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Synthesis of New (±)-1-(4-(3-fluorobenzyloxy)pyrrolidin-3-yl)-4-phenyl-1*H*-1,2,3-triazole Derivatives via Click Reaction and Study of Anti-cancer Activity against HCT 116, MDA-MB231, Mia-PaCa2 Cell Lines

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A SERIES of 16 new (±) -1-(4-(3-fluorobenzyloxy) pyrrolidin-3-yl)-4-phenyl-1*H*-1,2,3-triazole derivatives were synthesized from 2,5-dihydro-1*H*-pyrrole. Sixteen compounds are well characterized by their ^{1}H NMR, ^{13}C NMR and mass spectral data. Anticancer activities of these compounds were tested against HCT 116, MDA-MB231, Mia-PaCa2 cancer cell lines. Among these series of compounds, **8b** exhibited highest activity with IC_{50} of 42.5 µg/ mL against MDA-MB231 cell line. The compound **8o** and **8n** showed moderate activity with IC_{50} of 64.3 µg/ mL and 68.4 µg/ mL against HCT -116 and Mia-PaCa2 cancer cell lines respectively.

Keywords: **1**,2,3-Triazole, Anticancer, MDA-MB231, HCT 116, Mia-PaCa2.

Introduction

Mortality rate of cancer patients across the world was increased to alarming levels. Cancer was the second leading disease. 9.6 million People death was reported in 2018. Around the world, about 1 in 6 deaths due to cancer [1]. So the world was looking for potent anticancer compound. Pyrrolidine group was an important pharmachore in many natural and synthetic drugs for tremendous biological activities [2]. It has vast application in the medicinal chemistry like antimicrobial [3, 4], antiviral [5], anti convulsant [6], and anti-cancer activity [7]. These derivatives have been reported for a potent and selective MC4R agonist [8] so it gives treatment for obesity. Pyrrolidine derivatives are widely synthesizing in the laboratories to find out a solution for influenza virus [9]. These derivatives are useful for the progesterone receptor agonist [10] and for the treatment of isochoric stroke Na+ channel blockers [11].

1,2,3-Triazole are five membered heterocyclic compounds having three nitrogen atoms. These nitrogen atoms can easily form a favorable hydrogen bonding leading to easy solubility with biomolecular targets [12]. This type of triazole derivatives shows broad spectrum of application in biology, such as antibacterial [13], anti tuberacular [14], anti-allergic [15], antifungal [16, 17], anti-HIV [18], anti-cancer [19, 20], anti-inflammatory [21], a-glycoside inhibitor activity [22] tazobactum, β-lactum antibiotics. Carboxyamidotriazole (CAI) anti-cancer compound cefatrizine is the present drugs in the market that possess 1,2,3, triazole moiety[23]. In the recent years much research on 1,2,3,-triazole derivatives have been syntheized and found as potent antitubarculosis[24] in the evaluation of clinical trials. These triazole based heterocyclic compounds posses good anticancer potential targets in multiple types of tumors [19]. 1, 2,

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3-triazole frame work have been reported potent activity against human gastric cancer MAC-803 and human breast cancer MCF-7 Cell line [20].

During my previous work we had synthesized the 2-aryl-2, 3-dihydroquinizolin-4(1*H*)-ones derivatives [25], 2-Aryl and 2- Pyrazole-2,3-dihydroquinoline-4(1*H*)-ones derivatives [26], 2,5-disubstituted pyrimidine derivatives [27], Dihydropyrimidinone Derivatives [28] and evaluated the anticancer activities. Recently we had synthesized the phthalazine and 1,2,4-triazole units and evaluated their anti cancer properties against HCT 116 cell line [29]. So, in the present study, we considered to synthesize new derivatives in combination with pyrrolidine with 1,2,3-triazole pharmachore group and evaluated anti-cancer against HCT 116, MDA-MB231, Mia-PaCa2 cell lines.

Experimental

The reaction progress was monitored by TLC Merk silica gel plates. The novel compounds which synthesized were characterized by their ^{1}H NMR, ^{13}C NMR (400MHz) with TMS as the internal standard and mass spectrometer ESI Ms (M+H).

Preparation of *tert-butyl 2H-pyrrole-1(5H)-carboxylate* (**2**): 2,5-dihydro-1*H*-pyrrole (10 g, 144 mmol) was taken in dry THF (500 mL) at 0 °C in an ice bath. Di-*tert*-butyl dicarbonate (31.32 g, 144 mmol) was added drop wise to the reaction mixture, later the reaction mixture was stirred at room temperature for 2 hours. The completion of reaction was monitored by TLC. Saturated aqueous sodium bicarbonate (200 mL) was added to the reaction mixture. The reaction mixture was partitioned between water (2 x 500 mL) and DCM (2 x 250 mL). The DCM layer was separated, dried with Na_2SO_4 and concentrated under vacuum, the obtained semi solid compound forwarded to the next step.

Preparation of *tert-butyl 6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylate* (**3**): The crude compound (13 g, 76 mmol) obtained in step1 was reacted with mCPBA (15.7 g, 91 mmol) at room temperature in DCM (500 mL) solvent. The reaction mixture was stirred for 12 hours. The reaction completion was monitored with TLC. The reaction mixture was quenched with 1N aqueous NaOH solution (200 mL) and the aqueous layer was extracted with DCM (1 x 250 mL). The combined organic layer washed with brine solution and was dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material was forwarded to the next step.

Preparation of (±)-*tert-butyl 3-azido-4-hydroxy-pyrrolidine-1-carboxylate* (**4**): The crude compound (12 g, 64.86 mmol) was dissolved in 1, 4 dioxane (200 mL) and water (100 mL). NaN_3 (10.5 g, 162 mmol) was added to the reaction mixture at room temperature for 1 hour and reaction was stirred at 100 °C temperature for 24 hours. The reaction completion was monitored with TLC. After completion of reaction, water was added at 0 °C and extracted with ethyl acetate (2 x 500 mL) organic layer was washed with brine solution (1 x 100 mL) and was dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material was purified by column chromatography. The compound **4** was obtained as brown solid (6 g) Yield 18.18 %. Mp: 271.2 - 272.8 °C, TLC Rf. 0.51 (10% ethyl acetate in hexane as the eluent). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (s, 1H, CHO), 3.941 (s, 1H, CHN_3), 3.431-3.703 (m, 2H, CH_2N), 3.323 – 3.394 (m, 2H, CH_2N), 1.462 (s, 9H, $OC(CH_3)_3$). ESI MS (M+H) *m/z*: 129.1 (M-BOC). Anal.calcd. For $C_9H_{16}N_4O_3$ (228.12) Mol. C, 47.36; H, 7.07; N, 24.55. Found: C, 47.42; H, 7.12; N, 24.61.

Preparation of (±)-*tert-butyl 3-(3-fluorobenzyloxy)-4-azidopyrrolidine-1-carboxylate* (**5**): To a solution of compound **4** (6 g, 26.3 mmol) in THF (150 mL), sodium hydride (1.2 g, 52 mmol) was added at 0 °C and the reaction mixture was stirred at the same temperature for 30 minutes. The reaction mixture was slowly allowed to room temperature for 1 hour. A thick suspension formation was observed, it was disappeared by the addition of 3-fluoro benzyl bromide (4.9 g, 26.3 mmol). The reaction was stirred at 30 – 35 °C and was allowed to stir at ambient temperature for 16 hours. Reaction completion was observed by TLC and the reaction mixture was cooled to 0 °C and quenched with ice and extracted with ethyl acetate (1 x 250 mL) combined organic layer was dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material was purified by column chromatography. Compound **5** (5 g, Yield 56.8 %) was obtained as a brown solid. Mp: 231.4 - 232.8 °C, TLC Rf. 0.75 (10% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.35 (m, 1H, ArH), 6.98 – 7.09 (m, 3H, ArH), 4.43 – 4.58 (m, 2H, CH_2O), 4.01-4.04 (m, 1H, O-CH), 3.95 (s, 1H, CHN_3), 3.53 – 3.71 (m, 2H, CH_2N), 3.37 – 3.50 (m, 2H, CH_2N),

1.464 (s, 9H, $OC(CH_3)_3$). ESI MS (M+H) m/z: 237.0 (M-BOC). Anal.calcd. For $C_{16}H_{21}FN_4O_3$ (336.16), C, 57.13; H, 6.29; N, 16.66; Found: C, 57.18; H, 6.32; N, 16.69.

Preparation of *(±)-tert-butyl 3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl) pyrrolidine-1-carboxylate* (**6**)**:** A solution of compound **5** (5 g, 4.88 mmol) in *tert*-butanol (100 mL), phenyl acetylene (1.57 g, 14.88 mmol), sodium ascorbate (2.94 g, 14.88 mmol), $CuSO_4$ (0.23 g, 1.48 mmol) were added. The solution was stirred at room temperature for 4 hours, and the reaction completion was observed by TLC. Reaction mixture was diluted with water (1 x 500 mL) extracted with ethyl acetate (2 x 250 mL). The organic layer was dried over Na_2SO_4. The ethyl acetate layer was concentrated under reduced pressure. The obtained crude material was purified by column chromatography. The compound **6** (2.8 g, Yield 43.07 %) was obtained as white solid.Mp: 243.2 - 244.8 °C, TLC Rf. 0.45 (20% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.82 (d, *J* = 7.2 Hz, 2H, ArH), 7.73 (s, 1H, ArH), 7.33- 7.45 (m, 2H, ArH), 7.26 – 7.30 (m, 2H, ArH), 6.96 – 7.02 (m, 3H, ArH), 5.09 (s, 1H, O-CH), 4.53 – 4.60 (m, 2H, CH_2O), 4.43 (s, 1H, CHN), 4.04 – 4.14 (m, 1H, CH_2N), 3.84 – 3.98 (m, 2H, CH_2N), 3.48 – 3.58 (m, 1H, CH_2N), 1.48 (s, 9H, $OC(CH_3)_3$). ESI MS (M+H) m/z: 439.1. Anal.calcd. For $C_{24}H_{27}FN_4O_3$ (438.21), C, 65.74; H, 6.21; N, 12.78; Found: C, 65.78; H, 6.25; N, 12.80.

(±)-*1-(4-(3-fluorobenzyloxy) pyrrolidin-3-yl)-4-phenyl-1H-1,2,3-triazole*(**7**): Compound **6** (2.8 g, 6.38 mmol) was dissolved in dioxane (50 mL). HCl in dioxane (10 mL) was added at room temperature for 2 hours. Reaction completion was confirmed by TLC. The reaction mass was concentrated under reduced pressure, resulted brown solid was washed with MTBE, which gave the compound **7** as brown solid (1.68 g), yield 77.77 %.

Mp: 248.3 - 249.1 °C, TLC Rf. 0.35 (50% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 3H, ArH), 7.45 - 7.41 (m, 2H, ArH), 7.36 – 7.28 (m, 2H, ArH), 7.06 – 7.03 (m, 2H, ArH), 6.98 – 6.93 (m, 1H, ArH), 5.01 – 4.99 (m, 1H, O-CH), 4.60 – 4.59 (m, 2H, CH_2O), 4.39 – 4.37 (m, 1H, CHN), 3.62 – 3.60 (m, 1H, CH_2N), 3.59 – 3.50 (m, 1H, CH_2N), 3.49 – 3.32 (m, 1H, CH_2N), 3.14 – 3.10 (m, 1H, CH_2N). ESI MS (M+H) m/z: 339.0. Anal.calcd. For $C_{19}H_{19}FN_4O$ (338.21), C, 67.44; H, 5.66; N, 16.56; Found: C, 67.48; H, 5.69; N, 16.59.

General procedure for preparation of compounds (8a-8o): The compound (±)-**7** (100 mg, 0.295 mmol) was dissolved in DCM (5mL). Triethyl amine (0.354 mmol) was added to the reaction mixture at 0 °C. Appropriate acid chloride (0.295 mmol) was added to the reaction mixture and stirred for 30 minutes. Reaction mixture completion was confirmed by the TLC. After completion of reaction, the reaction mixture was quenched with $NaHCO_3$ solution (10 mL). The organic compound was extracted with DCM (20 mL) and DCM layer was washed with water (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by the silica gel chromatography to give **8a-8o** compounds were obtained. Yields, ^{1}H NMR, ESI MS (M+H) data of each compound was given below.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(2-chlorophenyl)methanone* **(8a):** White solid, yield 70.95%; Mp: 240.3 - 241.1 °C, TLC Rf. 0.30 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.86 - 7.76 (m, 3H, ArH), 7.47 – 7.28 (m, 8H, ArH), 7.08 – 6.96 (m, 3H, ArH), 5.23 – 5.12 (m, 1H, O-CH), 4.70 – 4.62 (m, 3H, CH_2O, CHN), 4.59 – 4.34 (m, 1H, CH_2N), 4.19 – 4.01 (m, 1H, CH_2N), 3.99 – 3.84 (m, 1H, CH_2N), 3.72 – 3.46 (m, 1H, CH_2N). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.33, 167.10, (C=O), 163.93, 163.89, 161.96, 161.93, 148.23, 148.09, 139.35, 139.31, 139.26, 135.97, 135.81, 131.79, 130.88, 130.83, 130.32, 130.28, 130.26, 130.21, 129.99, 129.93, 129.88, 128.98, 128.55, 128.53, 127.84, 127.77, 127.53, 125.75, 123.16, 123.14, 123.10, 123.08, 118.89, 115.29, 115.23, 115.12, 115.07, 114.62, 114.54, 114.45, 114.37, (Ar-C) 81.61, 80.39, (CH_2O), 71.49, 71.40, (O-CH), 63.56, 62.52, 51.35, 50.46, 49.26, 48.76, (CHN), ESI MS (M+H) *m/z*: 477.1, 478.1 Anal.calcd. For $C_{26}H_{22}ClFN_4O_2$ (476.14), C, 65.48; H, 4.65; N, 11.75; Found: C, 65.50; H, 4.69; N, 11.78.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(2-fluorophenyl)methanone* (**8b**): Brown solid, yield 58.79 %; TLC Rf. 0.35 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 –7.72 (m, 3H, ArH), 7.50 – 7.23 (m, 6H, ArH), 7.13 –7.12 (m, 1H, ArH), 7.08 – 6.97 (m, 4H, ArH), 5.25 – 5.24 (m, 1H, O-CH), 4.66 – 4.48 (m, 3H, CH_2O, CHN), 4.35 – 4.33 (m, 1H, CH_2N), 4.13 – 4.09 (m, 1H, CH_2N), 3.99 – 3.91 (m, 1H, CH_2N),

3.90 – 3.50 (m, 1H, CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.52, 167.25, (C=O), 163.99, 163.92, 161.96, 161.90, 148.33, 148.19, 139.55, 139.51, 139.44, 135.97, 131.89, 130.86, 130.44, 130.35, 130.28, 130.25, 129.90, 129.80, 128.91, 128.59, 128.43, 127.80, 127.70, 127.59, 125.79, 123.10, 123.09, 123.01, 123.14, 123.09, 118.92, 115.32, 115.28, 115.14, 114.69, 114.62, 114.54, 114.42, (Ar-C), 81.68, 80.55, (CH_2O), 71.55, 71.50, (O-CH), 63.59, 62.58, 51.39, 50.55, 49.38, 48.89, (CHN),; ESI MS (M+H) *m/z*: 461.0. Anal.calcd. For $C_{26}H_{22}F_2N_4O_2$ (460.17) C, 67.82; H, 4.82; N, 12.17; Found: C, 67.88; H, 4.89; N, 12.19.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(o-tolyl)methanone* (**8c**): White solid, yield 88.95 %; TLC Rf. 0.60 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 2H, ArH),7.79 – 7.68 (m, 1H, ArH), 7.47 – 7.41 (m, 2H, ArH), 7.38 – 7.36 (m, 1H, ArH),7.35 – 7.30 (m, 2H, ArH), 7.29 –7.21 (m, 3H, ArH), 7.08 – 6.97 (m, 3H, ArH), 5.19 – 5.01 (m, 1H, O-CH), 4.70 - 4.51 (m, 3H, CH_2O, CHN), 4.36 – 4.35 (m, 1H, CH_2N), 4.24 – 4.15 (m, 1H, CH_2N), 3.93 – 3.80 (m, 1H, CH_2N), 3.67 – 3.42 (m, 1H, CH_2N), 2.34 – 2.33 (m, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.55, 169.35, 163.88, 163.80, 161.90, 161.88, 148.20, 148.01, 139.55, 139.44, 139.28, 135.99, 135.78, 131.88, 130.98, 130.90, 130.38, 130.29, 130.22, 130.15, 129.88, 129.85, 129.78, 128.95, 128.59, 128.50, 127.90, 127.75, 127.56, 125.88, 123.42, 123.25, 123.18, 123.10, 118.95, 115.33, 115.30, 115.18, 115.05, 114.92, 114.85, 114.80, 114.35, (Ar-C), 81.69, 80.45, (CH_2O), 71.55, 71.51, (O-CH), 63.59, 62.59, 51.85, 50.90, 49.29, 48.79, (CHN), 21.20, 21.28, (CH_3); ESI MS (M+H) *m/z*: 457.1 Anal.calcd. For $C_{27}H_{25}FN_4O_2$ (456.2) C, 71.04; H, 5.52; N, 12.27; Found: C, 71.08; H, 5.55; N, 12.29.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(naphthalen-2-yl)methanone* (**8d):** White solid, yield 54.96 %; TLC Rf. 0.70 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.93 (m, 5H, ArH), 7.76 – 7.74 (m, 2H, ArH), 7.62 – 7.50 (m, 4H, ArH), 7.48 – 7.40 (m, 1H, ArH), 7.39 – 7.36 (m, 1H, ArH), 7.35 – 7.33 (m, 1H, ArH), 7.11 – 6.94 (m, 3H, ArH), 5.25 – 5.01 (m, 1H, O-CH), 4.73 – 4.61 (m, 1H, CH_2N), 4.50 – 4.47 (m, 3H, CH_2O, CHN), 4.35 – 4.10 (m, 1H, CH_2N), 3.95 – 3.68 (m, 1H, CH_2N), 3.65 – 3.41 (m, 1H, CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.01, 169.71, (C=O), 164.09, 164.02, 148.13, 139.36, 139.28, 139.22, 134.18, 134.02, 133.58, 130.34, 130.27, 130.22, 130.16, 130.02,129.91, 129.86, 129.09, 128.99, 128.93, 128.60, 128.57, 128.55, 127.50, 127.44, 126.63, 125.81, 125.75, 125.20, 124.64, 124.48, 124.33, 124.23, 123.16, 123.14, 122.98, 119.14, 118.90, 115.30, 115.19, 115.14, 115.02, 114.63, 114.46, 114.29, (Ar-C),81.58, 80.53, (CH_2O), 71.45, 71.26, (O-CH), 63.59, 62.77, 52.05, 51.26, 49.50, 49.05, (CHN). ESI MS (M+H) *m/z*: 493.1. Anal.calcd. For $C_{30}H_{25}FN_4O_2$ (492.2) C, 73.16; H, 5.12; N, 11.37; Found: C, 73.18; H, 5.16; N, 11.39.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(thiophen-2-yl)methanone* (**8e**): White solid, yield 90.53 %; TLC Rf. 0.45 (30% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.90 (m, 3H, ArH), 7.53 – 7.59 (m, 2H, ArH), 7.302 -7.37 (m, 2H, ArH), 7.28 – 7.29 (m, 2H, ArH), 7.09 -7.13 (m, 1H, ArH), 6.97 – 7.07 (m, 3H, ArH), 5.18 (s, 1H, O-CH), 4.64 (m, 3H, CH_2O, CHN), 4.39 (s, 2H, CH_2N), 4.18 – 4.23 (m, 1H, CH_2N), 3.90 – 3.99 (m. 1H, CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.08,169.12, 163.91, 162.40, 161.95, 148.22,139.35, 139.29, 137.78, 130.60, 130.36, 130.32, 130.25, 130.00, 128.94, 128.54, 127.44, 125.80, 123.15, 118.93, 115.29, 115.12, 114.62, 114.45, (Ar-C), 81.22, 81.34, (CH_2O), 80.50, 80.55, (O-CH),64.58, 64.72, 52.88, 52.92, 53.91, 53.94, (CHN). ESI MS (M+H) *m/z*: 449.2 Anal.calcd. For $C_{24}H_{21}FN_4O_2S$ (448.14). C, 64.27; H, 4.72; N, 12.49; Found: C, 64.29; H, 4.78; N, 12.52.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(3-cyanophenyl)methanone* (**8f**): Brown solid, yield 65.14 %; TLC Rf. 0.65 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.82 (m, 6H, ArH), 7.54 – 7.69 (m, 1H, ArH), 7.43 – 7.45 (m, 2H, ArH), 7.28 – 7.38 (m, 2H, ArH), 7.00 – 7.08 (m, 3H, ArH), 5.01 – 5.12 (m, 1H, O-CH), 4.56 – 4.70 (m, 3H, CH_2O, CHN), 4.38 - 4.40 (m, 1H, CH_2N), 4.00 – 4.36 (m, 2H, CH_2N), 3.60 – 3.99 (m, 1H, CH_2N).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.24, 169.12, (C=O), 164.04, 164.01, 148.22, 148.18, 139.21, 139.20, 139.15, 136.92, 136.85, 134.02, 133.93, 131.68, 131.65, 131.09, 131.00, 130.42, 130.39, 130.34, 129.64, 129.59, 128.99, 128.90, 128.72, 128.64, 125.84, 125.78, 123.20, 123.06, 119.39, 119.33, 117.88, 117.86, 115.42, 115.39, 115.28, 115.23, 114.58, 114.22, 114.20, (Ar-C),112.98, 112.90, 81.73, 80.21, (CH_2O), 71.62, 71.58, (O-CH), 63.78, 62.33, 53.23, 51.70,

49.98, 49.82, (CHN). ESI MS (M+H) *m/z*: 468.2 Anal.calcd. For $C_{27}H_{22}FN_5O_2$ (467.18) C, 69.37; H, 4.74; N, 14.98; Found: C, 69.39; H, 4.78; N, 14.99.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(4-fluorophenyl)methanone* (**8g**): White solid, yield 74.95 %; TLC Rf. 0.35 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.88 (m, 3H, ArH), 7.57 – 7.67 (m, 2H, ArH), 7.44 -7.55 (m, 2H, ArH), 7.42 -7.29 (m, 2H, ArH), 7.155 – 7.13 (m, 2H, ArH), 7.11 -6.99 (m, 3H, ArH), 5.13 -4.99 (m, 1H, O-CH), 4.66 – 4.30 (m, 3H, CH_2O, CHN), 4.18 -3.92 (m, 2H, CH_2N), 3.89 – 3.64 (m, 2H, CH_2N).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.22, 168.02, (C=O), 165.02, 164.93, 162.99, 162.93, 149.09, 149.02, 139.31, 139.25, 137.28, 137.22, 134.74, 134.24, 131.89, 131.84, 130.48, 130.42, 130.32, 130.26, 129.79, 129.75, 129.01, 128.97, 128.62, 128.58, 125.82, 125.78,123.12, 123.04, 119.06, 115.77, 115.60, 115.31, 115.15, 114.58, 114.54, 114.28, 114.25, (Ar-C), 82.02, 81.71, (CH_2O), 71.62, 71.50, (O-CH), 63.25, 62.63, 53.86, 53.24, 49.96, 49.56, (CHN). ESI MS (M+H) *m/z*: 461.1, Anal.calcd. For $C_{26}H_{22}F_2N_4O_2$ (460.17) C, 67.82; H, 4.82; N, 12.17; Found: C, 67.87; H, 4.88; N, 12.18.

(±)-*1-(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)-2-(4-fluorophenyl)ethanone* (**8h**): White solid, yield 78.44 %; TLC Rf. 0.35 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 2H, ArH), 7.61 – 7.45 (m, 1H, ArH), 7.43 -7.41 (m, 2H, ArH), 7.37- 7.21 (m, 5H, ArH), 7.03 – 6.98 (m, 5H, ArH), 5.08 – 5.07 (m, 1H, O-CH), 4.64 - 4.42 (m, 3H, CH_2O, CHN), 4.18 – 4.11 (m, 2H, CH_2CO), 3.92 – 3.85 (m, 2H, CH_2N), 3.67 -3.64 (m, 2H, CH_2N).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.85, 169.71, (C=O), 163.25, 163.025, 163.01, 162.93, 148.13, 148.03, 139.52, 139.44, 138.24, 138.22, 131.05, 131.10, 130.58, 130.55, 129.93, 129.80, 128.95, 128.56, 127.28, 127.24, 123.78, 123.72, 123.14, 123.10, 119.21, 119.01, 118.92, 118.88, 116.78, 116.76, 115.72, 115.69, 115.52, 115.35, 114.58, 114.55, 114.44, 114.36, (Ar-C), 80.77, 79.90, (CH_2O), 73.44, 73.32, (O-CH), 62.75, 62.88, (CH_2CO), 50.21, 49.88, 49.38, 49.14, 40.87, 40.92, (CHN)..ESI MS (M+H) *m/z*: 475.2, Anal.calcd. For $C_{27}H_{24}F_2N_4O_2$ (474.19) C, 68.34; H, 5.10; N, 11.81; Found: C, 68.38; H, 5.19; N, 11.87.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(2,6-dichlorophenyl)methanone* (**8i**): Yellow solid, yield 75.44 %; TLC Rf. 0.40 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 1H, ArH), 7.81 – 7.77 (m, 2H, ArH), 7.46 – 7.41 (m, 2H, ArH), 7.39 -7.28 (m, 5H, ArH), 7.08- 6.99 (m, 3H, ArH), 5.27 -5.26 (m, 1H, O-CH), 4.67- 4.63 (m, 2H, CH_2O), 4.62 – 4.60 (m, 1H, CHN), 4.56 – 4.36 (m, 1H, CH_2N), 4.21 – 3.72 (m, 2H, CH_2N), 3.58 – 3.43 (m, 1H, CH_2N).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.06, 170.02, (C=O), 164.19, 164.07, 148.17, 139.23, 135.17, 135.02, 131.61, 131.57, 131.45, 131.41, 131.09, 131.02, 130.32, 130.28, 130.25, 130.21, 130.00, 129.95, 128.98, 128.56, 128.53, 128.39, 128.38, 128.31, 128.23, 125.72, 125.70, 123.09, 118.53, 118.50, 115.30, 115.25, 115.13, 115.08, 114.56, 114.39, (Ar-C), 81.41, 80 .27, (CH_2O), 76.81, (O-CH), 71.40, 71.35, 63.39, 62.42, 50.50, 49.76, 49.02, 48.44 (CHN). ESI MS (M+H) *m/z*: 511.0, Anal.calcd. For $C_{26}H_{21}Cl_2FN_4O_2$ (510.1) C, 61.07; H, 4.14; N, 10.96; Found: C, 61.10; H, 4.19; N, 10.99.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(3,4-dimethoxyphenyl)methanone* (**8j**): Brown solid, yield 78.11 %; TLC Rf. 0.65 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.66 (m, 3H, ArH), 7.44 – 7.28 (m, 4H, ArH), 7.07 – 6.95 (m, 3H, ArH), 6.64 – 6.63 (m, 2H, ArH), 6.52 (s, 1H, ArH), 5.14 – 5.05 (m, 1H, O-CH), 4.68 – 4.55 (m, 3H, CH_2O, CHN), 4.36 – 4.08 (m, 2H, CH_2N), 3.97 – 3.94 (m, 1H, CH_2N), 3.88 – 3.85 (m, 6H, $O(CH_3)_2$), 3.69 -3.66 (m, 1H, CH_2N).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.12, (C=O), 164.12, 160.86, 148.04, 139.42, 139.34, 137.41, 130.28, 130.28, 130.20, 129.97, 128.94, 128.53, 125.76, 123.05, 119.24, 115.21, 115.01, 114.30, (Ar-C), 105.19, 105.06, 102.48, 81.57, 80.23, (CH_2O), 71.36, 71.38, (O-CH), 63.72, 62.54, (CHN), 55.61, 55.52, (OCH_3), 52.98, 51.86, 49.72, 49.33, (CHN). ESI MS (M+H) *m/z*: 503.2, Anal.calcd. For $C_{28}H_{27}FN_4O_4$ (502.2) C, 66.92; H, 5.42; N, 11.15; Found: C, 66.98; H, 5.49; N, 11.19.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)(3,5-dichlorophenyl)methanone* (**8k**): White solid, yield 82.05 %; TLC Rf. 0.40 (30% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.68 (m, 3H, ArH), 7.52 – 7.31 (m. 7H, ArH), 7.08 – 6.97 (m, 3H, ArH), 5.11 – 5.04 (m, 1H, O-CH), 4.69 – 4.54 (m, 3H, CH_2O, CHN), 4.38 –

4.21 (m, 1H, CH_2N), 4.18 -4.13 (m, 1H, CH_2N), 4.00 – 3.99 (m, 1H, CH_2N), 3.98 – 3.48 (m, 1H, CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.08, 168.02, (C=O), 165.08, 164.30, 146.32, 139.22, 139.17, 138.25, 135.52, 135.44, 130.63, 130.37, 130.31, 129.93, 128.99, 128.62, 126.13, 125.86, 125.78, 123.08, 119.31, 115.38, 115.22, 114.56, (Ar-C), 81.68, 80.16, (CH_2O), 71.56, 71.62, (O-CH), 62.74, 62.33, 53.13, 51.74, 49.93, 49.77, (CHN). ESI MS (M+H) *m/z*: 511.1. Anal.calcd. For $C_{26}H_{21}Cl_2FN_4O_2$ (510.1) C, 61.07; H, 4.14; N, 10.96; Found: C, 61.10; H, 4.19; N, 10.99.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl) (phenyl)-methanone* (**8l**): Pale white solid, yield 84.12 %; TLC Rf. 0.75 (30% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.66 (m, 3H, ArH), 7.55 – 7.536 (m, 2H, ArH), 7.46 – 7.42 (m, 5H, ArH), 7.38 – 7.28 (m, 2H, ArH), 7.078 – 6.95 (m, 3H, ArH), 5.15 – 5.07 (m, 1H, O-CH), 4.69 – 4.56 (m, 3H, CH_2O, CHN), 4.40 – 4.29 (m, 1H, CH_2N), 4.19 – 4.13 (m, 1H, CH_2N), 3.97 – 3.89 (m, 1H, CH_2N), 3.67 – 3.49 (m, 1H, CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13, 169.96, (C=O), 163.91, 161.95, 148.14, 148.06, 139.33, 133.93, 130.30, 130.23, 129.86, 128.89, 128.91, 128.89, 128.85, 128.56, 127.26, 127.16, 125.80, 123.13, 118.69, 115.27, 115.10, 114.58, 114.41, (Ar-C), 81.82, 79.98, (CH_2O), 71.48, 71.45, (O-CH), 63.80, 62.17, 50.54, 49.40, 49.28, 49.02, (CHN), ESI MS (M+H) *m/z*: 443.2. Anal. calcd. For $C_{26}H_{23}FN_4O_2$ (442.18) C, 70.57; H, 5.24; N, 12.66; Found: C, 70.60; H, 5.29; N, 12.69.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl) (cyclohexyl) methanone* (**8m**): Pink solid, yield 75.44 %; TLC Rf. 0.70 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 2H, ArH), 7.71 – 7.78 (m, 1H, ArH), 7.46 – 7.29 (m, 4H, ArH), 7.07- 6.99 (m, 3H, ArH), 5.19 – 5.08 (m, 1H, O-CH), 4.67 – 4.61 (m, 2H, CH_2O), 4.55 – 4.42 (m, 1H, CHN), 4.17 – 4.12 (m, 2H, CH_2N), 3.94 – 3.96 (m, 1H, CH_2N), 3.71 – 3.67 (m, 1H, CH_2N), 2.34 – 2.28 (m, 1H, CH) 1.80 – 1.68 (m, 5H, CH_2), 1.29 – 1.22 (m, 5H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.35, 175.22, (C=O), 161.97, 148.31, 148.02, 130.31, 130.24, 130.01, 128.94,128.55, 128.49, 125.78, 125.75, 123.13, 123.10, 118.85, 118.76, 115.26, 115.09, 114.62, 114.55, 114.44, 114.38, (Ar-C), 81.84, 79.79, (CH_2O), 71.55, 71.45, (O-CH), 63.92, 62.14, 50.33, 49.08, 49.00, 48.80, 42.64, 42.50, (CHN), 28.92, 28.81, 28.78, 25.69, (CH_2). ESI MS (M+H) *m/z*: 449.2. Anal.calcd. For $C_{26}H_{29}FN_4O_2$ (448.23) C, 69.62; H, 6.52; N, 12.49; Found: C, 69.67; H, 6.59; N, 12.52.

(±)-*(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl) (cyclopropyl) methanone* (**8n**): White solid, yield 79.92%; TLC Rf. 0.55 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 2H, ArH), 7.75 – 7.73 (m, 1H, ArH), 7.46 – 7.42 (m, 2H, ArH), 7.38 – 7.29 (m, 2H, ArH), 7.08 – 6.99 (m, 3H, ArH), 5.15 -5.09 (m, 1H, O-CH), 4.71 – 4.66 (m, 2H, CH_2O), 4.61 – 4.56 (m, 1H, CHN), 4.43 – 4.29 (m, 1H, CH_2N), 4.21 – 4.18 (m, 1H, CH_2N), 4.16 – 3.98 (m, 1H, CH_2N), 3.88 – 3.69 (m, 1H, CH_2N), 1.61 – 1.59 (m, 1H, CH), 1.07 – 1.04 (m, 2H, CH_2), 0.85 – 0.81 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.75, 172.62, (C=O), 161.92, 162.02, 147.96, 139.49, 130.30, 130.23, 130.00, 128.95, 128.54, 125.76, 123.13, 123.008, 118.96, 115.19, 115.03, 114.58, 114.51, 114.41, 114.34, (Ar-C), 81.68, 79.87, (CH_2O), 71.52, 71.42, (O-CH), 63.80, 62.22, (CHCO), 50.50. 49.29, 49.21. 48.99, (CHN), 12.44, 12.28, 8.13, 8.07, 7.98, 7.92, (CH_2). ESI MS (M+H) *m/z*: 407.2. Anal.calcd. For $C_{23}H_{23}FN_4O_2$ (406.18) C, 67.97; H, 5.70; N, 13.78; Found: C, 67.99; H, 5.75; N, 13.81.

(±)-*1-(3-(3-fluorobenzyloxy)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)-2-methoxyethanone* (**8o**): Brown solid, yield 72.55 %; TLC Rf. 0.55 (20% ethyl acetate in hexane as the eluent), ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 2H, ArH), 7.76 – 7.74 (m, 1H, ArH), 7.46 -7.42 (m, 2H, ArH), 7.38 -7.29 (m, 2H, ArH), 7.07 – 7.00 (m, 3H, ArH), 5.16 – 5.07 (m, 1H, O-CH), 4.66 – 4.55 (m, 2H, CH_2O), 4.46 – 4.44 (m, 1H, CHN), 4.24 - 4.23 (m, 1H, CH_2O), 4.23 - 4.22 (m, 1H, CH_2O), 4.19 – 4.10 (m, 1H, CH_2N), 4.08 – 4.07 (m, 1H, CH_2N), 3.98 – 3.93 (m, 1H, CH_2N), 3.73-3.70 (m, 1H, CH_2N), 3.44 (s, 3H, $O(CH_3)$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.43, 168.19, (C=O), 163.93, 148.24, 148.09, 139.33, 130.34, 130.31, 130.27, 130.24, 129.92, 128.95, 128.57, 128.55, 125.78, 123.16, 123.13, 123.09, 123.07, 118.94, 118.91, 115.30, 115.12,114.61, 114.55, 114.44, 114.38, (Ar-C) 81.93, 79.64, (CH_2O), 72.26, 72.03, (O-CH), 71.52, 71.44, (CH_2CO), 63.98, 61.79, 59.27, 59.22, (OCH_3) 49.73, 49.48, 49.18, 48.56. (CH_2N). ESI MS (M+H) *m/z*: 411.1. Anal. calcd. For $C_{22}H_{23}FN_4O_3$ (410.18) C, 64.38; H, 5.65; N, 13.65; Found: C, 64.40; H, 5.69; N, 13.69.

2.7.16 (±) *-1- (3-(3-fluorobenzyloxy) -4-(4-phenyl-*

1H-1,2,3-triazol-1-yl)pyrrolidin-1-yl)-2-phenylethanone (**8p**): White solid, yield 72.64 %; TLC Rf. 0.60 (20% ethyl acetate in hexane as the eluent), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.43 – 7.41(m, 2H, ArH), 7.39 – 7.25 (m, 7H, ArH), 7.04 – 6.97 (m, 3H, ArH), 5.09 – 5.08 (m, 1H, O-CH), 4.64 – 4.50 (m, 2H, CH_2O), 4.42 – 4.40 (m, 1H, CHN), 4.17 – 4.08 (m, 2H, CH_2N), 3.89 – 3.71 (m, 1H, CH_2N), 3.69 – 3.66 (m, 3H, CH_2CO, CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13, 169.96, (C=O), 163.91, 161.95, 148.14, 148.06, 139.33, 133.93, 130.30, 130.23, 129.86, 128.98, 128.91, 128.89, 128.85, 128.56, 127.26, 125.80, 123.13, 118.69, 115.27, 115.10, 114.58, 114.41, (Ar-C) 81.82, 79.98, (CH_2O), 71.45, (O-CH), 63.80,(CH_2CO), 62.17, 50.54, 49.40, 49.28, 49.02, (CH_2N). ESI MS (M+H) *m/z*: 457.1. Anal. calcd. For $C_{27}H_{25}FN_4O_2$ (456.2) C, 71.04; H, 5.52; N, 12.27; Found: C, 71.09; H, 5.56; N, 12.29.

Anticancer activity

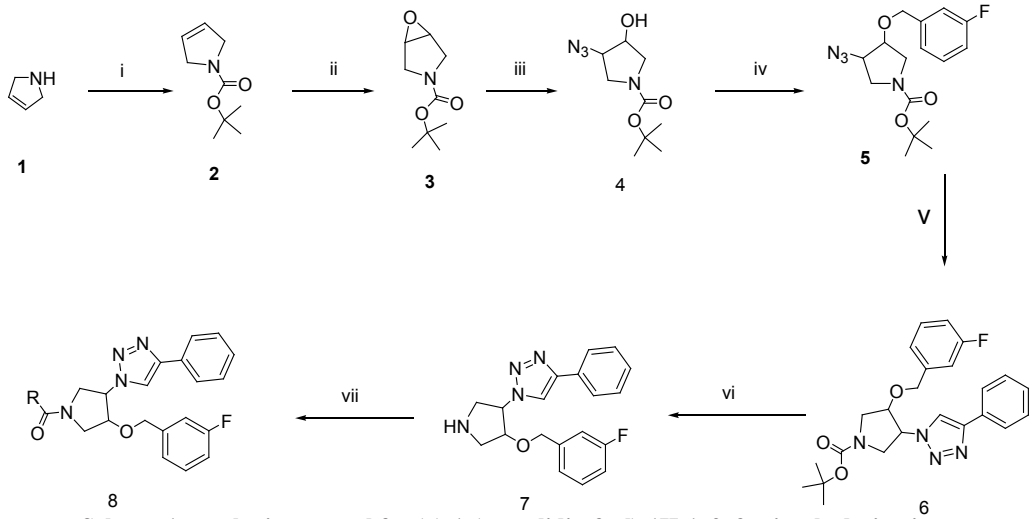
Cytotoxicity assay was performed using MTT [3-(4,5-dimethylthiazol -2yl) -2,5-diphenyltetrazolium bromide]. 10,000 cells per well were seeded in 93 well plates and treated with different concentrations (0-200 µg/ mL) of test compounds in duplicates. As controls, DMSO 0.5% (w/v) treated cells (Vehicle) were included in each experiment. Following treatments for 72 h, 10 µL of MTT (5mg/ mL) was added to each well and incubated for 3h at 37 °C in dark. Formazan crystals fromed were dissolved in 100 mL DMSO and the absorbance was measured at 570 nM using an ELISA reader.

Results and Discussion

Chemistry

The synthetic protocol for the 1-(pyrrolidin-3-yl)-1*H*-1,2,3-triazolederivatives has been shown in the **Scheme 1**. Amine group present in the 2,5-dihydro pyrrole was protected with di-*tert*-butyl dicarbonate gives the compound **2** [30] Boc protected pyrrole derivative on reaction with m-CPBA the compound **3** was obtained [30]. Compound **3** was reacted with sodiumazide in the presence of ammonium chloride, compound **4** was obtained [30]. The formed compound **4** on reaction with the sodium hydride, 3-fluoro benzyl bromide in THF solvent leads to compound **5** with moderate yield. The compound **5** on reaction with the phenyl acetylene, copper sulphate, and sodium ascorbate for 4h, the compound **6** was formed [31] in moderate yield. In the next step compound **6** reacted with the dry HCl in dioxane, the BOC group was deprotected and formed intermediate **7** in good yield. The novel triazole derivatives on reaction with appropriate acid halides in DCM in the presence of triethyl amine, compounds **8a-8o** were obtained; final step yields were mentioned in the Table 1.

Reagents and conditions: (i) Di-*tert*-butyl dicarbonate, THF, 0 °C, 2h. (ii) *m*-CPBA, DCM rt, 12h. (iii) NaN_3, Dioxane, NH_4Cl 100 °C, 24h. (iv) NaH, 3-fluoro benzyl bromide, THF, rt, 18h, 56.8%; (v) Phenyl acetylene, sodium ascorbate, $CuSO_4$, *tert*-butanol, H_2O, rt, 4h, 43.07%; (vi) HCl in dioxane, rt, 2h, 77.7%; (vii) Acid chloride, triethyl amine, DCM, 0 ˚C, 30 min.



Scheme 1. synthetic protocol for (±)-1-(pyrrolidin-3-yl)-1H-1, 2, 3-triazole derivatives.

TABLE 1. *In vitro* anticancer activity of the compounds 8a-8p.

Compound	R-	Final step mixture Yields	IC_{50} (μg/ mL)		
			HCT-116	**MDA-MB231**	**Mia-PaCa2**
8a	2-chloro phenyl	70.95	>200	>200	>200
8b	2-fluoro phenyl	58.79	**65.8**	**42.5**	**78.2**
8c	2-methyl phenyl	88.95	100.5	**96**	**99.1**
8d	2-napthyl	54.96	>200	>200	>200
8e	2-thiphene	90.53	>200	>200	>200
8f	3-cyano phenyl	65.14	>200	>200	>200
8g	4-fluoro phenyl	74.95	158.5	164.2	170.9
8h	4-fluoro ethyl benzene	78.44	168.5	123.4	155
8i	2,6-dichloro phenyl	75.44	>200	>200	>200
8j	3,4-dimethoxy phenyl	78.11	>200	>200	>200
8k	3,5-dichloro phenyl	82.05	>200	>200	>200
8l	Phenyl	84.12	>200	>200	>200
8m	Cyclo hexyl	75.44	95.4	**84.6**	110.2
8n	Cyclopropyl	79.92	**65.4**	**78.5**	68.4
8o	Methoxy methyl	72.55	**64.3**	**55.8**	72
8p	Benzyl	72.64	123.0	129.1	140.7
Doxorubicin			0.32	0.41	0.47

From Table 1, compound **8e** was found to be obtained with highest yield, 90.53 %. From the ^{1}H NMR spectra of compound **8e** reveals that two stereo isomers were present in equal proportion. Compound **8d** was obtained with lowest yield of 54.96 %. The acid halides having the substituent at the *meta* position exhibits higher yields. The electron releasing groups at the meta position increasing the positive charge at the reaction centre, this positive charge facilitate the attacking at the lone pair of nitrogen atom in the compound **7**. The compound **8f** having the electron withdrawing group (CN) at the *meta* position, it decreases the positive charge at the carbon so the less yields were obtained. The electron releasing groups at the ortho position also dcreases the positive charge at the carbon so after *meta* less yields were obtained in ortho isomers.

When come to the stereochemistry of the synthesized compounds in scheme 1 the compound **3** was synthesized by the reaction of m-CPBA with the compound **2,** during this reaction there is possibility of both exo and endo isomers formation for epoxide (Fig. 1). But, due to presence of N-BOC bulky group endo isomer is only product formed [30]. So in the next step, epoxide opening took place with attack of sodium azide on 3 and/or 4 positions in exo direction which leads to formation of enatiomers (**4**). This was confirmed by the use of achiral column HPLC with a single peak at a retention time of 12.769 min (column name: Zorbax SB-C18) using the Eluent system ACN:Water 70:30(V/V). Further, it was also observed that by the use of chiral column HPLC two peaks were observed for the same compound at retention times of 12.101, and 12.873 min with 50.335 % and 49.665 % (column: CHIRALCELOX-H 4.6 x 250 nm) in eluent system: MeOH/DEA). So, due to the same reason the final products (**8a-8p**) may be of racemic mixture of compounds in the same ratio with compound **4**. The ^{1}H NMR, and ^{13}C NMR of all compounds reveals that presence of isomers in equal proportion.

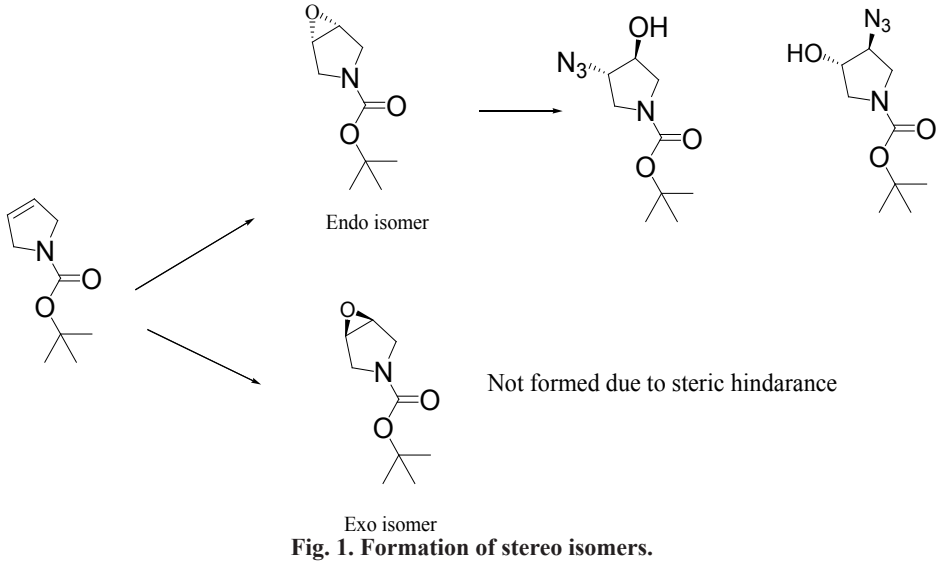


Fig. 1. Formation of stereo isomers.

All the synthesized compounds **8a-8p** were tested against the cancer cell lines, HCT-116, MDA-MB231, and Mia-PaCa2; among these synthesized compounds, 2-fluorophenyl derivative **8b** showed highest activity (IC_{50} = 42.5 µg/mL) on MDA-MB231 cancer cell line. The compound **8o** showed moderate activity (IC_{50} = 64.3 µg/mL) against the HCT -116 cancer cell line. Similarly the compound **8n** also showed the good results (IC_{50} = 68.4 µg/mL) with the Mia-PaCa2 cancer cell line. Compounds **8b, 8m, 8n**, and **8o** showed good results against the HCT-116 cancer cell line. Compounds **8c, 8m, 8n, 8o** showed the average results against the MDA-MB231 cancer cell lines. Compounds **8b, 8c, 8n** exhibited the moderate results against Mia-PaCa2 cancer cell line. The compounds **8a, 8d, 8e, 8f, 8i, 8j, 8k, 8l** showed poor results against the all three cancer cell lines. So these compounds in pure form if synthesized with reasonable activity make an interest to do further research to bring a potent anti cancer compounds for human beings.

SAR Study

Some of the synthesized compounds (**8a-8p)** were showed moderate activity on the tested cancer cell lines. Among the tested compounds five were found to be reasonably active towards MDA-MB231 breast cancer cell line; four were active on Mia-PaCa2 and only three were active on HCT-116 cell line. It was observed that the compound **8b** with 2-fluorophenyl substitution was showed highest activity (IC_{50} = 42.5 µg/mL) with MDA-MB231 breast cancer cell line**,** but the same fluorine substitution on 4th position i.e 4-fluorophenyl **(8g)** did showed considerable activity on the same cell line. Further, the compounds **8a** and **8k** with 2-chlorophenyl and 3,5-dichlorophenyl respectively did not showed good activity on the same cell line along with 3-cyano (**8f**) and simple phenyl (**8l**). However, the electron releasing 2-methyl phenyl substituted compound (**8c**) was found to be showed somewhat increased activity (IC_{50}<100 µg/mL). In case of HCT-116 cell line and Mia PaCa2 cell line the three compounds **8o, 8n** and **8b** with methoxy methyl, cyclopropyl and 2-fluorophenyl substitutions only showed considerable activity and remaining compounds did not showed any comparable activity except **8c** with 2-methylphenyl substitution on Mia PaCa2 cell line (IC_{50}<100 µg/mL).

Conclusion

In conclusion, we synthesized sixteen new(±)-1-(4-(3-fluorobenzyloxy)pyrrolidin-3-yl)-4-phenyl-1*H*-1,2,3-triazole derivatives. All derivatives **8a-8p** were tested against three cancer cell lines HCT- 116, MDA-MB231, and Mia-PaCa2. Compound **8b** showed highest activity with MDA-MB231 cancer cell line. The compound **8o** showed moderate activity against the HCT-116 cell line. Similarly the compound **8n** also showed the good results with the Mia-PaCa2 cell line. From the above results, the new chemical entities continue to be a major focus for contemporary drug discovery, it is expected that the present studies and their further extension will provide a best anti cancer compounds for human beings.

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Conflict of interest

The authors declare no conflict of interest.

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