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ORIGINAL RESEARCH

Design, synthesis and cytotoxic evaluation of quinazoline-2,4,6-triamine and 2,6-diaminoquinazolin-4(3*H*)-one derivatives

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Abstract

A series of quinazoline-2,4,6-triamine (quinazoline) and 2,6-diaminoquinazolin-4(3*H*)-one (quinazolinone) derivatives were designed, synthesized and evaluated as cytotoxic agents in three cancer cell lines (HCT-15, SKOV-3, and MDA-MB-231) using conventional MTT assay. Of the tested compounds, only eleven quinazoline derivatives showed activity against all the tested cell lines, at 24 h of exposure. Among them, the compounds **3e** and **3f** exhibited the highest cytotoxic activity, with the most important IC_{50} values ranging from 4.5 to 15.5 μM. They were more active than the reference drugs (Gefitinib, PD153035) which showed IC_{50} values ranging between 19.4 and 48.8 μM. These compounds open new possibilities for preparing novel analogous of quinazoline as antitumor agents.

Keywords Quinazoline-2,4,6-triamine · 2,6-diaminoquinazolin-4(3*H*)-one · Cytotoxic activity

Introduction

Cancer is continuing to be a major health problem in developing as well as undeveloped countries (WHO Media Center 2017). Despite the extensive research and rapid progress in cancer treatment, anticancer drugs used along with conventional radiotherapy and chemotherapy frequently evoke adverse side effects, severe immunosuppression and alarming increase in the incidence of drug resistance (Massagué and Obenauf 2016; Sbeity and Younes 2015; Dienstmann and Tabernero 2017; Sudhakar 2009; Charlton and Spicer 2016). Additionally, many cases of cancer generate sequels that affect the quality of life (Monsuez et al. 2010; Curigliano et al. 2010; Hartmann et al. 2009). So that, there is a growing demand to identify new agents and new targets for the treatment of neoplastic diseases.

Over the past years there has been a considerable interest in the development and pharmacology of heteroaromatic organic compounds (Kidwai et al. 2002; Asif 2017; Nikaljea and Bahetia 2017; Cavalli et al. 2009; Welsch et al. 2010). Among these structures both quinazoline and quinazolinone constitute an important class of pharmacophores in medicinal chemistry because of their potential in H-bonding and π–π stacking interactions with aromatic amino acid residues of receptors (Yadav et al. 2013; Ajani et al. 2016). These nuclei are associated with diverse pharmacological effects, including antiparasitic (Mendoza-Martínez et al. 2015), antibacterial (Jafari et al. 2016), antifungal (Khodarahmi et al. 2012), antiinflamatory (Tiwary et al. 2015; Alagarsamy and Saravanan 2013) and anticancer activities (Alanazi et al. 2014). Taking all the above findings into consideration, many research groups have dedicated efforts in developing molecules with a particular biological activity. Such is the case for the drugs Gefitinib, Erlotinib, and PD153035, all of which share the scaffold of quinazolin-4-amine and they were developed as therapies for the treatment of cancer by inhibiting the activity of the epidermal growth factor receptor (EGFR), which is involved in the regulation of cell growth, differentiation, and survival.

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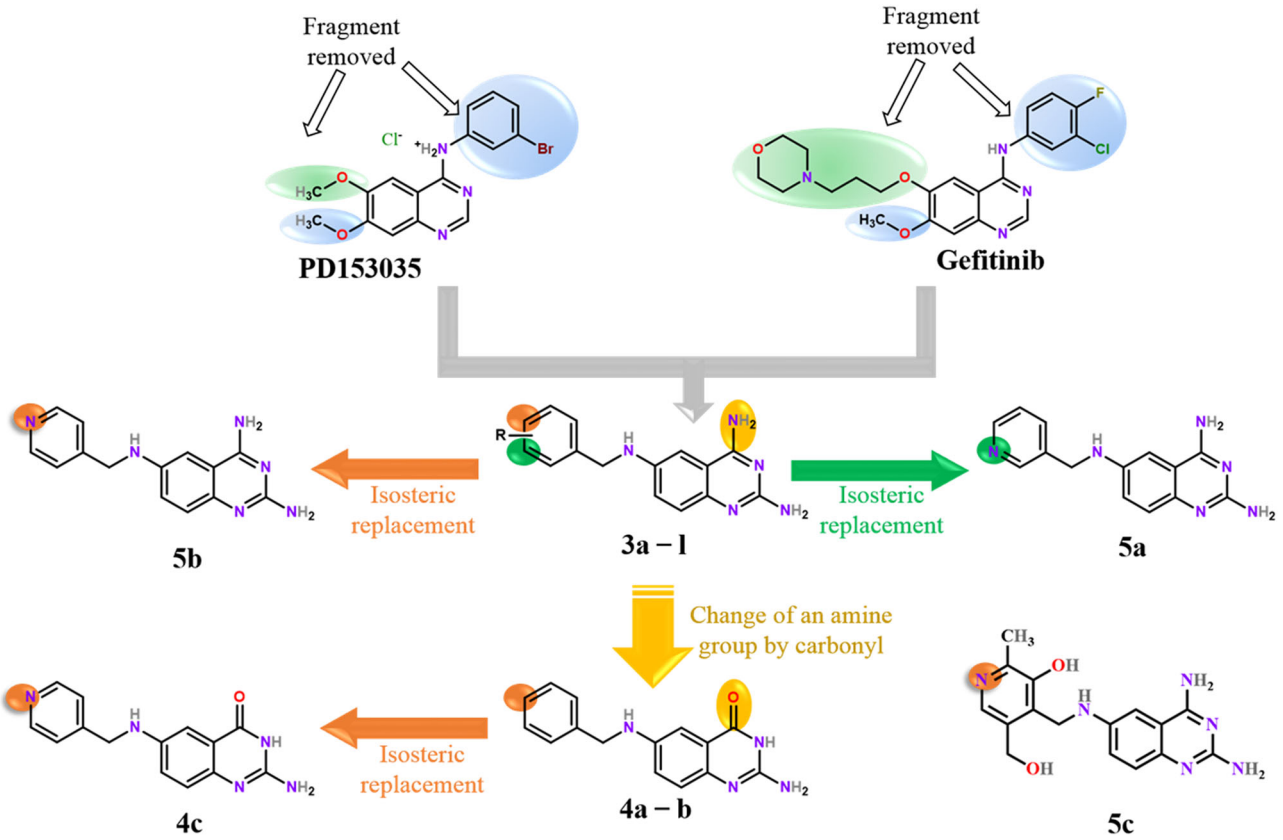


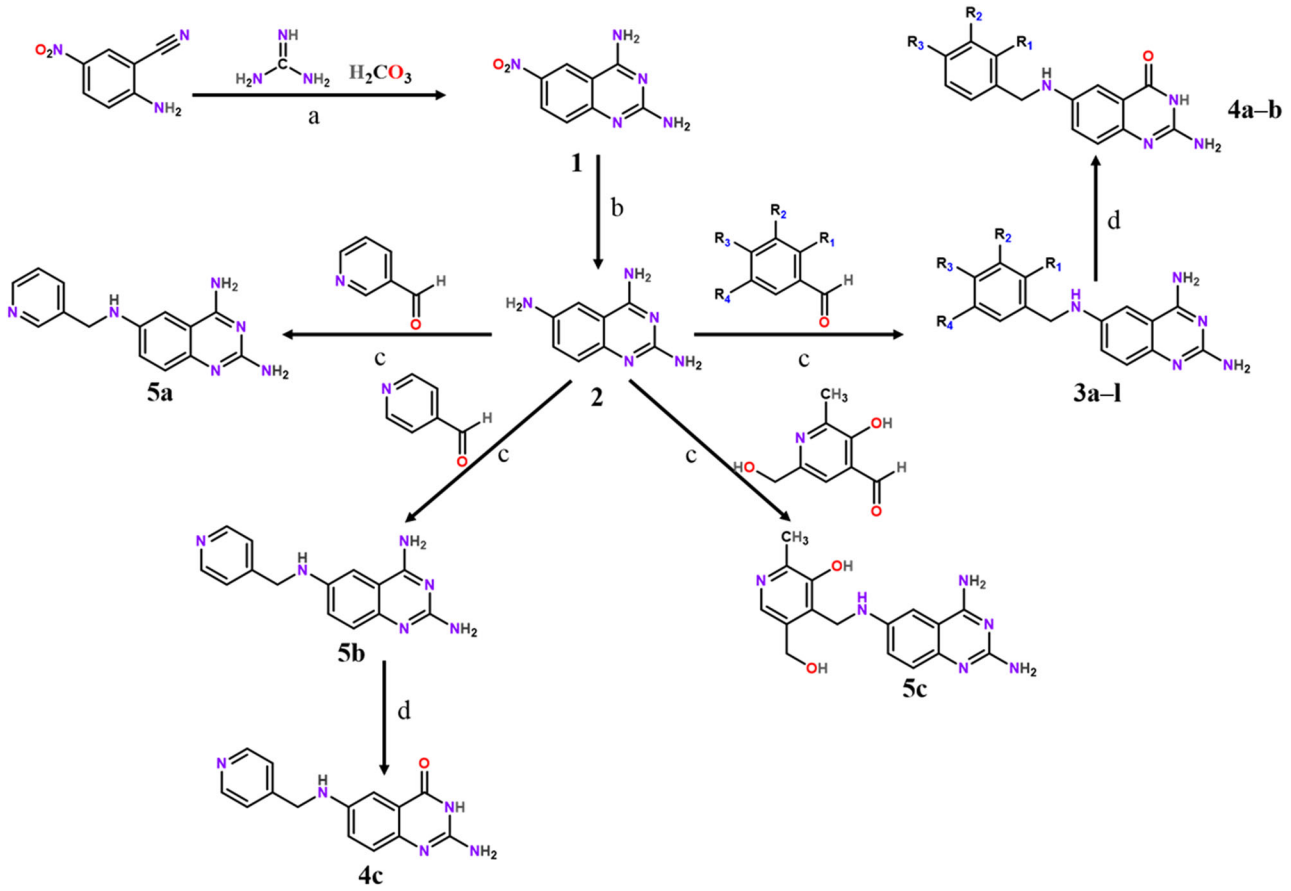
Fig. 1 Design of target compounds **3a–l**, **4a–c**, and **5a–c** analogs to Gefitinib and PD153035

Accordingly, as a part of our ongoing effort to develop potential anticancer drugs, in the present study we designed, synthesized, and characterized fifteen compounds derived from quinazoline-2,4,6-triamine and three compounds derived from quinazolin-4-(3*H*)-one. The quinazoline derivatives are structurally related to Gefitinib and PD153035; and the quinazolinone derivatives were designed in order to search if compounds with a hydrogen bond acceptor site favored cytotoxic activity. All compounds were screened in vitro by MTT assay using three cancer cell lines: HCT-15 (colorectal cancer), SKOV-3 (ovarian cancer), and MDA-MB-231 (breast cancer).

Chemistry

In our continued exploration for potential anticancer agents with multi-targeted molecular mechanisms, fifteen compounds were designed as quinazoline derivatives and three as quinazolinone derivatives (Fig. 1). Within the first group, twelve molecules (**3a–l**) were designed with reference to the drugs Gefitinib and PD153035, considering four modifications to quinazoline nucleus: (a) an amino group was added to the 2-position; (b) the phenyl group at the 4-position was removed; both changes increased the number of donor bonds per hydrogen bond; (c) benzylamine derivatives with different electron-donating and electron-withdrawing substituents were added at the 6-position in order that these substituents had electronic effects on the quinazoline nucleus and contributed to the modulation of activity; (d) the 7-position was left unsubstituted to achieve only the electronic effect of the substituents at 6-position. Additionally, three quinazoline-2,4,6-triamine with pyridine substituents at 6-position were proposed (**5a–c**) with the intention of analyzing the influence of a benzene ring change with a heterocycle. Finally, we decided to explore the relevance of the amino group at the 4-position by changing it for a carbonyl group to generate the quinazolinone derivatives **4a–c**.

The synthesis of **3a–l**, **4a–c**, and **5a–c** is shown in Scheme 1. The starting material, 2-amino-5-nitrobenzonitrile, was reacted with guanidine carbonate in a 1:1 ethanol/propanol mixture at 90 °C and the first intermediate, 6-nitroquinazoline-2,4-diamine (**1**), was obtained by a cyclocondensation reaction. Subsequently, **1** was subjected to a hydrogenation under a hydrogen atmosphere using palladium on charcoal (10%) to yield the second intermediate quinazoline-2,4,6-triamine (**2**). Reductive amination of this



Scheme 1 Synthetic route for the preparation of the compounds **3a–l**, **4a–c**, and **5a–c**. Reagents and conditions: **a** EtOH–PrOH, KOH, 1:1, 90 °C, 6 h; **b** H_2, Pd/C 10%, MeOH, 50 min; **c** DMF–DMA, $NaBH_4$, MeOH 8–12 h; **d** HCl 6N, 6 h

intermediate with various aryl aldehydes, DMF–DMA, $NaBH_4$ and MeOH provided amines **3a–l** and **5a–c**. The compounds **4a–b** were obtained from **3a** and **3f**, respectively, by refluxing conditions of a solution of HCl (6N) for 4 h; **4c** was obtained from **5b** under the same reaction conditions of **4a** and **4b**. The synthesis of compounds **1** and **2** has been previously reported (Mendoza-Martínez et al. 2015); in this work, the used solvent ratios and reaction times were modified to try to improve yields.

Result and discussion

Chemistry

The target compounds (**3a–l**, **4a–c**, and **5a–c**) were obtained in yields of moderate to acceptable (50–85%). It is important to mention that the target compounds (**3a–l** and **5a–c**) were synthesized directly without isolating the imine intermediate; their formation only was monitored by thin layer chromatography (TLC) and once observed, was added the $NaBH_4$ with an excess of methanol to increase the solubility of the imine intermediate and favor the reduction of the double bond.

On the other hand, the compounds **4a–c** were obtained directly from the **3a**, **3f**, and **5b**, respectively, because the reaction between the intermediate 2,6-diaminoquinazolin-4(3*H*)-one and the aldehydes generated greater impurities. Compounds **3a–l** and **5a–c** had no drawbacks in the reaction mixture; however, their purification was somewhat laborious.

All the synthesized compounds were characterized by ^{1}H NMR and ^{13}C NMR, infrared spectroscopy and high-resolution mass spectrometry (HRMS). All of them presented signals in common both in the IR and NMR spectra. In the ^{1}H NMR spectra of the final products, a double signal that is in the range of 4.21–4.68 ppm, which integrates for two protons, confirmed the presence of the methylene that binds the benzylamine substituent to the quinazoline nucleus. The same signal of the secondary carbon of the methylene was seen in the ^{13}C NMR spectra at δ value of 41.5–47 ppm for most of the compounds, except for **5c**, which presented it at 59.06 ppm. An important point to note in the ^{1}H NMR of all compounds was that they showed a

triple common signal corresponding to the amino group at 6-position of the quinazoline nucleus between 5.80 and 6.60 ppm, except for compounds **4a** and **5c**, (2-amino-6-(benzylamino)quinazolin-4(3*H*)-one and 4-(((2,4-diamino-quinazolin-6-yl)amino)methyl)-6-(hydroxymethyl)-2-methylpyridin-3-ol), respectively. The amino group at 2-position was commonly found between 5.49 and 5.57 ppm for **3b–i**, **3k–l**, and **5a–c**; at 8.61 and 5.78 ppm for **3a** and **3j**, respectively; and between 5.94 and 6.35 ppm for **4a–c**. The protons of the aromatic ring of quinazoline were commonly found overlapped with the amino group at 4-position. In the ^{13}C NMR for compounds **3e–f** and **3k**, C–F_3 couplings were observed as quartets, and C–F for **3j** as doublets (see Supplementary material).

Cytotoxic activity

All target compounds (**3a–l**, **4a–c**, and **5a–c**) and positive controls (Gefitinib and PD153035) were tested for their *in vitro* cytotoxic activity against the HCT-15 (human colon adenocarcinoma), MDA-MB-231 (human breast adenocarcinoma) and SKOV-3 (ovarian adenocarcinoma) cell lines through two-stage screening process. First, cells were exposed to a single concentration of each compound (50 μM) during 24 h. The effect on cell viability was estimated by MTT assay. The results from single concentration screening (Fig. 2) showed that quinazoline derivatives (**3a–g** and **3i–l**) reduced cell viability in 80%. On the other hand, the quinazolinone derivatives (**4a–c**) and the compounds (**3h**, **5a–c**) did not show a percentage of growth inhibition greater than 50%.

The quinazoline derivatives (**3a–g** and **3i–l**), that showed an excellent percentage of growth inhibition, have a benzylamine substituent at 6-position and amino group in the 2-positions and 4-positions. The exception the derivative **3h** which has a benzylamine substitutes with a hydroxyl group at the position meta. Both the quinazolinone derivatives (**4a–c**) and the quinazoline derivatives with a pyridine group at 6-position (**5a–c**) did not decrease cell growth by more than 50%. With these results, we can argue that it is indispensable to keep in this group of compounds amino groups in 2-positions and 4-positions, and benzylamine substituted in 6-position of the quinazoline nucleus. The isosters did not presented good biological activity at the tested concentration, and the biological activity can be modulated with the presence of different groups both electron-withdrawing and electron-donating on the aromatic ring.

Given these results, the compounds **3a–g** and **3i–l** were evaluated for the determination of IC_{50} at 24 h of exposure and this was calculated via a sigmoid curve fitting using GraphPad Prism 6.0 from at least three independent determination ± SD. The results are shown in Table 1.

Compounds **3e–f** have potent cytotoxic activity, showing a significant difference with Gefitinib and PD153035 in the

Table 1 IC_{50} values of **3a–l** against MDA-MB-231, SKOV-3, and HCT-15 cell lines

Compounds	IC_{50} (μM) ± SD		
	MDA-MB-231	SKOV-3	HCT-15
3a	21.81 ± 6.5*	29.34 ± 1.5*+	25.64 ± 1.7
3b	14.82 ± 4.3*	16.70 ± 2.3*	13.32 ± 2.7*+
3c	10.61 ± 2.8*+	14.32 ± 0.2*	10.57 ± 0.9*+
3d	8.89 ± 1.9*+	14.05 ± 0.7*	11.40 ± 0.3*+
3e	9.03 ± 2.9*+	10.58 ± 3.2*+	4.56 ± 0.4*+
3f	15.51 ± 7.2*	10.38 ± 3.5*+	6.23 ± 0.5*+
3g	19.54 ± 2.9*	22.97 ± 6.1*	22.87 ± 5.1*
3i	10.76 ± 1.1*+	14.62 ± 0.1*	11.53 ± 0.6*+
3j	13.72 ± 0.7*+	13.20 ± 3.7*	12.62 ± 1.3*+
3k	14.69 ± 9.6*	14.40 ± 1.0*	8.19 ± 2.8*+
3l	26.20 ± 2.4*	31.93 ± 1.3*+	23.79 ± 5.2
Gefitinib*	38.73 ± 3.0	48.76 ± 3.6	29.89 ± 2.8
PD153035+	25.35 ± 2.4	19.40 ± 1.3	25.58 ± 1.6

IC_{50}: concentration of compound (μM) producing 50% cell growth inhibition after 24 h of exposure

Statistical analyses were performed using ANOVA followed by Turkey's multiple comparison test, when comparing the IC_{50} of Gefitinib or PD153035 with each of the compounds (**3a–l**) with *$p < 0.05$ vs. Gefitinib; +$p < 0.05$ vs. PD153035

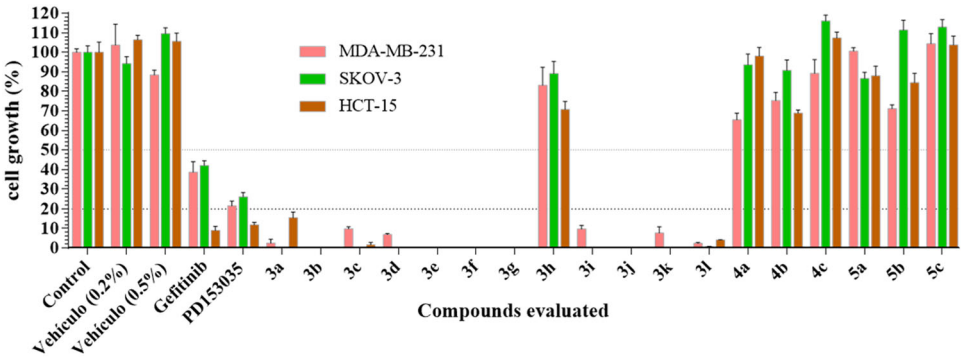


Fig. 2 Activity of compounds **3a–l**, **4a–c**, and **5a–c** on cell growth of MDA-MB-231, SKOV-3, and HCT-15 cell lines to 24 h of exposition. Cell viability was measured by MTT assay from at least two independent determination ± SD

three cell lines (MDA-MB-231, SKOV-3 and HCT-15). With exception of **3a** and **3l**, all other compounds only showed significant reductions vs. Gefitinib in the HCT-15 cell line. The result of cytotoxic activity appears to be related to the electronic effects of the substituents on the benzene group which connects through a methyl amine group with the quinazoline nucleus. In Table 1 it can be seen that most of the compounds have an IC_{50} below 20 μM except for **3a**, **3g**, and **3l**. The presence of an electro-attractant group, such as the nitro group, decreased cytotoxicity; however, the trifluoromethoxy group favored the cytotoxic activity, mainly when they are in the *ortho* position of the benzene ring, probably due to the electronegative and reactive nature of the fluorine atoms, which also is appreciated in the cytotoxic activities of compounds **3f**, **3j**, and **3k**.

Materials and methods

Melting points were determined in open capillary tubes with an IA9000 Series Melting Point Apparatus and they were uncorrected. The reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F254 plates (E. Merck) and visualized by irradiation with a UV lamp Spectroline Model ENF-240C. The mass spectrometry was performed by ESI-MS positive ion detection on a computer. The IR spectra were obtained on a spectrophotometer Pelkin ATX-Elmer. ^{1}H NMR spectra and ^{13}C NMR were acquired in $DMSO_{d6}$ on a Varian 300 and 400 MHz equipment; chemical shifts were obtained in parts per million (ppm), by using the deuterated solvent itself as reference. Splitting patterns have been designated as follows: s, singlet; d, doublet; q, quartet; dd, doublet of doublet; t, triplet; m, multiplet; br s, broad singlet. Catalytic hydrogenations were carried out in a Parr Shaker Hydrogenation apparatus. The starting materials 2-amine-5-nitrobenzonitrile, guanidine carbonate, and aldehydes are commercially available (Sigma Aldrich). PD153035 was synthetized following the synthesized reported by VanBrocklin et al. 2005 and Gefitinib was purchased of Santa Cruz Biotechnology (SC-202166).

Preparation of 6-nitroquinazoline-2,4-diamine (1)

A mixture of 5.00 g (30.64 mmol) of 2-amino-5-nitrobenzonitrile, 4.17 g (23.03 mmol) guanidine carbonate and 2.05 g (36.77 mmol) of KOH in 25 mL of ethanol and 50 mL propanol was refluxed for 6 h. The warm suspension was separated by filtration and the solid collected was washed successively with water and methanol to obtain 5.35 g (yield: 85%) of an orange solid; mp: 359–362 °C; IR (ν_{max}, cm^{-1}): 3463, 3440, 3106 (NH), 1614, 1460 (C=C), 1661 (C=N), 1325, 1295 (C–NO_2); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm, 9.07 (1H, d, $J = 2.50$ Hz, Ar–H), 8.21 (1H, dd, $J = 9.2$ Hz, 2.50 Hz, Ar–H), 7.83 (2H, s, Ar–NH_2), 7.21 (1H, d, $J = 9.20$ Hz, Ar–H), 6.76 (2H, s, Ar–NH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 163.23, 162.97, 157.24, 139.13, 126.58, 124.85, 121.88, 108.82 (Ar–C); MS: *m/z* (M + H) 206.

Preparation of quinazoline-2,4,6-triamine (2)

A mixture of 3.00 g (17.12 mmol) of **1**, 0.33 g (10%) of Pd/C in 270 mL of methanol were placed in a Parr hydrogenation flask at a pressure of 60 lb/in^2 for 1 h; the reaction end was consumed at 85 lb/in^2. The suspension was then filtered to remove Pd/C catalyst and the filtrate was evaporated in vacuo to yield 0.24 g (yield: 94%) of a light yellow solid, mp: 250–252 °C; IR (ν_{max}, cm^{-1}): 3399, 3326, 3146 (NH), 1559 (C=N), 1520 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz), δ ppm, 7.01 (1H, d, $J = 9.5$ Hz, Ar–H), 6.95–6.98 (1H, m, Ar–H), 6.94 (1H, s, Ar–H), 6.87 (2H, s, NH_2), 5.48 (2H, s, NH_2), 4.77 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 104.00, 110.95, 123.52, 125.08, 142.14, 145.03, 158.31, 161.40 (Ar–C); MS: *m/z* (M + H) 176.

General procedures for the synthesis of compounds 3a–l and 5a–c

To a solution of 0.50 g (2.85 mmol) of **2** in 15 mL of methanol was added 1.2 equivalents of the corresponding aryl aldehyde with ten drops of DMF-DMA. The mixture of the reaction was heated to 40 °C for 12 h. After cooling to room temperature, $NaBH_4$ (11.4 mmol) in 50 mL of methanol were added and then stirred for an additional 12 h. The mixture of the reaction was poured into a solution of $NaHCO_3$; the solid formed was filtered off and washed subsequent with water. After dried under vacuum condition, the crude product was purified by recrystallization from a methanol/water mixture.

General procedures for the synthesis of compounds 4a–c

Compounds **3a** or **3f** or **5b**, (0.43 mmol) were placed in 15 mL of HCl (6N) and stirred for 4 h to 90 °C. When reaction was completed, the mixture was cooled to 5 °C and neutralized by adding an appropriate amount of aqueous solution of NaOH (1 M). The precipitated solid formed was collected by filtration, washed with water, dried, and crystallized from a methanol/water mixture.

N^6-benzylquinazoline-2,4,6-triamine (3a) Yield: 70%, mp: 299–302 °C; IR (ν_{max}, cm^{-1}): 3317, 3148 (NH), 1633, 1588 (C=C aromatic), 1588, 1536 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 8.61 (2H, s, Ar–NH_2), 7.42 (2H, d, $J =$

7.4 Hz, Ar–H), 7.37 (2H, s, Ar–NH_2), 7.33–7.28 (2H, m, Ar–H), 7.32 (1H, d, $J = 1.9$ Hz, Ar–H), 7.25 (1H, dd, $J =$ 9.0, 2.1 Hz, Ar–H), 7.24–7.19 (1H, m, Ar–H), 7.20 (1H, d, $J = 8.93$ Hz, Ar–H), 6.56 (1H, t, $J = 6.1$ Hz, NH), 4.35 (2H, d, $J = 6.1$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 162.47, 153.65, 145.75, 139.56, 131.12, 128.21, 127.70, 126.76, 124.15, 117.82, 110.12, 101.72 (Ar–C), 46.51 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{16}N_5$ $[M + H]^+$ 266.1400, found 266.1404.

N^6-(2-chlorobenzyl)quinazoline-2,4,6-triamine (3b) Yield: 75%, mp: 72.7–74.1 °C; IR (ν_{max}, cm^{-1}): 3336, 3110 (NH), 1627 (C=C aromatic), 1543, 1521 (C=N), 1036, 740 (C–Cl); ^{1}H NMR (DMSO-d_6, 300 MHz,), δ ppm, 7.43–7.47 (2H, m, Ar–H), 7.24–7.31 (2H, m, Ar–H), 7.08–7.11 (1H, dd, $J = 9.1$, 1.9 Hz, Ar–H), 7.05–7.08 (1H, d, $J = 8.8$ Hz, Ar–H), 7.01 (2H, s, NH_2), 6.96 (1H, s, Ar–H), 5.92 (1H, t, $J = 6.1$ Hz, NH), 5.57 (2H, s, NH_2), 4.38 (2H, d, $J = 6.1$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz), δ ppm, 161.52, 158.46, 145.26, 142.65, 137.20, 132.69, 129.29, 129.22, 128.48, 127.06, 125.24, 123.24, 110.85, 100.41 (Ar–C), 44.89 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{15}N_5Cl$ $[M + H]^+$ 300.1010, found 300.1011.

N^6-(3-chlorobenzyl)quinazoline-2,4,6-triamine (3c) Yield: 80%, mp: 98.6–101.4 °C; IR (ν_{max}, cm^{-1}): 3441, 3351, 3132 (NH), 2817 (C–H), 1656, 1623 (C=C aromatic), 1574, 1523 (C=N), 1076, 830, 771 (C–Cl); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.44–7.50 (1H, m, Ar–H), 7.36–7.39 (1H, dt, $J = 7.7$, 1.5 Hz, Ar–H), 7.34 (1H, t, $J =$ 7.6 Hz, Ar–H), 7.26–7.29 (1H, dt, $J = 7.5$, 1.7 Hz, Ar–H), 7.05 (1H, s, Ar–H), 7.04 (1H, s, Ar–H), 6.99 (2H, s, NH_2), 6.94 (1H, s, Ar–H), 6.06 (1H, t, $J = 6.3$ Hz, NH), 5.57 (2H, s, NH_2), 4.31 (2H, d, $J = 6.3$ Hz, CH_2); ^{13}C NMR (101 MHz, DMSO-d_6), δ ppm, 158.29, 144.80, 143.07, 142.47, 132.94, 130.06, 127.38, 126.59, 126.31, 124.96, 123.36, 110.72, 100.58 (Ar–C), 46.17 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{15}N_5Cl$ $[M + H]^+$ 300.1010, found 300.1011.

N^6-(4-chlorobenzyl)quinazoline-2,4,6-triamine (3d) Yield: 80%, mp: 128.6–131.8 °C; IR (ν_{max}, cm^{-1}): 3348, 3115 (NH), 1621, 1566 (C=C aromatic), 1522 (C=N), 1013, 1089, 808 (C–Cl); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.43 (2H, d, $J = 8.6$ Hz, Ar–H), 7.36 (2H, d, $J = 8.5$ Hz, Ar–H), 7.06–7.03 (1H, dd, 1H, $J = 9.9$, 2.7 Hz, Ar–H), 7.02 (1H, d, $J = 7.6$ Hz, Ar–H), 6.93 (1H, d, $J = 1.3$ Hz, Ar–H), 6.92 (2H, s, NH_2), 5.98 (1H, t, $J = 6.3$ Hz, NH), 5.49 (2H, s, NH_2), 4.29 (2H, d, $J = 62$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.43, 158.44, 145.26, 142.49, 139.33, 131.15, 129.50, 128.13, 125.17, 123.37, 110.75, 100.56 (Ar–C), 46.17 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: Calcd for $C_{15}H_{15}N_5Cl$ $[M + H]^+$ 300.1010, found 300.1011.

N^6-(2-(trifluoromethoxy)benzyl)quinazoline-2,4,6-triamine (3e) Yield: 82%, decomp. point: 300.1–301.5 °C; IR (ν_{max}, cm^{-1}): 3629, 3444, 3428, 3356, 3112 (NH), 2817 (C–H), 1673, 1616 (C=C aromatic), 1569, 1526 (C=N), 1244, 1201, 1179, 1155, 815, 760 (C–F_3); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.51–7.56 (1H, ddd, $J = 7.3$, 1.8, 0.6 Hz, Ar–H), 7.32–7.42 (3H, m, Ar–H), 7.03–7.18 (2H, d, Ar–H), 6.97 (s, 3H, NH_2, Ar–H), 5.87 (t, 1H, $J = 6.1$ Hz, NH), 5.57 (s, 2H, NH_2), 4.37 (d, 2H, $J = 6.0$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.49, 158.38 (Ar–C), 146.72 (q, $J = 1.5$ Hz, Ar–C), 145.08, 142.62, 132.40, 129.81, 128.60, 127.33, 125.08, 123.15, 120.44 (Ar–C), 120.33 (q, $J = 256.5$ Hz, O–$\underline{C}F_3$), 110.78, 100.52, 41.54 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{16}H_{15}N_5OF$ $[M + H]^+$ 350.1223, found 350.1222.

N^6-(4-(trifluoromethoxy)benzyl)quinazoline-2,4,6-triamine (3f) Yield: 85%, mp: 213.0–214.1 °C; IR (ν_{max}, cm^{-1}): 3630, 3445, 3351, 3109 (NH), 2852 (C–H), 2060, 1896 (overtone = CH_2), 1673, 1621 (C=C aromatic), 1570, 1522 (C=N), 1288, 1257, 1216, 1196, 1158, 822 (C–F_3); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.54 (2H, d, $J =$ 8.7 Hz, Ar–H), 7.31 (2H, d, $J = 7.9$ Hz, Ar–H), 7.04 (2H, s, Ar–H), 6.96 (3H, s, NH_2, Ar–H), 6.01 (1H, t, $J = 6.2$ Hz, NH), 5.53 (2H, s, NH_2), 4.33 (2H, d, $J = 6.2$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.42, 158.43 (Ar–C), 147.11 (q, $J = 1.8$ Hz, Ar–C), 145.30, 142.51, 139.82, 129.39, 125.19, 123.33, 120.80 (Ar–C), 120.12 (d, $J = 255.8$ Hz, O$\underline{C}F_3$), 110.74, 100.46, 46.16 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{16}H_{15}N_5OF$ $[M + H]^+$ 350.1223, found 350.1223.

N^6-(4-nitrobenzyl)quinazoline-2,4,6-triamine (3g) Yield: 70%, mp: 299.4–302.0 °C; IR (ν_{max}, cm^{-1}): 3456, 3320, 3105 (NH), 1623, 1604 (C=C aromatic), 1564, 1506 (C=N), 1338, 821 (C–NO_2); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 8.19 (2H, d, $J = 8.7$ Hz, Ar–H), 7.66 (2H, d, $J = 8.7$ Hz, Ar–H), 7.05 (2H, s, Ar–H), 6.94 (2H, s, NH_2), 6.91 (1H, s, Ar–H), 6.20 (1H, t, $J = 6.4$ Hz, NH), 5.54 (2H, s, NH_2), 4.46 (2H, d, $J = 6.3$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.39, 158.40, 148.94, 146.35, 145.20, 142.18, 128.43, 125.19, 123.31, 123.21, 110.70, 100.61 (Ar–C), 46.19 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{15}N_6O_2$ $[M + H]^+$ 311.1251, found 311.1253.

3-(((2,4-diaminoquinazolin-6-yl)amino)methyl)phenol (3h) Yield: 50%, mp: 180.2–182.7 °C; IR (ν_{max}, cm^{-1}): 3372 (NH), 3147 (OH), 1656, 1619 (C=C aromatic), 1574, 1525 (C=N), 1252, 818, 782 (C–O); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 9.32 (1H, s, OH), 7.10 (1H, t, $J = 7.7$ Hz, Ar–H), 7.06 (1H, dd, $J = 9.0$, 2.1 Hz, Ar–H), 7.03 (1H, d, J = 8.8 Hz, Ar–H), 6.95 (1H, d, $J = 1.8$ Hz, Ar–H), 6.93 (2H, s, NH_2), 6.79–6.86 (2H, m, Ar–H), 6.62 (1H, ddd, $J = 8.1$,

2.3, 1.0 Hz, Ar–H), 5.84 (1H t, $J = 6.1$ Hz, NH), 5.49 (2H, s, NH_2), 4.21 (2H, d, $J = 6.0$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.42, 158.33, 157.35, 145.11, 142.91, 141.65, 129.11, 125.05, 123.34, 118.28, 114.45, 113.62, 110.79, 100.38 (Ar–C), 47.04 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{16}N_5O$ $[M + H]^+$ 282.1349, found 282.1353.

N^6-(4-methylbenzyl)quinazoline-2,4,6-triamine (3i) Yield: 85%, mp: 209.7–211.3 °C; IR (ν_{max}, cm^{-1}): 3634, 3439, 3346, 3114 (NH), 2974, 2922, 2853 (C–H), 2049, 1890 (overtone =CH_2), 1671, 1618 (C=C aromatic), 1565, 1515 (C=N), 1489, 1440, 1341, 820, 799 (CH_3); ^1H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.30 (2H, d, $J = 8.0$ Hz, Ar–H), 7.12 (2H, d, $J = 7.8$ Hz, Ar–H), 7.05 (1H, dd, $J =$ 9.0, 2.2 Hz, Ar–H), 7.02 (1H, d, $J = 8.6$ Hz, Ar–H), 6.95 (1H, d, $J = 1.8$ Hz, Ar–H), 6.94 (2H, s, NH_2), 5.84 (1H, t, $J = 6.1$ Hz, NH), 5.50 (2H, s, NH_2), 4.24 (2H, d, $J = 6.0$ Hz, CH_2), 2.26 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.45, 158.37, 145.13, 142.84, 137.02, 135.70, 128.78, 127.75, 125.04, 123.48, 110.77, 100.50 (Ar–C), 46.85 (Ar–$\underline{C}H_2$–NH), 20.73 ($\underline{C}H_3$); ESI-MS *m/z*: calcd for $C_{16}H_{18}N_5$ $[M + H]^+$ 280.1557, found 280.1558.

N^6-(2,4-difluorobenzyl)quinazoline-2,4,6-triamine (3j) Yield: 85%, mp: 183.1–184.8 °C; IR (ν_{max}, cm^{-1}): 3479, 3423, 3319 (NH), 1614 (C=C aromatic), 1558, 1520 (C=N), 1295, 1264, 1243 (CF) ^1H; NMR (DMSO-d_6, 300 MHz), δ ppm, 7.47 (1H, td, $J = 8.7$, 7.0 Hz, Ar–H), 7.19–7.28 (1H, m, Ar–H), 7.15 (2H, s, NH_2), 7.01–7.10 (3H, m, Ar–H), 6.98 (1H, s, Ar–H), 5.96 (1H, t, $J = 6.1$ Hz, NH), 5.78 (2H, s, NH_2), 4.31 (2H, d, $J = 6.0$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz), δ ppm, 161.52 (Ar–C), 159.81–163.05 (d, $J = 244.7$ Hz, Ar–$\underline{C}F$), 159.66–162.89 (d, $J = 244.3$ Hz, Ar–$\underline{C}F$), 158.52, 145.39, 142.47 (Ar–C), 130.66–130.87 (dd, $J = 9.7$, 6.3 Hz, Ar–$\underline{C}F$), 125.26, 123.37 (Ar–C), 122.92–123.17 (dd, $J = 15.2$, 3.5 Hz, Ar–$\underline{C}F$), 110.78–111.24 (dd, $J = 20.8$, 3.3 Hz, Ar–$\underline{C}F$), 110.78 (Ar–C), 103.69 (t, $J = 25.8$ Hz, Ar–$\underline{C}F$), 100.53 (Ar–C), 40.45 (d, $J = 3.2$ Hz, Ar–$\underline{C}H_2$–NH); ESI-MS *m*/z: calcd for $C_{15}H_{14}N_5F_2$ $[M + H]^+$ 302.1212, found 302.1214.

N^6-(2,5-bis(trifluoromethyl)benzyl)quinazoline-2,4,6-triamine (3k) Yield: 60 %, mp: 92.1–93.0 °C IR (ν_{max}, cm^{-1}): 3345, 3136 (NH), 1659, 1625 (C=C aromatic), 1594, 1565 (C=N), 1309, 1165, 1120, 1087, 836, 818 (C–F); ^1H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.99 (1H, d, $J = 8.2$ Hz, Ar–H), 7.96 (1H, s, Ar–H), 7.86 (1H, d, $J = 8.1$ Hz, Ar–H), 7.08 (1H, d, $J = 8.9$ Hz, Ar–H), 7.05 (1H, dd, $J = 9.0$, 2.2 Hz, Ar–H), 6.97 (1H, d, $J = 1.8$ Hz, Ar–H), 6.94 (2H, s, NH_2), 6.09 (1H, t, $J = 6.1$ Hz, NH), 5.53 (2H, s, NH_2), 4.54 (2H, d, $J = 5.8$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.50, 158.67, 145.73, 142.23, 140.81 (Ar–C), 132.56 (q, $J = 32.1$ Hz, Ar–$\underline{C}F$), 130.48 (q, $J = 31.1$ Hz, Ar–$\underline{C}F$), 127.35 (q, $J = 5.7$ Hz, Ar–$\underline{C}F$), 125.97 (q, $J =$ 3.5 Hz, Ar–$\underline{C}F$), 125.46 (Ar–C), 124.37 (q, $J = 3.6$ Hz, Ar–$\underline{C}F$), 122.92 (Ar–C), 122.47–125.20 (d, $J = 275.94$, Ar–$\underline{C}F$), 122.15–124.87 (d, $J = 274.07$ Hz, Ar–$\underline{C}F$), 110.79, 100.73 (Ar–C), 43.00–44.90 (m, Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{17}H_{14}N_5F_6$ $[M + H]^+$ 402.1148, found 402.1149.

N^6-(2-nitrobenzyl)quinazoline-2,4,6-triamine (3l) Yield: 70%, mp: 186.9–189.0 °C; IR (ν_{max}, cm^{-1}): 3423, 3322, 3178 (NH), 1630 (C=C aromatic), 1560, 1513 (C=N), 1326, 821 (C–NO_2); ^1H NMR (DMSO-d_6, 400 MHz), δ ppm, 8.07–8.13 (1H, m, Ar–H), 7.64–7.68 (1H, m, Ar–H), 7.63 (1H, dd, $J = 7.8$, 2.0 Hz, Ar–H), 7.50 (1H, ddd, $J =$ 8.7, 6.5, 2.3 Hz, Ar–H), 7.09 (1H, dd, $J = 8.9$, 2.3 Hz, Ar–H), 7.06 (1H, d, $J = 8.8$ Hz, Ar–H), 6.87 (2H, s, NH_2), 6.77 (1H, d, $J = 2.0$ Hz, Ar–H), 6.14 (1H, t, $J = 6.2$ Hz, NH), 5.49 (2H, s, NH_2), 4.68 (2H, d, $J = 6.2$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.38, 158.49, 148.23, 145.38, 142.08, 136.14, 133.72, 129.26, 127.93, 125.35, 124.93, 123.21, 110.72, 100.24 (Ar–C), 44.37 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{15}N_6O_2$ $[M + H]^+$ 311.1251, found 311.1252.

2-amino-6-(benzylamino)quinazolin-4(3H)-one (4a) Yield: 60%, mp: 267.8–268.5 °C; IR (ν_{max}, cm^{-1}): 3470, 3431, 3321 (NH), 3028 C–H), 1656 (C=O), 1615 (C=C aromatic), 1493 (C=N); ^1H NMR (DMSO-d_6, 400 MHz), δ ppm, 7.36 (2H, d, $J = 7.1$ Hz, Ar–H), 7.30 (2H, t, $J =$ 7.2 Hz, Ar–H), 7.20 (1H, t, $J = 6.7$ Hz, Ar–H), 7.05 (2H, s, Ar–H), 6.95 (1H, s, Ar–H), 6.35 (2H, s, NH_2), 4.28 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 163.97 (O=$\underline{C}$–NH), 150.30 (N=$\underline{C}$–NH), 144.34, 140.38, 140.13, 128.47, 127.28, 126.82, 123.38, 122.49, 117.67, 104.86 (Ar–C), 47.01 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{15}H_{15}N_4O$ $[M + H]^+$ 267.1240, found 267.1241.

2-amino-6-((4-(trifluoromethoxy)benzyl)amino)quinazolin-4(3H)-one (4b) Yield: 58%, mp: 335.6–336.0 °C; IR (ν_{max}, cm^{-1}): 3321, 3148 (NH), 2850 (C–H), 1643 (C=O), 1616 (C=C aromatic), 1551, 1532 (C=N), 1256, 1218, 1200, 1156, 820 (C–F); ^1H NMR (DMSO-d_6, 400 MHz), δ ppm, 10.80 (1H, s, NH), 7.48 (2H, d, $J = 8.6$ Hz, Ar–H), 7.31 (2H, d, $J = 8.0$ Hz, Ar–H), 7.02 (2H, s, Ar–H), 6.90 (1H, s, Ar–H), 6.30 (1H, t, $J = 6.0$ Hz, NH), 5.95 (2H, s, NH_2), 4.31 (2H, d, $J = 5.9$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 162.18 (O=$\underline{C}$–NH), 149.05 (N=$\underline{C}$–NH), 147.07, 143.67, 142.92, 139.72, 128.91, 125.04, 122.51, 121.00, 117.73 (Ar–C), 116.32–123.95 (q, $J = 255$ Hz, O$\underline{C}F_3$), 104.49, 46.12 (Ar–$\underline{C}H_2$–NH); ESI-MS *m/z*: calcd for $C_{16}H_{14}N_4O_2F_3$ $[M + H]^+$ 351.1063, found 351.1066.

2-amino-6-((pyridin-4-ylmethyl)amino)quinazolin-4(3H)-one (4c) Yield: 65%, mp: 241.0–242.2 °C; IR (ν_{max}, cm^{-1}): 3314, 3145 (NH), 2906, 2830 (C–H), 1647 (C=O), 1617 (C=C aromatic), 1561, 1531 (C=N); ^{1}H NMR (DMSO-d6, 400 MHz), δ ppm, 10.91 (1H, s, NH), 8.48 (2H, d, $J = 5.7$ Hz, Ar–H), 7.35 (2H, d, $J = 5.8$ Hz, Ar–H), 7.02 (2H, s, Ar–H), 6.86 (1H, s, Ar–H), 6.38 (1H, t, $J = 6.1$ Hz, NH), 6.05 (2H, s, NH_2), 4.33 (2H, d, $J = 6.0$ Hz, CH_2); ^{13}C NMR (DMSO-d6, 101 MHz), δ ppm, 162.36 (O=C–NH), 150.33 (N=C–NH), 149.56, 143.53, 124.97, 122.63, 122.26, 121.60, 117.69, 104.64 (Ar–C), 45.83 (Ar–CH_2–NH); ESI-MS *m/z*: calcd for $C_{14}H_{14}N_5O$ $[M + H]^+$ 268.1193, found 268.1201.

N^6-(pyridin-3-ylmethyl)quinazoline-2,4,6-triamine (5a) Yield: 70%, mp: 230.3–233.6 °C; IR (ν_{max}, cm^{-1}): 3459, 3331, 3089, 1417 (NH), 1666, 1629 (C=C aromatic), 1543, (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 8.64 (1H, d, $J = 1.7$ Hz, Ar–H), 8.43 (1H, dd, $J = 4.8$, 1.6 Hz, Ar–H), 7.80 (1H, dt, $J = 7.8$, 1.9 Hz, Ar–H), 7.34 (1H, ddd, $J = 7.8$, 4.8, 0.7 Hz, Ar–H), 7.04 (2H, s, Ar–H), 6.97 (1H, s, Ar–H), 6.95 (2H, s, NH_2), 6.02 (1H, t, $J = 6.3$ Hz, NH), 5.51 (2H, s, NH_2), 4.32 (2H, d, $J = 6.2$ Hz, CH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.41, 158.44, 149.23, 147.94, 145.32, 142.36, 135.49, 135.35, 125.18, 123.43, 123.37, 110.69, 100.61 (Ar–C), 44.48 (Ar–CH_2–NH); ESI-MS *m/z*: calcd for $C_{14}H_{15}N_6$ $[M + H]^+$ 267.1353, found 267.1361.

N^6-(pyridin-4-ylmethyl)quinazoline-2,4,6-triamine (5b) Yield: 70%, mp: 249.5–250.2 °C; IR (ν_{max}, cm^{-1}): 3408, 3334, 3074 (NH), 2847, 2803 (C–H), 1639 (C=C aromatic), 1565, 1516 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm, 8.45–8.52 (2H, m, Ar–H), 7.37–7.41 (2H, m, Ar–H), 7.06 (2H, d, $J = 1.4$ Hz, Ar–H), 6.93 (2H, s, NH_2), 6.90–6.92 (1H, m, Ar–H), 6.11 (1H, t, $J = 6.5$ Hz, NH), 5.53 (2H, s, NH_2), 4.35 (2H, d, $J = 6.4$ Hz, NH_2); ^{13}C NMR (DMSO-d_6, 101 MHz), δ ppm, 161.4, 158.49, 149.52, 149.37, 145.41, 142.27, 125.29, 123.22, 122.64, 110.73, 100.59 (Ar–C), 45.74 (Ar–CH_2–NH); ESI-MS *m/z*: calcd for $C_{14}H_{15}N_6$ $[M + H]^+$ 267.1353, found 267.1358.

4-(((2,4-diaminoquinazolin-6-yl)amino)methyl)-6-(hydroxymethyl)-2-methylpyridin-3-ol (5c) Yield: 60%, mp >350 °C; IR (ν_{max}, cm^{-1}): 3336, 3197 (NH), 1649, 1623 (C=C aromatic), 1562, 1535 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz), δ ppm, 7.85 (1H, s, Ar–H), 7.23 (1H, s, Ar–H), 7.02 (4Hs, Ar–H, NH_2), 5.57 (2H, s, NH_2), 4.53 (2H, s, CH_2), 4.31 (2H, s, CH_2), 2.35 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz), δ ppm, 161.69, 158.68, 151.45, 146.49, 145.71, 142.70, 138.30, 134.17, 130.75, 124.92, 123.98, 110.69, 102.37 (Ar–C), 59.06 (Ar–CH_2–OH), 19.95 (Ar–CH_3); ESI-MS *m/z*: calcd for $C_{16}H_{19}N_6O_2$ $[M + H]^+$ 327.1564, found 327.1565.

MTT cytotoxicity assay

The cytotoxicity activities of compounds **3a–l, 4a–c**, and **5a–c** were evaluated against HCT-15, MDA-MB-231, and SKOV-3 (colorectal, breast and ovarian cancer, respectively) using the standard MTT assay in vitro with Gefitinib and PD153035 as positive controls. The cell lines were acquired from American Type Culture Collection (ATCC).

The cell were maintained in RPMI-1640 medium (Invitrogen, 31800022) supplement with heat inactivated 10% fetal bovine serum (FBS) (Byproducts, SFB 500MX) in a humidified atmosphere of 5% CO_2, 95% air at 37 °C.

Each cell line was seeded overnight onto 96-well plate with RPMI-1640 medium, 10% FBS at a density of 8×10^3 cells per well. Thereafter, the tested compounds were added at 50 μM for the first screening and (50–0.78 μM) for IC_{50} determination. Cell viability was determined after 24 h by addition of an MTT solution (15 μL of 5 mg/mL MTT in PBS) and incubation at 37 °C for 2 h. In each of the wells, the supernatant was carefully removed and 100 μL of DMSO were added to dissolve the formazan crystals formed by the cellular reduction of MTT. The absorbance at 570 nm was measured with a microplate reader (Epoch Microplate Spectrophotometer, Biotek). The results were expressed as the IC_{50} (μM) which is the concentration of the compounds inducing a 50% inhibition of cell growth of the cells treated when compared to the growth of control cells. Each experiment was performed four times at least three independent experiments.

Conclusions

In order to develop new bioactive heterocyclic compounds, synthesis and screening of biological activity was performed using the MTT assay of quinazoline-2,4,6-triamine derivatives and 2,6-diaminoquinazolin-4(3*H*)-one. Cell viability assay data (50 μM at 24 h) revealed that among the eighteen compounds studied, quinazoline-2,4,6-triamine derivatives (**3a–l**) showed inhibition of cell growth greater than 50% compared to quinazolinone (**4a–c**) and pyridine derivatives (**5a–c**) against three cell lines (HCT-15, SKOV-3, and MDA-MB-231). Determination of the IC_{50} showed that the compounds **3e–f** exhibited high activity patterns against the three cell lines compared to the two controls (Gefitinib and PD153035). Compounds **3e–f** are characterized by having a trifluoromethoxy substituent in the benzene ring. Owing to significant results obtained, chemical studies are being conducted to improve the citotoxic activity of quinazoline-2,4,6-triamine diversified the pattern of trifluoromethoxy substitution.

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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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