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Synthesis of New Quinoline based Morpholine-1,2,3-Triazole Hybrids and their Cytotoxicity

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Regioselective synthesis of a series of 1-aryl 1,2,3-triazoles-4-methoxy methyl-3-quinoline-2-morpholine employing click reaction is presented. Highly selective and efficient copper(I)-catalyzed 1,3-dipolar cycloaddition between 2-morpholinoquinoline-3-methyl propargyl ether and various aryl azides **5a-j** yielded the title compounds **6a-j** in 71% to 85%. The structure of all the novel 1,2,3-triazoles was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis. The analogues were evaluated for their *in vitro* anticancer activity against MDA-MB-231 cell line. All the synthesized compounds were proven to have anticancer activity in comparison to reference drug doxorubicin. Especially, chloro and fluoro substituent compounds demonstrated potent activity with IC_{50} values of 17.20 ± 0.09 µM and 23.56 ± 0.09 µM, which proved their efficacy and could be further studied for the development of novel chemotherapeutics.

Keywords: 2-Morpholinoquinoline-3-methylpropargyl ether, Arylazides, 1,3-Dipolar cycloaddition, Regioselective.

INTRODUCTION

Cancer is a significant global health problem that causes fatalities across all age groups worldwide [1,2]. The global death toll in year 2020 amounted to 10 million and projections indicate that this figure will rise to 13 million by year 2030 [3,4]. Although there are multiple treatments and chemotherapeutics currently accessible, this ailment nevertheless presents a significant life-threatening danger. Therefore, it is imperative to persist in developing new anticancer medications [5]. Quinoline is a nitrogen containing pharmacophore occur in several natural compounds and synthetic derivatives used in numerous medications, such as chloroquine [6], amodiaquine [7], mefloquine [8], piperaquine [9] and primaquine [10] used as antimalarial agents, pitavastatin is used for lowering the cholesterol [11], lenvatinib [12], carbozatinib [13] and bosutinib [14] are used as anticancer agents, saquinavir [15] used as antiretroviral agent and lophocerine as antibiotic [16] are well known in literature.

Some of the naturally occurred quinoline alkaloids *viz*. 4-methoxy-2-phenylquinoline is isolated from *Lunasia amara* [17], graveolinine is found in *Ruta graveolens* and *Lunasia amara* [18], kokusaginine occur in *Haplophyllum thesioides* [19] and dictamnine is isolated from roots of *Haplophyllum bucharicum* [20] are reported have shown antitubercular activity in literature. Besides, 1,2,3-triazole has vital role in medicinal chemistry field by exhibit antimicrobial [21-24], anticancer [25-27], anti-HIV [28,29], antimalarial [30], anti-inflammatory [31,32], analgesic [33], antiepileptic [34], anti-Parkinson's [35], antiviral [36], antidepressant [37] and antitubercular [38] activities and versatile scaffolding.

Various naturally occurring substances having the morpholine moiety have been discovered to possess enhanced potency as biomolecules. For instance, polygonapholine alkaloid, utilized as a tonic medication in Taiwan, has been found to be particularly effective [39]. Additionally, chelonin has antibacterial and anti-inflammatory properties [40,41]. The morpholine containing alkaloids are believed to serve as starting materials for the manufacture of anticancer and antidiabetic medications [42,43]. There are several drugs that contain a morpholine cycle, for example, linezolid is an antibiotic [44], aprepitant is a neurokinin 1 receptor antagonist and the first drug approved by the FDA for chemotherapy [45] and gefitinib is a selective inhibitor of epidermal growth factor and is clinically used to treat lung cancer patients [46]. Inspired by medicinal significance of quinoline, triazole and morpholine nuclei, their hybridization results are extensive, need for discovery of novel anticancer agents, we have aimed to design and synthesize the novel quinoline based triazole and morpholine hybrids.

EXPERIMENTAL

All the synthetic reagents, catalysts and solvents were procured from Merck, Sigma-Aldrich and Avra chemicals and used without further purification. TLC was used to monitor the progress of the reactions using silica gel Merck $60F_{254}$ aluminum plates. Melting points of final compounds were recorded by utilizing Stuart SMP3 liquefying point mechanical assembly and are uncorrected. The mixtures were purified using the recrystallization method and the section chromatography strategy with silica gel 60-120 lattice. The IR spectra of the synthesized compounds were recorded on Shimadzu FTIR 8400 S spectrometer utilizing KBr pallets. The ^{1}H and ^{13}C NMR run on Bruker 400 spectrometer (400 and 100 MHz, respectively) by involving $CDCl_3$ and DMSO-d_6 as solvents and TMS as internal standard. Mass spectra were recorded on Shimadzu GC-MS QP 1000 spectrometer.

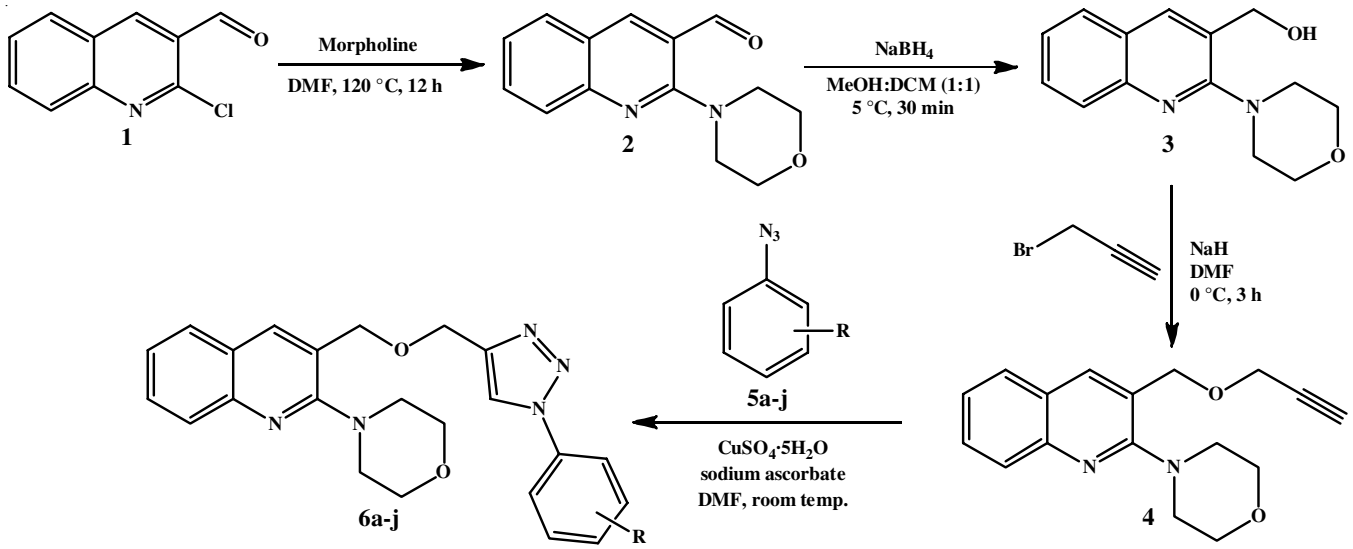
Synthesis of 2-morpholinoquinoline-3-carbaldehyde (2): 2-Chloroquinoline-3-carbaldehyde (**1**) (0.01 mmol, 1 equiv.) and morpholine (0.01 mmol, 1 equiv.) were dissolved in 25 mL of DMF and then the mixture was refluxed for 12 h at 120 ºC. Reaction monitored by TLC after completion of reaction, the reaction mass was poured on ice cold water and solid was filtered and dried under vacuum (**Scheme-I**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H), 8.73 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.75 (s, 2H), 7.44 (bs, 1H), 3.79 (s, 4H), 3.34 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 190.1, 157.8, 148.3, 143.9, 132.7, 129.5, 126.7, 124.5, 123.6, 121.8, 66.0, 50.7. ESI-MS *m/z* 243.12 $[M+H]^+$.

Synthesis of (2-morpholinoquinolin-3-yl)methanol (3): To a solution of 2-morpholinoquinoline-3-carbaldehyde (**2**) (0.01 mmol) in 25 mL of DCM, added $NaBH_4$ (0.005 mmol) at 5 ºC and continued the stirring for 30 min. The mixture was quenched saturated NH_4Cl solution in cold condition. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82-7.80 (m, 1H), 7.69 (s, 1H), 7.52-7.50 (m, 1H), 7.30-7.27 (s, 1H), 7.23-7.20 (s, 1H), 4.96 (s, 2H), 4.09 (s, 1H), 3.77-3.75 (m, 4H), 3.56-3.54 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.36, 149.58, 133.66, 129.64, 127.98, 127.58, 125.32, 124.83, 123.58, 65.59, 60.87, 45.92. ESI-MS *m/z* 245.14 $[M+H]^+$.

Synthesis of 4-(3-((prop-2-ynyloxy)methyl)quinolin-2-yl)morpholine (4): To a solution of (2-morpholinoquinolin-3-yl)methanol (**3**) (0.01 mmol) in 25 mL of DMF, added NaH (0.01 mmol, 1 equiv.) and propargyl bromide (0.012 mmol) dropwise continued the stirring 0 ºC for 3 h. The reaction mixture was poured on crushed ice and solid was filtered and dried. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.88-7.86 (m, H), 7.77-7.75 (m, 1H), 7.66-7.62 (m, 1H), 7.43-7.40 (s, 1H), 4.65 (s, 2H), 4.32 (d, J = 2.4 Hz, 2H), 3.79 (t, J = 4.0 Hz, 4H), 3.58 (t, J = 2.4 Hz, 1H), 3.26 (t, J = 4.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.4, 145.9, 138.5, 129.5, 127.4, 126.9, 124.8, 124.6, 124.3, 79.9, 77.8, 67.1, 66.2, 57.4, 50.4. ESI-MS *m/z* 283.14 $[M+H]^+$.

General procedure for the synthesis of 4-(3-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)quinolin-2-yl)-morpholine analogues (6a-j): Compound **4** (2 mmol) and azides (**5a-j**) (2 mmol) were dissolved in 10 mL of DMF. To this mixture, $CuSO_4{\cdot}5H_2O$ (25 mg, 0.1 mmol) and aqueous solution of sodium ascorbate (39 mg, 0.2 mmol) were added and stirred at 80 ºC for 1 h. The reaction mixture was poured into 25 mL of water and was extracted with $CHCl_3$ (3 × 25 mL). The organic layers were combined and washed with water (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to give the crude product. The crude product was purified by column chromatography using hexane:ethyl acetate (9:1-6:4%) as eluent to afford the pure compounds **6a-j**.

4-(3-(((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-methyl)quinolin-2-yl)morpholine (6a): White solid, yield: 81%, m.p. 187-189 ºC. IR (KBr, ν_{max}, cm^{-1}): 3138, 2853, 1600, 1432, 950, 754. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.29 (s, 1H), 7.93-7.86 (m, 3H), 7.76 (d, J = 7.6 Hz, 1H), 7.62-7.61 (m, 3H), 7.51-7.40 (m, 2H), 4.79 (s, 2H), 4.70 (s,



Scheme-I: Synthesis of 4-(3-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)quinoline-2-yl)morpholine analogues (**6a-j**)

2H), 3.71 (s, 4H), 3.23 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.9, 146.3, 145.1, 138.9, 137.1, 130.3, 129.9, 129.1, 127.9, 127.4, 125.5, 125.3, 124.8, 123.0, 120.5, 68.0, 66.6, 63.6, 50.9, 41.9, 31.1. m.f.: $C_{23}H_{23}N_5O_2$. ESI-MS *m/z* 424.30 $[M+Na]^+$.

4-(3-(((1-(4-Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6b): White solid, yield: 83%, m.p. 192-194 ºC. IR (KBr, ν_{max}, cm^{-1}): 3120, 2953, 2227, 1662, 840, 756. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.24 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.88 (t, *J* = 6.8 Hz, 3H), 7.63 (dd, *J* = 16.0, 7.9 Hz, 3H), 4.17-4.01 (m, 5H), 3.83-3.93 (m, 5H), 2.34-2.41 (m, 4H), 1.46 (q, *J* = 7.6 Hz, 2H), 1.06 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.95, 146.7, 145.3, 139.0, 138.6, 134.7, 130.3, 129.4, 127.4, 125.3, 124.6, 120.7, 68.6, 67.1, 63.9, 50.8, 21.1. m.f.: $C_{25}H_{27}N_5O_2$. ESI-MS *m/z* 430.35 $[M+H]^+$.

4-(3-(((1-(4-Isopropylphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6c): White solid, yield: 80%, m.p. 193-195 ºC. IR (KBr, ν_{max}, cm^{-1}): 3136, 2846, 2106, 1618, 825, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.40-7.35 (m, 1H), 4.71 (s, 4H), 4.29 (d, *J* = 2.4 Hz, 4H), 3.95-3.87 (m, 6H), 3.42-3.31 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.0, 158.8, 149.3, 143.2, 132.6, 129.2, 127.6, 124.8, 124.1, 122.0, 66.8, 51.4, 42.3. m.f.: $C_{26}H_{29}N_5O_2$. ESI-MS *m/z* 444.23 $[M+H]^+$.

4-(3-(((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6d): White solid, yield: 79%, m.p. 181-183 ºC. IR (KBr, ν_{max}, cm^{-1}): 3134, 2858, 1618, 1514, 1064, 877, 754. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.28-7.22 (m, 1H), 4.80 (d, *J* = 32.8 Hz, 4H), 3.87 (s, 4H), 3.35 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9, 146.7, 138.5, 133.0, 129.5, 127.4, 124.5, 121.9, 68.8, 67.1, 63.9, 50.9. m.f.: $C_{23}H_{22}BrN_5O_2$. ESI-MS *m/z* 480.25 $[M+H]^+$.

4-(3-(((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6e): White solid, yield: 85%, m.p. 185-187 °C. IR (KBr, ν_{max}, cm^{-1}): 3136, 2848, 1606, 1521, 1087, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.99-7.93 (m, 1H), 7.92-7.82 (m, 1H), 7.67 (d, *J* = 36.2 Hz, 5H), 7.32 (d, *J* = 46.3 Hz, 4H), 4.81 (d, *J* = 36.9 Hz, 4H), 3.85 (s, 4H), 3.35 (s, 4H), 2.99 (s, 1H), 1.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9, 146.7, 145.7, 138.5, 135.4, 134.7, 129.7, 127.4, 125.3, 124.5, 121.7, 120.7, 68.8, 67.1, 63.9, 50.8, 29.7. m.f.: $C_{23}H_{22}ClN_5O_2$. ESI-MS *m/z* 436.30 $[M+H]^+$.

4-(3-(((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6f): White solid, yield: 74%, m.p. 180-182 ºC. IR (KBr, ν_{max}, cm^{-1}): 3136, 2933, 1616, 1514, 1054, 824, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.28-7.22 (m, 1H), 4.80 (d, *J* = 32.8 Hz, 4H), 3.87 (s, 4H), 3.35 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9, 146.7, 145.7, 138.5, 135.4, 134.7, 129.7, 127.4, 125.34, 124.5, 121.7, 120.7, 68.8, 67.1, 63.9, 50.8, 29.7. m.f.: $C_{23}H_{22}FN_5O_2$. ESI-MS *m/z* 420.30 $[M+H]^+$.

4-(3-(((1-(4-Iodophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-methyl)quinolin-2-yl)morpholine (6g): White solid, yield: 78%, m.p. 190-192 ºC. IR (KBr, ν_{max}, cm^{-1}): 2839, 1612, 1425, 1365, 825, 754. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 7.70 (s, 3H), 7.60 (s, 1H), 7.37 (s, 1H), 7.21 (s, 2H), 4.80 (d, *J* = 34.2 Hz, 5H), 3.86 (s, 4H), 3.34 (s, 5H).$^+$). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.0, 158.8, 149.3, 143.3, 132.6, 129.2, 127.6, 124.8, 123.9, 122.0, 66.8, 51.4, 42.3. m.f.: $C_{23}H_{22}IN_5O_2$. ESI-MS *m/z* 528.30 $[M+H]^+$.

4-(4-(((2-Morpholinoquinolin-3-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile (6h): White solid, yield: 71%, m.p. 189-191 ºC. IR (KBr, ν_{max}, cm^{-1}): 3125, 1600, 1498, 1042, 815, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.20-8.14 (m, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 14.9, 7.1 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 4.85 (d, *J* = 20.5 Hz, 2H), 4.79 (s, 2H), 3.87 (d, *J* = 4.1 Hz, 4H), 3.35 (s, 4H), 1.81 (s, 2H), 1.26 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.7, 146.3, 144.9, 138.9, 130, 129.9, 127.9, 127.4, 125.4, 124.8, 122.9, 122.2, 115.3, 68.0, 66.6, 63.6, 56.0, 50.9, 39.8, 31.1. m.f.: $C_{24}H_{22}N_6O_2$. ESI-MS *m/z* 449.35 $[M+Na]^+$.

4-(3-(((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6i): White solid, yield: 74%, m.p. 195-197 ºC. IR (KBr, ν_{max}, cm^{-1}): 2950, 1619, 1581, 1062, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 6.9 Hz, 1H), 7.65 (d, *J* = 39.2 Hz, 4H), 7.37 (s, 1H), 7.24 (d, *J* = 21.3 Hz, 2H), 4.80 (d, *J* = 34.2 Hz, 4H), 3.86 (s, 4H), 3.34 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 148.9, 146.7, 138.5, 131.1, 129.5, 127.4, 125.6, 125.3, 124.6, 123.3, 115.2, 68.9, 67.1, 63.9, 50.9, 29.7. m.f.: $C_{23}H_{22}N_6O_4$. ESI-MS *m/z* 447.35 $[M+H]^+$.

4-(3-(((1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine (6j): White solid, yield: 79%, m.p. 197-199 ºC. IR (KBr, ν_{max}, cm^{-1}): 2838, 1612, 1425, 1112, 1041, 948, 734. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (s, 1H), 8.30 (s, 1H), 7.95-7.71 (m, 4H), 7.63 (dd, *J* = 11.2, 4.1 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 4.74 (d, *J* = 30.0 Hz, 4H), 3.84 (s, 3H), 3.77-3.68 (m, 4H), 3.29-3.13 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.7, 155.1, 141.9, 134.3, 129.1, 124.7, 122.7, 115.8, 107.7, 75.2, 65.3, 62.3, 59.1, 46.1, 31.7, 26.4. m.f.: $C_{24}H_{25}N_5O_3$. ESI-MS *m/z* 432.30 $[M+H]^+$.

MTT assay: Human breast adenocarcinoma cell lines MDA-MB-231 (triple negative) were procured from National Centre for Cell Sciences (NCCS), Pune India and were sub-cultured in-house at Maratha Mandal's Central Research Laboratory, Belgaum, India. Overnight, the cells were cultured in a 96-well flat-bottom microplate at 37 ºC with 95% humidity and 5% CO_2. Different concentrations of sample were employed, ranging from 100 to 3.125 µM. After 48 h, the cells were left to incubate and then 20 µL of MTT staining solution was applied to each well after two washing with PBS and the plate was then placed in an incubator set at 37 ºC. The formazan crystals were dissolved by adding 100 µL of DMSO to each well after 4 h and the absorbance was measured at 570 nm using a micro-plate reader. All the experiments were carried out in triplicate [47].

$$\text{Surviving cells (\%)} = \frac{\text{Mean OD of test compound}}{\text{Mean OD of negative control}} \times 100$$

RESULTS AND DISCUSSION

Synthesis of 4-(3-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)methyl)quinolin-2-yl)morpholine analogues (**6a-j**) is illustrated in **Scheme-I**. Initially, a mixture of 2-chloroquinoline-3-carbaldehyde (**1**) and morpholine was refluxed in DMF for 12 h to obtain 2-morpholinoquinoline-3-carbaldehyde (**2**). It was confirmed by appearance of signals of morpholine protons as two singlets at δ 3.79 and δ 3.34 ppm and the carbonyl proton was appeared as singlet at δ 10.10 ppm in ^{1}H NMR spectrum. In ^{13}C NMR, the carbonyl carbon signal was appeared at δ 190.1 ppm. The carbonyl group of compound **2** was converted to alcohol by using $NaBH_4$ as reducing agent in methanol-dichloromethane at 5 ºC for 30 min to afford (2-morpholinoquinolin-3-yl)methanol (**3**). Disappearance of singlet at δ 10.10 ppm and appearance of two singlets at δ 4.96 and δ 4.09 ppm corresponding to -CH_2- and -OH protons in ^{1}H NMR spectrum confirmed the functional group conversion of carbonyl to alcohol. Upon propargylation of alcohol group on intermediate **3** in presence of NaH in DMF obtained 4-(3-((prop-2-yn-1-yloxy)methyl)quinolin-2-yl)morpholine (**4**). It is confirmed by appearance of propargyl group -CH_2- protons as singlet δ 4.32 ppm and C≡CH proton as triplet at δ 3.58 ppm in ^{1}H NMR spectrum. The terminal alkyne of compound **4** was subjected to copper-catalyzed click reaction in presence of catalytic amounts of copper sulphate pentahydrate and sodium ascorbate with various aryl azides **5a-j** individually to obtain title compounds **6a-j**. The ESI-MS spectrum of compound 6**a** confirmed *m/z* peak as 424.30 $[M+Na]^+$.

Cytotoxicity studies: All the novel synthesized quinoline based morpholine-1,2,3-triazole hybrids (**6a-j**) were screened for their cytotoxicity against human breast cancer MDA-MB-231 cell line at various concentrations *viz*. 100, 50, 25, 12.5, 6.25 and 3.125 µM by employing doxorubicin as standard reference. The 4-chloro substituted compound **6e** displayed outstanding activity against MDA-MB-231 cell with an IC_{50} value of 17.20 ± 0.09 µM compared to reference doxorubicin IC_{50} value of 18.81 ± 0.03 µM. The 4-fluoro substituted compound **6f** showed good activity in comparison to reference compound with an IC_{50} value of 23.56 ± 0.09 µM. The activity of all other compounds was good to moderated with IC_{50} value ranging between 37.65-66.03 µM (Table-1). The presence of chlorine and fluoro groups on compounds **6e** and **6f** presented good activity, it may be attributed their electron withdrawing nature and ability to form H-bond interaction with biological targets. Replacement of chlorine or fluorine with various other substituents like bromo, ethyl, isopropyl, methoxy, cyano and nitro groups diminished their activity.

TABLE-1
IC_{50} VALUES OF COMPOUNDS **6a-j**
AGAINST MDA-MB-231 CELL LINE

Entry	IC_{50} value (µM)	Standard deviation (±)
6a	64.59	0.03
6b	56.80	0.02
6c	44.10	0.10
6d	37.65	0.05
6e	17.20	0.09
6f	23.56	0.09
6g	45.60	0.13
6h	66.03	0.08
6i	61.38	0.03
6j	82.69	0.18
Doxorubicin	18.81	0.03

Conclusion

In summary, the synthesis and characterization of some novel 1-aryl-1,2,3-triazoles-4-methoxy methyl-3-quinoline-2-morpholine (**6a-j**) is reported. Then structure of these triazoles was elucidated by the spectral studies. The synthesized compounds **6a-j** were evaluated for their *in vitro* anticancer activity against MDA-MB-231 cell line. All, these compounds were proven to have anticancer activity in comparison to reference drug doxorubicin. Especially, chloro and fluoro substituent compounds demonstrated potent activity with IC_{50} values of 17.20 ± 0.09 µM and 23.56 ± 0.09 µM, which proved their efficacy and could be further studied for the development of novel chemotherapeutics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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