Design, synthesis, cytotoxicity, and molecular docking studies of 1-(4-methoxyphenyl)-N-substituted phenyl-1H-1,2,3-triazole-4-carboxamide derivatives

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ABSTRACT
A new series of 1-(4-methoxyphenyl)-N-substituted phenyl-1H-1,2,3-triazole-4-carboxamide derivate (4A–4N) have been synthesized in excellent yields and structures were characterized by spectral techniques like 1H-NMR, 13C-NMR, LC-MS, and FT-IR. The newly synthesized derivatives were evaluated for anticancer activity against breast cancer cell lines MCF-7 and MDA-MB-231. Among them, compound 4H (IC50 = 13.11 and 23.61 μM) and compound 4M (IC50 = 11.55–31.87 μM) shows good cytotoxicity activity toward both cell line, while compounds 4B (IC50 = 9.48 μM), 4I (IC50 = 7.11 μM), and 4J (IC50 = 8.27 μM) showed promising cytotoxicity against MCF-7 cell line as compared with standard (Doxorubicin). Also explored docking study with binding mode of interactions and active site in EGFR tyrosinse (PDB ID: 2J5F) proteins and molecular docking study shows very good interaction with the tyrosine kinase active site. In addition to this targeted compounds were studied the pharmacokinetics and the compounds were follow Lipinski’s rule of five as well as compounds have acceptable good drug-likeness score properties.

GRAPHICAL ABSTRACT

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Supplemental data for this article is available online at https://doi.org/10.1080/00397911.2022.2137681
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Introduction

Triazoles have a high degree of solubility and the capacity to bind to the molecular targets of other molecules due to the non-covalent interactions that their derivatives may execute. Additionally, 1,2,3-triazole compounds work as bio isosteres of many functional groups, including carboxylic acids, amides, esters, and others.\textsuperscript{[1–4]} Triazoles may be synthesized in a variety of ways and have a wide range of pharmacological uses, therefore there are numerous medications on the market today that include derivatives of the 1\textit{H}-1,2,3-triazole. Currently, click reaction is the method of choice for synthesizing the 1,2,3-triazole ring.\textsuperscript{[5–7]} The 1,4-disubstituted 1,2,3-triazole building blocks can be produced using this click reaction, which is described as a copper (I) catalyzed azide-alkyne 1,3-dipolarcyclo-addition. 1,2,3-Triazole derivatives, such as hybrids, derivatives, and conjugates, have been used in medicinal chemistry and played a significant role in biological activities like anticonvulsant,\textsuperscript{[8]} antibacterial,\textsuperscript{[9]} anticancer,\textsuperscript{[10]} antiviral,\textsuperscript{[11]} anti-inflammatory,\textsuperscript{[12]} antihistaminic,\textsuperscript{[13]} and proliferative activities,\textsuperscript{[14]} \textit{β}-lactamase inhibitors,\textsuperscript{[15]} and DNA-alkylating cross-linking agents.\textsuperscript{[16,17]} The most potent and rapidly spreading illness in the world, cancer is also a life-threatening condition.\textsuperscript{[18,19]} There are many different anticancer medications that may be used to treat cancer, but it can be difficult to find and make anticancer medications that are both safe and efficient. Proliferation, apoptosis, and development are all processes in which signaling pathways are particularly essential. Because it was directly implicated in cell growth irregularity leading to cancer start, the signaling pathway change is the primary cause of cancer progression.\textsuperscript{[20]} Quinine, Galantamine, Artemisia, Aspirin, Elliptinium, Dolastatin 10, Salbutamol, Vincristine Salmeterol, Reserpine, Paclitaxel, Tubocurarine, Huperzine, and many other naturally occurring bioactive substances were employed in the treatment of many disorders.\textsuperscript{[21,22]} The use of natural medicines as oncological agents in drug development was already clinically established.\textsuperscript{[23]} The main issue throughout therapy is drug resistance. The main problems in contemporary research are to create and design novel anti-cancer drugs that are extremely effective and efficient, have fewer side effects, are less expensive, and provide speedy results. To address these issues, it is necessary to develop novel anti-cancer agents with selective action. As is well known, several heterocyclic scaffolds have been employed in the treatment of various malignancies, with 1,2,3-triazole serving as one of the most important of them. Some of the biologically active pharmacores were listed in Figure 1.

Results and discussion

Reagent and condition

Step a: 4-methoxyl aniline (1.0 eq.), NaNO\textsubscript{2} (1.5 eq.), NaN\textsubscript{3} (1.1 eq.), 6.0 N HCl (10 vol), 0–5\degree C; step b: propiolic acid (1.0 eq.), 4-methoxy phenyl azide (1.0 eq.), CuSO\textsubscript{4}.5H\textsubscript{2}O (0.05 eq.), Sodium ascorbate (0.1 eq.), tert-BuOH:Water (2:1) (10 vol), 50\degree C; step-c: comp-4 (1.0 eq.), substituted aniline (1.2 eq.), HATU (1.5 eq.), DIPEA (2.5 eq.), DMF (5.0 vol), RT.

Targeted molecules 1,2,3-triazole derivatives (4A–4N) has been synthesized as described in Scheme 1, as the 4-methoxy-phenyl azide (2) intermediate was synthesized from diazonium salts with sodium azide according to the procedure that was described
in the literature\cite{24} and reaction progress is monitored by TLC using 10% ethyl acetate: Hexanes as solvent system as well as LC-MS which shows complete consumption of 4-Methoxyaniline and formation of azide intermediate (2) which is confirm by mass (M – 1) m/z 148.1 and corresponding azide intermediate was further used toward click reaction\cite{25} in this chemical conversion CuSO₄·5H₂O and sodium ascorbate used as source of Cu in tert-butanol: water (2:1) combination of solvent and addition of propiolic acid and 4-methoxy-phenyl azide (2) in solution which gives the corresponding 1,2,3-triazole carboxylic acid (3) reaction conversion was monitored by LC-MS shows complete conversion of azide intermediate (2) into 1,2,3-triazole carboxylic acid (3) confirm by mass (M + 1) m/z (220.1) and ¹H-NMR as described in Scheme 1. Isolation of respective compound (3) with a simple workup and easy filtration from reaction mass with pure and high yield, compound 3 is used as such without further purification for the preparation of new series of compounds (4A–4N), we chose ortho, para, and meta substituted aniline containing electron donating and withdrawing groups for synthesis and finally, we carried out amide coupling with compound (3) and respective amines (R) using HATU, DIPEA, and DMF as a solvent, we majorly observed that nitro group (electron-withdrawing group) at ortho and para position which shows traces of product formation and in a reverse manner reaction conversion was faster in case of electron donation group on ortho and para-substituted aniline. All newly synthesized compounds were characterized by using a spectral technique like NMR (proton and carbon), LC-MS HPLC, elemental analysis, and FT-IR.

**Anti-cancer activity of triazole compounds**

The newly synthesized 1,2,3-triazole derivatives (4A–4N) were tested for the anticancer activity for two breast cancer cell lines (MCF-7 and MDA-MB-231) by using a standard MTT assay. Synthesized compounds consist of various functional groups on aromatic rings having different substitutions and the most of compounds having very good anticancer activity on both cell lines and some of the compounds were potent as compared with the standard drug Doxorubicin. The compounds 4B (IC₅₀ = 7.10 µM), 4I (IC₅₀ = 7.10 µM), 4J (IC₅₀ = 8.27 µM), and 4M (IC₅₀ = 9.83 µM) shows the highest

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**Figure 1.** 1,2,3-Trizole based potential pharmaceuticals.
promising inhibitory activity against MCF7 cell line and also the compounds 4A, 4C, 4E, 4F, and 4N shows moderate cytotoxicity as compared with standard (Doxorubicin), similarly for DMA-MB-231 cell line 4A, 4B, 4H, 4I, and 4M shows better cytotoxicity with (IC₁₀₀ = 13.11–23.61 μM) and rest of the compounds shown moderate inhibitory activity. Finally, compound 4M exhibited good cytotoxicity against MCF 7 and MDA-MB-231 cell lines in the range of IC₅₀ = 9.83–11.55 μM. According to cytotoxicity activity in Table 1, the cytotoxicity activity of compounds increases as compounds having an electronegative substituent on benzene ring on ortho and para position as compound 4M having 2,4-di-fluoro substitution of benzene ring as well as compound 4H having 2,4-dichloro derivatives shows very good activity in the range of (IC₅₀ = 13.11 and 23.61 μM) reported highest promising anticancer activity among the tested compounds against the cell lines MCF-7 and MDA-MB-231. The 4-fluoro substituted compound 4B (IC₅₀ = 9.48 and 22.54 μM) showed better activity against both cell lines. Compound 4I (3-Nitro derivative) exhibited its maximum activity against MCF-7 (IC₅₀ = 7.11 μM) as compared with MDA-MB-231 cell line (IC₅₀ = 31.87 μM). The rest of triazole shows the least anticancer activity in both cell lines. Other tested triazole derivatives like 4D, 4K, and 4L were less active in tested concentrations.

**Table 1.** Cytotoxicity activity of 4A–4N derivatives and the positive controls on two different breast cancer cell lines (μM).

| S.No. | Compound | IC₅₀ (μM) |
|-------|----------|-----------|
|       |          | MCF-7     | MDA-MB-231 |
| 1     | 4A       | 18.36     | 27.65      |
| 2     | 4B       | 9.48      | 22.54      |
| 3     | 4C       | 31.23     | >100       |
| 4     | 4D       | >100      | >100       |
| 5     | 4E       | 21.17     | >100       |
| 6     | 4F       | 17.90     | 86.44      |
| 7     | 4G       | >100      | >100       |
| 8     | 4H       | 13.11     | 23.61      |
| 9     | 4I       | 7.11      | 31.87      |
| 10    | 4J       | 8.27      | 63.75      |
| 11    | 4K       | >100      | 87.63      |
| 12    | 4L       | >100      | 92.78      |
| 13    | 4M       | 9.83      | 11.55      |
| 14    | 4N       | 23.18     | >100       |
| 15    | bDoxorubicin (Std.) | 3.90 | 1.23 |

aData were presented the mean value of three independent determinations.

bDoxorubicin is positive control.

Bold values indicates that these compounds having good anticancer activity on cell lines.
Kinase studies

Study of EGFR inhibitory activity

The ability of EGFR tyrosine kinase assay was performed to find the EGFR inhibitory activity of compounds 4H and 4M. The EGFR inhibition was found satisfactory in both compounds (4H and 4M) with IC$_{50}$ of 6.4–6.9 µM. According to Table 2, the compounds 4H and 4M were found to be active and have moderate IC$_{50}$ values for EGFR inhibition. The compound which has an electron-withdrawing substituent which found to be more active as compared with an electron-donating substituent. The outcome of this study supports the results of the cytotoxicity activity of cancer cell-based assays. In comparison to erlotinib the both compounds were found to be active EGFR inhibitors.

Molecular protocol study

The PDB ID for EGFR tyrosine kinase (PDB: 2J5F) was retrieved from the protein data bank. Themonomeric protein was established for the Protein Preparation Wizard with optimization of H bond and Epik for energy minimization. The receptor grid generation is performed with required co-ordinates. Total ligands were drawn in Cambridge Soft Chemdraw and converted into respective forms by Schrodinger Maestro 12.7 and Ligand preparation was done with LigPrep. The molecular docking was performed and screened for results (Fig. 2).

Table 2. Inhibitory activity of compounds M and N on EGFR.

| Compound | EGFR inhibition IC$_{50}$ + SEM (µM) |
|----------|--------------------------------------|
| 4H       | 6.4 ± 1.2                            |
| 4M       | 6.9 ± 0.8                            |
| Erlotinib| 0.09 ± 0.03                          |

Figure 2. Superimposition of all compounds with targeted protein.
Molecular docking studies

The docking studies revealed EGFR tyrosinse (PDB: 2J5F) as a lead target in the selected series derivatives (4A–4N). The results of docking revealed the derivatives of anticancer triazole were promising on the EGFR receptor. As structurally related nucleus are shown to exhibit inhibitory potential against Cancer cell line (MCF-7), the newly synthesized triazole molecules were docked against the epidermal growth factor receptor (EGFR) crystal structure to predict its inhibitory potential. The co-ordinates of EGFR were obtained from the protein data bank (2J5F). Docking studies were carried out for the selected molecules (4A–4N) of triazole compounds and the interactive poses of M and N into the scaffold of protein are represented in Figures 3 and 4. The compound M shows 2 hydrogen bonds in the active site of the protein, in which the first one was at a distance of 2.58 Å of C=O and the second at a distance of 2.36 Å methoxy group. Besides, two aromatic hydrogen bonds interacted with Met793 and Lys745. Further, hydrophobic interaction was found with Pro794, Leu792, and Phe 723. Interactions of compound N with hydrogen bond were seen at a distance of 2.21 Å of C=O and the next one was found at a distance of 2.28 Å methoxy. Besides, two aromatic hydrophylic bonding interactions were seen with Met793 and Lys745. Further, hydrophobic interaction was seen with Pro794, Leu792, Phe723, and Met790. In the analysis of this study, we got significant amino acid interactions. Further, with the conclusion from the docking study, all of the selected molecules were active in the binding scaffold and interacted with all the amino acid residues when compared with the co-crystal. Interaction poses of compounds M and N were found in the active site of the binding pocket of EGFR (PDB ID: 2J5F) showing the promising interaction with the amino acid. The selected compounds from docking also showed promising activity against the selected target. The compounds M and N were also found potent against the selected target. Super imposition of all 3D structures shown in the binding pocket with protein (PDB ID: 2J5F) is given below. It shows the different interactions with different
amino acids on one platform. The binding free energy of compounds shows promising results and also shows good binding interactions and the obtained values were tabulated in Table 3.

**ADME property**

ADME properties of newly synthesized molecules (4A–4N) were performed for prediction and calculated by using Molinspiration online property\textsuperscript{[26,27]} the values obtained were tabulated in Table 4. The entire synthesized compound shows good % ABS (% absorption) in the range of 69.36 to 85.18% and values were calculated as \( \text{% ABS} = \)
However, the criteria for developing the orally active drug candidate should not violate more than or equal to four criteria.\textsuperscript{30} n-OH, NH ≤ 5, miLog \(P_n\) ≤ 5, mol. Wt. ≤ 500 g/mol and \(n\)-ON (number of hydrogen bond acceptors) ≤ 10. Furthermore, all synthesized compounds were found potent to the orally active drug as they followed the required criteria therefore; synthesized compounds may have good potential as oral agents.

### Experimental

**Step a: Synthesis of 1-azido-4-methoxybenzene (2)\textsuperscript{24}**

To a stirred solution of 4-methoxy aniline (1) (1.0 eq.) in DCM (10.0 vol) in two neck round bottom flask was added 6.0 N HCl solution (10 vol) at 0–5°C, to this biphasic solution was dropwise added a saturated aqueous solution of NaNO\(_2\) (1.5 eq.) at 0–5°C, and continue stirring for 30 min, sodium azide (1.1 eq.) was added portion wise in reaction mass at 0–5°C, stirred for 30 min, and temperature of the reaction mass was allowed to warm to RT, monitored reaction by TLC to check the consumption of 4-methoxy aniline (1). After completion of the reaction stop stirring and separate the lower organic layer, the aqueous phase was extracted with DCM (2 x 10 vol). The combined organic layer was washed with saturated sodium bicarbonate solution, saturated brine solution, dried over anhydrous sodium sulfate, and filtered, in another round bottom flask charge combined organic layer and added activated charcoal (5% w/w) was stirred for 30 min and filter the reaction mass through celite bed and wash with DCM (1.0 vol.). Evaporation of the solvent in \textit{vacuo} gave the crude azide and was used as such in the next step without further purification.

**Step-b: Synthesis of 1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxylic acid (3)\textsuperscript{25}**

To a stirred aq. solution of CuSO\(_4\)·5H\(_2\)O (0.05 eq.) and sodium ascorbate (0.1 eq.), a solution of \textit{tert}-butanol: water (30 vol, 2:1) was added at RT. To the resulted solution, sequentially added propionic acid (1.0 eq.) and then 4-methoxy phenyl azide (2) (1.0 eq.) at RT. The reaction mixture was then stirred at 50°C for overnight, monitored reaction by

| Comp | % ABS | TPSA (A2) | \(n\)-ROTB | MV | MW | miLog \(P_n\) | \(n\)-ON | \(n\)-ONNH | Lipinski violation | Drug likeness model score |
|------|-------|-----------|-----------|----|----|-------------|--------|-----------|----------------|---------------------|
| 4A   | 85.18 | 69.05     | 4         | 274.38 | 328.76 | ≤ 5         | 6      | 1         | 0               | 0.47                |
| 4B   | 85.18 | 69.05     | 4         | 265.78 | 312.30 | 2.48        | 6      | 1         | 0.22             |
| 4C   | 81.99 | 78.28     | 5         | 286.39 | 324.34 | 2.37        | 7      | 1         | −0.07            |
| 4D   | 85.18 | 69.05     | 4         | 292.27 | 407.65 | 3.73        | 6      | 1         | −0.17            |
| 4E   | 85.18 | 69.05     | 4         | 274.38 | 328.76 | 2.97        | 6      | 1         | −0.08            |
| 4F   | 85.18 | 69.05     | 4         | 292.27 | 407.65 | 3.73        | 6      | 1         | 0.03             |
| 4G   | 85.18 | 69.05     | 4         | 298.37 | 454.65 | 4.00        | 6      | 1         | 0.20             |
| 4H   | 85.18 | 69.05     | 4         | 287.92 | 363.20 | 3.60        | 6      | 1         | 0.16             |
| 4I   | 69.37 | 114.87    | 5         | 284.18 | 339.31 | 2.25        | 9      | 1         | −0.54            |
| 4J   | 85.18 | 69.05     | 4         | 279.31 | 346.75 | 3.06        | 6      | 1         | 0.41             |
| 4K   | 85.18 | 69.05     | 4         | 278.73 | 373.21 | 3.12        | 6      | 1         | 0.05             |
| 4L   | 81.99 | 78.28     | 5         | 304.28 | 403.24 | 3.11        | 7      | 1         | −0.36            |
| 4M   | 85.18 | 69.05     | 4         | 270.71 | 330.29 | 2.57        | 6      | 1         | −0.02            |
| 4N   | 85.18 | 69.05     | 4         | 287.92 | 363.20 | 3.57        | 6      | 1         | 0.10             |
LC-MS and it shows the formation of product with mass [(M + 1), m/z 220.1] after completion, cool reaction mass at room temperature and added cold water (80 mL). The formed precipitate was collected by filtration under vacuum, washed with water and then diethyl ether and dried to give the titled compounds (3) as light brown solid (92%).

**Synthesis of N-(4-chlorophenyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamide (4A)**

To a stirred solution of compound (3) (300 mg, 1.36 mmol, 1.0 eq.), 4-chloroaniline (A) (208.2 mg, 1.63 mmol, 1.2 eq.) and DMF (5.0 mL) was added HATU (775.7 mg, 2.04 mmol, 1.5 eq.) at RT and stirred reaction mass for 10 min and DIPEA (0.59 ml, 3.40 mmol, 2.5 eq.) was added drop wise in reaction mass at 0–5°C, stir reaction mass for 4–5 h at RT, monitored reaction by LC-MS, after complete consumption of compound-3, pour reaction mass in to cold water (10 mL) the formed precipitate was filter through Buchner funnel under vacuum and wash with water (3 mL) and diethyl ether (3 mL), dried to give compound (4A) as an off-white solid (374.8 mg, 83.3%), HPLC purity: 99.45; LC-MS (M + 1) m/z 329.0, Melting point 243.6–246.2°C; IR (KBr) ν: 3336.99, 3136.39, 2961.8, 1672.36, 1595.20, 1556.62, 1510.33, 1252.82, 1035.82 cm⁻¹; ¹H-NMR (300 MHz, DMSO d-6) δ: 10.74(s, 1H), 9.36 (s, 1H), 7.90–7.93 (d, J = 9 Hz, 4H), 7.42–7.45 (d, J = 9Hz, 2H), 7.16–7.19 (d, J = 9Hz, 2H), 3.85 (s, 3H); ¹C-NMR (75 MHz, DMSO-d₆) δ: 56.09, 115.38, 122.45, 122.66, 126.04, 127.97, 129.01, 130.04, 138.00, 143.83, 158.76, 160.15 ppm; Elemental analysis (Found): C = 58.45%, H = 3.99%, N = 17.04%. Calculated: C = 58.42%, H = 4.01%, N = 17.14%.

**Conclusion**

In summary, we report the synthesis of a series of 1-(4-methoxyphenyl)-N-substituted phenyl-1H-1,2,3-triazole-4-carboxamide derivatives (4A–4N) were prepared and evaluated for anticancer activity against two breast cancer cell lines MCF-7 and MDA-MB-231. According to Table 2, The compounds 4H and 4M exhibited potent activity against both cell lines while few compounds like 4B, 4I, and 4J were shown good activity against MCF-7 cell line, and 4A, 4B, and 4I were shown good anticancer activity against the MDA-MB-231 cell line as compared with standard Doxorubicin. In general, all synthesized compounds were shown moderate to good anticancer activity. The molecular docking technique have been performed to support our experimental results and it shows good interaction with the tyrosinse kinase active site around potent compound 7M and 7N in tyrosinse kinase protein furthermore; the synthesized compounds cover the Lipinski’s rule of five and have good drug-like properties so, therefore, they can be developed as an oral drug candidate.

**Acknowledgments**

The author is thankful to Post Graduate and Research Centre, Maulana Azad College Aurangabad, 431001, India for providing laboratory facility and Navin Fluorine International Limited, Dewas, Madhya Pradesh, 455001, India for the analytical support and encouragement for the higher study and authors also thankful to Tata Memorial Centre-Advanced Centre for
Treatment, Research and Education in Cancer (ACTREC) Kharghar, Navi Mumbai for *In-vitro* anti-cancer activity.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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