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ARTICLE

One-pot synthesis and biological evaluation of novel 4-[3-fluoro-4-(morpholin-4-yl)]phenyl-1*H*-1,2,3-triazole derivatives as potent antibacterial and anticancer agents

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Abstract

In search of better antibacterial and anticancer agents, a series of novel 4-[3-fluoro-4-(morpholin-4-yl)]phenyl-1*H*-1,2,3-triazole derivatives were synthesized (**6a-l** and **8a-j**) by using 3-fluoro-4-morpholinoaniline, alkyne, and triflyl azide via an in situ generated 4-(4-azido-2-fluorophenyl)morpholine and evaluated for their antibacterial and anticancer activity in vitro. Antibacterial activity against three G+ bacterial strains and anticancer activity against breast cancer cell line (MCF-7) and cervical carcinoma cell line (HeLa) was evaluated. Among all the tested compounds, **6h**, **6i**, and **8b** exhibited potent antibacterial activity against tested gram-positive bacterial strains. The anticancer activity screening results of **8f**, **8h**, and **8i** exhibited potent cytotoxic activity against two cancer cell lines with IC_{50} values nearer to the standard drug, doxorubicin. The remaining compounds have shown good to moderate activity against the tested cell lines. On the basis of the results obtained, a structure-activity relationship (SAR) is discussed.

1 | INTRODUCTION

After cardiovascular diseases in humans, cancer is one of the most common causes of morbidity and mortality worldwide.[1] The biggest challenges for successful cancer treatment are its unwanted side effects and drug resistance in various types of cancer. The efficacy of many anticancer drugs is limited by the drug resistance acquired, and there are a number of side effects because of their toxicity to normal cells since the currently available anticancer drugs cannot distinguish between normal and cancer cells.[2] Similarly, the alarming rates of emerging and recurring microbial threats associated with increased antibacterial resistance in hospitals are of great importance for public health and science worldwide, particularly with respect to bacteria resistant to multidrug resistant gram-positive bacteria.[3,4]

Nitrogen containing heterocyclic compounds plays a very important role in pharmaceuticals and agrochemicals.[5] Of all the heterocyclic systems in organic chemistry, the five-member heterocyclic compounds containing 1,2,3-triazoles and their derivatives are of great importance because of their wide applications in medical, pharmaceutical, biochemical, and material sciences.[6–10] 1,2,3-Triazoles act as effective substitutes in bioactive molecules because they can exhibit hydrogen bonds, dipole-dipole moments, and π stacking interactions.[11] 1*H*-1,2,3-triazole containing compounds exhibited a wide range of biological activities, such as antimicrobial activity against gram-positive bacteria,[12] as well as important anticancer agents and a wide variety of human cancer cells, including those who resist multiple medications.[13–15] Heterocyclic compounds containing 4-(2-fluorophenyl) morpholine have shown potent

antibacterial activity, especially gram-positive bacteria. Linezolid is an potent antibacterial agent that specifically used for the treatment of gram-possitive infections. The 4-[3-fluoro-4-(morpholin-4-yl)]phenyl containing 1,2,3-triazole derivatives has demonstrated potent antibacterial activity reported by the Phillips research group.[17,18]

With this in mind, the research has begun to study biologically active properties, especially anticancer and antibacterial,[19–28] by merging two units of pharmacophore, both an anticancer active 1,2,3-triazole scaffold and an antibacterial active 4-(2-fluorophenyl) morpholine derived from linezolid, which are designed and synthesized (Figure 1), a substituent at the fourth position of the 1,2,3-triazole ring adapts the potency of anticancer and antibacterial activities.

A common approach for the synthesis of 1,2,3-triazoles is the copper catalyzed Huisgen [3 + 2] cycloaddition of alkynes with azides (CuAAC). However, the one-pot three-component regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles from in situ azides generated from amines has been found to be a very challenging task. However, low molecular weight organic azides are considered unstable entities that can decompose spontaneously, with which reactions are difficult or dangerous to manage.[29] Thus, a one-pot two-step process for the in situ generation of organic azides is highly required. Feldman et al[30] reported one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles by using using alkyl/aryl halides, alkyne, and sodium azide via an in situ generated azides. Also, Zhao et al[31] reported a successful synthesis of 1,4-disubstituted 1,2,3-triazoles from nitrobenzenes and terminal alkynes via an in situ generated azides. In 2012, Shabber and their group reported recyclable Cu (II) catalyzed tandem one-pot synthesis of 1-aryl-1,2,3-triazoles from aryl boronic acids and alkynes via an in situ generated azides at room temperature.[32]

Encouraged by the abovementioned successful synthesis of 1,4-disubstituted 1,2,3-triazoles via in situ generated azides, we report here an efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles by using 3-fluoro-4-morpholinoaniline, alkyne, and triflyl azide via an in situ generated 4-(4-azido-2-fluorophenyl)morpholine (Scheme 1).[33]

2 | RESULTS AND DISCUSSION

The syntheses of the final 4-(2-fluorophenyl)morpholine-1*H*-1,2,3-triazole derivatives **6a-l** and **8a-j** were performed as outlined in Schemes 2 and 3, starting from the readily available morpholine **1** and 3,4-difluoronitrobenzene **2** to give the 4-(2-fluoro-4-nitrophenyl)morpholine **3**. Reduction of **3** using Pd/C to give the 3-fluoro-4-morpholinoaniline **4** in good yields according to published procedures.[16,18] The proposed mechanism of the formation of in situ azide is shown in Scheme 4.

One-pot [3 + 2] cycloaddition reaction was performed by using morpholine derivative **4** with different alkynes (**5a-l** and **7a-j**) via an in situ generated azide[33,34] to form final 4-(2-fluorophenyl) morpholine-1*H*-1,2,3-triazole derivatives **6a-l** and **8a-j** in good to excellent yield. Our

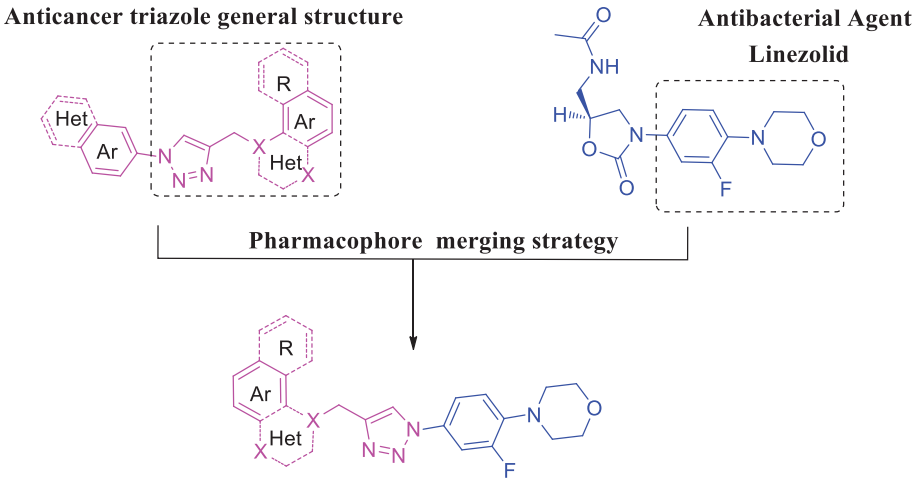
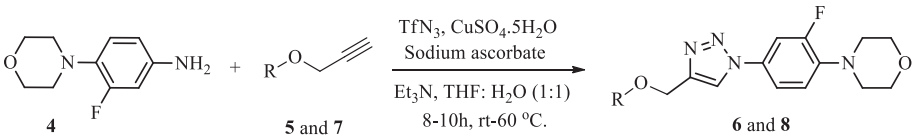
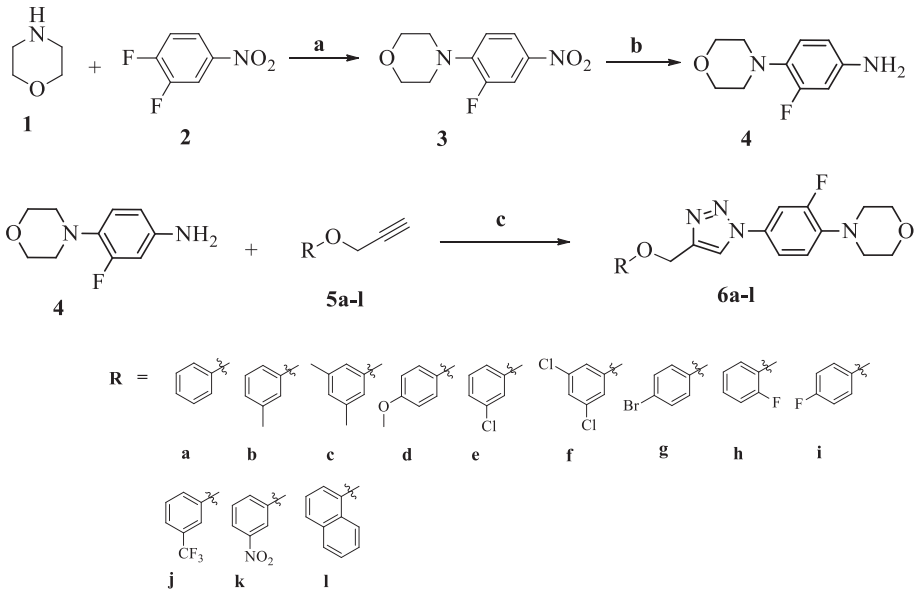


FIGURE 1 Dual modulator design through the pharmacophore merging strategy

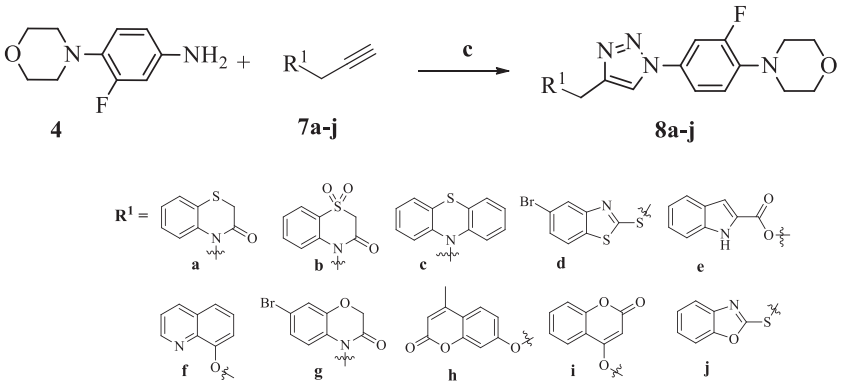


SCHEME 1 One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles

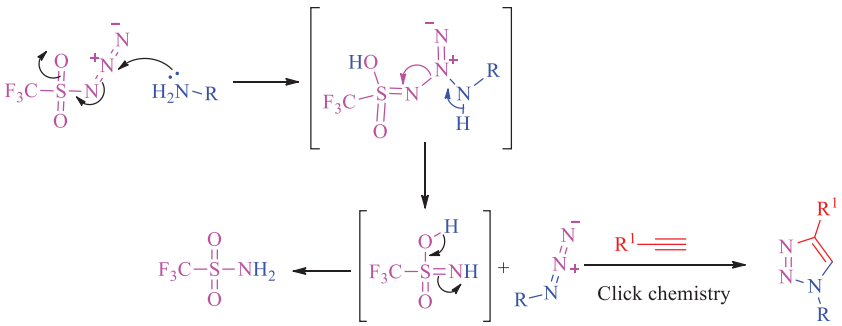
SCHEME 2 Reagents and conditions: (A) CH_3CN, reflux, 4 hours (82% yield); (B) H_2, 5% Pd/C, THF, 6 hours (63% Yield); and (C) TfN_3, $CuSO_4.5H_2O$, sodium ascorbate, Et_3N, THF: H_2O (1:1), 8 to 10 hours, 60°C



SCHEME 3 Reagents and conditions: (c) TfN_3, $CuSO_4.5H_2O$, sodium ascorbate, Et_3N, THF: H_2O (1:1), 8 to 10 hours, room temperature (rt): 60°C



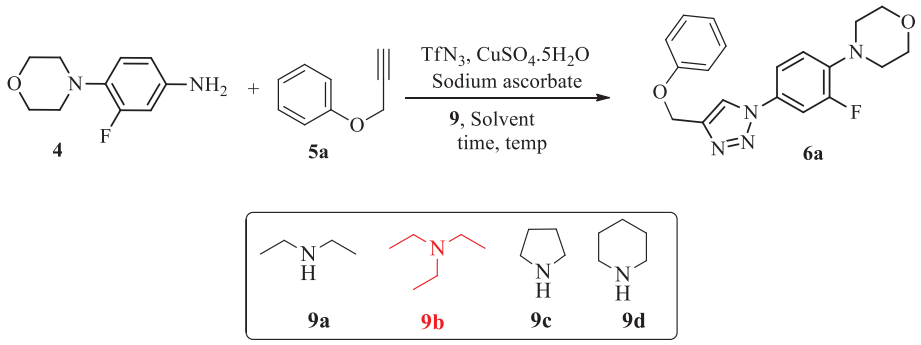
SCHEME 4 The proposed mechanism for the one-pot synthesis of 1,2,3-triazoles



initial investigation began with the [3 + 2] cycloaddition of in situ generated azide from amine (**4**), alkyne (**5a**), triflyl azide (TfN_3), catalyst, base, and solvent. During the course of the study, the combination of 10 mol% of $CuSO_4.5H_2O$ and 10 mol% sodium ascorbate with 3 equiv of triethylamine (TA) in the presence of 1:1 ratio of THF and water at 60°C was the optimum reaction condition for the synthesis of final 1,2,3-triazole derivatives (Table 1). When TEA was replaced with $NaHCO_3$, Na_2CO_3, K_2CO_3, and Cs_2CO_3, we could not get the desired product in good yield compared with TEA (Table 1, entries 10-13).

The structures of the newly synthesized compounds (**6a-l** and **8a-8j**) were confirmed by the spectral data (nuclear magnetic resonance [NMR], infrared [IR], and electrospray ionization mass spectrometry [ESI-MS]). All the spectral data of the synthesized compounds were in full agreement with the proposed structures and also

TABLE 1 Investigation of the reaction conditions for the synthesis of 1,2,3-triazole[a]



Entry	Base (2 eq)	Solvent, 20 mL	Time, h	Yield, %[b]
1	9a	THF	10	36
2	9b	THF	8	54
3	9c	THF	10	41
4	9d	THF	8	38
5	9b	H_2O	10	50
6	9b	DCM/MeOH	10	36
7	9b	MeOH	12	28
8[c]	9b	THF/H_2O(1:1)	8	78
9[d]	9b	THF/H_2O(1:1)	8	73
10[e]	$NaHCO_3$	H_2O and THF/H_2O(1:1)	10	NR and 16
11	Na_2CO_3	THF/H_2O(1:1)	10	21
12	K_2CO_3	THF/H_2O(1:1)	10	29
13	Cs_2CO_3	THF/H_2O(1:1)	10	34

Abbreviation: NR, no reaction.
[a]Reactions were performed with **4** (1.0 mmol), amine (1.5 mmol), TfN_3 (1.5 mmol), $CuSO_4.5H_2O$ (5 mol%), sodium ascorbate (5 mol%), and solvent (20 mL) at 60°C.
[b]Isolated yield.
[c]$CuSO_4.5H_2O$ (10 mol%), sodium ascorbate (10 mol%), and base (3.0 mmol).
[d]$CuSO_4.5H_2O$ (15 mol%), sodium ascorbate (15 mol%), and base (4.0 mmol).
[e]Base (3.0 mmol).

discussed for a representative compound **8a**. In the IR spectrum, the appearance of sharp absorption bands at 3136, 1660, and 1593 cm^{-1} are ascribed to ═CH (triazole), C═O, and —C═C stretching frequencies. In the ^1H NMR spectrum, the signals at δ 8.03-6.96 (Ar and CH-triazole) and 5.25 (s, 2H, N-CH_2) and the [M^+] ion peak at *m/z* 425.10 in the ESI mass spectrum confirmed the structure of compound **8a**.

2.1 | Antibacterial activity

The title compounds (**6a-l** and **8a-j**) were screened for their in vitro antibacterial activity against gram-positive (G+) bacterial strains by the standard broth micro-dilution technique[35,36] by using penicillin and streptomycin as positive controls. The minimum inhibitory concentrations (MICs) for all the synthesized compounds were reported in μg/mL, and the results are illustrated in Tables 2 and 3. It is evident from Tables 2 and 3 that the majority of the tested compounds exerted significant in vitro antibacterial activity against almost all the tested bacterial strains with MICs ranging from 1.56 to 12.5 μg/mL.

Compound **6a** with the MICs ranging from 25 ± 0.31 to 50 ± 0.37 μg/mL was selected as starting point for our initial SAR studies, which focused on phenoxymethyl group in fourth position of triazole ring. A wide variety of substituents were introduced to phenoxy group. As shown in Table 2, most of the compounds demonstrated significant in vitro antibacterial activities. The mono fluoro substituted at ortho or para position

TABLE 2 In vitro antibacterial and anticancer activity data of compounds **6a-6l**

	MIC, μg/mL[a]			IC_{50}, μM/mL[b]		
Analogs	***Bacillus subtilis***	***Staphylococcus aureus***	***Staphylococcus epidermidis***	**MCF-7**	**Hela**	**HEK-293**
6a	25 ± 0.31	25 ± 0.48	50 ± 0.37	84.85 ± 2.62	96.16 ± 1.05	>100
6b	-	50 ± 0.55	-	>100	>100	>100
6c	50 ± 0.25	-	-	>100	>100	>100
6d	-	-	50 ± 0.67	>100	>100	>100
6e	25 ± 0.28	25 ± 0.18	50 ± 0.33	59.41 ± 1.91	67.80 ± 1.65	>100
6f	12.5 ± 0.41	6.25 ± 0.21	12.5 ± 0.37	48.19 ± 1.12	61.58 ± 1.84	73.63 ± 2.72
6g	25 ± 0.61	25 ± 0.34	25 ± 0.26	81.69 ± 1.82	77.12 ± 2.02	68.83 ± 1.82
6h	3.12 ± 0.22	12.5 ± 0.37	6.25 ± 0.34	18.19 ± 1.32	33.15 ± 2.14	43.13 ± 1.65
6i	1.56 ± 0.72	3.12 ± 0.85	3.12 ± 0.65	11.18 ± 1.01	31.42 ± 1.64	66.59 ± 1.71
6j	12.5 ± 0.35	12.5 ± 0.84	25 ± 1.37	28.11 ± 0.64	37.84 ± 0.82	41.81 ± 1.58
6k	50 ± 0.32	50 ± 0.39	25 ± 0.41	68.16 ± 0.83	50.14 ± 2.06	64.31 ± 2.22
6l	-	50 ± 1.25	-	63.65 ± 0.31	41.36 ± 0.82	57.22 ± 1.39
Streptomycin	6.25 ± 0.21	6.25 ± 0.18	3.12 ± 0.25	NT	NT	NT
Penicillin	1.56 ± 0.19	1.56 ± 0.45	3.12 ± 0.20	NT	NT	NT
Doxorubicin	NT	NT	NT	2.63 ± 0.33	1.23 ± 0.21	5.68 ± 1.56

Note: "-" indicates concentration > 50 μg/mL.

Abbreviations: MIC, minimum inhibitory concentration; NT, not tested.

[a]Minimum inhibitory concentration (MIC) (μg/mL), ie, the lowest concentration of the test compound to inhibit the growth of bacteria completely.

[b]Values are mean ± SD of three replicates.

TABLE 3 In vitro antibacterial and anticancer activity data of compounds **8a-8j**

	MIC, μg/mL[a]			IC_{50}, μM[b]		
Analogs	***Bacillus subtilis***	***Staphylococcus aureus***	***Staphylococcus epidermidis***	**MCF-7**	**Hela**	**HEK-293**
8a	6.25 ± 0.31	6.25 ± 0.43	25 ± 0.62	33.62 ± 1.31	37.52 ± 1.12	44.81 ± 1.42
8b	3.12 ± 0.24	1.56 ± 0.51	50 ± 1.07	31.63 ± 1.34	36.54 ± 1.12	42.63 ± 1.13
8c	6.25 ± 0.41	12.5 ± 0.23	25 ± 0.56	61.88 ± 1.29	57.45 ± 1.52	63.87 ± 1.56
8d	25 ± 1.03	50 ± 1.27	50 ± 0.98	29.15 ± 0.92	7.44 ± 0.32	38.43 ± 1.24
8e	25 ± 0.32	25 ± 1.18	3.12 ± 0.21	29.41 ± 0.67	67.80 ± 1.65	57.80 ± 1.35
8f	25 ± 0.44	50 ± 1.27	25 ± 0.49	8.44 ± 0.22	6.29 ± 0.44	73.63 ± 1.52
8g	25 ± 1.21	25 ± 0.89	25 ± 1.35	30.62 ± 1.43	37.66 ± 1.92	44.81 ± 1.31
8h	50 ± 1.68	25 ± 1.51	25 ± 1.14	3.12 ± 0.38	2.77 ± 0.64	58.11 ± 1.22
8i	25 ± 1.19	50 ± 1.47	25 ± 0.25	5.19 ± 0.31	12.42 ± 0.31	66.38 ± 0.88
8j	12.5 ± 0.45	25 ± 1.68	6.25 ± 0.35	28.11 ± 0.64	9.84 ± 0.82	44.13 ± 1.32
Streptomycin	6.25 ± 0.21	6.25 ± 0.18	3.12 ± 0.25	NT	NT	NT
Penicillin	1.56 ± 0.19	1.56 ± 0.45	3.12 ± 0.20	NT	NT	NT
Doxorubicin	NT	NT	NT	2.63 ± 0.33	1.23 ± 0.21	5.68 ± 1.56

Abbreviations: MIC, minimum inhibitory concentration; NT, not tested.

[a]Minimum inhibitory concentration (MIC) (μg/mL), ie, the lowest concentration of the test compound to inhibit the growth of bacteria completely.

[b]Values are mean ± SD of three replicates.

of phenoxy group (compounds **6h** and **6i**) led to increase of activities; compound **6i** showed fourfold more potent activity against *Bacillus subtilis* (MIC = 1.56 ± 0.72 μg/mL) compared with standard streptomycin (MIC = 6.25 ± 0.21 μg/mL) and twofold more potent activity against *Staphylococcus aureus* (MIC = 3.12 ± 0.85 μg/mL) compared with standard streptomycin (MIC = 6.25 ± 0.18 μg/mL) and also equipotent activity against *Staphylococcus epidermidis* (MIC = 3.12 ± 0.65 μg/mL) compared with standard streptomycin (MIC = 3.12 ± 0.25 μg/mL). Also, compound **6h** effectively inhibited the *B. subtilis* (MIC = 3.12 ± 0.22 μg/mL; twofold more potent to streptomycin) and good activity against *S. aureus* (MIC = 12.5 ± 0.37 μg/mL) and *S. epidermidis* (MIC = 6.25 ± 0.34 μg/mL).

Introduction of two chloro groups at meta position led to increase of activity (compound **6f**; MIC ranging from 6.25 ± 0.21 to 12.5 ± 0.41 μg/mL) compared with mono chloro group at meta position of phenoxy group (compound **6e**; MIC ranging from 25 ± 0.18 to 50 ± 0.33 μg/mL). In addition, presence of methyl and methoxy groups at phenoxy group reduced inhibitory potency (compounds **6b**-**d**). The 3-(trifluoromethyl) at meta-position (compound **6**j) exhibited good activity against *B. subtilis* (MIC = 12.5 ± 0.35 μg/mL) and *S. aureus* (MIC = 12.5 ± 0.84 μg/mL).

Likewise, a wide variety of heterocyclic compounds has been introduced in the fourth position of the 1,2,3-triazole ring (compounds **8a**-**j**). As shown in Table 3, most of the compounds exhibited significant in vitro antibacterial activity. Of all the compounds, **8b** was effective and demonstrated equipotent inhibitory efficacy and a broader antibacterial spectrum than that of the reference drugs. Compound **8b** exhibited excellent inhibiting activity than the standard streptomycin (MIC = 6.25 μg/mL) and equipotent to that of penicillin (MIC = 1.56 μg/ mL) against *B. subtilis* and *S. aureus* with MIC values 3.12 ± 0.24 and 1.56 ± 0.51 μg/mL. Also, compounds **8a** and **8c** showed significant activity against *B. subtilis* and *S. aureus* with MIC values ranging 6.25 ± 0.31 to 12.5 ± 0.23 μg/mL. Similarly, compounds **8e** and **8j** could effectively inhibit the growth of *S. epidermidis* with MIC values 3.12 ± 0.21 and 6.25 ± 0.35 μg/mL, while the rest of the compounds have shown modest activity against all the tested strains with MIC values ranging from 12.5 to 50 μg/mL.

2.2 | Anticancer activity

In vitro anticancer activity was performed against two cancer lines (MCF-7and HeLa) and normal cell line (HEK-293) by MTT assay[37] using doxorubicin as a positive control, and the results are tabulated in Tables 2 and 3.

From the screening results in Table 2 (compounds **6a**-**6l**), it was observed that majority of compounds exhibited good to moderate anticancer activity against MCF-7 and HeLa. Among all compounds, **6h** and **6i** showed good activity against MCF-7 with IC_{50} values ranging from 11.18 ± 1.01 to 33.15 ± 2.14 μM. Remaining compounds have shown moderate to poor activity against MCF-7 and HeLa with IC_{50} values ranging from 28.11 ± 0.64 to 96.16 ± 1.05 μM, respectively. On the basis of SAR, it was observed from experimental data compounds derived from 4-fluoro and 2-fluorophenoxy groups at fourth position on 1,2,3-triazole (**6i**) and (**6h**) have exhibited good anticancer activity against MCF-7 when compared with the others.

From Table 3 (compounds **8a**-**8j**), it is clear that majority of the compounds showed potent activity against tumor cell lines. Among all the synthesized compounds, **8h**, **8i**, and **8f** showed the highest cytotoxicity towards both the cancer cell lines. Compound **8h**, which contains 7-hydroxy-4-methylcoumarin at fourth position of 1,2,3-triazole, exhibited potent activity against both MCF-7 and HeLa cell lines with IC_{50} values 3.12 ± 0.38 and 2.77 ± 0.64 μM, respectively. These results are comparable with the standard drug, doxorubicin. Similarly, the introduction of 4-hydroxycoumarin at fourth position of 1,2,3-triazole (**8i**) significantly enhanced the cytotoxicity against the two cancer cell lines MCF-7 and HeLa with IC_{50} values 8.44 ± 0.22 and 6.29 ± 0.44 μM, respectively. Introduction of 8-hydroxy quinoline at fourth position exhibits potent activity against MCF-7 (IC_{50} 5.19 ± 0.31 μM) and Hela (IC_{50} 512.42 ± 0.31 *μM*). The potential activity of these compounds (**8h**, **8i**, and **8f**) may be attributed due to the presence of hydroxymethyl heterocyclic compounds fourth position of triazole ring. Compounds **8d** and **8j** that contains 2-mercapto benzothiazole and 2-mercapto benzoxazole derivatives on triazole exhibit potent cytotoxicity against Hela, with IC_{50} values 7.44 ± 0.32 and 9.84 ± 0.82 μM, respectively. These results are comparable with the standard doxorubicin (MCF-7, IC_{50} 2.63 ± 0.33; and HeLa, IC_{50} 1.23 ± 0.21 μM). The rest of the compounds exhibited moderate to poor cytotoxic activity against the two cancer cell lines with IC_{50} values ranging from 28.11 ± 0.64 to 67.80 ± 1.65 μM.

3 | CONCLUSION

In conclusion, a new series of 1,2,3-triazole derivatives containing 4-(2-fluorophenyl) morpholine using 3-fluoro-4-morpholinoaniline, alkyne, and triflyl azide was synthesized through an in situ generated azide. In this

method, the separation of the intermediates azide does not require and should be mainly useful when unstable azides are required for the synthesis of 1,2,3-triazoles. All compounds were selected for their in vitro cytotoxic activity against MCF-7 and HeLa cancer cell lines. Compounds **8f**, **8h**, and **8i** exhibited potent cytotoxic activity against two cancer cell lines with IC_{50} values closer to standard doxorubicin. in vitro antibacterial activity against three gram-positive bacterial strains and compounds, **6h**, **6i**, and **8b**, showed a potent antibacterial activity against the bacterial strains analyzed. Further simple structural modifications of the titled compounds, which could provide more interesting results and new lead molecules for further studies.

4 | EXPERIMENTAL

4.1 | Materials and methods

All the reactants were purchased from the Aldrich chemical company. All the reagents and solvents were purchased from SD. Fine chemicals limited and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60F254 precoated plates (0.25 mm), and silica gel (particle size 60–120 mesh) was used for column chromatography. ^1H and ^{13}C NMR spectra were recorded on a 400-MHz instrument. ^1H NMR spectra were reported relative to Me_4Si and residual $CDCl_3$. ^{13}C NMR was reported relative to $CDCl_3$ or DMSO. Mass spectra were recorded on a Jeol JMC-300 spectrometer (ESI, 70 eV). Elemental analyses were performed on Carlo Erba 106 and PerkinElmer model 240 analyzers. Melting points were determined using a Cintex apparatus and are uncorrected.

4.1.1 | General procedure for the synthesis of 4-[3-fluoro-4-(morpholin-4-yl)] phenyl-1H-1,2,3-triazole derivatives (6a-l and 8a-j)

To a mixture of alkyne (1.0 mmol), 3-fluoro-4-morpholinoaniline (1.5 mmol), and triflyl azide (1.5 mmol) in THF-H_2O (20 mL). To this solution, add TEA, $CuSO_4.5H_2O$ (10 mmol%), and sodium ascorbate (10 mmol%). The reaction mixture was stirred for 2 hours at room temperature and then heated at 60°C for 6 to 8 hours. After completing the reaction by TLC, the reaction mixture was carefully poured into ice water (50 mL). The resulting solid was filtered, washed with excess water, and dried under vacuum for 1 hour, and the crude product obtained was purified by column chromatography (hexane/ethyl acetate gradient) to afford the pure desired 4-[3-fluoro-4-(morpholin-4-yl)]phenyl-1*H*-1,-2,3-triazole derivatives in good yields.

4.2 | 4-(2-fluoro-4-(4-[phenoxymethyl]-1*H*-1,2,3-triazol-1-yl)phenyl) morpholine (6a)

White solid (Yield 78%); mp: 89-91°C; IR (KBr, cm^{-1}): 3145 (CH-triazole), 3082 (CH, Ar), 1592 (C═C), 1490 (N═N); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.05 (s, 1H, tri), 7.84 (t, $J = 4.0$ Hz, Ar, 1H), 7.74-7.71 (m, Ar, 1H), 7.53-7.50 (m, Ar, 2H), 7.49-7.30 (m, Ar, 3H), 7.06-7.04 (m, Ar, 1H), 5.27 (s, 2H, O—CH_2), 3.91-3.87 (m, 4H, morpholine), 3.17-3.13 (m, 4H, morpholine); MS (ESI) *m/z*:355 $[M + H]^+$; Anal Cal for $C_{19}H_{19}FN_4O_2$: C, 64.40; H, 5.40; N, 15.81; found: C, 64.46; H, 5.35; N, 15.77.

4.2.1 | 4-(2-fluoro-4-(4-([m-tolyloxy] methyl)-1*H*-1,2,3-triazol-1-yl)phenyl) morpholine (6b)

White solid (Yield 65%); mp: 94-96°C; IR (KBr, cm^{-1}): 3132 (CH, triazole), 3096 (CH, Ar), 1589 (C═C), 1496 (N═N); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.88 (s, 1H, triazole), 7.62-7.59 (m, 2H, Ar), 7.36-7.29 (m, 3H, Ar), 7.19-7.14 (m, 2H, Ar), 5.23 (s, 2H, O-CH_2), 3.93-3.87 (m, 4H, morpholine), 3.18-3.13 (m, 4H, morpholine), 2.26 (s, 3H, Ar-CH_3); ESI-MS (*m/z*): 369 $[M + H]^+$. Anal Cal for $C_{20}H_{21}FN_4O_2$: C, 65.20; H, 5.75; N, 15.21; found: C, 65.27; H, 5.70; N, 15.26.

4.2.2 | 4-(4-(4-([3,5-dimethylphenoxy] methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluorophenyl)morpholine (6c)

White solid (Yield 68%); mp: 101-103°C; IR (KBr, cm^{-1}): 3127 (CH, triazole), 3096 (CH, Ar), 1592 (C═C), 1467 (N═N); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.63 (brs, 1H, triazole), 7.48-7.42 (m, 2H, Ar), 7.36 (s, 2H, Ar), 7.24-7.20 (m, 1H, Ar), 7.17 (s, 1H, Ar), 5.26 (s, 2H, O—CH_2), 3.88 (t, $J = 4.0$ Hz, 4H, morpholine), 3.15-3.12 (m, 4H, morpholine), 2.39 (s, 6H, Ar—CH_3); ESI-MS (*m/z*): 383 $[M + H]^+$. Anal Cal for $C_{21}H_{23}FN_4O_2$: C, 65.95; H, 6.06; N, 14.65; found: C, 65.89; H, 6.02; N, 14.61.

4.2.3 | 4-(2-fluoro-4-(4-([4-methoxyphenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)morpholine (6d)

White solid (Yield 70%); mp: 108-110°C; IR (KBr, cm^{-1}): 3136 (CH, triazole), 3094 (CH, Ar), 1587 (C═C), 1496 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.96 (s, 1H, triazole), 7.71-7.68 (m, 2H, Ar), 7.63-7.60 (m, 1H, Ar), 7.20-7.13 (m, 2H, Ar), 7.01-6.98 (d, J = 12.0 Hz, 2H, Ar), 5.21 (s, 2H, O-CH_2), 3.95-3.90 (m, 4H, morpholine), 3.85 (s, 3H, O-CH_3), 3.16 (t, J = 4.0 Hz, 4H, morpholine); ESI-MS (m/z): 385 $[M + H]^+$. Anal Cal for $C_{20}H_{21}FN_4O_3$: C, 62.49; H, 5.51; N, 14.57; found: C, 62.56; H, 5.59; N, 14.51.

4.2.4 | 4-(4-(4-([3-chlorophenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluorophenyl)morpholine (6e)

Pale yellow solid (Yield 69%); mp: 117-119°C; IR (KBr, cm^{-1}): 3130 (CH, triazole), 3088 (CH, Ar), 1590 (C═C), 1486 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.06 (s, 1H, triazole), 7.76 (s, 1H, Ar), 7.61 (d, J = 8.0 Hz, 1H, Ar), 7.49-7.43 (m, 3H, Ar), 7.20-7.14 (m, 2H, Ar), 5.22 (s, 2H, O-CH_2), 3.90-3.87 (m, 4H, morpholine), 3.15-3.12 (m, 4H, morpholine); ESI-MS (m/z): 389 $[M + H]^+$. Anal Cal for $C_{19}H_{18}ClFN_4O_2$: C, 58.69; H, 4.67; N, 14.41; found: C, 58.74; H, 4.61; N, 14.47.

4.2.5 | 4-(4-(4-([3,5-dichlorophenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluorophenyl)morpholine (6f)

Pale yellow solid (Yield 71%); mp: 124-126°C; IR (KBr, cm^{-1}): 3131 (CH, triazole), 3092 (CH, Ar), 1593 (C═C), 1489 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.08 (s, 1H, triazole), 7.67 (s, 2H, Ar), 7.45-7.42 (m, 2H, Ar), 7.20-7.14 (m, 2H, Ar), 5.25 (s, 2H, O-CH_2), 3.88 (t, J = 4.0 Hz, 4H, morpholine), 3.15-3.12 (m, 4H, morpholine); ESI-MS (m/z): 424 $[M + H]^+$. Anal Cal for $C_{19}H_{17}Cl_2FN_4O_2$: C, 53.91; H, 4.05; N, 13.24; found: C, 53.83; H, 4.09; N, 13.17.

4.2.6 | 4-(4-(4-([4-bromophenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluorophenyl)morpholine (6g)

White solid (Yield 68%); mp: 118-120°C; IR (KBr, cm^{-1}): 3130 (CH, triazole), 3095 (CH, Ar), 1591 (C═C), 1478 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.05 (s, 1H, triazole), 7.66-7.58 (m, 4H, Ar) 7.50-7.47 (m, 1H, Ar), 7.20-7.14 (m, 2H, Ar), 5.21 (s, 2H, O—CH_2), 3.91-3.88 (m, 4H, morpholine), 3.16 (t, J = 4.0 Hz, 4H, morpholine); ESI-MS (m/z): 434 $[M + 2H]^+$. Anal Cal for $C_{19}H_{18}BrFN_4O_2$: C, 52.67; H, 4.19; N, 12.93; found: C, 52.71; H, 4.13; N, 12.87.

4.2.7 | 4-(2-fluoro-4-(4-([2-fluorophenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)morpholine (6h)

Pale yellow solid (Yield 54%); mp: 102-104°C; IR (KBr, cm^{-1}): 3137 (CH, triazole), 3097 (CH, Ar), 1576 (C═C), 1467 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.53 (s, 1H, triazole), 8.31 (d, J = 8.0 Hz, 1H, Ar) 8.19-8.13 (m, 2H, Ar), 7.77-7.72 (m, 1H, Ar), 7.48-7.45 (m, 1H, Ar), 7.21-7.15 (m, 2H, Ar), 5.30 (s, 2H, O—CH_2), 3.90-3.87 (m, 4H, morpholine), 3.15-3.12 (m, 4H, morpholine); ESI-MS (m/z): 373 $[M + H]^+$. Anal Cal for $C_{19}H_{18}F_2N_4O_2$: C, 61.28; H, 4.87; N, 15.05; found: C, 61.35; H, 4.84; N, 15.03.

4.2.8 | 4-(2-fluoro-4-(4-([4-fluorophenoxy]methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)morpholine (6i)

Pale yellow solid (Yield 59%); mp: 106-108°C; IR (KBr, cm^{-1}): 3128 (CH, triazole), 3083 (CH, Ar), 1592 (C═C), 1487 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.11 (s, 1H, triazole), 7.82-7.79 (m, 2H, Ar), 7.65-7.62 (m, 1H, Ar), 7.45-7.42 (m, 1H, Ar), 7.37-7.35 (m, 1H, Ar), 7.30-7.26 (m, 1H, Ar), 7.07-7.05 (m, 1H, Ar), 5.27 (s, 2H, O—CH_2), 3.91-3.88 (m, 4H, morpholine), 3.18-3.15 (m, 4H, morpholine); ESI-MS (m/z): 373 $[M + H]^+$. Anal Cal for $C_{19}H_{18}F_2N_4O_2$: C, 61.28; H, 4.87;N, 15.05; found: C, 61.32; H, 4.93; N, 15.01.

4.2.9 | 4-(2-fluoro-4-(4-((3-(trifluoromethyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)morpholine (6j)

Pale yellow solid (Yield 53%); mp: 123-125°C; IR (KBr, cm^{-1}): 3130 (CH, triazole), 3093 (CH, Ar), 1589 (C═C), 1490 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.12 (s, 1H, triazole), 7.98 (s, 1H, Ar), 7.84-7.79 (m, 1H, Ar), 7.74-7.62 (m, 2H, Ar), 7.49-7.39 (m, 2H, Ar), 7.12-7.09 (m, 1H, Ar), 5.24 (s, 2H, O-CH_2), 3.91-3.87 (m, 4H, morpholine), 3.17-3.13 (m, 4H, morpholine): ESI-MS (m/z): 423 $[M + H]^+$. Anal Cal for $C_{20}H_{18}F_4N_4O_2$: C, 56.87; H, 4.30; N, 13.26; found: C, 56.77; H, 4.33; N, 13.21.

4.2.10 | 4-(2-fluoro-4-(4-([3-nitrophenoxy] methyl)-1*H*-1,2,3-triazol-1-yl)phenyl) morpholine (6k)

Yellow solid (Yield 65%); mp: 137-139°C; IR (KBr, cm^{-1}): 3122 (CH, triazole), 3086 (CH, Ar), 1595 (C═C), 1488 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.13 (s, 1H, triazole), 8.00 (s, 1H, Ar), 7.95 (d, J = 4.0 Hz, 1H, Ar), 7.72-7.66 (m, 2H, Ar), 7.47 (d, J = 8.4 Hz, 1H, Ar), 7.20-7.18 (m, 1H, Ar), 7.15 (d, J = 4.4 Hz, 1H, Ar), 5.34 (s, 2H, O—CH_2), 3.90-3.87 (m, 4H, morpholine), 3.18-3.13 (m, 4H, morpholine); ESI-MS (m/z): 400 $[M + H]^+$. Anal Cal for $C_{19}H_{18}FN_5O_4$: C, 57.14; H, 4.54; N, 17.54; found: C, 57.21; H, 4.49; N, 17.48.

4.2.11 | 4-(2-fluoro-4-(4-([naphthalen-1-yloxy]methyl)-1*H*-1,2,3-triazol-1-yl) phenyl)morpholine (6l)

Pale yellow solid (Yield 66%); mp: 141-143°C; IR (KBr, cm^{-1}): 3139 (CH, triazole), 3098 (CH, Ar), 1590 (C═C), 1477 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.04 (s, 1H, triazole), 7.90-7.85 (m, 2H, Ar), 7.71-7.69 (m, 1H, Ar), 7.63-7.58 (m, 3H, Ar), 7.34-7.25 (m, 4H, Ar), 5.30 (s, 2H, O—CH_2), 3.91-3.88 (m, 4H, morpholine), 3.17-3.15 (m, 4H, morpholine); ESI-MS (m/z): 405 $[M + H]^+$. Anal Cal for $C_{23}H_{21}FN_4O_2$: C, 68.30; H, 5.23; N, 13.85; found: C, 68.37; H, 5.29; N, 13.81.

4.2.12 | 4-((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methyl)-2*H*-benzo [*b*][1,4]thiazin-3(4*H*)-one (8a)

White solid (Yield 59%); mp: 152-154°C; IR (KBr, cm^{-1}): 3136 (CH, triazole), 2933 (CH, Ar), 1660 (C═O), 1593 (C═C), 1472 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, tri), 7.83-7.81 (m, Ar, 1H), 7.50-7.47 (dd, J = 8.8, 2.5 Hz, Ar, 1H), 7.42-7.29 (m, Ar, 3H), 7.06-6.99 (m, Ar, 2H), 5.25 (s, 2H, N-CH_2), 3.90-3.87 (m, 4H, morpholine), 3.42 (s, 2H, S-CH_2), 3.15-3.12 (m, 4H, morpholine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 154.6, 139.6, 138.1, 134.4, 129.6, 129.3, 128.4, 127.7, 126.3, 123.5, 122.4, 121.8, 120.7, 117.4, 65.8, 47.6, 38.5, 33.4; ESI-MS m/z: 425.10 $[M]^+$. Anal Cal for $C_{21}H_{20}FN_5O_2S$: C, 59.28; H, 4.74; N, 16.46; found: C, 59.55; H, 4.83; N, 16.53.

4.2.13 | 4-((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one 1,1-dioxide (8b)

White solid (Yield 66%); mp: 171-173°C; IR (KBr, cm^{-1}): 3121 (CH, triazole), 3076 (CH, Ar), 1694 (C═O), 1593 (C═C), 1499 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, Ar, 1H), 8.03 (s, 1H, tri), 7.95 (dd, J = 7.7, 1.4 Hz, Ar, 1H), 7.75-7.73 (m, Ar, 1H), 7.47 (dd, J = 12.8, 2.4 Hz, Ar 1H), 7.37 (dt, J = 12.1, 4.6 Hz, Ar, 2H), 7.01 (t, J = 8.8 Hz, Ar, 1H), 5.35 (s, 2H, N—CH_2), 4.25 (s, SO_2—CH_2, 2H), 3.89-3.87 (m, 4H, morpholine), 3.15-3.12 (m, 4H, morpholine); ESI-MS m/z: 458.34 $[M + H]^+$. Anal Cal for $C_{21}H_{20}FN_5O_4S$: C, 55.13; H, 4.41; N, 15.31; found: C, 55.09; H, 4.48; N, 15.34.

4.2.14 | 4-(4-(4-([10*H*-phenothiazin-10-yl] methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluoro phenyl)morpholine (8c)

Yellow solid (Yield 63%); mp:159-161°C; IR (KBr, cm^{-1}): 3144 (CH, triazole), 1594 (C═C), 1514 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H, tri), 7.44-7.41 (dd, J = 8.8, 2.5 Hz, Ar, 1H), 7.40-7.32 (dd, J = 8.6, 2.5 Hz, Ar, 1H), 7.15-7.12 (dd, J = 7.6, 1.4 Hz, 2H), 7.07-7.04 (m, Ar, 2H), 6.97-6.91(m, Ar, 3H), 6.81 (d, J = 8.0 Hz, Ar, 2H), 5.28 (s, 2H, N—CH_2), 3.87 (t, J = 4.0 Hz, 4H, morpholine), 3.12-3.09 (m, 4H, morpholine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 144.6, 139.8, 134.6, 129.8, 129.7, 128.2, 124.3, 124.1, 121.9, 116.8, 116.4, 65.6, 47.8, 43.3; ESI-MS m/z: 482.30 $[M + Na]^+$. Anal Cal for $C_{25}H_{22}FN_5OS$: C, 65.34; H, 4.83; N, 15.24; found: C, 65.38; H, 4.77; N, 15.29.

4.2.15 | 4-(4-(4-(((5-bromobenzo[*d*] thiazol-2-yl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)-2-fluorophenyl)morpholine (8d)

Pale yellow solid (Yield 57%); mp: 169-171°C; IR (KBr, cm^{-1}): 3152 (CH, triazole), 3077 (CH, Ar),1594 (C═C) 1513 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 1.8 Hz, Ar, 1H), 7.96 (s, 1H, tri), 7.61 (d, J = 8.4 Hz, Ar, 1H), 7.46-7.43 (m, Ar, 2H), 7.37 (d, J = 8.7 Hz, Ar, 1H), 7.01 (t, J = 8.8 Hz, Ar, 1H), 4.75 (s, 2H, S—CH_2), 3.89-3.87 (m, 4H, morpholine), 3.14-3.12 (m, 4H, morpholine); ESI-MS m/z: 505.13 $[M + 2H]^+$. Anal Cal for $C_{20}H_{17}BrFN_5OS_2$: C, 47.43; H, 3.38; N, 13.83; found: C, 47.51; H, 3.29; N, 13.90.

4.2.16 | (1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methyl 1*H*-indole-2-carboxylate (8e)

White solid (Yield 50%); mp: 148-150°C; IR (KBr, cm^{-1}): 3447 (NH), 3152 (CH, triazole), 3084 (CH, Ar), 1654 (C═O), 1587 (C═C), 1477 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H, NH), 8.07 (s, 1H, tri), 7.68 (d, J = 8.0 Hz, Ar, 1H), 7.50 (dd, J = 12.6, 2.5 Hz, Ar, 1H), 7.49-7.42 (m, Ar, 2H), 7.41-7.29 (m, Ar, 2H), 7.28-7.15(m, Ar, 1H), 7.04 (t, J = 8.8 Hz, Ar, 1H), 5.57 (s, O—CH_2, 2H), 3.90-3.88 (m, 4H, morpholine), 3.16-3.13 (m, 4H, morpholine); ESI-MS *m/z*: 421.20 $[M]^+$. Anal Cal for $C_{22}H_{20}FN_5O_3$: C, 62.70; H, 4.78; N, 16.62; found: C, 62.62; H, 4.69; N, 16.70.

4.2.17 | 4-(2-fluoro-4-(4-([quinolin-8-yloxy]methyl)-1*H*-1,2,3-triazol-1-yl) phenyl)morpholine (8f)

Pale red solid (Yield 64%); mp: 172-174°C; IR (KBr, cm^{-1}): 3147 (CH, triazole), 3046 (CH, Ar), 1588 (C═C), 1493 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98-8.95 (m, Ar, 1H), 8.17 (s, 1H, tri), 7.45-7.32 (m, 6H), 7.00 (t, J = 8.6 Hz, Ar, 2H), 5.62 (s, O—CH_2, 2H), 3.88-3.86 (m, 4H, morpholine), 3.14-3.12 (m, 4H, morpholine); ESI-MS *m/z*: 406.19 $[M + H]^+$. Anal Cal for $C_{22}H_{20}FN_5O_2$: C, 65.17; H, 4.97; N, 17.27; found: C, 65.22; H, 4.91; N, 17.35.

4.2.18 | 7-bromo-4-((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (8g)

Pale yellow solid (Yield 60%); mp: 164-166°C; IR (KBr, cm^{-1}): 3141 (CH, triazole), 3094 (CH, Ar), 1659 (C═O), 1580 (C═C), 1496 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, tri), 7.50-7.45 (m, Ar, 2H), 7.40-7.37 (m, Ar, 1H), 7.19-7.13 (m, Ar, 2H), 7.01 (t, J = 8.8 Hz, Ar, 1H), 5.21 (s, N—CH_2, 2H), 4.63 (s, 2H, O—CH_2), 3.88 (t, J = 4.4 Hz, 4H, morpholine), 3.14 (t, J = 4.4 Hz, 4H, morpholine); ESI-MS *m/z*: 488.37 $[M + 2H]^+$. Anal Cal for $C_{21}H_{19}BrFN_5O_3$: C, 51.65; H, 3.92; N, 14.34; found: C, 51.59; H, 3.84; N, 14.43.

4.2.19 | 7-((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methoxy)-4-methyl-2*H*-chromen-2-one (8h)

White solid (Yield 51%); mp: 180-182°C; IR (KBr, cm^{-1}): 3155 (CH, triazole), 3016 (CH, Ar), 1704 (C═O), 1587 (C═C), 1497 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, tri), 7.54-7.42 (m, Ar, 3H), 7.06-6.96 (m, Ar, 3H), 6.16 (s, Coumarine—H, 1H), 5.34 (s, 2H,O—CH_2), 3.90-3.88 (m, 4H, morpholine), 3.16-3.14 (m, 4H, morpholine), 2.40 (s, 3H, CH_3); ESI-MS *m/z*: 437.34 $[M + H]^+$. Anal Cal for $C_{23}H_{21}FN_4O_4$: C, 63.30; H, 4.85; N, 12.84; found: C, 63.38; H, 4.81; N, 12.79.

4.2.20 | 4-((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methoxy)-2*H*-chromen-2-one (8i)

White solid (Yield 69%); mp: 178-180°C; IR (KBr, cm^{-1}): 3163 (CH, triazole), 3077 (CH, Ar), 1674 (C═O), 1588 (C═C), 1483 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H, tri), 7.83-7.80 (m, Ar, 1H), 7.55-7.50 (m, Ar, 2H), 7.45-7.33 (m, Ar, 2H), 7.31-7.25 (m, Ar, 1H), 7.06 (t, J = 8.8 Hz, Ar, 1H), 5.90 (s, Coumarine—H, 1H), 5.42 (s, 2H, O—CH_2), 3.91-3.88 (m, 4H, morpholine), 3.17-3.15 (m, 4H, morpholine); ESI-MS *m/z*: 422.17 $[M]^+$. Anal Cal for $C_{22}H_{19}FN_4O_4$: C, 62.55; H, 4.53; N, 13.26; found: C, 62.62; H, 4.59; N, 13.33.

4.2.21 | 2-(((1-[3-fluoro-4-morpholinophenyl]-1*H*-1,2,3-triazol-4-yl) methyl)thio)benzo[*d*]oxazole (8j)

Pale red solid (Yield 68%); mp: 163-165°C; IR (KBr, cm^{-1}): 3133(CH, triazole), 2997 (CH, Ar), 1591 (C═C), 1499 (N═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, tri), 7.64 (d, J = 7.6 Hz, Ar, 1H), 7.47-7.43 (m, Ar, 2H), 7.39-7.36 (m, Ar, 1H), 7.33-7.27 (m, Ar, 2H), 7.00 (t, J = 8.8 Hz, Ar, 1H), 4.70 (s, 2H, S-CH_2), 3.89-3.87 (m, 4H, morpholine), 3.14-3.11 (m, 4H, morpholine); ESI-MS *m/z*: 412.15 $[M + H]^+$. Anal Cal for $C_{20}H_{18}FN_5O_2S$: C, 58.38; H, 4.41; N, 17.02; found: C, 58.43; H, 4.37; N, 17.08.

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