



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

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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 selectivity, 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

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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 H₂O, Et₂O, 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-H₂O and washed with saturated aqueous NaHCO₃ solution (three times) followed by brine. The organic layer was dried over MgSO₄, filtered, and the solvent was evaporated in vacuo. Recrystallization 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 Et₂O, 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 (CH₃)₂CO (30 mL) was added conc. HCl (5 mL, 6 M) and the reaction mixture was cooled to −5 °C. A solution of NaNO₂ (932 mg, 13.5 mmol) in H₂O (2 mL) was added dropwise over 10 min and the reaction mixture was then stirred for a further 30 min. A solution of NaN₃ (878 mg, 13.5 mmol) in H₂O (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, H₂O was added and the resulting precipitate was filtered, washed with cold EtOH, cold Et₂O, and dried to afford **9** (2.14 g, 98% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 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 C₁₆H₁₅N₆O₂ [M + H]⁺ 323.1256, found 323.1250. Anal. calcd. for C₁₆H₁₄N₆O₂: 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:H₂O (2:1, 9 mL) was added alkyne (1.86 mmol) and sodium ascorbate (0.50 mmol). A fresh solution of CuSO₄·5H₂O (0.25 mmol) in H₂O (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 H₂O (50 mL). The resulting precipitate was sonicated, filtered, and the filter cake was washed with cold H₂O, cold Et₂O, 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}; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 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 C₂₄H₂₁N₆O₂ [M + H]⁺ 425.1726, found 425.1729; Anal. calcd. for C₂₄H₂₀N₆O₂: 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}; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 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-dimethoxyquinazolin-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-(phenoxyethyl)-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 $\mu g/mL$). 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% CO₂ 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 (2×10^4 cells/well) and SKOV-3 (2×10^4 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 $\text{control-test/control} \times 100$ 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**

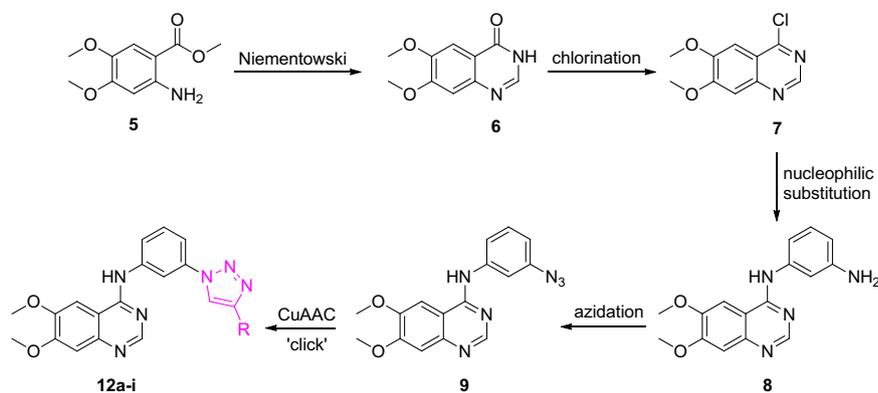
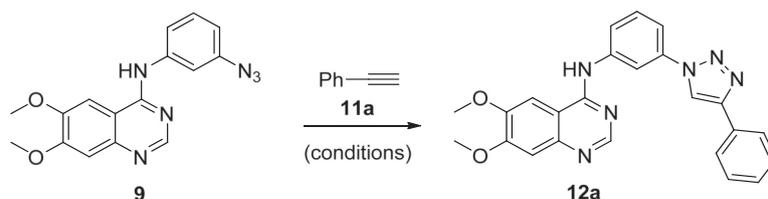


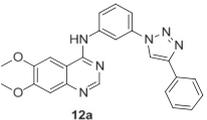
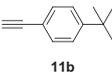
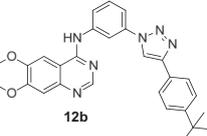
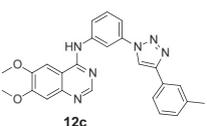
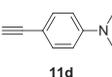
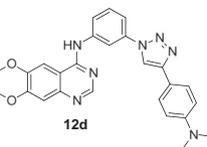
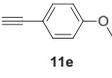
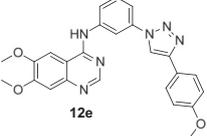
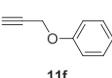
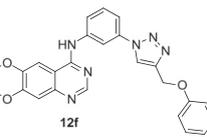
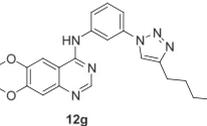
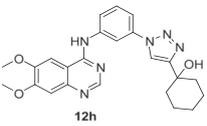
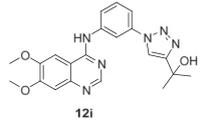
Table 1 Optimization of the click reaction using azido quinazoline **9** and phenylacetylene **11a** as substrates for the synthesis of triazolyl 4-anilinoquinazoline **12a**



Entry	Phenylacetylene 11a (equiv.)	<i>T</i> (°C)	Yield (%) ^a
1	1.5	rt	No reaction
2	1.5	60	61
3	1.5	80	79
4	3	80	96

^aAll reactions were carried out using **9** (0.62 mmol), **11a** (equiv.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (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

^aIC₅₀ = concentration that induces 50% inhibition (IC₅₀ values above are the average of three independent experiments)

^bHuman breast adenocarcinoma

^cOvarian 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 (IC₅₀) 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 IC₅₀ 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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References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68:394
- Garofalo A, Goossens L, Baldeyrou B, Lemoine A, Ravez S, Six P, David-Cordonnier MH, Bonte JP, Depreux P, Lansiaux A, Goossens JF (2010) Design, synthesis, and DNA-binding of *N*-alkyl(anilino)quinazoline derivatives. *J Med Chem* 53:8089
- Garofalo A, Goossens L, Lemoine A, Ravez S, Six P, Howsam M, Farce A, Depreux P (2011) [4-(6,7-Disubstituted quinazolin-4-ylamino)phenyl] carbamic acid esters: a novel series of dual

- EGFR/VEGFR-2 tyrosine kinase inhibitors. *MedChemComm* 2:65
- Garske AL, Peters U, Cortesi AT, Perez JL, Shokat KM (2011) Chemical genetic strategy for targeting protein kinases based on covalent complementarity. *Proc Natl Acad Sci USA* 108:15046
- Giardina D, Martarelli D, Sagratini G, Angeli P, Ballinari D, Gulini U, Melchiorre C, Poggesi E, Pompei P (2009) Doxazosin-related α 1-adrenoceptor antagonists with prostate antitumor activity. *J Med Chem* 52:4951
- Hassan HMA (2018) A short and efficient total synthesis of ficu-septamines A and B. *Molecules* 23:1865
- Hassan HMA, Brown FK (2010) A convenient approach to acyclic unsaturated amino acids via ring-closing metathesis. *Chem Commun* 46:3013
- Hassan HMA, Denetiu I, Sakkaf K, Khan KA, Pushparaj PN, Gauthaman K (2017) Synthesis and biological evaluation of triazolyl monastrol analogues using Cu-catalyzed click chemistry. *Heterocycles* 94:1856
- Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer* 13:714
- Kolb HC, Sharpless KB (2003) The growing impact of click chemistry on drug discovery. *Drug Discov Today* 8:1128
- Lauria A, Delisi R, Mingoia F, Terenzi A, Martorana A, Barone G, Almerico AM (2014) 1,2,3-Triazole in heterocyclic compounds, endowed with biological activity, through 1,3-dipolar cycloadditions. *Eur J Org Chem* 2014:3289
- Li F, Lu L, Liu P (2016) Acceptorless dehydrogenative coupling of *o*-aminobenzamides with the activation of methanol as a C1 source for the construction of quinazolinones. *Org Lett* 18:2580
- Liu F, Barsyte-Lovejoy D, Allali-Hassani A, He Y, Herold JM, Chen X, Yates CM, Frye SV, Brown PJ, Huang J, Vedadi M, Arrowsmith CH, Jin J (2011) Optimization of cellular activity of G9a inhibitors 7-aminoalkoxy-quinazolines. *J Med Chem* 54:6139
- Odingo J, O'Malley T, Kesicki EA, Alling T, Bailey MA, Early J, Ollinger J, Dalai S, Kumar N, Singh RV, Hipskind PA (2014) Synthesis and evaluation of the 2,4-diaminoquinazoline series as anti-tubercular agents. *Bioorg Med Chem* 22:6965
- Smits RA, Adami M, Istyastono EP, Zuiderveld OP, van Dam CM, de Kanter FJ, Jongejan A, Coruzzi G, Leurs R, de Esch IJ (2010) Synthesis and QSAR of quinazoline sulfonamides as highly potent human histamine H₄ receptor inverse agonists. *J Med Chem* 53:2390
- Thirumurugan P, Matosiuk D, Jozwiak K (2013) Click chemistry for drug development and diverse chemical–biology applications. *Chem Rev* 113:4905
- VanBrocklin HF, Lim JK, Coffing SL, Hom DL, Negash K, Ono MY, Gilmore JL, Bryant I, Riese DJ (2005) Anilinoalkoxyquinazolines: screening epidermal growth factor receptor tyrosine kinase inhibitors for potential tumor imaging probes. *J Med Chem* 48:7445
- Van Horn KS, Burda WN, Fleeman R, Shaw LN, Manetsch R (2014) Antibacterial activity of a series of *N*²,*N*⁴-disubstituted quinazoline-2,4-diamines. *J Med Chem* 57:3075
- Verhaeghe P, Azas N, Gasquet M, Hutter S, Ducros C, Laget M, Rault S, Rathelot P, Vanelle P (2008) Synthesis and antiparasitic activity of new 4-aryl-2-trichloromethylquinazolines. *Bioorg Med Chem Lett* 18:396
- Yang Z, Wang T, Wang F, Niu T, Liu Z, Chen X, Long C, Tang M, Cao D, Wang X, Xiang W (2015) Discovery of selective histone deacetylase 6 inhibitors using the quinazoline as the cap for the treatment of cancer. *J Med Chem* 59:1455
- Zhang J, Yang PL, Gray NS (2009) Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 9:28