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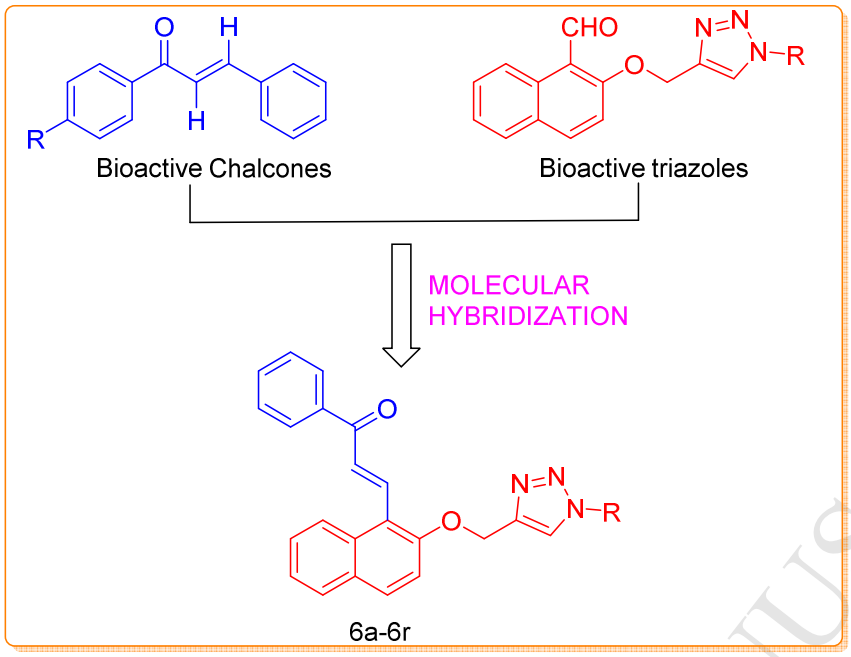

Designed chalcone-1,2,3-triazole conjugates as potential antimicrobial agents

Synthesis, crystal structure and antimicrobial potential of some fluorinated chalcone-1,2,3-triazole conjugates

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Abstract

A simple and green synthesis of some fluorinated chalcone-triazole hybrids from propargylated chalcones and organic azides catalyzed by cellulose supported copper nanoparticles click reaction is reported. All the synthesized compounds were well characterized by various analytical and spectroscopic methods. The X-rays crystallographic study of compounds **6k** revealed the self assembling properties. The antimicrobial screening results of all the synthesized compounds revealed that most of the triazole hybrids exhibited significant efficacy against tested bacterial and fungal strains. The activity results showed the synergistic effect of biological activity when two pharmacophoric units, i.e. chalcone and 1,2,3-triazole are conjugated. Further, docking simulation of the most active compounds **6p** into *Escherichia coli* topoisomerase II DNA Gyrase B was also carried out.

Key words: Fluoronated compounds, Chalcones, 1,2,3-triazoles, antimicrobial activity, docking studies

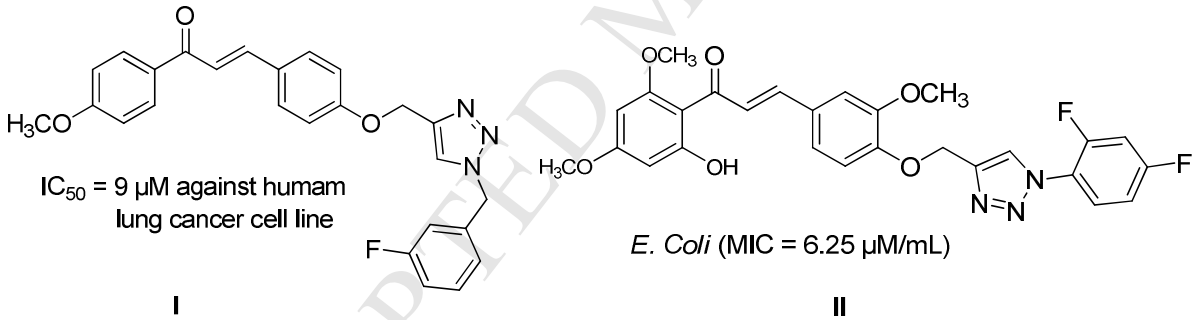
1. Introduction

The development of fluorine containing scaffolds has gain a real interest especially in organic and pharmaceutical areas due to their unique chemical and physiological properties.[1-4] Due to unique properties of fluorine, there is an enormous progress of fluorine-containing drugs which continue to stimulate research on fluorine in medicinal chemistry for drug discovery.[5] Fluorination of an organo-molecule significantly affects its biological properties. Introduction of fluorine atom could somewhere alter the course and biological activity of the compounds. Due to the size of the fluorine atom and its electro negativity, the insertion of a fluorine atom or a trifluoromethyl (CF_3) group in the moiety also changes both pharmacodynamics and pharmacokinetics of the molecule. Somewhere the replacement of the oxidizable C-H bond by a C-F bond acts as a key factor that increases the biological half life of a drug and also increases its metabolic stability.[5]

1,2,3-triazoles are the important class of heterocyclic compounds that received enhanced significant attention from last decade because of the wide applications in the field of pharmaceutical, biochemical and material science.[6-11] 1,4-Disubstituted 1,2,3-triazoles have attracted significant attention because of their broad range of biological activities including antimicrobial,[12-17] anticancer,[18-23] antitubercular,[24-26] antiviral,[27] anti-inflammatory,[28] antimalarial,[29] anti-HIV,[30] antidiabetic,[31-32] anti-oxidant,[33] antiallergic,[34] etc. These are attractive connecting units, since they are stable to oxidative/reductive conditions, metabolic degradation and participate in hydrogen bonding and dipole-dipole interactions.[35] The cellulose supported copper nanoparticles catalyzed cycloaddition between terminal alkynes and organic azides is an excellent method for the click synthesis of 1,2,3-triazoles in eco-friendly conditions in good yield.[36] The insertion of 1,2,3-triazoles and fluorine atom in the substrate led to excellent pharmacological activity like anticancer activity,[37] antimicrobial activity,[38] antitubercular activity,[39] etc.

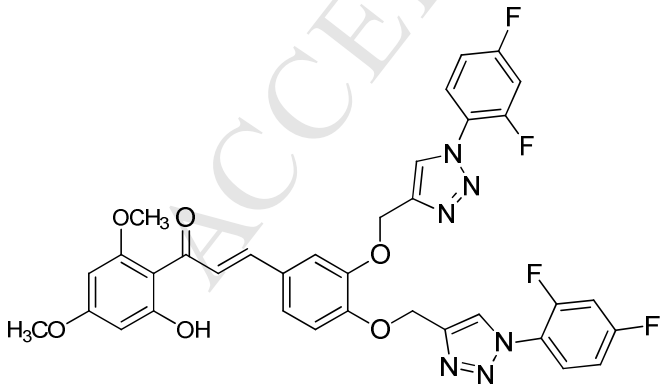
In addition, chalcones, also known as α,β-unsaturated ketones, are not only important precursors for synthetic manipulation but also form a major component of the natural products.[40-41] Chalcones as well as their synthetic analogues show enormous biological activities[42-47] and

widely used as frameworks in drug design. The presence of double bond in conjugation with carbonyl functionalities is known to be responsible for the biological activities. In view of this, Yadav *et al*. efficiently synthesized benzaldehyde chalcone-triazole analogs for anticancer activity towards human cancer cell lines and the study revealed that analog **I** was found as potential anticancer agent (Figure 1).[19] Interestingly, among the series of novel 1,2,3-triazole-chalcone hybrids, compounds **II** and **III** in Figure 1 showed broad-spectrum antimicrobial activity and antiplasmodial activity with MIC values of 6.25 µg/mL and IC_{50} values of 8.86 µg/mL, respectively.[48] Recently we have also reported some naphthaldehyde linked 1,2,3-triazoles as good antimicrobial compounds. Moreover, chalcones have also been reported as biologically active molecules. Therefore, it was envisioned that the conjugation of chalcone and naphthaldehyde linked 1,2,3-triazoles may lead to better antimicrobial agents. Therefore, on the basis of aforementioned and as a part of our programme towards the development of triazole based molecules of biological importance it was planned to synthesize some fluorinated chalcone-triazole hybrids. Herein we report the synthesis of a series of chalcone-1,2,3-triazole hybrids in water as potential antimicrobial agents.



I

II



III

Figure 1: Structures of some biological active fluorinated 1,2,3-triazoles

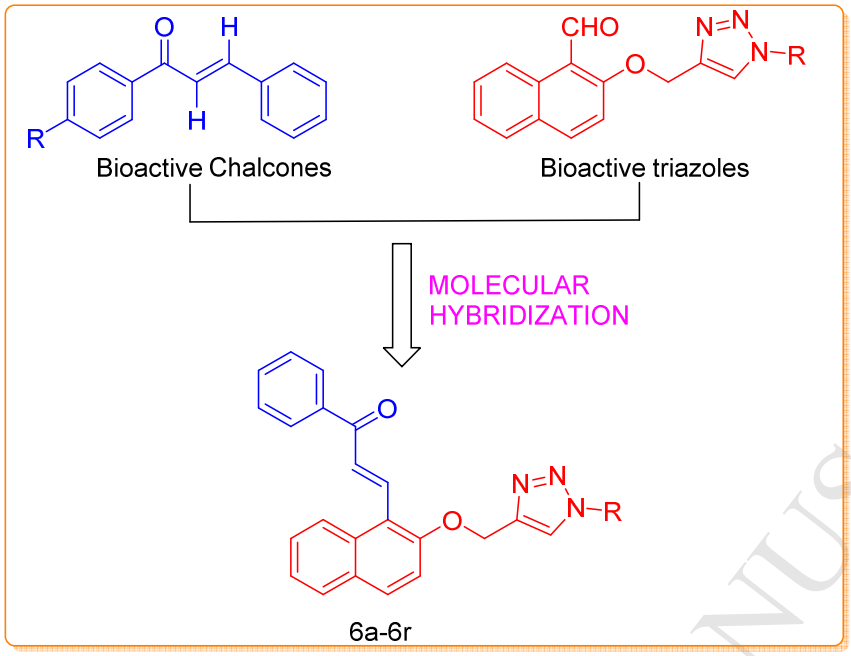
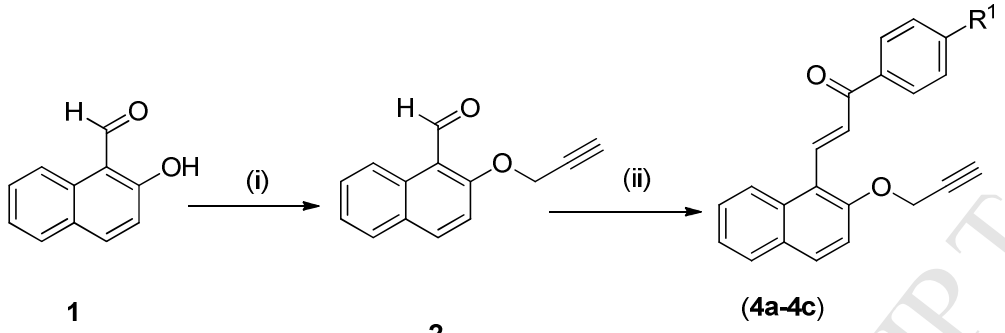


Figure 2: Design of chalcone-1,2,3-triazole conjugates

2. Results and Discussion

2.1 *Chemistry*

The synthetic route for propargylated chalcones and chalcone-triazole hybrids is presented in scheme 1 and 2. Commercially available 2-hydroxynaphthaldehyde (**1**) was subjected to O-alkylation with 1.2 eq of propargyl bromide in presence of K_2CO_3 (1.5 eq) in DMF at room temperature. Propargylated naphthaldehyde (**2**) thus obtained was further condensed with variedly substituted acetophenones (**3a-3c**) *via* base catalyzed Claisen-Schmidt condensation in presence of NaOH (60 %) to furnish propargylated chalcones in excellent yield (**4a-4c**) and recrystallized with ethyl acetate/hexane.

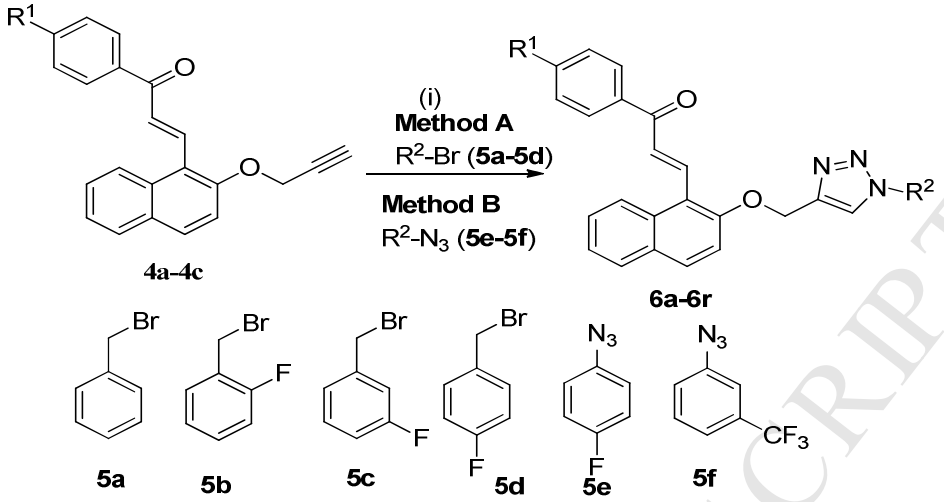


1 **2** (**4a-4c**)

4a $R^1 = OCH_3$; **4b** $R^1 = Br$; **4c** $R^1 = NO_2$

Scheme 1: Reagent and conditions: (i) propargyl bromide, K_2CO_3, acetone, reflux (ii) acetophenones (**3a-3c**), NaOH (60 %), Ethanol, RT, 4 h.

The synthesis of the substituted 1,2,3-triazoles (**6a-6r**) was accomplished from propargylated chalcones utilizing azide-alkyne cycloaddition reaction with appropriate azide using cellulose supported copper nanoparticles (**Scheme 2**).[36] Propargylated chalcones (**4a-4c**) were then subjected to click reaction with sodium azide and various benzyl bromides (**5a-5d**; method A) and organic azides (**5e-5f**; method A) catalyzed by cellulose supported copper nanoparticles in water at 70 °C to yield 1,2,3-triazoles (**6a-6r**) in good yield. The organic azides (**5e-5f**) were synthesized from aniline derivatives *via* reported method.[49] The cellulose supported copper catalyst can be reused to next turn without loss of significant activity. The reactions proceeded very smoothly and afforded the desired products in excellent yield. The plausible mechanism for the transformation of Propargylated chalcones and Sod./ Aryl azides in to chalcone-triazole derivatives (scheme1; supplementary material).[36]



6a = R^1 = Br, R^2 = $C_6H_5CH_2$-	**6j = R^1 = OCH_3, R^2 = 4-$FC_6H_4CH_2$-**
6b = R^1 = Br, R^2 = 2-$FC_6H_4CH_2$-	**6k = R^1 = OCH_3, R^2 = 4-FC_6H_4-**
6c = R^1 = Br, R^2 = 3-$FC_6H_4CH_2$-	**6l = R^1 = OCH_3, R^2 = 3-$CF_3C_6H_4$-**
6d = R^1 = Br, R^2 = 4-$FC_6H_4CH_2$-	**6m = R^1 = NO_2, R^2 = $C_6H_5CH_2$-**
6e = R^1 = Br, R^2 = 4-FC_6H_4-	**6n = R^1 = NO_2, R^2 = 2-$FC_6H_4CH_2$-**
6f = R^1 = Br, R^2 = 3-$CF_3C_6H_4$-	**6o = R^1 = NO_2, R^2 = 3-$FC_6H_4CH_2$-**
6g = R^1 = OCH_3, R^2 = $C_6H_5CH_2$-	**6p = R^1 = NO_2, R^2 = 4-$FC_6H_4CH_2$-**
6h = R^1 = OCH_3, R^2 = 2-$FC_6H_4CH_2$-	**6q = R^1 = NO_2, R^2 = 4-FC_6H_4-**
6i = R^1 = OCH_3, R^2 = 3-$FC_6H_4CH_2$-	**6r = R^1 = NO_2, R^2 = 3-$CF_3C_6H_4$-**

Scheme 2: Reagent and conditions: (i) NaOH (60 %), Ethanol, RT, 4 h (ii) **Method A**: copper nanoparticles; sodium azide; water; 70 °C; 4-7 h, **Method B:** copper nanoparticles; water; 70 °C; 4-7 h.

The chemical structures of all the synthesized compounds (**6a-6r**) were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and MS data.

IR analysis

The IR spectra of propargyl chalcones (**4a-4c**) exhibited two bands at 3178-3275 and 2114-2133 cm^{-1} due to alkyne ≡C-H stretching and C≡C stretching, respectively and were not present in the spectra of all the triazoles (**6a-6r**). The IR spectrum of compound **6n** exhibited a characteristic band due to =C-H stretching of triazole at 3151 cm^{-1}. The synthesized triazole **6n** displayed two absorption bands at 1579 cm^{-1} and 1658 cm^{-1}, which were assigned to the stretching vibrations of =C-H and C=O stretching, respectively.

^{1}H NMR analysis

The ^{1}H NMR spectrum of compound **6n** exhibited two characteristic doublets at δ 8.04 and δ 8.58 with a coupling constant (*J*) of 15.6 Hz. The high value of coupling constant established the *E*-geometry of double bond in chalcones. A characteristic singlet at δ 7.70 due to triazolyl proton confirmed the formation of triazole ring. Two singlets of methylene protons of NCH_2 and OCH_2 each integrating for two protons resonated in the region δ 5.46 and δ 5.62.

^{19}F NMR analysis

The ^{19}F NMR spectrum of **6n** showed a signal at δ -117.95 (dd, J^1 = 22.56, J^2 = 7.57 Hz) which confirmed the presence of 2-fluoro benzene in the compound.

^{13}C NMR analysis

The ^{13}C NMR spectrum of **6n** exhibited peaks of C-4 and C-5 carbon atoms of triazole at δ 143.18 and δ 123.12, respectively. The signal due to C_α and C_β carbon atoms of the α,β-unsaturated carbonyl moiety of compound **6n** were observed at δ 121.45 and δ 143.49, respectively. The peak in the region δ 189.52 was attributed to the carbonyl carbon atom. Two peaks of methylene carbons of OCH_2 and NCH_2 appeared at δ 62.52 and δ 47.61, respectively.

Mass analysis

The mass spectrum of compound **6n** showed a peak at *m*/*z* 510.1 $(M+H)^+$, which is in good agreement with the molecular formula of the compound. The chemical shifts of proton and carbon atoms were designated on the basis of DEPT-135, HSQC and HMBC spectra.

X-rays crystallography

X-rays crystallography of the compound **6k** (recrystallized from ethanol) confirmed the anticipated structure (Figure 3; Table 1 in supplementary material). Compound **6k** crystallizes in monoclinic crystal system with the space group $\boldsymbol{P}2_1/c$. The asymmetric unit contains one crystallographically independent molecule. Crystal structure shows that the plane of chalcone group and triazole group is different. Five–membered triazole ring is almost in gauche conformation with respect to the central biphenyl ring of the chalcone. Hence, the attached flurobenzene ring is almost perpendicular to the chalcone moiety. The molecular structure is stabilized by nonclassical hydrogen-bonding interactions. Here, the hydrogen donor atom is carbon and acceptors are F, N and O atoms (Table 2 in supplementary material). C–H···O interactions are mainly observed for intramolecular stabilization whereas C–H···F and C–H···N interactions are observed for supramolecular stabilization (Figure 4). In the packing structure, one can find the 2_1 screw-axis is extended along the crystallographic *b*-axis. .It is noteworthy that

the weak C–H···F and C–H···N interactions are responsible for the three-dimensional packing and such week interactions can play a crucial role for the biological activity.

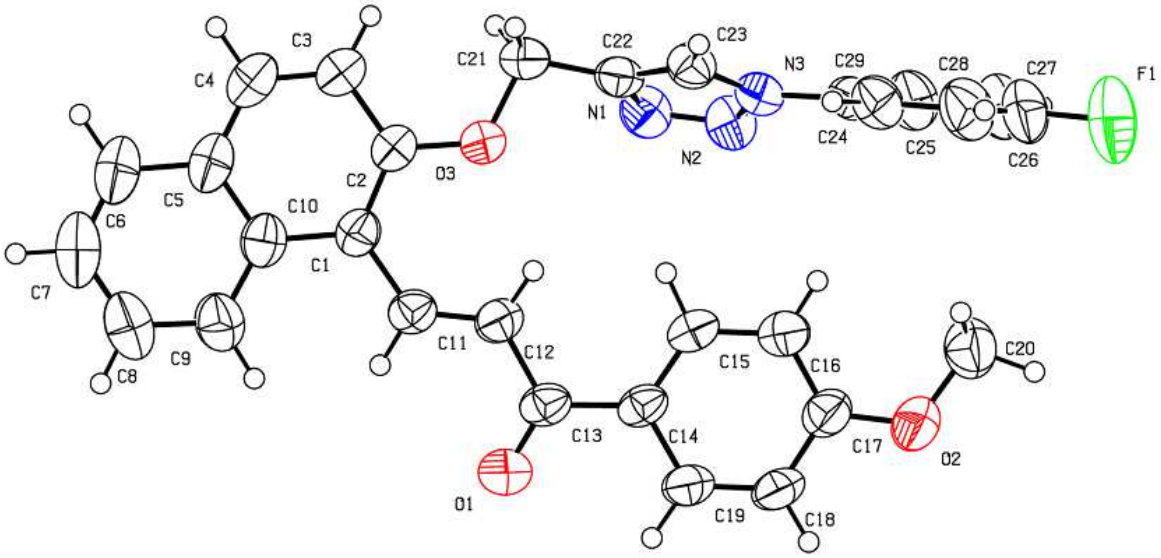


Figure 3: Ortep diagram of the compound **6k**

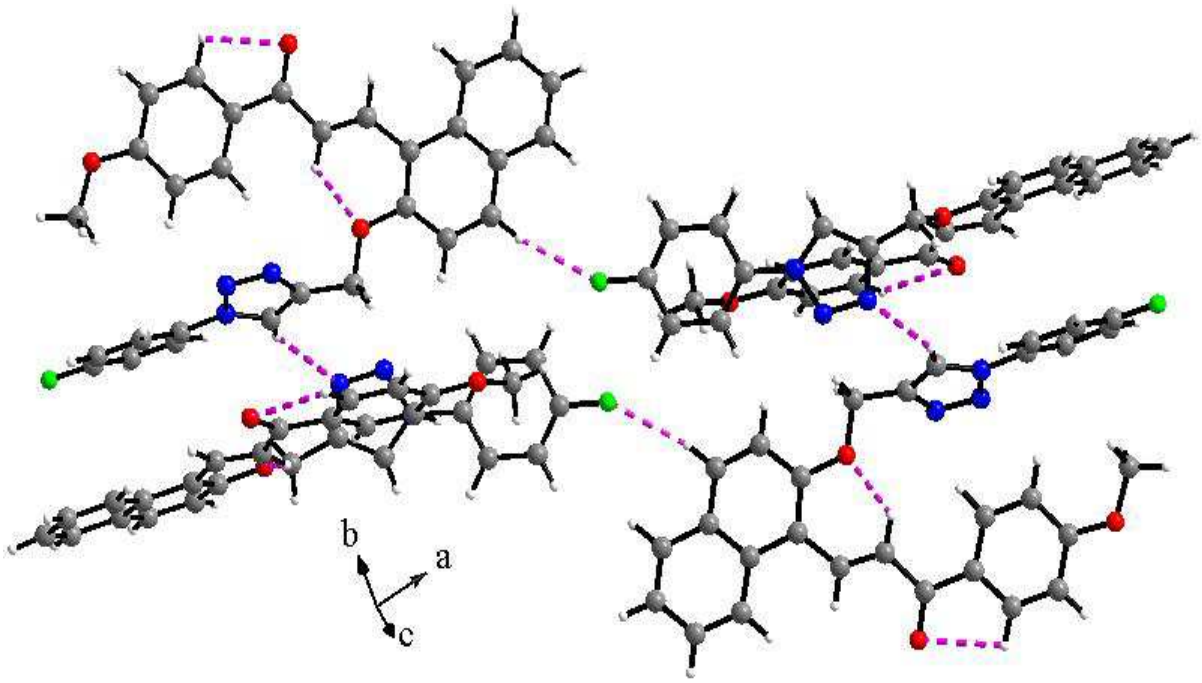


Figure 4: Hydrogen bonded supramolecular packing diagram of the compound **6k (**Pink color dotted lines correspond to the observed hydrogen boning interactions).

2.2 Pharmacology

Antimicrobial activity

The target compounds and chalcone alkynes were examined towards Gram-positive bacteria *S. epidermidis* (MTCC 6880), *B. subtilis (*MTCC 441), Gram-negative bacteria *E. coli* (MTCC 16521), *P. aeruginosa* (MTCC 424) and two fungal strains viz. *A. niger* (MTCC 8189) and *C. albicans* (MTCC 227) by standard serial dilution method.[50] Ciprofloxacin and Fluconazole were used as standard drug for antibacterial and antifungal analysis, respectively. Minimum inhibitory concentrations (MIC in µmol/mL) of all the synthesized compounds as well as positive controls **II** and **III** (Fig. 1) are depicted in Table 1.

Table 1: *In vitro* antimicrobial screening of the compounds **4a-4c; 6a-6r** (MIC in µmol/mL).

Entry	Compounds	*E. coli*	*B. subtilis*	*S. epidermidis*	*P. aeruginosa*	*C. albicons*	*A. niger*
1.	**4a**	0.0731	0.0731	0.1462	0.0731	0.0731	0.0731
2.	**4b**	0.0637	0.0637	0.1274	0.0637	0.0637	0.1274

3.	**4c**	0.0700	0.1400	0.0700	0.0700	0.0700	0.0700
4.	**6a**	0.0119	0.0239	0.0119	0.0119	0.0119	0.0119
5.	**6b**	0.0116	0.0116	0.0116	0.0232	0.0232	0.0232
6.	**6c**	0.0116	0.0116	0.0232	0.0232	0.0232	0.0232
7.	**6d**	0.0058	0.0058	0.0058	0.0116	0.0058	0.0058
8.	**6e**	0.0237	0.0474	0.0474	0.0474	0.0474	0.0237
9.	**6f**	0.0108	0.0217	0.0217	0.0108	0.0217	0.0108
10.	**6g**	0.0263	0.0263	0.0526	0.0263	0.0526	0.0526
11.	**6h**	0.0063	0.0253	0.0253	0.0126	0.0063	0.0253
12.	**6i**	0.0126	0.0253	0.0253	0.0253	0.0126	0.0126
13.	**6j**	0.0032	0.0253	0.0253	0.0253	0.0063	0.0126
14.	**6k**	0.0130	0.0261	0.0522	0.0261	0.0130	0.0522
15.	**6l**	0.0118	0.0236	0.0236	0.0236	0.0118	0.0118
16.	**6m**	0.0128	0.0063	0.0063	0.0128	0.0128	0.0063
17.	**6n**	0.0063	0.0063	0.0063	0.0248	0.0063	0.0063
18.	**6o**	0.0063	0.0126	0.0063	0.0063	0.0063	0.0063
19.	**6p**	0.0032	0.0063	0.0032	0.0063	0.0032	0.0032
20.	**6q**	0.0253	0.0126	0.0253	0.0253	0.0126	0.0126
21.	**6r**	0.0230	0.0459	0.0230	0.0230	0.0115	0.0459
22.	**Ciprofloxacin**	**0.0047**	**0.0047**	**0.0047**	**0.0047**	----	----
23.	**Fluconazole**	----	----	----	----	**0.0102**	**0.0051**
24.	**II**[44]	**0.0956**	----	-----	**>0.191**	**>0.191**	**0.0956**
25.	**III**[44]	**>0.143**	----	-----	**>0.143**	**0.0714**	**0.1428**

The preliminary *in vitro* antibacterial screening indicated that the majority of the synthesized compounds exhibited good activity. Compound **6p** with 4-nitro group was found to be more active than the standard with MIC value of 0.0032 µmol/mL against *E. coli* and *S. epidermidis*. Moreover, **6j** also showed excellent potency against *E. coli* with the MIC value of 0.0032 µmol/mL and was found to be more active than standard used. In case of *B. subtilis*, compounds **6d** exhibited high potency amongst all the tested compounds with MIC values of

0.0058 µmol/mL. In case of *P. aeruginosa*, compounds **6o** and **6p** were found to be more active compared to the all other tested compounds with MIC values of 0.0063 µmol/mL.

Most of the synthesized hybrids also exhibited good antifungal activity. Compound **6p** showed better potency compared to Fluconazole (MIC = 0.0102 µmol/mL) against *A. niger* and *C. albicans* with MIC value of 0.0032 µmol/mL. Similarly, **6h**, **6j**, **6n** and **6o** showed excellent activity against *A. niger* and *C. albicans* with the MIC value of 0.0032 µmol/mL which is better than Fluconazole (MIC = 0.0102 µmol/mL). Against *C. albicans*, **6d** with bromine group exhibited comparable activity to that of standard with MIC values of 0.0054 µmol/mL.

Structure Activity Relationship

i) Most of the fluorinated triazoles exhibited good results than the non-fluorinated compound **6a**.[51]

ii) The synthesized triazole analogues with a substituted benzene showed better activity than naphthaldehyde-chalcone alkynes (**4a-4c)**, exhibiting the significance of 1,2,3-triazole. These outcomes revealed the additive effect of biological activity when two pharmacophoric moieties, i.e. chalcone and 1,2,3-triazole are conjugated.[52]

iii) Compounds with electron withdrawing substituents on benzene displayed more activity than having electron releasing groups.[53]

iv) It was observed that compounds with nitro and methoxy substituents on benzene ring demonstrated better activity against majority of the microorganisms under test.

v) Molecule **6p** containing *p*-nitro group exhibited good antifungal activity and was more effective than Fluconazole.

vi) Activity results also revealed that most of the triazole hybrids exhibited superior antifungal potency compared to antibacterial activity.

vii) Further, the biological activity of the synthesized compounds has been compared with the positive control (II and III; Fig. 1) reported in the literature.[44] It was observed that all the synthesized triazoles were found to be more potent than the positive control II and III against all the tested microbial strains.

Docking studies

The docking simulations most potent antibacterial compound **6p** into ligand binding region of *E. coli* topoisomerase II DNA gyrase B were carried out to get probable modes of binding. The most stable binding conformation of **6p** into active site of topoisomerase II DNA

gyrase B and cartoon diagram are shown in Figure 5 and Figure 6, respectively. The carbonyl group participated in hydrogen bonding with His95, Ala96 and Ser121 residues. Triazole ring as well as phenyl ring attached to triazole is engaged in pi-alkyl interactions with Ile 78, while same phenyl ring also demonstrated pi-alkyl interactions with Val120. The phenyl ring showed pi-alkyl interactions with Ala 96 and pi-sigma interactions with Ile 90. Hence, it can be thought that these chalcone triazole conjugates possibly inhibit DNA topoisomerase.

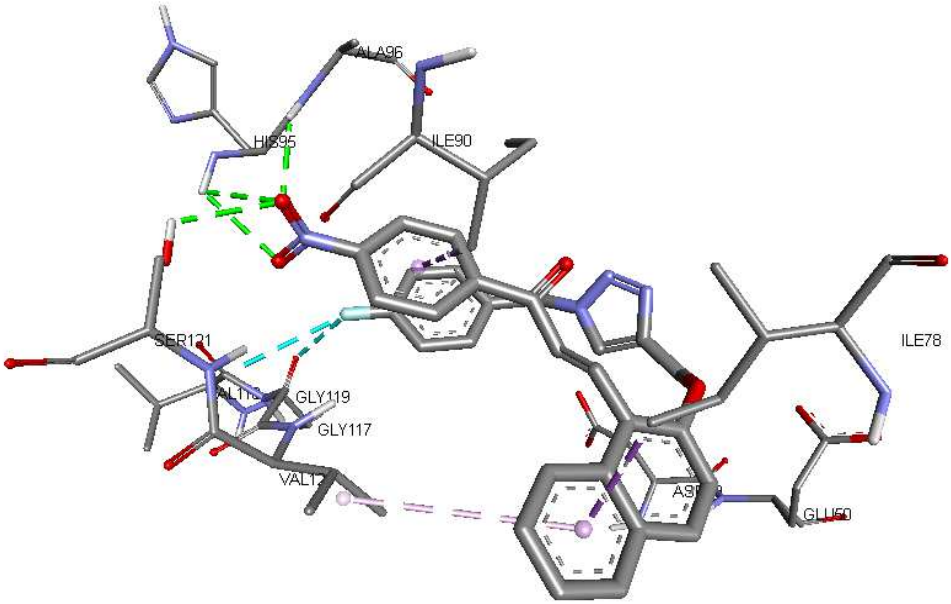


Figure 5: Binding conformation of compound **6p** into topoisomerase II DNA Gyrase showing different interactions i.e hydrogen bond (green lines), pi-alkyl (pink lines), pi-sigma (magenta lines).

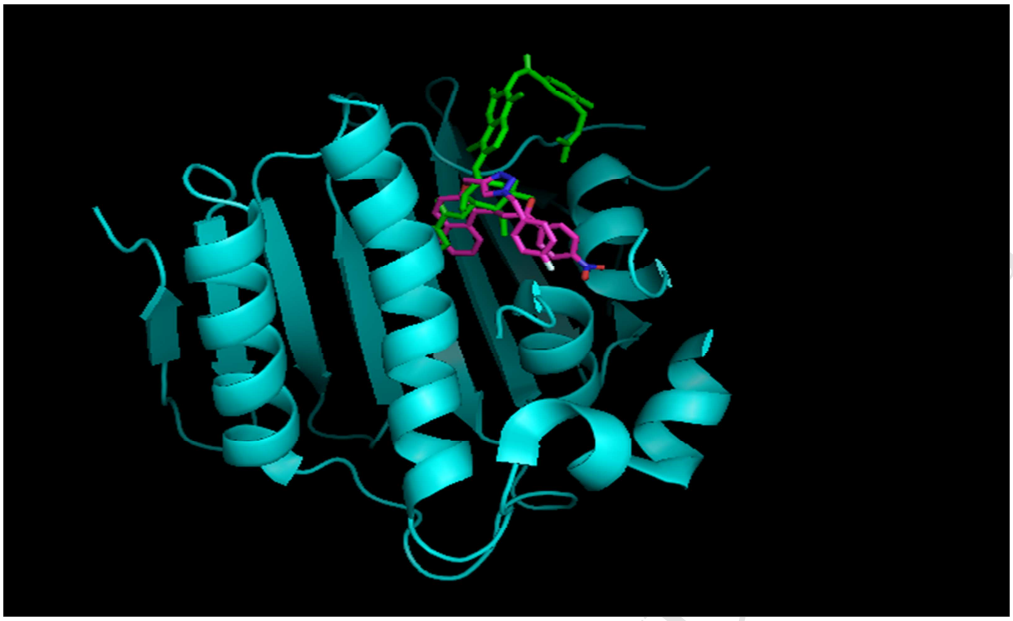


Figure 6: Cartoon diagram of topoisomerase II DNA Gyrase alongwith docked **6p**.

Molecular dynamics studies

We performed a 50 ns molecular dynamics simulation of ligand-protein complex obtained after molecular docking study in order to reveal the dynamics of ligand binding into the active site of enzyme. MD simulation gives important insight into the dynamics of interaction between the partners and the overall stability of the complex which overcomes the limitation of x-ray crystallography or molecular docking as these methods provides a still picture of the interaction. The Fig. 7A represent the all atom (blue), backbone (green) root means square deviation (RMSD) plot for the protein and ligand RMSD (magenta) plot. The RMSD plot indicates that the protein remains stable throughout the 50 ns simulation period with very small fluctuations at the starting point of simulation. The ligand RMSD remains fluctuating owing to its dynamic nature and in order to accommodate and bind itself strongly in the protein binding pocket. It is also observed that the ligand RMSD stabilized during the later half of simulation period. Further, radius of gyration plot of Cα atoms of protein provided a measure of overall compactness of the protein structure during simulation (**Fig. 7B**).

Additionally, in order to evaluate the flexibility of the protein structure throughout the simulation, we calculated root mean square fluctuation (RMSF) of individual amino acid residues of the protein (**Fig. 7C).** The whole protein had a RMSF value between 0.05 to 0.45 indicating a simulation.

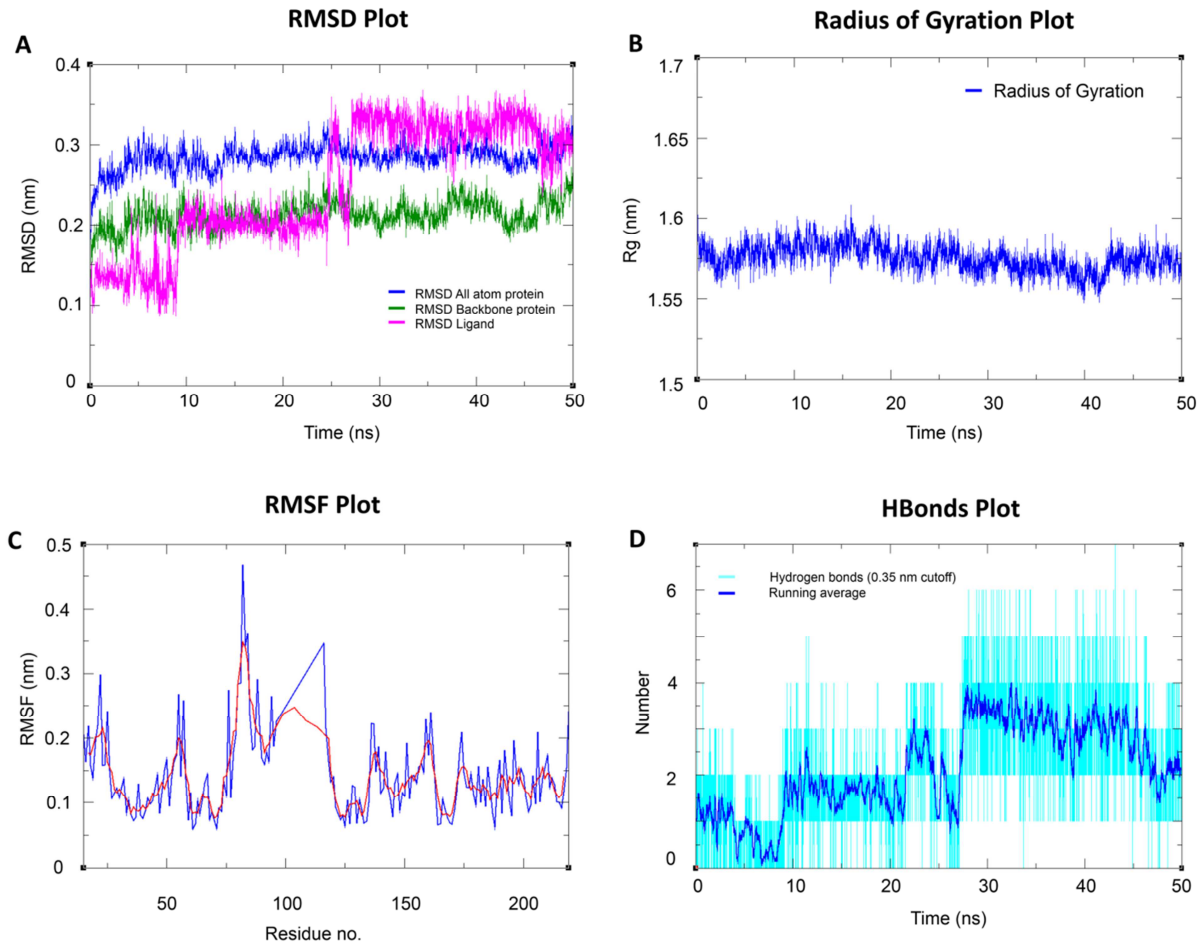


Figure 7: Qualitative analysis of the Molecular dynamics trajectory. RMSD plot of protein and ligand (**A**). Radius of gyration plot of the protein (**B**). RMSF plot of the protein (**C**) and the plot of hydrogen bonds formed between protein and ligand during the 50 ns simulation period. (**D**).

One of important forces involved during protein ligand interaction is the hydrogen bonding and it plays an indispensable role in stabilizing the protein-ligand complex. The average number of hydrogen bonds formed during the simulation was calculated using a soft cut-off value of 3.5 Å with the help of h-bond utility in GROMACS and are plotted in **Fig. 7D**. It was observed that the ligand not only preserved the hydrogen bonds formed during the docking simulation, but also makes new hydrogen bonds and thus stabilizes the complex. Especially, during the later half of the simulation period, compound forms on an average 3 hydrogen bonds with the protein. It indicates that the compound stabilizes itself into the binding pocket of the protein through formation of additional contacts with the binding site amino acid residues.

Finally, we extracted the coordinates from trajectory at 0, 15 and 50 ns time interval and made a comparison. The structures are given in **Fig. 7**

3. Conclusion

We have synthesized some new fluorinated-chalcone-1,2,3-triazoles with potential antimicrobial activity from substituted propargylated chalcones and organic azides by click reaction under environmentally benign conditions. The X-ray crystallographic studies suggested that molecular structure is stabilized by nonclassical hydrogen-bonding interactions. The antimicrobial evaluation revealed that most of the compounds showed significant activity. The antimicrobial screening results demonstrated the additive effect of activity when two pharmacophoric moieties, i.e. 1,2,3-triazole and chalcone are connected. Docking studies also showed that compound **6k** interacts with DNA topoisomerase via various non covalent interactions. Additionally, molecular dynamics study was also performed to get an insight into the dynamics of ligand interaction.

4. Materials and Methods

4.1. Experimental section

General

All the melting points (ºC) were recorded in open capillaries and are uncorrected. The IR spectra were taken on SHIMAZDU IR AFFINITY-I FTIR spectrophotometer using potassium bromide (KBr). The ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively on Bruker Avance III 400 nano bay using tetramethysilane (TMS). DEPT-135, HMQC (heteronuclear multiple quantum coherence) or HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple bond correlation), ^{19}F NMR experiments were also parformed out for characterization of some compounds. MS spectra were recorded on Q-TOF micromass (ESI-MS) Waters high resolution mass spectrometer. The analytical TLC was recorded on readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under ultraviolet lamp. Starting materials were procured from Aldrich, Across, Hi-media, S. D. fine, SRL etc. and were used as recieved.

Single-Crystal Structure Determination

A suitable light yellow single crystal was carefully selected under a polarizing microscope and glued to a thin glass fiber with a cyanoacrylate (superglue) adhesive. The single-crystal data were collected on a Bruker D8 Advance diffractometer at 295(2) K. The data were reduced using SAINTPLUS,[54] and an empirical absorption correction was applied using the SADABS program.[55] The structure was solved and refined using SHELXL97[56] present in the WinGx suit of programs (Version 1.63.04a).[57] All the hydrogen atoms were located from difference Fourier map and refined using the riding model. The final refinement included atomic positions for all of the atoms, anisotropic thermal parameters for all of the non-hydrogen atoms, and isotropic thermal parameters for all the non-hydrogen atoms. Full-matrix least-squares refinement against F^2 was carried out using the WinGx package of programs. Details of the structure solution and final refinements for the structure are given in Table 1. The crystallographic data for the compound can be found in CCDC No: 1587460 by free of charge from The Cambridge Crystallographic Data Center (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of chalcone alkyne (4a-4c)[19]:

An aqueous solution of NaOH (3 mL, 60%) was added dropwise to a solution of substituted acetophenone **3** (1 mmol) and 4-*O*-propargylated naphthaldehyde **2** (1 mmol) in ethanol (5-10 mL) with constant stirring. The reaction mixture was stirred for 3-4 h at room temperature. Upon completion of the reaction as monitored by the TLC, reaction mixture was diluted with ice cold water and filtered. The solid thus obtained was washed with ethanol 2-3 times followed by water and recrystallized from methanol: chloroform (7:3) to yield the chalcones (**4a-4c**).

(E)-3-(4-methoxyphenyl)-1-(2-(prop-2-yn-1-yloxy)naphthalen-1-yl)prop-2-en-1-one (**4a**), Yield 89%; Yellow solid; mp 168–170 °C; IR (KBr, cm^{-1}): 3283, 3056 (C-H), 2930, 2862, 2127 (C≡C), 1658 (C=O), 1592 (C=C), 1575, 1520, 1426, 1377, 1344, 1296, 1253, 1215, 1176, 1068, 1036, 1008, 989, 778, 743, 692, 642, 586, 537. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.61 (t, 1H), 3.90 (s, OCH_3, 3H), 4.92 (s, 2H, OCH_2), 7.01 (d, *J* = 8.0 Hz, 2H), 7.38-7.46 (m, 2H), 7.54-7.59 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 15.6 Hz, 1H, =C-H), 8.11-8.15 (m, 2H), 8.28 (d, *J* = 8.4 Hz, 2H), 8.47 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.35 (C=O), 163.38, 154.76, 136.48, 133.04, 131.44, 131.32, 130.98, 129.62, 128.61,

127.98, 127.48, 124.45, 123.75, 119.05, 114.39, 113.82, 78.56, 57.18 (OCH_2), 55.48 (OCH_3). MS: m/z (M^+) Cacld. for $C_{23}H_{18}O_3$: 342.1; found: 343.0 $(M+H)^+$.

(E)-3-(4-bromophenyl)-1-(2-(prop-2-yn-1-yloxy)naphthalen-1-yl)prop-2-en-1-one (**4b**), Yield 91%; Yellow solid; mp 170–172 °C; IR (KBr, cm^{-1}): 3287, 3058 (C-H), 2932, 2864, 2128 (C≡C), 1662 (C=O), 1596 (C=C), 1577, 1520, 1430, 1373, 1349, 1297, 1258, 1217, 1179, 1062, 1038, 1002, 988, 770, 739, 689, 639, 587, 540. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.62 (t, 1H), 4.94 (s, 2H,OCH_2), 7.39-7.44 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.56-7.61 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.91 (m, 1H), 7.94 (d, *J* = 15.6 Hz, 1H, =C-H), 7.98 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 8.4 Hz, 2H), 8.51 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.07 (C=O), 155.07, 137.84, 137.23, 133.06, 131.87, 130.24, 129.56, 128.70, 127.77, 127.71, 127.29, 124.56, 123.53, 118.42, 114.14, 78.37, 57.15 (OCH_2). MS: m/z (M^+) Cacld. for $C_{22}H_{15}BrO_2$: 390.0; found: 391.1 $(M+H)^+$.

(E)-3-(4-nitrophenyl)-1-(2-(prop-2-yn-1-yloxy)naphthalen-1-yl)prop-2-en-1-one (**4c**), Yield 83%; Yellow solid; mp 174–176 °C; IR (KBr, cm^{-1}): 3287, 3058 (C-H), 2928, 2872, 2131 (C≡C), 1656 (C=O), 1594 (C=C), 1576, 1524, 1428, 1379, 1346, 1297, 1261, 1215, 1177, 1069, 1037, 1010, 983, 777, 746, 696, 644, 589, 538. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.64 (t, 1H), 4.96 (s, 2H, OCH_2), 7.40-7.48 (m, 2H), 7.58-7.63 (m, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.93 (m, 1H), 7.97 (d, *J* = 15.6 Hz, 1H, =C-H), 8.38 (d, *J* = 8.4 Hz, 2H), 8.55 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.72 (C=O), 155.23, 143.38, 139.08, 133.06, 132.45, 129.57, 128.80, 127.93, 126.83, 124.66, 123.79, 123.28, 117.64, 113.37, 76.30, 56.89 (OCH_2). MS: m/z (M^+) Cacld. for $C_{22}H_{15}NO_4$: 352.1; found: 353.3 $(M+H)^+$.

General procedure for the synthesis of triazoles (6a-6r)[36, 38]:

A suspension of propargylated chalcones (**4a-4c)** (1 mmol), substituted benzyl bromides (1 mmol), sodium azide (1.2 mmol), water (2 mL) and cellulose supported CuI nanoparticles (0.1 g) was heated at 70 °C for 4-7 h. Upon completion of reaction as monitored by TLC, the reaction mixture was filtered and residue was washed with ethyl acetate three times (3×30 mL). The organic extract was washed with water followed by brine and dried over Na_2SO_4 and concentrated under vacuum. The solid obtained was recrystallized from methanol: chloroform (7:3) to yield the pure products (**6a-6r**).

(E)-3-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-bromophenyl)prop-2-en-1-one (**6a**), Yield 88%; Yellow solid; mp 184–186 °C; IR (KBr, cm^{-1}): 3177, 3162 (C-H,

triazole), 3048 (C-H), 2953, 2879, 1669 (C=O), 1594 (C=C), 1578, 1524, 1459, 1399, 1289, 1258, 1222, 1178, 1078, 1048, 1010, 828, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.44 (s, 2H, NCH_2), 5.52 (s, 2H, OCH_2), 7.20–7.22 (m, 2H), 7.31–7.33 (m, 3H), 7.43-7.47 (m, 2H), 7.56 (s, 1H, triazolyl–H), 7.56-7.60 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.85-7.92 (m, 5H), 8.04 (d, *J* = 15.6 Hz, 1H, =C-H), 8.25 (d, *J* = 8.8 Hz, 2H), 8.49 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.92 (C=O), 155.82, 143.94 (C-4), 137.75, 137.13, 134.23, 133.13, 132.12, 131.19 130.20, 129.38, 129.17, 128.88, 128.02, 127.77, 127.70, 126.90, 124.42, 123.40, 122.91 (C-5), 117.95, 114.19, 63.21 (OCH_2), 54.32 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{22}BrN_3O_2$: 523.1; found: 525.7 $(M+2H)^+$.

(E)-1-(4-bromophenyl)-3-(2-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)prop-2-en-1-one (**6b**), Yield 89%; Yellow solid; mp 188–190 °C; IR (KBr, cm^{-1}): 3189, 3148 (C-H, triazole), 3046 (C-H), 2949, 2879, 1658 (C=O), 1591 (C=C), 1577, 1522, 1458, 1397, 1295, 1258, 1218, 1177, 1075, 1045, 1009, 828, 774, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.44 (s, 2H, NCH_2), 5.58 (s, 2H, OCH_2), 7.06-7.11 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.32–7.34 (m, 1H), 7.43-7.48 (m, 2H), 7.56-7.58 (m, 2H), 7.60-7.67 (m, 2H), 7.83-7.93 (m, 5H, triazolyl–H, =C-H + 3ArH), 8.26 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.90 (C=O), 161.71, 159.23, 155.83, 143.88 (C-4), 137.65, 137.10, 133.14, 132.11, 131.85, 131.11, 131.03, 130.18, 129.35, 128.71, 127.69, 126.87, 124.84, 124.40, 123.38, 123.15, 121.63, 121.51 (C-5), 117.88, 115.98, 116.77, 114.12, 63.10 (OCH_2), 47.94 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}BrN_3O_2$: 541.1; found: 543.8 $(M+2H)^+$.

(E)-1-(4-bromophenyl)-3-(2-((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)prop-2-en-1-one (**6c**), Yield 87%; Yellow solid; mp 196–198 °C; IR (KBr, cm^{-1}): 3179, 3149 (C-H, triazole), 3052 (C-H), 2947, 2882, 1655 (C=O), 1593 (C=C), 1576, 1524, 1458, 1397, 1295, 1258, 1218, 1177, 1075, 1045, 1009, 828, 774, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 6.91-6.94 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.01–7.06 (m, 1H), 7.26-7.32 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.56-7.61 (m, 2H), 7.63-7.65 (m, 2H), 7.84-7.93 (m, 5H, triazolyl–H, =C-H + 3ArH), 8.25 (d, *J* = 12 Hz, 1H), 8.48 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.90 (C=O), 164.18, 161.72, 155.72, 144.18 (C-4), 137.80, 137.08, 136.56, 133.06, 132.15, 131.89, 130.87, 130.79, 130.19, 129.37, 128.74, 127.80, 127.73, 126.91, 124.45, 123.48, 123.45, 123.39, 122.99 (C-5), 117.98, 116.02, 115.81, 115.08, 114.86,

114.16, 63.18 (OCH_2), 53.52 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}BrN_3O_2$: 541.1; found: 543.8 $(M+2H)^+$.

(E)-1-(4-bromophenyl)-3-(2-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)prop-2-en-1-one (**6d**), Yield 88%; Yellow solid; mp 196–198 °C; IR (KBr, cm^{-1}): 3182, 3153 (C-H, triazole), 3074 (C-H), 2946, 2884, 1655 (C=O), 1594 (C=C), 1577, 1531, 1459, 1398, 1296, 1257, 1220, 1179, 1077, 1046, 1009, 827, 775, 522. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.44 (s, 2H, NCH_2), 5.48 (s, 2H, OCH_2), 6.98-7.03 (m, 2H), 7.19-7.22 (m, 2H), 7.43–7.47 (m, 2H), 7.56-7.60 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.83-7.92 (m, 5H, triazolyl–H, =C-H + 3ArH), 8.25 (d, *J* = 12 Hz, 1H), 8.47 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.88 (C=O), 164.09, 161.54, 155.69, 144.03 (C-4), 137.80, 137.08, 133.06, 132.12, 131.90, 130.18, 129.95, 129.38, 128.72, 127.80, 127.73, 126.95, 124.46, 123.40, 122.79 (C-5), 118.03, 116.29, 116.08, 114.20, 63.23 (OCH_2), 53.54 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}BrN_3O_2$: 541.1; found: 543.8 $(M+2H)^+$.

(E)-1-(4-bromophenyl)-3-(2-((4-fluorophenyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-prop-2-en-1-one (**6e**), Yield 92%; Yellow solid; mp 188–190 °C; IR (KBr, cm^{-1}): 3184, 3156 (C-H, triazole), 3049 (C-H), 2953, 2876, 1657 (C=O), 1592 (C=C), 1575, 1530, 1467, 1388, 1295, 1259, 1219, 1170, 1084, 1049, 1008, 829, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.52 (s, 2H, OCH_2), 7.21-7.26 (m, 2H), 7.45–7.49 (m, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.55-7.58 (m, 2H), 7.60-7.62 (m, 1H), 7.64-7.67 (m, 2H), 7.82-7.87 (m, 3H), 7.90-7.97 (m, 2H), 8.06 (s, 1H, triazolyl-H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.72 (C=O), 155.83, 144.57 (C-4), 137.93, 137.11, 133.12, 132.26, 131.91, 130.08, 129.47, 128.74, 127.83, 126.96, 124.55, 123.45, 122.49 (C-5), 122.41, 121.22, 118.08, 116.97, 116.74, 114.12, 63.21 (OCH_2). MS: m/z (M^+) Cacld. for $C_{28}H_{19}BrFN_3O_2$: 527.1; found: 529.8 $(M+H)^+$.

(E)-1-(4-bromophenyl)-3-(2-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy) naphthalene-1-yl)prop-2-en-1-one (**6f**), Yield 92%; Yellow solid; mp 196–198 °C; IR (KBr, cm^{-1}): 3187, 3164 (C-H, triazole), 3039 (C-H), 2948, 2879, 1657 (C=O), 1590 (C=C), 1578, 1520, 1458, 1398, 1287, 1264, 1218, 1170, 1068, 1040, 1011, 829, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.56 (s, 2H, OCH_2), 7.45-7.51 (m, 2H), 7.55-7.62 (m, 3H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.85-7.92 (m, 5H), 7.95 (d, *J* = 9.2 Hz, 1H), 8.06 (m, 1H), 8.21 (s, 1H,

triazolyl–H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.52 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.72 (C=O), 155.58, 144.94 (C-4), 137.95, 137.13, 137.02, 133.03, 132.74, 132.40, 132.18, 131.89, 130.63, 130.07, 129.57, 128.76, 127.85, 127.80, 127.63, 125.64, 125.61, 124.58, 123.50, 123.39 (C-5), 121.88, 121.01, 117.38, 114.27, 63.21 (OCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{19}BrF_3N_3O_2$: 577.1; found: 579.2 $(M+2H)^+$.

(E)-3-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (**6g**), Yield 79%; Yellow solid; mp 188–190 °C; IR (KBr, cm^{-1}): 3182, 3152 (C-H, triazole), 3044 (C-H), 2948, 2877, 1657 (C=O), 1590 (C=C), 1575, 1520, 1457, 1398, 1294, 1256, 1217, 1170, 1074, 1040, 1008, 827, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, OCH_3, 3H), 5.44 (s, 2H, NCH_2), 5.48 (s, 2H, OCH_2), 7.00 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.29-7.32 (m, 3H), 7.42-7.47 (m, 2H), 7.56 (s, 1H, triazolyl–H), 7.57 (dd, *J* = 4.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.87-7.91 (m, 2H, =C-H +1ArH), 8.02 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.23 (C=O), 163.37, 155.41, 144.17 (C-4), (C-4), 136.56, 134.28, 133.03, 131.59, 131.30, 130.93, 129.40, 129.11, 128.78, 128.63, 127.99, 127.60, 127.49, 124.33, 123.62, 122.98 (C-5), 118.59, 114.43, 113.85, 63.43 (OCH_2), 55.52 (NCH_2), 54.25 (OCH_3). MS: m/z (M^+) Cacld. for $C_{30}H_{25}N_3O_3$: 475.2; found: 476.0 $(M+H)^+$.

(E)-3-(2-((2-fluorobenzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxy phenyl)prop-2-en-1-one (**6h**), Yield 90%; Yellow solid; mp 192–194 °C; IR (KBr, cm^{-1}): 3186, 3158 (C-H, triazole), 3047 (C-H), 2958, 2873, 1658 (C=O), 1591 (C=C), 1575, 1522, 1458, 1399, 1290, 1256, 1218, 1170, 1084, 1043, 1013, 827, 777, 522. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 3H, OCH_3), 5.44 (s, 2H, NCH_2), 5.48 (s, 2H, OCH_2), 7.00 (d, *J* = 8.0 Hz, 2H), 7.17-7.19 (m, 2H), 7.31–7.32 (m, 3H), 7.42-7.47 (m, 2H), 7.54-5 (m, 2H, triazolyl–H + 1ArH), 7.84 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 4.0 Hz, 1H), 7.89 (d, *J* = 15.6 Hz, 1H, =C-H), 8.02 (d, *J* = 12 Hz, 2H), 8.26 (d, *J* = 12.0 Hz, 1H), 8.43 (d, *J* = 16.0 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.12 (C=O), 163.37, 155.30, 144.17 (C-4), 136.56, 134.28, 133.03, 131.59, 131.30, 130.93, 129.40, 129.11, 128.78, 128.63, 127.99, 127.60, 127.49, 124.33, 123.62, 122.98 (C-5), 118.59, 114.43, 113.85, 109.14, 63.43 (OCH_2), 55.52 (NCH_2), 54.25 (OCH_3). MS: m/z (M^+) Cacld. for $C_{30}H_{24}FN_3O_3$: 492.8; found: 493.9 $(M+H)^+$.

(E)-3-(2-((3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxy

phenyl)prop-2-en-1-one (**6i**), Yield 88%; Yellow solid; mp 188–190 °C; IR (KBr, cm^{-1}): 3186, 3155 (C-H, triazole), 3049 (C-H), 2958, 2867, 1659 (C=O), 1594 (C=C), 1576, 1524, 1457, 1399, 1294, 1257, 1218, 1170, 1075, 1040, 1008, 828, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 3H, OCH_3), 5.46 (s, 2H, NCH_2), 5.48 (s, 2H, OCH_2), 6.90-7.04 (m, 4H), 7.23-7.27 (m, 2H), 7.43-7.47 (m, 2H), 7.55-7.59 (m, 2H), 7.60 (s, 1H, triazolyl–H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 15.6 Hz, =C-H, 1H), 8.08 (d, *J* = 12 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.0 Hz, 2H), 8.43 (d, *J* = 15.6 Hz, 1H, =C-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.21 (C=O), 164.15, 163.38, 161.69, 155.31, 144.48 (C-4), 136.69, 136.67, 136.62, 131.61, 131.24, 130.93, 129.44, 128.65, 127.67, 127.52, 124.37, 123.65, 123.47, 123.03 (C-5), 118.72, 115.92, 115.71, 114.85, 114.46, 113.85, 63.49 (OCH_2), 55.52 (NCH_2), 53.57 (OCH_3). MS: m/z (M^+) Cacld. for $C_{30}H_{24}FN_3O_3$: 492.8; found: 493.9 $(M+H)^+$.

(E)-3-(2-((4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxy phenyl)prop-2-en-1-one (**6j**), Yield 86%; Yellow solid; mp 184–186 °C; IR (KBr, cm^{-1}): 3186, 3155 (C-H, triazole), 3048 (C-H), 2949, 2876, 1657 (C=O), 1591 (C=C), 1576, 1524, 1458, 1399, 1295, 1256, 1219, 1177, 1078, 1047, 1012, 828, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 3H, OCH_3), 5.44 (s, 2H,NCH_2), 5.45 (s, 2H, OCH_2), 6.95-7.01 (m, 4H), 7.15-7.19 (m, 2H), 7.42-7.46 (m, 2H),7.55-7.59 (m, 2H), 7.70 (s, 1H, triazolyl–H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 15.6 Hz, 1H, =C-H). 8.08 (d, *J* = 12 Hz, 2H), 8.42 (d, *J* = 15.6 Hz, 1H, =C-H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.19 (C=O), 164.06, 163.41, 161.58, 155.30, 144.41 (C-4), 136.69, 132.96, 131.58, 131.24, 130.92, 130.16, 130.13, 129.93, 129.84, 129.44, 128.64, 127.70, 127.53, 124.38, 123.65, 122.81 (C-5), 118.77, 116.23, 116.01, 114.49, 113.86, 63.54 (OCH_2), 55.52 (NCH_2), 53.48 (OCH_3). MS: m/z (M^+) Cacld. for $C_{30}H_{24}FN_3O_3$: 492.8; found: 493.9 $(M+H)^+$.

(E)-3-(2-((4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxy phenyl)prop-2-en-1-one (**6k**), Yield 90%; Yellow solid; mp 200–202 °C; IR (KBr, cm^{-1}): 3188, 3158 (C-H, triazole), 3064 (C-H), 2956, 2878, 1657 (C=O), 1591 (C=C), 1575, 1522, 1457, 1399, 1295, 1256, 1218, 1177, 1074, 1048, 1008, 828, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.48 (s, 3H, OCH_3), 5.54 (s, 2H, OCH_2), 6.90-6.93 (m, 2H), 7.16-7.20 (m, 2H), 7.44-7.51 (m, 2H), 7.57-7.65 (m, 3H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.92-7.97 (m, 2H), 8.07 (s, 1H, triazolyl–H), 8.28 (d, *J* = 8.8 Hz, 1H), 8.49 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.36 (C=O), 168.17, 160.65, 155.23, 146.17, 143.73 (C-4), 142.35, 139.16, 138.94, 131.99, 131.05,

130.36, 130.26, 130.22, 130.18, 130.16, 130.08, 130.00, 129.89, 128.78, 123.57 (C-5), 122.47, 120.92, 119.15, 118.99, 117.62, 115.03, 102.36, 61.86, (OCH_2), 53.57 (OCH_3). MS: m/z (M^+) Cacld. for $C_{29}H_{22}FN_3O_3$: 479.1; found: 480.2 $(M+H)^+$.

(E)-1-(4-methoxyphenyl)-3-(2-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy) naphthalene-1-yl)prop-2-en-1-one (**6l**), Yield 90%; Yellow solid; mp 192–194 °C; IR (KBr, cm^{-1}): 3185, 3159 (C-H, triazole), 3064 (C-H), 2958, 2868, 1657 (C=O), 1592 (C=C), 1575, 1522, 1457, 1388, 1294, 1257, 1218, 1170, 1077, 1040, 1009, 827, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.80 (s, 3H, OCH_3), 5.52 (s, 2H, OCH_2), 6.88 (d, *J* = 8.8 Hz, 2H), 7.43-7.46 (m, 2H), 7.55-7.63 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.83-7.93 (m, 4H), 7.98 (d, *J* = 8.8 Hz, 2H), 8.08 (m, 1H), 8.24 (s, triazolyl–H, 1H). 8.26 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.15 (C=O), 163.38, 155.26, 145.21 (C-4), 137.16, 136.69, 132.98, 131.69, 131.13, 130.84, 130.51, 129.55, 128.69, 127.74, 127.61, 125.42, 124.48, 123.67, 123.29 (C-5), 121.10, 118.87, 117.39, 114.41, 113.82, 63.50 (OCH_2), 55.22, 29.70. HRMS: m/z (M^+) Cacld. for $C_{29}H_{22}FN_3O_3$: 479.1645 found: $(M+H)^+$. MS: m/z (M^+) Cacld. for $C_{30}H_{22}F_3N_3O_3$: 529.1; found: 530.0 $(M+H)^+$.

(E)-3-(2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitrophenyl)prop-2-en-1-one (**6m**), Yield 86%; Yellow solid; mp 186–188 °C; IR (KBr, cm^{-1}): 3178, 3162 (C-H, triazole), 3046 (C-H), 2958, 2876, 1658 (C=O), 1592 (C=C), 1576, 1522, 1458, 1388, 1296, 1257, 1218, 1176, 1075, 1046, 1009, 827, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (s, 2H, NCH_2), 5.62 (s, 2H, OCH_2), 7.04–7.12 (m, 2H), 7.30–7.36 (m, 2H), 7.45-7.49 (m, 2H), 7.61 (t, 1H), 7.70 (s, 1H, triazolyl–H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 15.6 Hz, =C-H, 1H), 8.14 (d, *J* = 12 Hz, 2H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 2H), 8.58 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.56 (C=O), 164.15, 161.74, 156.22, 149.99, 143.82, 143.17 (C-4), 138.80, 132.71, 129.63, 128.83, 127.94, 126.42, 124.55, 123.77, 123.15 (C-5), 117.38, 116.04, 115.83, 115.04, 114.82, 113.92, 62.87 (OCH_2), 53.66 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{22}N_4O_4$: 490.1; found: 491.2 $(M+H)^+$.

(E)-3-(2-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitro phenyl)prop-2-en-1-one (**6n**), Yield 89%; Yellow solid; mp 194–196 °C; IR (KBr, cm^{-1}): 3183, 3156 (C-H, triazole), 3057 (C-H), 2938, 2849, 1656 (C=O), 1593 (C=C), 1572, 1524, 1459, 1395, 1356, 1295, 1256, 1218, 1170, 1075, 1040, 1012, 827, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (s, 2H, NCH_2), 5.62 (s, 2H, OCH_2), 7.04–7.12 (m, 2H), 7.30–7.36 (m, 2H), 7.45-

7.49 (m, 2H), 7.61 (t, 1H), 7.70 (s, 1H, triazolyl–H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 15.6 Hz, =C-H, 1H). 8.14 (d, J = 12 Hz, 2H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 2H), 8.58 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.52 (C=O), 161.79, 159.27, 156.15, 149.85, 143.49, 143.18 (C-4), 138.41, 133.22, 132.56, 131.18, 131.10, 130.70, 130.67, 129.61, 129.30, 128.82, 127.91, 126.28, 124.90, 124.50, 123.75, 123.23, 123.12 (C-5), 121.59, 121.45, 117.20, 115.98, 115.77, 62.52 (OCH_2), 47.61 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}FN_4O_4$: 508.1; found: 509.1 $(M+H)^+$.

(E)-3-(2-((1-(3-fluorobenzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitro phenyl)prop-2-en-1-one (**6o**), Yield 91%; Yellow solid; mp 192–194 °C; IR (KBr, cm^{-1}): 3184, 3157 (C-H, triazole), 3048 (C-H), 2938, 2857, 1657 (C=O), 1591 (C=C), 1576, 1522, 1458, 1398, 1345, 1295, 1257, 1217, 1179, 1074, 1043, 1008, 827, 776, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.45 (s, 2H, NCH_2), 5.56 (s, 2H, OCH_2), 7.22–7.25 (m, 2H), 7.31–7.33 (m, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.58-7,62 (m, 2H, triazolyl–H + 1ArH), 7.85 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 15.6 Hz, =C-H, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 2H), 8.57 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.56 (C=O), 156.32, 149.99, 143.56, 143.19 (C-4), 138.72, 134.20, 133.26, 132.70, 129.62, 129.32, 129.16, 128.89, 128.01, 127.92, 126.35, 124.52, 123.78, 123.13, 122.97 (C-5), 117.29, 113.91, 62.87 (OCH_2), 54.35 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}FN_4O_4$: 508.1; found: 509.1 $(M+H)^+$.

(E)-3-(2-((1-(4-fluorobenzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitro phenyl)prop-2-en-1-one (**6p**), Yield 94%; Yellow solid; mp 188–190 °C; IR (KBr, cm^{-1}): 3184, 3157 (C-H, triazole), 3054 (C-H), 2948, 2876, 1654 (C=O), 1590 (C=C), 1576, 1521, 1458, 1399, 1356, 1295, 1257, 1218, 1170, 1075, 1048, 1008, 827, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (s, 2H, NCH_2), 5.53 (s, 2H, OCH_2), 7.01 (t, *J* = 8.0 Hz, 2H), 7.23–7.26 (m, 2H), 7.45-7.48 (m, 2H), 7.59 (s, 1H, triazolyl–H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 15.6 Hz, =C-H, 1H). 8.16 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 2H), 8.55 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.53 (C=O), 164.11, 156.21, 150.00, 143.74, 143.17 (C-4), 138.83, 133.19, 132.69, 130.07, 129.98, 129.89, 129.63, 129.35, 128.83, 127.95, 126.46, 124.50, 123.78, 123.16, 122.81 (C-5), 117.43, 116.31, 116.09, 113.96, 62.92 (OCH_2), 53.59 (NCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{21}FN_4O_4$: 508.1; found: 509.1 $(M+H)^+$.

(E)-3-(2-((4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitrophenyl) prop-2-en-1-one (**6q**), Yield 87%; Yellow solid; mp 198–200 °C; IR (KBr, cm^{-1}): 3185, 3157 (C-H, triazole), 3064 (C-H), 2958, 2897, 1657 (C=O), 1595 (C=C), 1576, 1530, 1458, 1388, 1295, 1257, 1217, 1174, 1077, 1040, 1018, 827, 777, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.57 (s, 2H,OCH_2), 7.23-7.27 (m, 2H), 7.46–7.54 (m, 2H), 7.60-7.63 (m, 1H), 7.71-7.74 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.98-8.01 (m, 1H), 8.06 (d, *J* = 15.6 Hz, =C-H, 1H). 8.13-8.16 (m, 3H), 8.28-8.30 (m, 3H), 8.61 (d, *J* = 15.6 Hz, =C-H, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.40 (C=O), 163.52, 156.21, 154.86, 143.25 (C-4), 142.88, 138.58, 134.49, 133.18, 132.64, 132.25, 132.23, 129.40, 129.34, 128.87, 128.27, 127.68, 126.81, 126.53, 126.32, 124.64, 123.77, 123.21, 122.43 (C-5), 122.31, 121.21, 117.03, 116.83, 113.90, 62.91 (OCH_2). MS: m/z (M^+) Cacld. for $C_{28}H_{19}FN_4O_4$: 493.4; found: 494.5 $(M+H)^+$.

(E)-1-(4-nitrophenyl)-3-(2-((1-(3-trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy) naphthalene-1-yl)prop-2-en-1-one (**6r**), Yield 89%; Yellow solid; mp 194–196 °C; IR (KBr, cm^{-1}): 3185, 3157 (C-H, triazole), 3057 (C-H), 2953, 2839, 1657 (C=O), 1589 (C=C), 1576, 1524, 1457, 1379, 1294, 1257, 1217, 1177, 1074, 1049, 1008, 827, 775, 522. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62 (s, 2H, OCH_2), 6.63 (m, 2H), 7.45-7.54 (m, 3H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.83-7.92 (m, 5H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.08 (m, 1H), 8.20 (s, 1H, triazolyl–H), 8.44 (d, *J* = 15.6 Hz, =C-H, 1H), 9.26 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.73 (C=O), 162.31, 156.20, 144.62 (C-4), 141.70, 137.63, 137.22, 131.53, 131.14, 130.67, 130.04, 129.79, 129.03, 128.53, 128.31, 128.20, 125.75, 125.71, 125.22, 124.91, 123.68 (C-5), 121.07, 121.01, 117.66, 117.62, 117.57, 113.97, 113.92, 113.76, 63.21 (OCH_2). MS: m/z (M^+) Cacld. for $C_{29}H_{19}F_3N_4O_4$: 544.1; found: 545.2 $(M+H)^+$.

Pharmacology

The antimicrobial activities were carried out by following the procedure as reported by Kaushik *et al* .[58]

Docking details

The most potent compound **6p** was docked into the active sites of Docking studies were carried out by following procedure as given by Kaushik *et al* using Auto Dock Vina 1.1.2.[58]

Molecular dynamics simulation

A 50 ns long molecular dynamics simulation of the docked complex between 1kzn and 6p was carried out in order to elucidate the binding mode of 6p into the active site of 1kzn as described

earlier[59] using GROMACS 5.1.4 code and Gromos43a1 force field [60-61].The force field parameters of ligand 6p were obtained from PRODRG web server[62]. Briefly, the docked complex of 1kzn-6p obtained from molecular docking was solvated in a cubic box of 255.26 nm^3 using simple point charge (SPC/E) water model keeping a distance of 1.0 nm between each side. The final simulation system was solvated and ionized with Na+ and Cl− ions at a concentration of 100 mM and the final system consisting of one protein molecule, one ligand molecules, 7465 water molecules, 24 Na+ and 15 Cl− ions was minimized using the steepest descent algorithm until the maximum force became less than 500 kJ/mol/nm.

Position restrained equilibration was performed in association with constant Numbers of particles, Volume and Temperature (NVT) and constant number of particles, Pressure, and Temperature (NPT) also called as isothermal-isobaric ensemble.NVT equilibration was performed at constant temperature at 300K using V-rescale (modified Berendsen thermostat) temperature coupling [63]for a time duration of 500 ps. After stabilization of temperature the NPT equilibration was performed using both temperature and Parrinello–Rahman pressure coupling [64]to maintain the system at 300 K temperature and 1 bar pressure along with coupling constant of 0.1 picosecond (ps) for temperature and 2 ps for pressure. Position restraints were applied during both NVT and NPT ensemble equilibration. Long-range electrostatic interactions and van der Walls interactions were calculated using the Particle mesh Ewald (PME) method [65], and the cut-off for short-range van der Waals was set to 1 nm. All bonds were constrained using LINCS algorithm [66] and the time step of the simulation was set to 0.002 ps. Finally, a 50 ns production simulation was performed.

The analysis of MD trajectory was performed using modules present in GROMACS 5.1.4. The trajectory was analyzed quantitatively by determining RMSD, RMSF and radius of gyration using rms, rmsf, and gyrate functionalities. Structural analysis was performed by analyzing the hydrogen bonds formed throughout the simulation period of 50 ns using the h-bond utility. Graphs were plotted using the XMgrace program[67].

Conflict of interest

The authors declare that they have no conflict of interest.

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Highlights

Some fluorinated chalcone-1,2,3-triazole conjugates were synthesized via click reaction.

The X-rays crystallographic study of compounds **6k** revealed the self assembling properties.

Some conjugates demonstrated better activity compared to reference drug.

Conjugates exhibited synergistic effects in the activity.