SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SOME NEW 1,2,4-TRIAZOLO QUINAZOLINE DERIVATIVES

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ABSTRACT

Cancer is a major public health problem in all countries and remains as one of the top leading causes of death worldwide. Herein we report the synthesis of novel series of triazoloquinazolines as potential anticancer agents. Structures of this set of compounds were confirmed by different spectral data including IR, ^{1}H NMR, ^{13}C NMR, Mass spectra, and elemental analyses. All the newly synthesized compounds were evaluated for their anti-proliferative activity against four human cancer cell lines namely; Hepatocellular carcinoma (HePG-2), Mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and Colorectal carcinoma (HCT-116)). Results of cytotoxicity evaluation showed that the synthesized compounds displayed moderate cytotoxic activity against the selected cancer cell lines. Compound **9** showed the highest anti-proliferative effect followed by compound **7** against colorectal carcinoma cell line (HCT-116) with IC_{50} values of 17.35 and 27.05 µM respectively. As well, both compounds showed moderate activity against hepatocellular carcinoma (HePG2) with IC_{50} values of 29.47 and 39.41 µM respectively.

Keywords**:** Triazoloquinazolines, Anticancer activity, cytotoxicity evaluation, doxorubicin.

Introduction

Quinazoline derivatives are biologically important heterocycles and are known to possess a variety of biological activities such as antitumor (Fedorov et al. 2014), antimicrobial (Sun et al. 2011; Sun, Wei, et al. 2010), anti-inflammatory (Sun, Hu, et al. 2010), antihistaminic (Awadallah, El-Eraky, and Saleh 2012), antidepressant (Olmo et al. 2006), anticonvulsant (Abulkhair et al. 2016) and antihypertensive (Holló et al. 2014). Quinazoline scaffold is in the core structure of many commercially available anticancer drugs like, Gefitinib (**1**) (Eldehna et al. 2017) Erlotinib (**2**) (Gaber et al. 2018), and Lapatinib (**3**) **(Figure 1)** which were approved by FDA in the last decade for the treatment certain types of cancers (wood E. R. *et al.* 2004). On the other hand, Triazole moieties were reported to possess antitumor activity (Ezzat et al. 2020; Turky, Bayoumi, et al. 2020; Turky, Sherbiny, et al. 2020). Recently, two research articles (Alesawy et al. 2020; Ewes et al. 2020) reported the 1,2,4-triazolo[4,3-*c*]quinazolines as a new class of anticancer agents with potential inhibitory effects of EGFR-TK, and topoisomerase II. These latter studies documented the EGFR inhibition activity of **4** with IC_{50} value of 0.69 to 1.8 µM. Cell cycle study of MCF-7 cancer cell showed that the same compound could arrest cell cycle at G2/M phase and induced the apoptotic cell death. Considering the above-mentioned facts and in continuation of our recent works (El-Shershaby et al. 2020; Hannoun et al. 2020) to develop a new potential molecules with potent bioactivity, molecular hybridization between triazole and quinazoline as effective antitumor moieties was carried out. All the synthesized compounds were evaluated for their *in vitro* anticancer activity against four cancer cell lines namely; hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), human prostate cancer (PC3) and colorectal carcinoma (HCT-116).

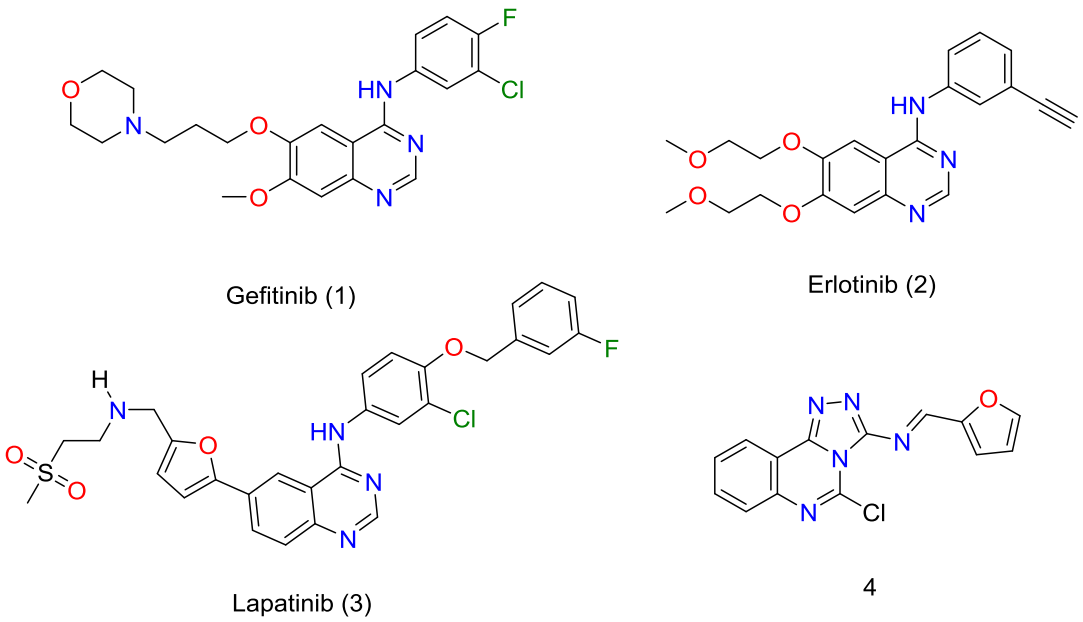
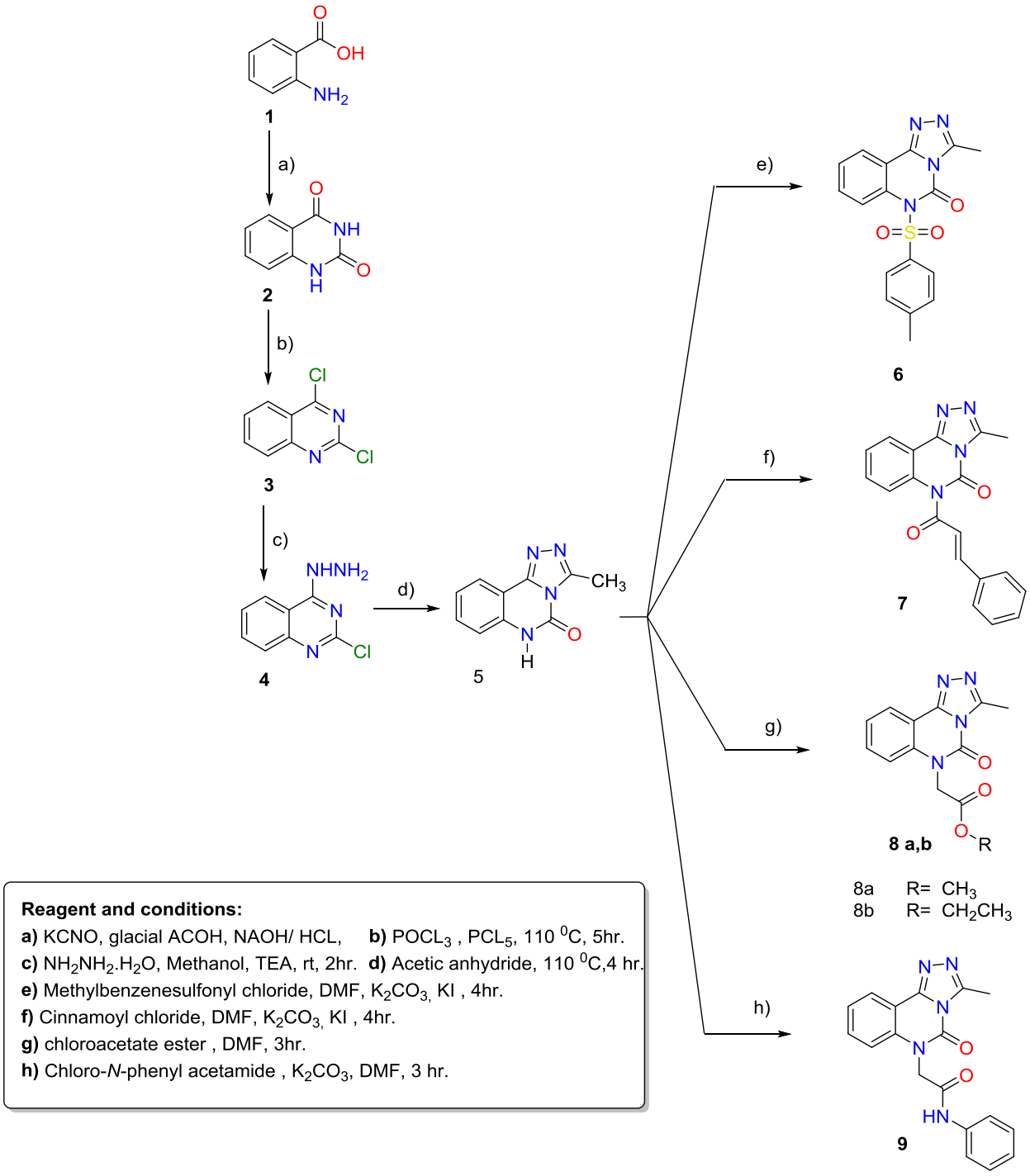


Figure 1: Structures of some anticancer agents containing quinazoline and triazoloquinazoline nuclei

Results and discussion

Chemistry: The general route for the synthesis of starting triazoloquinazolines is presented in **Scheme 1**. The *o*-ureidobenzoic acids was prepared from the corresponding anthranilic acid **1** and potassium cyanate (Asif 2014). The ureido acids are then easily cyclized to the respective quinazoline-2,4(1*H*, 3*H*)-dione **2** by heating with acid or alkali. Treating of quinazoline-2,4(1*H*, 3*H*)-dione **2** with Phosphorus oxychloride (Fujino et al. 2001) in the presence of diisopropylethylamine (DIPEA) or *N*,*N*-dimethylaniline to provide 2,4-dichloroquinazoline **3**. 2-Chloroquinazolin-4-yl)hydrazine **4** was prepared by adding hydrazine hydrate (Abul-Khair et al. 2013; Abulkhair et al. 2020) dropwise to alcoholic solution of 2,4-dichloro quinazoline **3** at 0-5°C. The resulting mixture was stirred for 0.5 h below 10°C then at room temperature for additional 2 hours. Compound **4** was heated in water bath with acetic anhydride (40 mL) for 3-4 hours then leaved to cool to obtain 3-methyl[1,2,4]triazolo[4,3-*c*]quinazolin-5(6*H*)-one (**5**) in a reasonable good yield. treating the latter with *p*-methylbenzenesulfonyl chloride in DMF for 4 hr afforded compound **6**.

6-cinnamoyl-3-methyl[1,2,4]triazolo[4,3-c]quinazolin-5(6*H*)-one (**8**) synthesized by reaction of **5** with cinnamoyl chloride in the presence of potassium iodide as a catalyst and dry DMF as a solvent. Reaction of compounds **5** with the appropriate the chloroesters in DMF and heating for 3-5 hr afforded the desired alkyl 2-(3-substituted-5-oxo-[1,2,4] triazolo[4,3-c]quinazolin-6(5H)-yl) acetate derivatives **8a** and **8b**. Compound **5** was also allowed to react with 2-chloro–*N*-phenylacetamide in DMF and in the presence of sodium acetate. this alternative route successfully afforded the final product **9** in a satisfactory yield and reasonable purities.



Scheme 1: Synthetic routes for preparation of target triazoloquinazolines.

Anticancer evaluation: Anticancer activities of the synthesized compounds were assessed on four cancer cell lines namely; hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), human prostate cancer (PC3) and colorectal carcinoma (HCT-116) using MTT assay (Mosmann 1983). Doxorubicin was used as a reference anticancer agent. The results of preliminary anticancer evaluation are shown in **Table 1**. The results of cytotoxicity evaluation showed that the majority of the synthesized compounds displayed moderate cytotoxic activities against the selected cell lines. Compound **9**showed the highest inhibitory effect followed by compound **7** against colorectal carcinoma cell line (HCT-116) with IC_{50} values of 17.35 and 27.05 µM respectively. The same two compounds also showed moderate activity against hepatocellular carcinoma (HePG2) with IC_{50} values of 29.74 and 39.41 µM respectively. Compounds (**5, 6** and **8a,b**) displayed relatively lower inhibitory potencies than all other compounds.

Table 1: *In vitro* anticancer activity of the new triazoloquinazolines.

***In vitro* Cytotoxicity IC_{50} (µM)$^{\bullet}$**				
Compound No.	**HePG2**	**MCF-7**	**PC3**	**HCT-116**
5	88.66 ± 4.8	94.47 ± 5.2	>100	65.46 ± 4.1
6	71.90 ± 3.9	73.80 ± 3.8	48.29 ± 2.9	42.48 ± 3.2
7	39.41 ± 2.7	45.20 ± 2.9	53.10 ± 3.2	27.05 ± 2.2
8a	91.45 ± 4.9	>100	>100	74.18 ± 4.4
8b	67.04 ± 3.7	90.27 ± 5.0	83.86 ± 4.6	57.13 ± 3.8
9	29.47±2.3	26.39±2.5	32.75±2.5	17.35±1.5
Doxorubicin	4.50±0.2	4.17±0.2	8.87±0.6	5.23±0.3

* **IC_{50} (µM)** : 1 – 10 (very strong). 11 – 20 (strong). 21 – 50 (moderate). 51 – 100 (weak) and above 100 (non-cytotoxic).

Experimental Section

General: All melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker-400-MHz spectrophotometer using DMSO-d_6 as a solvent and TMS as internal reference. ^{13}C NMR spectra were recorded on Bruker-100-MHz spectrophotometer using DMSO-d_6 as a solvent and TMS as internal reference. Chemical shifts were recorded in δ ppm downfield the TMS signal. Mass spectra were recorded on Hewlett Packard 5988 spectrometer. Elemental analyses were performed on CHN analyzer. All spectral measurements have been performed at the Regional Center for Mycology & Biotechnology, Al-Azhar University, Cairo, Egypt. Anticancer evaluation was carried out at the Holding Company for Biological Products and Vaccines, Egypt (Vacsera).

Synthesis of (3-methyl -[1,2,4]triazolo[4,3-c]quinazolin-5(6*H*)-one (5).

A mixture of 2-chloro-4-hydrazinylquinazoline 4 (4.0 g, 0.020 mol) and acetic anhydride (40 ml) was heated in water bath for 4 h, and leaved to cool overnight. The obtained solid was filtered and washed with water and dried, crystallized with methanol to give the target compound **5** as a yellow crystal. The structure of compound **5** was confirmed by both elemental and spectral analysis.

Yellow solid, Yield: 92%; m.p. 259-261°C. IR (KBr) cm^{-1}: 3186 (NH), 3062 (CH aromatic), 2985 (CH aliphatic), 1743 (C=O), 1627 (C=N), 1597 (C=C aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 12.19 (S, 1H, NH), 8.06-8.08 (d, *J* = 8.4 Hz, 1H, H-10 of quinazoline), 7.64 -7.66 (dd, *J* = 7.6 Hz, 1H, H-8 of quinazoline), 7.39-7.41 (d, *J* = 8.4 Hz, 1H, H-7 of quinazoline), 7.35-7.37 (dd, *J* = 8.4 Hz, 1H, H-9 of quinazoline), 2.48 (S,3H, CH_3). MS (*m/z*): 200 ($C_{١٠}H_{٨}N_4O$, 88.71%, M^+), 199 ($C_{10}H_7N_4O$, 15.67 %). ^{13}C NMR (DMSO-*d6*) δ ppm: 163.36, 153.15, 144.13, 137.32, 132.98, 124.38, 123.92, 116.42, 110.57, and 14.53. Anal. Calc. for: ($C_{10}H_8N_4O$) (M.W. = 200): C, 59.99; H, 4.03; N, 27.99 %; Found: C, 61.89; H, 4.85; N, 25.98%.

Synthesis of 3-methyl-6-tosyl-[1,2,4]triazolo[4,3-c]quinazolin-5(6H)-one (6).

To a mixture of compound **5** (0.200 g, 0.001 mole) and K_2CO3 in dry DMF (20 mL), 4-methylbenzenesulfonyl chloride (0.190 g, 0.001 mole) was added in presence of catalytic amount of KI and heated under refluxing using water bath for 4 h. After cooling to room temperature, the reaction mixture was poured onto ice-water (100 ml) and stirred for 1 h. The obtained solid was filtered and crystallized from ethanol.

Brown solid, Yield: 79%; m.p. 276-278°C. IR (KBr) cm^{-1}: 3031 (CH aromatic), 2924 (CH aliphatic),1734 (C=O), 1595 (C=C aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 7.93 (d,, 1H,, *J* = 8 Hz,H-10 of quinazoline), 7.52 (dd, 2H,, *J* = 8 Hz, H-2, H-3 of tosyl), 7.43 (dd, 1H,, *J* = 7.6 Hz, H-8 of quinazoline), 7.27 (d,,1H,, *J* = 8.4Hz, H-7 of quinazoline), 7.14 (dd, 2H,, *J* = 8 Hz, 5H,6H of tosyl) 7.02 (dd, 1H,, *J* = 8.4 Hz, H-9 of quinazoline), 2.44 (S, 3H, CH_3), 2.28 (S, 3H, CH_3 of tosyl). MS (*m/z*): 354 ($C_{17}H_{14}N_4O_3S$, 58.36%, M^+), 339 ($C_{16}H_{11}N_4O_3S$, 10.15 %), 324 ($C_{15}H_8N_4O_3S$, 10.15 %).^{13}C NMR (DMSO-*d6*) δ ppm: 167.46, 161.09, 153.35, 149.38, 146.99, 145.16, 138.69, 131.22, 129.94, 128.68, 127.97, 126.00, 123.41, 122.99, 120.23, 21.30 and 14.72. Anal. Calc. for: ($C_{17}H_{14}N_4O_3S$) (M.W. = 354): C, 57.62; H, 3.98; N, 15.81 %; Found: C, 57.85; H, 4.12; N, 16.07 %.

Synthesis of 6-cinnamoyl-3-methyl-[1,2,4]triazolo[4,3-c]quinazolin-5(6H)-one (7).

To a mixture of Compound **5** (0.200g, 0.001 mole) and K_2CO3 in dry DMF (20 mL), Cinnamoyl chloride (0.166g, 0.001 mole) was added in presence of catalytic amount of KI and heated under refluxing using water bath for 6 h. After cooling to room temperature, the reaction mixture was poured onto ice-water (100 ml) and stirred for 1 h. The obtained solid was filtered and crystallized from ethanol.

Brown solid, Yield: 76%; m.p. 281-283°C. IR (KBr) cm^{-1}: 3065 (CH aromatic), 2925 (CH aliphatic),1689 (C=O), 1654 (C=O aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 8.46 (d,, 1H,, *J* = 8 Hz, H-10 of quinazoline), 7.46 (dd, 1H,, *J* = 7.6 Hz, H-8 of quinazoline),7.34 (d, 2H, H-2, H-6 of phenyl), 7.32 (d,,1H,, *J* = 8.4 Hz, H-7 of quinazoline), 7.31 (d, 2H, H-3, H-5 of phenyl), 7.26 (dd, 1H,, *J* = 8.4 Hz, H-9 of quinazoline), 7.00 (t, 1H, H-4 of phenyl), 6.32 (S, 2H, H of alkene). MS (*m/z*): 330 ($C_{19}H_{14}N_4O_2$, 55.58 %, M^+), 298 ($C_{19}H_{14}N_4$, 12.9 %), 283 ($C_{18}H_{11}N_4$, 26.96 %). Anal. Calc. for: ($C_{19}H_{14}N_4O_2$) (M.W. = 330): C, 69.08; H, 4.27; N, 16.96 %; Found: C, 69.31; H, 4.50; N, 17.23 %.

Synthesis of alkyl 2-(3-methyl -5-oxo-[1,2,4]triazolo[4,3-c]quinazolin-6(5H)-yl) acetate derivatives (8a, 8b).

General procedure:

To a mixture of Compound **5** (0.200g, 0.001 mole) and K_2CO3 in dry DMF (20 mL), an appropriate Methyl chloroacetate or Ethyl chloroacetate (0.002 mole) was added and heated using water bath for 3 h. After cooling to room temperature, the reaction mixture was poured onto ice-water (100 ml) and stirred for 1 h. The obtained solid was filtered and crystallized from ethanol.

Synthesis of Methyl 2-(3-methyl -5-oxo-[1,2,4]triazolo[4,3-c]quinazolin-6(5H)-yl) acetate (8a).

Yellowish solid, Yield: 86%; m.p. 233-235°C. IR (KBr) cm^{-1}: 3047 (CH aromatic), 2997 (CH aliphatic), 1716 (C=O), 1620 (C=C aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 8.10 (d,, 1H, *J* = 8 Hz, H-10 of quinazoline), 7.50 (dd, 1H, *J* = 7.6 Hz, H-8 of quinazoline), 7.42 (d,,1H, *J* = 8 Hz, H-7 of quinazoline), 7.38 (dd, 1H, *J* = 8.4 Hz, H-9 of quinazoline), 5.21 (S, 2H, N-CH2), 3.74 (S, 3H, OCH_3), 2.45 (S, 3H, CH_3). MS (*m/z*): 272 ($C_{13}H_{12}N_4O_3$), 213 ($C_{11}H_9N_4O$, 26.96 %).^{13}C NMR (DMSO-*d6*) δ ppm: 168.76, 153.19, 152.39, 144.71, 137.64, 133.73, 125.20, 123.29, 116.46, 110.60, 53.06, 45.54 and 14.54. Anal. Calc. for: ($C_{13}H_{12}N_4O_3$) (M.W. = 272): C, 57.35; H, 4.44; N, 20.58 %; Found: C, 57.49; H, 4.63; N, 20.39 %.

Synthesis of Ethyl 2-(3-methyl -5-oxo-[1,2,4]triazolo[4,3-c]quinazolin-6(5H)-yl) acetate (8b).

Yellowish white solid, Yield: 79%; m.p. 238-240°C. IR (KBr) cm^{-1}: 3059 (CH aromatic), 2993 (CH aliphatic), 1728 (C=O), 1624 (C=C aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 8.13 (d,, 1H, *J* = 8 Hz, H-10 of quinazoline), 7.51 (dd, 1H, *J* = 7.6 Hz, H-8 of quinazoline), 7.42 (d,,1H, *J* = 8.4 Hz, H-7 of quinazoline), 7.38 (dd, 1H, *J* = 8.4 Hz, H-9 of quinazoline), 5.20 (S, 2H, N-CH2), 4.20 (q, 2H, *J* = 8.0 Hz, OCH_2), 2.51 (t, 3H, *J* = 7.6 Hz, OCH_2 –CH_3), 1.24 (s, 3H, CH_3). MS (*m/z*): 286 ($C_{14}H_{14}N_4O_3$, 15.79%, M^+), 213 ($C_{11}H_9N_4O$, 20.44 %). ^{13}C NMR (DMSO-*d6*) δ ppm: 168.25, 164.22, 152.39, 144.72, 137.66, 133.74, 125.21, 124.80, 116.04, 111.05, 110.59, 62.02, 45.63, 14.47 and 14.46. Anal. Calc.

for: ($C_{14}H_{14}N_4O_3$) (M.W. = 286): C, 58.74; H, 4.93; N, 19.57 %; Found: C, 58.53; H, 4.79; N, 19.81 %.

Synthesis of 2-(3-methyl-5-oxo-[1,2,4]triazolo[4,3-c]quinazolin-6(5H)-yl)-N-phenylacetamide (9).

To a mixture of Compound **5** (0.200 g, 0.001 mole) and K_2CO3 in dry DMF (20 mL), 2-chloro-*N*- phenyl acetamide (0.169 g, 0.001 mole) was added and heated using water bath for 3 hours. After cooling to room temperature, the reaction mixture was poured onto ice-water (100 ml) and stirred for 1 h. The obtained solid was filtered and crystallized from Ethanol.

Brown solid, Yield: 66%; m.p. 253-255°C. IR (KBr) cm^{-1}: 3258 (NH), 3062 (CH aromatic), 2978 (CH aliphatic), 1687 (C=O), 1592 (C=C aromatic). ^{1}H NMR (DMSO-*d6*) δ ppm: 10.21 (S, 1H, NH, D_2O exchanged), 7.90 (d,1H, *J* = 8.4 Hz, H-10 of quinazoline), 7.88 (d, 1H, *J* = 8Hz, H-7 of quinazoline), 7.62 (d, 2H, phenyl), 7.42 (dd,,1H, *J* = 7.6 Hz, H-8 of quinazoline), 7.38 (t, 2H, phenyl), 7.08 (dd, 1H, *J* = 8.4 Hz, H-9 of quinazoline),), 7.04 (t, 1H, phenyl), 4.14 (S, 2H, N-CH_2), 2.45 (S, 3H, CH_3). MS (*m/z*): 333 ($C_{18}H_{15}N_5O_2$, M^+), 168 ($C_9H_4N_4$, 10.43%). ^{13}C NMR (DMSO-*d6*) δ ppm: 168.94, 156.94, 144.43, 139.34, 138.85, 134.19, 129.34, 129.30, 123.76, 121.06, 119.63, 115.91, 57.80, and 13.20. Anal. Calc. for: ($C_{18}H_{15}N_5O_2$) (M.W. = 333): C, 64.86; H, 4.54; N, 21.01 %; Found: C, 65.09; H, 4.63; N, 20.89 %.

Anticancer activity: All the synthesized compounds were subjected to MTT proliferation assay to investigate their *in-vitro* cytotoxic activity. Hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and colorectal carcinoma (HCT-116) cell lines was chosen for investigation.

Conclusion

A series of triazoloquinazoline derivatives was synthesized and evaluated for their anticancer activity against four human cancer cell lines (Hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and Colorectal carcinoma (HCT-116)). The results of anticancer evaluation showed that most of the synthesized compounds displayed moderate cytotoxic activities against the selected cell lines. Compound **9** showed the highest inhibitory effect followed by compound **7** against hepatocellular carcinoma and colorectal carcinoma cell lines.

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تشييد وتقييم أقربازينى لبعض مشتقات (٤،١،٢) ترايازولو كينازولين الجديدة

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الملخص:

يُعدُّ السَّرطان أحدُ الأسبابِ الرئيسيَّةُ للوفاةِ في جميع أنحاء العالم خلال العقد الماضي. في محاولة لتطوير عامل مضاد للسرطان، تم تشييد سلسلة جديدة من مشتقات التريازولوكينازولين وتقييم نشاطها المضاد للسرطان ضد أربعة أنواع لخلايا السرطان البشرية وهي: سرطان خلايا الكبد وسرطان الثدي وسرطان البروستاتا وسرطان القولون والمستقيم.
أظهرت نتائج تقييم السمِّية الخلوية أن معظم المركبات أنتجت أنشطة سامة للخلايا متوسطة ضد أنواع الخلايا السرطانية المُختارة. أظهر المركب **٩** أعلى تأثير مثبِّط للخلايا السرطانية يليه المركب **٧** ضد كل من سرطان الكبد و سرطان القولون والمستقيم.