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NEW 1,2,3-TRIAZOLE TETHERED IMIDAZOLE HYBRIDS AS ANTICANCER AGENTS

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Abstract

With an aim to discover new anticancer agents, synthesized new 1,2,3-triazole tethered imidazole hybrids **7a-l** by involving a multicomponent and click chemistry reactions. The structures were characterized by interpretation of ^{1}H NMR, ^{13}C NMR and Mass spectral data. The novel hybrids were screened for their cytotoxicity against human breast adenocarcinoma MDA-MB-231 cell line by employing *Doxorubicin* as standard drug. The compounds **7c** and **7d** demonstrated better activity with IC_{50} value of 17.20±0.09 µM and 23.56±0.09 µM in comparison to reference drug IC_{50} value of 18.81±0.03 µM. Molecular docking study of best active compound 7d displayed considerable docking score value of -9.9 kcal and binding interactions against EGFR.

Keywords

Click chemistry, cytotoxicity, Imidazole, molecular docking, 1,2,3-triazole

Introduction

In the field of heterocyclic chemistry, imidazoles and their substituted derivatives had a elite place [1]. It is present as structural component of natural products such as histidine[2], histamine[3], and purine[4,5]

Imidazoles have a wide range of biological applications, including compounds that are antimicrobial[6], antiviral[7], antiprotozoal[8], anti-inflammatory[9], anticancer[10], antifungal[11], antitubercular[12], antiparasitic[13], antihypertensive[14], etc. In addition to their significance in medicinal chemistry, imidazoles have commercial uses as corrosion inhibitors[15], flame retardants[16], photographic[17] and electronics[18]. Numerous studies have demonstrated that imidazole reduces cancer cell development through interacting with biological receptors such as DNA, vascular endothelial growth factor receptors, histone deacetylases, topoisomerases, and epidermal growth factor receptor tyrosine kinases.[19–23] Several imidazoles, such as tipifarnib, dacarbazine, temozolomide and zoledronic acid are currently utilised in clinics to treat a variety of malignancies[24–27] (**Fig 1**). Condensation of 1,2-diketones with substituted aldehydes in presence of ammonium acetate under N_2 atmosphere[28,29] is a facile protocol for synthesis of imidazoles with better yields.

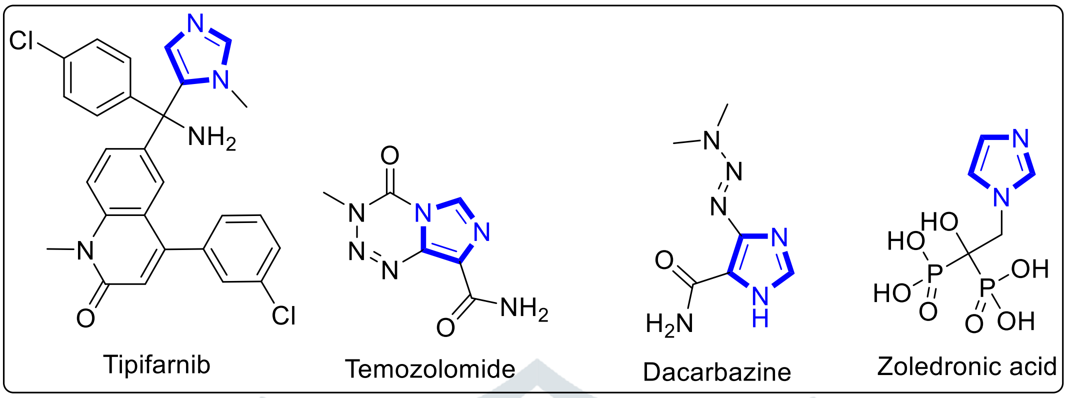


Fig 1. Anticancer drugs containing imidazole moiety.

Molecular hybridization is a popular method in which two or more nuclei are combined with a proper linker to envisage increased activity or novel biological features[30]. In the literature, hybridization of imidazoles with 1,2,3-triazoles is reported to have enriched pharmacological activities, such as inhibition of HIV-1 protease[31], inhibition of CYP17 lyase[32], antitubercular activity[33], anticancer activity[34] etc. Cancers are characterized by the unchecked growth and spread of abnormal cells[35]. It caused death of 10 million worldwide in 2020, and by 2030, that number is predicted to rise to 13 million[36–38]. The most prevalent type of cancer among women is breast cancer. which typically develops because of genetic abnormalities and aberrant enzyme activity[39,40]. It is still a condition that poses a serious risk to life, and research into novel anticancer medications must continue as the available medications have undesired side-effects[41,42].

Inspired by the significant medicinal applications of imidazoles and their 1,2,3-triazole hybrids, we have synthesised novel 4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole analogues, evaluated their anticancer activity against human breast adeno carcinoma cell line MDA-MB-231 and performed molecular docking studies.

Experimental

Material and methods

All chemicals and reagents were obtained from commercial sources (Spectrochem, TCI and Avra chemicals) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualisation on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz instrument. Chemical shifts (d) are reported in ppm downfield from internal TMS standard. Mass spectra were recorded on Shimadzu GC-MS QP 1000 spectrometer. Melting points were determined with an electrothermal melting point apparatus, and are uncorrected.

Procedure for the synthesis of 2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazole (4):

To the solution of benzil **3** (10 mmol) in glacial acetic acid (25 mL), added ammonium acetate **2** (0.1 mmol) and refluxed the reaction mixture for 1 hour, under nitrogen atmosphere at 100 ^{o}C. At this stage, added 1-naphthaldehyde **1** (10 mmol) in acetic acid (5 mL) drop wise continued the reflux for another 3 hr to obtain 2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazole **4**. TLC monitored and after completion of reaction, the reaction mixture was poured on crushed ice (100 g), the precipitate was collected by filtration and the dried compounds were chromatographic over silica gel using pet ether: ethyl acetate (60:40) solvent system as eluent.

Procedure for the synthesis of 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole (5): To the solution of 2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazole **4** (0.01 mmol) in DMF (25 mL), added K_2CO_3 (0.02 mmol) and stirred the solution for 20 minutes at room temperature. Then, added propargyl bromide (0.01 mmol) to the same and reaction mixture was stirred at 80 ^{o}C for 4 hours to yield 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole. The progress of the reaction was monitored by TLC, after completion, poured reaction mixture in ice cold water, filtered and dried the solid under vaccum.

General procedure for synthesis of 4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole analogues (7a-l): To the solution of 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole **5** (0.01 mmol) in 25 ml of DMF:H_2O(1:1), was added sodium ascorbate (0.01 mmol), copper sulphate pentahydrate (0.01 mmol) and an appropriate substituted aryl azide **6a-l** individually. The resulting reaction mixture was stirred for 2 – 4 hours to afforded 4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole analogues **7a-l**. After completion, the reaction mixture was poured in ice cold water, the separated solid was purified by column chromatography using ethyl acetate : pet ether solvent mixture as eluents.

Spectra

4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole (7a): White solid. Yield: 72 %. m.p.: 157 – 158 ^{o}C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 7.98 (d, J = 8.00 Hz, 2H), 7.90 (d, J = 8.43 Hz, 1H), 7.82 (d, J = 7.85 Hz, 1H), 7.74 (d, J = 7.57 Hz, 2H), 7.70 (d, J = 7.85 Hz, 2H), 7.70 (dd, J = 8.73, 7.06 Hz, 1H), 7.45 (d, J = 7.85 Hz, 4H), 7.43 (dd, J =8.00, 7.06 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.40 (t, J = 7.45 Hz, 1H), 7.39 (dd, J = 7.85, 7.47 Hz, 1H), 7.35 (t, J = 7.20 Hz, 1H), 7.34 (dd, J = 7.57, 7.20 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.4, 140.7, 136.3, 135.7, 132.6, 132.1, 130.9, 129.4, 128.9, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 127.1, 126.4, 126.2, 125.8, 125.1, 123.6, 121.6, 47.3. ESI-MS: *m/z* 503 $[M+H]^{+}$.

1-(4-bromophenyl)-4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (7b): Pale white solid. Yield: 70 %. m.p.: 165 – 167 ^{o}C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.88 (d, J = 8.30 Hz, 2H), 7.73 (d, J = 7.85 Hz, 1H), 7.70 (d, J = 7.85 Hz, 2H), 7.51 (d, J = 8.30 Hz, 2H), 7.50 (dd, J = 8.43, 7.06 Hz, 1H), 7.46 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45

Hz, 1H), 7.39 (t, J = 7.85 Hz, 2H), 7.39 (d, J = 7.85 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.0, 140.9, 135.7, 134.7, 132.9, 132.2, 132.1, 130.9, 128.9, 128.9, 128.2, 128.1, 127.9, 127.8, 127.1, 126.6, 126.6, 126.4, 126.1, 125.2, 123.6, 123.4, 121.6, 120.8, 47.7. ESI-MS: *m/z* 582 $[M+H]^+$.

1-(2-chlorophenyl)-4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (7c): White solid. Yield: 75 %. m.p.: 158 – 160 °C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.46 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H0, 7.93 (d, J = 8.43 Hz, 1H), 7.73 (d, J = 7.85 Hz, 1H), 7.70 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.49 (d, J = 7.85 Hz, 1H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.46 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 3H), 7.33 (t, J = 7.45 Hz, 1H), 7.30 (dd, J = 7.85, 7.44 Hz, 1H), 7.22 (dd, J = 7.85, 7.44 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.0, 140.7, 140.6, 135.1, 132.6, 132.2, 132.1, 130.9, 130.0, 129.7, 129.0, 128.9, 128.2, 127.9, 127.8, 127.3, 127.1, 126.4, 16.1, 125.5 125.2, 124.6, 123.1, 47.3. ESI-MS: *m/z* 538 $[M+H]^+$.

1-(4-chlorophenyl)-4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (7d): White solid. Yield: 71 %. m.p.: 155 – 157 °C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.82 (d, J = 7.85 Hz, 1H), 7.73 (d, J = 8.43 Hz, 2H), 7.69 (d, J = 7.85 Hz, 2H), 7.52 (d, J = 8.43 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.46 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 3H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.0, 140.7, 136.1, 134.7, 132.6, 132.2, 132.1, 131.7, 130.9, 129.7, 128.9, 128.2, 127.9, 127.8, 127.3, 127.1, 126.4, 125.5, 125.2, 123.6, 123.1, 121.6, 47.3. ESI-MS: *m/z* 538 $[M+H]^+$.

4-(4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenol (7e): White solid. Yield: 70 %. m.p.: 152 – 154 °C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.44 (s, 1H), 8.60 (s, 1H), 8.03 (d, J = 8.00 Hz, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.90 (d, J = 8.43 Hz, 1H), 7.82 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.57 (d, J = 8.43 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 8.00, 7.06 Hz, 3H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 3H), 7.33 (t, J = 7.45 Hz, 1H), 6.78 (d, J = 8.43 Hz, 2H), 5.35 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 157.3, 150.3, 145.2, 140.7, 138.7, 135.7, 132.6, 132.2, 132.1, 130.9, 128.9, 128.6, 128.2, 127.8, 127.3, 127.1, 125.5, 125.2, 123.8, 121.6, 119.1, 115.2, 47.3. ESI-MS: *m/z* 520 $[M+H]^+$.

1-(2-methoxyphenyl)-4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (7f): White solid. Yield: 73 %. m.p.: 156 – 158 °C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.47 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.70 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.44 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 3H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 2H), 7.39 (t, J = 7.85 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 7.26 (dd, J = 7.85, 7.45 Hz, 1H), 7.16 (dd, J = 7.85, 7.44 Hz, 1H), 7.10 (d, J = 7.85 Hz, 1H), 5.31 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.8, 150.1, 145.0, 140.7, 140.6, 134.4, 132.4, 132.2, 132.1, 130.9, 128.9, 128.2, 127.9, 127.8, 127.7, 127.1, 126.4, 126.3, 125.5, 125.2, 124.3, 122.4, 121.6, 114.4, 56.9, 47.7. ESI-MS: *m/z* 534 $[M+H]^+$.

1-(4-methoxyphenyl)-4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (7g): White solid. Yield: 68 %. m.p.: 162 – 164 ºC. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.60 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.82 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.44 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (d, J = 8.43 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 3H), 7.33 (t, J = 7.45 Hz, 1H), 7.12 (d, J = 8.43 Hz, 2H), 5.33 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 158.2, 150.1, 145.0, 140.7, 135.7, 134.7, 132.4, 132.2, 132.1, 130.9, 128.9, 128.2, 127.9, 127.8, 127.1, 126.4, 126.3, 125.2, 123.8, 121.6, 114.4, 55.4, 47.7. ESI-MS: *m/z* 534 $[M+H]^+$.

4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-(o-tolyl)-1H-1,2,3-triazole (7h): White solid. Yield: 79 %. m.p.: 148 – 150 ºC. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.40 (s, 1H), 8.03 (d, J = 8.00 Hz, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.90 (d, J = 8.43 Hz, 1H), 7.70 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 8.00, 7.06 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 2H), 7.39 (t, J = 7.85 Hz, 1H), 7.34 (dd, J = 7.85, 7.44 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 7.32 (d, J = 7.85 Hz, 1H) 7.15 (d, J = 7.85 Hz, 1H), 7.14 (dd, J = 7.85, 7.44 Hz, 1H), 5.33 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.2, 140.7, 139.6, 138.7, 134.6, 132.6, 132.2, 132.1, 130.9, 129.4, 128.9, 128.6, 128.3, 128.2, 127.8, 127.3, 127.1, 127.0, 125.5, 125.2, 124.1, 122.2, 121.6, 47.3, 17.6. ESI-MS: *m/z* 518 $[M+H]^+$.

4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-(p-tolyl)-1H-1,2,3-triazole (7i): White solid. Yield: 79 %. m.p.: 145 – 147 ºC. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.03 (d, J = 8.00 Hz, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.90 (d, J = 8.43 Hz, 1H), 7.82 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 8.00, 7.06 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (d, J = 7.85 Hz, 2H), 7.39 (t, J = 7.85 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 7.32 (d, J = 8.60 Hz, 2H), 7.15 (d, J = 9.05 Hz, 1H), 5.33 (s, 2H), 2.36 (s, 3H) 13C NMR (125 MHz, *DMSO-d6*) δ 150.3, 145.2, 140.7, 138.7, 138.5, 135.2, 132.6, 132.2, 132.1, 130.9, 129.4, 128.9, 128.6, 128.2, 127.8, 127.3, 127.1, 125.5, 125.2, 123.6, 122.2, 121.6, 47.3, 21.4. ESI-MS: *m/z* 518 $[M+H]^+$.

1-(3-(4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one (7g): White solid. Yield: 70 %. m.p.: 167 – 169 ºC. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.50 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.90 (s, 1H), 7.73 (d, J = 7.85 Hz, 1H), 7.70 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.54 (t, J = 7.85 Hz, 1H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.47 (d, J = 7.85 Hz, 1H), 7.45 (dd, J = 785, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (t, J = 7.85 Hz, 1H), 7.37 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 197.5, 150.1, 145.0, 140.7, 135.9, 134.7, 133.2, 132.4, 132.2, 132.1, 130.9, 129.0, 128.8, 128.7, 128.3, 128.2, 128.0, 127.9, 127.8, 127.3, 127.1, 126.4, 125.5, 125.2, 123.8, 12.7, 122.6, 121.6, 115.9, 47.7, 26.5. ESI-MS: *m/z* 546 $[M+H]^+$.

1-(4-(4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one (7k): White solid. Yield: 74 %. m.p.: 167 – 169 °C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.80 (d, J = 8.43 Hz, 2H), 7.73 (d, J = 7.85 Hz, 1H), 7.71 (d, J = 8.43 Hz, 2H), 7.69 (d, J = 7.85 Hz, 2H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (t, J = 7.85 Hz, 1H), 7.37 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 198.6, 150.1, 145.0, 140.7, 134.7, 133.4, 132.4, 132.2, 132.1, 130.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.8, 127.3, 127.1, 126.4, 125.5, 125.2, 123.6, 122.7, 121.6, 47.7, 27.2. ESI-MS: *m/z* 546 $[M+H]^+$.

4-((2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (7l): Pale yello solid. Yield: 72 %. m.p.: 162 – 164°C. ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.37 (d, J = 9.20 Hz, 1H), 8.37 (d, J = 10.00 Hz, 1H), 8.02 (d, J = 7.85 Hz, 1H), 7.99 (d, J = 8.00 Hz, 1H), 7.93 (d, J = 8.43 Hz, 1H), 7.43 (d, J = 7.85 Hz, 1H), 7.69 (d, J = 7.85 Hz, 2H), 7.67 (d, J = 9.20 Hz, 1H), 7.67 (d, J = 10.00 Hz, 1H), 7.47 (dd, J = 8.43, 7.06 Hz, 1H), 7.45 (dd, J = 7.85 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.42 (dd, J = 8.00, 7.06 Hz, 1H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (t, J = 7.85 Hz, 1H), 7.37 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (125 MHz, *DMSO-d6*) δ 150.1, 145.4, 145.0, 140.7, 135.3, 134.7, 132.4, 132.2, 132.1, 130.9, 128.8, 128.7, 128.3, 128.2, 128.0, 127.9, 127.8, 127.3, 127.1, 126.4, 125.5, 125.2, 124.1, 123.3, 121.6, 47.7. ESI-MS: *m/z* 549 $[M+H]^+$.

MTT Assay

The Human breast adenocarcinoma cell lines MDA-MB-231 (triple negative) were procured from the National Centre for Cell Sciences (NCCS), Pune India, and were sub-cultured in-house at Maratha Mandal's Central Research Laboratory, Belgaum, India. The cells were seeded in a 96-well flat-bottom microplate and maintained at 37ºC in 95% humidity and 5% CO_2 overnight. Different concentration (100, 50, 25, 12.5, 6.25, 3.125 µM) of samples were treated. The cells were incubated for another 48 hours. The wells were washed twice with PBS and 20 µL of the MTT staining solution was added to each well, and the plate was incubated at 37°C. After 4h, 100 µL of DMSO was added to each well to dissolve the formazan crystals, and absorbance was recorded with a 570 nm using microplate reader. All the experiments were carried out in triplicate[43].

$$\text{Surviving cells (\%)} = \frac{\text{Mean OD of test compound}}{\text{Mean OD of Negative control}}\, x\, 100$$

Molecular Docking Protocol

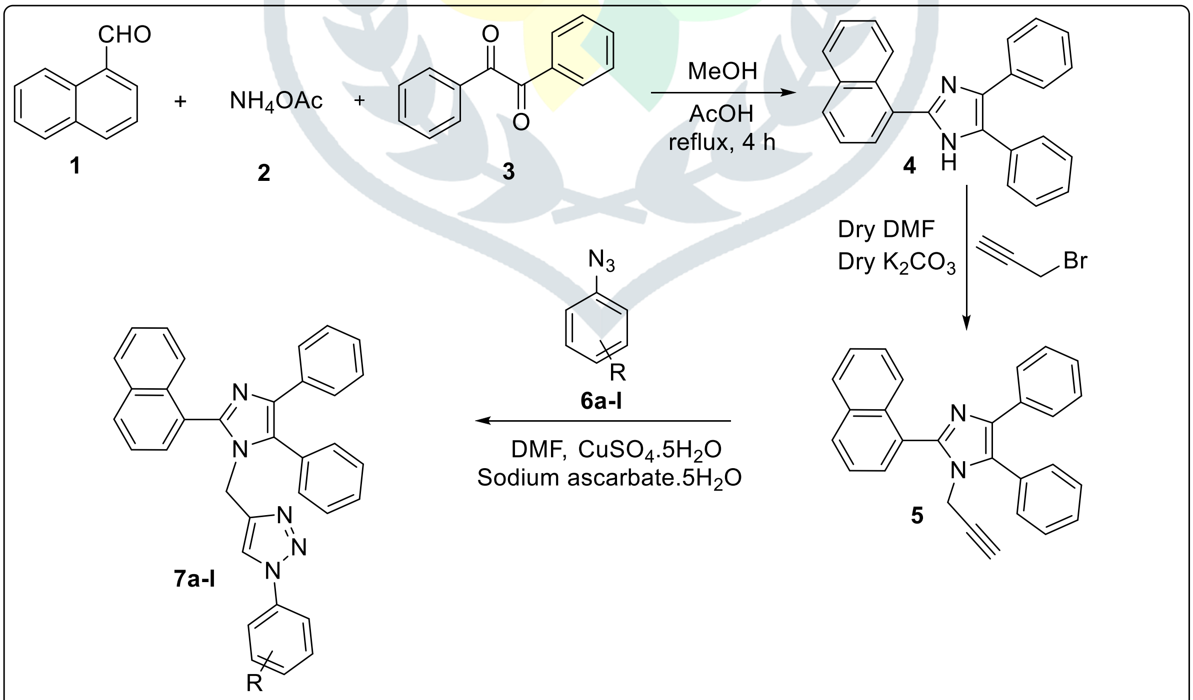
Autodock Vina integrated PyRx tool was employed for docking simulations[44]. The crystal structure of Epidermal Growth Factor Receptor (EGFR) (PDB ID: 2J6M) was retrieved from Protein Data Bank (www.rcsb.org). Initially, water molecules and heteroatoms of protein were removed and added polar hydrogens. The ligands were sketched using ChemDraw Professional 16.0 in MDL file format. Minimized the energies of all ligands after loading into PyRx and converted to PDBQT file format. The 3D grid box was configured with dimensions of center_x = -54.3301870193, center_y = -1.2835053849, center_z = -

23.6434711185, size_x = 19.7790909323, size_y = 16.8231182695 and size_z = 14.9566869842, docking simulations were performed after assigning the exhaustiveness value of 8. The docking result were visualized using Pymol and Biovia Discovery Studio Visualizer.

Result and Discussion

Chemistry

The synthetic protocol for the synthesis of 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole analogues **7a-l** presented in the **Scheme 1**. Initially, multicomponent reaction between the precursors *viz.* 1-napthaldehye **1**, ammonium acetate **2** and benzil **3** in methanol produced the 2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazole **4.** Propargylation of imidazole nitrogen of intermediate compound **4** with propargyl bromide in presence of dry K_2CO_3 obtained the 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole **5**. The terminal alkyne of compound **5** was allowed to react with various substituted aryl azides **6a-l** individually via copper catalysed – click chemistry reaction to obtain 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole analogues **7a-l**. The structure of the title compounds was analysed by interpretation of ^{1}H NMR, ^{13}C NMR and Mass spectral data. For instance, compound **7a**, the triazole proton appeared as singlet at δ 8.49, the methylene protons planked between imidazole and triazole ring appeared as singlet at δ 5.35, and all aromatic protons appeared in the range between δ 7.98 – 7.33 in ^{1}H NMR spectrum. The methylene carbon signal was observed at δ 47.3, whereas all aromatic carbon signals appeared in the range δ 150.3 – 121.6 in ^{13}C spectrum. The structure for **7a** was further confirmed from mass spectrum by showing the protonated molecular ion peak at m/z 503.



R = **7a**: H; **7b**: 4-Br; **7c**: 2-Cl; **7d**: 4-Cl; **7e**: 4-OH; **7f**: 2-OMe; **7g**: 4-OMe; **7h**: 2-Me; **7i**: 4-Me; **7j**: 3-acetyl; **7k**: 4-acetyl; **7l**: 4-NO_2

Scheme 1. Synthesis of 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole analogues (**7a-l**).

Cytotoxicity

All the novel synthesized imidazole – 1,2,3 triazole hybrids **7a-l** 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 IC_{50} value of compounds **7a-l** are presented in **Table 1.** The 4-chloro substituted compound **7d** 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 2-chloro substituted compound **7c** showed good activity in comparison with reference compound with IC_{50} value of 23.56±0.09 µM. The activity of all other compounds was good moderated with IC_{50} value ranging between 37.65 – 66.03 µM. The presence of chlorine function on compound 7c and 7d presented good activity, it may be attributed their electron withdrawing nature and ability to form H-bond interaction with biological targets. Replacement of chlorine with various other substituents like bromo, methyl, methoxy, acetyl and nitro groups diminished their activity.

Table 1. IC_{50} values of compounds **7a-l** against MDA-MB-231 cell line.

Entry	IC_{50} value (µM)	Standard Deviation (±)
7a	44.10	0.10
7b	45.60	0.13
7c	23.56	0.09
7d	17.20	0.09
7e	64.59	0.03
7f	56.80	0.02
7g	66.03	0.08
7h	61.38	0.03
7i	82.69	0.18
7j	55.03	0.02
7k	37.65	0.05
7l	64.59	0.20
Doxorubicin	18.81	0.03

Molecular Docking against EGFR

To understand the binding interactions, the best active ligand **7d** was docked into the active site pockets of the Epidermal Growth Factor Receptor (EGFR) (PDB ID: 2J6M) [45]. EGFR plays an important role by inducting tyrosine phosphorylation and receptor dimerization with other family members leading to enhanced uncontrolled proliferation[46], and could be a suitable target for Insilco screening. The docking results were validated by re-docking the co-crystallized ligand AEE788 into EGFR cavity. The AEE788 presented RMSD values of 1.07 Å and indicated the binding affinity value of -9.1 kcal/mol against EGFR.

Whereas, the compound **7d** scored best binding energy affinity than AEE788 with value of -9.9 kcal/mol. The **7d**, displayed an H-bond interaction with amino acid site Asp855 of EGFR, the bond distance is 2.73 Å. And hydrophobic interactions were observed with amino acid sites viz. Leu718, Val726, Ala743, Lys745, Met766, Leu777, Leu788, Arg841 and Leu844 of EGFR. The co-crystallized ligand AEE788, showed H-bond interactions with Gln791 and Thr854, and hydrophobic interactions with Leu718, Val726, Ala743, Lys745, Leu788, Thr790, Met793, Cys797 and Leu844 of EGFR (**Fig 2 & 3**). The binding affinity value of **7d** is greater than AEE788, and the hydrophobic interactions are comparable to reference ligand, it is proven to be best fit into the cavity of EGFR.

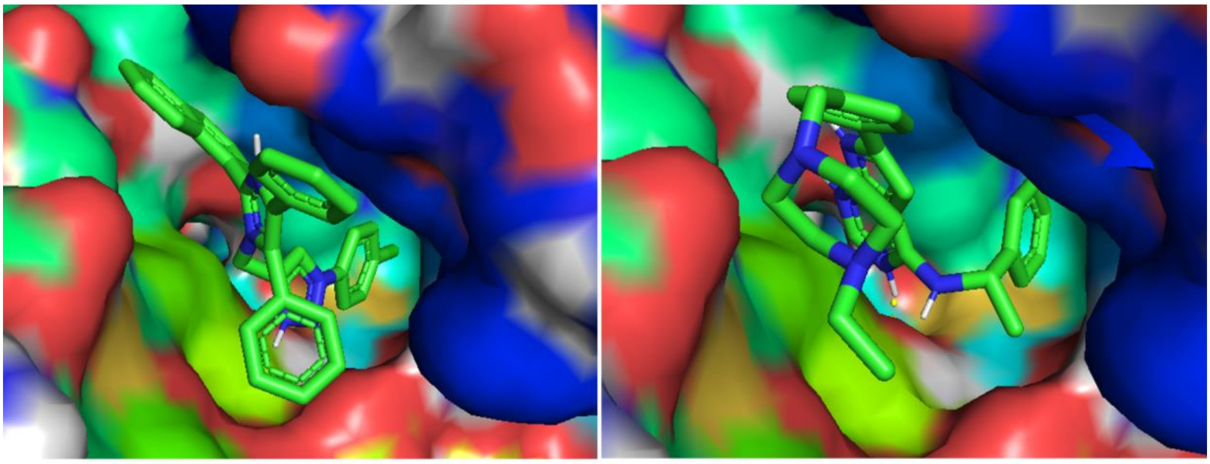


Fig 2. Docking pose of compound **7d** and AEE788

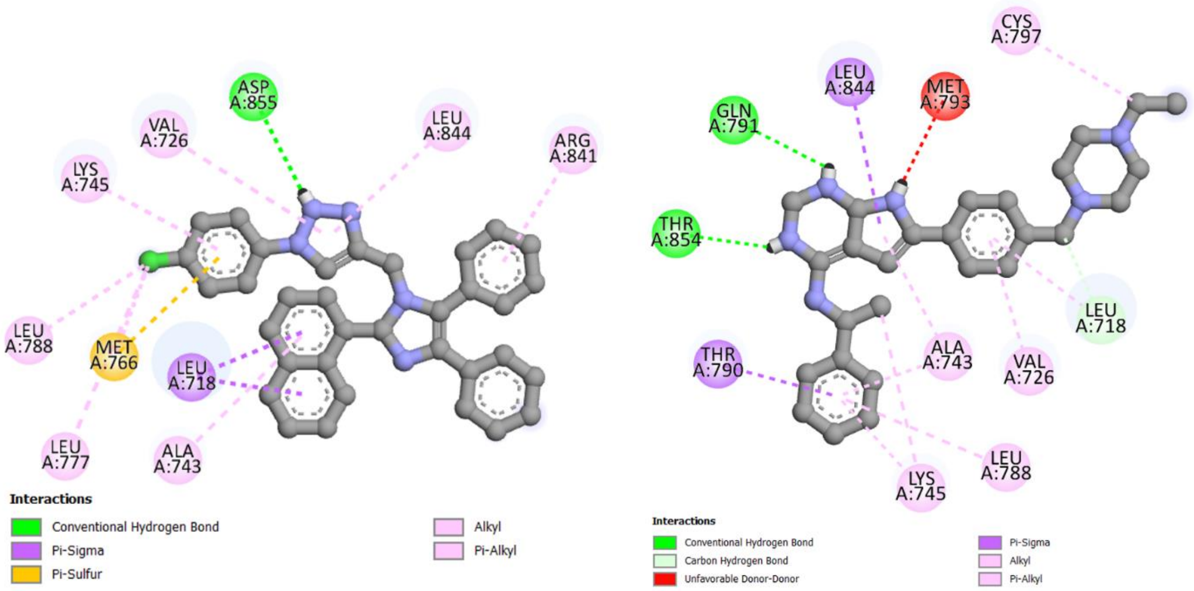


Fig 3. Binding interactions of compound 7d and AEE788

Conclusion

In conclusion, synthesized new 1,2,3-triazole tethered imidazoles by involving a multicomponent and click chemistry reactions. The structures were characterized by interpretation of ^{1}H NMR, ^{13}C NMR and Mass spectral data. The novel hybrids were screened for their cytotoxicity against human breast adenocarcinoma MDA-MB-231 cell line by employing *Doxorubicin* as standard drug. The compounds **7c** and **7d** demonstrated notable activity with IC_{50} value of 17.20±0.09 µM and 23.56±0.09 µM in comparison to reference drug IC_{50}

value of 18.81±0.03 µM. Molecular docking study of best active compound 7d displayed considerable docking score value of -9.9 kcal and binding interactions against EGFR. Hence, these novel 2-(naphthalen-1-yl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazole analogues (**7a-l**) could be the lead molecules in the process of drug discovery and can be investigated for the development of novel chemotherapeutic agents.

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