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SYNTHESIS AND REACTIONS OF A NEW SERIES OF 1,2,4-TRIAZOLO[4,3-*c*]QUINAZOLINES

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Abstract – 3-Ethoxycabonyl-1,2,4-triazolo[4,3-*c*]quinazoline (**2**) has been synthesized in excellent yield by the condensation of 4-hydrazinoquinazoline (**1**) with diethyl oxalate and was converted into 3-carbohydrazide **3**. The later product was treated with potassium thiocyanate, phenylisothiocyanate or carbon disulfide followed by reaction with hydrazine hydrate to give the respective new 1,2,4-triazolo[4,3-*c*]quinazoline derivatives **4**, **8** or **12**. Dehydrative cyclization of the later compounds with concentrated sulphuric acid, sodium hydroxide, m-bromobenzoic acid, carbon disulfide, oxalic acid, phenacyl bromide or benzoin yielded the target heterocycles namely, 1,3,4-thiadiazole, 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole or 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine incorporating 1,2,4-triazolo[4,3-*c*]quinazoline ring. The structure of the above compounds was confirmed from their spectral characteristics.

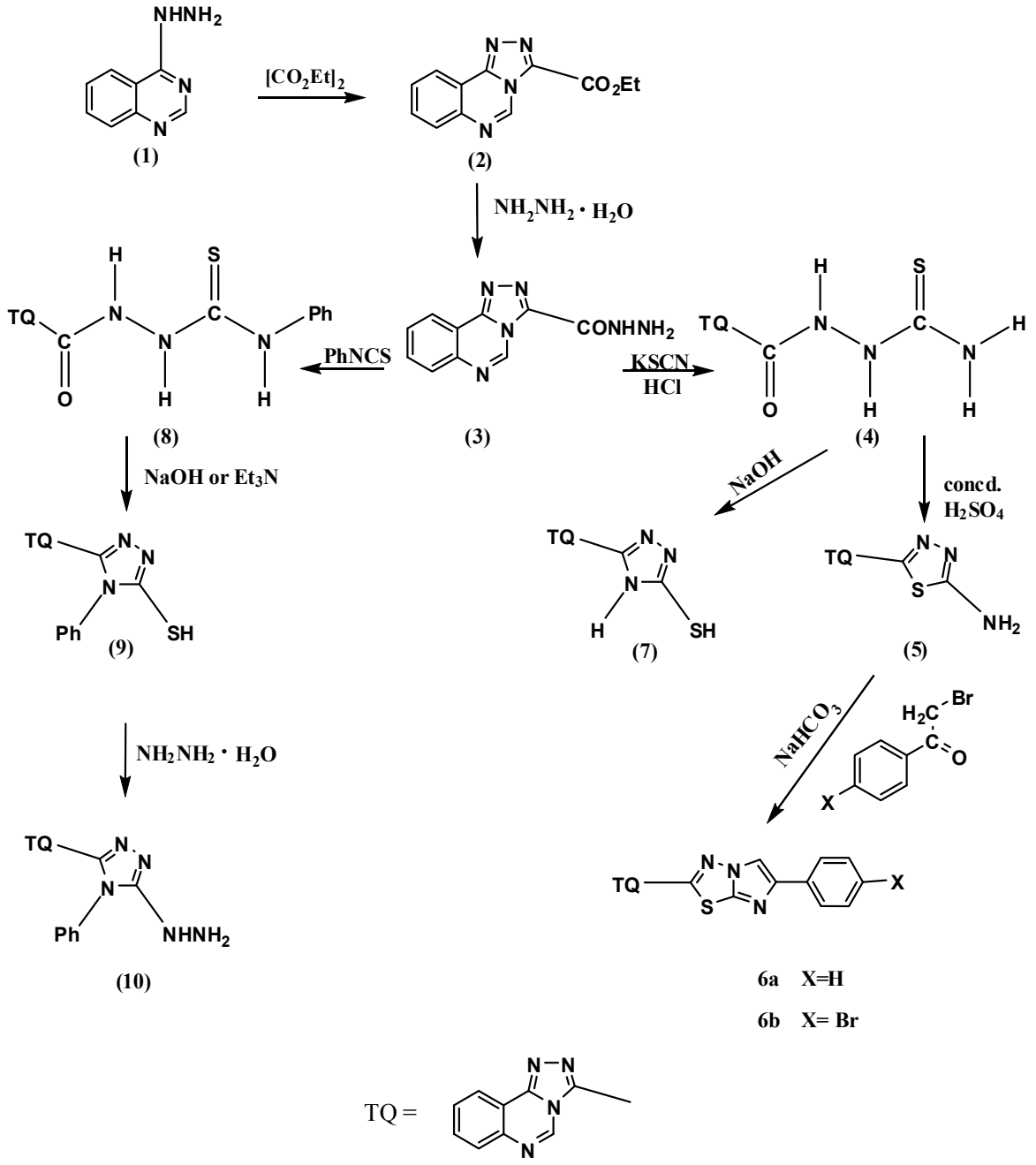
Quinazoline derivatives are multitarget agents with a broad spectrum of biological activity.[1–12] A number of quinazolines act as anticancer,[13,14] which have a wide range of activity against different kinds of human cancer.[8,13,15,16] Some of them (ZD1836, ZD 6474, OSI-774 and GW-2016) are currently in clinical testing. Also, certain 1,2,4-triazoles have a broad spectrum of pharmacological activities.[17] Several methods are reported for the synthesis of 1,2,4-triazoloquinazoline from 4-hydrazino-quinazolines.[18-21]

Based on the above mentioned behavior of quinazoline and triazole rings, a new series of 1,2,4-triazolo[4,3-*c*]quinazoline system bearing a variety of mono- and fused heterocyclic moiety were synthesized.

Condensation of 4-hydrazinoquinazoline (**1**)[22] with diethyl oxalate yielded 3-ethoxycarbonyl-1,2,4-triazolo[4,3-*c*]quinazoline (**2**) (Sheme 1). Its formation can be explained to be a consequence of the role of ethyl oxalate that acts as oxaloylating agent for the hydrazine moiety, forming the oxaloyl hydrazine residue that underwent dehydrative cyclization to form the triazoloquinazoline **2**. The structure of **2** was deduced from its spectral analysis. Thus, the IR spectrum of **2** showed an absorption band at 1746 cm^{-1} for the ester group. Also, it's ^1H NMR spectrum revealed the absence of NH signal and the presence of ethyl ester group as triplet at δ 1.33 ($C\underline{H}_3$) and a quartet at δ 4.29 ($C\underline{H}_2$). Treatment of compound **2** with hydrazine hydrate in ethanolic solution afforded the key compound 1,2,4-triazolo[4,3-*c*]quinazoline-3-carbohydrazide (**3**) as confirmed from its spectral data. Its IR spectrum showed the absence of ester absorption band and the presence of amide absorption band at 1670 cm^{-1}.

Reaction of the key compound **3** with potassium thiocyanate in the presence of concentrated hydrochloric acid led to the formation of hydrazinecarbothioamide **4**. Dehyrative cyclization of **4** can be attempted either in acidic or alkaline medium whereupon two different heterocycles were obtained; 1,3,4-thiadiazole or 1,2,4-triazole, respectively. Therefore, treatment of compound **4** with concentrated sulfuric acid yielded 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-1,3,4-thiadiazole-2-amine (**5**). Its IR spectrum showed the presence of NH_2 group absorption band at 3424 and 3330 cm^{-1}, while it's MS revealed a molecular ion peak at m/z 269. On the other hand, dehydrative cyclization of compound **4** with sodium hydroxide gave 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4*H*-1,2,4-triazole-3-thiol (**7**).

Refluxing of compound **5** with phenacyl bromides in the presence of sodium bicarbonate afforded imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives **6a**,**b** as confirmed from their IR spectra, which showed the disappearance of NH_2 stretching bands. The mass spectrum of **6a** showed a molecular ion peak at m/z 369. Moreover, the reaction of hydrazide **3** with phenylisothiocyanate afforded 2-(1,2,4-triazolo[4,3-*c*]-quinazoline-3-carbonyl)-*N*-phenylhydrazinecarbothioamide (**8**). Ringclosure of the later to 3-thiolo-1,2,4-triazole **9** was attempted with either triethylamine in ethanol or with sodium hydroxide solution, which gave better yield. The IR spectrum showed the disappearance of the carbonyl absorption band and appearance of SH stretching band at 2632 cm^{-1},[23] in addition to the characteristic absorption bands of the triazoloquinazoline nucleus. The mass spectrum of **9** revealed a molecular ion peak at m/z 345. Hydrazinolysis of **9** yielded 5-hydrazino-4-phenyl-4*H*-1,2,4-triazole derivative **10**. Its IR spectrum showed only $NHNH_2$ absorptions at 3419, 3320 and 3280 cm^{-1},[24] which can be used for further conversion to fused heterocycles.[25]

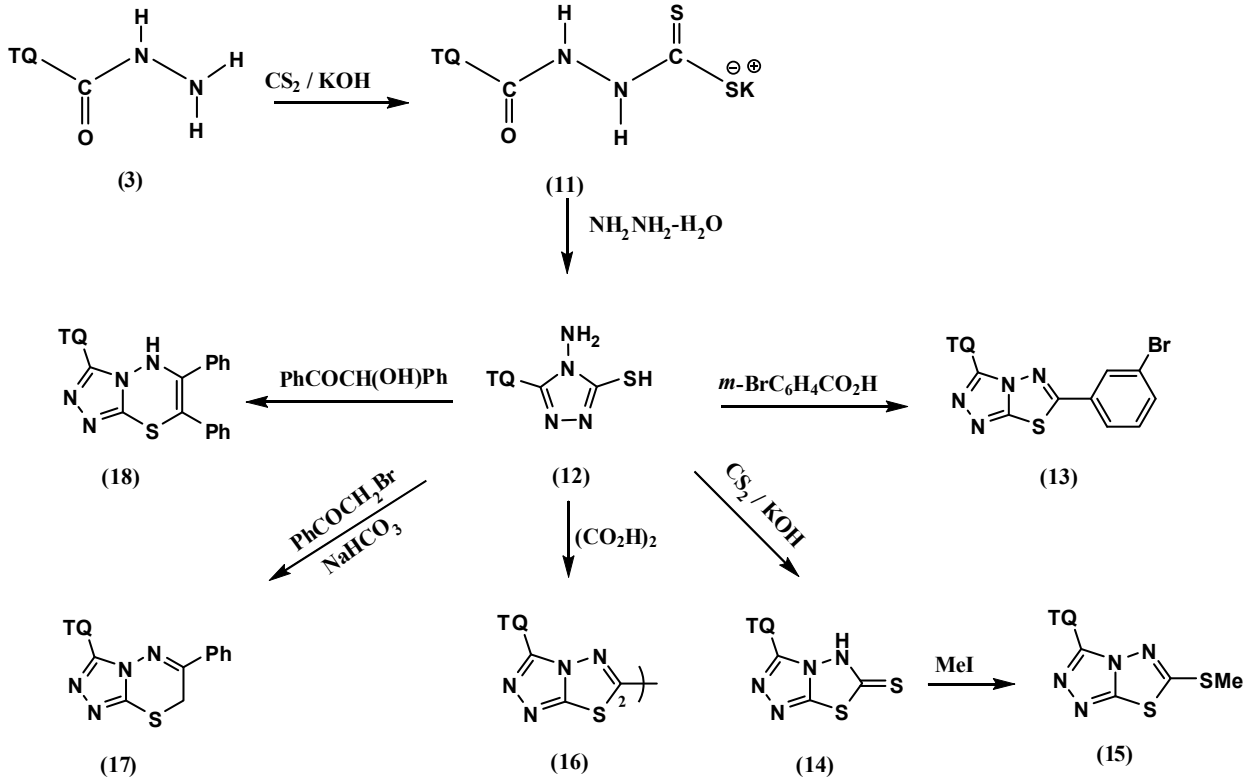


Scheme 1

Furthermore, the hydrazide **3** reacted with carbon disulfide in the presence of potassium hydroxide to produce the potassium salt **11** (Scheme 2), which underwent dehydrative cyclization upon treatment with hydrazine hydrate to give 4-amino-4*H*-1,2.4-triazole-3-thiol derivative **12**. The structure of **12** was confirmed by spectral data. It's ^{1}H NMR spectrum revealed three exchangeable singlets at δ 8.26, 8.29 and 13.51 for NH_2 and SH protons, respectively.

5-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**) is considered as key starting for the synthesis of diverse heterocyclic compounds upon treatment in one-step with one and two

carbon cyclizing reagents (Scheme 2). Thus, the reaction of compound **12** with m-bromobenzoic acid yielded 3-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-6-(3-bromophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**13**). It's ^{1}H NMR spectrum showed the disappearance of NH_2 and SH proton signals of the starting material. Moreover, treatment of compound **12** with carbon disulfide in the presence of potassium hydroxide led to the formation of 3-([1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazole-6(5*H*)-thione (**14**). The mass spectrum of **14** showed a molecular ion peak at m/z 326. The structure of **14** was also confirmed by methylation with methyl iodide affording 3-(1,2,4-triazolo[4,3-*c*]-quinazolin-3-yl)-6-(methylthio)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**15**). On the other hand, the reaction of **14** with oxalic acid in the presence of phosphoryl chloride gave 3,3'-di([1,2,4]triazolo[4,3-*c*]-quinazolin-3-yl)]-6,6'-bi[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole) (**16**). It's ^{1}H NMR spectrum showed the disappearance of NH_2 and SH proton signals. Compound **12** can be also used as a precursor for the synthesis of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives. Thus, treatment of **12** with phenacyl bromide under reflux afforded 3-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**17**), whereas its reaction with benzoin gave 3-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-6,7-diphenyl-5*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**18**). The structures of both compounds was confirmed from their spectral data. The mass spectrum of **18** showed a molecular ion peak at m/z 460. The spectroscopic data and elemental analyses of these compounds were consistent with the assign structures.



Scheme 2

EXPERIMENTAL

Melting points were determined on a Kofler Block and are uncorrected. TLC were done on Merck Kiesel gel 60-f 254 precoated plastic plates. Infrared spectra were measured with Fourier Transform infrared 8400 spectrophotometer for potassium bromide pellets. The ^{1}H NMR spectra were recorded on a JEOL JNM ECA 500 MHZ with tetramethylsilane as internal standard. Mass spectra were recorded at 70 ev by 5980 series II GC coupled with 5989 B mass spectrometer. Microanalysis were performed by the microanalytical unit, Cairo university, Cairo.

4-Hydrazinoquinazoline (1).

This compound **1** was prepared as described earlier.[22]

3-Ethoxycarbonyl-1,2,4-triazolo[4,3-*c*]quinoxaline (2). A mixture of 4-hydrazinoquinoxaline (**1**, 5 g, 31.2 mmol) and diethyl oxalate (100 mL) was heated under reflux for 3 h. The reaction mixture was evaporated under reduced pressure the residue was poured onto crushed ice and kept in refrigerator overnight. The product was filtered, washed with Et_2O and crystallized from EtOH to give the titled compound **2** as colorless needles (6 g, 80% yield); mp 175-176 ^{o}C; IR: 1746 (CO_2Et), 1590 (triazole ring C=N), 1476 (pyrimidine ring C=N) and 1420 cm^{-1} (pyrimidine ring C=C); ^{1}H NMR (DMSO-d_6): δ 1.33 (t, 3H, -$CH_2C\underline{H}_3$), 4.29 (q, 2H, -$C\underline{H}_2CH_3$), 7.25 (t, 1H, aromatic-H), 8.03 (t, 1H, aromatic-H), 8.19 (d, 1H, aromatic-H), 8.60 (d, 1H, aromatic-H) and 8.82 (s, 1H, pyrimidine-H); MS: m/z (%): 242 (M^+, 48), 197 (M^+ -CO_2Et, 6), 170 (M^+ -$CO_2C_2H_4$, 100), 115 (M^+ -$C_4H_5N_3O_2$, 9) and 89 (M^+ -$C_5H_5N_4O_2$, 3); Anal. Calcd for $C_{12}H_{10}N_4O_2$ (242.08): C, 59.5; H, 4.2; N 23.1%. Found: C, 59.4; H, 4.6; N, 23.3%.

1,2,4-Triazolo[4,3-*c*]quinazoline-3-carbohydrazide (3). A solution of 3-ethoxycarbonyl-1,2,4-triazolo[4,3-*c*]quinazoline (**2**, 0.5 g, 2 mmol) and hydrazine hydrate (99%, 0.5 mL) in EtOH (40 mL) was heated under reflux for 10 h. The reaction mixture on cooling gave a solid mass, which was filtered, washed with EtOH and crystallized from DMF to give the titled compound **3** as colorless needles (0.4 g, 85% yield); mp 245-246 °C; IR: 3326 (NH), 3100, 3071 (NH_2), 1670 (CON), 1595 (triazole ring C=N), 1474 (pyrimidine ring C=N) and 1438 cm^{-1} (pyrimidine ring C=C); ^{1}H NMR (DMSO-d_6): δ =7.33 (t, 1H, aromatic-H), 8.03 (t, 1H, aromatic-H), 7.93 (d, 1H, aromatic-H), 8.09 (d, 1H, aromatic-H), 9.40 (s, 1H, pyrimidine-H), 12.81 (s, 1H, exchangeable, NH) and 13.29, 13.50 (2s, 2H, exchangeable, NH_2); MS: m/z (%): 228 (5, M^+), 213 (50, M^+ -NH), 197 (5, M^+ -$NHNH_2$), 143 (17, M^+ -$C_2H_3N_3O$) and 117 (8, M^+ -$C_3H_3N_4O$); Anal. Calcd for $C_{10}H_8N_6O$ (228.21): C, 52.63; H, 3.53; N, 36.83%. Found: C, 52.41; H, 3.12; N, 37.01%.

2-(1,2,4-Triazolo[4,3-*c*]quinazoline-3-carbonyl)hydrazinecarbothioamide (4). A mixture of 1,2,4-triazolo[4,3-*c*]quinazoline-3-carbohydrazide (**3**, 1 g, 4 mmol) and potassium thiocyanate (1 g, 10 mmol)

was added to 5 mL of water containing 1 mL of concd HCl. The mixture was warmed on a water bath for 2 h, then cooled, poured onto crushed ice and the product was filtered, washed with water, dried and crystallized from EtOH to give the titled compound **4** as colorless needles (1g, 83% yield); mp 221-222 °C; IR: 3181 (NH), 3388, 3290 (NH_2), 1691 (CON), 1520 (triazole ring C=N), 1448 (pyrimidine ring C=N), 1420 (pyrimidine ring C=C) and 1310 cm^{-1} (C=S); ^1H NMR (DMSO-d_6): δ = 7.27 (t, 1H, aromatic-H), 7.45 (t, 1H, aromatic-H), 8.19 (d, 1H, aromatic-H), 8.67 (d, 1H, aromatic-H), 8.79 (s, 1H, pyrimidine-H), 9.37 (s, 1H, exchangeable, NH), 10.84 (s, 1H, exchangeable, NH), 12.79 and 14.57 (2s, 2H, exchangeable, NH_2); Anal. Calcd for $C_{11}H_9N_7OS$ (287.30): C, 45.99; H, 3.16; N, 34.13; S, 11.16%. Found: C, 46.3; H, 3.01; N, 34.02; S, 11.65%.

5-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-1,3,4-thiadiazole-2-amine (5). A mixture of 2-(1,2,4-triazolo-[4,3-*c*]quinazolin-3-carbonyl)hydrazinecarbothioamide (**4**, 0.4 g, 1.3 mmol) in cold concd H_2SO_4 (4 mL) was stirred for 10 min. Then, the mixture was allowed to cool at room temperature. After stirring for an additional 30 min, the resulting solution was poured onto ice-cold water and made alkaline to pH 8 with 20% NH_4OH. The precipitated product was filtered, washed with water, dried and crystallized from EtOH to give the titled compound **5** as brown needles (0.24 g, 64% yield); mp 261-262 °C; IR: 3424, 3330 (NH_2), 1548 (triazole ring C=N), 1492 (pyrimidine ring C=N) and 1382 cm^{-1} (pyrimidine ring C=C); MS: m/z (%): 269 (10, M^+), 213 (14, M^+ -CH_2N_3), 185 (100, M^+ -CH_2N_5), 129 (30, M^+ -$C_3H_2N_5S$), 76 (4, M^+ -$C_5H_3N_7S$) and 78 (98, M^+ -C_5HN_7S); Anal. Calcd for $C_{11}H_7N_7S$ (269.29): C, 49.06; H, 2.62; N, 36.41; S, 11.91%. Found: C, 49.20; H, 2.43; N, 36.75; S, 11.51%.

2-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (6a). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-1,3,4-thiadiazole-2-amine (**5**, 0.1 g, 0.3 mmol) and phenacyl bromide (0.15 g, 0.7 mmol) in absolute EtOH (10 mL) was heated under reflux for 24 h. The reaction mixture was slowly quenched onto crushed ice with stirring and it was neutralized with 10% aqueous sodium bicarbonate solution. The precipitate which separated out after standing overnight was filtered, washed with cold water, dried and crystallized from absolute EtOH to give the titled compound **6a** as brown needles (0.1 g, 76% yield); mp 181-182 °C; IR: 1593 (triazole ring C=N), 1496 (pyrimidine ring C=N) and 1468 cm^{-1} (pyrimidine ring C=C); MS: m/z (%): 369 (2, M^+), 313 (2, M^+ -$2N_2$), 185 (100, M^+ -$C_9H_6N_5$) and 129 (30, M^+ -$C_{11}H_6N_5S$); Anal. Calcd for $C_{19}H_{11}N_7S$ (369.40): C, 61.78; H, 3.00; N, 26.54; S, 8.68%. Found: C, 61.61; H, 3.10; N, 26.30; S, 8.24%**.**

2-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6-(4-bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole (6b). A solution 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-1,3,4-thiadiazole-2-amine (**5**, 0.15 g, 0.3 mmol) and 4-bromophenacyl bromide (0.15 g, 0.5 mmol) in absolute EtOH (10 mL) was heated under reflux for 24 h.

The reaction mixture was slowly quenched onto crushed ice with stirring and it was neutralized with 10% aqueous sodium bicarbonate solution. The precipitate which separated out after standing overnight was filtered, washed with cold water, dried and crystallized from absolute EtOH to give the titled compound **6b** as brown needles (0.1 g, 62% yield); mp 159-160 °C; IR: 1587 (triazole ring C=N), 1482 (pyrimidine ring C=N) and 1425 cm^{-1} (pyrimidine ring C=C); Anal. Calcd for $C_{19}H_{10}BrN_7S$ (448.30): C, 50.90; H, 2.25; Br, 17.82; N, 21.87%. Found: C, 50.80; H, 2.60; Br, 17.41; N, 21.90%.

5-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-4*H*-1,2,4-triazole-3-thiol (7). To a solution of (20 mL, 5% NaOH) and 2-(1,2,4-triazolo[4,3-*c*]quinazolin-3-carbonyl)hydrazinecarbothioamide (**4**, 2.87 g, 10 mmol) was added and refluxed for 3 h. The reaction mixture was cooled, poured onto crushed ice, neutralized with concd HCl . The resulting solid was filtered, washed with water, dried and crystallized from EtOH to give the titled compound **7** as pale yallow needles (2 g, 74% yield); mp 281-282 °C; IR: 3458 (NH), 2586 (SH), 1595, 1548 (triazole ring C=N), 1478 (pyrimidine ring C=N) and 1420 cm^{-1} (pyrimidine ring C=C); ^{1}H NMR (DMSO-d_6): δ = 6.96 (t, 1H, aromatic-H), 7.24 (t, 1H, aromatic-H), 7.92 (d, 1H, aromatic-H), 8.59 (d, 1H, aromatic-H), 8.80 (s, 1H, pyrimidine-H), 14.03 (s, 1H, exchangeable, SH/NH) and 14.25 (s, 1H, exchangeable, SH/NH); Anal. Calcd for $C_{11}H_7N_7S$ (269.29): C, 49.06; H, 2.62; N, 36.41; S, 11.91%. Found: C, 49.20; H, 2.82; N, 36.11; S, 11.54%.

2-(1,2,4-Triazolo[4,3-*c*]quinazoline-3-carbonyl)-*N*-phenylhydrazinecarbothioamide (8). A mixture of 1,2,4-triazolo[4,3-*c*]quinazoline-3-carbohydrazide (**3**, 2.28 g, 10 mmol) and phenylisothiocyanate (1.79 ml, 15 mmol) in EtOH (50 mL) under reflux for 10 h. The reaction mixture was cooled and the product was filtered, washed with EtOH and crystallized from dioxan to give the titled compound **8** as pale yellow needles (2.6 g, 71% yield); mp 324-325 °C; IR: 3424, 3226 (3NH), 1680 (CON), 1590 (triazole ring C=N), 1454 (pyrimidine ring C=N), 1420 (pyrimidine ring C=C) and 1308 cm^{-1} (C=S); Anal. Calcd for $C_{17}H_{13}N_7OS$ (363.40): C, 56.19; H, 3.61; N, 26.98; S, 8.82%. Found: C, 56.00; H, 3.50; N, 27.31; S, 8.34%.

5-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (9). Method A. A solution of 2-(1,2,4-triazolo[4,3-*c*]quinazoline-3-carbonyl)-*N*-phenylhydrazinecarbothioamide (**8**, 36.3 g, 10 mmol) in 2 N NaOH (20 mL) was refluxed for 3 h. The resulting solution was cooled to room temperature, poured onto crushed ice and acidified to pH 3-4 with 37% HCl. The product formed was filtered, washed with cooled water, dried and crystallized from EtOH to give the titled compound **9** as colorless needles (1.5 g, 61% yield); mp 291-292 °C; IR: 2632 (SH), 1596, 1543 (triazole ring C=N), 1498 (pyrimidine ring C=N) and 1461 cm^{-1} (pyrimidine ring C=C); MS: m/z (%): 345 (7, M^+), 184 (4, M^+ -$C_8H_5N_2S$), 185 (100, M^+ -$C_8H_4N_2S$) and 158 (14, M^+ -$C_9H_5N_3S$); Anal. Calcd for $C_{17}H_{11}N_7S$ (345.38): C,

59.12; H, 3.21; N, 28.39; S, 9.28%. Found: C, 59.30; H, 3.10; N, 28.74; S, 9.71%.

Method B. A solution of 2-(1,2,4-triazolo[4,3-*c*]quinazoline-3-carbonyl)-*N*-phenylhydrazinecarbothioamide (**8**, 1 g, 2.7 mmol) and Et_3N (15 mL) in EtOH (50 mL) was refluxed for 24 h. The resulting solution was cooled to room temperature and the product was filtered, washed with EtOH and crystallized from EtOH to give the titled compound **9** as colorless needles (0.5 g, 52% yield); mp and mixed mp 291-292 °C.

3-(5-Hydrazinyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1,2,4-triazolo[4,3-*c*]quinazoline (10). A suspension of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**9**, 0.3 g, 0.8 mmol) and hydrazine hydrate (99%, 3 mL) in EtOH (50 mL) was heated under reflux for 24 h. The product was filtered, washed with EtOH and crystallized from dioxan to give the titled compound **10** as colorless needles (0.18 g, 64% yield); mp 229-230 °C; IR: 3419 (NH), 3320, 3280 (NH_2), 1591, 1517 (triazole ring C=N), 1463 (pyrimidine ring C=N) and 1420 cm^{-1} (pyrimidine ring C=C); MS: m/z (%): 343 (3, M^+), 185 (100, M^+ -$C_8H_6N_4$), 158 (18, M^+ -$C_9H_7N_5$) and 159 (6, M^+ -$C_9H_6N_5$); Anal. Calcd for $C_{17}H_{13}N_9$ (343.35): C, 59.47; H, 3.82; N, 36.72%. Found: C, 59.40; H, 3.44; N, 36.91%.

Potassium 2-(1,2,4-triazolo[4,3-*c*]quinazolin-3-carbonyl)hydrazinecarbodithioate (11). To a solution of KOH (0.84 g, 15 mmol) in absolute EtOH (250 mL), 1,2,4-triazolo[4,3-*c*]quinazoline-3-carbohydrazide (**3**, 2.28 g, 10 mmol) and carbon disulfide (1.14 g, 15 mmol) in absolute EtOH (250 mL) were added. The reaction mixture was agitated for 12-16 h, where upon a yellow precipitate was separated. Dry Et_2O (200 mL) was then added to complete the precipitation of the titled compound. The obtained product was collected by filtration, washed with dry Et_2O and dried in a desiccator. The potassium salt prepared as described above, was obtained in nearly quantitative yield and was employed without further purification for the next step.

5-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (12). A suspension of potassium dithiocarbazinate (**11**, 3.43 g, 10 mmol) and hydrazine hydrate (95%, 1 mL, 20 mmol) in water (5 mL) was heated and stirred under reflux for 2 h. The color of the reaction mixture changed to green, hydrogen sulfide evolved and homogenous solution resulted. The reaction mixture was cooled, diluted with ice-cold water (100 mL) and subsequent acidification with concd HCl gave a white precipitate. It was collected by filtration, washed with ice-cold water (100 mL), dried and crystallized from EtOH to give the titled compound **12** as colorless needles (2 g, 70% yield); mp 223-224 °C; IR: 3308, 3260 (NH_2), 2360 (SH), 1550 (triazole ring C=N), 1449 (pyrimidine ring C=N) and 1385 cm^{-1} (pyrimidine ring C=C); ^1H NMR (DMSO-d_6): δ = 7.29 (t, 1H, aromatic-H), 7.52 (t, 1H, aromatic-H), 7.95 (s, 1H, pyrimidine-H), 8.14 (d, 1H, aromatic-H), 8.26, 8.29 (2s, 2H, exchangeable, NH_2), 8.60 (d, 1H, aromatic-H) and 13.51 (s,

1H, exchangeable, SH); MS: m/z (%): 284 (100, M^+), 256 (7, M^+ -N_2), 255 (11, M^+ -HN_2), 227 (15, M^+ -HN_5), 185 (50, M^+ -CH_3N_7), 129 (60, M^+ -$C_3H_3N_7S$) and 103 (14, M^+ -$C_4H_3N_8S$); Anal. Calcd for $C_{11}H_8N_8S$ (284.30): C, 46.47; H, 2.84; N, 39.41; S, 11.28%. Found: C, 46.70; H, 2.54; N, 39.11; S, 11.78%.

3-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6-(3-bromophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (13). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**, 0.28 g, 1 mmol) and m-bromobenzoic acid (0.22 g, 1.1 mmol) in $POCl_3$ (5 mL) was refluxed for 7 h. The reaction mixture was slowly quenched onto crushed ice with stirring and neutralized with 10% aqueous sodium bicarbonate solution. The product which separated after standing overnight was filtered, washed with cold water, dried and crystallized from $CHCl_3$-EtOH to give the titled compound **13** as yellow needles (0.2 g, 56% yield); mp 131-132 °C; IR: 1560, 1541 (triazole ring C=N), 1505 (pyrimidine ring C=N), 1461 (pyrimidine ring C=C), 1261 (N-N=C) and 679 cm^{-1} (C –S-C); ^{1}H NMR (DMSO-d_6): δ = 7.25 (s, 1H, aromatic-H), 7.31 (t, 1H, aromatic-H), 7.42 (t, 1H, aromatic-H), 7.52 (t, 1H, aromatic-H), 7.84 (d, 2H, aromatic-H), 8.12 (d, 2H, aromatic-H) and 8.33 (s, 1H, pyrimidine-H); Anal. Calcd for $C_{18}H_9BrN_8S$ (449.29): C, 48.12; H, 2.02; Br, 17.78; N, 24.94; S, 7.14%. Found: C, 48.20; H, 2.22; Br, 17.54; N, 24.87; S, 7.61%.

3-([1,2,4]Triazolo[4,3-*c*]quinazolin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione (14). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**, 0.28 g, 10 mmol), KOH (0.6 g, 10 mmol) and carbon disulfide (4 mL) in MeOH (100 mL) was refluxed for 24 h, and then evaporated to dryness and 50% aqueous HCl (50 mL) was added, the product was filtered off, washed with water, dried and crystallized from MeOH to give the titled compound **14** as yellow needles (0.2 g, 61% yield); mp 259-260 °C; IR: 3414 (NH), 1593, 1538 (triazole ring C=N), 1472 (pyrimidine ring C=N), 1429 (pyrimidine ring C=C) and 1304 cm^{-1} (C=S); MS: m/z (%): 326 (2, M^+), 197 (2, M^+ -$C_8H_5N_2$), 198 (2, M^+ -$C_8H_4N_2$), 122 (2, M^+ -$C_9H_4N_2S_2$), 123 (2, M^+ -$C_9H_3N_2S_2$), 108 (13, M^+ -$C_9H_4N_3S_2$), 109 (2, M^+ -$C_9H_3N_3S_2$) and 68 (13, M^+ -$C_{10}H_4N_5S_2$); Anal. Calcd for $C_{12}H_6N_8S_2$ (326.36): C, 44.16; H, 1.85; N, 34.33; S, 19.65%. Found: C, 44.00; H, 2.01; N, 34.62; S, 19.34%.

3-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6-(methylthio)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (15). A solution of 3-([1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione (**14**, 0.3 g, 1 mmol) and anhydrous sodium acetate (1 g, 15 mmol) in dioxan (100 mL) was treated with CH_3I (0.14 mL, 1 mmol) gradually with constant stirring for 24 h. The solvent was removed and the residue was poured into ice-cold water. The compound that precipitated was filtered, washed, dried and crystallized from EtOH to give the titled compound **15** as pale green needles (0.2 g, 64% yield); mp 229-

230 °C; IR: 3107 (SCH_3), 1591, 1544 (triazole ring C=N), 1459 (pyrimidine ring C=N) and 1427 cm^{-1} (pyrimidine ring C=C); Anal. Calcd for $C_{13}H_8N_8S_2$ (340.39): C, 45.87; H, 2.37; N, 32.92; S, 18.84%. Found: C, 45.81; H, 2.61; N, 32.54; S, 19.27%.

3,3'-Di([1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-6,6'-bi([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole) (16). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**, 0.5 g, 17 mmol), oxalic acid (0.08 g, 0.8 mmol) and phosphoryl chloride (1.4 mL) was refluxed for 1 h. The reaction mixture was poured onto crushed ice and the product was filtered, washed with cold water, dried and crystallized from EtOH to give the titled compound **16** as colorless needles (0.37 g, 67% yield); mp 239-240 °C; IR: 1560, 1543 (triazole ring C=N), 1463 (pyrimidine ring C=N), 1420 (pyrimidine ring C=C) and 690 cm^{-1} (C–S-C); ^{1}H NMR (DMSO-d_6): δ = 7.68 (t, 2H, aromatic-H), 7.93 (t, 2H, aromatic-H), 8.53 (d, 2H, aromatic-H), 8.70 (d, 2H, aromatic-H) and 9.18 (s, 2H, pyrimidine-H); Anal. Calcd for $C_{24}H_{10}N_{16}S_2$ (586.57): C, 49.14; H, 1.72; N, 38.21; S, 10.93%. Found: C, 49.40; H, 1.90; N, 38.11; S, 10.44%.

3-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (17). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**, 0.27 g, 1 mmol) and phenacyl bromide (0.24 g, 1.2 mmol) in absolute EtOH (20 mL) was refluxed for 24 h. The reaction mixture was slowly quenched onto crushed ice with stirring and was neutralized with 10% aqueous sodium bicarbonate. The product which separated after standing overnight was filtered, washed with cold water, dried and crystallized from MeOH to give the titled compound **17** as yellow needles (0.22 g, 61% yield); mp 281-282 °C; IR: 1592, 1539 (triazole ring C=N), 1505 (pyrimidine ring C=N), 1463 (pyrimidine ring C=C), 1232 (N-N=C) and 677 cm^{-1} (C–S-C); Anal. Calcd for $C_{19}H_{12}N_8S$ (384.42): C, 59.36; H, 3.15; N, 29.15; S, 8.34%. Found: C, 59.31; H, 3.51; N, 29.00; S, 8.80%.

3-(1,2,4-Triazolo[4,3-*c*]quinazolin-3-yl)-6,7-diphenyl-5*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (18). A mixture of 5-(1,2,4-triazolo[4,3-*c*]quinazolin-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol (**12**, 1.59 g, 0.005 mol) and benzoin (1.06 g, 5 mmol) in EtOH (30 mL) was heated to get a clear solution and to the hot solution was added 2N KOH solution (0.5 mL). The reaction mixture was refluxed with stirring for 2h, then concentrated and cooled to room temperature. The product was filtered, washed with water, dried and crystallized from EtOH to give the titled compound **18** as pale yellow needles (1.6 g, 64% yield); mp 299-300 °C; IR: 3455 (NH), 1593, 1576 (triazole ring C=N), 1450 (pyrimidine ring C=N), 1389 (pyrimidine ring C=C) and 640 cm^{-1} (C–S-C); MS: m/z (%): 460 (2, M^+), 355 (3, M^+ -$C_6H_5N_2$), 105 (65, M^+ -$C_{21}H_{15}N_4S$) and 78 (100, M^+ -$C_{22}H_{16}N_5S$); Anal. Calcd for $C_{25}H_{16}N_8S$ (460.51): C, 65.20; H, 3.50; N, 24.33; S, 6.96%. Found: C, 65.41 H, 3.44; N, 24.62; S, 7.35%.

REFERENCES

1. T. M. Abdel-Rahman, *Boll. Chim. Farm*., 1998, **137**, 43.
2. A. M. Farghaly, I. Chaaban, M. A. Khalil, and A. A. Bekhit, *Arch. Pharmacol*., 1990, **323**, 833.
3. E. Pomarnacka, S. Angielski, and A. Hoppe, *Acta Polon. Pharm*., 1984, **4**, 141.
4. M. J. Kornet, *J. Heterocycl. Chem*., 1992, **29**, 103.
5. M. Shimoyama, K. Ogino, Y. Tanaka, T. Ikeda, and I. Hisatome, *Diabetes*, 1999, **3**, 609.
6. C. M. Sorenson and M. A. Barry, *J. Natl. Cancer Inst.*, 1990, **82**, 749.
7. P. K. Naithani, G. Palit, V. K. Srivastava, and K. Shankar*, Indian J. Chem.*, 1989, **28B**, 745.
8. S. Jantova, M. Urbancikova, T. Maliar, M. Mikulasova, and P. Rauko, *Neoplasma*, 2001, **1**, 52.
9. S. Jantova, M. Theiszova, and M. Mikulasova, *Neoplasma*, 2004, **51**, 436.
10. S. Jantova, R. Ovadekova, S. Letasiova, K. Spirkova, and S. Stankovsky, *Folia Moicrobiol.*, 2005, **50**, 90.
11. S. Jantova, S. Letasiova, A. Repicky, R. Ovadekova, and B. Lakatos, *Cell Biochem. Funct.*, 2006, **24**, 519.
12. S. Jantova, A. Repicky, and L. Cipak, *Neoplasma*, 2009, **56**, 494.
13. M. Loriga, G. Vitale, and G. PagliettIi, *Farmaco*., 1998, **53**, 139.
14. R. R. Sotelo-Mundo, J. Ciesla, and J. M. Dzik, *Biochemistry*, 1990, **38**, 1087.
15. M. Ranson, *Br. J. Cancer*, 2004, **90**, 2250.
16. S. B. Kaye, *Br. J. Cancer*, 1998, **78**, 1.
17. K. Sztanke, T. Tuzimski, J. Rzymowska, K. Pastemak, and M. Kandefer, *Eur. J. Med. Chem*., 2008, **43**, 404.
18. P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Leda, A. L. P. de Miranda, C. A. M. Fraga, and E. J. Barreiro, *Eur. J. Med. Chem*., 2000, **35**, 187.
19. M. El. Enany and S. Botros, *Pharmazie*, 1981, **36**, 62.
20. G. S. Sidhu, G. Thyarajan, and N. Rao, *Naturwissenschaften*., 1963, **50**, 732 (*Chem. Abstr*., 1964, **60**, 684).
21. M. A. E. Shaban and A. Z. Nasr, *Adv. Heterocycl. Chem.,* 1990, **49**, 277.
22. M. Claesen and H. Vanderhaeghe, *Bull. Soc. Chim. Belg*., 1959, **68**, 220 (*Chem. Abstr*., 1960, **54**, 9939h).
23. S. K. Pandey, A. Singh, and Nizamuddin, *Eur. J. Med. Chem*., 2009, **44**, 1188.
24. L. J. Bellany, "*The Infrared Spectra of Complex Mol.," Matheuew London*, 1959, 249.
25. K. F. Atta and M. G. Marei, unpublished results.