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Synthesis and characterization of some new 4-heteroaryl quinazoline and fused triazolo quinazoline derivatives

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ABSTRACT

Treatment of chloroquinazoline (2) with primary amines (2-aminothiazoles and sulpha drugs) and secondary amines (morpholine, piperidine, and piperazine) furnished 4-substituted aminoquinazolines (3a,b and 4a,b), 4-aryl quinazolines (5a,b), and bisquinazoline (6). Hydrazinolysis of compound 2 using hydrazine hydrate, phenyl hydrazine, and sulphonyl hydrazine afforded compound 8 and 9a,b. 1,2,4-Trizolo-quinazoline derivatives (7a-c) were obtained via a one-pot reaction of chloroquinazoline (2), hydrazine hydrate, and aromatic aldehydes. Additionally, 1,2,4-trizolo-quinazoline derivatives (10a,b) were furnished when compound 2 was treated with acid hydrazides like acetyl and benzoyl hydrazides. Pyrimidino quinazoline (13) has been constructed via a three-step conversion of chloroquinazoline 2 using interaction with malononitrile followed by partial hydrolysis and hetero-ring cyclization. All the synthesized compounds were fully characterized using physical and spectral data like, FT-IR, ^{1}H NMR, ^{13}C NMR, and HR-MS.

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1. Introduction

2,4-Disubstituted quinazoline derivatives possess a broad spectrum of biological and pharmaceutical activities [1-5]. Such as, antitumor agents [6], anticancer [7], CD38 inhibitors [8], kinases inhibitors [9,10], antimicrobial agents [11,12], immune activators [13], and modulators of adenosine A3 receptors [14].

For the above findings and in continuation of our program [15-19] on the synthesis of novel heterocyclic systems exhibit-ting biological activity. We synthesis varieties of quinazoline derivatives with the aim obtaining a source of functionalized molecules as well as getting quinazoline derivatives bearing a second chromophore which possess some interesting biological and pharmaceutical applications. Herein, we report the reactions of 2-[(*E*)-2-(furan-2-yl)ethenyl]-4-chloro-quinazoline (**2**) with some nitrogen and carbon nucleophiles.

2. Experimental

2.1. Instrumentation

All reagents and solvents were dried and purified before use by the usual procedures. M.p.: Büchi® melting point apparatus; uncorrected. TLC: Merck TLC aluminium sheets, silica gel 60F_{254} with detection by UV quenching at 254 nm. IR spectra: FT-IR Nicolet Impact 400D; KBr pellets; ν in cm^{-1}. ^{1}H and ^{13}C NMR spectra: Bruker at 400 and 100 MHz, respectively; in $CDCl_3$ or DMSO-d_6; δ in ppm relative to Me_4Si as internal standard, *J* in Hz. DEPT135 NMR spectroscopy: used where appropriate, to aid the assignment of signals in the ^{1}H and ^{13}C NMR spectra. HRMS (FAB+): JEOL JMS-SX 102A. Elemental analyses were carried out at Technical University of Dortmund.

2.2. Synthesis

2.2.1. Synthesis of 2-[(E)-2-(furan-2-yl)ethenyl]-4-chloro-quinazoline (2) [20]

A mixture of quinazolinone (**1**) (2.38 g, 0.01 mole) and PCl_5 (0.01 mole) in $POCl_3$ (5 mL) was refluxed for 2 h under Ar atmosphere. The excess $POCl_3$ was distilled under reduced pressure and the residue was poured on ice.

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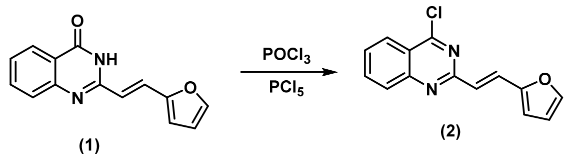
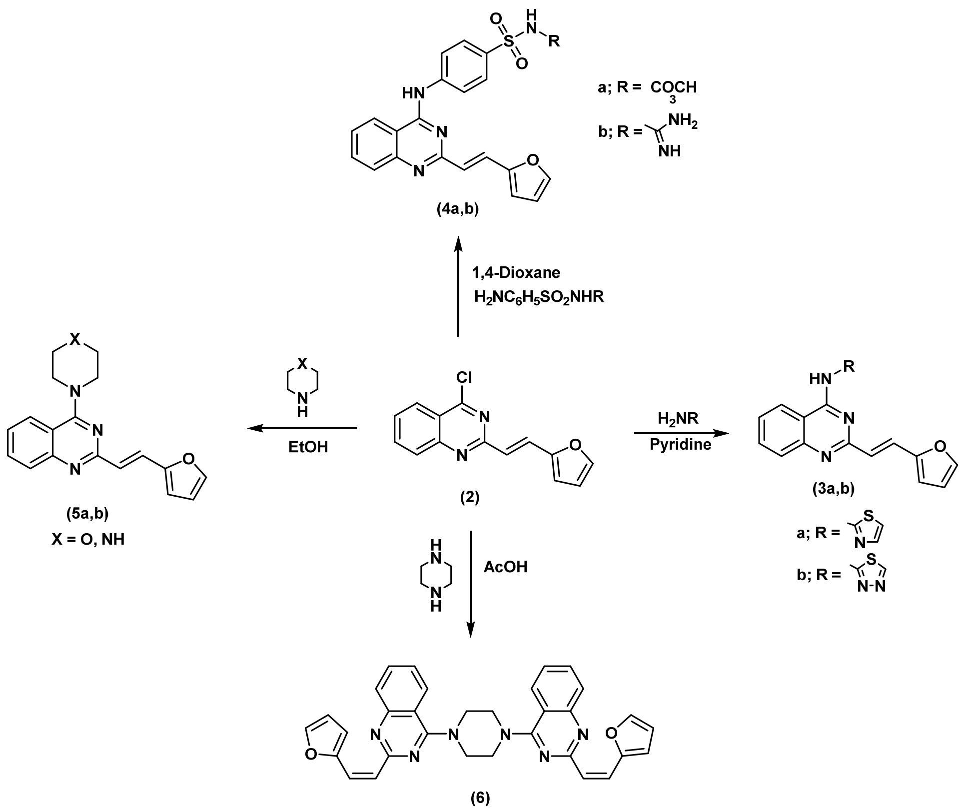


Scheme 1



Scheme 2

The separated solid precipitated was filtered off, dried and crystallized from ethanol to afford chloroquinazoline **2** (Scheme 1). Color: Brown. Yield: 65%. M.p.: 269-271 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.75 (s, 1H, Furyl-*H*), 6.92 (d, *J* = 3.3Hz, 1H, Furyl-*H*), 7.07 (d, *J* = 14.3 Hz, 1 H, =C*H*), 7.59 (t, *J* = 7.05 Hz, 2 H, Ar-*H*), 7.94 (m, 3 H, =C*H* + 2 Ar-*H*), 8.14 (d, *J*= 7.05 Hz, 1 H, furyl-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.5 (C), 153.1 (C), 150.3 (C), 147.4 (C), 135.5 (CH), 130.3 (CH), 127.5 (CH), 126.4 (2CH), 122.5 (CH), 119.9 (C), 117.9 (CH), 113.5 (CH), 112.7 (CH). HRMS (EI, *m/z*) calcd. for $C_{14}H_{10}ClN_2O$, 257.0493; found 257.0482. Anal. calcd. for $C_{14}H_9ClN_2O$: C, 65.5; H, 3.5; N, 10.9. Found: C, 65.3; H, 3.6; N, 11.4%.

2.2.2. Synthesis of quinazolin-4-amines 3a,b

A mixture of 4-chloroquinazoline **2** (2.57 g, 0.01 mol) and 2-aminothiazole and/or 2-aminothiadiazole (0.01 mol) in dry pyridine (20 mL) was heated under reflux for 2 h. The reaction mixture after cooling was poured over HCl/crushed ice. The reaction mixture was concentrated, cooled and the solid obtained was filtered off and recrystallized from EtOH to give compound **3a** and **3b**, respectively (Scheme 2)

2-[(E)-2-(furan-2-yl)ethenyl]-N-(1,3-thiazol-2-yl)quinazolin-4-amine (**3a**): Color: Beige. Yield: 79%. M.p.: 194-196 °C. FT-IR (KBr, ν, cm^{-1}): 3164 ν(NH), 3059 ν(CH arom.), 2938 ν(CH aliph.), 1624 ν(C=N), 1162 ν(CS). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.49 (s, 1H, furyl-*H*), 6.64 (d, *J* = 3.3 Hz, 1 H, furyl-*H*), 6.79 (d, *J* = 14.8 Hz, 1 H, =C*H*), 6.91 (d, *J* = 3.1 Hz, 1 H, tiazole-*H*), 7.44-7.52 (m, 4 H, =C*H*, thiazole-*H* + 2 Ar-*H*), 7.73-7.78 (m, 2 H, Ar-*H*), 8.16 (d, *J* = 8.3 Hz, 1 H, Ar-*H*), 9.08 (brs, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.2 (C), 156.9 (C), 155.4 (C), 150.8 (C), 146.8 (CH), 142.9 (CH), 138.6 (CH), 135.5 (CH), 129.4 (CH), 127.7 (CH), 116.9 (C), 116.4 (C), 115.1 (CH), 114.3 (CH), 113.6 (CH), 112.7 (CH). HRMS (EI, *m/z*) calcd. for $C_{17}H_{12}N_4OS$, 320.0732; found 320.0736. Anal. calcd. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49. Found: C, 63.86; H, 3.81; N, 17.34%.

2-[(E)-2-(furan-2-yl)ethenyl]-N-(1, 3, 4-thiadiazol-2-yl) quinazolin-4-amine (**3b**): Color: Beige. Yield: 66%. M.p.: 213-215 °C. FT-IR (KBr, ν, cm^{-1}): 3159 ν(NH), 3061 ν(CH arom.), 1626 ν(C=N), 1158 ν(CS). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.53 (s, 1H, , furyl-*H*), 6.63 (d, *J* = 3.3 Hz, 1 H, furyl-*H*), 6.84 (d, *J* = 14.8 Hz, 1 H, =C*H*), 7.21 (t, *J* = 8.13 Hz, 1 H, Ar-*H*), 7.39-7.74 (m, 4 H, =C*H*, thiazole-*H* + 2 Ar-*H*), 8.13 (d, *J* = 8.13 Hz, 1 H, Ar-*H*), 8.63 (s, 1 H, thiazole-*H*), 9.06 (brs, 1 H, NH). HRMS (EI, *m/z*) calcd. for $C_{16}H_{11}N_5OS$, 321.0784; found 321.0788. Anal. calcd.

for $C_{16}H_{11}N_5OS$: C, 59.80; H, 3.45; N, 21.79. Found: C, 59.96; H, 3.59; N, 21.58%.

2.2.3. Synthesis of sulfonamides 4a,b

A solution of compound **2** (0.01 mol) and sulfa drugs namely, sulfacetamide and/or sulfaguanidine (0.01 mol) in 1,4-dioxane (20 mL) was refluxed for 5 h. The mixture was concentrated and the formed precipitate was washed with water, filtered off, and crystallized from the proper solvent to give compound **4a** and **4b**, respectively (Scheme 2).

N-[4-({2-[(E)-2-(furan-2-yl)ethenyl] quinazolin-4-yl} amino) benzene-1-sulfonyl]acetamide (**4a**): Color: Pale yellow. Yield: 83%. M.p.: 208-210 °C ($PhCH_3$). FT-IR (KBr, ν, cm^{-1}): 3164, 3357 ν(NH), 3055 ν(CH arom.), 1598, 1628 ν(C=N), 1198 ν(SO_2). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.07 (s, 3H, CH_3), 6.51 (s, 1H, furyl-*H*), 6.61-6.72 (m, 2 H, furyl-*H* + =C*H*), 7.28-7.46 (m, 5 H, furyl-*H*, =C*H* + 3 Ar-*H*), 7.68-7.77 (m, 4 H, Ar-*H*), 8.13 (d, *J* = 8.13 Hz, 1 H, Ar-H), 8.68 (s, 1 H, NH), 8.93 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 168.5 (C), 162.3 (C), 154.3 (C), 153.4 (C), 147.9 (C), 144.7 (CH), 141.2 (CH), 139.5 (CH), 136.4 (CH), 131.7 (CH), 129.1 (CH), 127.3 (CH), 126.8 (C), 117.2 (C), 115.7 (CH), 114.3 (CH), 112.7 (CH), 112.3 (CH), 109.8 (CH), 24.3 (CH_3). HRMS (EI, *m/z*) calcd. for $C_{22}H_{18}N_4O_4S$, 434.1049; found 434.1053. Anal. calcd. for $C_{22}H_{18}N_4O_4S$: C, 60.82; H, 4.18; N, 12.90. Found: C, 60.68; H, 4.23; N, 12.99%.

N-carbamimidoyl-4-({2-[(E)-2-(furan-2-yl)ethenyl] quinazo lin-4-yl}amino)benzene-1-sulfonamide (**4b**): Color: Pale yellow. Yield: 74%. M.p.: 196-198 °C (AcOH). FT-IR (KBr, ν, cm^{-1}): 3189, 3368 ν(NH), 3058 ν(CH arom.), 1623 ν(C=N), 1179 ν(SO_2). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.49 (s, 1H, furyl-*H*), 6.63 (d, *J* = 3.2 Hz, 1 H, furyl-*H*), 6.69-6.74 (m, 2 H, =C*H* + Ar-*H*), 7.28 (t, *J* = 8.13 Hz, 1 H, Ar-*H*), 7.42-7.51 (m, 4 H, furyl-*H*, =C*H* &+ 2 Ar-*H*), 7.73-7.79 (m, 4 H, Ar-*H*), 8.16 (d, *J* = 8.13 Hz, 1 H, Ar-*H*), 9.30 (s, 4 H, NH`s). HRMS (EI, *m/z*) calcd. for $C_{21}H_{19}N_6O_3S$, 435.1239; found 435.1243. Anal. calcd. for $C_{21}H_{18}N_6O_3S$: C, 58.05; H, 4.18; N, 19.34. Found: C, 58.32; H, 4.36; N, 19.12%.

2.2.4. Synthesis of quinazolines 5a,b

A mixture of chloroquinazoline **2** (3.92 g, 0.01 mol) and morpholine and/or piperidine (0.01 mol) was heated at 140 °C for 5 min then 20 mL of ethanol was added and the reaction mixture was refluxed for 3 h. The excess solvent was distilled off and the solid that separated after cooling was collected and recrystallized from ethanol to give compound **5a** and **5b**, respectively (Scheme 2).

2-[(E)-2-(furan-2-yl)ethenyl]-4-(morpholin-4-yl)quinazoline (**5a**): Color: Beige. Yield: 72%. M.p.: 293-295 °C. FT-IR (KBr, ν, cm^{-1}): 3055 ν(CH arom.), 2939 ν(CH aliph.), 1627 ν(C=N). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.42-2.49 (m, 4H, $2CH_2$), 3.67-3.74 (m, 4H, $2CH_2$), 6.52 (s, 1H, furyl-*H*), 6.61-6.69 (m, 3 H, furyl-*H*, =C*H* + Ar-*H*), 7.23 (t, *J* = 8.15 Hz, 1 H, Ar-*H*), 7.46-7.58 (m, 2 H, furyl-*H* + =C*H*), 7.72-7.81 (m, 2 H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 159.3 (C), 155.6 (C), 152.5 (C), 147.8 (C), 145.9 (CH), 137.4 (CH), 129.1 (CH), 128.2 (CH), 127.7 (CH), 126.8 (CH), 115.9 (C), 112.6 (CH), 112.3 (CH), 108.9 (CH), 66.2 ($2CH_2$), 49.7 ($2CH_2$). HRMS (EI, *m/z*) calcd. for $C_{18}H_{17}N_3O_2$, 307.1321; found 307.1326. Anal. calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.61; H, 5.67; N, 13.48%.

2-[(E)-2-(furan-2-yl)ethenyl]-4-(piperazin-1-yl)quinazoline (**5b**): Color: Pale yellow. Yield: 77%. M.p.: 302-304 °C. FT-IR (KBr, ν, cm^{-1}): 3186 ν(NH), 3062 ν(CH arom.), 2941 ν(CH aliph.), 1624 ν(C=N). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.51-2.56 (m, 4H, $2CH_2$), 3.49-3.54 (m, 4H, $2CH_2$), 6.55 (s, 1H, furyl-*H*), 6.61-6.68 (m, 3 H, furyl-*H*, =C*H* + Ar-*H*), 7.16 (t, *J* = 8.13 Hz, 1 H, Ar-*H*), 7.52-7.67 (m, 4 H, furyl-*H*, =C*H* + 2Ar-*H*), 7.81 (d, *J* = 8.13 Hz, 1 H, Ar-*H*). HRMS (EI, *m/z*) calcd. for $C_{18}H_{18}N_4O$, 306.1481; found 306.1483. Anal. calcd. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.29; H, 5.80; N, 18.08%.

2.2.5. Synthesis 4,4'-(piperazine-1,4-diyl)bis(2-[(E)-2-(furan-2-yl)ethenyl]quinazoline) (6)

A mixture of chloroquinazoline **2** (3.92 g, 0.01 mol) and piperidine (1.73 g, 0.02 mol) was heated at 140 °C for 5 min then 20 mL of ethanol was added and the reaction mixture was refluxed for 3 h. The excess solvent was distilled off and the solid that separated after cooling was collected and recrystallized from ethanol to give compound **6** (Scheme 2). Color: Brown. Yield: 58%. M.p.: 230-231 °C. FT-IR (KBr, ν, cm^{-1}): 3056 ν(CH arom.), 2937 ν(CH aliph.), 1624 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.58-3.82 (m, 8 H, 4 CH_2), 6.43 (s, 2 H, furyl-*H*), 6.61-6.88 (m, 8 H, 2 furyl-*H*, 4 =C*H* + 2 Ar-*H*), 7.22 (t, *J* = 8.11 Hz, 2 H, 2 Ar-*H*), 7.52-7.69 (m, 6 H, 2 furyl-*H* + 4 Ar-*H*). HRMS (EI, *m/z*) calcd. for $C_{32}H_{26}N_6O_2$, 526.2117; found 526.2122. Anal. calcd. for $C_{32}H_{26}N_6O_2$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.27; H, 5.06; N, 16.17%.

2.2.6. Synthesis of triazolo quinazolines 7a-c

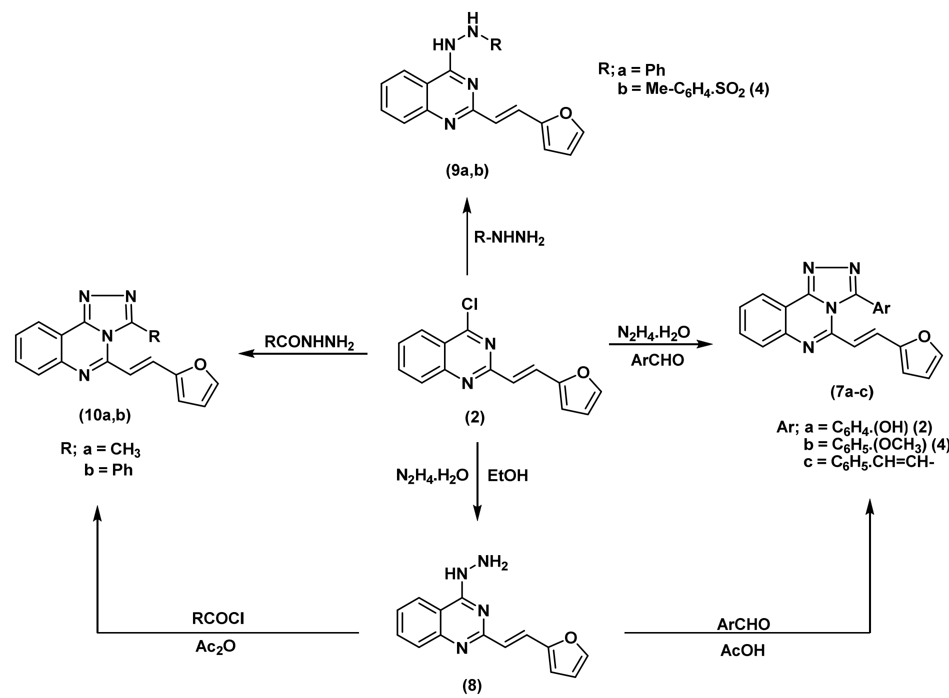
Procedure A: A mixture of compound **2** (2.57 g, 0.01 mol), hydrazine hydrate (0.75 g, 0.015 mol), and aromatic aldehydes namely, salicylaldehyde, 4-methoxy benzaldehyde, and cinnamaldehyde in 20 mL of *N*,*N*-dimethylformamide was refluxed for 4 h. The reaction mixture was concentrated, cooled and the residue was poured over cold water. The solid that formed was filtered off and crystallized from the suitable solvent to afford compound **7a**-**c** (Scheme 3).

Procedure B: A mixture of 4-hydrazinylquinazoline **8** (2.52 g, 0.01 mol) and aromatic aldehydes namely, salicylaldehyde, 4-methoxy benzaldehyde, and cinnamaldehyde in glacial acetic acid (30 mL) was heated under reflux for 6 h. The excess solvent was distilled off and the residue was left overnight, then the solid that separated was collected, dried, and crystallized from the proper solvent to give compound **7a**-**c** (Scheme 3).

2-{5-[(E)-2-(furan-2-yl)ethenyl][1,2,4]triazolo[4, 3-c] quina-zolin-3-yl}phenol (**7a**): Color: Pale yellow. Yield: 63%. M.p.: 232-233 °C. FT-IR (KBr, ν, cm^{-1}): 3448 ν(OH), 3058 ν(CH arom.), 1623 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.24 (brs, 1H, OH), 6.49 (s, 1H, furyl-*H*), 6.63-6.79 (m, 3 H, furyl-*H*, =C*H* + Ar-*H*), 7.13-7.26 (m, 3 H, Ar-*H*), 7.51 (d, *J* = 3.4 Hz, 1 H, furyl-*H*), 7.78 (d, *J* = 15.4 Hz, 1 H, =C*H*), 8.09-8.18 (m, 4 H, Ar-*H*). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}N_4O_2$, 354.1117; found 354.1121. Anal. calcd. for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.42; H, 4.17; N, 16.07%.

5-[(E)-2-(furan-2-yl)ethenyl]-3-(4-methoxyphenyl)[1, 2, 4] triazolo[4,3-c]quinazoline (**7b**): Color: Beige. Yield: 67%. M.p.: 208-209 °C (AcOH). FT-IR (KBr, ν, cm^{-1}): 3054 ν(CH arom.), 2942 ν(CH aliph.), 1625 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.81 (s, 3 H, CH_3), 6.52 (s, 1 H, furyl-*H*), 6.63-6.82 (m, 4 H, furyl-*H*, =C*H*, 2 Ar-*H*), 7.21 (t, *J* = 8.39 Hz, 1 H, Ar-*H*), 7.49-7.66 (m, 2 H, furyl-*H* + =C*H*), 8.09-8.21 (m, 5 H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 159.4 (C), 154.7 (C), 151.3 (C), 149.3 (C), 146.2 (C), 139.5 (CH), 138.9 (C), 132.1 (CH), 128.6 (2CH), 127.1 (2CH), 125.9 (C), 124.2 (C), 118.6 (2CH), 117.8 (CH), 114.8 (CH), 112.0 (CH), 110.4 (CH), 109.1 (CH), 54.3 (CH_3). HRMS (EI, *m/z*) calcd. for $C_{22}H_{17}N_4O_2$, 369.1352; found 369.1355. Anal. calcd. for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.97; H, 4.26; N, 15.43%.

5-[(E)-2-(furan-2-yl)ethenyl]-3-[(E)-2-phenylethenyl][1,2, 4] triazolo[4,3-c]quinazoline (**7c**): Color: Beige. Yield: 67%. M.p.: 208-209 °C (AcOH). FT-IR (KBr, ν, cm^{-1}): 3057 ν(CH arom.), 1624 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.47 (s, 1H, furyl-*H*), 6.61-6.72 (m, 2 H, furyl-*H* + =C*H*), 7.13 (t, *J* = 8.13 Hz, 1 H, Ar-*H*), 7.21 (d, *J* = 15.4 Hz, 1 H, =C*H*-Ar), 7.34-7.46 (m, 7 H, furyl-*H*, =C*H*-Ar + 5 Ar-*H*), 7.72 (d, *J* = 15.4 Hz, 1 H, =C*H*),



Scheme 3

8.11-8.17 (m, 3 H, Ar-*H*). HRMS (EI, *m/z*) calcd. for $C_{23}H_{16}N_4O$, 364.1324; found 364.1329. Anal. calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.07; H, 4.29; N, 15.17%.

2.2.7. Synthesis of 2-[(E)-2-(furan-2-yl)ethenyl]-4-hydrazinylquinazoline (8)

A solution of compound **2** (2.57 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in absolute ethanol (30 mL) in the presence of a few drops of piperidine was heated under reflux at 70 °C for 6 h. The excess solvent was distilled off under reduced pressure and the solid that obtained after cooling was collected and crystallized from EtOH/H_2O to afford compound **8** (Scheme 3). Color: Beige. Yield: 81%. M.p.: 362-363 °C. FT-IR (KBr, ν, cm^{-1}): 3168, 3305 ν(NH), 3054 ν(CH arom.), 1628 ν(C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.87 (brs, 3 H, NH`s), 6.53 (s, 1H, furyl-*H*), 6.63-6.70 (m, 2 H, furyl-*H* + =C*H*), 7.12 (d, *J* = 15.6 Hz, 1 H, =C*H*), 7.42-7.49 (m, 2 H, furyl-*H* + Ar-*H*), 7.76-7.89 (m, 3 H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.5 (C), 154.9 (C), 153.8 (C), 151.0 (C), 146.7 (CH), 139.2 (CH), 137.9 (CH), 126.9 (CH), 126.3 (CH), 121.8 (CH), 118.9 (C), 116.8 (CH), 113.3 (CH), 112.5 (CH). HRMS (EI, *m/z*) calcd. for $C_{14}H_{12}N_4O$, 252.1011; found 252.1017. Anal. calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.89; H, 4.63; N, 21.94%.

2.2.8. Synthesis of hydrazinyl quinazolines 9a,b

An equimolar mixture of compound **2** (2.57 g, 0.01 mol) and phenyl hydrazine and/or sulphonyl hydrazine (0.01 mol) in *N*,*N*-dimethylformamide (30 mL) was heated under reflux at 100 °C for 4 h. The reaction mixture after cooling was poured over cold water and the precipitate that separated was filtered off and crystallized from the proper solvent to afford compound **9a** and **9b**, respectively (Scheme 3).

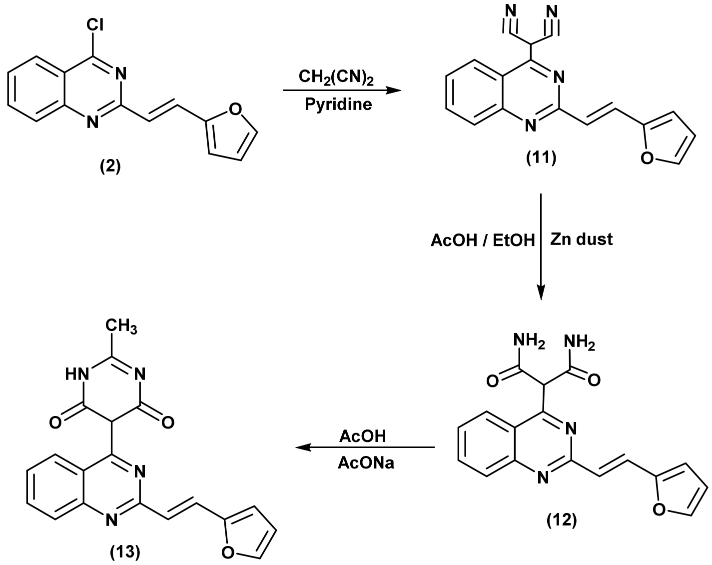
2-[(E)-2-(furan-2-yl)ethenyl]-4-(2-phenylhydrazinyl) quinazoline (**9a**): Color: Yellow. Yield: 78%. M.p.: 183-185 °C ($PhCH_3$). FT-IR (KBr, ν, cm^{-1}): 3189 ν(NH), 3055 ν(CH arom.), 1609, 1596 ν(C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.50 (s, 1H, furyl-*H*), 6.63-6.84 (m, 6 H, furyl-*H*, 2 =C*H* + 3 Ar-*H*), 7.18 (d, *J* = 8.14 Hz, 1 H, Ar-*H*), 7.39-7.47 (m, 3 H, furyl-H + 2 Ar-*H*), 7.76-7.91 (m, 2 H, Ar-*H*), 8.27 (d, *J* = 8.14 Hz, 1 H, Ar-*H*), 9.08 (brs, 2 H, 2 NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 168.2 (C), 154.1 (C), 153.4 (C), 144.8 (C), 143.5 (C), 141.3 (CH), 139.8 (CH), 138.3 (CH), 129.2 (2CH), 126.8 (CH), 126.4 (CH), 119.7 (CH), 114.8 (2CH), 114.3 (C), 113.9 (CH), 112.4 (CH), 112.1 (CH), 109.9 (CH). HRMS (EI, *m/z*) calcd. for $C_{20}H_{16}N_4O^+$; calc. 328.1324; found 328.1329. Anal. calcd. for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.33; H, 5.04; N, 17.23%.

N'-{2-[(E)-2-(furan-2-yl)ethenyl]quinazolin-4-yl}-4-methyl benzene-1-sulfonohydrazide (**9b**): Color: Yellow. Yield: 76%. M.p.: 294-296 °C (EtOH). FT-IR (KBr, n, cm-1): 3200, 3361 ν(NH), 3057 ν(CH arom.), 2942 ν(CH aliph.), 1614 ν(C=N), 1183 ν(SO_2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.13 (s, 3 H, CH_3), 6.49 (s, 1H, furyl-*H*), 6.64-6.73 (m, 2 H, furyl-*H* + =C*H*), 6.93 (d, *J* = 15.4 Hz, 1 H, =C*H*), 7.38-7.46 (m, 4 H, furyl-*H* + 3 Ar-*H*), 7.78-7.85 (m, 3 H, Ar-*H*), 8.09-8.18 (m, 2 H, Ar-*H*), 9.14 (brs, 1 H, NH), 9.67 (brs, 1 H, NH). HRMS (EI, *m/z*) calcd. for $C_{21}H_{18}N_4O_3S$, 406.1100; found 406.1107. Anal. calcd. for $C_{21}H_{18}N_4O_3S$: C, 62.05; H, 4.46; N, 13.78. Found: C, 62.27; H, 4.35; N, 14.02%.

2.2.9. Synthesis of quinazolines 10a,b

***Procedure A*:** A solution of chloro compound **2** (2.57 g, 0.01 mol) and acid hydrazide namely, acetyl hydrazide and/or benzoyl hydrazide (0.015 mol) in glacial acetic acid (20 mL) and 5 mL of freshly distilled acetanhydride was heated at 110 °C for 5 h. The excess solvent was distilled off and the solid that separated after cooling was filtered off, washed with light petroleum ether (B.p. 60-80 °C), and recrystallized from *n*-butanol to afford compound **10a** and **10b**, respectively (Scheme 3).

***Procedure B*:** A solution of 4-hydrazinoquinazoline **8** (2.52 g, 0.01 mol) and acid chlorides namely, acetyl chloride and/or benzoyl chloride in freshly distilled acetanhydride (10



Scheme 4

mL) was heated in water bath at 70 °C for 3 h. The reaction mixture was cooled and the solid that formed was collected washed with light petroleum ether (B.p.: 60-80 °C) and crystallized from *n*-butanol to give compound **10a** and **10b**, respectively (Scheme 3).

5-[(E)-2-(furan-2-yl)ethenyl]-3-methyl[1, 2, 4]triazolo[4, 3-c]quinazoline (**10a**): Color: Yellow. Yield: 84%. M.p.: 297-298 °C. FT-IR (KBr, ν, cm^{-1}): 3055 ν(CH arom.), 2938 ν(CH aliph.), 1619 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.51 (s, 3 H, CH_3), 6.48 (s, 1H, furyl-*H*), 6.68-6.85 (m, 2 H, furyl-*H* + =C*H*), 7.31-7.43 (m, 2 H, furyl-*H* + Ar-*H*), 7.76 (d, *J* = 15.4 Hz, 1 H, =C*H*), 8.07-8.11 (m, 2 H, Ar-*H*), 8.31 (d, *J* = 8.14 Hz, 1 H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 159.1 (C), 157.3 (C), 151.4 (C), 149.3 (C), 143.9 (CH), 139.6 (CH), 137.1 (C), 133.6 (CH), 127.4 (CH), 126.8 (CH), 123.1 (C), 117.7 (CH), 114.9 (CH), 112.4 (CH), 110.8 (CH), 18.2 (CH_3). HRMS (EI, *m/z*) calcd. for $C_{16}H_{13}N_4O$, 277.1089; found 277.1095. Anal. calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.67; H, 4.52; N, 20.56%.

5-[(E)-2-(furan-2-yl)ethenyl]-3-phenyl[1, 2, 4]triazolo[4, 3-c]quinazoline (**10b**): Color: Yellow. Yield: 81%. M.p.: 306-308 °C. FT-IR (KBr, ν, cm^{-1}): 3054 ν(CH arom.), 1598, 1623 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.51 (s, 1H, furyl-*H*), 6.61-6.74 (m, 2 H, furyl-*H* + =C*H*), 7.19(t, *J* = 8.39 Hz, 1 H, Ar-*H*), 7.39-7.51 (m, 7 H, furyl-*H*, =C*H* + 5 Ar-*H*), 7.91-7.97 (m, 2 H, Ar-*H*), 8.19 (d, *J* = 8.39 Hz, 1 H, Ar-*H*). HRMS (EI, *m/z*) calcd. for $C_{21}H_{15}N_4O$, 339.1246; found 339.1249. Anal. calcd. for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.73; H, 4.29; N, 16.81%.

2.2.10. Synthesis of {2-[(E)-2-(furan-2-yl)ethenyl] quinazolin-4-yl}propanedinitrile **(11)**

A mixture of 4-chloroquinazoline **2** (2.57 g, 0.01 mol) and malononitrile (0.99 g, 0.015 mol) in dry pyridine (20 mL) was heated under reflux for 2h. The reaction mixture after cooling was poured over HCl/crushed ice. The reaction mixture was concentrated, cooled and the solid obtained was filtered off and recrystallized from EtOH/H_2O to give compound **11** (Scheme 4). Color: Reddish brown. Yield: 86%. M.p.: 317-319 °C. FT-IR (KBr, ν, cm^{-1}): 3061 ν(CH arom.), 2943 ν(CH aliph.), 2200, 2220 ν(CN), 1624 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.86 (s, 1 H, $CH(CN)_2$), 6.48 (s, 1H, furyl-*H*), 6.68-6.91 (m, 3 H, furyl-*H* + 2 =C*H*), 7.34-7.45 (m, 2 H, furyl-*H* + Ar-*H*), 7.98-8.05 (m, 2 H, Ar-*H*), 8.43 (d, *J* = 8.3 Hz, 1 H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 158.7 (C), 150.9 (C), 149.8 (C), 147.1 (C), 143.2 (CH), 139.0 (CH), 137.4 (CH), 129.8 (CH), 126.7 (CH), 119.6 (C), 116.2 (CH), 114.9 (CH), 112.4 (2C), 111.3 (CH), 109.6 (CH), 38.7 (CH). HRMS (EI, *m/z*) calcd. for $C_{17}H_{10}N_4O$, 286.0855; found 286.0863. Anal. calcd. for $C_{17}H_{10}N_4O$: C, 71.32; H, 3.52; N, 19.57. Found: C, 71.14; H, 3.63; N, 19.36%.

2.2.11. Synthesis of 2-{2-[(E)-2-(furan-2-yl)ethenyl] quinazolin-4-yl}propanediamide **(12)**

To a solution of propanedinitrile **11** (3.22 g, 0.01 mol) in a mixture glacial AcOH:EtOH (2:1) a catalytic amount of Zn dust was added and the reaction mixture was heated under reflux for 3 h. The reaction mixture after cooling was poured on ice water and the solid that separated was filtered off and crystallized from EtOH to afford compound **12** (Scheme 4). Color: Beige. Yield: 82%. M.p.: 286-287 °C. FT-IR (KBr, ν, cm^{-1}): 3200, 3367 ν(NH), 2937 ν(CH aliph.), 1684 ν(CO), 1625 ν(C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.91 (s, 1 H, $CH(CONH_2)_2$), 6.51 (s, 1H, furyl-*H*), 6.64-6.82 (m, 3 H, furyl-*H* + 2 =C*H*), 6.90 (brs ,4 H, NH`s), 7.48-7.59 (m, 3 H, furyl-*H* + 2 Ar-*H*), 8.21-8.33 (m, 2 H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 166.6 (2C), 157.2 (C), 153.7 (C), 151.4 (C), 147.2 (C), 140.9 (CH), 137.1 (CH), 132.9 (CH), 127.9 (CH), 126.4 (CH), 121.8 (C), 114.3 (CH), 111.6 (CH), 109.7 (CH), 109.1 (CH), 63.5 (CH). HRMS (EI, *m/z*) calcd. for $C_{17}H_{14}N_4O_3$, 322.1066; found: 322.1073. Anal. calcd. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.58; H, 4.52; N, 17.16%.

2.2.12. Synthesis of 5-{2-[(E)-2-(furan-2-yl)ethenyl] quinazolin-4-yl}-2-methylpyrimidine-4,6(1H,5H)-dione **(13)**

To a solution of propane diamide **12** (3.22 g, 0.01 mol) in glacial acetic acid (30 mL) a catalytic amount of sod. acetate was added and the reaction mixture was heated under reflux for 4h. The reaction mixture after concentration and cooling, the solid that separated was filtered off and crystallized from EtOH to afford compound **13** (Scheme 4). Color: Beige. Yield: 74%. M.p.: 232-234 °C. FT-IR (KBr, ν, cm^{-1}): 3216 ν(NH), 3054 ν(CH arom.), 2944 ν(CH aliph.), 1678, 1685 ν(CO), 1623 ν(C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 3 H, CH_3), 3.19 (s, 1 H, pyrimidine-*H*), 6.49 (s, 1H, furyl-*H*), 6.66-6.84 (m, 3 H, furyl-*H* + 2 =C*H*), 7.51-7.58 (m, 3 H, furyl-*H* + 2 Ar-*H*), 8.23-8.31 (m, 2 H, Ar-*H*), 9.87 (brs, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 181.7 (C), 169.1 (C), 159.2 (C), 156.9 (C), 153.2 (C), 151.4 (C), 146.8 (C), 141.3 (C), 139.8 (CH), 137.6 (CH), 131.2 (CH), 129.0 (CH), 126.8 (CH), 123.4 (CH), 113.8 (CH), 111.7 (CH), 110.7 (CH), 109.2 (CH), 23.9 (CH_3). HRMS (EI, *m/z*) calcd. for $C_{19}H_{14}N_4O_3$, 346.1066; found 346.1071. Anal. calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18. Found: C, 66.11; H, 3.92; N, 15.97%.

3. Results and discussion

The key starting material 4-chloro-2-(furan-2-yl)-vinyl-quinazoline (**2**) has been synthesized in good yield via chlorination of the corresponding 4-oxoquinazoline analog compound **1** (prepared according to a reported method [20]) using a mixture of phosphorus oxychloride and phosphorus pentachloride in boiling water bath (Scheme 1).

It was envisioned that compounds like compound **2** are considered as key starting materials for a diversity of heterocyclic compounds [21], since they have a hydrolysable chloroatom which can be easily exchanged. Moreover, 4-substituted aminoquinazoline derivatives are exploited as promising pharmacological active agents [22-23]. Under such circumstance, the interaction of chloroquinazoline **2** with primary amines like 2-aminothiazole and/or 2-aminothia diazole afforded the 4-aryl aminoquinazoline derivatives **3a**,**b**, respectively (Scheme 2). The structure of compounds **3a** and **b** were confirmed from correct analytical data and their spectroscopic analysis, where their FT-IR spectra displayed strong absorption bands at 3159 and 3164 cm^{-1} for NH group, ^{1}H NMR gave bands at δ 9.06 and 9.08 ppm characteristic for D_2O exchangeable NH (c.f. experimental section).

Sulfa drugs were proven to be of therapeutic importance and are used against a wide spectrum of bacterial elements [24]. Since quinazoline derivatives also have antibacterial activity, it was of interest to incorporate with sulfa drugs in the quinazoline nucleus in order to have promising antibacterial agents. Indeed, the interaction of sulfa drugs such as sulfacetamide and/or sulfaguanidine with chloroquinazoline **2** in 1,4-dioxane furnished the corresponding 4-*N*-substituted quinazolines **4a**,**b**, respectively (Scheme 2). The IR spectra of compound **4a** and **b** revealed strong absorption bands at 3164, 3189, 3357, and 3368 cm^{-1} assignable for NH groups, ^{1}H NMR spectra substantiated signals for each compound at δ 8.68, 8.93, and 9.30 ppm expected for sulfonamide NH's and NH groups respectively (c.f. experimental section).

Condensation of 4-chloroquinazoline derivative **2** with secondary amines namely morpholine and piperazine in boiling ethanol afforded the 4-arylquinazoline derivatives **5a**,**b**, respectively. While the bisquinazoline piperazine **6** was resulted when the stiochmeteric ratio are changed and the reaction was conducted in glacial acetic acid Structures of compound **5a**,**b** and **6** were elucidated from their spectral and elemental data (c.f. Scheme 2 and experimental section).

Some of the 1,2,4-triazole containing compounds are reported to have anticonvulsants and muscle relaxant activities [25]. Incorporate 1,2,4-triazole moiety at 4 position of quinazoline derivatives is proven as a new class of H_1-antihistaminic [26]. In this respects, a successful attempt for synthesizing 1,2,4-trizole-quinazoline derivatives was achieved via a one-pot reaction, where the hydrazinolysis of chloroquinazoline **2** and subsequent condensation with different aromatic aldehydes, namely salicylaldehyde, 4-methoxy benzaldehyde, and cinnamaldehyde furnished a series of 5-substituted trizolo-quinazolines **7a**-**c**. Additionally, the course of such reaction is chemically investigated via generating the 4-hydrazino-quinazoline system **8** as an isolated intermediate. Thereafter, the obtained hydrazine quinazoline **8** was submitted to react with the above-mentioned aromatic aldehydes and the 5-substituted triazolo-quinazolines **7a**-**c** were attained, elemental analysis and spectral data for compounds **7a**-**c** were found to be in full agreement with the proposed structures. IR spectrum of compound **7a** revealed broad absorption band at 3448 cm^{-1} corresponding to the hydroxyl group. In addition, ^{13}C NMR of compound **7b** showed a resonated signals at δ 159.4, 154.7, and 151.3 ppm attributed to C-OMe, C=N of triazoloquinazoline, and C=N of C2 quinazoline. On the other hand, IR spectrum of hydrazinoquinazoline compound **8** revealed two absorption bands at 3168 and 3305 cm^{-1} confirming the two NH groups. ^{1}H NMR and ^{13}C NMR data afforded a further evidence of the structure. Its ^{1}H NMR displayed signal at δ 4.87ppm attributable to NH`s. ^{13}C NMR of compound **8** showed a resonated signals at δ 161.5, 154.9, and 153.8 ppm attributable to C-NH, C=N, and C-O (c.f. Scheme 3 and experimental section).

A similar hydrazinolysis of chloroquinazoline **2** using phenyl hydrazine and/or sulphonyl hydrazine in boiling ethanol afforded 4-*N*-substituted quinazoline derivatives **9a**,**b** (Scheme 3). The IR and ^{1}H NMR spectra for both compound **9a** and **b** exhibited the characteristic signals for the NH groups, HRMS, ^{13}C NMR and elemental analysis confirmed their structures. In the same fashion, the reaction of chloroquinazoline **2** with acid hydrazides like acetyl and/or benzoyl hydrazides in a mixture of glacial acetic acid and freshly distilled acetanhydride (4:1) at 120 °C has afforded new interesting triazoloquinazoline derivatives **10a**,**b**, respectively. IR spectrum of compound **9b** recorded the absorption band at 3361, 3200 cm^{-1} attributted to NH`s, in addition at 1614 and 1183 cm$^{-1}$ attributed to C=N and $SO_2$. $^{1}$H NMR spectrum of compound **9b** displayed signals at δ 2.13, 9.14, and 9.67 ppm attributable to $CH_3$ and NH`s. On the other hand, IR spectra of compounds **10a**,**b** revealed strong absorption bands at 1598, 1619, and 1623 cm^{-1} attributed to C=N. ^{13}C NMR of compound **10a** showed a resonated signals at δ 159.1, 157.3, and 153.4 ppm attributable to C4 quinazoline, C=N (C2 quinazoline), and C-O (c.f. Scheme 3 and experimental section).

It is worthwhile to investigate the behavior of our chloroquinazoline system **2** towards carbon nucleophiles. Indeed, the interaction of chloroquinazoline **2** with malononitrile was conducted in dry pyridine and the 4-substituted quinazoline **11** was furnished. IR spectrum for compound **11** displayed two absorption bands at $ν_{max}$ 2200 and 2220 cm^{-1} assignable for the two C≡N groups. ^{1}H NMR spectrum of compound **11** displayed signal at δ 4.86 ppm attributable to C*H*$(CN)_2$. Its ^{13}C NMR spectrum showed a resonated signal at δ 38.7 ppm attributable to CH of malononitrile. Partial hydrolysis of the two cyano groups of compound **11** into amides using acetic acid/ethanol mixture and a catalytic amount of Zn dust gave quinazoline derivative **12**. Former structure of compound **12** has been deduced from the corrected elemental analysis and spectral data. IR spectrum of compound **12** exhibited strong absorption band at 1684 cm^{-1} due to amide group and at 3200 and 3367 cm^{-1} attributed to NH_2 absorption. Its ^{1}H NMR gave resonated band at δ 6.90 ppm characteristic for D_2O exchangeable NH. ^{13}C NMR of compound **12** showed a resonated signal at δ 166.6 ppm attributable to CO amide. Finally, quinazoline derivative **12** was submitted to hetero-ring cyclization and afforded the interesting spiro compound pyrimidine-quinazoline derivative **13**. The IR spectrum of compound **13** showed strong absorption bands at $ν_{max}$ = 1678, 1685 cm^{-1} for the 2C=O groups and at 3216 cm^{-1} for the NH group, ^{1}H NMR and ^{13}C NMR data were carried out also and were found to be consistent with the proposed structure for compound **13**. Its ^{1}H NMR gave resonated signals at δ 2.31 and 3.19 ppm characteristic for CH_3 and pyrimidine-H. ^{13}C NMR of compound **13** revealed a resonated signal at δ 181.7, 169.1, and 159.2

ppm attributed to 2C=O and C=N (c.f. Scheme 4 and experimental section).

4. Conclusion

We successfully obtained a novel series of 4-heteroaryl quinazolines as well as triazolo quinazolines and spiro compound **13** via the simple replacement of the chlorine atom at 4 position of quinazoline nucleus with different amines, hydrazines, and nitriles respectively. Such interesting functionalized quinazoline derivatives obtained are promising anticipated biological activities.

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