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Pyrazoline tethered 1,2,3-triazoles: Synthesis, antimicrobial evaluation and *in silico* studies

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ABSTRACT

A new series of pyrazoline-amide linked 1,2,3-triazole hybrids was wisely designed and synthesized using 1,3-dipolar cycloaddition between pyrazoline linked alkynes and 2-bromo-*N*-arylacetamide. All the newly synthesized compounds were evaluated *in vitro* against different microbial strains *viz. Escherichia coli, Bacillius subtilis, Staphylococcus aureus, Aspergillus niger,* and *Candida albicans*. Pyrazoline linked terminal alkynes (**4a–c**) showed MIC = 0.062–0.078 μmol/mL against different bacterial and fungal strain. However, pyrazoline-amide linked 1,2,3-triazole hybrids (**6a-6t**) showed MIC = 0.0229–0.050 μmol/mL. Compound **6e** exhibited better efficacy against *E. coli* and both the fungal strains compared to standard drugs used. Docking studies of the most potent compounds were carried out against bacterial DNA Gyr A and fungal 14α-steroldemethylase were also performed. The binding potential of **4a** and **6e** with both the target using molecular dynamics simulations was also investigated.

1. Introduction

As the COVID-19 pandemic started taking the world by storm, both World Health Organization (WHO) and Pew Charitable Trust (Pew) assessed the global antibiotic pipeline [1]. Microbial infections and their associated effects are problematic and most challenging issue to global researchers, and represent one of the top 10 causes of mortality and the primary cause of death from microbial agents [2]. The ever-increasing antimicrobial resistance over the ages along with the evolution of drugs emphasizes the urgent need for discovering and developing newer and effective drugs that can either kill or inhibit the growth of the microbes inside the host body. In contrast, a general belief is that drugs affecting more than a single target or multiple sites of the single target showed higher potency and lower resistance as compared to solo targeting agents.

This can easily be achieved by the molecular hybridization approach in which two different active pharmacophores are clubbed together with or without the help of a linker [3–5]. These days, this approach is the most popular one in the development of novel drug entities to target multiple sites [5]. Therefore, hybrid molecules can attenuate the risk of multiple drug resistance as well as a drug-drug interaction which could be useful for humanity to resist microbial resistance.

1,2,3-Triazoles have attracted much attention in designing new lead molecules simply because of ease of preparation by a Cu(I)-catalyzed azide-alkyne cycloaddition and broad spectrum of pharmacological activities including anti-viral [6–8], anti-cancer [9–17], anti-bacterial [18–23], anti-fungal [24–30], α-glucosidase inhibition [31,32], anti-tubercular [33–35], anti-protozoal [36], anti-oxidant [37], anti-inflammatory [38], anti-proliferative [39,40]. 1,2,3-Triazoles have also been found to be the constituent of some of the well-known drugs such as Tazobactam, Cefatrizine, Carboxyamidotriazole and Rufinamide. Vanegasa *et al.* synthesized small library of diverse 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives using click reaction and tested for activity against filamentous fungi and Candidal species. Some compounds exhibited comparable or better activity compared to standard itraconazole [25]. Aouad *et al.* synthesized new 1,2,3-triazoles with a lipophilic side chain *via* cycloaddition of diethylacetylene dicarboxylate and various surfactant azides and screened for their antimicrobial activities. Compound 5,5-(1-hexadecyl-1*H*-1,2,3-triazole-4,5-diyl)bis(4-amino-1,2,4-triazole-5(4*H*)-thione) was found to be the most potent antimicrobial agents relative to the standard antimicrobial agents[23]. Molecular hybridization approach has been utilized for the fusion of 1,2,3-triazole ring with other antimicrobial pharmacophores including urea, thiourea, oxazoles, pyrazoles, imi-

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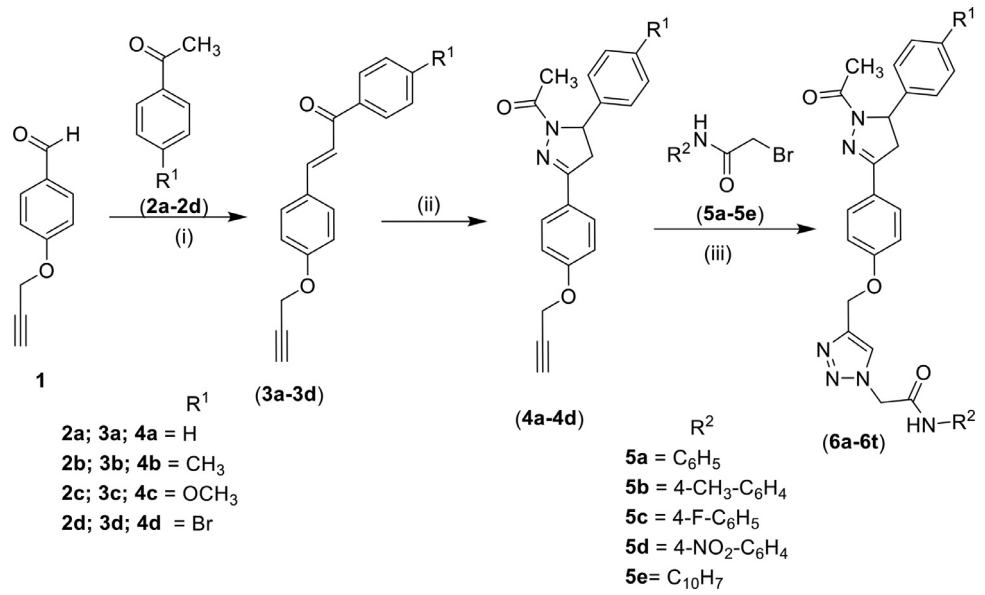


Scheme 1. Reagents and conditions: (i) 40% NaOH, EtOH, MW, 5-7 min; (ii) Hydrazine hydrate, Glacial acetic acid, Reflux, 2,3 h; (iii) NaN_3, sodium ascorbate, copper sulphate pentahydrate, DMF: H_2O (8:2, v/v).

dazoles, pyrazolines, semicarbazones, thiosemicarbazones, purines, pyrimidines, among others to develop hybrid drug candidates with broad biological spectrum, reduced toxicity and enhanced efficacy compared to their parent units [41]. A number of 1,2,3-triazole hybrids containing an amide functionality have also been reported as efficient anti-microbial agents [42,43].

Pyrazoline, five membered heterocylcle with two nitrogen atoms at 1- and 2-positions has attracted considerable attention from organic and medicinal chemists because of its tremendous pharmacological significance and potential for structural diversification. Many pyrazoline derivatives have shown remarkable biological activities such as anti-oxidant [44] anti-tumor [45], antimicrobial [46–48], anti-viral [49], and anti-malarial [50]. Beside these, pyrazoline pharmacophore has been clubbed with other bioactive moieties for designing of hybrid molecules with potential pharmacological activities.

Therefore, in view of the biological importance of these three phamacophoric units *i.e.,* 1.2.3-triazole, an amide and pyrazoline, herein, we report synthesis some pyrazoline-amide linked 1,2,3-triazole hybrids. We have also investigated their antimicrobial potential against a series of pathogenic bacteria and fungi. Molecular docking analysis of most potent compounds with bacterial DNA gyrase and fungal CYP51 was also performed.

2. Result and discussion

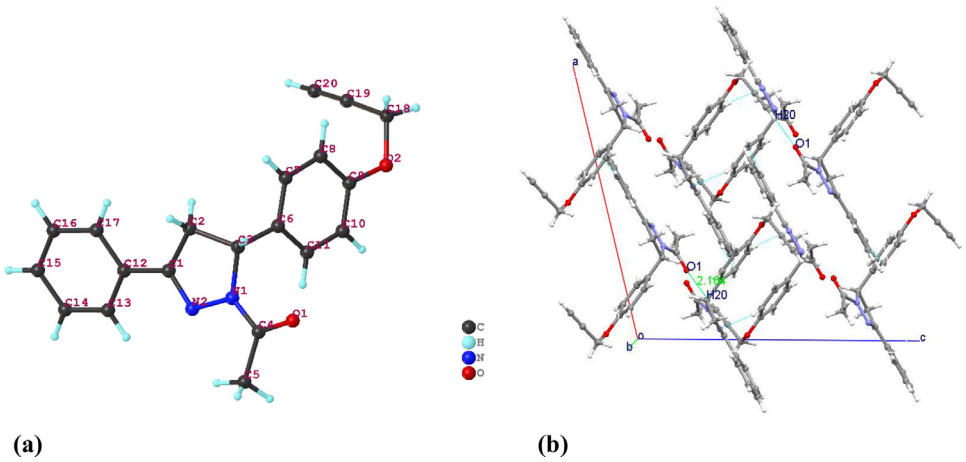
2.1. Chemistry

Pyrazoline linked terminal alkynes (**4a–d**) were used as dipolarophiles for the synthesis of pyrazoline linked 1,2,3-triazole hybrids (**6a–-t**). 2-Bromo-*N*-arylacetamide derivatives (5a–f) and pyrazoline linked terminal alkynes (**4a–d**) used for the purpose were synthesized using synthetic strategies as shown in Scheme 1. At first, propargylation of 4-hydroxybenzaldehyde by propargyl bromide was carried out using K_2CO_3 at room temperature [51]. After that, propargylated benzaldehyde was reacted with various *p*-substituted acetophenones (2**a–d**) *via* Claisen-Schmidt reaction under microwave irradiation for 5–10 min. to yield propargylated chalcones (**3a–d**) [52]. In the next step, chalcones bearing a terminal alkyne moiety (**3a–d**) were reacted with hydrazine hydrate under reflux to obtain pyrazoline linked terminal alkynes (**4a–d**) [53]. 2-Bromo-*N*-arylacetamides (**5a–f**) were prepared by reacting various aniline derivatives with bromoacetyl bromide using K_2CO_3 in dichloromethane [54]. In the final step, pyrazoline-amide-1,2,3-triazole hybrids (**6a–t**) were synthesized by using copper(I)-catalyzed azide-alkyne cycloaddition between pyrazolines linked terminal alkynes (**4a–d**) and 2-bromo-*N*-arylacetamides (**5a–f**) using sodium azide, $CuSO_4.5H_2O$ and sodium ascorbate in DMF: Water as solvent (Scheme 1 [53].

All the synthesized pyrazoline-amide-1,2,3-triazole hybrids (**6a–t**) and their alkyne precursors (**4a–d**) were characterized using different spectral techniques like FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. The IR spectra of compounds (**4a–d**) showed a characteristic absorption band due to alkyne C-C stretching at 2123–2113 cm^{-1}. The disappearance of this band and appearance of a band at 3158–3104 cm^{-1} showed the formation of a triazole ring. The ^{1}H NMR spectra of compounds (**4a–d**) exhibited a characteristics doublet and a triplet at δ 4.67–4.75 and δ 2.43–2.44 corresponding to a propargyl unit. The disappearance of these peaks and appearance of a characteristic peak at δ 7.84–7.54 ppm due to C-5 proton in the ^{1}H NMR spectra of compounds (**6a–t**) further confirmed the formation of triazole ring. The presence of three doublet of doublet at δ 5.57–5.14, δ 3.73–3.65 and δ 3.17–3.10 ppm were observed due to diasterotopic protons of pyrazoline moiety. Also, a sharp singlet in range of δ 11.10–8.40 ppm appeared due to the presence of -NH proton of amide unit in the spectra of all the triazoles. The ^{13}C NMR spectra of compounds (**4a–d**) exhibited a characteristics peaks at δ 74.54–78.56 and δ 72.58–75.60 due the alkyne carbons and the absence of these peaks in the spectra of all the triazoles (**6a–t**) and the presence of a peak at δ 144–143 due to C_4 of the triazole carbon further supported the formation of triazole ring. A signal at δ 169–168 ppm for carbonyl carbon of the acetyl group on pyrazoline ring was also present in ^{13}C NMR spectra of all the triazoles. HRMS data for the compounds (**6a–t**) were in good conformity with their theoretically calculated values.

2.2. X-ray crystallography

The X-ray single crystal data showed that the compounds **4a** is crystallized in monoclinic cell having space group *C2/c*. Crystal structure for asymmetric unit of **4a** was represented in Fig. 1. It has been observed from the crystal structure of **4a** that pyrazo-



(a) (b)

Fig. 1. (a) Crystal structure of compound (**4a**); (b) Crystal packing and intermolecular interactions of (**4a**).

Table 1
Crystal data and structure refinement parameters for compound **4a**.

Empirical formula	$C_{20}H_{18}N_2O_2$
Formula weight	318.36
Crystal system	Monoclinic
Space group	*C2/c*
a (Å)	16.9143(6)
b (Å)	11.9473(4)
c (Å)	17.0055(5)
α (°)	90.00
β (°)	103.5680(10)
γ (°)	90.00
V (Å^3)	3340.57(19)
Z	8
D (calc/gcm^{-3})	1.266
μ (mm^{-1})	0.083
λ (Mo Kα/Å)	0.71073
θ range (°)	2.46–25.00
Total data collected	16879
Unique data Rint R indexes R indexes (all data) CCDC Number	2935 0.0225 R1 = 0.0435; wR2 = 0.1210 R1 = 0.0522; wR2 = 0.1261 1953240

line is upright to benzene ring consisting of propargyl group linked *via* oxygen atom. The propargyl moiety is parallel/*cis* to pyrazoline ring. The packing diagram along a-axis for **4a** has displayed Fig. 1. Suitable hydrogen bonding interactions are not observed in the present compound as analyzed by the PLATON program in WinGX suite. The details of the crystallographic data are provided in Table 1.

2.3. Antimicrobial activity

All the synthesized pyrazoline linked terminal alkynes (**4a–d**) and pyrazoline-amide tethered 1,2,3-triazole hybrids (**6a–t**) were evaluated for their *in vitro* antimicrobial activity towards Gram negative bacterium; *Escherichia coli* (MTCC 16521) and two Gram positive bacteria- *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 6880). The compounds were also explored against two fungal strains *viz. Aspergilus niger* (MTCC 8189) and *Candida albicans* (MTCC 227) following standard serial dilution method [59]. Ciprofloxacin and Fluconazole were used as standard drugs against bacteria and fungi, respectively. The standard drugs were used in order to compare the bio-efficacy of the developed molecular hybrids. Results of anti-microbial activity were expressed in minimum inhibitory concentration values (μmol/mL) and are tabulated in Table 2.

The preliminary *in vitro* antimicrobial evaluation revealed that compounds **6b–e**, **m**, **s** and **t** were found to be the more active among the tested compounds having MIC value for antibacterial activity in the range of 0.022−0.050 μmol/mL and antifungal efficacy in the range of 0.022−0.046 μmol/mL. From the table, it was concluded that pyrazoline-linked terminal alkynes scaffolds (**4a–d**) were less active against bacteria and fungi used, but when these pyrazoline moieties linked with triazole scaffold, activity of synthesized hybrid compounds was increased showing the effect of molecular hybridization. Compounds **6a–f** against *E. coli*; **6m** against *B. subtilis*; **6a–f**, **s**, **t** against *A. niger*; **6a**, **b**, **m**, **s**, **t** against *C. albicans* were found to be more active than the respective standard drugs. From careful analysis of antimicrobial activity following SAR was established:

1 The significance of molecular hybridization approach was established as pyrazolineamide-triazoles showed better activity then their precursors.
2 Greater activity was observed for compounds with electron withdrawing -bromo group at the pharmacophore nucleus *i.e.,* pyrazoline.
3 Compounds with naphthyl group exhibits better activity than with phenyl ring.
4 Moreover, compounds with nitro group on phenyl ring exhibited better potency than those containing methyl group.

2.4. Docking studies

In order to reveal the bio-efficacy of pyrazoline linked triazoles, the *in silico* docking studies of **4a, 6e**, **m** and **t** was performed in the active site of DNA gyrase of *E. coli* (PDB ID 2Y3P), 14-α steroldemethylase of (PDB ID CYP51A) for *A. niger,* DNA gy-

Table 2
Antimicrobial activity of synthesized compounds (**4a–d**; **6a–t**) in terms of MIC in μmol/mL.

Compounds	Minimum inhibitory concentration (MIC, μmol/mL)						
	R^1	R^2	*E. coli*	*B. subtilis*	*S. aureus*	*A. niger*	*C. albicans*
4a	—	—-	0.0783	0.0783	0.0783	0.0783	0.0783
4b	—	—	0.0750	0.0750	0.0750	0.0750	0.0750
4c	—	—	0.0716	0.0716	0.0716	0.0716	0.0716
4d	—	—	0.0628	0.0628	0.0628	0.0628	0.0628
6a	H	C_6H_5	0.0252	0.0505	0.0505	0.0252	0.0252
6b	H	4-$CH_3C_6H_4$	0.0245	0.0491	0.0491	0.0245	0.0245
6c	H	4-FC_6H_4	0.0244	0.0487	0.0487	0.0244	0.0487
6d	H	4-$NO_2C_6H_4$	0.0231	0.0463	0.0463	0.0231	0.0463
6e	H	α-$C_{10}H_7$	0.0229	0.0459	0.0459	0.0229	0.0459
6f	CH_3	C_6H_5	0.0245	0.0491	0.0491	0.0245	0.0491
6g	CH_3	4-$CH_3C_6H_4$	0.0478	0.0478	0.0956	0.0478	0.0478
6h	CH_3	4-FC_6H_4	0.0474	0.0948	0.0474	0.0474	0.0474
6i	CH_3	4-$NO_2C_6H_4$	0.0451	0.0451	0.0451	0.0451	0.0451
6j	CH_3	α-$C_{10}H_7$	0.0447	0.0447	0.0447	0.0447	0.0447
6k	OCH_3	C_6H_5	0.0476	0.0476	0.0476	0.0476	0.0476
6l	OCH_3	4-$CH_3C_6H_4$	0.0464	0.0464	0.0464	0.0464	0.0464
6m	OCH_3	4-FC_6H_4	0.0460	0.0230	0.0460	0.0460	0.0230
6n	OCH_3	4-$NO_2C_6H_4$	0.0438	0.0876	0.0438	0.0438	0.0438
6o	OCH_3	α-$C_{10}H_7$	0.0435	0.0435	0.0870	0.0435	0.0435
6p	Br	C_6H_5	0.0435	0.0435	0.0435	0.0435	0.0435
6q	Br	4-$CH_3C_6H_4$	0.0425	0.0850	0.0425	0.0425	0.0425
6r	Br	4-FC_6H_4	0.0422	0.0422	0.0422	0.0422	0.0422
6s	Br	4-$NO_2C_6H_4$	0.0404	0.0404	0.0404	0.0404	0.0404
6t	Br	α-$C_{10}H_7$	0.0401	0.0802	0.0401	0.0401	0.0401
Ciprofloxacin	—	—	0.0377	0.0377	0.0377	—	—
Fluconazole	—	—	—	—	—	0.0408	0.0408

rase of *S. aureus* (PDB ID 3U2K) and 14 α steroldemethylase of *C. albicans* (PDB ID -5TZ1) as shown in Fig. 2. Compounds **6e, m and t** was found to be most efficacious among all the tested compounds (lowest MIC) therefore, **6e, m and t** and its precursors (**4a**) bearing a pyrazoline unit were selected for docking studies. Compounds **4a, 6e, m and t** were docked in the same binding site using Autodock Vina program. All of these have been reported as good targets for antibacterial and antifungal activities. It has been revealed from docking studies that all the ligands fit snuggly in the binding site of DNA gyrase which resulted into binding free energy of -5.642 Kcal/mol for **6e** and -10.15 Kcal/ mol for **6t** higher than that of alkyne derivative (**4a**, -3.998 Kcal/mol). The binding energy of **6e and m** and **4a** in the active site of CYP51a and (PDB ID 5TZ1) was -9.857 Kcal/mol, -9.96 Kcal/ mol and -9.114 Kcal/mol, respectively. The higher binding energies of **6a** and **m** than that of **4a** supported the activity data and the same is also in line with molecular hybridization concept. It has been revealed from the ligand interaction diagram that mainly non-covalent interactions are responsible for the stabilization of **6e, m** and **t** in the binding cavity of both DNA gyrase, 5TZ1 and CYP51a.

2.4.1. Simulation studies

Based on experimental as well as *in silico* docking results, we opted for investigating the binding potential of **6e** with both the target using MD Simulations. Two systems have been chosen, one with **6e** + *E. coli* GyrA and another with **6e** + *A. niger* CYP51a. The protein backbone RMSD for both the systems showed a stable behavior after an initial surge. These targets have exhibited good interaction with the **6e** having average interaction energy -83.59 kcal/mol and -82.55 kcal/mol for *E. coli* GyrA and *A. niger* CYP51a, respectively. Diffusion coefficient calculated from the initial docked positions for both these ligands to relate their displacement, showed that during the Molecular Dynamics run both of these ligands are tightly held back inside the active site having a diffusion coefficient of 0.10 e^{-5} cm^2/s and 0.11 e^{-5} cm^2/s inside *E. coli* GyrA and *A. niger* CYP51a, respectively **Fig. 3**.

3. Conclusion

We have synthesized a series of pyrazoline linked 1,2,3-triazole hybrids *via* Cu(I)-catalyzed azide alkyne [3 + 2] cycloaddition. All the compounds were characterized fully by using various spectroscopic methods like NMR, IR, HRMS. Further the structure of compound **4a** was elucidated with single X-Ray crystal diffraction. All these compounds were evaluated for their antimicrobial activity against three different strains of bacteria and two fungal strains. The *In-vitro* results showed that compounds (**6a–t**) exhibited moderate to good antibacterial and antifungal activity in comparisons with standard drugs. In particular, compounds **6e** and **f** showed potent activity against all the tested bacterial and fungal strains comparable to or even better than the standard drugs. Compound **6e** showed better activity against bacteria *E. Coli* and both the fungal strains than the standard drugs used. Molecular docking of most potent compounds with bacterial DNA gyrase and fungal CYP51 as well as molecular dynamics studies of **6e** supported the *in vitro* antibacterial activity results. The activity result clearly showed that hybrid compounds showed greater activity comparable to pyrazolines with terminal alkyne. The results of present study may be utilized for further development of lead for various microorganisms.

4. Experimental section

4.1. Materials and measurements

The chemical reagents were procured from CDH, Sigma-Aldrich, and Loba, India. All yields refer to isolated products after purification. Microwave synthesizer Make-Anton Paar used for the synthesis of chalcones at elevated temperature and pressure capacity up to 260 °C and 20 bar. Products were characterized by comparing with authentic samples and by spectroscopic techniques, that is, ^1H and ^{13}C NMR, elemental analysis. The ^1H and ^{13}C were recorded on Bruker Avance II 400 MHz at 400 MHz and 100 MHz, respectively, using $CDCl_3$ relative to tetramethylsilane (TMS) (0.00 ppm). Chemical shifts were reported in δ using the internal standard

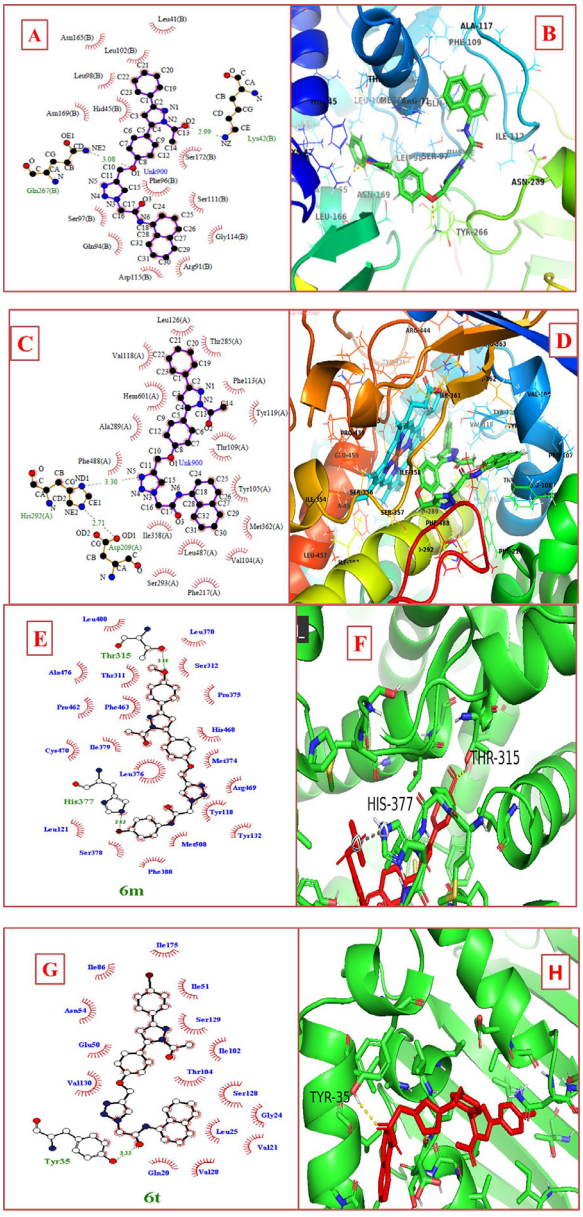


Fig. 2. (A) Docking interaction diagram for 6e + *E. coli* GyrA; (B) 3D Interaction diagram of 6e in the binding pocket of *E. coli*; (C) Docking interaction diagram for 6e + *A. niger* CYP51a; (D) 3D Interaction diagram of 6e in the binding pocket of *A. niger*; (E) Docking interaction diagram for 6m + *C.albicans*; (F) 3D Interaction diagram of 6m in the binding pocket of *C. albicans*; (G) Docking interaction diagram for 6t + *S. aureus* GyrA; (H) 3D Interaction diagram of 6t in the binding pocket of *S. aureus*;

(TMS). Melting points were determined in open capillaries and are reported uncorrected. IR spectra were obtained on Shimazdu IR Affinity-I FT-IR spectrophotometer with KBr.

4.2. General procedure for the synthesis of pyrazoline linked terminal alkynes (4a–d) [53]

Microwave irradiation has been applied in synthesis of propargylated chalcones using Claisen-Schmidt reaction. A solution of 4-*O*-propargylated benzaldehyde (**1**) (1.0 mmol), various *p*-substituted acetophenones (**2a–d**) (1.0 mmol), and NaOH (0.2 mmol) in EtOH (10 mL) were irradiated in microwave at 30–40 °C for 5–7 min. After the completion of reaction as checked by TLC analysis, the precipitates were collected by filtration, washed with water and EtOH and dried under vacuum to afford propargylated chalcones (**3a–d**) in 90–96% yields. After that, propargylated chalcones (**3a–d**) (1.0 mmol) were reacted with hydrazine hydrates (2.0 mmol; 99%) under refluxing for 4–5 h in acetic acid. After completion of the reaction, the reaction mixture was concentrated and poured onto crushed ice (approx. 100 g). Solid product was filtered, washed with plenty of cold water and recrystallized from ethanol to get the pure pyrazoline linked terminal alkynes **(4a–d)**. Purity of the compound was checked on TLC plates in the solvent system ethylacetate: hexane (8:2).

4.2.1. 1-(3-phenyl-5-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone
(4a)

Brown solid; Yield 82%; m.p.: 140–142 °C; FT-IR (KBr, υ_{max} cm^{-1}): 3214 (≡C-H str.), 3038 (C-H str., aromatic ring), 2927, 2113 (C≡C str) 1654 (C=O str), 1618 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, J = 6.7, 3.0 Hz, 2H, Ar-H), 7.46–7.44 (m, 3H, Ar-H), 7.20 (d, J = 8.7 Hz, 2H, Ar-H), 6.94 (d, J = 8.7 Hz, 2H, Ar-H), 5.58 (dd, J = 11.8, 4.5 Hz, 1H, Pyrazoline-H), 4.67 (d, J = 2.3 Hz, 2H, -OCH_2), 3.75 (dd, J = 17.7, 11.8 Hz, 1H, Pyrazoline-H), 3.18 (dd, J = 17.7, 4.5 Hz, 1H, Pyrazoline-H), 2.52 (t, J = 2.4 Hz, 1H, Propagylated proton), 2.44 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9 (C=O), 157.0 (Ar-C), 153.9 (Pyrazoline-C), 135.0 (Ar-C), 131.4 (Ar-C), 130.3 (Ar-C), 128.8 (Ar-C), 126.9 (Ar-C), 126.6 (Ar-C), 115.2 (Ar-C), 78.5 (*C*≡CH), 75.6 (C≡*CH*), 59.4 (Pyrazoline-C), 55.8 (OCH_2), 42.3 (Pyrazoline-C), 22.0 ($COCH_3$). HRMS: (m/z) $[M+H]^+$calculated for $C_{20}H_{18}N_2O_2$: 319.1441 found: 319.1394.

4.2.2. 1-(5-(4-(prop-2-yn-1-yloxy)phenyl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone
(4b)

Brown solid; Yield 80%; m.p.: 151–153 °C; FT-IR (KBr, υ_{max} cm^{-1}): 3217 (≡C-H str.), 3033 (C-H str., aromatic ring), 2933, 2114 (C≡C str) 1654 (C=O str), 1612 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.2 Hz, 2H, Ar-H), 7.25 (d, J = 8.0 Hz, 2H, Ar-H), 7.20 (d, J = 8.7 Hz, 2H, Ar-H), 6.94 (d, J = 8.7 Hz, 2H, Ar-H), 5.57 (dd, J = 11.7, 4.4 Hz, 1H, Pyrazoline-H), 4.67 (d, J = 2.2 Hz, 2H), 3.72 (dd, J = 17.6, 11.8 Hz, 1H, Pyrazoline-H), 3.16 (dd, J = 17.6, 4.5 Hz, 1H, Pyrazoline-H), 2.52 (t, J = 2.4 Hz, 1H), 2.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.84 (C=O), 156.04 (Ar-C), 152.37 (Pyrazoline-C), 134.94 (Ar-C), 130.44 (Ar-C), 130.22 (Ar-C), 127.75 (Ar-C), 126.64 (Ar-C), 126.28 (Ar-C), 115.29 (Ar-C), 74.54 (C≡CH), 72.58 (C≡CH), 53.39 (Pyrazoline-C), 55.63 (O-CH_2), 42.68 (Pyrazoline-C), 29.30 ($COCH_3$), 22.18 (CH_3) HRMS: (m/z) $[M+H]^+$calculated for $C_{21}H_{20}N_2O_2$: 333.1598 found: 333.1578.

4.2.3. 1-(3-(4-methoxyphenyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone
(4c)[53]

[53]Appearance: Brown solid; Yield 70%; m.p.: 110–112 °C (Lt.); FT-IR (KBr, υ_{max} cm^{-1}): 3197 (≡C-H str.), 3020 (C-H str., aromatic ring), 2935, 2123 (C≡C) 1683 (C=O Amide), 1514 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.95 (t, J = 9.2 Hz, 4H), 5.56 (dd, J = 11.6, 4.3 Hz, 1H, Pyrazoline-H), 4.67 (d, J = 2.3 Hz, 2H), 4.67 (d, J = 2.3 Hz, 2H), 3.87 (s, 3H), 3.72 (dd, J = 17.6, 11.7 Hz, 1H, Pyrazoline-H), 3.17 (dd, 1H, Pyrazoline-H), 2.52 (t, J = 2.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.69 (s) (C=O), 161.34 (s) (Ar-C), 156.96 (s) (Ar-C), 153.73 (s) (Ar-C), 135.15 (s) (Ar-C), 128.18 (s) (Ar-C), 126.94 (s) (Ar-C), 124.07 (s) (Ar-C), 115.18 (s) (Ar-C), 114.17 (s) (Ar-C), 78.56 (s) (C≡CH), 75.56 (s) (C≡CH), 59.25 (s) (O-CH_2), 55.83 (s) (N-CH_2), 55.42 (s), 42.38 (s), 21.98 (s); HRMS (m/z) $[M+H]^+$calculated for $C_{21}H_{20}N_2O_3$ 349.1552 found: 349.1582.

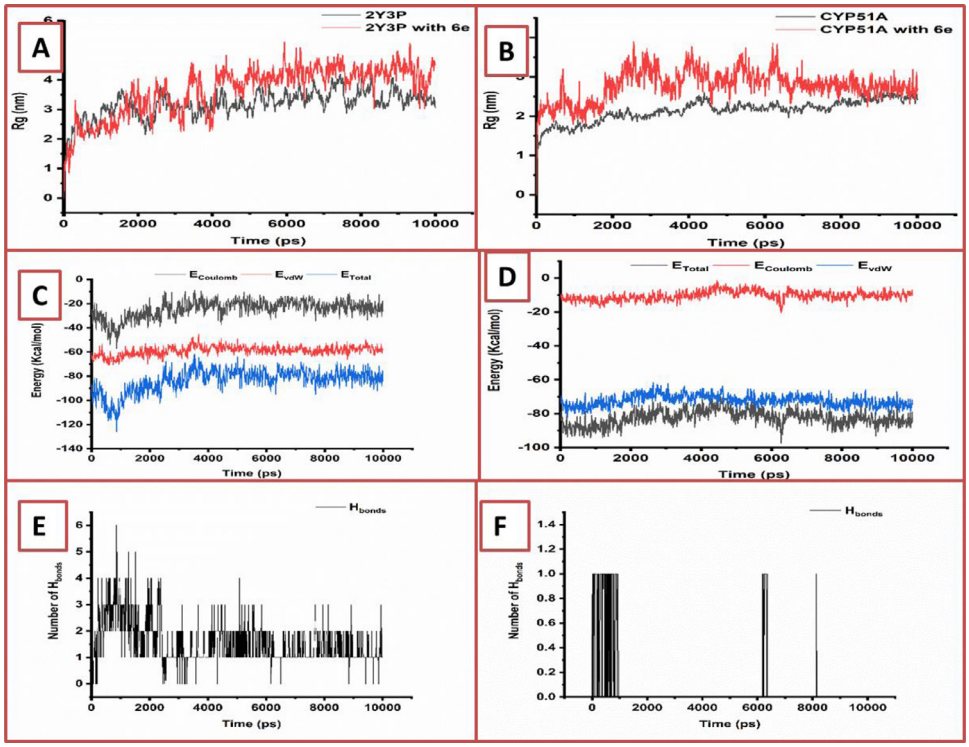


Fig. 3. (A) Rmsd plot for 6e + *E. coli* GyrA; (B) Rmsd plot for 6e + CYP51; (C) Energy plot for 6e + *E. coli* GyrA; (D) Energy plot for 6e + *A. niger* CYP51; (E) Hbond plot for 6e + *E. coli* GyrA; (F) Hbond plot for 6e + *A. niger* CYP51.

*4.2.4. 1-(3-(4-bromophenyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (4d)*

[53]

Appearance: Brown solid; Yield 64%; m.p.: 114-117°C (Lt.); FT-IR (KBr υ_{max}, cm^{-1}):3219 (≡C-H str.), 3049 (=C-H str., aromatic ring), 2951, 2113 (C≡C), 1658 (C=O), 1531(C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.6 Hz, 3H), 7.55 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 9.1 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 5.86 (dd, J = 11.9, 4.8 Hz, 1H, Pyrazoline-H), 4.75 (s, J = 4.3 Hz, 2H), 3.74 (dd, J = 17.7, 11.9 Hz, 1H, Pyrazoline-H), 3.08 (dd, J = 17.7, 4.8 Hz, 1H, Pyrazoline-H), 2.49 (t, J = 2.4 Hz, 1H), 2.48 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$):δ 168.89 (s), 154.16 (s) (Ar-C), 153.66 (s) (Ar-C), 131.84 (s) (Ar-C), 130.64 (s) (Ar-C), 129.61 (s) (Ar-C), 128.64 (s) (Ar-C), 128.03 (s) (Ar-C), 126.24 (s) (Ar-C), 124.41 (s) (Ar-C), 121.71 (s) (Ar-C), 112.53 (s) (Ar-C), 78.51 (s) (C≡CH), 75.60 (s) (C≡CH), 56.13 (s) (N-CH_2), 41.30 (s) (O-CH_2), 21.98 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{20}H_{17}BrN_2O_2$: 397.0552 found: 397.0587.

*4.3. General Procedure for the synthesis of 1, 2, 3-triazoles (**6a–t**)*

[53]

To a solution of sodium azide (3.0 mmol in 1 mL H_2O) was added to a stirred solution of 2-bromo-*N*-arylacetamides (**5a–e**; 1.0 mmol) in DMF (8 mL) at 30–40 °C under stirring. After 30 min, pyrazoline linked terminal alkynes (**3a–d**; 1.0 mmol), copper sulfate pentahydrate (0.1 mmol in 1 mL H_2O) and sodium ascorbate (0.4 mmol) were added to it and stirring was continued for 4–6 h. After completion of the reaction, 25 mL ice cold water was added to reaction mixture, precipitated product thus obtained was filtered and washed with aqueous ammonia solution to get desired triazole hybrids **(6a–t).**

*4.3.1. 2-(4-((4-(1-acetyl-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**6a**)*

Brown solid; Yield 82%; m.p.: 141–143 °C; FT-IR (KBr, υ_{max} cm^{-1}): 3276 (N-H str.), 3137 (C-H str., triazole ring), 3067 (C-H str., aromatic), 2935 (C-H str., aliphatic), 1630 (C=O str., amide), 1509, 1443 (C=C str., aromatic) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H, N*H*), 7.81–7.72 (m, 3H, 2Ar-H & C-H triazole), 7.56 (d, J = 7.8 Hz, 2H, Ar-*H*), 7.46 (d, J = 3.9 Hz, 3H, Ar-*H*), 7.32 (t, J = 7.6 Hz, 2H, Ar-*H*), 7.14 (t, J = 7.0 Hz, 3H), 6.86 (d, J = 8.0 Hz, 2H), 5.55 (dd, J = 11.6, 4.4 Hz, 1H, Pyrazoline-H), 5.07 (s, 2H, NCH_2), 4.68 (s, 2H, OCH_2), 3.77 (dd, J = 17.6, 11.8 Hz, 1H, Pyrazoline-H), 3.16 (dd, J = 17.7, 4.4 Hz, 1H, Pyrazoline-H), 2.50 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C=O), 166.9 (C=O), 163.3 (Ar-C), 157.7 (Ar-C), 154.7 (Pyrazoline-C), 144.1 (C_4 triazole), 137.6 (Ar-C), 134.6 (Ar-C), 131.1 (Ar-C), 130.6 (Ar-C), 129.0 (Ar-C), 128.8 (Ar-C), 126.8 (Ar-C), 126.7 (Ar-C), 124.8 (C_5 triazole), 124.6 (Ar-C), 119.9 (Ar-C), 115.1 (Ar-C), 61.9 (Pyrazoline-C), 59.7 (OCH_2), 52.7 (NCH_2), 42.7 (Pyrazoline-C), 22.2 ($COCH_3$). HRMS: (m/z) $[M+H]^+$calculated for $C_{28}H_{26}N_6O_3$: 495.2139 found: 495.2143.

*4.3.2. 2-(4-((4-(1-acetyl-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide (**6b**)*

Brown solid; Yield 88%; m.p.: 178-180°C; FT-IR (KBr, υ_{max} cm^{-1}): 3278 (N-H amide str.), 3128 (C-H str., triazole ring), 3066 (C-H str., aromatic ring), 2927 (C-H str., aliphatic), 1639 (C=O str., amide), 1509, 1420 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H, N*H*), 7.78 (s, 1H, C-H triazole), 7.76 (d, J = 5.4 Hz, 2H, Ar-H), 7.46 (s, 2H, Ar-H), 7.44 (d, J = 3.0 Hz, 2H, Ar-H), 7.42 (s, 1H, Ar-H), 7.12 (dd, J = 13.6, 8.2 Hz, 4H), 6.86 (d, J = 8.2 Hz, 2H), 5.55 (dd, J = 11.5, 4.3 Hz, 1H, Pyrazoline ring), 5.05 (s, 2H, -OCH_2), 4.66 (s, 2H, -NCH_2), 3.77 (dd, J = 17.6,

11.8 Hz, 1H, Pyrazoline ring), 3.16 (dd, J = 17.8, 4.4 Hz, 1H, Pyrazoline ring), 2.47 (d, J = 18.7 Hz, 3H), 2.31 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.37 (C=O), 163.24, 157.69 (Ar-C), 154.77 (Pyrazoline-C), 143.89 (C_4 triazole), 135.08 (Ar-C), 134.59 (Ar-C), 134.18 (Ar-C), 131.12 (Ar-C), 130.60 (Ar-C), 129.49 (Ar-C), 128.81 (Ar-C), 126.82 (Ar-C), 126.71 (Ar-C), 124.80 (C_5 triazole), 119.91 (Ar-C), 115.06 (Ar-C), 61.87 (Pyrazoline-C), 59.74 (OCH_2), 52.52 (NCH_2), 42.61 (Pyrazoline-C), 22.17 ($COCH_3$), 20.90 (CH_3); HRMS: (m/z) $[M+H]^+$ calculated for $C_{29}H_{28}N_6O_3$: 509.2296 found: 509.2323

4.3.3. 2-(4-((4-(1-acetyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)acetamide (**6c**)

Brown solid; Yield 86%; m.p.: 124–127 °C; FT-IR (KBr, υ_{max} cm^{-1}): 3296 (N-H amide str.), 3152 (C-H str., triazole ring), 3091 (C-H str., aromatic ring), 2929 (C-H str., aliphatic), 1641 (C=O str., amide), 1509, 1435 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H, N*H*), 7.77 (s, 3H, 2Ar-H & C-H triazole), 7.49 (s, 2H, Ar-H), 7.46 (s, 3H, Ar-H), 7.16 (s, 2H), 7.00 (s, 2H), 6.87 (s, 1H), 5.56 (dd, 1H, Pyrazoline-H), 5.12 (s, 2H, -OCH2), 4.87 (s, 2H,-NCH2), 3.76 (dd, 1H, Pyrazoline-H), 3.16 (dd, J = 17.7 Hz, 1H, Pyrazoline-H), 2.47 (s, 3H, $COCH_3$).^{13}C NMR (100 MHz, $CDCl_3$): δ 169.37 (C=O), 163.24, 157.69 (Ar-C), 154.77 (Pyrazoline-C), 143.89 (C_4 triazole), 135.08 (Ar-C), 134.59 (Ar-C), 134.18 (Ar-C), 131.12 (Ar-C), 130.60 (Ar-C), 129.49 (Ar-C), 128.81 (Ar-C), 126.82 (Ar-C), 126.71 (Ar-C), 124.80 (C_5 triazole), 119.91 (Ar-C), 115.06 (Ar-C), 61.87 (Pyrazoline-C), 59.74 (OCH_2), 52.52 (NCH_2), 42.61 (Pyrazoline-C), 22.17 ($COCH_3$), 20.90; HRMS: (m/z) $[M+H]^+$calculated for $C_{28}H_{25}FN_6O_3$: 513.2045 found: 513.2049

4.3.4. 2-(4-((4-(1-acetyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (**6d**)

Brown solid; Yield 81%; m.p.: 164–166 °C; FT-IR (KBr, υ_{max} cm^{-1}): 3260 (N-H amide str.), 3158 (C-H str., triazole ring), 3079 (C-H str., aromatic ring), 2929 (C-H str., aliphatic), 1636 (C=O str., amide), 1511, 1435 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H, N*H*), 8.22 (d, J = 7.5 Hz, 2H, Ar-H), 7.78 (s, 5H, 4Ar-H & C-H triazole), 7.47 (d, J = 6.1 Hz, 3H, Ar-H), 7.17 (d, J = 7.9 Hz, 2H), 6.89 (d, J = 7.5 Hz, 2H), 5.56 (dd, J = 11.6, 3.8 Hz, 1H, Pyrazoline-H), 5.11 (s, 2H, -OCH_2), 4.71 (s, 2H, -NCH_2), 3.80 (dd, J = 18.0, 11.1 Hz, 1H, Pyrazoline-H), 3.19 (dd, J = 17.9, 5.1 Hz, 1H, Pyrazoline-H), 2.51 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.37 (C=O), 163.24, 157.69 (Ar-C), 154.77, 143.89 (C_4 triazole), 135.08 (Ar-C), 134.59 (Ar-C), 134.18 (Ar-C), 131.12 (Ar-C), 130.60 (Ar-C), 129.49 (Ar-C), 128.81 (Ar-C), 126.82 (Ar-C), 126.71 (Ar-C), 124.80 (C_5 triazole), 119.91 (Ar-C), 115.06 (Ar-C), 61.87 (Pyrazoline-C), 59.74 (OCH_2), 52.52 (NCH_2), 42.61 (Pyrazoline-C), 22.17 ($COCH_3$), 20.90 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{28}H_{25}N_7O_5$: 540.1990 found: 540.1985

4.3.5. 2-(4-((4-(1-acetyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(naphthalen-1-yl)acetamide (**6e**)

Brown solid; Yield 90%; m.p.: 153-154°C; FT-IR (KBr, υ_{max} cm^{-1}): 3284 (N-H amide str.), 3104 (C-H str., triazole ring), 3049 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1645 (C=O str., amide), 1511, 1432 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H, N*H*), 7.95 (d, J = 14.5 Hz, 2H, Ar-H), 7.75 (t, J = 8.1 Hz, 2H, 1Ar-H & C-H triazole), 7.65–7.61 (m, 3H, Ar-H), 7.42–7.34 (m, 6H, Ar-H), 7.06 (d, J = 7.4 Hz, 2H), 6.85 (d, J = 7.2 Hz, 2H), 5.44 (dd, J = 11.5, 4.2 Hz, 1H, Pyrazoline-H), 5.34 (s, 2H, OCH_2), 5.10 (s, 2H, NCH_2), 3.64 (dd, J = 16.3, 13.1 Hz, 1H, Pyrazoline-H), 3.05 (dd, J = 17.7, 4.3 Hz, 1H, Pyrazoline-H), 2.30 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.69 (C=O), 164.34, 157.59 (Ar-C), 153.93 (Pyrazoline-C), 143.06 (C_4 triazole), 134.64 (Ar-C), 134.02 (Ar-C), 132.04 (Ar-C), 131.30 (Ar-C), 130.26 (Ar-C), 128.67 (Ar-C), 128.41 (Ar-C), 127.50 (Ar-C), 126.86 (Ar-C), 126.53 (Ar-C), 126.11(Ar-C), 126.03 (Ar-C), 125.49 (C_5 triazole), 121.84 (Ar-C), 121.42 (Ar-C), 115.03 (Ar-C), 61.86 (Pyrazoline-C), 59.32 (OCH_2), 53.15 (NCH_2), 42.27 (Pyrazoline-C), 21.94 ($COCH_3$); HRMS (m/z) $[M+H]^+$calculated for $C_{32}H_{28}N_6O_3$ 545.2296 found: 545.2288

4.3.6. 2-(4-((4-(1-acetyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (**6f**)

Brown solid; Yield 88%; m.p.: 105-107°C; FT-IR (KBr, υ_{max} cm^{-1}): 3278 (N-H amide str.), 3134 (C-H str., triazole ring), 3035 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1636 (C=O str., amide), 1509, 1448 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H, N*H*), 7.74 (s, 1H, C-H triazole), 7.66 (d, J = 8.2 Hz, 2H, Ar-H), 7.56 (d, J = 7.8 Hz, 2H, Ar-H), 7.32 (t, J = 7.9 Hz, 2H), 7.26 (d, J= 8.1 Hz, 2H), 7.13 (m, 3H), 6.86 (d, J = 8.6 Hz, 2H), 5.54 (dd, J = 11.7, 4.6 Hz, 1H, Pyrazoline-H), 5.08 (s, 2H, -OCH_2), 4.66 (s, 2H, -NCH_2), 3.75 (dd, J = 17.7, 11.7 Hz, 1H, Pyrazoline-H), 3.15 (dd, J = 16.9, 8.5 Hz, 1H, Pyrazoline-H), 2.49 (s, 3H, -OCH_3), 2.42 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.28 (C=O), 163.33 (C=O), 157.66 (Ar-C), 154.88 (Pyrazoline-C), 144.03(C_4 triazole), 141.03 (Ar-C), 137.62 (Ar-C), 134.74 (Ar-C), 129.52 (Ar-C), 129.02 (Ar-C), 128.35 (Ar-C), 126.85 (Ar-C), 126.69 (Ar-C), 124.76 (C_5 triazole), 124.61 (Ar-C), 119.89 (Ar-C), 115.05 (Ar-C), 61.92 (Pyrazoline-C), 59.66 (OCH_2), 52.60 (NCH_2), 42.66 (Pyrazoline-C), 22.16 ($COCH_3$), 21.55 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{28}N_6O_3$: 509.2296 found: 509.2295

4.3.7. 2-(4-((4-(1-acetyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (**6g**)

Brown solid; Yield 84%; m.p.: 117-119°C; FT-IR (KBr, υ_{max} cm^{-1}): 3284 (N-H amide str.), 3122 (C-H str., triazole ring), 3067 (C-H str., aromatic ring), 2929 (C-H str., aliphatic), 1638 (C=O str., amide), 1525, 1445 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H, N*H*), 7.75 (s, 1H, C-H triazole), 7.66 (d, J = 8.2 Hz, 2H, Ar-H), 7.43 (d, J = 8.3 Hz, 2H, Ar-H), 7.26 (d, J = 8.1 Hz, 2H, Ar-H), 7.14 (t, J = 9.1 Hz, 4H), 6.87 (d, J = 8.4 Hz, 2H), 5.54 (dd, J = 11.7, 4.6 Hz, 1H, Pyrazoline-H), 5.09 (s, 2H,-OCH_2), 4.71 (s, 2H, -NCH_2), 3.75 (dd, J = 17.7, 11.7 Hz, 1H, Pyrazoline-H), 3.15 (dd, J = 17.7, 4.6 Hz, 1H, Pyrazoline-H), 2.48 (s, 3H, -OCH3), 2.42 (s, 3H, -CH_3), 2.32 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.19 (C=O), 163.06, 157.63 (Ar-C), 154.71 (Pyrazoline-C), 144.17 (C_4 triazole), 140.96 (Ar-C), 134.88 (Ar-C), 134.76 (Ar-C), 134.34 (Ar-C), 129.52 (Ar-C), 128.39 (Ar-C), 126.87 (Ar-C), 126.66 (Ar-C), 124.68 (C_5 triazole), 119.96 (Ar-C), 115.04 (Ar-C), 61.93 (Pyrazoline-C), 59.60 (OCH_2), 52.73 (NCH_2), 42.61 (Pyrazoline-C), 22.14 ($COCH_3$), 21.54 (CH_3), 20.91(CH_3); HRMS (m/z) $[M+H]^+$calculated for $C_{30}H_{30}N_6O_3$: 523.2452 found: 523.2446

4.3.8. 2-(4-((4-(1-acetyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)acetamide (**6h**)

Brown solid; Yield 89%; m.p.: 142-143°C; FT-IR (KBr, υ_{max} cm^{-1}): 3214 (N-H amide str.), 3155 (C-H str., triazole ring), 3042 (C-H str., aromatic ring), 2920 (C-H str., aliphatic), 1637 (C=O str., amide), 1509, 1458 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1H, N*H*), 7.76 (s, 1H, C-H triazole), 7.66 (d, J = 6.2 Hz, 2H, Ar-H), 7.52 (d, J = 5.8 Hz, 2H, Ar-H), 7.26 (d, J = 7.1 Hz, 2H), 7.15 (d, J = 7.1 Hz, 2H), 7.02 (d, J = 7.4 Hz, 2H),

6.86 (d, J = 7.0 Hz, 2H), 5.53 (dd, J = 9.8, 3.6 Hz, 1H, Pyrazoline-H), 5.08 (s, 2H, -OCH_2), 4.70 (s, 2H, -NCH_2), 3.76 (dd, J = 17.7, 11.8 Hz, 1H, Pyrazoline-H), 3.15 (dd, J = 17.7, 4.2 Hz, 1H, Pyrazoline-H), 2.48 (s, 3H, -$COCH_3$), 2.42 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.29 (C=O), 163.53 (C=O), 163.22 (Ar-C), 157.60 (Ar-C), 154.88 (Pyrazoline-C), 144.06 (C_4 triazole), 141.04 (Ar-C), 136.13 (Ar-C), 133.55 (Ar-C), 131.85 (Ar-C), 129.52 (Ar-C), 128.31 (Ar-C), 126.87 (Ar-C), 126.77 (Ar-C), 124.76 (C_5 triazole), 121.68 (Ar-C), 115.67 (Ar-C), 115.05 (Ar-C), 61.87 (Pyrazoline-C), 59.63 (OCH_2), 52.62 (NCH_2), 42.66 (Pyrazoline-C), 22.16 ($COCH_3$), 21.54 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{27}FN_6O_3$: 527.2201 found: 527.2196

*4.3.9. 2-(4-((4-(1-acetyl-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide (**6i**)*

Brown solid; Yield 82%; m.p.: 150-152°C; FT-IR (KBr, υ_{max} cm^{-1}): 3276 (N-H amide str.), 3152 (C-H str., triazole ring), 3046 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1635 (C=O str., amide), 1512, 1452 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (s, 1H, N*H*), 8.06 (d, J = 8.2 Hz, 2H, Ar-H), 7.83 (s, 1H, C-H triazole), 7.69 (d, J = 8.0 Hz, 2H, Ar-H), 7.52 (d, J = 7.4 Hz, 2H), 7.11 (d, J = 7.4 Hz, 2H), 7.04 (d, J = 7.2 Hz, 2H), 6.81 (d, J = 7.6 Hz, 2H), 5.41 (dd, J = 12.0, 3.5 Hz, 1H, Pyrazoline-H), 5.15 (s, 2H, -OCH_2), 5.06 (s, 2H, -NCH_2), 3.62 (dd, J = 17.3, 12.0 Hz, 1H, Pyrazoline-H), 3.01 (dd, J = 18.0, 2.9 Hz, 1H, Pyrazoline-H), 2.56 (s, 3H, -CH_3), 2.28 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 169.18 (C=O), 164.26, 157.49 (Ar-C), 154.10 (Pyrazoline-C), 144.03 (C_4 triazole), 143.38 (Ar-C), 140.60 (Ar-C), 134.69 (Ar-C), 129.35 (Ar-C), 128.43 (Ar-C), 126.82 (Ar-C), 126.48 (Ar-C), 124.79 (C_5 triazole), 119.35 (Ar-C), 114.95 (Ar-C), 61.77 (Pyrazoline-C), 59.19 (OCH_2), 52.9 (NCH_2), 52.90, 42.31 (Pyrazoline-C), 21.93($COCH_3$), 21.42 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{27}N_7O_3$: 554.2146 found: 554.2138

*4.3.10. 2-(4-((4-(1-acetyl-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(naphthalen-1-yl)acetamide (**6j**)*

Brown solid; Yield 92%; m.p.: 156-158°C; FT-IR (KBr, υ_{max} cm^{-1}): 3284 (N-H amide str.), 3145 (C-H str., triazole ring), 3033 (C-H str., aromatic ring), 2928 (C-H str., aliphatic), 1640 (C=O str., amide), 1529, 1430 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H, N*H*), 7.84 (m, 4H, 3Ar-H & C-H triazole), 7.68 (d, J = 8.1 Hz, 1H, Ar-H), 7.63 (d, J = 8.0 Hz, 2H), 7.49-7.40 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H), 5.50 (dd, J = 11.6, 4.3 Hz, 1H, Pyrazoline-H), 5.11 (s, 2H, -OCH_2), 5.01 (s, 2H, -NCH_2), 3.70 (dd, J = 17.7, 11.8 Hz, 1H, Pyrazoline-H), 3.10 (dd, J = 17.7, 4.4 Hz, 1H, Pyrazoline-H), 2.41 (s, 6H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.16 (C=O), 164.17, 157.59 (Ar-C), 154.61(Pyrazoline-C), 144.37 (C_4 triazole), 140.90 (Ar-C), 134.78 (Ar-C), 134.04 (Ar-C), 131.72 (Ar-C), 129.49 (Ar-C), 128.56 (Ar-C), 128.43 (Ar-C), 127.09 (Ar-C), 126.87 (Ar-C), 126.64 (Ar-C), 126.44 (Ar-C), 126.19 (Ar-C), 126.10 (Ar-C), 125.55 (C_5 triazole), 124.91 (Ar-C), 121.15 (Ar-C), 120.86 (Ar-C), 115.07 (Ar-C), 61.88 (Pyrazoline-C), 59.54 (OCH_2), 52.99 (NCH_2), 42.54 (Pyrazoline-C), 22.06 ($COCH_3$), 21.53 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{33}H_{30}N_6O_3$: 559.2452 found: 559.5447

*4.3.11. 2-(4-((4-(1-acetyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**6k**)*

Brown solid; Yield 86%; m.p.: 175-177°C; FT-IR (KBr, υ_{max} cm^{-1}): 3246 (N-H amide str.), 3135 (C-H str., triazole ring), 3068 (C-H str., aromatic ring), 2937 (C-H str., aliphatic), 1609 (C=O str., amide), 1509, 1446 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H, N*H*), 7.73 (s, 1H, C-H triazole), 7.71 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 6.9 Hz, 2H), 7.31 (t, J = 8 Hz, 2H), 7.13 (d, J = 6.5 Hz, 3H), 6.96 (d, J = 7.3 Hz, 2H), 6.84 (d, J = 7.3 Hz, 2H), 5.52 (dd, J = 11.4, 4.2 Hz, 1H), 5.03 (s, 2H), 4.58 (s, 2H), 3.87 (s, 3H), 3.74 (dd, J = 16.9, 11.9 Hz, 1H), 3.13 (dd, J = 15.7, 2.1 Hz, 1H), 2.49 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.18 (C=O), 163.48 (C=O), 161.58 (Ar-C), 157.69 (Ar-C), 154.69 (Pyrazoline-C), 143.82 (C_4 triazole), 137.81 (Ar-C), 134.72 (Ar-C), 128.99 (Ar-C), 128.38 (Ar-C), 126.81 (Ar-C), 124.80 (C_5 triazole), 124.48 (Ar-C), 123.71 (Ar-C), 119.84 (Ar-C), 115.03 (Ar-C), 114.23 (Ar-C), 61.91 (Pyrazoline-C), 59.67 (OCH_2), 55.45 (NCH_2), 52.40 ($COCH_3$), 42.74 (Pyrazoline-C), 22.17 (CH3); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{28}N_6O_4$: 525.2245 found: 525.2232

*4.3.12. 2-(4-((4-(1-acetyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(*p*-tolyl)acetamide (**6l**)*

Brown solid; Yield 89%; m.p.: 171-174°C; FT-IR (KBr, υ_{max} cm^{-1}): 3272 (N-H amide str.), 3128 (C-H str., triazole ring), 3067 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1625 (C=O str., amide), 1524, 1435 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H, N*H*), 7.74 (s, 1H, C-H triazole), 7.71 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.13 (t, J = 9.3 Hz, 4H), 6.96 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.53 (dd, J = 11.4, 4.2 Hz, 1H), 5.08 (s, 2H), 4.69 (s, 2H), 3.88 (s, 3H), 3.73 (dd, J = 17.7, 11.8 Hz, 1H), 3.13 (dd, J = 17.6, 4.2 Hz, 1H), 2.47 (s, 3H), 2.32 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.05 (C=O), 163.10 (C=O), 161.54 (Ar-C), 157.67 (Pyrazoline-C), 154.40 (Ar-C), 144.12 (C_4 triazole), 134.96 (Ar-C), 134.80 (Ar-C), 134.29 (Ar-C), 129.50 (Ar-C), 128.32 (Ar-C), 126.86 (Ar-C), 124.67 (C_5 triazole), 123.83 (Ar-C), 119.98 (Ar-C), 115.08 (Ar-C), 114.22(Ar-C), 61.97 (Pyrazoline-C), 59.59 (OCH_2), 55.43, 52.71 (NCH_2), 42.65 (Pyrazoline-C), 22.09 ($COCH_3$), 20.88 (CH_3); HRMS: (m/z) $[M+H]^+$calculated for $C_{30}H_{30}N_6O_4$: 539.2401 found: 539.2405

*4.3.13. 2-(4-((4-(1-acetyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide (**6m**)*

Brown solid; Yield 91%; m.p.: 107-109°C; FT-IR (KBr, υ_{max} cm^{-1}): 3278 (N-H amide str.), 3152 (C-H str., triazole ring), 3066 (C-H str., aromatic ring), 2971 (C-H str., aliphatic), 1637 (C=O str., amide), 1509, 1459 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (s, 1H, N*H*), 7.73 (d, J = 4.6 Hz, 2H, Ar-H), 7.70 (s, 1H, C-H triazole), 7.53 (dd, J = 9.1, 4.8 Hz, 2H, Ar-H), 7.15 (d, J = 8.6 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.53 (dd, J = 11.6, 4.5 Hz, 1H, Pyrazoline-H), 5.06 (s, 2H, -OCH_2), 4.64 (s, 2H, -NCH_2), 3.88 (s, 3H, -OCH_3), 3.76 (dd, J = 17.6, 11.6 Hz, 1H, Pyrazoline-H), 3.14 (dd, J = 17.6, 4.5 Hz, 1H, Pyrazoline-H), 2.48 (s, 3H, -CH3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.16 (C=O), 163.25 (C=O), 161.59 (Ar-C), 157.65 (Pyrazoline-C), 154.63 (Ar-C), 144.27 (C_4 triazole), 134.82 (Ar-C), 128.37 (Ar-C), 126.85 (Ar-C), 124.71 (C_5 triazole), 123.70 (Ar-C), 121.63 (Ar-C), 121.55 (Ar-C), 115.79 (Ar-C), 115.57 (Ar-C), 115.04 (Ar-C), 114.23 (Ar-C), 61.95 (Pyrazoline-C), 59.64 (OCH_2), 55.45, 52.47 (NCH_2), 42.72 (Pyrazoline-C), 22.17 ($COCH_3$); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{27}FN_6O_4$: 543.2151 found: 543.2138

4.3.14.
*2-(4-((4-(1-acetyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide*
(6n)

Brown solid; Yield 86%; m.p.: 117-120°C; FT-IR (KBr, υ_{max} cm^{-1}): 3278 (N-H amide str.), 3152 (C-H str., triazole ring), 3091 (C-H str., aromatic ring), 2927 (C-H str., aliphatic), 1641 (C=O str., amide), 1509, 1435 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 11.10 (s, 1H, N*H*), 8.26 (d, *J* = 7.0 Hz, 3H, Ar-H), 7.83 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.73 (d, *J* = 6.9 Hz, 2H, 1Ar-H & C-H triazole), 7.12 (d, *J* = 6.1 Hz, 2H), 7.01 (s, 4H), 5.49 (dd, 1H, *J* = 11.6, 4.5 Hz), 5.44 (s, 2H), 5.16 (s, 2H), 3.81 (dd, *J* = 16.6, 11.6 Hz, 1H), 3.79 (s, 3H), 3.10 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.51 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.53 (C=O), 165.81 (C=O), 161.38 (Ar-C), 157.65 (Ar-C), 154.46 (Pyrazoline-C), 144.97 (C_4 triazole), 143.08 (Ar-C), 135.40 (Ar-C), 128.76 (Ar-C), 127.25 (Ar-C), 126.73 (Ar-C), 125.60 (Ar-C), 124.13 (C_5 triazole), 119.52 (Ar-C), 115.18 (Ar-C), 114.68 (Ar-C), 61.48 (Pyrazoline-C), 59.17 (OCH_2), 55.81, 52.79 (NCH_2), 42.62 (Pyrazoline-C), 22.22 ($COCH_3$); HRMS: (m/z) $[M+H]^+$calculated for $C_{29}H_{27}N_7O_6$: 570.2096 found: 570.2099

*4.3.15. 2-(4-((4-(1-acetyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(naphthalen-1-yl)acetamide*
(6o)

Brown solid; Yield 92%; m.p.: 130-132°C; FT-IR (KBr, υ_{max} cm^{-1}): 3272 (N-H amide str.), 3146 (C-H str., triazole ring), 3050 (C-H str., aromatic ring), 2936 (C-H str., aliphatic), 1628 (C=O str., amide), 1509, 1458 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H, N*H*), 7.87 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.85 (s, 1H), 7.79 (s, 1H, C-H triazole), 7.68 (d, *J* = 8.6 Hz, 3H), 7.48 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.50 (dd, *J* = 11.6, 4.3 Hz, 1H, Pyrazoline-H), 5.11 (s, 2H, -OCH_2), 5.01 (s, 2H, -NCH2), 3.87 (s, 3H), 3.68 (dd, *J* = 17.6, 11.7 Hz, 1H, Pyrazoline-H), 3.09 (dd, *J* = 17.6, 4.4 Hz, 1H, Pyrazoline-H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.00 (C=O), 164.16 (C=O), 161.48 (Ar-C), 157.60 (Ar-C), 154.28 (Ar-C), 144.43 (C_4 triazole), 134.80 (Ar-C), 134.04 (Ar-C), 131.75 (Ar-C), 128.53 (Ar-C), 128.27 (Ar-C), 127.10 (Ar-C), 126.84 (Ar-C), 126.40 (Ar-C), 126.16 (Ar-C), 126.08 (Ar-C), 125.53 (C_5 triazole), 124.88 (Ar-C), 123.85 (Ar-C), 121.17 (Ar-C), 120.85 (Ar-C), 115.08 (Ar-C), 114.19 (Ar-C), 61.90 (Pyrazoline-C), 59.51 (OCH_2), 55.41, 52.99 (NCH_2), 42.57(Pyrazoline-C), 22.02 ($COCH_3$); HRMS: (m/z) $[M+H]^+$calculated for $C_{33}H_{30}N_6O_4$: 575.2401 found: 575.2413

*4.3.16. 2-(4-((4-(1-acetyl-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide*
(6p)

Brown solid; Yield 86%; m.p.: 127-129°C; FT-IR (KBr, υ_{max} cm^{-1}): 3244 (N-H amide str.), 3152 (C-H str., triazole ring), 3091 (C-H str., aromatic ring), 2926 (C-H str., aliphatic), 1641 (C=O str., amide), 1509, 1435 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 9.07 (s, 1H, N*H*), 7.74 (s, 1H, C-H triazole), 7.71 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.43 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.13 (t, *J* = 9.3 Hz, 4H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 5.53 (dd, *J* = 11.4, 4.2 Hz, 1H, Pyrazoline-H), 5.08 (s, 2H, OCH_2), 4.69 (s, 2H, NCH_2), 3.88 (s, 3H), 3.73 (dd, *J* = 17.7, 11.8 Hz, 1H, Pyrazoline-H), 3.13 (dd, *J* = 17.6, 4.2 Hz, 1H, Pyrazoline-H), 2.47 (s, 3H), 2.32 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.18 (C=O), 163.48 (C=O) (Ar-C), 161.58 (C=O), 157.69 (Ar-C), 154.69 (Pyrazoline-C), 143.82 (C_4 triazole), 137.81 (Ar-C), 134.72 (Ar-C), 128.99 (Ar-C), 128.38 (Ar-C), 126.81 (Ar-C), 124.80 (C_5 triazole), 124.48 (Ar-C), 123.71 (Ar-C), 119.84 (Ar-C), 115.03 (Ar-C), 114.23 (Ar-C), 61.91 (Pyrazoline-C), 59.67 (OCH_2), 55.45, 52.40 (NCH_2), 42.74 (Pyrazoline-C), 22.17 ($COCH_3$); HRMS: (m/z) calculated for $C_{28}H_{25}BrN_6O_3$ $[M+H]^+$: 573.1244, $[M+2]^+$: 575.1224 found: 573.1246, 575.1234

*4.3.17. 2-(4-((4-(1-acetyl-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide*
(6q)

Brown solid; Yield 86%; m.p.: 141-142°C; FT-IR (KBr, υ_{max} cm^{-1}): 3267 (N-H amide str.), 3134 (C-H str., triazole ring), 3068 (C-H str., aromatic ring), 2938 (C-H str., aliphatic), 1664 (C=O str., amide), 1511, 1420 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H, N*H*), 7.78 (s, 1H, C-H triazole), 7.60 (q, *J* = 8.6 Hz, 4H, Ar-H), 7.38 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.14 (t, *J* = 9.2 Hz, 4H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.56 (dd, *J* = 11.8, 4.7 Hz, 1H, Pyrazoline-H), 5.16 (s, 2H, -OCH_2), 4.93 (s, 2H, NCH_2), 3.73 (dd, *J* = 17.7, 11.9 Hz, 1H, Pyrazoline-H), 3.13 (dd, *J* = 17.7, 4.7 Hz, 1H, Pyrazoline-H), 2.45 (s, 3H, $COCH_3$), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.11 (C=O), 162.79 (Ar-C), 157.70 (Pyrazoline-C), 153.15 (Ar-C), 148.02 (Ar-C), 142.99 (C_4 triazole), 134.70 (Ar-C), 134.60 (Ar-C), 132.01 (Ar-C), 130.27 (Ar-C), 129.56 (Ar-C), 128.05 (Ar-C), 126.92 (Ar-C), 124.78 (C_5 triazole), 124.60 (Ar-C), 120.15 (Ar-C), 115.19(Ar-C), 61.98 (Pyrazoline-C), 59.77 (OCH_2), 53.23 (NCH_2), 42.28 (Pyrazoline-C), 22.03 ($COCH_3$), 20.87(CH_3).; HRMS (m/z) calculated for $C_{29}H_{27}BrN_6O_3$ $[M+H]^+$:587.1401, $[M+2]^+$: 589.1380 found: 587.1303, 589.1283

*4.3.18. 2-(4-((4-(1-acetyl-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide*
(6r)

Brown solid; Yield 90%; m.p.: 120-122°C; FT-IR (KBr, υ_{max} cm^{-1}): 3284 (N-H amide str.), 3154 (C-H str., triazole ring), 3067 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1639 (C=O str., amide), 1509, 1431 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, N*H*), 7.56 (d, *J* = 7.8 Hz, 2H, 1Ar-H & C-H triazole), 7.50 (d, *J* = 7.7 Hz, 4H, Ar-H), 7.28 (s, 1H, Ar-H), 7.10 (s, 2H), 6.93 (s, 4H), 5.50 (dd, *J* = 7.3, 4.1 Hz, 1H, Pyrazoline-H), 5.17 (s, 2H, -OCH2), 5.12 (s, 2H, -NCH_2), 3.67 (dd, *J* = 17.2, 11.7 Hz, 1H, Pyrazoline-H), 3.07 (dd, *J* = 17.6, 3.7 Hz, 1H, Pyrazoline-H), 2.35 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.18 (C=O), 163.48 (C=O), 161.58 (Ar-C), 157.69 (Ar-C), 154.69 (Pyrazoline-C), 143.82 (C_4 triazole), 137.81 (Ar-C), 134.72 (Ar-C), 128.99 (Ar-C), 128.38 (Ar-C), 126.81 (Ar-C), 124.80 (C_5 triazole), 124.48 (Ar-C), 123.71 (Ar-C), 119.84 (Ar-C), 115.03 (Ar-C), 114.23 (Ar-C), 61.91(Pyrazoline-C), 59.67 (OCH_2), 55.45, 52.40 (NCH_2), 42.74 (Pyrazoline-C), 22.17 ($COCH_3$); HRMS: (m/z) calculated for $C_{28}H_{24}BrFN_6O_3$ $[M+H]^+$: 591.1150, $[M+2]^+$: 593.1130 found: 591.1159, 593. 1138

4.3.19.
*2-(4-((4-(1-acetyl-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide*
(6s)

Brown solid; Yield 83%; m.p.: 225-228°C; FT-IR (KBr, υ_{max} cm^{-1}): 3248 (N-H amide str.), 3152 (C-H str., triazole ring), 3082 (C-H str., aromatic ring), 2931 (C-H str., aliphatic), 1632 (C=O str., amide), 1508, 1451 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 10.26 (s, 1H, N*H*), 8.19 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.86 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H, 1Ar-H & C-H triazole), 7.58 (d, *J* = 11.8 Hz, 4H, Ar-H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 5.55 (dd, *J* = 11.3, 4.1 Hz, 1H, Pyrazoline-H), 5.19 (d, 2H, -OCH2), 5.14 (d, 2H, -NCH2), 3.72 (dd, *J* = 17.6, 11.9 Hz, 1H, Pyrazoline-H), 3.12 (dd, *J* = 19.3, 4.4 Hz, 1H, Pyrazoline-H), 2.41 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.18 (C=O), 163.48 (C=O), 161.58 (Ar-C), 157.69 (Ar-C), 154.69 (Pyrazoline-C), 143.82 (C_4 triazole), 137.81(Ar-C), 134.72 (Ar-C), 128.99 (Ar-C), 128.38 (Ar-C), 126.81 (Ar-C), 124.80 (C_5 triazole), 124.48 (Ar-C), 123.71(Ar-C), 119.84 (Ar-C), 115.03

(Ar-C), 114.23 (Ar-C), 61.91 (Pyrazoline-C), 59.67 (OCH_2), 55.45, 52.40 (NCH_2), 42.74 (Pyrazoline-C), 22.17 ($COCH_3$); HRMS (m/z) calculated for $C_{28}H_{24}BrN_7O_5$ $[M+H]^+$::618.1095, $[M+2]^+$: 620.1075 found: 618.1107,

*4.3.20. 2-(4-((4-(1-acetyl-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(naphthalen-1-yl)acetamide*
(***6t***)

Brown solid; Yield 90%; m.p.: 178-180°C; FT-IR (KBr, υ_{max} cm^{-1}): 3260 (N-H amide str.), 3140 (C-H str., triazole ring), 3055 (C-H str., aromatic ring), 2928 (C-H str., aliphatic), 1661 (C=O str., amide), 1515, 1423 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H, N*H*), 7.90 (s, 2H, Ar-H), 7.77 (d, J = 7.1 Hz, 2H, 1Ar-H & C-H triazole), 7.65 (d, J = 7.2 Hz, 1H), 7.55-7.37 (m, 7H), 7.08 (d, J = 7.4 Hz, 2H), 6.88 (d, J = 6.8 Hz, 2H), 5.47 (dd, J = 10.9, 4.7 Hz, 1H, Pyrazoline-H), 5.34 (s, 2H, -OCH2), 5.14 (s, 2H, -NCH2), 3.63 (dd, J = 17.4, 12.1 Hz, 1H, Pyrazoline-H), 3.04 (dd, J = 17.7, 4.5 Hz, 1H, Pyrazoline-H), 2.32 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.84 (C=O), 164.38 (Ar-C), 157.64 (Ar-C), 152.96 (Pyrazoline-C), 144.05 (C_4 triazole), 134.44 (Ar-C), 134.04 (Ar-C), 131.89 (Ar-C), 130.29 (Ar-C), 128.46 (Ar-C), 128.03 (Ar-C), 127.50 (Ar-C), 126.85 (Ar-C), 126.21 (Ar-C), 126.07 (Ar-C), 125.51 (C_5 triazole), 124.89 (Ar-C), 124.53 (Ar-C), 121.71 (Ar-C), 121.46 (Ar-C), 115.11 (Ar-C), 61.86 (Pyrazoline-C), 59.53 (OCH_2), 53.04 (NCH_2), 42.14 (Pyrazoline-C), 21.95 ($COCH_3$). HRMS (m/z) calculated for $C_{32}H_{27}BrN_6O_3$ $[M+H]^+$: 623.1401, $[M+2]^+$: 625.1380 found: 623.1306, 625.1287."

4.4. X-ray Crystallographic analysis

A yellow colour best quality single crystal of **4a** was selected below a polarizing microscope and mounted on a fine glass fiber using cyanoacrylate as a adhesive. Single-crystal X-ray diffraction data were obtained on Bruker D8 Quest PHOTON II diffractometer having monochromatic Mo *Kα* radiation (λ = 0.71073 Å) at 296 (2) *K* by using ω and ϕ *s*can. The X-ray generator has been used at 50 kV and 20 mA. After collection of data, it was reduced by APEX3 and for diffraction profiles integration SAINTPLUS program has been utilized [55]. The absorption correction (multiscan) was done with the help of SADABS program [56]. The structure was firstly solved and refined using full matrix least square process on F^2 with SHELXL97 program of WinGx package (version 1.63.04 a) [57,58]. The positions of all hydrogen atoms were primarily placed in difference Fourier maps, while, during final refinement, the hydrogens were located in geometrically perfect locations and refined in the riding mode. Final refinement included the atomic positions of all the atoms, anisotropic thermal parameters for every non-hydrogen atoms and isotropic thermal parameters for all hydrogens. The detailed structural parameters after final refinement of the structures are given in Table 1. The Crystallographic data of **4a** can be found in CCDC No: 1953240 from The Cambridge Crystallographic Data Centre (CCDC) *via*www.ccdc.cam.ac.uk/data_request/cif.

4.5. In-vitro *antimicrobial activity*

In vitro antimicrobial evaluation of synthesized pyrazoline tethered 1,2,3-triazoles (**6a–t**) was carried out against three bacterial strains, namely, *E. Coli* (MTCC 16521), *S. aureus* (MTCC 6880), *B. Subtilis* (MTCC 441) and two fungi, namely, *C. albicans* (MTCC 227) and *A. niger* (MTCC 8189), employing serial dilution method using a stock solution of 100 µg/mL concentration. Double-strength nutrient broth and dimethylsulfoxide (DMSO) were used as media and solvent control. Stock solutions (100 µg/mL) of the test compounds were serially diluted with 1 mL of sterile medium to get the concentration of 50 µg/mL in first culture tube and then serially diluted to obtain a concentration of 25.5–3.12 µg/mL in next tubes. Then all culture tubes were inoculated with 100 µL of suspension of respective microorganism in sterile saline. The inoculated culture tubes were incubated at 37 ± 1 °C for 24 h (bacteria), 37 ± 1 °C for 48 h (*C. albicans*), and 25 ± 1 °C for 7 days (*A. niger*). Ciprofloxacin and fluconazole were also screened under similar experimental conditions [59]. Results of antimicrobial evaluation were noted after incubation in terms MIC by checking the microbial growth visually.

4.6. In silico *studies*

4.6.1. Docking studies

The crystal structure of topoisomerase II DNA Gyrase B was obtained from the Brookhaven Protein Data Bank http://www.rcsb.org/pdb (PDB entry: -2Y3P, 3U2K, 5TZ1 and). To carry out docking studies, the 2D structures of various ligands were drawn and these were converted to 3D and their energy was minimized (Marvin Sketch, 1998–2008). Ligand files were prepared in pdb format with explicit hydrogen addition. Co-crystallized ligand was removed from pdb files and protein molecule was prepared by deleting solvent molecules and non-complex ions using Chimera (UCSF Chimera, 2000–2011). Incomplete side chains were replaced using Dun Brack Rotamer library (Dunbrack, 2002). Hydrogens were added and gasteiger charges were calculated using Antechamber (Wang et al., 2006). The prepared file was saved as pdb format and is used for further studies. All pdb files were transformed into pdbqt format. Docking studies were carried out by using Auto Dock Vina 1.1.2. Grid center was placed on the active site. The sizes and center of grid box were center_*x* = 126, center_*y* = 104, center_*z* = 108, size_*x* = 25.0, size_*y* = 25.0, size_*z* = 25.0 and center_*x* = 19.5975431717, center_*y* = 30.2651505494, center_*z* = 35.2957776043, size_*x* = 25.0, size_*y* = 23.0014700724, size_*z* = 23.651263131 for 1JIJ and 1kzn, respectively. Exhaustiveness of the global search algorithmwas set to be 8. Then, finally docking results were viewed using pdb and pdbqt files (Discovery Studio Visualizer, 2005–2009; PyMol, 2008). Compounds **4a**, **e, m and t** docked against their respective targets, bacterial DNA gyrase and fungal CYP51. Based on our experimental MIC values, we have chosen the *E.coli* GyrA (PDB ID: 2Y3P) as bacterial target and *A. Niger* 14-alpha sterol demethylase as the fungal target. The crystal structure for *A. Niger* CYP51a was not available; hence we opt for homology model. Sequence for *A. niger* cyp51A gene retrieved from UniProt (G4WW85) and modelled using Swiss Model [60] with a template identity of 65% with our submitted sequence. Docking was performed using Autodock tools [61], and docking pose visualised using LigPlus [62].

4.6.2. Molecular dynamics

Two systems, one with **6e** + *E. coli* GyrA and another with **6e** + *A. niger* CYP51a were investigated using the same procedure as reported by Kumar et al. [53].

Declaration of Competing Interest

None

CRediT authorship contribution statement

Lokesh Kumar: Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Kashmiri Lal:** Conceptualization, Methodology, Resources, Data curation, Supervision. **Ashwani Kumar:** Software, Data curation. **Avijit Kumar Paul:** Formal analysis, Investigation. **Anil Kumar:** Investigation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131154.

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