



Click chemistry inspired syntheses of new amide linked 1,2,3-triazoles from naphthols: biological evaluation and in silico computational study

Satish V. Akolkar¹ · Mubarak H. Shaikh^{1,2} · Mininath K. Bhalmode¹ · Prabhakar U. Pawar³ · Jaiprakash N. Sangshetti⁴ · Manoj G. Damale⁵ · Bapurao B. Shingate¹

Received: 1 December 2022 / Accepted: 21 March 2023 / Published online: 30 March 2023
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Abstract

In search of new active molecules, a small focused library of new 1,2,3-triazoles derived from naphthols were efficiently prepared via the click chemistry approach. The synthesized triazole derivatives were evaluated for their antifungal, antioxidant and antitubercular activities. Furthermore, to rationalize the observed biological activity data, the molecular docking study has also been carried out against the active site of cytochrome P450 lanosterol 14 α -demethylase of *C. albicans* to understand the binding affinity and binding interactions of enzyme and synthesized derivatives, which revealed a significant correlation between the binding score and biological activity for these compounds. The results of the in vitro and In Silico study suggest that the 1,2,3-triazole derivatives may possess the ideal structural requirements for the further development of novel therapeutic agents.

Keywords Click chemistry · 1,2,3-triazoles · Naphthol · Antifungal activity · Antioxidant activity · Molecular docking · Alkynes

Introduction

Invasive fungal infections remain a significant threat to public health in critically ill patients in the last few decades [1]. The occurrence of fungal infections has risen significantly in recent years due to the regular use of modern medical devices including, stents, catheters and ventilators. Also, in organ transplantation,

Dedicated to Carolyn R. Bertozzi, Morten Meldal and K. Barry Sharpless for the Nobel Prize in Chemistry 2022.

✉ Bapurao B. Shingate
bapushingate@gmail.com

Extended author information available on the last page of the article

anticancer chemotherapy, HIV infection and neutropenia in the case of immune compromised individuals [2]. Apart from the medical factors which leads to the expansion of fungal pathogens, the production of newly pathogenic fungal species can be related to changes in the environment as well as global climate change [3]. Fungal infections in the immunocompromised patients are severe and difficult to treat. Nevertheless, a separate class of chemotherapeutic agents such as pyrimidines, polyenes, azoles, echinocandins and allylamines were used to treat fungal infections with a different mode of action including ergosterol inhibition, protein, glucan, chitin, microtubule and nucleic acid synthesis [4]. Currently, azole-based antifungal agents were commonly used in the treatment of fungal infections. Eflinaconazole, Isavuconazole, Voriconazole, Fluconazole and Posaconazole are the recently introduced triazole containing antifungal drugs [5, 6]. However, azoles are the major source of anti-fungal treatment, which results into pathogen resistance [7]. Nevertheless, the development of a new chemical structure, which will enhance clinical results associated with fungal infections, remains a key challenge for researchers. All of the above facts indicates the need for new azoles with enhanced efficacy, oral bioavailability, elaborated potency and minimized adverse effects with toxicity.

Azole is also a selective inhibitor of the CYP51 fungal enzyme and used to treat fungal infections caused by *Candida albicans* and *Aspergillus fumigatus*. Triazoles have been commonly used in the treatment of fungal infections due to their wide therapeutic index. Triazoles inhibit the growth and replication of fungi through a mechanism including interaction with cytochrome P450 14 α -demethylase (CYP51), which plays a vital role in ergosterol biosynthesis. The CYP51 enzyme catalyzes oxidative removal of a 14 α -methyl group of lanosterol by monooxygenase activity [8]. Azoles disrupt this oxidative removal by binding *N*-4 azole to CYP51 iron protoporphyrin unit, which results in ergosterol depletion and 14 α -methylated sterol accumulation. This affects membrane fluidity and membrane enzyme activity, which leads to fungal growth being retarded [9].

The conjugation of functional molecules through 1,2,3-triazole has received great attention in drug design and discovery [10, 11]. The triazole has two H-bond acceptors and capable of interacting with the biomolecular targets through H-bonding, π - π stacking, and dipole interaction. The triazole ring exhibits better chemical stability in biological environments, and improves the pharmacokinetic and toxicity properties. The formation of 1,2,3-triazole compounds via a Cu(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition (CuAAC) reaction, often referred to as click chemistry, is widely used for the rapid assembly of heterocyclic molecules that may be subsequently used as candidate leads in drug development [12]. The 1,2,3-triazoles based compounds exhibited a wide range of biological activities such as antiangiogenesis [13], selective sphingosine kinase-2 inhibitors [14], antiproliferative agents [15], antitubercular [16], antifungal [17], antioxidant [18], anti-prostate cancer agent [19] and xanthine oxidase inhibition activity [20].

There are some 1,2,3-triazole-containing molecules are available in the market or in the clinical trials. Some of the 1,2,3-triazoles based potential pharmaceuticals consist of the Rufinamide, Carboxyamidotriazole (CAI), tert-butyl-dimethylsilyl-spiroaminooxathioledioxide (TSAO), Tazobactam, Cefatrizine and I-A09 (Fig. 1).

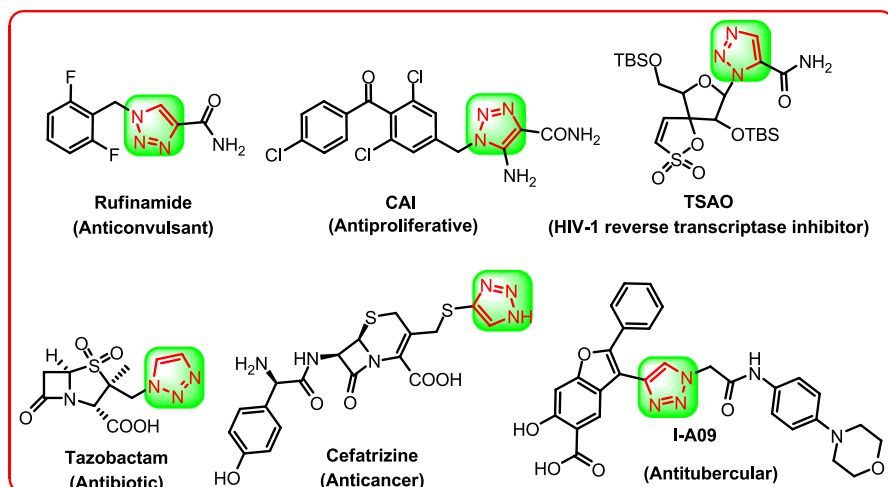


Fig. 1 1,2,3-Triazole based marketed drugs

1,4-Disubstituted-1,2,3-triazoles bearing amide functionality displays various biological activities and some representative examples are shown in Fig. 2. Pal et al. [21] synthesized amide based 1,3,4-oxadiazole-tethered 1,2,3-triazoles as antibacterial agents. Wang et al. synthesized [22] amide linked triazine-triazole and amide linked 2,4,5-triarylimidazole-1,2,3-triazole [23] as potential α -glucosidase inhibitors. Ferroni et al. reported [24] amide linked 1,4-disubstituted 1,2,3-triazole as nonsteroidal anti-androgens for prostate cancer treatment (Fig. 2).

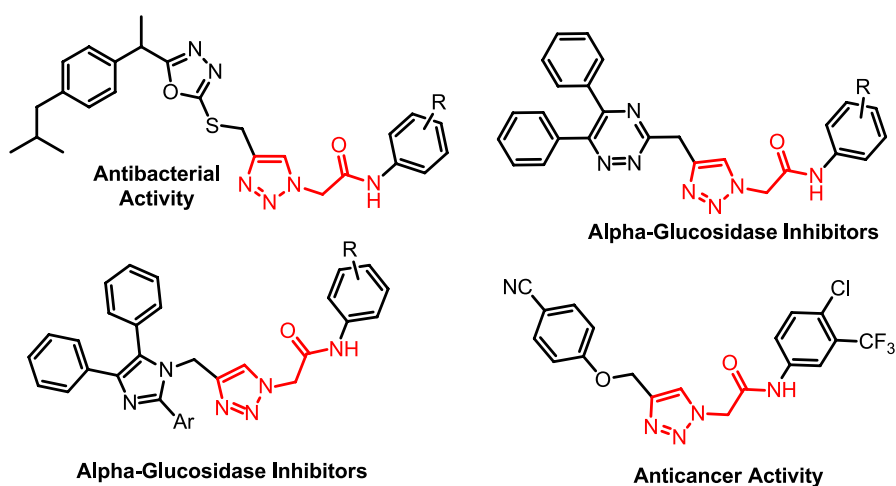


Fig. 2 Bioactive amide linked 1,4-di-substituted-1,2,3-triazoles

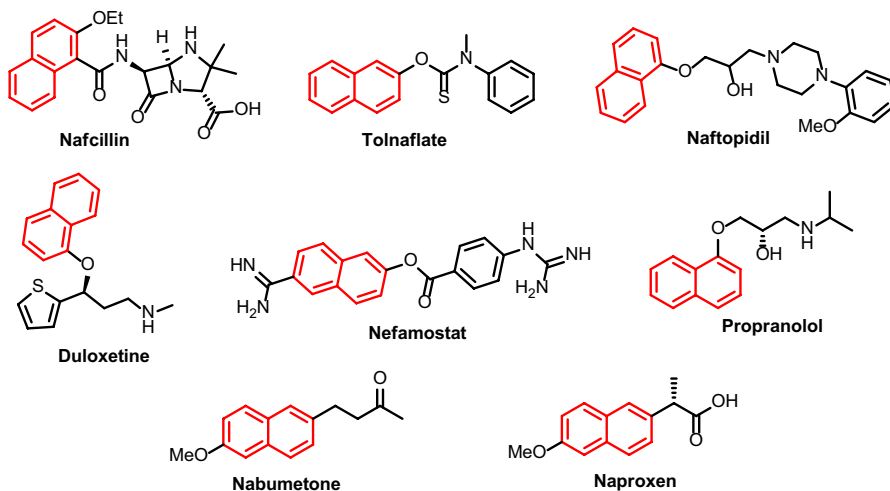


Fig. 3 Naphthol based drugs/bioactive compounds

Naphthol containing/derived drugs like Nafcillin [25] (Fig. 3) act as an antibiotic.

Tolnaftate (INN) drug is used to treat fungal infections, which inhibit squalene epoxidase, a vital enzyme in the ergosterol biosynthesis [26]. Naftopidil acts as a selective α_1 -adrenergic receptor antagonist [27]. Duloxetine acts as antidepressant agent [28]. Nefamostat is an anticoagulant agent (Fig. 3). [29]

Propranolol is used to treat high blood pressure and irregular heart rate as a β -adrenergic blocking agent [30]. Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) [31]. Naproxen is also nonsteroidal anti-inflammatory drug (NSAID) used to treat pain, inflammatory diseases and menstrual cramps and a nonselective COX inhibitor (Fig. 3) [32].

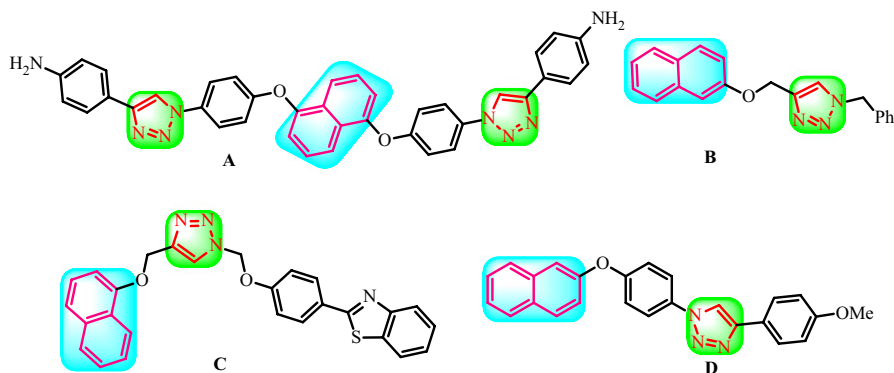


Fig. 4 Naphthol based 1,2,3-triazole derivatives

In recent years, a library of naphthol derivatives conjugated with 1,2,3-triazole were synthesized and shown in the Fig. 4. Balasubramanian et al. [33] synthesized naphthol derived bis-1,2,3-triazole derivative (**A**). Castillo et al. [34] synthesized β -naphthol fused with 1,2,3-triazole derivatives (**B**), Nehra and coworkers reported [35] derivatives of α -naphthol fused with 1,2,3-triazole and benzthiazole heterocycle (**C**), Tai et al. [36] synthesized β -naphthol fused with 1,2,3-triazole derivatives (**D**).

Mycobacterium Tuberculosis (MTB) bacteria causes Tuberculosis (TB), which is a communicable disease and the major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (COVID-19) pandemic in 2019, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. World Health Organization (WHO) in its 2020 report included a provisional assessment of the impact of the COVID-19 pandemic on TB services, TB disease burden and progress towards targets [37]. In TB, the major cause of tissue inflammation is oxidative stress. Due to the poor dietary intake of micronutrients, free radicals burst from activated macrophages and anti-tuberculosis drugs during illness. The free radicals can lead to pulmonary inflammation, if they are not neutralized by the antioxidants [38]. To inhibit the pulmonary inflammation progress, antioxidants can prevent the formation of free radicals by scavenging or inhibiting the generation of reactive oxygen species (ROS) [39].

Considering the medicinal importance of amide linked 1,2,3-triazoles derived from phenols, naphthalene/naphthol based bioactive compounds/drugs, herein we would like to incorporate these scaffolds in a single molecular motif via molecular hybridization approach which may displays better bioactivities. In continuation to our earlier work [16–18, 40–46], we have designed and synthesized a small focused library of 1,2,3-triazole incorporated naphthol derivatives via click chemistry and their antifungal, antitubercular and antioxidant activities. In addition to this, we have performed molecular docking study for antifungal activity and ADME prediction of synthesized 1,2,3-triazole derivatives were also performed.

Experimental section

Chemistry

Materials and methods

All the solvents and reagents were purchased from commercial suppliers, Sigma Aldrich, Rankem India Ltd. and Spectrochem Pvt. Ltd. and were used without further purification. The completion of the reactions was monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel $^{60}\text{F}_{254}$, 0.25 mm thickness (Merck). The detection of the components were made by exposure to iodine vapours or UV light. Melting points were determined by open capillary methods and are uncorrected. ^1H NMR spectra were recorded in $\text{DMSO}-d_6$ on a Bruker DRX-400 and 500 MHz spectrometer. ^{13}C NMR spectra were recorded in $\text{DMSO}-d_6$ on a Bruker DRX-100 and 125 MHz spectrometer. IR spectra were recorded using

a Bruker ALPHA ECO-ATR FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) mass spectrometer.

General procedure for the synthesis of (prop-2-yn-1-yloxy)naphthalene (2a-b)

To the stirred solution of 1-naphthol or 2-naphthol **1a-b** (20 mmol) in DMF (20 mL), K_2CO_3 (24 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, which results into the corresponding oxyanion. To this mixture, propargyl bromide (20 mmol) was added and stirred for 2 h [47, 48]. The progress of the reaction was monitored by TLC using *n*-hexane:ethyl acetate (9:1) as a solvent system. The reaction was quenched by crushed ice. The reaction mixture was extracted with ethylacetate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and obtained thick oily product was used for further reaction without purification.

General experimental procedure for the synthesis of 2-chloro-*N*-phenylacetamides (4a-m)

The stirred solution of appropriate anilines **3a-m** (20 mmol) in dichloromethane (DCM) (20 mL), triethylamine (20 mmol) was added. The reaction mixture was stirred at 0 °C till the addition of chloroacetyl chloride (20 mmol) and then stirred at room temperature for 3–5 h. This resulted into the corresponding 2-chloro-*N*-phenylacetamide [21, 40]. The progress of the reaction was monitored by TLC using *n*-hexane:ethyl acetate (9:1) as a solvent system the reaction was quenched by crushed ice. In case of solid product, it was filtered and the obtained crude solid product and used for the further reaction without purification. In case of liquid product, the reaction mixture was extracted with ethylacetate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and obtained liquid was used for further step without purification.

General experimental procedure for the synthesis of 2-azido-*N*-phenylacetamides (5a-m)

The stirred solution of appropriate 2-chloro-*N*-phenylacetamides **4a-m** (20 mmol) and sodium azide (NaN_3) (30 mmol) in toluene:water (20 mL, 8:2), refluxed for 5–7 h [21, 40]. The progress of the reaction was monitored by TLC using hexane:ethyl acetate (9:1) as a solvent system. After the completion of reaction, toluene was removed under reduced pressure and then the reaction was quenched by crushed ice. In case of solid product, it was filtered and the obtained crude solid product was crystallized using ethanol. The crystallized products were taken for next step. When the products are liquid, it has been extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 . The solvent was removed under reduced pressure and used for the further reaction without purification.

General experimental procedure for the synthesis of substituted 2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (6a-m and 7a-m)

To the stirred solution of (prop-2-yn-1-yloxy)naphthalene **2a-b** (0.5 mmol), appropriate substituted 2-azido-*N*-phenylacetamide **5a-m** (0.5 mmol) and copper diacetate ($\text{Cu}(\text{OAc})_2$) (10 mol %) in *t*-BuOH- H_2O (3:1, 8 mL) were added and the resulting mixture was stirred at room temperature for 6–8 h. The progress of the reaction was monitored by TLC using hexane:ethyl acetate (8:2) as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2×15 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. The obtained crude compounds were recrystallized by using ethanol.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (6a)

The compound **6a** was obtained via 1,3-dipolar cycloaddition reaction between azide **5a** and alkyne **2a**. IR ν_{max} cm^{-1} : 3262 (–NH), 3078 (–CH), 1671 (C=O), 1599 (C=C, Ar), 1303 (–C–N) and 1254 (–C–O).

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide (6b)

The compound **6b** was obtained via 1,3-dipolar cycloaddition reaction between azide **5b** and alkyne **2a**. IR ν_{max} cm^{-1} : 3292 (–NH), 2990 (–CH), 1682 (C=O), 1587 (C=C, Ar), 1504 (–NO₂ asymmetric), 1340 (–C–N) and 1275 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 5.38 (s, 2H, –NCH₂CO–), 5.48 (s, 2H, –OCH₂), 7.20 (d, 1H, *J*=8.0 Hz, Ar-*H*), 7.40–7.54 (m, 5H, Ar-*H*), 7.72 (t, 2H, *J*=8.0 Hz, Ar-*H*), 7.87 (d, 1H, *J*=8.0 Hz, Ar-*H*), 8.0 (d, 1H, *J*=8.0 Hz), 8.12 (d, 1H, *J*=8.0 Hz), 8.36 (s, 1H, triazole) and 10.79 (s, 1H, –NH). ¹³C NMR (100 MHz, DMSO-*d*₆, δ ppm): 52.0, 61.6, 105.8, 120.3, 121.6, 124.9, 125.1, 125.4, 125.6, 126.0, 126.2, 126.3, 126.5, 127.5, 130.4, 134.2, 142.4, 142.8, 153.5 and 165.0. HRMS calculated [M+H]⁺ for C₂₁H₁₈N₅O₄: 404.1359 and found: 404.1348.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl)acetamide (6c)

The compound **6c** was obtained via 1,3-dipolar cycloaddition reaction between azide **5c** and alkyne **2a**. IR ν_{max} cm^{-1} : 3302 (–NH), 3150 (–CH), 1676 (C=O), 1601 (C=C, Ar), 1535 (–NO₂ asymmetric), 1295 (–C–N) and 1209 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 5.40 (s, 2H, –NCH₂CO–), 5.46 (s, 2H, –OCH₂), 7.22 (d, 1H, *J*=8.0 Hz, Ar-*H*), 7.43–7.55 (m, 4H, Ar-*H*), 7.65 (t, 1H, *J*=8.0 Hz, Ar-*H*), 7.86–7.98 (m, 3H, Ar-*H*), 8.13 (d, 1H, *J*=8.0 Hz, Ar-*H*), 8.40 (s, 1H, triazole), 8.61 (s, 1H, Ar-*H*) and 11.02 (s, 1H, –NH). ¹³C NMR (100 MHz, DMSO-*d*₆, δ ppm): 52.6, 61.9, 106.1, 113.7, 118.7, 120.6, 121.8, 125.2, 125.6, 125.7, 126.5, 126.6,

126.8, 127.8, 130.8, 134.4, 139.8, 143.0, 148.3, 153.8 and 165.5. HRMS calculated $[M+H]^+$ for $C_{21}H_{18}N_5O_4$: 404.1359 and found: 404.1338.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (6d)

The compound **6d** was obtained via 1,3-dipolar cycloaddition reaction between azide **5d** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3260 (–NH), 3089 (–CH), 1683 (C=O), 1591 (C=C, Ar), 1504 (–NO₂ asymmetric), 1292 (–C–N) and 1219 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 5.39 (*s*, 2H, –NCH₂CO–), 5.48 (*s*, 2H, –OCH₂), 7.22 (*d*, 1H, *J*=8.0 Hz, Ar–*H*), 7.46–7.53 (*m*, 4H, Ar–*H*), 7.83–7.89 (*m*, 3H, Ar–*H*), 8.13 (*d*, 1H, *J*=8.0 Hz, Ar–*H*), 8.26 (*d*, 2H, *J*=8.0 Hz, Ar–*H*), 8.40 (*s*, 1H, triazole) and 11.13 (*s*, 1H, –NH). HRMS calculated $[M+H]^+$ for $C_{21}H_{18}N_5O_4$: 404.1359 and found: 404.1338.

N-(2-Methoxyphenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6e)

The compound **6e** was obtained via 1,3-dipolar cycloaddition reaction between azide **5e** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3302 (–NH), 3150 (–CH), 1676 (C=O), 1601 (C=C, Ar), 1295 (–C–N) and 1209 (–C–O). HRMS calculated $[M+H]^+$ for $C_{22}H_{21}N_4O_3$: 389.1614 and found: 389.1630.

N-(3-Methoxyphenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6f)

The compound **6f** was obtained via 1,3-dipolar cycloaddition reaction between azide **5f** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3204 (–NH), 3054 (–CH), 1666 (C=O), 1631 (C=C, Ar), 1269 (–C–N) and 1216 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 3.81 (*s*, 3H, Ar-OMe), 5.39 (*s*, 2H, –NCH₂CO–), 5.45 (*s*, 2H, –OCH₂), 6.77 (*d*, 1H, *J*=8.0 Hz, Ar–*H*), 7.19 (*d*, 1H, *J*=8.0 Hz, Ar–*H*), 7.25–7.40 (*m*, 3H, Ar–*H*), 7.45 (*t*, 1H, *J*=8.0 Hz, Ar–*H*), 7.57 (*t*, 1H, *J*=8.0 Hz, Ar–*H*), 7.63 (*s*, 1H, Ar–*H*), 7.93 (*d*, 3H, *J*=8.0 Hz, Ar–*H*), 8.41 (*s*, 1H, triazole), and 10.59 (*s*, 1H, –NH). HRMS calculated $[M+H]^+$ for $C_{22}H_{21}N_4O_3$: 389.1614 and found: 389.1630.

N-(4-Methoxyphenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6g)

The compound **6g** was obtained via 1,3-dipolar cycloaddition reaction between azide **5g** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3262 (–NH), 3093 (–CH), 1694 (C=O), 1657 (C=C, Ar), 1287 (–C–N) and 1236 (–C–O). HRMS calculated $[M+H]^+$ for $C_{22}H_{21}N_4O_3$: 389.1614 and found: 389.1630.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (6 h)

The compound **6 h** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 h** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3260 (–NH), 3089 (–CH), 1683 (C=O), 1591 (C=C, Ar), 1292 (–C–N) and 1219 (–C–O). ^1H NMR (200 MHz, CDCl_3 , δ ppm): 2.08 (s, 3H, Ar–Me), 5.21 (s, 2H, –NCH₂CO–), 5.41 (s, 2H, –OCH₂), 6.93 (d, 1H, $J=8.0$ Hz, Ar–H), 7.0–7.26 (m, 4H, Ar–H), 7.33–7.49 (m, 4H, Ar–H), 7.72–7.81 (m, 2H, Ar–H), 7.89 (s, 1H, triazole) and 8.16–8.24 (m, 1H, Ar–H). HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_2$: 373.1665 and found: 373.1678.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(m-tolyl)acetamide (6i)

The compound **6i** was obtained via 1,3-dipolar cycloaddition reaction between azide **5i** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3266 (–NH), 3083 (–CH), 1675 (C=O), 1596 (C=C, Ar), 1273 (–C–N) and 1221 (–C–O). ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ ppm): 2.28 (s, 3H, Ar–Me), 5.37 (s, 2H, –NCH₂CO–), 5.38 (s, 2H, –OCH₂), 6.91 (d, 1H, $J=8.0$ Hz, Ar–H), 7.21 (t, 2H, $J=8.0$ Hz, Ar–H), 7.37 (d, 1H, $J=8.0$ Hz, Ar–H), 7.43 (s, 1H, Ar–H), 7.45–7.52 (m, 4H, Ar–H), 7.88 (d, 1H, $J=8.0$ Hz, Ar–H), 8.13 (d, 1H, $J=8.0$ Hz, Ar–H), 8.38 (s, 1H, triazole), and 10.44 (s, 1H, –NH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ ppm): 21.0, 52.1, 61.4, 105.6, 116.2, 119.6, 120.1, 121.3, 124.3, 124.7, 125.2, 126.0, 126.3, 127.3, 128.6, 133.9, 138.0, 138.2, 142.4, 148.3, 153.3 and 164.0. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_2$: 373.1665 and found: 373.1678.

2-(4-((Naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (6j)

The compound **6j** was obtained via 1,3-dipolar cycloaddition reaction between azide **5j** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3248 (–NH), 3075 (–CH), 1698 (C=O), 1614 (C=C, Ar), 1243 (–C–N) and 1193 (–C–O). ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm): 2.22 (s, 3H, Ar–Me), 5.22 (s, 2H, –NCH₂CO–), 5.31 (s, 2H, –OCH₂), 6.91–7.03 (m, 3H, Ar–H), 7.29–7.40 (m, 5H, Ar–H), 7.61 (d, 1H, $J=8.0$ Hz, Ar–H), 7.71 (d, 1H, $J=8.0$ Hz, Ar–H), 8.03 (s, 1H, triazole), 8.14 (d, 1H, $J=8.0$ Hz, Ar–H) and 10.10 (s, 1H, –NH). ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm): 19.8, 51.7, 61.0, 104.2, 118.6, 119.5, 120.0, 120.9, 121.2, 121.6, 124.0, 124.1, 124.3, 124.8, 125.4, 126.3, 126.9, 128.2, 132.5, 133.3, 145.4, and 162.4. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_2$: 373.1665 and found: 373.1649.

N-(2-Chlorophenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6 k)

The compound **6 k** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 k** and alkyne **2a**. IR ν_{\max} cm^{-1} : 3267 (–NH), 2934 (–CH), 1671 (C=O), 1590 (C=C, Ar), 1289 (–C–N), 1212 (C–O) and 743 (–C–Cl). ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ ppm): 5.40 (s, 2H, –NCH₂CO–), 5.53 (s, 2H, –OCH₂), 7.22 (t, 2H, $J=8.0$ Hz, Ar–H), 7.34 (t, 1H, $J=8.0$ Hz, Ar–H), 7.43–7.54 (m, 5H, Ar–H), 7.78 (d, 1H, $J=8.0$ Hz, Ar–H), 7.87 (d, 1H, $J=8.0$ Hz, Ar–H), 8.14 (d, 1H, $J=8.0$ Hz,

Ar-*H*), 8.41 (*s*, 1H, triazole) and 10.14 (*s*, 1H, -NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 52.1, 61.7, 105.8, 120.4, 119.5, 121.6, 124.9, 125.4, 125.9, 126.2, 126.4, 126.5, 126.8, 127.5, 127.6, 129.7, 134.2, 142.7, 153.5 and 165.0. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{ClN}_4\text{O}_2$: 393.1118 and found: 393.1109.

N-(3-Chlorophenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6 l)

The compound **6 l** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 l** and alkyne **2a**. IR ν_{max} cm^{-1} : 3257 (-NH), 3080 (-CH), 1672 (C=O), 1595 (C=C, Ar), 1349 (-C-N), 1237 (C-O) and 742 (-C-Cl). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 5.39 (*s*, 2H, -NCH₂CO-), 5.41 (*s*, 2H, -OCH₂), 7.15–7.23 (*dd*, 2H, Ar-*H*), 7.38 (*t*, 1H, $J=8.0$ Hz, Ar-*H*), 7.45–7.53 (*m*, 6H, Ar-*H*), 7.79 (*s*, 1H, Ar-*H*), 7.88 (*d*, 1H, $J=8.0$ Hz, Ar-*H*), 8.13 (*d*, 1H, $J=8.0$ Hz, Ar-*H*), 8.39 (*s*, 1H, triazole) and 10.71 (*s*, 1H, -NH). HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{ClN}_4\text{O}_2$: 393.1118 and found: 393.1109.

N-(4-Chlorophenyl)-2-(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6 m)

The compound **6 m** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 m** and alkyne **2a**. IR ν_{max} cm^{-1} : 3291 (-NH), 3071 (-CH), 1678 (C=O), 1606 (C=C, Ar), 1287 (-C-N), 1136 (-C-O) and 785 (-C-Cl). HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{ClN}_4\text{O}_2$: 393.1118 and found: 393.1112.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (7a)

The compound **7a** was obtained via 1,3-dipolar cycloaddition reaction between azide **5a** and alkyne **2b**. IR ν_{max} cm^{-1} : 3260 (-NH), 3034 (-CH), 1670 (C=O), 1592 (C=C, Ar), 1289 (-C-N) and 1210 (-C-O).

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide (7b)

The compound **7b** was obtained via 1,3-dipolar cycloaddition reaction between azide **5b** and alkyne **2b**. IR ν_{max} cm^{-1} : 3197 (-NH), 3087 (-CH), 1658 (C=O), 1598 (C=C, Ar), 1503 (-NO₂), 1341 (-C-N) and 1255 (-C-O). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 5.29 (*s*, 2H, -NCH₂CO-), 5.46 (*s*, 2H, -OCH₂), 7.20 (*d*, 1H, $J=8.0$ Hz, Ar-*H*), 7.34–7.49 (*m*, 3H, Ar-*H*), 7.53 (*s*, 1H, Ar-*H*), 7.68–7.76 (*m*, 2H, Ar-*H*), 7.84 (*d*, 3H, $J=8.0$ Hz, Ar-*H*), 7.99 (*d*, 1H, $J=8.0$ Hz, Ar-*H*), 8.29 (*s*, 1H, triazole) and 10.79 (*s*, 1H, -NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 52.6, 61.7, 107.8, 119.4, 124.4, 125.7, 126.2, 126.6, 127.1, 127.4, 128.2, 129.2, 123.0, 130.9, 134.8, 143.1, 156.6 and 165.6. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{N}_5\text{O}_4$: 404.1359 and found: 404.1345.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl)acetamide (7c)

The compound **7c** was obtained via 1,3-dipolar cycloaddition reaction between azide **5c** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3257 (–NH), 3066 (–CH), 1688 (C=O), 1593 (C=C, Ar), 1506 (–NO₂), 1338 (–C–N) and 1259 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 5.31 (*s*, 2H, –NCH₂CO–), 5.44 (*s*, 2H, –OCH₂), 7.21 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.36 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.47 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.54 (*s*, 1H, Ar-*H*), 7.65 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.84 (*d*, 3H, *J*=8.0 Hz, Ar-*H*), 7.89–7.97 (*m*, 2H, Ar-*H*), 8.35 (*s*, 1H, triazole), 8.61 (*s*, 1H, Ar-*H*) and 11.01 (*s*, 1H, –NH). ¹³C NMR (100 MHz, DMSO-*d*₆, δ ppm): 52.5, 61.3, 107.4, 113.6, 118.6, 119.0, 124.0, 125.5, 126.7, 127.0, 127.8, 128.8, 129.6, 130.7, 134.4, 139.7, 142.7, 148.2, 156.2 and 165.4. HRMS calculated [M+H]⁺ for C₂₁H₁₈N₅O₄: 404.1359 and found: 404.1364.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (7d)

The compound **7d** was obtained via 1,3-dipolar cycloaddition reaction between azide **5d** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3207 (–NH), 3047 (–CH), 1690 (C=O), 1606 (C=C, Ar), 1501 (–NO₂), 1310 (–C–N) and 1205 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 5.31 (*s*, 2H, –NCH₂CO–), 5.46 (*s*, 2H, –OCH₂), 7.21 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.37 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.47 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.54 (*s*, 1H, Ar-*H*), 7.82–7.84 (*m*, 5H, Ar-*H*), 8.26 (*d*, 2H, *J*=8.0 Hz, Ar-*H*), 8.34 (*s*, 1H, triazole) and 11.11 (*s*, 1H, –NH). HRMS calculated [M+H]⁺ for C₂₁H₁₈N₅O₄: 404.1359 and found: 404.1364.

N-(2-Methoxyphenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7e)

The compound **7e** was obtained via 1,3-dipolar cycloaddition reaction between azide **9e** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3204 (–NH), 3054 (–CH), 1666 (C=O), 1631 (C=C, Ar), 1269 (–C–N) and 1216 (–C–O). ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 3.86 (*s*, 3H, Ar-OMe), 5.29 (*s*, 2H, –NCH₂CO–), 5.47 (*s*, 2H, –OCH₂), 6.92 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.10 (*q*, 2H, *J*=8.0 Hz, Ar-*H*), 7.20 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.37 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.47 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.54 (*s*, 1H, Ar-*H*), 7.84 (*d*, 3H, *J*=8.0 Hz, Ar-*H*), 7.93 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 8.31 (*s*, 1H, triazole) and 9.77 (*s*, 1H, –NH). ¹³C NMR (100 MHz, DMSO-*d*₆, δ ppm): 48.6, 55.7, 61.1, 107.1, 111.3, 118.7, 120.3, 121.8, 123.7, 124.9, 126.5, 126.8, 127.6, 128.6, 129.4, 134.2, 142.4, 149.6, 156.0 and 164.5. HRMS calculated [M+H]⁺ for C₂₂H₂₁N₄O₃: 389.1614 and found: 389.1624.

N-(3-Methoxyphenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7f)

The compound **7f** was obtained via 1,3-dipolar cycloaddition reaction between azide **5f** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3235 (–NH), 3025 (–CH), 1670 (C=O),

1615 (C=C, Ar), 1290 (–C–N) and 1226 (–C–O). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 3.72 (*s*, 3H, Ar-OMe), 5.30 (*s*, 2H, –NCH₂CO–), 5.36 (*s*, 2H, –OCH₂), 6.67 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.10 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.19–7.26 (*m*, 2H, Ar-*H*), 7.29 (*s*, 1H, Ar-*H*), 7.36 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.48 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.54 (*s*, 1H, Ar-*H*), 7.84 (*d*, 3H, *J*=8.0 Hz, Ar-*H*), 8.32 (*s*, 1H, triazole) and 10.50 (*s*, 1H, –NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 51.5, 55.0, 60.3, 106.4, 110.6, 118.0, 119.6, 121.0, 123.0, 124.2, 125.8, 126.1, 126.8, 127.9, 128.7, 133.5, 141.7, 148.9, 155.2 and 163.8. HRMS calculated $[\text{M}+\text{H}]^+$ for C₂₂H₂₁N₄O₃: 389.1614 and found: 389.1629.

N-(4-Methoxyphenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7 g)

The compound **7 g** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 g** and alkyne **2b**. IR ν_{max} cm⁻¹: 3263 (–NH), 3065 (–CH), 1667 (C=O), 1594 (C=C, Ar), 1297 (–C–N) and 1213 (–C–O). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 3.72 (*s*, 3H, Ar-OMe), 5.30 (*s*, 2H, –NCH₂CO–), 5.32 (*s*, 2H, –OCH₂), 6.91 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.21 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.36 (*t*, 1H, Ar-*H*), 7.48–7.54 (*m*, 4H, Ar-*H*), 7.84 (*d*, 2H, *J*=8.0 Hz, Ar-*H*), 8.31 (*s*, 1H, triazole) and 10.35 (*s*, 1H, –NH). HRMS calculated $[\text{M}+\text{H}]^+$ for C₂₂H₂₁N₄O₃: 389.1614 and found: 389.1629.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (7 h)

The compound **7 h** was obtained via 1,3-dipolar cycloaddition reaction between azide **5 h** and alkyne **2b**. IR ν_{max} cm⁻¹: 3235 (–NH), 3025 (–CH), 1670 (C=O), 1615 (C=C, Ar), 1290 (–C–N) and 1226 (–C–O). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 2.24 (*s*, 3H, Ar-Me), 5.30 (*s*, 2H, –NCH₂CO–), 5.42 (*s*, 2H, –OCH₂), 7.11 (*d*, 1H, *J*=8.0 Hz, Ar-*H*), 7.15–7.24 (*m*, 3H, Ar-*H*), 7.36 (*t*, 1H, *J*=8.0 Hz, Ar-*H*), 7.42–7.49 (*m*, 2H, Ar-*H*), 7.54 (*s*, 1H, Ar-*H*), 7.84 (*d*, 3H, *J*=8.0 Hz, Ar-*H*), 8.32 (*s*, 1H, triazole) and 9.82 (*s*, 1H, –NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 18.5, 52.7, 61.8, 107.8, 119.4, 124.4, 125.4, 126.3, 126.8, 127.2, 127.5, 128.2, 129.3, 130.1, 131.2, 132.3, 134.9, 136.2, 143.1, 156.7 and 165.1. HRMS calculated $[\text{M}+\text{H}]^+$ for C₂₂H₂₁N₄O₂: 373.1665 and found: 373.1679.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(m-tolyl)acetamide (7i)

The compound **7i** was obtained via 1,3-dipolar cycloaddition reaction between azide **5i** and alkyne **2b**. IR ν_{max} cm⁻¹: 3248 (–NH), 3075 (–CH), 1698 (C=O), 1614 (C=C, Ar), 1243 (–C–N) and 1193 (C–O). ^1H NMR (200 MHz, CDCl₃, δ ppm): 2.09 (*s*, 3H, Ar-Me), 5.24 (*s*, 2H, –NCH₂CO–), 5.39 (*s*, 2H, –OCH₂), 7.08–7.20 (*m*, 4H, Ar-*H*), 7.31–7.49 (*m*, 3H, Ar-*H*), 7.73–7.83 (*m*, 5H, Ar-*H*) and 7.88 (*s*, 1H, triazole). HRMS calculated $[\text{M}+\text{H}]^+$ for C₂₂H₂₁N₄O₂: 373.1665 and found: 373.1655.

2-(4-((Naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (7j)

The compound **7j** was obtained via 1,3-dipolar cycloaddition reaction between azide **5j** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3302 (–NH), 3150 (–CH), 1676 (C=O), 1601 (C=C, Ar), 1315 (–C–N) and 1235 (–C–O). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 2.25 (s, 3H, Ar–Me), 5.30 (s, 2H, –NCH₂CO–), 5.35 (s, 2H, –OCH₂), 7.14 (d, 2H, $J=8.0$ Hz, Ar–H), 7.21 (d, 1H, $J=8.0$ Hz, Ar–H), 7.36 (t, 1H, $J=8.0$ Hz, Ar–H), 7.47 (d, 3H, $J=8.0$ Hz, Ar–H), 7.54 (s, 1H, Ar–H), 7.84 (d, 3H, $J=8.0$ Hz, Ar–H), 8.32 (s, 1H, triazole) and 10.41 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 21.2, 52.9, 61.8, 107.8, 119.4, 119.9, 124.4, 127.2, 127.5, 128.3, 129.3, 130.0, 130.1, 133.5, 134.9, 136.6, 143.1, 156.7 and 164.7. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_2$: 373.1665 and found: 373.1650.

N-(2-Chlorophenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7k)

The compound **7k** was obtained via 1,3-dipolar cycloaddition reaction between azide **5k** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3280 (–NH), 3075 (–CH), 1662 (C=O), 1594 (C=C, Ar), 1373 (–C–N), 1259 (–C–O) and 686 (–C–Cl). HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{ClN}_4\text{O}_2$: 393.1118 and found: 393.1129.

N-(3-Chlorophenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7l)

The compound **7l** was obtained via 1,3-dipolar cycloaddition reaction between azide **5l** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3327 (–NH), 3075 (–CH), 1683 (C=O), 1589 (C=C, Ar), 1334 (–C–N), 1237 (–C–O) and 748 (–C–Cl). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 5.31 (s, 2H, –NCH₂CO–), 5.40 (s, 2H, –OCH₂), 7.16 (d, 1H, $J=8.0$ Hz, Ar–H), 7.21 (d, 1H, $J=8.0$ Hz, Ar–H), 7.37 (t, 2H, $J=8.0$ Hz, Ar–H), 7.46 (d, 2H, $J=8.0$ Hz, Ar–H), 7.54 (s, 1H, Ar–H), 7.80–7.85 (m, 4H, Ar–H), 8.34 (s, 1H, triazole) and 10.72 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 52.5, 61.3, 107.4, 117.9, 118.9, 119.0, 123.8, 124.0, 126.7, 127.0, 127.8, 128.8, 129.6, 130.9, 133.5, 134.4, 140.1, 142.7, 156.2 and 164.9. HRMS calculated $[\text{M} + \text{H}]^+$ for $\text{C}_{21}\text{H}_{18}\text{ClN}_4\text{O}_2$: 393.1118 and found: 393.1132.

N-(4-Chlorophenyl)-2-(4-((naphthalen-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (7m)

The compound **7m** was obtained via 1,3-dipolar cycloaddition reaction between azide **5m** and alkyne **2b**. IR ν_{\max} cm^{-1} : 3257 (–NH), 3078 (–CH), 1671 (C=O), 1609 (C=C, Ar), 1258 (–C–N), 1218 (–C–O) and 738 (–C–Cl). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 5.30 (s, 2H, –NCH₂CO–), 5.38 (s, 2H, –OCH₂), 7.21 (d, 1H, $J=8.0$ Hz, Ar–H), 7.34–7.41 (m, 3H, Ar–H), 7.48 (t, 1H, $J=8.0$ Hz, Ar–H), 7.54 (s, 1H, Ar–H), 7.62 (d, 2H, $J=8.0$ Hz, Ar–H), 7.84 (d, 3H, $J=8.0$ Hz, Ar–H), 8.33 (s, 1H, triazole) and 10.65 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 52.4, 61.2, 107.3, 118.8, 120.9, 123.9, 126.6, 126.9, 127.5, 127.7, 128.7,

129.0, 129.5, 134.3, 137.5, 142.5, 156.1 and 164.6. HRMS calculated $[M+H]^+$ for $C_{21}H_{18}ClN_4O_2$: 393.1118 and found: 393.1133.

Experimental protocol for biological activity

Antifungal activity

Antifungal activity was determined by the standard agar dilution method as per the CLSI (formerly, NCCLS) guidelines [49, 50]. The newly synthesized compounds were screened for their in vitro antifungal activity against five human pathogenic fungal strains including *Candida albicans* (NCIM 3471), *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *Aspergillus niger* (NCIM 1196), and *Cryptococcus neoformans* (NCIM 576). The synthesized compounds and the standard Miconazole were dissolved in DMSO. The medium yeast nitrogen base was dissolved in phosphate buffer of pH 7 and was autoclaved at 110 °C for 10 min. With each set, a growth control without the antifungal agent and solvent control DMSO were included. The fungal strains were freshly subcultured onto sabouraud dextrose agar (SDA) and incubated at 25 °C for 72 h. The fungal cells were suspended in sterile distilled water and diluted to get 10⁵ cells per mL. Ten mL of the standardized suspension was inoculated onto the control plates and the media incorporated with the antifungal agents. The inoculated plates were incubated at 25 °C for 48 h. The readings were taken at the end of 48 and 72 h. MIC is the lowest concentration of the drug preventing the growth of macroscopically visible colonies on the drug-containing plates when there is visible growth on the drug-free control plates.

Antitubercular activity using XRMA assay

MTB H37Ra was obtained from Astra Zeneca, India. It was grown in Diffco Dubos medium and was used for further study. The stock culture was maintained at -70 °C and subcultured once in *M. pheli* medium before inoculation into experimental culture. *MTB* was grown to a logarithmic phase (up to OD₆₂₀-1.0) in a defined *M. pheli* medium. They were solubilized in dimethyl sulfoxide (DMSO) and stored in aliquots at -20 °C. XTT sodium salt powder (Sigma) was prepared as a 1.25 mM stock solution in sterile 1X PBS and used immediately. Even Menadione (Sigma) was prepared as a 6 mM solution in DMSO and used immediately. Briefly, 2.5 µL of these inhibitor solutions were added into the 96 well plates. After that total volume was made up to 250 µL by using *M. pheli* medium consisting of 1 percent of 1 OD tubercular bacilli. The assay plates were incubated at 37 °C incubator. The incubation was terminated on the 8th day for *MTB* cultures. The XRMA was then performed to estimate the viable cells present in different wells of the assay plate. For that, in all wells of assay plate 200 µM XTT was added as a final concentration and incubate at 37 °C for 20 min. Then 60 µM Menadione was added as a final concentration and incubated at 37 °C for 40 min. The optical density (OD) was read on a micro plate reader (Spectramax plus 384 plate reader, Molecular Devices Inc.) at 470 nm filter against a blank prepared from cell free wells. Absorbance given

by cells treated with the vehicle DMSO alone was taken as 100% cell growth. All experiments were carried out in triplicates and the quantitative value was expressed as the average \pm standard.

The % inhibition of bacilli was measured by using following formula,

$$\% \text{ Inhibition} = (A_1 - \text{Blank}) / (A_2 - \text{Blank}) \times 100$$

where A_1 : Culture absorbance at 470 nm in the presence of the compound after addition of menadione. A_2 : Culture absorbance at 470 nm (DMSO solvent control) after addition of menadione. Blank: Culture absorbance at 470 nm of the respective data points before addition of XTT/menadione.

DPPH radical scavenging activity (Antioxidant activity)

The hydrogen atom or electron donation ability of the some compounds were measured from the bleaching of the purple colored methanol solution of 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 $\mu\text{g/mL}$) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. The reaction mixture was incubated at 37 °C. The scavenging activity on DPPH was determined by measuring the absorbance at 517 nm after 30 min. All tests were performed in triplicate and the mean values were entered. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation.

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

Where, A_{control} is the absorbance of the control (DPPH radical without test sample)

A_{sample} is the absorbance of the test sample (DPPH radical with test sample).

The control contains all reagents except the test samples.

Computational study

Molecular docking study

In current study we have tried to focus mostly on understand and analyze binding affinity, binding poses and pattern of molecular interactions of synthesized compounds with antifungal drug target cytochrome P450 lanosterol 14 α -demethylase of *C. albicans*. Molecular docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence, docking plays an important role in the rational design of drugs [51]. The three-dimensional homology model structure of cytochrome P450 lanosterol 14 α -demethylase of *C. albicans* was predicted using the theoretical methods of protein structure prediction, i.e. comparative modelling using the Biopredicta module of VLifeMDS 4.3 Pro-Model. The protein sequence of cytochrome P450 lanosterol 14 α -demethylase for *C. albicans* was retrieved from the protein knowledge database Universal Protein Resource

(UniProtKB) (<http://www.uniprot.org/>) (accession code: P10613) and its homologous template was identified from the protein structural database, i.e., Protein Data Bank (PDB) using Basic Local Alignment Search Tool for proteins (BLASTp). The homologous template identified using BLASTp solved the three-dimensional crystal structure of human lanosterol 14 α -demethylase (CYP51) complex with azole (PDB ID: 3LD6). To construct a basic framework and to build the loop regions of *C. albicans* cytochrome P450 lanosterol 14 α -demethylase, pairwise sequence alignment and loop refinement of CA-CYP51 (P10613) and human CYP51 (3LD6_B) were performed. Three-dimensional modelled protein structures were subjected to structural quality check programs such as PROCHECK and its other structural validation parameters [31].

Results and discussion

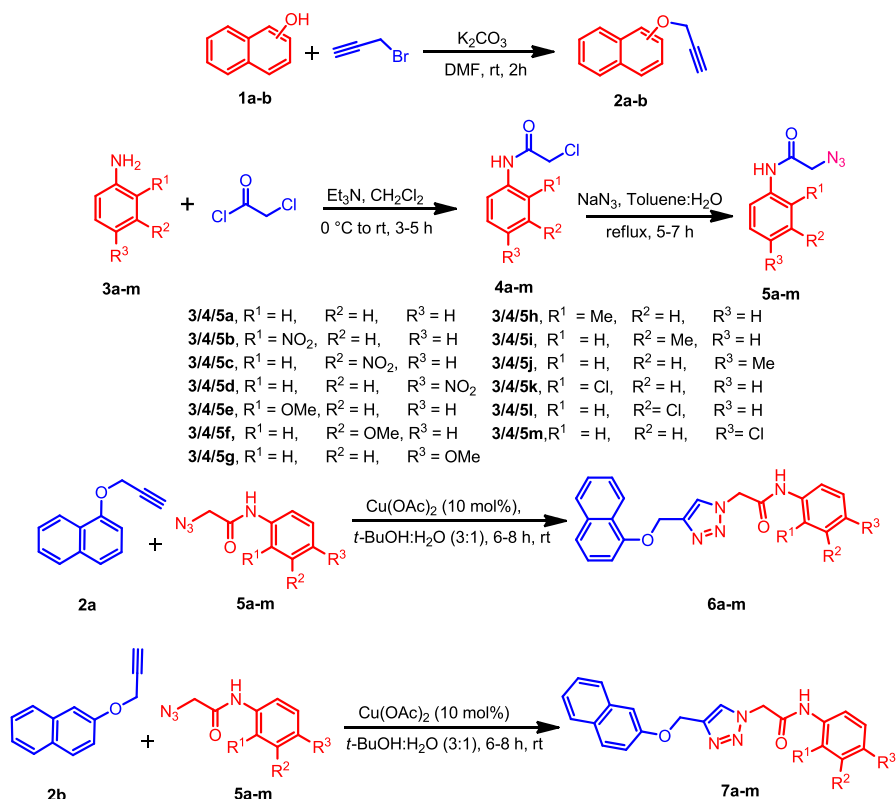
Chemistry

The 1,4-disubstituted-1,2,3-triazole derivatives **6a-m** and **7a-m** have been obtained by the 1,3-dipolar cycloaddition of 1-(prop-2-yn-1-yloxy)naphthalene **2a** or 2-(prop-2-yn-1-yloxy)naphthalene **2b** and 2-azido-*N*-phenylacetamides **5a-m** via click chemistry approach (Scheme 1).

The commercially available α -naphthol and β -naphthol were alkylated separately with propargyl bromide in the presence of K_2CO_3 as a base in *N,N*-dimethylformamide (DMF) afforded the corresponding alkyne based naphthalene derivatives **2a** and **2b** respectively in 83–93% yields (Scheme 1) [47, 48]. The synthesis of 2-azido-*N*-phenylacetamides **5a-m** have been achieved from the corresponding anilines **3a-m** via chloroacetylation using chloroacetyl chloride, followed by nucleophilic substitution with sodium azide in excellent yields (Scheme 1) [21, 40].

The Huisgen's CuAAC 1,3-dipolar cycloaddition reaction has been performed on (prop-2-yn-1-yloxy)naphthalene **2a** with 2-azido-*N*-phenylacetamides **5a** in the presence of $Cu(OAc)_2$ in *t*-BuOH- H_2O (3:1) at room temperature for 6.5 h to afford the naphthalene based 1,4-disubstituted-1,2,3-triazole **6a** in 89% yield (Scheme 1). Similarly, the 2-azido-*N*-phenylacetamides **5a-m** on 1,3-dipolar cycloaddition reaction with alkynes **2a-b** using $Cu(OAc)_2$ as catalyst in *t*-BuOH- H_2O at room temperature for 6–8 h resulted into the corresponding 1,4-disubstituted-1,2,3-triazole derivatives **6b-m** and **7a-m** in quantitative isolated yields (84–93%) (Scheme 1). The structures, time required, yield of the product and physical constants of all the 1,2,3-triazole **6a-m** and **7a-m** derivatives are shown in Fig. 5.

The preliminary synthetic data 1,4-disubstituted-1,2,3-triazole derivatives **6b-m** suggested that the quantitative isolated yields of the compounds are ranging in between 84 and 93% suggesting that the synthetic scheme has very efficient. The molecular docking result of 1,4-disubstituted-1,2,3-triazole derivatives **6b-m** also suggest that they have excellent binding affinity against antifungal drug target cytochrome P450 lanosterol 14 α -demethylase of *C. albicans* ranging from 8.9252 to 6.2874 (-log Ki) value.



Scheme 1. Synthesis of 1,2,3-triazole derivatives from naphthols

The formation of compounds **6a-m** and **7a-m** has been confirmed by physical data and spectral methods such as IR, ^1H NMR, ^{13}C NMR and HRMS. In the IR spectrum of compound **6c**, the characteristic peak was observed at 3261 cm^{-1} due to NH group and 1671 cm^{-1} for carbonyl of amide group. In the ^1H NMR spectrum of compound **6c**, the two sharp singlet peaks at δ 5.40 and 5.46 ppm for two methylene protons of $-\text{N}-\text{CH}_2$ and $-\text{CH}_2-\text{O}-$, respectively. The singlet peak was observed at δ 8.40 ppm due to the proton of triazole ring of compound **6c**.

The synthesis of the 1,4-disubstituted-1,2,3-triazole ring **6c** was also proven by the ^{13}C NMR spectrum. The peak appears at δ 52.6 ppm shows the methylene carbon connected to the nitrogen of triazole ring and peak at δ 61.9 ppm assigned for methylene carbon near to oxygen and peak at δ 165.5 ppm indicating carbonyl of amide for compound **6c**. In addition, the formation of compound **6c** was confirmed by the HRMS spectrum and the calculated mass for **6c** $[\text{M} + \text{H}]^+$ is 404.1359 and in HRMS, the $[\text{M} + \text{H}]^+$ peak observed at 404.1338.

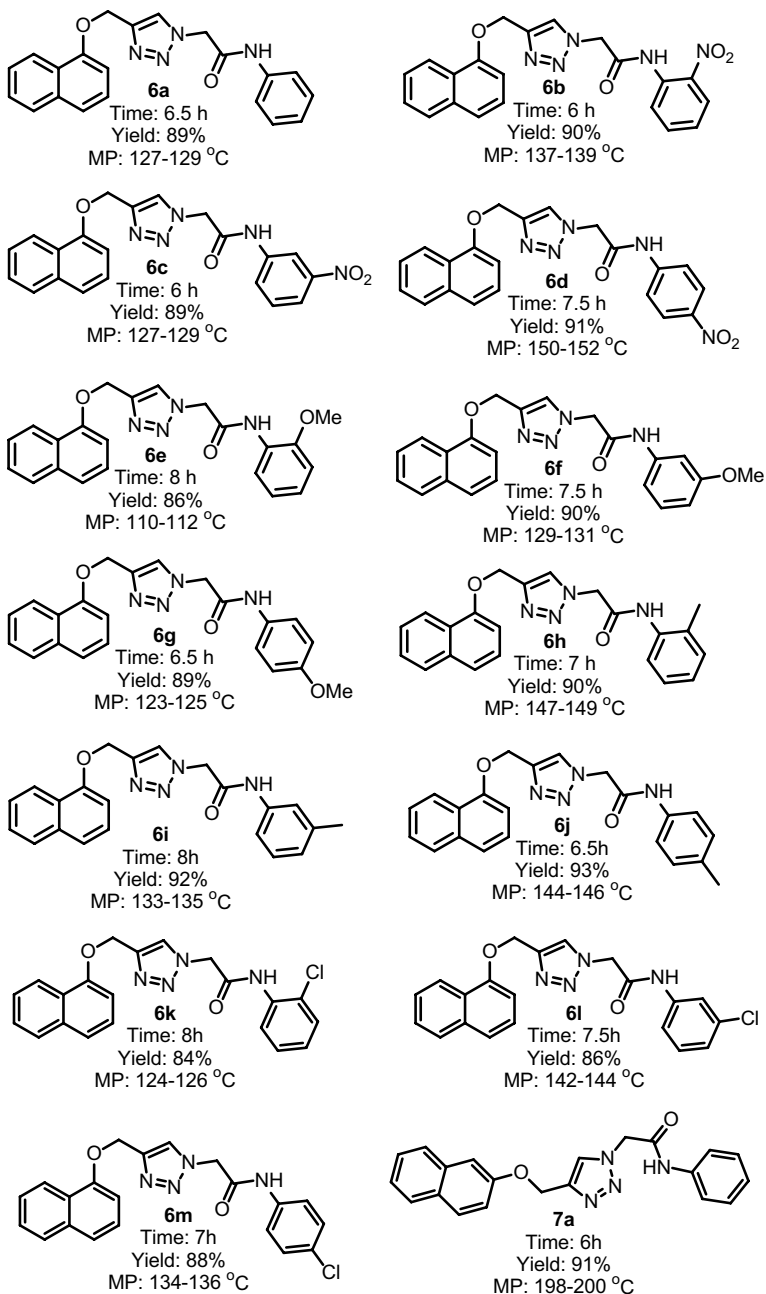


Fig. 5 Structures, time required, yield of the product and physical constants of 2-(4-((naphthalen-1/2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives **6a-m** and **7a-m**

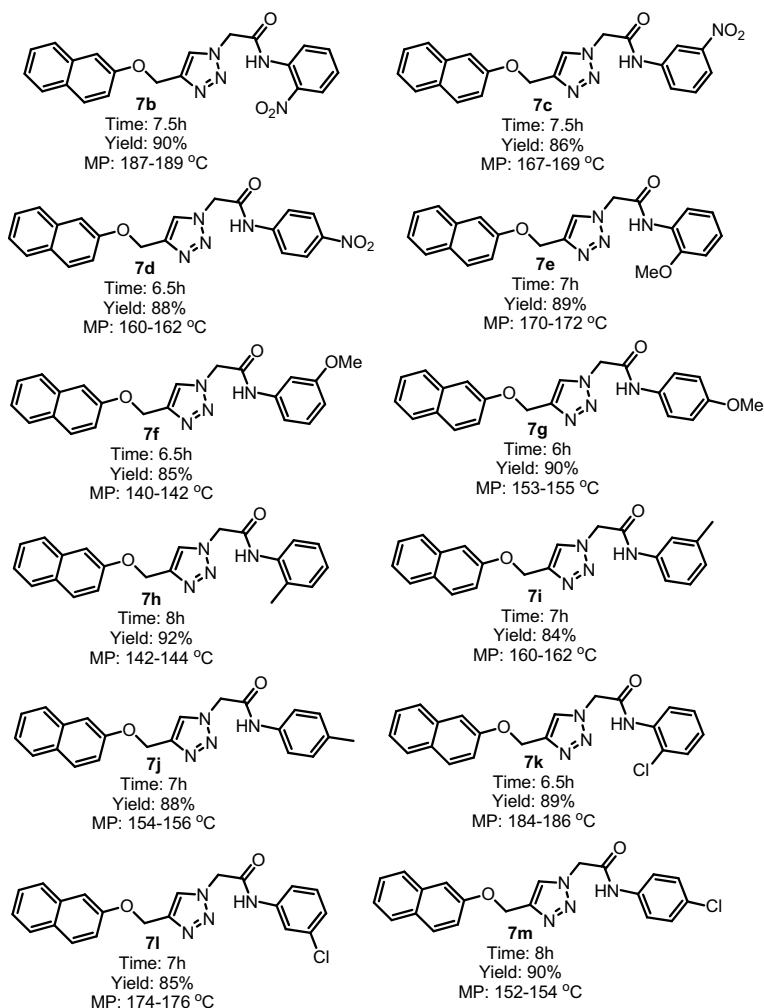


Fig. 5 (continued)

Biological evaluation

Antifungal activity

All the newly synthesized compounds were screened for their *in vitro* antifungal activity against five different fungal strains, viz. *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. The minimum inhibitory concentration (MIC, $\mu\text{g/mL}$) values of all the newly synthesized compounds were determined and summarized in Table 1. DMSO was used as the negative control and Miconazole was used as the standard antifungal drug for the comparison of antifungal activity.

Table 1 In vitro biological evaluation of synthesized compounds **6a-m** and **7a-m**

Cpd	Antifungal activity MIC ($\mu\text{g/mL}$)					Anti TB activity (% Inhibition) at 30 $\mu\text{g/mL}$	Antioxidant activity
	CA	FO	AF	AN	CN	MTB H37Ra	DPPH IC ₅₀ ($\mu\text{g/mL}$)
6a	12.5	37.5	50	100	62.5	52.54	85.05
6b	125	100	125	175	*	20.07	91.19
6c	25	50	50	100	50	44.21	94.34
6d	50	100	25	100	*	37.51	*
6e	100	200	175	*	162.5	NT	82.41
6f	175	175	200	175	150	NT	78.66
6 g	37.5	25	100	37.5	125	50.17	118.49
6 h	150	150	175	200	*	52.29	119.24
6i	12.5	37.5	75	100	25	65.19	*
6j	12.5	25	50	25	50	55.64	120.71
6 k	150	*	*	*	175	39.80	123.22
6 l	75	100	125	75	100	37.99	115.70
6 m	25	25	12.5	25	25	33.04	112.11
7a	25	50	100	175	25	1.42	79.04
7b	75	100	150	150	*	-38.87	*
7c	25	50	25	75	50	1.91	96.39
7d	150	125	150	150	*	33.53	*
7e	*	*	100	125	150	64.87	79.19
7f	100	150	100	*	*	50.30	*
7 g	*	*	*	*	200	61.47	77.09
7 h	62.5	75	50	75	50	29.91	*
7i	150	125	150	150	*	32.42	105.90
7j	100	12.5	25	25	50	17.24	110.80
7 k	100	*	100	*	*	-22.68	*
7 l	*	*	*	125	150	-18.79	120.16
7 m	150	200	175	200	150	NT	*
MA	25	25	12.5	25	25	NA	NA
RIF	NA	NA	NA	NA	NA	90 (0.03 $\mu\text{g/mL}$ Conc.)	NA
BHT	NA	NA	NA	NA	NA	NA	16.47

Cpd: compounds; CA: *Candida albicans*; FO: *Fusarium oxysporum*; AF: *Aspergillus flavus*; AN: *Aspergillus niger* and CN: *Cryptococcus neoformans*. MA: miconazole, DPPH: 2, 2-diphenyl-1-picrylhydrazyl; RIF: rifampicin; BHT: butylated hydroxy toluene.

*No activity was observed, NA: not applicable, NT: not tested.

The triazole derivatives **6a-m** and **7a-m** derived from alkynes **2a** and **2b** displayed good to moderate activity against all the fungal strains. However, most of the triazoles derived from alkyne **2a** (from α -naphthol) displayed excellent anti-fungal activity against all the tested strains. The compounds **6a**, **6i** and **6j** having MIC value of 12.5 $\mu\text{g/mL}$ were found to be more potent; compounds **6c**, **6 m**, and **7a** having MIC value of 25 $\mu\text{g/mL}$ were found to be equipotent as compared

to the standard drug Miconazole against the fungal strain *Candida albicans*. The compounds **6 g**, **6 i** and **6 m** with MIC value of 25 $\mu\text{g/mL}$ were found to be equivalent to Miconazole. Compound **7 j** with MIC value of 12.5 $\mu\text{g/mL}$ was more potent than the Miconazole against the fungal strain *F. oxysporum*. Compound **6 m** with MIC value of 12.5 $\mu\text{g/mL}$ exhibited equivalent activity as compared to Miconazole against *A. flavus*. For the fungal strain *A. niger*, the compounds **6 j**, **6 m** and **7 j** with MIC value of 25 $\mu\text{g/mL}$ displayed equivalent antifungal activity as compared to Miconazole. For the fungal strain *C. neoformans*, the compounds **6 i**, **6 m** and **7 a** with MIC value of 25 $\mu\text{g/mL}$ were equivalent to Miconazole. The remaining compounds displayed moderate to low antifungal activity against all the tested fungal strains.

The antifungal activity depends on the various substituents present on phenyl rings of azides. Among the series, the compounds derived from α -naphthol **6 a-m** were the most active against all the tested fungal strains. Compounds **6 j** and **6 m** were the most active in the series as they possessed a methyl and chloro group at *para* position.

Antitubercular activity

The anti-tubercular activity of all the newly synthesized compounds were assessed at concentrations of 30 $\mu\text{g/mL}$ using an established XTT Reduction Menadione assay (XRMA) anti-tubercular screening protocol [52] using first-line antitubercular drugs Rifampicin as reference standard. In vitro anti-tubercular activity determined by measuring inhibition of growth against avirulent strain of MTB (*MTB H37Ra*; ATCC 25,177) in liquid medium and the obtained results are presented in Table 1.

The triazole derivatives derived from α -naphthol **6 a**, **6 g**, **6 h**, **6 i**, **6 j** and derived from β -naphthol **7 e**, **7 f** and **7 g** displayed moderate activity against *MTB* having 52.54, 50.17, 52.29, 65.19, 55.64, 64.87, 50.30 and 61.47% inhibition at 30 $\mu\text{g/mL}$, respectively (Table 1). The remaining compounds from the series were shows < 50% inhibition against *MTB* strain.

Antioxidant activity

Antioxidant activity of the synthesized compounds **6 a-m** and **7 a-m** were measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay [53]. DPPH radical scavenging activity is the most commonly used method for screening the antioxidant activity of the various natural as well as synthetic antioxidants. A lower IC_{50} value indicates the greater antioxidant activity. The IC_{50} (concentration required to scavenge 50% of the radicals) were calculated to evaluate the potential antioxidant activities. Butylated hydroxytoluene (BHT) has been used as a standard drug for the comparison of antioxidant activity and the observed results are summarized in Table 1. None of the synthesized derivatives displayed better antioxidant activity compared to the standard drug BHT.

Computational studies

Molecular docking study

The molecular docking study of all the synthesized triazole derivatives **6a-m** and **7a-m** was performed against modeled three dimensional structure of cytochrome P450 lanosterol 14 α -demethylase of *C. albicans* to understand the binding affinity and binding interactions of enzyme and synthesized derivatives using SYBEL 2.1.1 package following standard procedures [54]. The data obtained from molecular docking study is presented in Table 2.

The docking result indicates that, triazole scaffold in the synthesized derivatives **6a-m** and **7a-m** appropriately incorporated in the active site of CYP450 and from various kinds of non-bonded interactions such as hydrogen bond and π -bond interactions with active site of amino acid residues. Among all the synthesized derivatives **6 m** (8.9252), **6j** (8.8571), **7j** (8.586) and **6i** (8.373) are most active triazole derivatives when compared with standard Miconazole (6.4895). The most active triazole derivative **6 m** (8.9252) contain hydrophilic as well as hydrophobic amino acids in the active site, such as histidine, valine, methionine, tyrosine, leucine and phenylalanine. Hydrophobic amino acid Tyr168 forms, conventional hydrogen bond with ether bridge oxygen ($-O$) atom in between triazole core and naphthalene ring of distance 1.89 Å. Met342 who contains non polar side chain forms hydrogen bond with a carbonyl oxygen atom of distance 2.94 Å. The amino acids such as Tyr154 and Phe264 forms π - π stacking interactions with chloro-phenyl ($-Cl$) ring and naphthalene ring π electron cloud. The amino acids Val545, His346 and Leu157 from other forms of weak π interactions such as alkyl and π -alkyl interactions with a chlorine atom of phenyl ring and π electron cloud of the naphthalene ring of various distances shown in Fig. 6.

The second most active triazole derivative **6j** (8.8571) interact with active site amino acids forms non covalent bonded interactions such as hydrogen bond interaction and π bond interaction. The hydrophobic amino acids such as Met546 who contain non polar side chain which interact with carbonyl ($C=O$) oxygen to form a conventional hydrogen bond interaction of distance of 2.13 Å. Nonpolar amino acid Met544 whose sulfur atom interact with triazole core π electron cloud to forms π -Sulfur interactions of distance 4.89 Å. The amino acids such as Try105 and Phe108 forms strong Van der Waals interactions such as π - π stacking and π - π T shaped interactions with naphthalene ring π electron cloud.

Hydrophobic amino acids such as Leu157, Phe264 and Phe266 interact with an alkyl group ($-CH_3$) of phenyl ring and a π electron cloud of phenyl ring and naphthalene ring to form alkyl and π -alkyl interactions shown in Fig. 7.

In silico ADME prediction

The success of a drug is determined not only by good efficacy but also by an acceptable ADMET (absorption, distribution, metabolism, excretion and toxicity) profile (Table 3).

Table 2 Molecular docking score for the compounds **6a-m** and **7a-m**

Compounds	Total score (-log Ki)	Crash score	Polar score
<i>Molecular docking score</i>			
6a	8.1051	-1.3314	1.032
6b	6.7417	-1.8979	2.8358
6c	7.8064	-0.7068	3.1512
6d	6.3354	-0.903	2.8137
6e	6.7621	-1.6855	0.0001
6f	6.4228	-1.5496	1.329
6 g	7.7585	-0.8561	1.6365
6 h	7.0001	-1.8541	1.6268
6i	8.3753	-1.7978	0.8948
6j	8.8571	-1.9308	2.0096
6 k	6.2874	-1.4782	1.4928
6 l	6.8562	-1.1515	0.7682
6 m	8.9252	-1.4554	0.826
7a	6.8677	-1.5073	0.8615
7b	7.2492	-1.4724	2.5093
7c	8.0641	-1.2431	0.8622
7d	7.6297	-2.0632	2.1796
7e	6.8	-2.3164	0.0067
7f	7.5755	-1.6427	1.8529
7 g	5.8618	-1.1163	0.6528
7 h	7.6373	-0.7882	1.9817
7i	7.451	-1.7643	1.717
7j	8.5886	-0.7624	0
7 k	6.4946	-1.3407	0.7534
7 l	7.4334	-1.1128	3.094
7 m	6.8304	-1.024	1.6887
Miconazole	6.4895	-1.4009	1.0311

Total score: total docking score; *Crash*: degree of inappropriate penetration by the ligand into the protein and of interpenetration between ligand atoms that are separated by rotatable bonds; *Polar*: contribution of the polar non-hydrogen bonding interactions to the total score.

Lipinski's rule of five also known as Pfizer's rule of five (RO5) and this approach has been widely used as a filter for substances that would likely be further utilized as a leads for drug design programs. We have also analyzed parameters like number of rotatable bonds (> 10) and the number of rigid bonds, which implies that the compound may have a good oral drug bio-availability and very good intestinal absorption rate while pass through the GI track [55].

The values of polar surface area (PSA) for synthesized triazole derivatives **6a-m** and **7a-m** indicated these agents have very high solubility and also have good oral

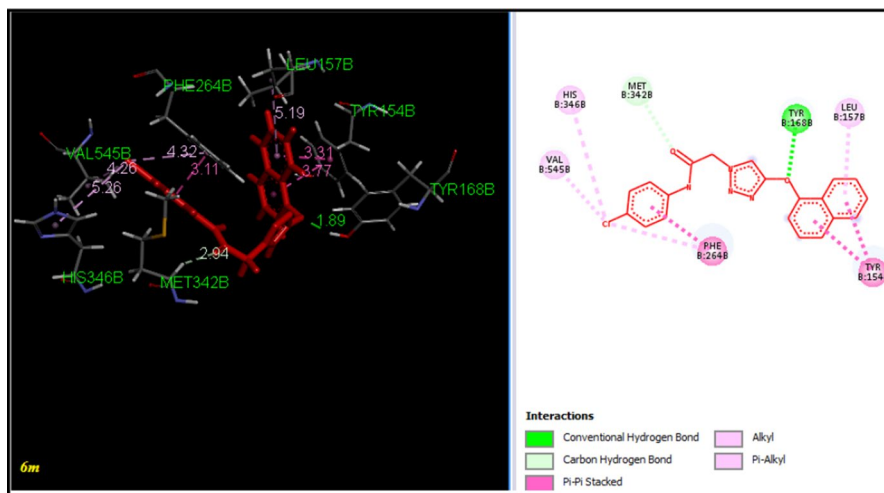


Fig. 6 Binding pose and molecular interactions of **6 m** in the active site of *C. albicans* lanosterol 14 α -demethylase

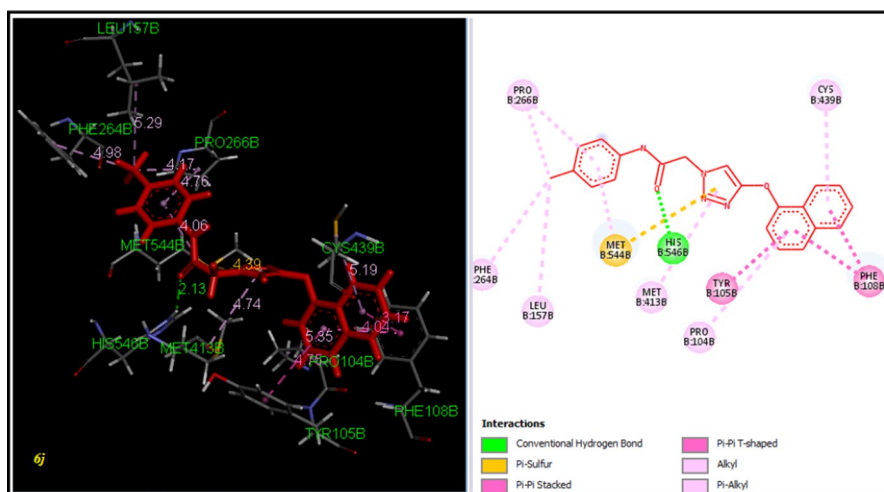


Fig. 7 Binding pose and molecular interactions of **6 j** in the active site of *C. albicans* lanosterol 14 α -demethylase

bioavailability. These parameters, molecular weight, number of hydrogen bond donor and number of hydrogen bond acceptors, LogP, max size ring and ratio of H/C are associated with the oral absorption rate, showed that all synthesized compounds **6a-m** and **7a-m** had good absorption. The percentage of absorption (% ABS) was calculated using TPSA by using formula $\% \text{ ABS} = 109 - (0.345 \times \text{TPSA})$ [56]. All the analyzed

Table 3 Pharmacokinetic parameters for in silico ADME prediction

Cpd	MW	LogP	% ABS	TPSA	n-ROB	n-RIB	HBD	HBA	Ratio H/C	Toxicity
6a	344.36	3.93	85.18	69.04	5	24	1	4	0.3	NT
6b	390.37	4.25	69.75	113.74	6	25	2	6	0.45	NT
6c	390.37	4.25	69.75	113.74	6	25	2	6	0.45	NT
6d	390.37	4.25	69.75	113.74	6	25	2	6	0.45	NT
6e	374.39	3.94	81.99	78.27	6	24	1	5	0.33	NT
6f	374.39	3.94	81.99	78.27	6	24	1	5	0.33	NT
6 g	374.39	3.94	81.99	78.27	6	24	1	5	0.33	NT
6 h	358.39	4.24	85.18	69.04	5	24	1	4	0.28	NT
6i	358.39	4.24	85.18	69.04	5	24	1	4	0.28	NT
6j	358.39	4.24	85.18	69.04	5	24	1	4	0.28	NT
6 k	378.81	4.58	85.18	69.04	5	24	1	4	0.35	NT
6 l	378.81	4.58	85.18	69.04	5	24	1	4	0.35	NT
6 m	378.81	4.58	85.18	69.04	5	24	1	4	0.35	NT
7a	358.39	3.72	85.18	69.04	6	24	1	4	0.28	NT
7b	404.39	4.04	69.75	113.74	7	25	2	6	0.42	NT
7c	404.39	4.04	69.75	113.74	7	25	2	6	0.42	NT
7d	404.39	4.04	69.75	113.74	7	25	2	6	0.428	NT
7e	388.41	3.73	81.99	78.27	7	24	1	5	0.31	NT
7f	388.41	3.73	81.99	78.27	7	24	1	5	0.31	NT
7 g	388.41	3.73	81.99	78.27	7	24	1	5	0.31	NT
7 h	372.41	4.03	85.18	69.04	6	24	1	4	0.27	NT
7i	372.41	4.03	85.18	69.04	6	24	1	4	0.27	NT
7j	372.41	4.03	85.18	69.04	6	24	1	4	0.27	NT
7 k	392.83	4.37	85.18	69.04	6	24	1	4	0.33	NT
7 l	392.83	4.37	85.18	69.04	6	24	1	4	0.33	NT
7 m	392.83	4.37	85.18	69.04	6	24	1	4	0.33	NT

Cpd: compounds, *MW*: molecular weight, *LogP*: logarithm of partition coefficient of compound between *n*-octanol and water, *%ABS*: percentage of absorption, *PSA*: polar surface area, *n-ROB*: number of rotatable bonds, *n-RIB*: number of rigid bonds, *HBD*: hydrogen bond donor, *HBA*: hydrogen bond acceptors, *NT*: non toxic.

physical, chemical descriptors and pharmaceutically relevant properties for ADMET prediction by using FAF-Drugs2 and data are summarized in Table 3.

The ADMET prediction data obtained from all the synthesized triazole derivatives **6a-m** and **7a-m** are within the range of accepted values, none of the synthesized triazole derivatives have violated the Lipinski's rule of five (RO5).

Conclusions

We have synthesized twenty six (26) 1,4-disubstituted-1,2,3-triazole derivatives by using click chemistry approach from commercially available starting materials in excellent yields. The synthesized triazole derivatives were evaluated for their anti-fungal, antioxidant and antitubercular activities. The compounds **6a**, **6c**, **6d**, **6g**, **6i**, **6j**, **6m**, **7a**, **7c** and **7j** shows potential antifungal activity as compared to the standard drug Miconazole with lower MIC values. Also, all the synthesized compounds were tested for in vitro anti-tubercular activity against avirulent strain of *MTB H37Ra* and antioxidant activity. The compounds shows moderate anti-tubercular and antioxidant activity as compared to the respective standard drugs. In addition to this, In silico molecular docking study have supported the experimental results and demonstrated that 1,2,3 triazole derivatives **6j** and **6m** are the most active forms of synthesized derivatives and have the potential to inhibit survival of fungal species. Predictions of pharmacokinetics parameter suggest that the synthesized derivatives have potential to have high oral drug bio-availability.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11164-023-05008-4>.

Acknowledgements One of the author, Satish V. Akolkar, is very much grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of research fellowship. Authors are also thankful to the Head, Department of Chemistry, Dr Babasaheb Ambedkar Marathwada University Aurangabad for providing laboratory facility.

Author's contribution SVA and MKB performed the experimental work, characterization and prepared manuscript. MHS and PUP helped in the optimization of reaction conditions, characterization and performed in silico ADME evaluation. JNS and MGD carried out biological activity and molecular docking study. Dr. BBS designed and monitored the project and also reviewed the manuscript.

Funding No funding received.

Data availability Not Applicable.

Declarations

Conflict of interest The authors declares that they have no conflict of interest.

Ethical approval Not applicable.

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Authors and Affiliations

Satish V. Akolkar¹ · Mubarak H. Shaikh^{1,2} · Mininath K. Bhalmode¹ · Prabhakar U. Pawar³ · Jaiprakash N. Sangshetti⁴ · Manoj G. Damale⁵ · Bapurao B. Shingate¹

Satish V. Akolkar
akolkarsatish137@gmail.com

Mubarak H. Shaikh
mubbarakshaikh01@gmail.com

Mininath K. Bhalmode
milindbhalmode11@gmail.com

Prabhakar U. Pawar
prabhakarupawar@gmail.com

Jaiprakash N. Sangshetti
jnsangshetti@rediffmail.com

Manoj G. Damale
pharmalink1985@gmail.com

¹ Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra 431004, India

² Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar, Maharashtra 414001, India

- ³ Department of Chemistry, Indian Institute of Science Education and Research Pune, Pune, Maharashtra 411008, India
- ⁴ Y. B. Chavan College of Pharmacy, Rafiq Zakaria Campus, Aurangabad, Maharashtra 431001, India
- ⁵ Department of Pharmaceutical Chemistry, Srinath College of Pharmacy, Aurangabad, Maharashtra 431136, India