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ORIGINAL RESEARCH



# Synthesis and biological evaluation of novel triazolyl 4-anilinoquinazolines as anticancer agents

Hani Mutlak A. Hassan[1] · Iuliana Denetiu[1] · Salman A. Khan[2] · Mohd Rehan[1] · Kaltoom Sakkaf[3] · Kalamegam Gauthaman[4]

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**Abstract**
The synthesis of novel triazolyl 4-anilinoquinazolines in five sequential synthetic steps via copper-catalyzed click chemistry and their anticancer biological evaluation is described.

**Keywords** Quinazolines · Triazoles · Click chemistry · Anticancer

## Introduction

Despite advances in chemotherapy, cancer remains one of the leading causes of morbidity and mortality worldwide (Bray et al. 2018). The current anticancer drugs have shortcomings such as lack of efficacy and poor selectively, the latter of which could lead to adverse side effects. In addition, the emergence of drug resistance (Holohan et al. 2013) has hampered the effectiveness of these drugs in the clinic. Thus, there is a necessity to develop efficacious, safe, and selective anticancer agents with enhanced properties that could overcome current limitations in chemotherapy treatment. Quinazolines exert their anticancer activity through inhibition of various enzymes such as protein kinases (Zhang et al. 2009), protein lysine methyltransferase (Liu et al. 2011), DNA topoisomerase (Garofalo et al. 2010), and histone deacetylase (Yang et al. 2015). Besides their anticancer activity (Giardina et al. 2009; Garofalo et al. 2011), quinazolines exhibit a wide spectrum of pharmacological properties such as anti-inflammatory (Smits et al. 2010) antimalarial (Verhaeghe et al. 2008), antibacterial, (Van Horn et al. 2014), and antitubercular activities (Odingo et al. 2014).

As part of our research program in the use of metal-catalyzed reactions for the synthesis of molecules of interest (Hassan et al. 2017, 2018; Hassan and Brown 2010), we were interested in designing and synthesizing novel 4-anilinoquinazolines that possess the 1,2,3-triazole motif (Lauria et al. 2014) embedded in their structure using copper-catalyzed click chemistry, a highly useful synthetic tool that has been extensively utilized in medicinal chemistry (Thirumurugan et al. 2013; Kolb and Sharpless 2003). We hypothesized that the incorporation of a second pharmacophore to the quinazoline nucleus could lead to pharmacologically potent quinazolines. Herein, we report the synthesis of a small molecule library of triazolyl 4-anilinoquinazolines using copper-catalyzed azide-alkyne cycloaddition (CuAAC) 'click' reactions to generate 1,4-disubstituted triazole products **12a–i** in a regioselective fashion for anticancer evaluation.

## Materials and methods

### General chemistry

Chemical reactions were carried out under a nitrogen atmosphere with anhydrous solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates with

✉ Hani Mutlak A. Hassan
hmahassan@kau.edu.sa

[1] King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia

[2] Department of Chemistry, Faculty of Science, King Abdulaziz University, P. O. Box 80203, Jeddah 21589, Saudi Arabia

[3] Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, P. O. Box 80216, Jeddah 21589, Saudi Arabia

[4] Center of Excellence in Genomic Medicine Research, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia

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fluorescent indicator (254 nm) and visualized using ultraviolet (UV) irradiation and/or staining with aqueous basic solution of potassium permanganate. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-$d_6$ as the solvent and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts and coupling constants (*J*-values) are reported in parts per million (ppm) and Hertz (Hz), respectively. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, triplet = t, quintet = quin, sext = sextet, and m = multiplet. Elemental analyses were performed on a 2400 Perkin Elmer Series II analyzer and high-resolution mass spectrometry (HRMS) was conducted using a Micromass Q-ToF mass spectrometer.

## Experimental procedures for chemical synthesis

### 6,7-Dimethoxyquinazolin-4(3*H*)-one (6)

A mixture of methyl 2-amino-4,5-dimethoxybenzoate **5** (5.00 g, 23.67 mmol) in formamide (50 mL) was stirred at 170 °C overnight under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and the precipitate was collected by filtration and washed with $H_2O$, $Et_2O$, and dried. Recrystallization from EtOH provided **6** (4.29 g, 88% yield) as a beige solid. Analytical data for compound **6** are in agreement with the literature (Li et al. 2016).

### 4-Chloro-6,7-dimethoxyquinazoline (7)

A mixture of compound **6** (4.00 g, 19.40 mmol) and phosphoryl chloride (40 mL) was stirred at 120 °C for 6 h. The solvent was removed in vacuo and the residue was dissolved in ice-$H_2O$ and washed with saturated aqueous $NaHCO_3$ solution (three times) followed by brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Recrystallizaton from EtOH afforded the chlorinated product **7** (3.58 g, 82%) as a yellow solid. Analytical data for compound **7** are in agreement with the literature (VanBrocklin et al. 2005).

### *N*$^1$-(6,7-dimethoxyquinazolin-4-yl)benzene-1,3-diamine (8)

A mixture of compound **7** (2.00 g, 8.90 mmol) and 1,3-phenylenediamine (1.06 g, 9.79 mmol) in EtOH (35 mL) was stirred at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the precipitate was then collected by filtration, washed with cold EtOH, cold $Et_2O$, and dried to afford **8** (2.51 g, 95%) as a green solid. Analytical data for compound **8** are in agreement with the literature (Garske et al. 2011).

### *N*-(3-azidophenyl)-6,7-dimethoxyquinazolin-4-amine (9)

To a stirred mixture of compound **8** (2.00 g, 6.75 mmol) in $(CH_3)_2CO$ (30 mL) was added conc. HCl (5 mL, 6 M) and the reaction mixture was cooled to −5 °C. A solution of $NaNO_2$ (932 mg, 13.5 mmol) in $H_2O$ (2 mL) was added dropwise over 10 min and the reaction mixture was then stirred for a further 30 min. A solution of $NaN_3$ (878 mg, 13.5 mmol) in $H_2O$ (3 mL) was then added dropwise over a period of 20 min and the reaction mixture was stirred for 1 h. After the starting material was consumed, $H_2O$ was added and the resulting precipitate was filtered, washed with cold EtOH, cold $Et_2O$, and dried to afford **9** (2.14 g, 98% yield) as a brown solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta = 11.62$ (s, 1H), 8.84, (s, 1H), 7.63–7.58 (m, 1H), 7.51 (t, $J = 8.4$ Hz, 1H), 7.42 (s, 1H), 7.07–7.06 (m, 1H), 4.04 (s, 3H), 3.99 (s, 3H) ppm; HRMS (ESI) calcd. for $C_{16}H_{15}N_6O_2$ $[M + H]^+$ 323.1256, found 323.1250. Anal. calcd. for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.56; H, 4.34; N, 25.98.

## General procedure for the preparation of triazolyl 4-anilinoquinazolines 12a–12i (click reaction)

To a stirred mixture of compound **11a** (0.62 mmol) in EtOH:$H_2O$ (2:1, 9 mL) was added alkyne (1.86 mmol) and sodium ascorbate (0.50 mmol). A fresh solution of $CuSO_4{\cdot}5H_2O$ (0.25 mmol) in $H_2O$ (1 mL) was added dropwise and the reaction mixture was vigorously stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and poured into $H_2O$ (50 mL). The resulting precipitate was sonicated, filtered, and the filter cake was washed with cold $H_2O$, cold $Et_2O$, and dried. Recrystallization from EtOH afforded the triazole products.

### 6,7-Dimethoxy-*N*-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl] quinazolin-4-amine (12a)

Brown solid, 96% yield; IR (KBr): 1616, 1563 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta = 10.22$ (s, 1H), 9.33 (s, 1H), 8.48 (s, 1H), 8.13 (s, 1H), 7.99–7.96 (m, 3H), 7.74–7.66 (m, 2H), 7.53–7.49 (m, 2H), 7.39 (t, $J = 7.3$ Hz, 1H), 4.00 (s, 3H), 3.99 (s, 3H) ppm; HRMS (ESI) calcd. for $C_{24}H_{21}N_6O_2$ $[M + H]^+$ 425.1726, found 425.1729; Anal. calcd. for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.88; H, 4.70; N, 19.73.

### *N*-{3-[4-(4-*tert*-butylphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}-6,7-dimethoxyquinazolin-4-amine (12b)

Brown solid, 89% yield; IR (KBr): 1620, 1562 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta = 9.84$ (s, 1H), 9.26 (s, 1H), 8.50 (s, 1H), 8.03 (s, 1H), 7.88 (d, $J = 8.2$ Hz, 2H),

7.68–7.61 (m, 2H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.39 (s, 1H), 4.00 (s, 6H), 1.32 (s, 9H) ppm; HRMS (ESI) calcd. for $C_{28}H_{29}N_6O_2$ $[M + H]^+$ 481.2352, found 481.2348; Anal. calcd. for $C_{28}H_{28}N_6O_2$: C, 69.98; H, 5.87; N, 17.49. Found: C, 69.90; H, 5.82; N, 17.41.

#### 6,7-Dimethoxy-*N*-{3-[4-(3-methylphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}quinazolin-4-amine (12c)

Brown solid, 79% yield; IR (KBr): 1626, 1560 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.82$ (s, 1H), 9.29 (s, 1H), 8.52 (s, 1H), 8.04 (s, 1H), 7.80–7.75 (m, 3H), 7.67–7.62 (m, 2H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.20 (d, $J = 7.4$ Hz, 1H), 4.01 (s, 6H), 2.39 (s, 3H) ppm; HRMS (ESI) calcd. for $C_{25}H_{23}N_6O_2$ $[M + H]^+$ 439.1882, found 439.1875; Anal. calcd. for $C_{25}H_{22}N_6O_2$: C, 68.48; H, 5.06; N, 19.17. Found: C, 68.53; H, 4.99; N, 19.11.

#### *N*-(3-{4-[4-(dimethylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}phenyl)-6,7-dimethoxyquinaz-olin-4-amine (12d)

Brown solid, 79% yield; IR (KBr): 1618, 1564 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.81$ (s, 1H), 9.62 (s, 1H), 9.07 (s, 1H), 8.48 (s, 1H), 8.02 (s, 1H), 7.77 (d, $J = 7.8$ Hz, 2H), 7.70–7.61 (m, 3H), 7.40 (m, 1H), 6.82 (d, $J = 7.8$ Hz, 2H), 4.00 (s, 6H), 2.95 (s, 6H) ppm; HRMS (ESI) calcd. for $C_{26}H_{26}N_7O_2$ $[M + H]^+$ 468.2148, found 468.2141; Anal. calcd. for $C_{26}H_{25}N_7O_2$: C, 66.79; H, 5.39; N, 20.97. Found: C, 66.83; H, 5.35; N, 20.92.

#### 6,7-Dimethoxy-*N*-{3-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}quinazolin-4-amine (12e)

Brown solid, 85% yield; IR (KBr): 1623, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.79$ (s, 1H), 9.18 (s, 1H), 8.84 (s, 1H), 8.50 (s, 1H), 8.03 (m, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.65–7.60 (m, 2H), 7.06 (d, $J = 8.2$ Hz, 2H), 4.00 (s, 6H), 3.80 (s, 3H) ppm; HRMS (ESI) calcd. for $C_{25}H_{23}N_6O_3$ $[M + H]^+$ 455.1832, found 455.1826; Anal. calcd. for $C_{25}H_{22}N_6O_3$: C, 66.07; H, 4.88; N, 18.49. Found: C, 65.99; H, 4.91; N, 18.45.

#### 6,7-Dimethoxy-*N*-{3-[4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl]phenyl}quinazolin-4-amine (12f)

Brown solid, 77% yield; IR (KBr): 1622, 1554 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.81$ (s, 1H), 8.95 (s, 1H,), 8.48 (s, 1H), 8.02 (s, 1H), 7.61 (m, 2H), 7.34–7.28 (m, 3H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.98–6.96 (m, 2H), 5.24 (s, 2H), 4.00 (s, 6H) ppm; HRMS (ESI) calcd. for $C_{25}H_{23}N_6O_3$ $[M + H]^+$ 455.1832, found 455.1826. Anal. calcd. for $C_{25}H_{22}N_6O_3$: C, 66.07; H, 4.88; N, 18.49. Found: C, 66.12; H, 4.85; N, 18.42.

#### *N*-[3-(4-butyl-1*H*-1,2,3-triazol-1-yl)phenyl]-6,7-dimethoxyquinazolin-4-amine (12g)

Brown solid, 94% yield; IR (KBr): 1626, 1566 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.80$ (s, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 7.98 (s, 1H), 7.58 (m, 3H), 5.28 (s, 1H), 3.99 (s, 6H), 2.73–2.70 (m, 2H), 1.66 (quin, $J = 7.2$ Hz, 2H), 1.38 (sext, $J = 7.2$ Hz, 2H), 0.92 (t, $J = 7.2$ Hz, 3H) ppm; HRMS (ESI) calcd. for $C_{22}H_{25}N_6O_2$ $[M + H]^+$ 405.2039, found 405.2037; Anal. calcd. for $C_{22}H_{24}N_6O_2$: C, 65.33; H, 5.98; N, 20.78. Found: C, 65.31; H, 5.97; N, 20.75.

#### 1-(1-{3-[(6,7-Dimethoxyquinazolin-4-yl)amino]phenyl}-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (12h)

Brown solid, 76% yield; IR (KBr): 3236, 1625, 1558 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.78$ (s, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.01 (s, 1H), 7.64–7.58 (m, 2H), 5.01 (s, 1H), 3.99 (s, 6H), 1.99–1.31 (m, 10H) ppm; HRMS (ESI) calcd. for $C_{24}H_{27}N_6O_3$ $[M + H]^+$ 447.2144, found 447.2149; Anal. calcd. for $C_{24}H_{26}N_6O_3$: C, 64.45; H, 5.87; N, 18.82. Found: C, 64.50; H, 5.90; N, 18.74.

#### 2-(1-{3-[(6,7-Dimethoxyquinazolin-4-yl)amino]phenyl}-1*H*-1,2,3-triazol-4-yl)propan-2-ol (12i)

Brown solid, 72% yield; IR (KBr): 3285, 1627, 1564 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 9.90$ (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 7.97 (s, 1H), 7.65–7.57 (m, 2H), 5.28 (s, 1H), 4.00 (s, 6H), 1.55 (s, 6H) ppm; HRMS (ESI) calcd. for $C_{21}H_{23}N_6O_3$ $[M + H]^+$ 407.1831, found 407.1828; Anal. calcd. for $C_{21}H_{22}N_6O_3$: C, 62.06; H, 5.46; N, 20.68. Found: C, 62.01; H, 5.43; N, 20.63.

## General biology

The human breast adenocarcinoma (MCF-7) and ovarian adenocarcinoma (SKOV-3) cell lines were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). Both cell lines were independently cultured in Dulbecco's minimal essential medium containing low glucose (DMEM-LG) supplemented with 10% fetal bovine serum (FBS), 2 mM Glutamax, antibiotic solution of penicillin (50 IU), and streptomycin (50 µg/mL). Additionally, 0.01 mg/mL bovine insulin was added to the media used for MCF-7. Both cancer cell lines were cultured at 37 °C in a humidified 5% $CO_2$ atmosphere.

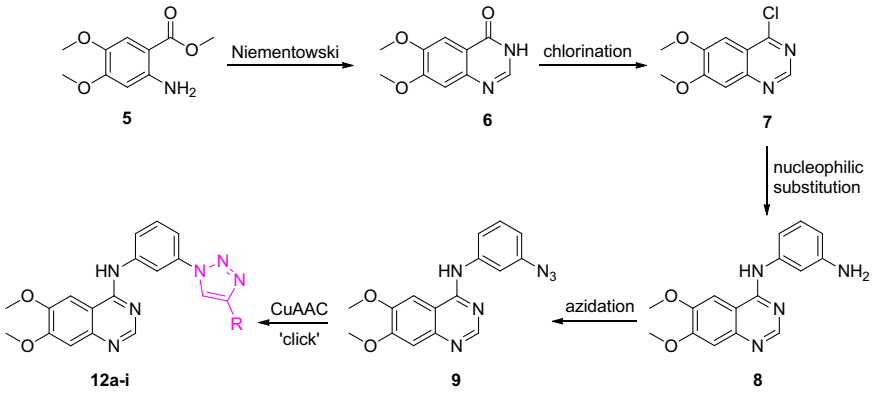
## Experimental procedure for anticancer biological evaluation

The inhibition of proliferation on human cancer cell lines (MCF-7 and SKOV-3) of triazolyl 4-anilinoquinazolines

**12a–12i** was analyzed using the MTT reagent [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide]. Briefly, the human cancer cell lines MCF-7 ($2 \times 10^4$ cells/well) and SKOV-3 ($2 \times 10^4$ cells/well) were seeded in 24-well tissue culture plates and allowed to attach overnight. The cells were then treated with different concentrations of each compound (0.1, 1, 3, 10, 30, 100 µM) and incubated at 37 °C in a humidified atmosphere of 5% $CO_2$ for 24, 48, and 72 h. Following the treatment period, the MTT reagent (5 mg/ml) in 100 µL of fresh culture medium was added to each well and incubated for 3 h. The formazan crystals formed after MTT treatment were solubilized with DMSO and the optical density was measured at 570 nm with a reference wavelength of 630 nm using a microplate ELISA reader (SpectraMax i3 Multimode Reader; Molecular Devices, Sunnyvale, USA). Percentage of inhibition was calculated as control–test/control × 100 and $IC_{50}$ for each compound was estimated.

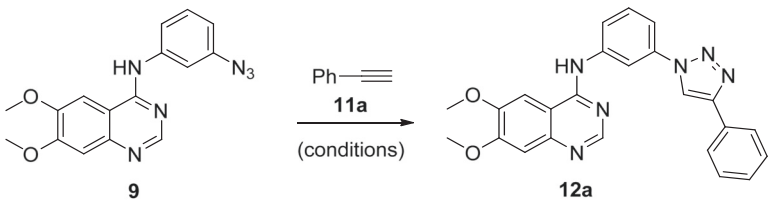
## Results and discussion

The synthetic approach to prepare the designed triazolyl 4-anilinoquinazolines **12a–i** is outlined in Scheme 1, commencing the synthesis from the commercially available methyl 2-amino-4,5-dimethoxybenzoate **5**. The quinazolinone ring system of **6** was constructed using a modified Niementowski quinazolinone reaction through cyclocondensation reaction of **5** with formamide at 170 °C, which afforded 6,7-dimethoxyquinazolin-4(3*H*)-one **6** in 88% yield. Chlorination of **6** was accomplished with phosphoryl chloride to provide 4-chloro-6,7-dimethoxyquinazoline **7** in




**Scheme 1** A click chemistry synthetic approach towards the synthesis of triazolyl 4-anilinoquinazolines **12a–i**

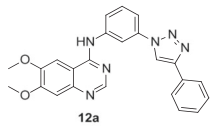
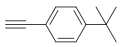
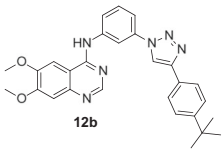
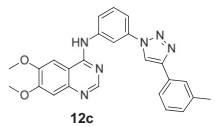
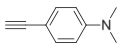
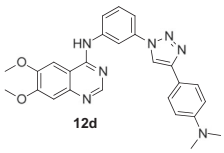
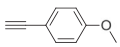
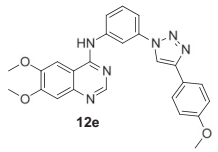
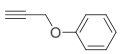
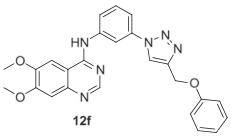
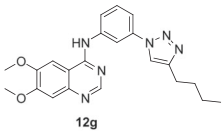
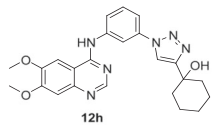
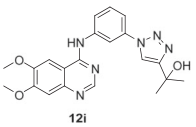
**Table 1** Optimization of the click reaction using azido quinazoline **9** and phenylacetylene **11a** as substrates for the synthesis of triazolyl 4-anilinoquinazoline **12a**




| Entry | Phenylacetylene **11a** (equiv.) | *T* (°C) | Yield (%)[a] |
|---|---|---|---|
| 1 | 1.5 | rt | No reaction |
| 2 | 1.5 | 60 | 61 |
| 3 | 1.5 | 80 | 79 |
| 4 | 3 | 80 | 96 |

[a]All reactions were carried out using **9** (0.62 mmol), **11a** (equiv.), $CuSO_4 \cdot 5H_2O$ (20 mol%), NaAsc (40 mol%), and temperature for 16 h

**Table 2** Small library synthesis of triazolyl 4-anilinoquinazolines **12a–i** employing alkynes **11a–i**

| Entry | Alkyne | Product | Yield (%) |
|---|---|---|---|
| 1 |  11a |  12a | 96 |
| 2 |  11b |  12b | 89 |
| 3 |  11c |  12c | 79 |
| 4 |  11d |  12d | 79 |
| 5 |  11e |  12e | 85 |
| 6 |  11f |  12f | 77 |
| 7 |  11g |  12g | 94 |
| 8 |  11h |  12h | 76 |
| 9 |  11i |  12i | 72 |

82% yield. Treatment of compound **7** with 1,3-phenylenediamine under refluxing EtOH displaced the chlorine substituent and delivered amino quinazoline **8** in 95% yield. Conversion of the amino group to an azido group was achieved through diazotisation under the influence of sodium nitrite and HCl followed by nucleophilic substitution reaction with sodium azide to provide the key click chemistry precursor **9** in quantitative yield (98%).

**Table 3** Anticancer activity of triazolyl 4-anilinoquinazolines **12a–i** against MCF-7 and SKOV-3 cell lines

| Compounds | $IC_{50}$ values (μM)[a] | |
|---|---|---|
| | MCF-7[b] | SKOV-3[c] |
| **12a** | 9.7 | 10.2 |
| **12b** | 8.9 | 9.8 |
| **12c** | 9.0 | 7.9 |
| **12d** | 7.8 | 14.2 |
| **12e** | 9.4 | 15.2 |
| **12f** | 6.7 | 7.8 |
| **12g** | 7.7 | 9.1 |
| **12h** | 10.5 | 9.4 |
| **12i** | 11.7 | 9.2 |
| **5-FU** | 42.7 | 26.3 |

[a]$IC_{50}$ = concentration that induces 50% inhibition ($IC_{50}$ values above are the average of three independent experiments)

[b]Human breast adenocarcinoma

[c]Ovarian carcinoma

For the click chemistry reaction, we opted to utilize azido quinazoline **9** and phenylacetylene **11a** to explore suitable click reaction conditions. We began by performing a CuAAC reaction between compounds **9** and **11a** at room temperature for 16 h, which proved unfruitful as no triazole product formation was observed to provide **12a** (Table 1, entry 1). When we increased the temperature to 60 °C, compound **12a** was generated in 61% yield while increasing the temperature further to 80 °C afforded **12a** in 79% yield (Table 1, entries 2 and 3). In a bid to improve the yield further, we conducted the reaction using three equivalents of **11a** at 80 °C, which resulted in the formation of **12a** in a high yield of 96% (Table 1, entry 4; Table 2, entry 1).

Azido quinazoline **9** was then subjected to click reactions with alkyne substrates **11b–i** using our optimized reaction conditions to afford triazole products **12b–i** (Table 2, entries 2–9).

All the synthesized triazolyl 4-anilinoquinazoline products **12a–i** were evaluated for their anticancer activity using an MTT-based assay against human breast adenocarcinoma (MCF-7) and ovarian carcinoma (SKOV-3) cell lines. The biological results revealed compounds **12a–i** showed promising anticancer activity against both cell lines with half-maximal inhibitory concentration ($IC_{50}$) values from 6.7–15.2 μM, most of which were in the single digit micromolar range (Table 3). Compound **12f** was the most potent compound identified and was highly active against both cell lines (6.7 μM for MCF-7; 7.8 μM for SKOV-3). Compound **12f** was sixfold (MCF-7) and threefold (SKOV-3) more potent than the drug 5-fluorouracil (5-FU). Compounds **12c** and **12f** were equipotent (~7.9 μM) against SKOV-3 cell line while compound **12f** was slightly more potent against MCF-7 cell line with an $IC_{50}$ of 6.7 μM.

Compounds **12d** and **12e** were selective towards MCF-7 cell line (7.8 and 9.4 μM, respectively) than SKOV-3 cell line (14.2 and 15.2 μM, respectively). In contrast, compounds **12h** and **12i** were slightly more active towards SKOV-3 cell line (9.4 μM and 9.2 μM, respectively) than MCF-7 cell line (10.5 μM and 11.7 μM, respectively). A phenyl group directly attached at C4 of the triazole heterocycle does not seem to be important for the anticancer activity as replacement of the phenyl group with a non-phenyl moiety also gave molecules with similar potencies (compare e.g. compound **12b** vs. **12g** in both cell lines). On the basis of the above biological results, compound **12f** could be used as a starting point for further structural optimization for the discovery of more potent derivatives.

## Conclusions

A novel triazolyl 4-anilinoquinazolines **12a–i** were synthesized through a copper-catalyzed click chemistry approach for anticancer biological evaluation against MCF-7 and SKOV-3 cell lines. The biological tests revealed the identification of highly active anticancer compounds with triazolyl 4-anilinoquinazoline **12f** emerged as the most potent anticancer molecule. Compound **12f**, therefore, could be used as a template for optimization studies. Further studies are required to elucidate the exact mechanism of action of these molecules.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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