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Synthesis of new 2-propenoylamides and 3-*H*-quinazolin-4-one derivatives

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ABSTRACT

A series of novel quinazolinones, pyrazolo [5, 1-b] quinazolines, beside acrylonitrile derivatives were synthesized by reaction of 3,1-benzoxazinone **(1)** and 4- chloroquinazoline **(8)** with different nitrogen nucleophiles. The structures of all novel compounds were identified by correct elemental and physical analysis.

KEYWORDS

3, 1-benzoxazinone;
3H-quinazolinone;
Pyrazoloquinazolinone.

INTRODUCTION

Due to their interesting biological and other properties, 4*H*-3,1-benzoxazin-4-one derivatives are an important class of compounds[1,2]. 2-Substituted benzoxazinone derivatives show bioactivities on human leukocyte elastase[3-5], human chymase[5], anti-HCOVS and ICAMVS inhibitors[6], besides their antiinflammatory and anti-platelet aggregation agents[7], antifungal and antibacterial agents[8-11], antimusclar contraction properties and can be used as hypnotic drugs[12,13]. On the other hand, 4*H*-3,1-benzoxazinone derivatives are mainly used as starting materials for synthesis of the highly important 3H-quinazolin-4-one derivatives via the precursors amides. The natural quinazolinones and their synthetic analogous, possess a variety of biological activities, including antimalarial[14-16], anticonvulsant[17-19], antibacterial[20-24], antidiabetic[25,26], anticancer[27-30], analgesic and anti-inflammatory[31-33], antiviral[34], antihelminitic[35], antitubercular[36], besides other activities[37].

RESULTS AND DISCUSSION

In continuation[38-41] of our interest in synthesis and reactions of important benzoxazinones and quinazolinones, we report herein, the reaction of 3,1-benzoxazin-4-one[42] **(1)** with different nitrogen nucleophiles.

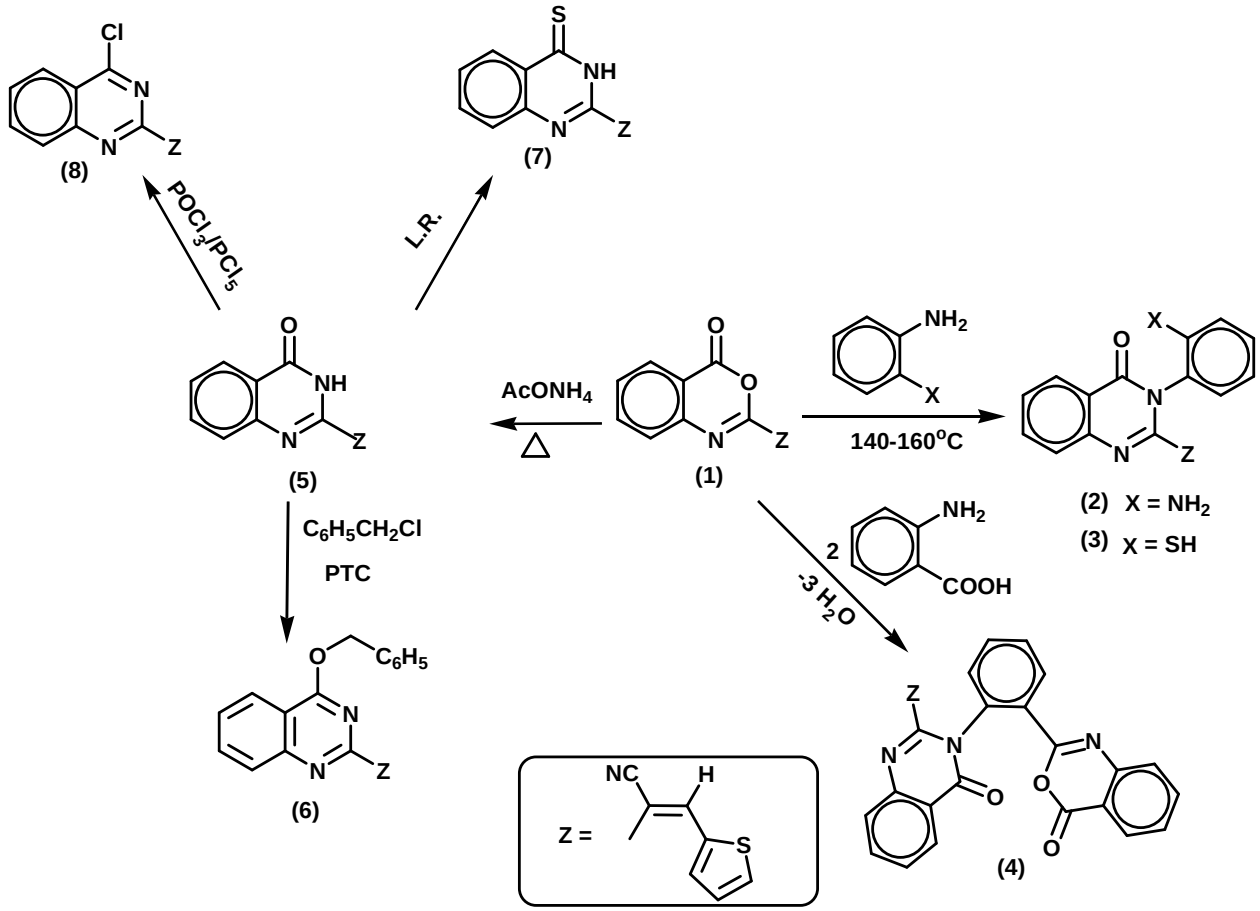
Fusion of **(1)** with *o*-phenylenediamine and/or *o*-aminothiophenol at 160°C gave the N-aryl quinazolinones **(2&3)**, respectively (Scheme 1) via ring-opening ring-closure mode of reaction. With anthranilic acid at elevated temperature, **(1)** yielded the unexpected quinazolinone derivative **(4)**. One of our targets is to get the 3*H*-quinazolin-4-one[42] **(5)** upon heating of **(1)** with ammonium acetate (Scheme 1), which can be used as starting material for several important reactions.

Alkylation of **(5)** with benzyl chloride under PTC conditions gave the 4-benzyloxy quinazoline derivative **(6)** (Scheme 1). On the other hand, thiation of **(5)** with Lawesson's reagent gave the expected quinazoline-4-thione derivative **(7)**.

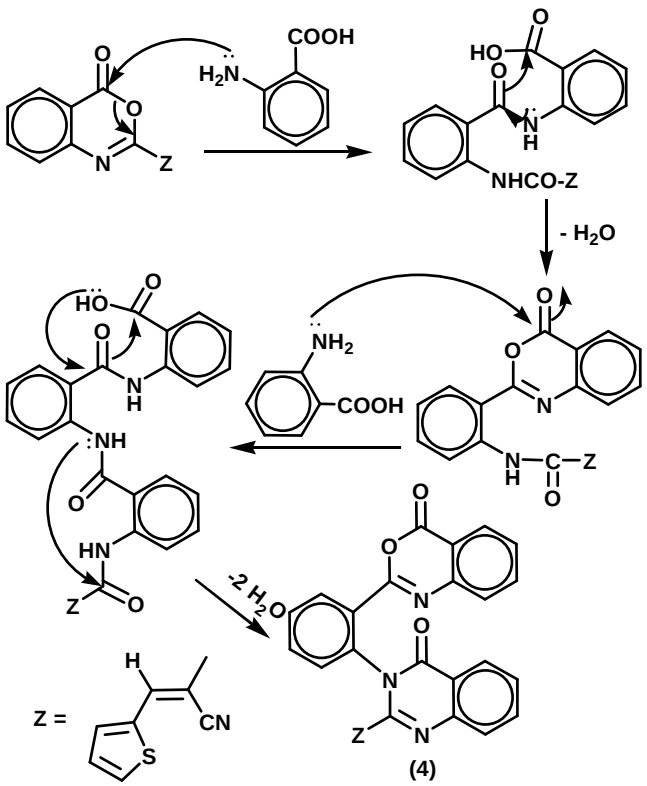
Chlorination of **(5)** with $POCl_3/PCl_5$ mixture gave the 4-chloroquinazoline derivative[42] **(8)** (Scheme 1). **(8)** was used in wide scales in nucleophilic substitution reactions (Scheme 6).

Formation of compound **(4)** can be achieved by the following pathway:

Full Paper



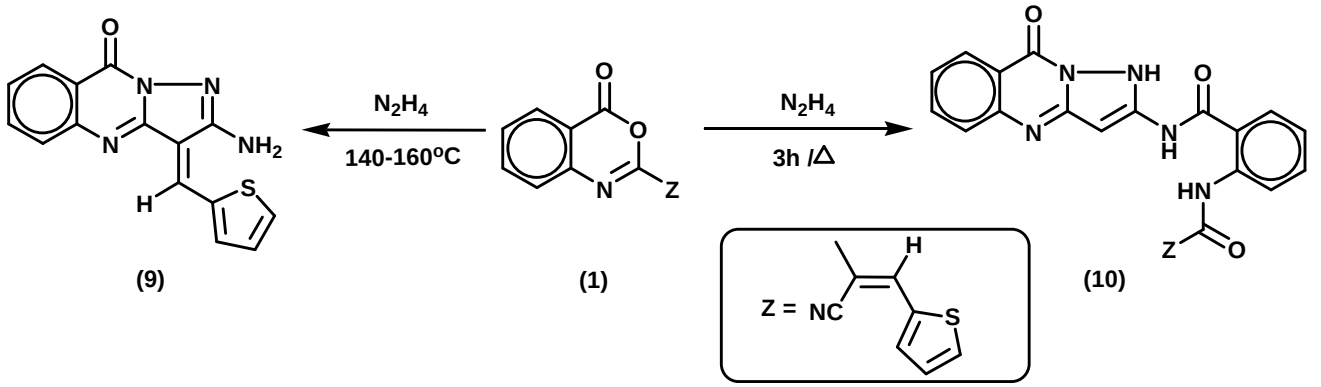
Scheme 1



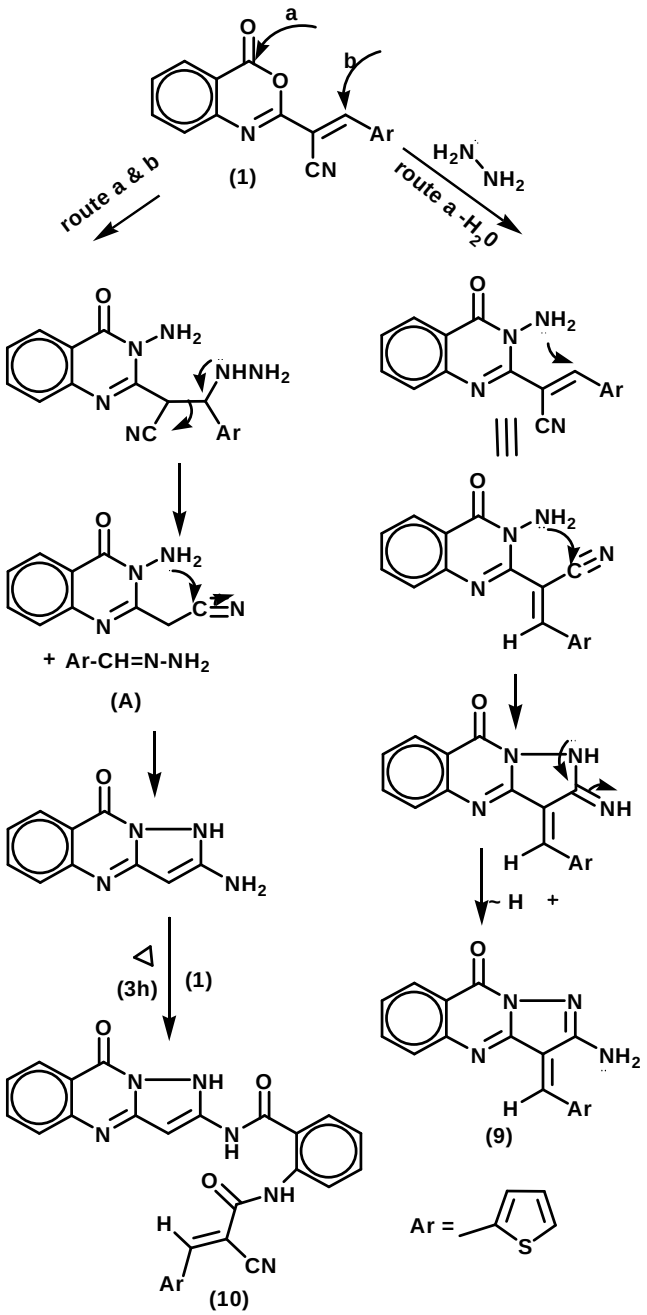
Fusion of **(1)** with hydrazine hydrate at 160°C without solvent gave the pyrazole[5,1-b]quinazolin-9-one derivative **(9)** (Scheme 2). On the other hand, heating of the above reagents for 3 hours in dioxane gave further analogs of this system **(10)** (Scheme 2), which prove the high nucleophilicity of hydrazine hydrate and also the reactivity of α,β-unsaturated nitrile at position 2 towards these types of reagents.

Formation of **(9&10)** could be explained in the following general mechanism:

Furthermore, fusion of **(1)** with *p*-anisidine and/or 2-aminophenol afforded only the open system 2-propenoylamide derivatives **(11 & 12)**, respectively (Scheme 3). Ring opening of **(1)** with ethanolamine gave the corresponding amide **(13)** which used as precursors on synthesis of its chloro derivative **(14)** and N-chloro ethyl quinazolinone **(15)** upon treatment with phosphorous pentachloride. (Scheme 3). With phenyl hydrazine, **(1)** gave a mixture of hydrazide **(16)** and phenyl hydrazone **(17)**, while with benzoyl hydrazine **(1)** gave the open system **(18)** (Scheme 3).



Scheme 2



Reaction of **(1)** with N-methyl thiourea and/or thiosemicarbazide gave only the normal open system 2-propenoylamides **(19)** and **(20)**, respectively (Scheme 3).

Condensation of **(8)** with benzoyl hydrazine gave only the benzoylhydrazine derivative **(21)** rather than the triazolo[3,4-a]-quinazoline **(22)** (Scheme 4), while with hydrazine hydrate in ethanol we got a mixture of hydrazone derivative **(23)**, azo derivative **(24)** and the bis-quinazoline derivative **(25)** (Scheme 6). On the other hand, thione **(7)** condensed with hydrazine hydrate to get **(24)** as sole product (Scheme 4).

One pot reaction of chloroquinazoline **(8)** with N_2H_4 and piperonal afforded the hydrazone **(26)** (Scheme 4). Condensation of chloroquinazoline **(8)** with thiourea in refluxing ethanol gave the N,N'-bisquinazoline thiourea **(27)** instead of thione **(7)** (Scheme 4).

Structures of all compounds are confirmed by elemental analysis and spectroscopic data (IR, MS. and ^{1}H-NMR spectra).

EXPERIMENTAL

Melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. ^{1}H-NMR spectra were determined on Varian Gemini 300 MHz using TMS as internal standard. All chemical shifts (δ) are expressed in ppm. All the NH or OH protons are exchangeable on addition of D_2O. The mass spectra were determined using MP model MS-5988 and Shimadzu single focusing mass spectrometer (70 eV). Elemental analyses were investigated by Elementar analyzer Vario EL III.

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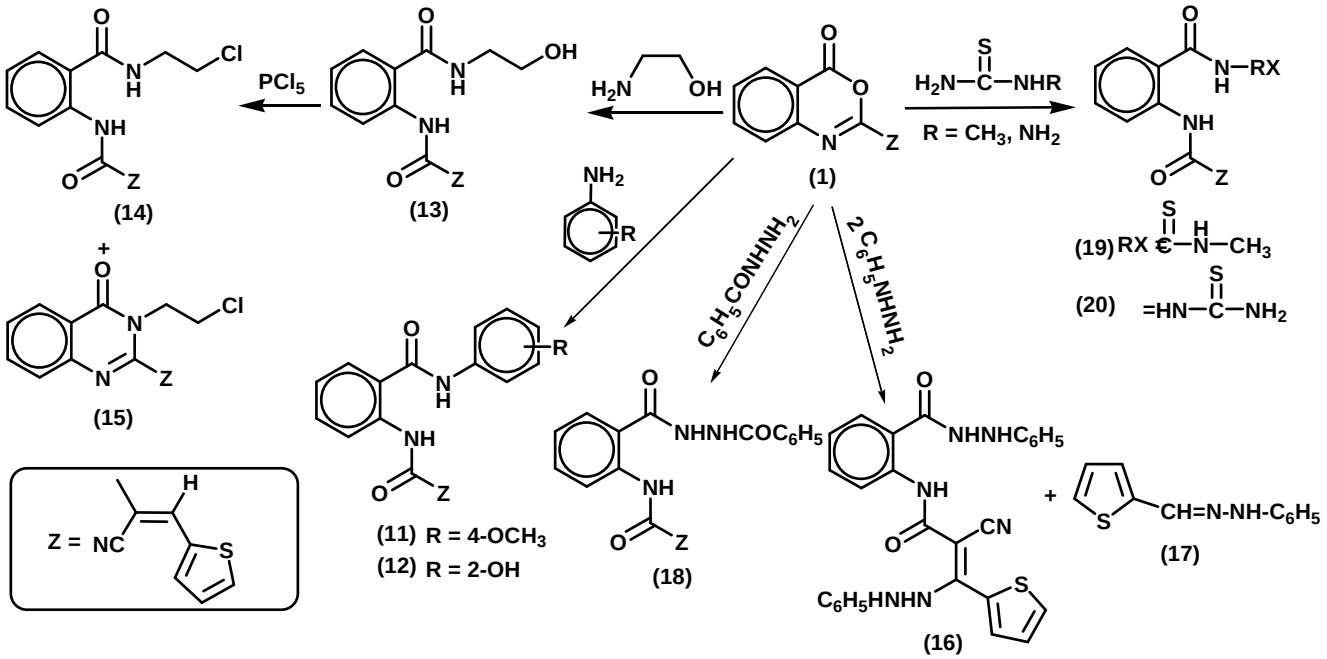
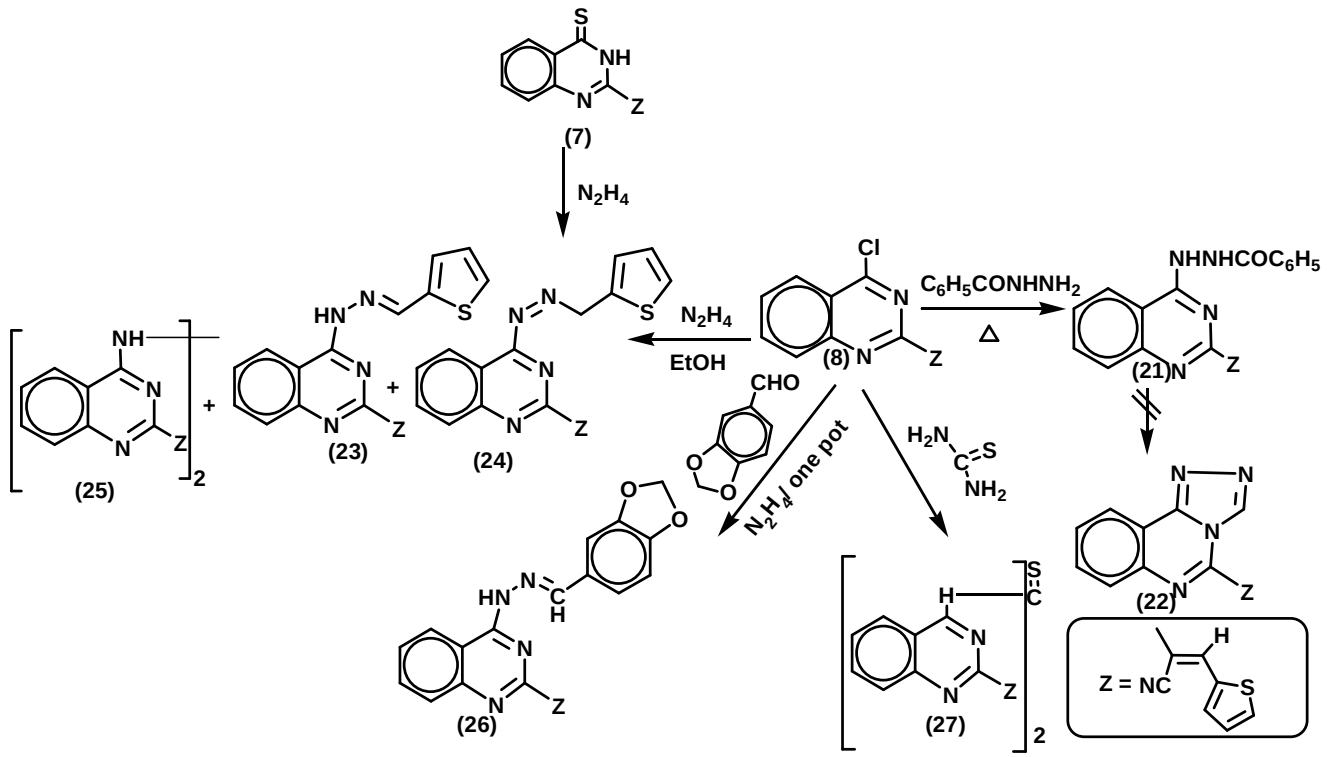


Scheme 3



Scheme 4

(E)-2-(3-(2-Aminophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(thiophen-2-yl) acrylonitrile (2)

A mixture of benzoxazinone **(1)** (1.48 g, 0.005 mol) and o-phenylenediamine (0.54 g, 0.005 mol) was fused in sand bath at 160-170°C for 2h. The reaction mixture was triturated with ethanol and crystallized from benzene to give **(2)** as yellow crystals; m.p.: 119-120°C, yield 44%. Anal. Calcd. for $C_{21}H_{14}N_4OS$ (370.416): C, 68.09; H, 3.81; N, 15.13. Found C, 68.18; H, 3.72; N, 15.22. IR (KBr, νcm^{-1}): 3474, 3369 (NH_2), 2218 (C≡N), 1654, (C=O). ^{1}H-NMR (DMSO-d_6)δ (ppm)

6.50 (t, 1H Ar-H), 6.74 (d, 1H, J = 12, Ar-H), 7.18-7.85 (m, 9H, Ar-H), 8.55 (s, 1H, =CH), 13.0 (s_{br}, 2H, NH_2). MS: $M^{+\cdot}$ not observed, 258 (52), 250 (100), 92 (28), 77 (8).

(E)-2-(3-(2-Mercaptophenyl)-4-oxo-3,4-dihydro-quinaz-olin-2-yl)-3-(thiophen-2-yl)acrylonitrile (3)

A mixture of benzoxazinone **(1)** (1.48 g, 0.005 mol) and 2-aminothiophenol (0.63 g, 0.005 mol) was fused in sand bath at 160-170°C for 2h. The reaction mixture was triturated with diethyl ether and crystallized from petroleum ether 80-100°C to give **(3)** as orange crystals; m.p. 202-204°C, yield 27%. Anal. Calcd. for $C_{21}H_{13}N_3OS$ (387.480): C, 65.09; H, 3.38; N, 10.84. Found C, 65.19; H, 3.29; N, 10.64. IR (KBr, νcm^{-1}): 2211 (C≡N), 1674, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 7.29-8.28 (m, 10H, Ar-H), 8.66 (s, 1H, =CH), 8.75 (d, 1H, J = 9, Ar-H), 12.87 (s, 1H, SH). MS: 387 ($[M]^{+\cdot}$, 21), 254 (21), 253 (100), 134 (34), 109 (30), 107 (10), 76 (11).

(E)-2-(4-Oxo-3-(2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-phenyl)-3,4-dihydroquinazolin-2-yl)-3-(thiophen-2-yl) acrolnitrile (4)

A mixture of benzoxazinone **(1)** (1.48 g, 0.005 mol) and anthranilic acid (0.54 g, 0.005 mol) was fused in sand bath at 160-170°C for 2h. The residue was triturated with few ethanol then filtered, dried and crystallized from toluene to afford the product **(4)** as yellow crystals; m.p. 189-190°C, yield 30%. Anal. Calcd. for $C_{29}H_{16}N_4O_3S$ (500.53): C, 69.59; H, 3.22; N, 11.19. Found C, 69.51; H, 3.31; N, 11.28. IR (KBr, νcm^{-1}): 2212 (C≡N), 1765, 1683 (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 7.34-8.2 (m, 15H, Ar-H), 8.65 (s, 1H, =CH). *MS: 500 ($[M^{+\cdot}]$*, 0.9), 278 (11), 252 (4), 354 (14), 264 (20), 236 (3), 222 (5), 162 (39), 146 (39), 107 (10), 90 (100).

(E)-2-(4-oxo-3,4 dihydroquinazolime-2-yl)-3(thiophen-2-yl)acrylamide (5)[42]

A mixture of benzoxazinone **(1)** (5 g, 0.01 mol) and ammonium acetate (20 g, 0.04 mol) was heated without solvent at 160-170°C for 8h. The reaction mixture was triturated with warm water (10 mL). The solid separated was filtered, washed with water (20 mL), dried and crystallized from dioxane to give **(5)** as yellow crystals; m.p. 330-331°C, yield 60%.

(E)-2-(4-Benzyloxy)quinazolin-2-yl)-3-(thiophen-2-yl)acrylonitrile (6)

A mixture of quinazoline **(5)** (1.4 g, 0.005 mol) in acetonitrile (50 ml), potassium carbonate anhydrous (1.38 g, 0.01 mol), tertabutyl ammonium bromide (TBAB) (0.4 g, 0.002 mol) was stirred at 80-82°C for 30 minutes. After addition of benzyl chloride (0.69 g, 0.006 mol), the reaction mixture was stirred for 2h. The reaction mixture was poured into ice/HCl. The solid separated was filtered, washed with water several times, dried and crystallized from tolueneto give **(6)** as yellow crystals; m.p. 190-192°C, yield 65%. Anal. Calcd. for $C_{22}H_{15}N_5OS$ (397.45): C, 66.48; H, 3.80; N, 17.62. Found C, 66.23; H, 3.62; N, 17.50. IR (KBr, νcm^{-1}): 2212 (C≡N). ^{1}H-NMR (DMSO-d_6) δ (ppm) 5.80 (s, 2H, CH_2), 7.34-8.19 (m, 12H, Ar-H), 9.00 (s, 1H, =CH). MS: 369 ($[M^{+\cdot}]$, 42), 368 ($[M^{+\cdot}-1]$, 62), 278 (13), 262 (4), 230 (13), 91 (100).

(E)-3-(Thiophen-2-yl)-2-(4-thioxo-3,4-dihydroquinazolin-2-yl) acrylonitrile (7)

A mixture of **(5)** (208 g, 0.01 mol) and Lawson's reagent (1.19 g, 0.015 mol) in dry toluene (50 ml) was refluxed for 10h. The residue was filtered, washed with toluene. The formed solid was crystallized from petroleum ether 80-100°C to give **(7)** as yellow crystals; m.p. 178-180°C, yield 60%. Anal. Calcd. for $C_{15}H_9N_3S_2$ (295.4): C, 60.99; H, 3.07; N, 14.23. Found C, 60.98; H, 3.17; N, 14.32. IR (KBr, νcm^{-1}): 3267 (NH,), 2224 (C≡N). ^{1}H-NMR (DMSO-d_6) δ (ppm) 6.40 (t, 1H, (J = 7), thienyl-H), 7.65 (d, 2H, (J = 8), thienyl-H), 7.87 (m_{br}, 3H, Ar-H + NH), 8.19 (d, 1H, (J = 8), Ar-H), 8.60 (d, 1H, (J = 8), Ar-H), 8.87 (s, 1H, =CH). MS: 295 ($[M^{+\cdot}]$, 100), 262 (77), 230 (59), 135 (15), 102 (53).

(Z)-2-(4-Chloroquinazolin-2-yl)-3-(thiophen-2-yl)acrylo-nitrile (8)[42]

A mixture of **(5)** (5 g, 0.01 mol), phosphorus oxychloride (40 mL) and phosphorus pentachloride (5 g) was heated on water bath for 5h. After cooling the reaction mixture was poured on crushed ice (50 g). The solid separated was filtered, washed with water (60 mL), dried and crystallized from toluene to give **(8)** as yellow crystals; m.p. 222-223°C, yield 55%.

Full Paper

(E)-2-Amino-3-(thiophen-2-ylmethylene) pyrazolo[5,1-b] quinazolin-9(3H)-one (9)

A solution of benzoxazinone **(1)** (1.48 g, 0.005 mol) and hydrazine hydrate (0.3 ml, 0.005 mol) was fused in sand bath at 160-170°C for an hour. The reaction mixture was triturated with ethanol. The solid separated was filtered, dried and crystallized from toluene to give **(9)** as yellow crystals; m.p. 148-150°C, yield 26%. Anal. Calcd. for $C_{15}H_{10}N_4OS$ (294.06): C, 61.21; H, 3.42; N, 19.04. Found C, 60.98; H, 3.25; N, 18.96. IR (KBr, νcm^{-1}): 3326, 3198 NH_2, 1680(s), 1642 (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 5.31 (s_{br}, 2H, NH_2,), 7.21 (t, 2H, (J = 8), Ar-H), 7.40 (d, 2H, (J = 8), Ar-H), 7.65 (s+d, 2H, Ar-H + =CH), 8.10 (d, 2H, (J = 9), Ar-H). Also, the characteristic signals at 8.50 for =CH in (1) and related structures not observed. MS: $M^{+\cdot}$ at 294 (77), 200 (100), 144 (26), 145 (40), 119 (18), 118 (12), 104 (7).

(E)-2-(2-Cyano-3-(thiophen-2-yl)acrylamido)-N-(9-oxo-1,9-dihydropyrazolo[5,1-b]quinazolin-2-yl)benzamide (10)

A solution of benzoxazinone **(1)** (1.48 g, 0.005 mol) and hydrazine hydrate (0.3 mL, 0.005 mol) in dioxane (50 ml) was refluxed for 3h. The solvent was concentrated and the separated solid was filtered, dried and crystallized from toluene to give **(10)** as yellow crystals, m.p. 222-223°C yield 58%. Anal. Calcd. for $C_{25}H_{16}N_6O_3S$ (480.49): C, 62.49; H, 3.36; N, 17.49. Found C, 62.23; H, 3.18; N, 17.30. IR (KBr, νcm^{-1}): 3197, 3303, 3447 (NH,), 2222(C≡N), 1681, 1646 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.05 (s_{br}, 3H, NH), 6.98-8.42 (m, 12H, Ar-H), 8.78 (s, 1H, =CH). MS: 480 (20), 312 (14), 184 (14), 182 (7), 91 (100).

(E)-2-(2-Cyano-3-(thiophen-2-yl)acrylamido)-N-(4-methoxyphenyl) benzamide (11)

A mixture of benzoxazinone **(1)** (1.48 g, 0.005 mol) and p-anisidine (0.62 g, 0.005 mol) was fused in sand bath at 160-170°C for 2h. The reaction mixture was triturated with ethyl alcohol. The crude solid product was filtered, dried and crystallized from toluene to afford the product **(11)** as orange crystals; m.p. 168-170°C, yield 35%. Anal. Calcd. for $C_{22}H_{17}N_3O_3S$ (403.50): C, 65.49; H, 4.25; N, 10.42. Found C, 65.58; H, 4.33; N, 10.51. IR (KBr, νcm^{-1}): 3447 (NH,), 2212 (C≡N), 1684, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 10,12 (s, 2H NH) 7.04-7.97 (m, 11H, Ar-H), 8.18 (s, 1H, =CH). 3.87 (s, 3H, OCH_3). MS: 385 ([M-H_2O], 13), 354 (2), 278 (9), 250 (83), 162 (35), 144 (5), 134 (27), 108 (14), 102 (24), 63 (100).

(E)-2-(2-Cyano-3-(thiophen-2-yl)acrylamido)-N-(2-hydroxyphenyl) benzamide (12)

A mixture of benzoxazinone **(1)** (1.48 g, 0.005 mol) and 2-aminophenol (0.5 g, 0.005 mol) was fused in sand bath at 170-180°C for an hour. The residue was triturated with ethanol, filtered, dried and crystallized from toluene to give **(12)** as orange crystals. m.p. 208-210°C, yield 31%. Anal. Calcd. for $C_{21}H_{15}N_3O_3S$ (389.43): C, 64.77; H, 3.88; N, 10.79. Found C, 64.23; H, 3.68; N, 10.30. IR (KBr, νcm^{-1}): 3284 (NH, OH), 2211 (C≡N), 1680, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 6.94-8.22 (m, 11H, Ar-H), 8.68 (s, 1H, =CH), 9.90 (s_{br}, 2H, 2 NH), 11.92 (s_{br}, 1H, OH,). MS: 289 ([$M^{+\cdot}$], 3), 281 (41), 255 (1), 162 (29), 119 (6), 134 (34), 109 (100), 108 (5), 90 (28).

(E)-2-(2-Cyano-3-(thiophen-2-yl)acrylamido)-N-(2-hydroxyethyl) benzamide (13)

A solution of benzoxazinone **(1)** (1.48 g, 0.005 mol) and ethanol amine (0.305 g, 0.005 mol) in dioxane (50 ml) was heated under reflux for 2 h. The solid separated after evaporation of the solvent was collected, dried and crystallized from toluene to give **(13)** as yellow crystals; m.p.: 219-220°C, yield 95%. Anal. Calcd. for $C_{17}H_{15}N_3O_3S$ (341.38): C, 59.81; H, 4.43; N, 12.31. Found C,59.73; H, 4.52; N, 12.21. IR (KBr, νcm^{-1}): 3524, 3298 (NH, OH), 2210 (C≡N), 1679, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 12.38(s, 1H, NH), 8.90(t_{br}, 1H, NH), 8.60 (s,1H, =CH), 8,45(d,1HAr-H,J=8), 8,16 (d,1HAr-H,J=8), 8,00 (d,1HAr-H,J=9), 7.86 (d,1HAr-H,J=8), 7,56 (t,1HAr-H,J=7), 7,35 (t,1HAr-H,J=7), 7,23 (t,1HAr-H,J=7), 4.75 (t,1H, OH J=5.6), 3,56 (t,2H, H=5.56), 3,37 (t,2H, J=5.6), MS: 341 ([$M^{+\cdot}$], 10), 310 (12), 281 (57), 253 (21), 188 (18), 161 (59), 146 (97), 134 (76), 90 (100).

(E)-N-(2-Chloroethyl)-2-(2-cyano-3-(thiophen-2-yl)acryl-amido)benzamide (14) and (E)-2-(3-(2-chloroethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(thiophen-2-yl)acrylonitrile (15)

A solution of **(13)** (1 g, 0.003 mol) and

phosphourous pentachloride (1 g, 0.005 mol) in dioxane (50 ml) heated under reflux for 3h. The reaction mixture was poured into ice/water. The solid separated was filtered, washed with water several times, dried and crystallized from petroleum ether 80-100°C afforded the product **(14)** as yellow crystals, and then recrystallized from toluene to give **(15)** as orange crystals.

(14): m.p 170-172°C, yield 30%. Anal. Calcd. for $C_{17}H_{14}ClN_3O_2S$ (359.83): C, 56.74; H, 3.92; N, 11.68. Found C, 56.64; H, 3.82; N, 11.77. IR (KBr, νcm^{-1}): 3301 (NH), 2205 (C≡N), 1679, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 12.18(s,1H, NH), 9.02(t_{br}, 1H, NH), 8.63 (s,1H, =CH), 8,60 (d,1H, Ar-H, J=8), 8,17 (d,1H, Ar-H, J=8), 8,02 (d,1H,Ar-H, J=9), 7.84 (d,1H Ar-H, J=8), 7,58 (t,1H Ar-H, J=7), 7,36 (t,1H Ar-H, J=7), 7,26 (t,1H Ar-H, J=6), 3,80 (t,2H, J=8.5), 3,65 (t,2H, J=6). MS: 359 ([M$^{+\cdot}$], 2), 323 (38), 189 (87), 146 (100), 90 (100).

(15): m.p 200-202°C, yield 28%. Anal. Calcd. for $C_{17}H_{12}ClN_3OS$ (341.80): C, 59.73; H, 3.54; N, 12.29. Found C, 59.81; H, 3.45; N, 12.38. IR (KBr, νcm^{-1}): 2215 (C≡N), 1678, (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.96 (t, 2H, J = 5.4, CH_2N), 4.51 (t, 2H, J = 5.6, CH_2Cl), 7.35-8.29 (m, 7H, Ar-H), 8.75 (s, 1H, =CH). MS: 343 ([M$^{+\cdot}$+2], 6), 341 ([M$^{+\cdot}$], 12), 304 (16), 280 (3), 272 (9), 247 (20), 102 (65), 149 (15), 134 (26), 76 (63), 63 (100).

1,4-diphenyl-3,6-di(thiophen-2-yl)-1,2,4,5-tetrahydrazine (16) and (E)-1-Phenyl-2-(thiophen-2-ylmethylene) hydrazine (17)

A solution of benzoxazinone **(1)** (1.48 g, 0.005 mol) and phenyl hydrazine (0.54 g, 0.005 mol) in dioxane (50 ml) was heated under reflux for 8h. The reaction mixture was concentrated and left to cool. The solid separated was filtered, dried and crystallized from toluene to give **(17)** as yellow crystals and then recrystallized from ethanol to give **(16)** as orange crystals.

(16): m.p.209-210°C, yield 28%. Anal. Calcd. for $C_{27}H_{22}N_6O_2S$ (494.60): C, 65.57; H, 4.48; N, 16.99. Found C, 65.66; H, 4.56; N, 16.91. IR (KBr, νcm^{-1}): 3251(br) (NH),2216 (C≡N), 1681, 1683 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm) 11.12 (s, 1H, NH), 6.70-8.25 (m, 17 H, Ar-H), 3.91 (s, 1H, NH), 3.97 (s, 1H, NH), 4.19 (s, 1H, NH), 4.26 (s, 1H, NH), the characteristic signals for (=CH) not observed. MS: 494 ([M$^{+\cdot}$], 4), 369 (6), 279 (8), 253 (3), 221 (5), 236 (7), 146 (15), 131 (11), 103 (13), 89 (13), 77 (100).

(17): m.p 160-162 °C, yield 23%. Anal. Calcd. for $C_{11}H_{10}N_2S$ (202.30): C, 65.32; H, 4.98; N, 13.98. IR (KBr, νcm^{-1}): 3217(NH), 1623(C≡N), 3082(ArCH). ^{1}H-NMR ($CDCl_3$) δ (ppm) 6.85 (t, 1H, J = 6, Ar-H), 6.88-7.10 (m, 4H, Ar-H), 7.25-7.31 (m, 3H, Ar-H), 7.49 (s_{br}, 1H, NH), 7.87 (s, 1H, =CH). MS: 202(35), 119(7), 110(6), 107(14) 106(70), 105(61), 78(36), 77(100).

(2E)-N-[2-[(2-Benzoylhydrazino)carbonyl]phenyl]-2-cyano-3-thien-2-ylarylamide (18)

A mixture of benzoxazinone **(1)** (0.56 g, 0.002 mol) and benzoyl hydrazine (0.27 g, 0.002 mol) in dioxane (50 ml) was heated under reflux for 12h. The solid separated after evaporation of the solvent was collected, dried and crystallized from petroleum ether 80-100°C to give **(18)** as yellow crystals; m.p. 219-220°C, yield 54%. $C_{22}H_{16}N_4O_3S$ (416.50): C, 63.45; H, 3.87; N, 13.45. Found C, 63.36; H, 3.79; N, 13.54. IR (KBr, νcm^{-1}): 3209 (br) (NH), 2209 (C≡N), 1668, 1632 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.04-8.24 (m, 12H, Ar-H), 8.46 (s, 1H, =CH), 8.95 (s_{br}, 1H, NH), 9.40 (s, 2H, 2CH). MS: 304 (12), 293 (31), 200 (12), 146 (23), 133 (23), 119 (27), 90 (100), 76 (42).

(E)-1-(2-(2-Cyano-3-(thiophen-2-yl)acrylamido) benzoyl)-3-methyl thiourea (19)

A mixture of benzoxazinone **(1)** (0.7 g, 0.003 mol) and N-methylthiourea (0.22 g, 0.003 mol) in dioxane (50 ml) was heated under reflux for 8h. The solid separated after evaporation of the solvent was collected, dried and crystallized from petroleum ether 80-100°C to give **(19)** as yellow crystals; m.p. 229-230°C, yield 62%. $C_{17}H_{14}N_4O_2S_2$ (370.45): C, 55.12; H, 3.81; N, 15.12. Found C, 55.03; H, 3.89; N, 15.03. IR (KBr, νcm^{-1}): 3247 (br) (NH), 2220 (C≡N), 1676 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.07 (s, 3H, N-CH_3), 6.40 (s_{br}, 1H, NH), 7.20-8.20 (m, 7H, Ar-H), 8.45 (s, 1H, =CH), 12.06 (s, 1H, NH), 12.29 (s, 1H, NH). MS: 368 ([M-2]$^{+\cdot}$, 3), 367 ([M-3]$^{+\cdot}$, 8), 314 (3), 281 (12), 253 (17), 198 (5), 163 (5), 162 (71), 134 (65), 119 (6), 104 (9), 91 (24), 90 (100).

(E)-1-(2-(2-Cyano-3-(thiophen-2-yl)acrylamido) benzoyl thiosemicarbazide (20)

A mixture of benzoxazinone **(1)** (0.56 g, 0.001

mol) and thiosemicarbazide (0.54 g, 0.003 mol) in pyridine (30 ml) was heated under reflux for 3h. The reaction mixture was poured into ice/HCl. The solid separated was filtered, washed with water several times, dried and crystallized from toluene to give **(20)** as yellow crystals; m.p. 258-260°C, yield 53%. $C_{16}H_{13}N_5O_2S_2$ (371.44): C, 51.74; H, 3.53; N, 18.85. Found C, 51.83; H, 3.61; N, 18.76. IR (KBr, νcm^{-1}): 3319 (br) (NH), 2210 (C≡N), 1695 (C=O). MS: 370 ([M-1]$^{+\cdot}$, 24), 230 (21), 155 (17), 119 (31), 106 (59), 91 (28), 65 (100).

(E)-N-(2-(1-Cyano-2-(thiophen-2-yl)vinyl) quinazolin-4-yl) benzohydrazide (21)

A mixture of **(8)**[42] (1.48 g, 0.005 mol) and benzoyl hydrazine (0.68 g, 0.005 mol) was fused at 160-170°C for 2h. after cooling, the mixture was triturated with ethanol. The separated solid was filtered, dried and crystallized from toluene to give **(21)** as orange crystals; m.p. 259-260°C, yield 38%. $C_{22}H_{15}N_5OS$ (397.45): C, 66.48; H, 3.80; N, 17.62. Found C, 66.56; H, 3.79; N, 17.54. IR (KBr, νcm^{-1}): 3394,3214 (NH), 2210 (C≡N). ^{1}H-NMR (DMSO-d$_6$) δ (ppm) 7.26 (t, 1H, (J = 6), thienyl-H), 7.48-8.04 (m, 10H, Ar-H), 8.37 (d, 1H, (J = 8), Ar-H), 8.65 (s, 1H, =CH), 10.68 (s$_{br}$, 2H, 2NH). MS: 397 ([M$^{+\cdot}$], 16), 292 (4), 262 (2), 105 (100), 77 (61).

(2E)-3-Thien-2-yl-2-[4-[(2E)-2-(thien-2-ylmethylene)-hyd-razine]quinazolin-2-yl]acrylonitrile (23), (2E)-3-thien-2-yl-2-{4-[(2)-thien-yl methyl)diazenyl]quinazolin-2-yl}acrylonitrile (24) and (Z)-2-(4-methylamino)quinazolin-2-yl)-3-(thiophen-2-yl)acrylonitrile (25)

A mixture of **(8)** (1.6 g, 0.005 mol) and hydrazine hydrate (0.16 g, 0.005 mol) in ethanol (50 ml) was refluxed for 5h. The solvent was removed and the crude solid was crystallized from petroleum ether 80-100°C to give **(23)** as yellow crystals, and crystallized from toluene to give **(24)** as yellow crystals, and from ethanol to give **(25)** as brown crystals.

(23): m.p. 270-271°C, yield 28%. $C_{20}H_{13}N_5S_2$ (387.48): C, 61.99; H, 3.38; N, 18.07. Found C, 61.91; H, 3.29; N, 18.15. IR (KBr, νcm^{-1}): 3265 (NH), 2214 (C≡N). ^{1}H-NMR (DMSO-d$_6$) δ (ppm) 7.17 (t, 1H, (J = 6), thienyl-H), 7.20 (t, 1H, (J = 6), thienyl-H), 7.53-8.20 (m, 8H, Ar-H), 8.78 (s, 1H, N=CH), 8.95 (s, 1H, =CH), 12.12 (s$_{br}$, 1H, NH). MS: 387 ([M$^{+\cdot}$], 84), 386 ([M$^{+\cdot}$-1], 23), 304 (17), 277 (100), 262 (31), 245 (24), 134 (8), 129 (10), 108 (9), 103 (12), 75 (9).

(24): m.p. 290-291°C, yield 32%. $C_{20}H_{13}N_5S_2$ (387.48): C, 61.99; H, 3.38; N, 18.07. Found C, 61.89; H, 3.49; N, 18.17. IR (KBr, νcm^{-1}): 2216 (C≡N). ^{1}H-NMR (DMSO-d$_6$) δ (ppm) 4.80 (s, 2H, CH$_2$-N), 7.23-7.37 (m, 3H, Ar-H), 7.56 (d, 1H, (J = 7), Ar-H), 7.67 (t, 1H, (J = 6), Ar-H), 7.94-8.12 (m, 5H, Ar-H), 8.99 (s, 1H, =CH). MS: 387 (19), 385 (100), 384 (28), 262 (28), 230 (13), 161 (5), 123 (4), 102 (7).

(25): m.p. >300°C, yield 23%. $C_{30}H_{18}N_8S_2$ (555.00): C, 64.96; H, 3.27; N, 20.20. Found C, 64.88; H, 3.11; N, 20.09. IR (KBr, νcm^{-1}): 3302 (NH), 2210 (C≡N). ^{1}H-NMR (DMSO-d$_6$) showed the following signals for symmetrical 4-aminoquinazoline at δ (ppm) 7.20 (m, 2H, Ar-H), 7.74 (t, 1H, (J = 8), Ar-H), 7.87-7.97 (m, 3H, Ar-H), 8.32 (s, 1H, =CH), 8.58 (d, 1H, (J = 8), Ar-H), 10.82 (s$_{br}$, 1H, NH). MS: 554 (5), 277 (100), 278 (50), 262 (8), 252 (23), 145 (38), 144 (8), 118 (36), 117 (20), 108 (8).

(2E)-2-{4-(2E)-2-(1,3-Benzodioxol-5-ylmethylene)hydr-azine]quinazolin-2-yl}-3-thien-2-ylacrylonitrile (26)

A mixture of **(8)** (1.6 g, 0.005 mol), hydrazine hydrate (0.16 g, 0.005 mol) and piperonal (0.75 g, 0.005 mol) in ethanol (50 ml) was heated under reflux for 5 h. The solid was collected, washed with ethyl alcohol, dried and crystallized from toluene to give **(26)** as brown crystals; m.p. 180-182°C, yield 58%. $C_{23}H_{15}N_5O_2S$ (425.46): C, 64.93; H, 3.55; N, 16.46. Found C, 64.89; H, 3.42; N, 16.33. IR (KBr, νcm^{-1}): 3267 (NH), 2216 (C≡N). ^{1}H-NMR (DMSO-d$_6$) δ (ppm) 6.13 (s, 2H, O-CH$_2$O), 7.15-8.54 (m, 11H, Ar-H + NH), 8.78 (s, 1H, N=CH), 8.95 (s, 1H, =CH). MS: 425 ([M$^{+\cdot}$], 34), 277 (100), 278 (44), 262 (24), 245 (26), 145 (11), 108 (15), 83 (7), 51 (19).

1,3-Bis-(2-[(E)-1-cyano-2-(thiophen-2-yl)vinyl]quinazolin-4-yl)thiourea (27)

A solution of **(8)** (1.6 g, 0.005 mol), thiourea (0.38 g, 0.005 mol) in ethanol (50 ml) was refluxed for 5 h.

The solvent was removed and the crude solid was crystallized from dioxane to give **(27)** as brown crystals; m.p. 290-291°C, yield 68%. $C_{31}H_{18}N_8S_3$ (598.72): C, 62.19; H, 3.03; N, 18.72. Found C, 62.28; H, 3.11; N, 18.63. IR (KBr, νcm^{-1}): 3420 (NH), 2212 (C≡N). ^{1}H-NMR (DMSO-d_6) showed the classical signals of aromatic protons (14 H) as multiplet at 7.22-8.23, 2 x olefinic signals at 8.66, and 2NH at 12.22 (exchangeable with D_2O. MS: $M^{+\cdot}$ not obtained, 279 (83), 278 (100), 145 (57), 117 (50), 90 (55). $M^{+\cdot}$ not obtained, 279 (83), 278 (100), 145 (57), 117 (50), 90 (55).

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