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Synthesis of novel substituted quinazoline and quinazolin-4(3*H*)-one derivatives of expected antitumor activity

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ABSTRACT

Series of 2,4-disubstituted quinazoline and 2-substituted or 2,3-disubstituted quinazolin-4(3H)-one derivatives as antitumor agents were designed and synthesized. The structures of the newly synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses. The antitumor activity of the target compounds were evaluated using the National Cancer Institute disease oriented antitumor screening protocol. It was found that all the tested compounds showed activity against two cell lines (CNS and renal) and compound ***21*** *was the most active derivative in this study with GI% 59.44 against HOP-92.*

Keywords: quinazolinones, quinazolines, antitumor activity.

INTRODUCTION

Cancer is a worldwide public health concern as it is currently the leading cause of death in many of high-developed and as well as the undeveloped countries and will probably become a major cause of mortality worldwide [1]. It is characterized by uncontrolled growth of abnormal cells in the body [2]. Nowadays, chemotherapy is one of the most widely used approaches for cancer treatment [3]. Since many of the used cytotoxic agents showed many problems as toxicity and drug-resistance [4] so the design of potent anticancer agents with higher specificity and reduced toxicity is becoming a major interest in many of the research laboratories all over the world [5].

Quinazoline is a core nucleus for designing of many potential bioactive agents as antitumor [6-10], analgesic [11], antifungal [12], antibacterial [13, 14], antiviral [15], anticonvulsant [16-19] and anti-inflammatory activities [20, 21].

Literature survey revealed that 4-anilinoquinazoline and quinazolinone derivatives are important scaffold used in drug design of effective antitumor agents as gefitinib **I** [22], thymitaq **II** [23], raltitrexed **III** [24], lapatinib **IV** [25], erlotinib **V** [26], vandetanib **VI** [27] and verubulin **VII** [28]. (Fig.1) This activity was enhanced by additional substitution at position 2 of the 4-anilinoquinazoline [29]. Also, substitution at position 2 dramatically affect the antitumor activity of the quinazolinones [30, 31], many literature revealed the importance of presence of 2,3-disubstituted quinazolinones as a broad-spectrum antitumor [7].

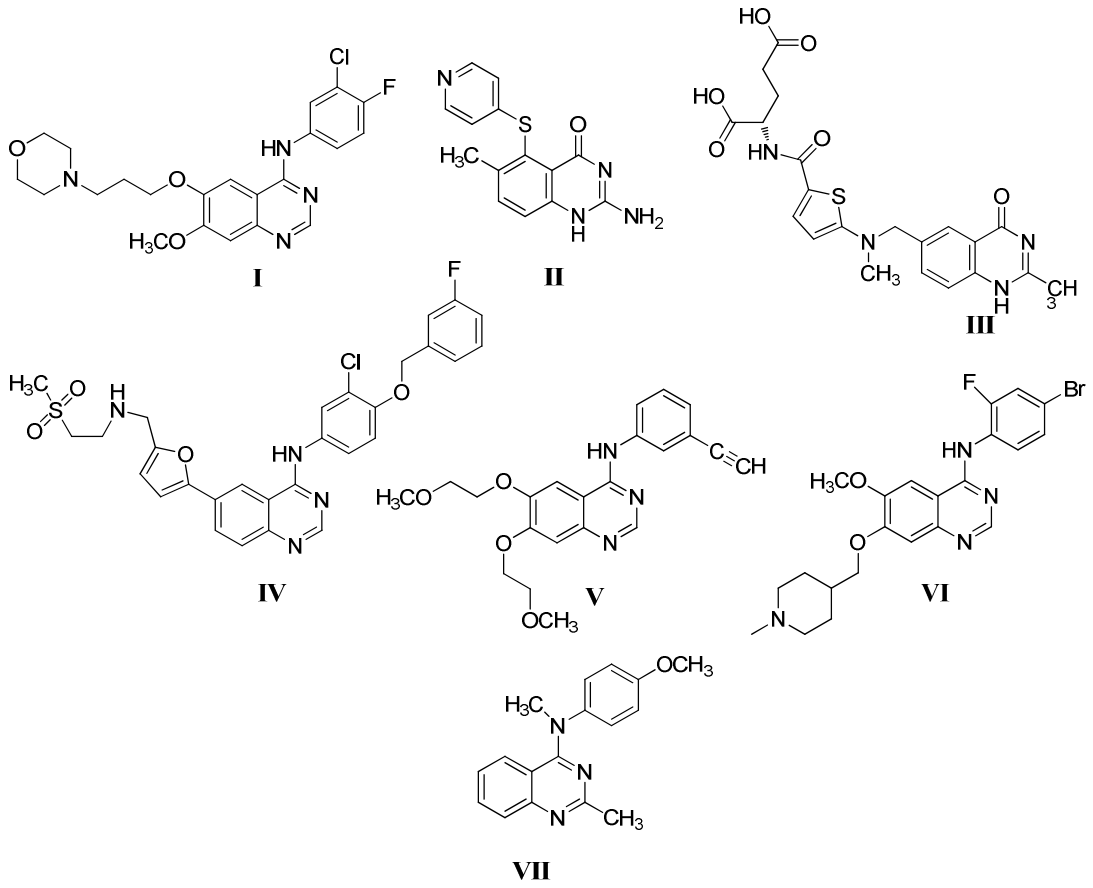


Fig.1. Chemical structures of some biologically active quinazoline and quinazolinone derivatives.

On the other hand, it is well known that aliphatic and aromatic amino acids and its conjugates represent an antitumor activity through inhibition of cell growth as result of DNA interactions [32-34]. Similarly to amino acid, the incorporation of aromatic acid hydrazide moiety especially 3-methoxy analog was found to increase the antitumor activity of their substrates [35a, 36]. Furthermore, several types of antitumor agents have sulfonamide moieties in their structures which explain that sulfonamide play a great role in antitumor activity [37-41]. Moreover, pyrazoles and 1,3,4 oxadiazoles play a major role in anticancer drug design as they displayed potent and selective action against various cell lines [35b, 42-44].

Encouraged by these findings and in an attempt to synthesize potential anti-tumor agents, a hybrid pharmacophoric approach was applied in which a new series of monosubstituted or disubstituted quinazoline or quinazolinone were designed to be hybridized with biologically active moieties including natural amino acid, aromatic acid hydrazide, sulfonamide, pyrazoles and 1,3,4 oxadiazoles in order to enhance the antitumor activity.

MATERIALS AND METHODS

2.1. Chemistry

Melting points were carried out by open capillary tube method using IA 9100 MK-Digital Melting Point Griffin Apparatus and are uncorrected. Elemental Microanalyses were carried out using Vario El III, CHNSO analyzer (Germany) at Faculty of Pharmacy, Al-azhar University. Infrared Spectra were done on Bruker FT-IR spectrophotometer Vector 22, Schimadzu 435, Perkin-Elmer 457 and Jasco FT.IR plus 460 Japan, and expressed in wave number (cm^{-1}), using KBr discs. ^{1}H NMR Spectra were carried out using Varian Mercury VX-300 NMR spectrometer at 300 MHz. and Bruker Avance III at 400 MHz (Bruker AG, Switzerland) using DMSO-d_6 or otherwise stated as a solvent. The chemical shifts were expressed in δ ppm units using trimethylsilane as the internal standard. ^{13}C NMR spectra were carried out using Bruker Avance III at 100 MHz (Bruker AG, Switzerland) using DMSO-d_6 as a solvent. Mass Spectra was done on Shimadzu Qp- 2010 plus. All the reactions were monitored by thin layer chromatography. Silica gel/TLC-cards DC- Alufolien-Kieselgel with fluorescent indicator 254 nm; layer thickness 0.2mm. Petroleum ether: ethyl acetate (1:1) or (1:2) was the adopted solvent system. All chemicals used in this study were of analytical grade. Compounds **2** [45], **3** [46], **6** [47], **13** [48], **14** [49], **15** and **16** [50] were synthesized acorrding to the reported methods.

2.1.1. General procedure for the synthesis of compounds 4a-d

To a solution of sodium carbonate (1.23 g, 15 mmole) in water (15 mL), the appropriate amino acid (5 mmole) was added and stirred till dissolution. Then, the mixture was added to 4-chloro-2-methylquinazoline (**3)** (0.89 g, 5 mmole) and refluxed for 24 h. The reaction mixture was filtered while hot and left to cool. The solution was then acidified with acetic acid (pH 6). The resulting precipitate was filtered, washed with water, dried and recrystallized from aqueous ethanol.

2.1.1.1. 2-((2-Methylquinazolin-4-yl)amino)propanoic acid (4a)

Yield 65%; mp 178–180 °C. IR (ν_{max}/cm^{-1}): 3483, 3425, 3391, 3082, 2920, 2850, 2746 (NH, CH aromatic, CH aliphatic, OH), 1627 (CO), 1597 (NH bending). ^{1}H NMR δ ppm: 2.29 (s, 3H, CH_3), 2.40 (d, 3H, CH-$\underline{CH_3}$, J = 1.8 Hz), 3.33 (m, 1H, CH), 7.41-8.08 (m, 5H, CH aromatic, NH exch. D_2O), 12.15 (s, 1H, OH, exch. D_2O). Mass (m/z): 231 (M^+, 19.13), 69 (100). Anal. Calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.34; H, 5.67; N, 18.18. Found: C, 62.15; H, 5.76; N, 18.47%

2.1.1.2. 2-((2-Methylquinazolin-4-yl)amino)succinic acid (4b)

Yield 64%; mp 150–152 °C. IR (ν_{max}/cm^{-1}): 3414, 3259, 3147, 3035, 2978, 2744 (NH, CH aromatic, CH aliphatic, 2OHs), 1658, 1612 (2COs), 1566 (NH bending). ^{1}H NMR δ ppm: 2.07 (s, 3H, CH_3), 2.34 (d, 2H, CH_2-CO, J = 5.1 Hz), 3.34 (m, 1H, CH), 7.41-8.08 (m, 5H, CH aromatic, NH exch. D_2O), 12.16 (s, 2H, 2OHs, exch. D_2O). Mass (m/z): 275 (M^+, 0.16), 160 (100). Anal. Calcd for $C_{13}H_{13}N_3O_4$ (275.26): C, 56.72; H, 4.77; N, 15.27. Found: C, 56.83; H, 4.81; N, 15.52%

2.1.1.3. 2-((2-Methylquinazolin-4-yl)amino)pentanedioic acid (4c)

Yield 62%; mp 175–177 °C. IR (ν_{max}/cm^{-1}): 3414, 3263, 3174, 3035, 2978, 2789 (NH, CH aromatic, CH aliphatic, 2OHs), 1658, 1612 (2COs), 1562 (NH bending). ^{1}H NMR δ ppm: 2.12 (s, 3H, CH_3), 2.33 (q, 2H, $\underline{CH_2}$-CH_2-COOH, J = 3.6 Hz), 2.41 (t, 2H, CH_2-$\underline{CH_2}$-COOH, J = 2.45 Hz), 5.89 (t, 1H, NH-$\underline{CH}$-CH_2, J = 3.22 Hz), 6.20 (s, 1H, NH, exch. D_2O), 7.32-8.46 (m, 4H, CH aromatic), 13.98, 14.31 (s, 2H, 2OHs, exch. D_2O). Mass (m/z): 289 (M^+, 1.54), 92 (100). Anal. Calcd for $C_{14}H_{15}N_3O_4$ (289.29): C, 58.13; H, 5.24; N, 14.53. Found: C, 58.18; H, 5.32; N, 14.90%

2.1.1.4. 2-((2-Methylquinazolin-4-yl)amino)-3-phenylpropanoic acid (4d)

Yield 57%; mp 218–220 °C. IR (ν_{max}/cm^{-1}): 3417, 3170, 3032, 2978, 2746 (NH, CH aromatic, CH aliphatic, OH), 1670 (CO), 1562 (NH bending). ^{1}H NMR δ ppm: 2.23 (s, 3H, CH_3), 2.34 (d, 2H, CH-$\underline{CH_2}$, J = 1.8 Hz), 3.29 (m, 1H, $\underline{CH}$-CH_2), 7.41 -8.07 (m, 10H, CH aromatic, NH exch. D_2O), 12.20 (s, 1H, OH, exch. D_2O). ^{13}C NMR δ ppm: 21.9 (CH_3), 39.3 (CH_2), 44.2 (CH), 121.1, 126.1, 126.3, 127.0, 134.8 (aromatic carbons), 162.2 (C=O); Mass (m/z): 307 (M^+, 1.06), 160 (100). Anal. Calcd for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.36; H, 5.58; N, 13.68. Found: C, 70.49; H, 5.62; N, 13.93%

2.1.2. General procedure for the synthesis of compounds 5a-c

A mixture of 4-chloro-2-methylquinazoline (**3)** (0.89 g, 5 mmole) and appropriate acid hydrazide (5 mmole) was refluxed in dioxane (15 mL) for 24 h in presence of triethylamine (1 mL). The excess solvent was distilled off. The residue was poured onto ice/water and the separated solid was filtered off, dried and crystallized from ethanol to give the desired compound.

2.1.2.1. 3,5-Dimethoxy-N'-(2-methylquinazolin-4-yl)benzohydrazide (5a)

Yield 72%; mp 125–127 °C. IR (ν_{max}/cm^{-1}): 3257, 3172 (2NHs), 3012 (CH aromatic), 2939 (CH aliphatic), 1693 (CO), 1600 (NH bending). ^{1}H NMR δ ppm: 2.44 (s, 3H, CH_3), 3.89 (s, 6H, 2OCH_3), 6.79 (s, 1H, NH, exch. D_2O), 7.17-8.17 (m, 7H, CH aromatic), 10.28 (s, 1H, CONH, exch. D_2O). Mass (m/z): 338 (M^+, 0.81), 165 (100). Anal. Calcd for $C_{18}H_{18}N_4O_3$ (338.36): C, 63.89; H, 5.36; N, 16.56. Found: C, 64.17; H, 5.42; N, 16.74%

2.1.2.2. 3,4,5-Trimethoxy-N'-(2-methylquinazolin-4-yl)benzohydrazide (5b)

Yield 68%; mp 100–102 °C. IR (ν_{max}/cm^{-1}): 3161, 3100 (2NHs), 3050 (CH aromatic), 2920 (CH aliphatic), 1663 (CO), 1558 (NH bending). ^{1}H NMR δ ppm: 1.93 (s, 3H, CH_3), 3.85 (s, 6H, 2OCH_3), 3.94 (s, 3H, OCH_3), 7.17-7.77 (m, 7H, CH aromatic, NH exch. D_2O), 9.74 (s, 1H, $\underline{NH}$-CO, exch. D_2O). ^{13}C NMR δ ppm: 39.3 (CH_3), 56.4 (3,5-OCH_3), 60.5 (4-OCH_3), 104.9, 105.4, 128.1, 128.9, 140.2, 140.9, 153.1, 153.2 (aromatic carbons), 165.9 (C=O). Mass (m/z): 368 (M^+, 82.11), 82 (100). Anal. Calcd for $C_{19}H_{20}N_4O_4$ (368.39): C, 61.95; H, 5.47; N, 15.21. Found: C, 62.09; H, 5.53; N, 15.73%

2.1.2.3. N'-(2-Methylquinazolin-4-yl)benzohydrazide (5c)

Yield 70%; mp 192–194°C. IR (ν_{max}/cm^{-1}): 3412, 3261 (2NHs), 3035 (CH aromatic), 2977 (CH aliphatic), 1660 (CO), 1611 (NH bending). ^{1}H NMR δ ppm: 2.35 (s, 3H, CH_3), 7.43-8.52 (m, 10H, CH aromatic, NH exch. D_2O),

8.74 (s, 1H, NH-CO, exch. D_2O). Mass (m/z): 279 (M^{+1}, 3.79), 106 (100). Anal. Calcd for $C_{16}H_{14}N_4O$ (278.31): C, 69.05; H, 5.07; N, 20.13. Found: C, 69.20; H, 5.18; N, 20.35%

2.1.3. General procedure for compounds 7a-f

A mixture of compound **6** (2.24 g, 10 mmole) and the appropriate sulphanilamide derivative (10 mmole) was refluxed in ethanol (10 mL) for 24 h in presence of anhydrous potassium carbonate (1.38 g, 10 mmole). The reaction mixture was filtered while hot and the filtrate was cooled and poured onto ice/water, then it was acidified with acetic acid (pH 6). The resulting precipitate was filtered, washed with water, dried and recrystallized from ethanol except **7d,e** which recrystallized from water as they were insoluble in organic solvents.

2.1.3.1. 4-((4-Oxo-3,4-dihydroquinazolin-2-yl)methylamino)benzenesulfonamide (7a)

Yield 64%; mp 150–152 °C. IR (ν_{max}/cm^{-1}): 3411, 3387 (2NHs, NH_2), 3070 (CH aromatic), 2927 (CH aliphatic), 1635 (CO), 1600 (NH bending), 1315, 1149 (SO_2). ^{1}H NMR δ ppm: 2.08 (s, 2H, CH_2), 5.81 (s, 3H, CH_2-NH, NH_2 exch. D_2O), 6.55-7.48 (m, 9H, CH aromatic, NH exch. D_2O). Mass (m/z): 330 (M^+, 86.59), 75(100). Anal. Calcd for $C_{15}H_{14}N_4O_3S$ (330.36): C, 54.53; H, 4.27; N, 16.96. Found: C, 54.71; H, 4.36; N, 17.32%

2.1.3.2. N-(4-((4-Oxo-3,4-dihydroquinazolin-2-yl)methylamino)phenylsulfonyl)acetamide (7b)

Yield 62%; mp 169–171 °C. IR (ν_{max}/cm^{-1}): 3394, 3305 (3NHs), 3075 (CH aromatic), 2920 (CH aliphatic), 1670, 1643 (2COs), 1396, 1126 (SO_2). ^{1}H NMR δ ppm: 2.13 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 6.92 (s, 1H, CH_2-NH, exch. D_2O), 7.30-8.25 (m, 9H, CH aromatic, NH exch. D_2O), 10.35 (s, 1H, SO_2-NH-CO, exch. D_2O). Mass (m/z): 372 (M^+, 62.2), 57 (100). Anal. Calcd for $C_{17}H_{16}N_4O_4S$ (372.40): C, 54.83; H, 4.33; N, 15.04. Found: C, 54.59; H, 4.38; N, 15.37%

2.1.3.3. 1-(4-((4-Oxo-3,4-dihydroquinazolin-2-yl)methylamino)phenylsulfonyl)guanidine (7c)

Yield 62%; mp 155–157 °C. IR (ν_{max}/cm^{-1}): 3431, 3372, 3331, 3223 (4NHs, NH_2), 3070 (CH aromatic), 2923 (CH aliphatic), 1633 (CO), 1306, 1130 (SO_2). ^{1}H NMR δ ppm: 2.07 (s, 2H, CH_2), 5.68 (s, 4H, CH_2NH, SO_2NH, NH_2), 6.59 (s, 1H, C=NH, exch. D_2O), 6.51-7.39 (m, 9H, CH aromatic, NH exch. D_2O). Mass (m/z): 372 (M^+, 16.24), 57(100). Anal. Calcd for $C_{16}H_{16}N_6O_3S$ (372.40): C, 51.60; H, 4.33; N, 22.57. Found: C, 51.72; H, 4.38; N, 22.73%

2.1.3.4. N-(Isoxazol-3-yl)-4-((4-oxo-3,4-dihydroquinazolin-2-yl)methylamino)benzenesulfonamide (7d)

Yield 54%; mp >400 °C. IR (ν_{max}/cm^{-1}): 3425, 3251 (3NHs), 3079 (CH aromatic), 2927 (CH aliphatic), 1635 (CO), 1373, 1126 (SO_2). ^{1}H NMR (D_2O) δ ppm: 2.08 (s, 3H, CH_3), 2.29 (s, 2H, CH_2), 6.91-7.99 (m, 9H, CH aromatic). Mass (m/z): 411 (M^+, 6.83), 69 (100). Anal. Calcd for $C_{19}H_{17}N_5O_4S$ (411.44): C, 55.47; H, 4.16; N, 17.02. Found: C, 55.43; H, 4.22; N, 17.24%

2.1.3.5. 4-((4-Oxo-3,4-dihydroquinazolin-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (7e)

Yield 58%; mp >400 °C. IR (ν_{max}/cm^{-1}): 3352, 3232 (3NHs), 3070 (CH aromatic), 2927 (CH aliphatic), 1662 (CO), 1369, 1126 (SO_2). ^{1}H NMR (D_2O) δ ppm: 2.08 (s, 2H, CH_2), 6.85-8.35 (m, 11H, CH aromatic). Mass (m/z): 408 (M^+, 21.85), 69 (100). Anal. Calcd for $C_{19}H_{16}N_6O_3S$ (408.43): C, 55.87; H, 3.95; N, 20.58. Found: C, 56.06; H, 4.02; N, 20.91%

2.1.3.6. N-(4,6-Dimethylpyrimidin-2-yl)-4-((4-oxo-3,4-dihydroquinazolin-2-yl)methylamino) benzenesulfon amide (7f)

Yield 60%; mp 271–273 °C. IR (ν_{max}/cm^{-1}): 3530, 3455, 3359 (3NHs), 3071 (CH aromatic), 2924 (CH aliphatic), 1644 (CO), 1618 (NH bending), 1305, 1139 (SO_2). ^{1}H NMR δ ppm: 2.02 (s, 6H, $2CH_3$), 2.49 (s, 2H, CH_2), 5.27 (s, 2H, CH_2NH, SO_2NH, exch. D_2O), 6.12-7.52 (m, 10H, CH aromatic, NH exch. D_2O). Mass (m/z): 435 (M^{-1}, 12.97), 69 (100). Anal. Calcd for $C_{21}H_{20}N_6O_3S$ (436.49): C, 57.79; H, 4.62; N, 19.25. Found: C, 57.83; H, 4.70; N, 19.38%

2.1.4. Synthesis of 4-((4-chloroquinazolin-2-yl)methylamino)benzenesulfonamide (8)

A mixture of compound **7a** (1.49 g, 5 mmole) and phosphorous oxychloride (7.5 g, 4.5 mL, 50 mmole) was refluxed for 2 h. The excess phosphorus oxychloride was distilled off. The reaction mixture was cooled and poured onto ice/water and the resulting precipitate was filtered, dried and recrystallized from ethanol. Yield 68%; mp 228–230 °C. IR (ν_{max}/cm^{-1}): 3477, 3375 (NH, NH_2), 3215 (CH aromatic), 2920 (CH aliphatic), 1627 (NH bending), 1313, 1147 (SO_2). ^{1}H-NMR δ ppm: 1.51 (s, 2H, CH_2-NH), 4.68, 4.70 (s, 3H, NH-CH_2, NH_2 exch. D_2O), 6.61-8.17 (m, 8H, CH aromatic). Mass (m/z): 349 (M^+, 15.82), 64 (100). Anal. Calcd for $C_{15}H_{13}ClN_4O_2S$ (348.81): C, 51.65; H, 3.76; N, 16.06. Found: C, 51.88; H, 3.73; N, 16.24%

2.1.5. General procedure for the synthesis of compounds 9a-d

To a solution of sodium carbonate (1.23 g, 15 mmole) in water (15 mL), the appropriate amino acid (5 mmole) was added and stirred till dissolution. Then the mixture was added to 4-((4-chloroquinazolin-2-

yl)methylamino)benzenesulfonamide **(8)** (1.75 g, 5 mmole) and refluxed for 24 h. The reaction mixture was filtered while hot and left to cool. The solution was then acidified with acetic acid (pH 6). The resulting precipitate was filtered, washed with water, dried and recrystallized from ethanol.

2.1.5.1. 2-((2-(((4-Sulfamoylphenyl)amino)methyl)quinazolin-4-yl)amino)propanoic acid (9a)
Yield 64%; mp 206–208 °C. IR (ν_{max}/cm^{-1}): 3464, 3356, 3282, 3047, 2920, 2850 (2NHs, NH_2, CH aromatic, CH aliphatic, OH), 1678 (CO), 1411, 1157 (SO_2). ^{1}H NMR δ ppm: 1.35 (d, 3H, CH_3, J = 2.7 Hz), 1.95 (s, 2H, CH_2-NH), 3.37 (m, 1H, NH-CH-COOH), 7.32-8.72 (m, 12H, CH aromatic, NHs, NH_2 exch. D_2O), 10.93 (s, 1H, OH exch. D_2O). Mass (m/z): 401 (M^+, 1.15), 90 (100). Anal. Calcd for $C_{18}H_{19}N_5O_4S$ (401.44): C, 53.85; H, 4.77; N, 17.45. Found: C, 53.94; H, 4.81; N, 17.66%

2.1.5.2. 2-((2-(((4-Sulfamoylphenyl)amino)methyl)quinazolin-4-yl)amino)succinic acid (9b)
Yield 62%; mp 139–141 °C. IR (ν_{max}/cm^{-1}): 3464, 3356, 3282, 3074, 2920, 2850 (2NHs, NH_2, CH aromatic, CH aliphatic, OH), 1681 (2COs), 1411, 1157 (SO_2). ^{1}H NMR δ ppm: 1.52 (s, 2H, CH_2-NH), 2.87 (d, 2H, CH_2-COOH, J = 4.8 Hz), 4.69 (t, 1H, NH-CH-COOH, J = 7.0 Hz), 6.59-8.20 (m, 12H, CH aromatic, NHs, NH_2 exch. D_2O), 7.19 (s, 2H, 2OHs, exch. D_2O). Mass (m/z): 446 (M^{+1}, 1.51), 160 (100). Anal. Calcd for $C_{19}H_{19}N_5O_6S$ (445.45): C, 51.23; H, 4.30; N, 15.72. Found: C, 51.27; H, 4.38; N, 15.95%

2.1.5.3. 2-((2-(((4-Sulfamoylphenyl)amino)methyl)quinazolin-4-yl)amino)pentanedioic acid (9c)
Yield 60%; mp 170–172 °C. IR (ν_{max}/cm^{-1}): 3350, 3210, 3116, 3074, 2916, 2850 (2NHs, NH_2, CH aromatic, CH aliphatic, OH), 1643 (2COs), 1415, 1157 (SO_2). ^{1}H NMR δ ppm: 1.91 (s, 2H, CH_2-NH), 2.39 (q, 2H, CH_2-CH_2-COOH, J = 2.4 Hz), 3.38 (m, 2H, CH_2 CH_2-COOH), 4.69 (t, 1H, NH-CH-COOH, J = 3.6 Hz), 5.84 (s, 4H, NH, CH_2-NH, NH_2 exch. D_2O), 6.57-8.20 (m, 8H, CH aromatic), 7.19 (s, 2H, 2OHs, exch. D_2O). Mass (m/z): 459 (M^+, 0.28), 65 (100). Anal. Calcd for $C_{20}H_{21}N_5O_6S$ (459.48): C, 52.28; H, 4.62; N, 15.24. Found: C, 52.51; H, 4.59; N, 15.41%

2.1.5.4. 3-Phenyl-2-((2-(((4-sulfamoylphenyl)amino)methyl)quinazolin-4-yl)amino)propanoic acid (9d)
Yield 63%; mp 173–175 °C. IR (ν_{max}/cm^{-1}): 3464, 3356, 3278, 3066, 2920, 2850 (2NHs, NH_2, CH aromatic, CH aliphatic, OH), 1681 (CO), 1600 (NH bending), 1408, 1157 (SO_2). ^{1}H NMR δ ppm: 1.90 (s, 2H, CH_2-NH), 2.57 (d, 2H, CH-CH_2-C_6H_5, J = 2.4 Hz), 3.38 (m, 1H, CH-COOH), 6.45 (s, 4H, NHs, NH_2 exch. D_2O), 7.29-8.70 (m, 13H, CH aromatic), 10.87 (s, 1H, OH, exch. D_2O). Mass (m/z): 477 (M^+, 0.70), 84 (100). Anal. Calcd for $C_{24}H_{23}N_5O_4S$ (477.53): C, 60.63; H, 4.85; N, 14.67. Found: C, 60.62; H, 4.89; N, 14.85%

2.1.6. General procedure for the synthesis of compounds 10a,c,d
A mixture of 4-((4-chloroquinazolin-2-yl)methylamino)benzenesulfonamide (**8**) (1.75 g, 5 mmole) and appropriate acid hydrazide (5 mmole) was refluxed in dioxane (15 mL) for 24 h in presence of triethylamine (1 mL). The excess solvent was distilled off. The residue was poured onto ice/water and the separated solid was filtered off, dried and crystallized from ethanol.

2.1.6.1. 4-((4-(2-Isonicotinoylhydrazinyl)quinazolin-2-yl)methylamino)benzenesulfonamide (10a)
Yield 72%; mp 180–182 °C. IR (ν_{max}/cm^{-1}): 3411, 3342, 3287 (3NHs, NH_2), 3100 (CH aromatic), 2922 (CH aliphatic), 1660 (CO), 1642 (NH bending), 1411, 1156 (SO_2). ^{1}H NMR δ ppm: 1.47 (s, 2H, CH_2-NH), 6.60-8.70 (m, 16H, CH aromatic, NHs, NH_2 exch. D_2O), 10.11 (s, 1H, NHCO, exch. D_2O). Mass (m/z): 449 (M^+, 2.76), 78 (100). Anal. Calcd for $C_{21}H_{19}N_7O_3S$ (449.49): C, 56.11; H, 4.26; N, 21.81. Found: C, 56.23; H, 4.31; N, 22.13%

2.1.6.2. 4-((4-(2-(3,5-Dimethoxybenzoyl)hydrazinyl)quinazolin-2-yl)methylamino)benzenesulfonamide (10c)
Yield 58%; mp 153–155 °C. IR (ν_{max}/cm^{-1}): 3414, 3338 (3NHs, NH_2), 3064 (CH aromatic), 2958 (CH aliphatic), 1689 (CO), 1419, 1165 (SO_2). ^{1}H NMR δ ppm: 1.30 (s, 2H, CH_2-NH), 3.86 (s, 6H, $2OCH_3$), 6.72-7.86 (m, 16H, CH aromatic, NHs, NH_2 exch. D_2O). Mass (m/z): 508 (M^+, 3.23), 182 (100). Anal. Calcd for $C_{24}H_{24}N_6O_3S$ (508.55): C, 56.68; H, 4.76; N, 16.53. Found: C, 56.89; H, 4.84; N, 16.79%

2.1.6.3. 4-((4-(2-(3,4,5-Trimethoxybenzoyl)hydrazinyl)quinazolin-2-yl)methylamino)benzenesulfonamide (10d)
Yield 62%; mp 183–185 °C. IR (ν_{max}/cm^{-1}): 3332, 3239, 3215 (3NHs, NH_2), 3073 (CH aromatic), 2922 (CH aliphatic), 1677 (CO), 1415, 1156 (SO_2). ^{1}H NMR δ ppm: 1.93 (s, 2H, CH_2-NH), 3.88 (s, 6H, $2OCH_3$), 3.94 (s, 3H, OCH_3), 7.13-8.72 (m, 14H, CH aromatic, NHs, NH_2 exch. D_2O), 10.36 (s, 1H, NHCO, exch. D_2O). Mass (m/z): 538 (M^+, 32.13), 57 (100). Anal. Calcd for $C_{25}H_{26}N_6O_3S$ (538.57): C, 55.75; H, 4.87; N, 15.60. Found: C, 55.92; H, 4.91; N, 15.87%

2.1.6.4. Synthesis of 4-((4-(2-benzoylhydrazinyl)quinazolin-2-yl)methylamino)benzenesulfonamide (10b)
Method A: by applying the same procedure adopted for the synthesis of compounds **10a,c,d.**
Method B: mixture of compound **11** (3.57 g, 10 mmole) and sulfanilamide (1.72 g, 10 mmole) was refluxed in ethanol (10 mL) for 24 h in presence of anhydrous potassium carbonate (1.38 g, 10 mmole). The reaction mixture was filtered while hot and the filtrate was cooled and poured into ice/water, then acidified with acetic acid (pH 6). The resulting precipitate was filtered, washed with water, dried and crystallized from ethanol. Yield 70% (method A) and 60% (method B); mp 176–178 °C. IR (ν_{max}/cm^{-1}): 3202, 3186 (3NHs, NH_2), 3053 (CH aromatic), 2924 (CH aliphatic), 1668 (CO), 1630 (NH bending), 1411, 1156 (SO_2). ^{1}H NMR δ ppm: 1.30 (s, 2H, $\underline{CH_2}$-NH), 7.27-8.03 (m, 17H, CH aromatic, NHs, NH_2 exch. D_2O), 10.57 (s, 1H, NHCO, exch. D_2O). Mass (m/z): 448 (M^+, 56.84), 91 (100). Anal. Calcd for $C_{22}H_{20}N_6O_3S$ (448.50): C, 58.92; H, 4.49; N, 18.74. Found: C, 59.08; H, 4.53; N, 18.97%

2.1.7. Synthesis of N'-(2-(bromomethyl)quinazolin-4-yl)benzohydrazide (11)
A mixture of N'-(2-methylquinazolin-4-yl)benzohydrazide (**5c)** (2.78 g, 10 mmole) and *N*-bromosuccinimde (1.77 g, 10 mmole) was stirred in dry dimethyl formamide (10 mL) at room temperature for 18 h. The reaction mixture was poured into ice/water; the obtained solid was filtered off, washed with water, dried and crystallized from ethanol. Yield 63 %; m.p. 275-277 °C. IR (ν_{max}/cm^{-1}): 3537, 3410 (2NHs), 3074 (CH aromatic), 2924 (CH aliphatic), 1654 (CO). ^{1}H NMR δ ppm: 3.09 (s, 2H, CH_2), 6.85-8.36 (m, 10H, CH aromatic), 11.08 (s, 1H, NH-CO, exch. D_2O). Mass (m/z): 356 (M^{-1}, 0.62), 80 (100). Anal. Calcd for $C_{16}H_{13}BrN_4O$ (357.20): C, 53.80; H, 3.67; N, 15.68. Found: C, 54.06; H, 3.71; N, 15.93%

2.1.8. Synthesis of 1-(2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetyl)pyrazolidine-3,5-dione (17)
A mixture of 2-(2-Methyl-4-oxoquinazolin-3(4H)-yl)acetohydrazide **(16)** (0.89 g, 5 mmole) and diethylmalonate (0.8 g, 0.8 mL, 5 mmole) was refluxed in sodium ethoxide (1%) (10 mL) for 24 h. The mixture was distilled off and the residue was poured onto ice/water. The separated solid was filtered off, dried and crystallized from ethanol. Yield 54%; mp 185–187 °C. IR (ν_{max}/cm^{-1}): 3421 (NH), 3075 (CH aromatic), 2924 (CH aliphatic), 1674-1732 (4COs). ^{1}H NMR δ ppm: 1.18 (s, 3H, CH_3), 3.15 (s, 2H, CH_2-CO), 4.15 (s, 2H, CO-CH_2-CO), 7.28-8.69 (m, 4H, CH aromatic), 13.03 (s, 1H, NH, exch. D_2O). Mass (m/z): 300 (M^+, 2.30), 80 (100). Anal. Calcd for $C_{14}H_{12}N_4O_4$ (300.27): C, 56.00; H, 4.03; N, 18.66. Found: C, 55.96; H, 4.08; N, 18.78%

2.1.9. Synthesis of 3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-2-methylquinazolin-4(3H)-one (18)
A mixture of compound **16** (0.89 g, 5 mmole) and acetyl acetone (0.5 g, 0.5 mL, 5 mmole) was refluxed in ethanol (10 mL) for 24 h in presence of glacial acetic acid (5 mL). The mixture was poured onto ice/water and the separated solid was filtered off, dried and crystallized from ethanol. Yield 62%; mp 117–119 °C. IR (ν_{max}/cm^{-1}): 3074 (CH aromatic), 2920 (CH aliphatic), 1681 (2COs). ^{1}H NMR δ ppm: 1.63 (s, 6H, $2CH_3$), 2.34 (s, 3H, CH_3), 3.35 (s, 2H, CH_2-CO), 6.36 (s, 1H, CH), 6.49-8.40 (m, 4H, CH aromatic). Mass (m/z): 296 (M^+, 9.58), 64 (100). Anal. Calcd for $C_{16}H_{16}N_4O_2$ (296.32): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.97; H, 5.85; N, 19.14%

2.1.10. Synthesis of 2-methyl-3-(2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)quinazolin-4(3H)-one (19)
A mixture of compound **16** (0.89 g, 5 mmole) and ethylacetoacetate (2.5 g, 2.4 mL, 20 mmole) was refluxed in ethanol (10 mL) for 24 h. The mixture was poured onto ice/water and the separated solid was filtered off, dried and crystallized from ethanol. Yield 59%; mp 170–172°C. IR (ν_{max}/cm^{-1}): 3076 (CH aromatic), 2920 (CH aliphatic), 1689, 1658 (3COs). ^{1}H NMR δ ppm: 2.08 (s, 3H, N-N=C-CH_3), 2.16 (s, 3H, CH_3), 3.84 (2H, CH_2-CO), 4.10 (s, 2H, N-N-CO-CH_2), 7.31-8.57 (m, 4H, CH aromatic). Mass (m/z): 297.65 (M^+, 1.56), 92 (100). Anal. Calcd for $C_{15}H_{14}N_4O_3$ (298.30): C, 60.40; H, 4.73; N, 18.78. Found: C, 60.65; H, 4.79; N, 19.04%

2.1.11. Synthesis of N'-formyl-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetohydrazide (20)
A mixture of compound **16** (0.89 g, 5 mmole) and formic acid (10 mL) was refluxed in acetic acid (10 mL) for 24 h. The mixture was poured onto ice/water and the separated solid was filtered off, dried and crystallized from ethanol. Yield 55%; mp 176–178 °C. IR (ν_{max}/cm^{-1}): 3153 (2NHs), 3070 (CH aromatic), 2924 (CH aliphatic), 2856 (CHO), 1666 (2COs). ^{1}H NMR δ ppm: 1.91 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.28-8.69 (m, 4H, CH aromatic), 9.17 (s, 1H, CHO), 12.77-12.98 (s, 2H, 2NH, exch. D_2O). Mass (m/z): 260 (M^+, 4.23), 119 (100). Anal. Calcd for $C_{12}H_{12}N_4O_3$ (260.25): C, 55.83; H, 4.65; N, 21.53. Found: C, 55.43; H, 4.74; N, 21.91%

2.1.12. Synthesis of 3-((1,3,4-oxadiazol-2-yl)methyl)-2-methylquinazolin-4(3H)-one (21)
A mixture of compound **20** (1.3 g, 5 mmole) and phosphorus pentaoxide (1.1 g, 10 mmole) was refluxed in dry toluene (10 mL) for 24 h in presence of celite (1 g). The excess toluene was distilled off and the mixture was cooled, poured onto ice/water, filtered and dried to give the desired compound. Yield 58%; mp 240–242 °C. IR (ν_{max}/cm^{-1}): 3012 (CH aromatic), 2931 (CH aliphatic), 1685 (CO). ^{1}H NMR δ ppm: 1.32 (s, 3H, CH_3), 4.05 (s, 2H, CH_2),

7.00-8.75 (m, 5H, CH aromatic). Mass (m/z): 242 (M^+, 6.46), 64 (100). Anal. Calcd for $C_{12}H_{10}N_4O_2$ (242.23): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.73; H, 4.11; N, 23.41%

2.2. Antitumor Screening

Fourteen derivatives **4a**, **5b**, **7a-e**, **9a**, **9d**, **10a**, **17**, **18**, **19** and **21** were chosen by the U.S. National Cancer Institute for the antitumor evaluation. The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 µL at plating densities ranging from 5000 to 40000 cells/well depending on the doubling time of individual cell lines. After cell incubation, the microtiter plates are incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, two plates of each cell line are fixed *in situ* with trichloroacetic acid (TCA), to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed *in situ* by the gentle addition of 50 µl of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4 °C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4% (w/v) in 1% acetic acid is added to each well, and plates are incubated for 10 minutes at room temperature. After staining, unbound dye is removed by washing five times with 1% acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI_{50}) is calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

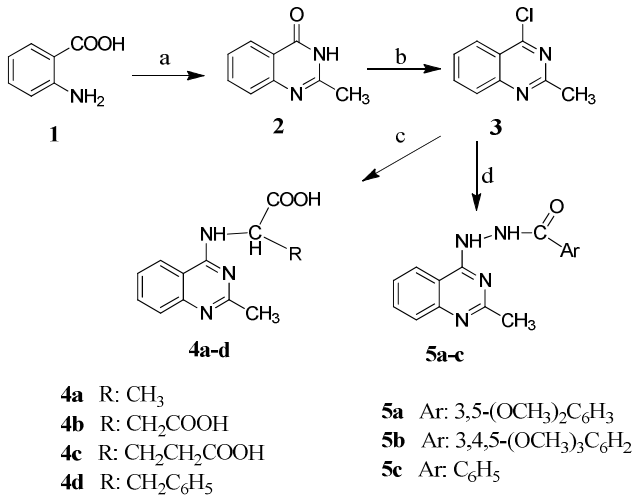
RESULTS AND DISCUSSION

3.1 Chemistry

The synthetic strategies adopted to obtain target compounds are displayed in **Schemes 1-5**. As shown in **scheme 1**, the published 4-chloro-2-methylquinazoline intermediate (**3)** was prepared according to the previously reported method from anthranilic acid (**1)** in two steps [45, 46]. The target compounds **4a-b** were synthesized through the reaction of 4-chloro-2-methyl-quinazoline (**3)** with different amino acids in the presence of sodium carbonate. IR spectra of these compounds revealed the presence of continuous series of overlapping bands due to zwitter ion vibrating at 3483-2744 cm^{-1} corresponding to amino and hydroxyl groups, in addition to CH aromatic and CH aliphatic. Moreover, ^1H NMR spectra showed the presence of peak at δ 3.29-5.89 ppm corresponding to NHCH group. Furthermore, ^{13}C NMR of compound **4d** represented the presence of peaks at δ 21.9, 39.3, 44.2 and 162.2 corresponding to methyl, CH_2, CH and carbonyl group, respectively. The reaction of 4-chloro-2-methyl-quinazoline (**3)** with appropriate acid hydrazide in dioxane and trimethylamine afforded the corresponding quinazoline

derivatives **5a-c**. IR spectra of these compounds showed the presence of a bands vibrating at 3412-3100 cm^{-1} corresponding to amino groups and bands at 1693-1660 corresponding to carbonyl groups. Moreover, ^1H NMR spectra showed the presence of singlet peaks at δ 3.80-3.94 ppm representing OCH_3 protons of acid hydrazide. Also, ^{13}C NMR of compound **5b** exhibited the presence of peaks at δ 56.4, 60.5, 165.9 corresponding to 3,5-OCH_3, 4-OCH_3 and carbonyl group, respectively.

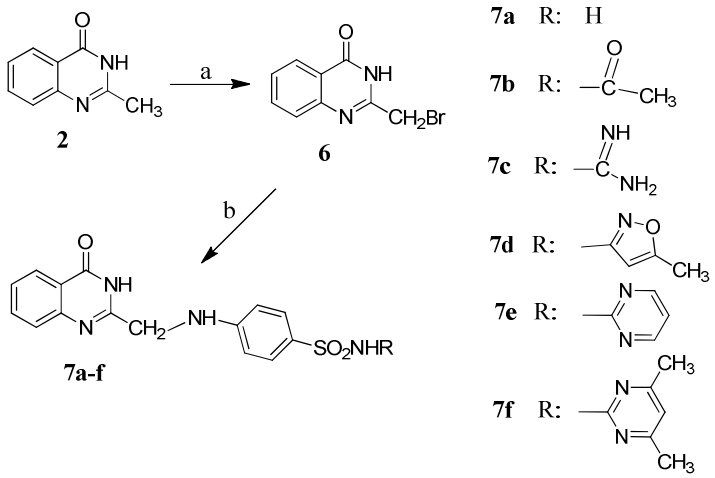
Scheme 1:



Scheme 1. Reagents and conditions: (a) thioacetamide, reflux, 2 h; (b) $POCl_3$, reflux, 2 h; (c) amino acids, Na_2CO_3, water reflux, 24 h; (d) acid hydrazides, triethylamine, dry dioxane, reflux, 24 h.

In **scheme 2**, the key intermediate 2-(bromomethyl)quinazolin-4(3*H*)-one **(6)** was synthesized in good yield according to the reported procedure [51]. Reflux of 2-(bromomethyl) quinazolin-4(3*H*)-one **(6)** with the appropriate sulfonamide in absolute ethanol in the presence of anhydrous potassium carbonate yielded compounds **7a-f**. The structures of these compounds were confirmed by the presence of singlet peak at δ 2.07-2.49 ppm corresponding to CH_2 in their ^1H NMR. As compounds **7d,e** showed high solubility in water and insolubility in organic solvents, so ^1H NMR were carried out in D_2O.

Scheme 2

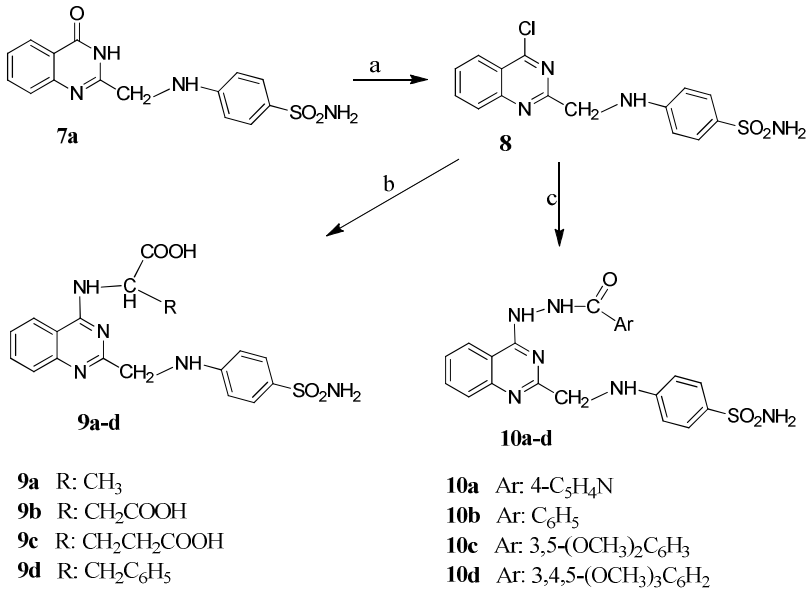


Scheme 2. Reagents and conditions: (a) N-bromosuccinimide, DMF, stir, room tempreature, 18 h; (b) sulphanilamide derivatives, anh. K_2CO_3, absolute ethanol, reflux, 24 h.

Chlorination of compound **7a** with phosphorus oxychloride resulted in the formation of compound **8**, which was reacted with different amino acids in the presence of sodium carbonate gave compounds **9a-d** and their structures were proved by the IR spectra which revealed the presence of continuous series of overlapping bands due to zwitter

ion vibrating at 3464-2850 cm^{-1} corresponding to amino and hydroxyl groups. Furthermore, ^1H NMR spectra that showed the presence of peak at δ 3.37-4.69 corresponding to NHCH proton. Also, compound **8** was refluxed with appropriate acid hydrazide to give compounds **10a-d**. The structures of **10a-d** were confirmed by their spectral data where IR spectra displayed bands in the range of 1689-1660 cm^{-1} relative to the carbonyl group. (**Scheme 3**)

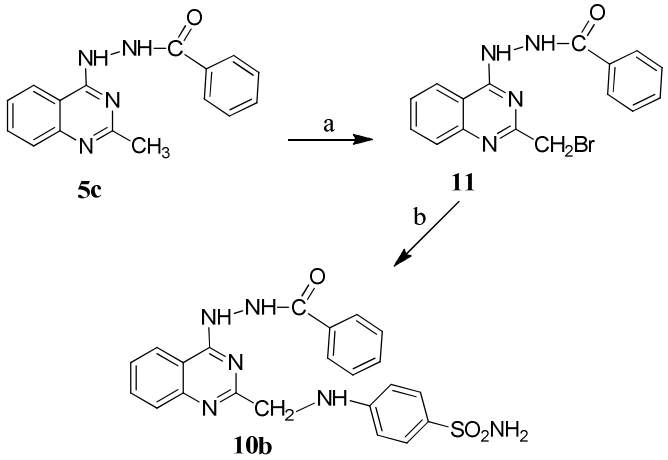
Scheme 3



Scheme 3. Reagents and conditions: (a) $POCl_3$, reflux, 2 h; (b) amino acids, Na_2CO_3, water, reflux, 24 h; (c) acid hydrazides, triethylamine, dry dioxane, reflux, 24 h.

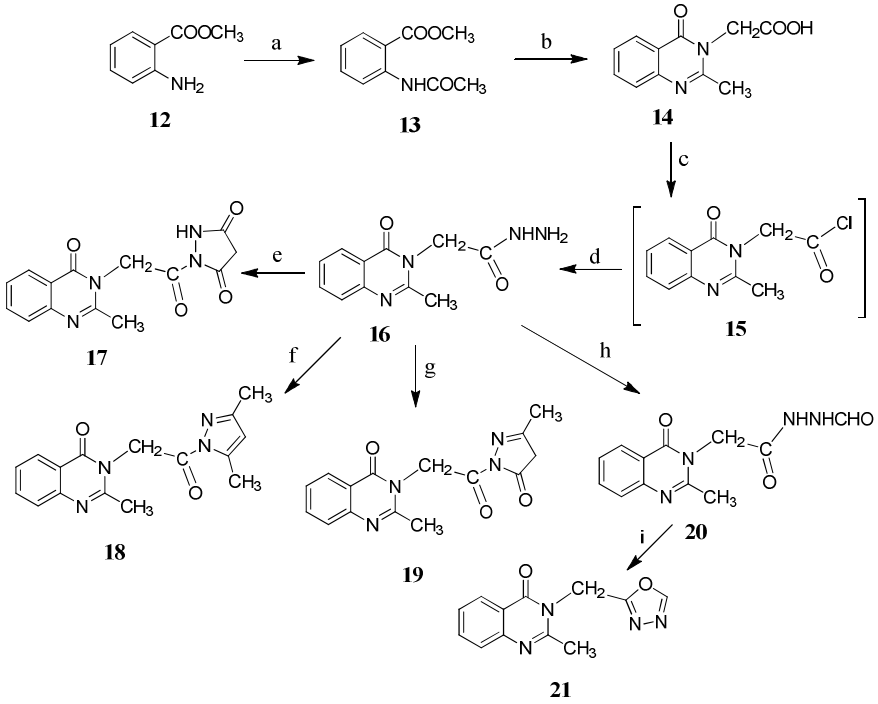
In an attempt to apply another technique for synthesis of compound **10b** through substitution at position 4 followed by substitution at position 2, as shown in **scheme 4**, it was found that the product produced in lower yield. As described in **scheme 5**, the known 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetohydrazide intermediate (**16)** was synthesized according to previously reported method from methyl anthranilate (**12)** in several steps [48-50]. The reaction of intermediate **16** with diethylmalonate in sodium ethoxide, acetyl acetone in ethanol using acetic acid, ethyl acetoacetate in ethanol and formic acid afforded the target compounds **17, 18, 19** and **20,** respectively. The structures of these compounds were confirmed through IR spectra which revealed the presence of bands corresponding to their carbonyl groups and ^1H NMR spectra which displayed the peaks representing their aliphatic protons. Cyclization of compound **20** with phosphorus pentaoxide in dry toluene afforded compound **21** ^1H NMR spectrum revealed the disappearance of singlet peak representing CHO protons.

Scheme 4



Scheme 4. Reagents and conditions: (a) N-bromosuccinimide, DMF, stir, room tempreature, 18 h; (b) sulphanilamide , anh. K_2CO_3, absolute ethanol, reflux, 24 h.

Scheme 5



Scheme 5. Reagents and conditions: (a) acetic anhydride, reflux, 2 h;(b) glycine, fusion, 5 h;(c) thionyl chloride, reflux, 1 h; (d) hydrazine hydrate, stirr, room tempreature, 1 hr; (e) diethylmalonate, absolute ethanol, sodium metal, reflux, 24 h; (f) acetyl acetone, absolute ethanol, acetic acid, reflux, 24 h; (g) ethylacetoacetate ,absolute ethanol, acetic acid, reflux, 24 h;(h) formic acid, glacial acetic, reflux, 24 h;(i) P_2O_5, dry toluene,celite, reflux, 24 h.

3.2. Preliminary anti-tumor screening

Fourteen quinazolines derivatives **4a**, **5b**, **7a-e**, **9a**, **9d**, **10a**, **17**, **18**, **19** and **21** were selected by the U.S. National Cancer Institute for *in vitro* antitumor screening assay. All the tested compounds were subjected to full NCI 60 cell line panel assay which includes nine subpanels (non-small cell lung cancer, leukemia, CNS, colon, melanoma, ovarian, prostate, breast and renal cancer). The results obtained as mean graph of the percent growth of treated cell, and represented as percent of growth inhibition (GI%) in **tables 1** and **2** [52-54]. From these results, it was observed that the tested quinazoline derivatives showed a broad-spectrum antitumor activity especially against renal cancer UO-31 and CNS cancer SNB-75.

Concerning selectivity toward certain cell lines, tested quinazoline derivatives exhibited distinctive pattern of selectivity. Lung cancer HOP-92 found to be remarkably sensitive to **5b** and **21** with GI% values of 30.04 and 59.44, respectively. Compounds **19** and **21** displayed selective activity against renal cancer UO-31 and ACHN with GI% values of 30.43 and 36.49, respectively, while compounds **5b** and **7b** proved to be sensitive to melanoma UACC-257 and LOX-IMVI with GI% values of 20.88 and 37.92, respectively. In addition, compounds **7b** and **18** showed GI% values of 21.46 and 24.06 against leukemia HL-60(TB) and MOLT-4, respectively. Regarding breast cancer MDA-MB-231/ATCC, compounds **5b**, **9a**, **9d**, **10a** and **19** represented remarkable activity with GI% values of 27.31, 24.58, 31.93, 30.56 and 25.3, respectively. Moreover, compound **7a** showed selective potency to CNS cancer SNB-75 with GI% value of 25.92. Regarding wide spectrum antitumor activity, results revealed that compounds **7b**, **9d**, **18** and **21** exhibited activity toward various cell lines belong to different tumor subpanels.

Concerning the quinazolinones derivatives, it was found that substitution at position 2 with acetamido sulphonamide moiety **7b** lead to broad activity with higher antitumor activity against melanoma cell (LOX IMVI and UACC-257). Moreover, substitution at position 3 especially with oxadiazole **21** revealed marked increase in the antitumor activity toward lung cancer (HOP-92), while presence of 3,5-dimethylpyrazole moiety **18** lead to high activity against leukemia (CCRF-CEM and MOLT-4).

Concerning the quinazolines derivatives, it was found that substitution at position 4 with 3,4,5-trimethoxybenzoylhydrazide **5b** showed good selectivity toward lung cancer (HOP-92), while disubstituted quinazolines at position 2,4 as shown in **9a,d** and **10a** lead to marked decrease in the antitumor activity except for CNS cancer (SNB-75).

Table 1: Percentage growth inhibition (GI %) of in-vitro subpanel tumor cell lines of compounds 4a, 5b, 7a-e

Subpanel tumor cell lines	Growth Inhibition % (GI %)						
	4a	5b	7a	7b	7c	7d	7e
leukemia							
CCRF-CEM	L	L	–	–	L	–	–
HL-60(TB)	nt	17.7	L	21.46	nt	–	nt
K-562	L	L	L	–	–	L	L
MOLT-4	–	–	–	18.26	–	–	–
RPMI-8226	–	–	–	–	L	L	L
SR	–	–	–	–	–	L	L
Non-small cell lung cancer							
A549\ATCC	–	–	–	16.87	–	–	–
HOP-62	L	L	–	L	L	L	L
HOP-92	–	30.04	–	L	L	–	16.16
NCI-H226	–	–	–	–	–	L	–
NCI-H322M	–	L	L	–	–	–	L
NCI-H460	L	–	L	L	L	L	L
NCI-H522	nt	nt	–	nt	nt	–	12.38
colon cancer							
COLO 205	nt	nt	L	nt	nt	L	L
HCC-2998	L	L	L	L	L	L	L
HCT-116	–	–	L	19.23	–	–	–
HT29	L	L	L	L	L	L	L
KM12	L	L	L	–	L	nt	nt
SW-620	–	–	–	L	L	–	L
CNS cancer							
SF-268	L	L	L	L	–	L	L
SF-295	–	L	–	L	–	L	L
SF-539	–	–	–	L	–	–	–
SNB-19	L	–	–	–	L	–	L
SNB-75	14.01	18.56	25.92	15.77	12.93	13.02	16.2
U251	–	–	–	L	L	L	–
Melanoma							
LOX IMVI	L	–	–	37.92	–	L	L
MALME-3M	L	L	L	13.18	L	L	L
M14	–	–	L	–	–	–	–
MDA-MB-435	–	L	L	–	L	–	L
SK-MEL-28	L	–	L	L	L	L	L
SK-MEL-2	L	L	–	nt	L	L	L
UACC-257	15.89	20.88	–	28.37	–	–	18.06
UACC-62	L	–	–	–	L	–	L
ovarian cancer							
IGROV1	L	–	–	–	L	L	L
OVCAR-3	L	L	L	L	L	L	L
OVCAR-4	L	L	–	L	L	–	–
OVCAR-5	–	–	–	L	13	–	12.24
OVCAR-8	–	–	–	–	–	L	–
NCI/ADR-RES	L	L	L	L	L	L	L
SK-OV-3	–	–	–	L	–	L	–
Renal cancer							
786-0	L	L	L	L	–	–	–
A498	–	–	–	L	L	–	L
CAKI-1	–	12.42	13.3	–	–	–	–
RXF 393	L	–	L	L	L	L	L
SN 12C	L	–	L	L	L	L	L
UO-31	15.61	23.57	22.57	20.66	21.77	12.93	21.81
Prostate cancer							
PC-3	–	–	13.73	15.47	–	–	–
DU-145	L	L	L	L	L	L	L
Breast cancer							
MCF7	L	12.49	–	19.14	L	L	L
MDA-MB-231/ATCC	L	27.31	–	L	L	–	L
HS 578T	–	–	–	L	L	L	L
BT-549	L	–	L	–	L	L	L
T-47D	–	–	–	L	–	L	–
MDA-MB-468	–	–	L	–	–	–	L

– GI % not significant; nt, not tested; L, compound proved lethal to the cancer cell line.

Table 2: Percentage growth inhibition (GI %) of in-vitro subpanel tumor cell lines of compounds 9a, 9d, 10a, 17, 18, 19 and 21

Subpanel tumor cell lines	Growth Inhibition % (GI %)						
	9a	9d	10a	17	18	19	21
leukemia							
CCRF-CEM	L		–	L	23.94	–	21.11
HL-60(TB)	L	L	L	–	–	nt	L
K-562	nt	–	L	–	13.57	L	–
MOLT-4	–	–	13.35	–	24.06	13.47	13.55
RPMI-8226	–	19.55	–	L	–	–	L
SR	–	–	–	L	L	L	L
Non-small cell lung cancer							
A549\ATCC	L	L	L	–	L	–	L
HOP-62	L	L	–	L	–	L	–
HOP-92	nt	nt	–	L	L	13.01	59.44
NCI-H226	12.67	19.42	–	–	–	14.12	–
NCI-H460	–	–	–	L	L	L	L
NCI-H522	–	–	nt	–	19.84	15.77	Non
colon cancer							
COLO 205	L	L	L	L	L	L	L
HCC-2998	L	L	L	–	L	L	L
HCT-15	–	–	–	L	17.05	L	19.18
HT29	L	L	L	L	L	L	L
KM12	L	L	L	nt	–	nt	L
SW-620	–	–	–	L	L	–	–
CNS cancer							
SF-268	L	L	L	L	–	–	–
SF-295	–	–	–	L	–	–	–
SF-539	–	L	–	–	L	–	–
SNB-19	L	–	–	L	L	L	L
SNB-75	18.03	20.35	20.67	8.74	16.92	15.31	10.6
U251	–	–	L	L	L	L	L
Melanoma							
LOX IMVI	L	–	–	–	15.23	L	14.44
MALME-3M	L	–	–	L	–	L	L
MDA-MB-435	L	L	L	L	–	L	–
SK-MEL-28	–	–	L	L	–	L	L
SK-MEL-2	L	L	L	L	L	L	L
UACC-257	–	–	nt	–	L	–	nt
UACC-62	–	–	–	L	–	L	13.26
ovarian cancer							
IGROV1	–	L	13.48	L	L	–	–
OVCAR-3	L	L	–	L	–	–	L
OVCAR-4	–	–	L	L	–	L	L
OVCAR-5	–	–	14.39	L	L	–	13.2
OVCAR-8	–	L	–	L	L	L	L
NCI/ADR-RES	L	L	L	L	L	L	L
SK-OV-3	L	L	–	–	L	–	L
Renal cancer							
786-0	L	L	L	–	L	–	L
A498	L	–	–	–	L	L	L
ACHN	–	15.7	18.98	L	27.48	13.57	36.49
CAKI-1	14	19.51	14.55	L	–	–	–
RXF 393	L	L	L	L	L	L	–
SN 12C	–	–	L	L	L	–	L
UO-31	27.5	25.75	26.86	17.67	22.05	30.43	20.43
Prostate cancer							
PC-3	15.65	12.15	17	–	–	–	–
DU-145	L	L	L	L	L	L	L
Breast cancer							
MCF7	–	12.38	–	L	L	–	–
MDA-MB-231/ATCC	24.58	31.93	30.56	L	L	25.3	–
HS 578T	L	13.35	–	L	L	L	–
BT-549	–	L	L	–	–	L	–
T-47D	–	–	–	L	14.56	18.83	–
MDA-MB-468	L	L	L	–	–	L	–

– GI % not significant; nt, not tested; L, compound proved lethal to the cancer cell line.

CONCLUSION

From the previous results, it was found that all the tested compounds showed activity against two cell lines (CNS and renal) and compound **21** was the most active derivative in this study with GI% 59.44 against HOP-92.

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