Design, Synthesis, and Anticancer Activity of Novel Benzothiazole Analogues

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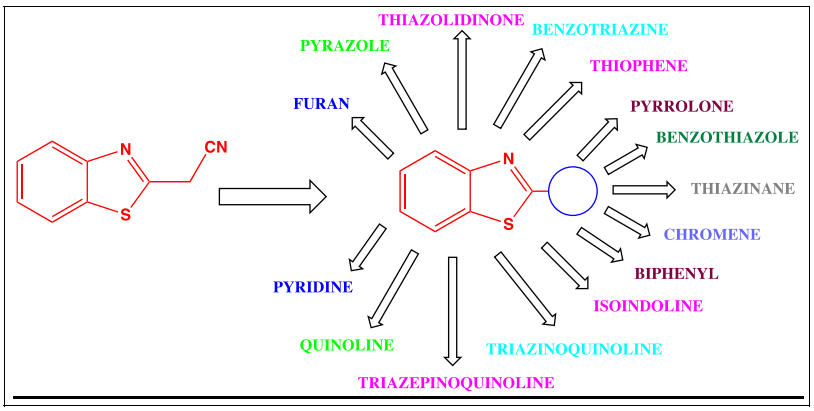

On the pharmaceutical account of the reported anticancer activity of benzothiazole derivatives, differently substituted benzothiazole derivatives **2a**–**c** to **34a**,**b**, attached at 2-position to different heterocyclic moieties, were synthesized *via* different chemical reactions. Thirteen of the newly synthesized compounds were selected by the National Cancer Institute, Bethesda, Maryland, USA, and evaluated for their *in vitro* antitumor activity against 60 human tumor cell lines in a one-dose screening panel among which two compounds **4** and **17** showed high activity and were selected for further evaluation in the five-dose full panel assay, in which compound **4** exerted powerful growth inhibitory activity against all cell lines with GI_{50} ranging from 0.683 to 4.66 μM/L in addition to excellent lethal activity against most of the cell lines.

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INTRODUCTION

Benzothiazole derivatives represent an important class of biologically active molecules having diverse pharmacological activities including anticancer [1–3], antimicrobial [4,5], anti-inflammaotory [6], antiviral [7], antioxidant [8], antitubercular [9], anticonvulsant [10], antimalarial [11], and antileshmanial [12] activities. Besides, many benzothiazole derivatives were found to be responsible for inhibition of topoisomerase II [13–15] and tyrosine kinase histone deacetylase [16] enzymes.

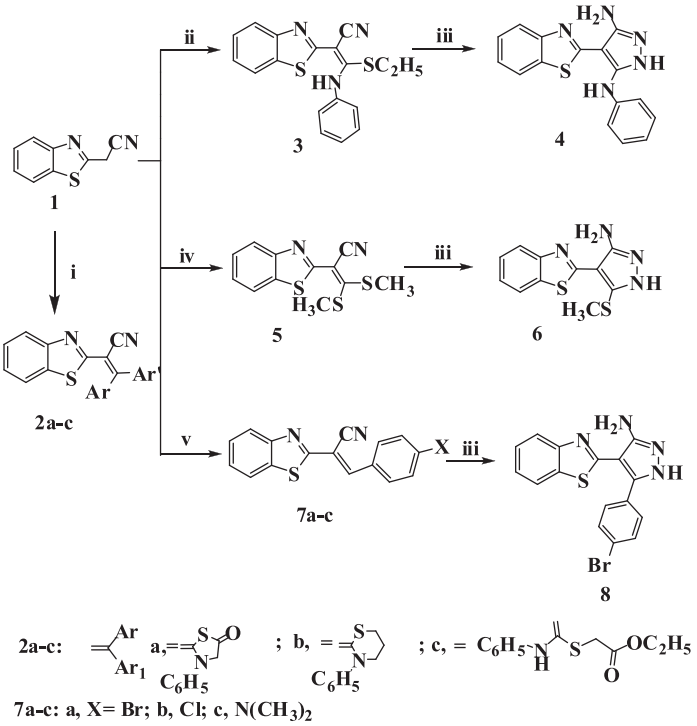
Therefore, it was aimed to synthesize novel compounds comprising a benzothiazole moiety attached at the 2-position to various substituted heterocyclic rings such as thiazole, thiazinane, pyrazole, thiophene, pyrrole, thienopyrimidine, indole, furan, pyridine, chromen, quinoline, triazoloquinoline, and triazepinoquinoline rings, in which benzothiazol-2-acetonitrile was an excellent synthone for these syntheses. The newly synthesized heterocyclic compounds possessed variable substituents, which were designed to fulfill the objectives of the target anticancer activity.

DISCUSSION

Chemistry. 2-(Benzo[*d*]thiazol-2-yl)acetonitrile **1** was synthesized adopting the reported method [17] (Scheme 1). However, the base-catalyzed reaction of active methylene bearing compounds with phenyl isothiocyanate was reported to yield their corresponding ketene *N*,*S*-acetals that were further subjected to cyclization *via* their reaction with alkylating agent. Therefore, compound **1** was reacted with phenyl isothiocyanate in the presence of finely powdered potassium hydroxide and dimethyl formamide that was followed by addition of chloroacetyl chloride, 1,3-dichloropropane, or ethyl bromoacetate to afford the thiazolidinone **2a**, thiazinane **2b**, or the open-chain ester derivative **2c**, respectively.

^{1}H NMR spectrum of compound **2a** revealed a singlet integrated for two protons at δ 4.17 ppm corresponding to thiazolidinone–CH_2 protons. While compound **2b** showed a multiplet and two triplets each integrated for two protons at δ 3.22–3.29 ppm and 3.59 and 3.97 ppm assigned for thiazinane–C_5, C_4, and C_6–H, respectively,

Scheme 1. Reagents and conditions: (i) phenyl isothiocyanate/KOH/DMF/0°C, chloroacetyl chloride or 1,3-dichloropropane or ethyl bromoacetate/0°C/RT; (ii) phenyl isothiocyanate/KOH/DMF/RT, ethyl iodide; (iii) hydrazine hydrate 99%/absolute ethanol/reflux; (iv) carbon disulfide/KOH/DMF/10°C, dimethyl sulfate; (v) 4-X-C_6H_4-CHO/absolute ethanol/TEA/reflux.



compound **2c** revealed a deuterium oxide exchangeable singlet signal at δ 10.12 ppm attributed to NH proton.

Aminopyrazoles have been widely reported to be synthesized *via* several methods [21–28]. Therefore, compound **1** was reacted with phenyl isothiocyanate/ethyl iodide, carbon disulfide/dimethyl sulfate, or differently 4-substituted benzaldehyde derivatives to afford the corresponding acrylonitrile derivatives **3**, **5**, and **7a–c**, respectively, which were further subjected to hydrazinolysis through their reaction with hydrazine hydrate 99% in ethanol to yield the target aminopyrazole derivatives **4**, **6**, and **8**, respectively. It is worth mentioning that compounds **7b** and **7c** upon hydrazinolysis failed to yield the target aminopyrazole derivatives.

^{1}H NMR spectra of compounds **4** and **6** revealed two deuterium oxide exchangeable singlet signals at δ 6.86–6.16 and 9.36–11.45 ppm attributed to NH_2 and pyrazole-NH protons, respectively.

It is to be noted that C-acylation [29] of compound **1** was achieved *via* reaction with benzoyl chloride in toluene containing a catalytic amount of triethyl amine to yield the target compound **9** (Scheme 2). Also, compound **1** upon heating under reflux with thiosemicarbazide in glacial acetic acid yielded unexpectedly the acyclic hydrazinyl acrylonitrile derivative **10**.

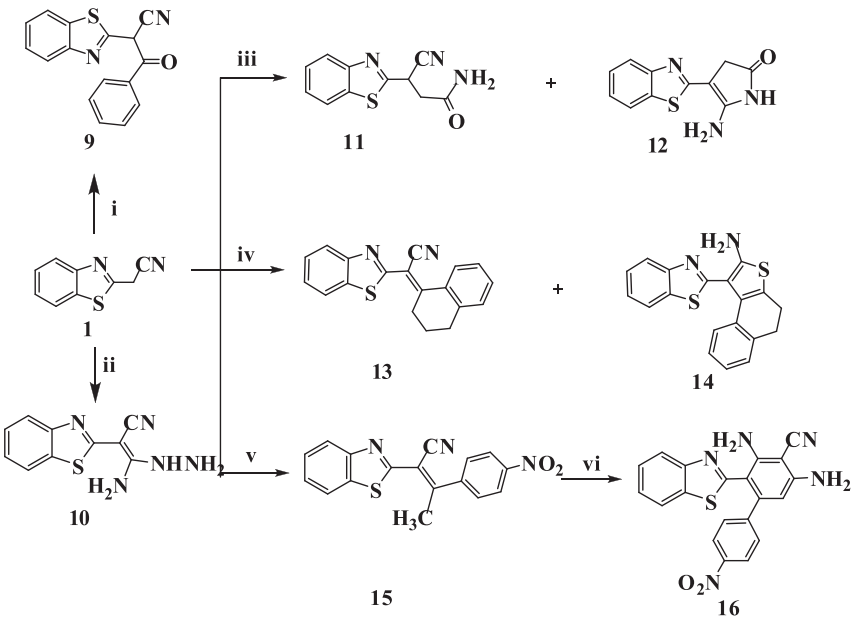
^{1}H NMR spectrum of compound **10** showed three dueterium oxide exchangeable singlet signals at δ 4.74, 7.18 and 9.66 ppm attributed to NH_2, NH–NH_2, and NH protons, respectively.

The reaction of acetonitrile derivatives with chloroacetamide analogues was reported to afford the corresponding aminopyrrolone derivatives [30]. However, 2-(benzo[*d*]thiazol-2-yl)acetonitrile derivative **1** upon reaction with chloroacetamide in ethanol containing a catalytic amount of potassium carbonate yielded both the alkylated β-cyanoamide derivative **11** and the cyclic aminopyrrolone derivative **12**.

^{1}H NMR spectrum of compounds **11** revealed one deuterium oxide exchangeable singlet signal in compound **11** at δ 7.26 ppm integrated for two protons corresponding to NH_2 protons, while the spectrum of compound **12** showed two deuterium oxide exchangeable singlet signals at δ 4.10 and 7.68 ppm assigned for NH_2 and NH protons, respectively.

It is well documented that Gewald multicomponent reaction of activated nitriles with ketones and elemental sulfur in the presence of a basic catalyst led to the synthesis of the corresponding aminothiophene derivatives [31–35] through the formation of non-isolated acrylonitrile intermediate [31,35].

Scheme 2. Reagents and conditions: (i) benzoyl chloride/toluene/TEA/reflux; (ii) thiosemicarbazide, glacial acetic acid/reflux; (iii) chloroacetamide/K_2CO_3/absolute ethanol/reflux; (iv) 1-tetralone/sulfur, absolute ethanol/TEA/reflux; (v) 4-nitroacetophenone/NH_4OAc/fusion at 160–170°C; (vi) malononitrile/absolute ethanol/TEA/reflux.



One pot reaction of 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1**, 1-tetralone, and elemental sulfur in ethanol containing a catalytic amount of triethyl amine was carried out to afford the acrylonitrile intermediate **13** and the cyclic aminothiophene derivative **14**. ^{1}H NMR spectra of compounds **13** and **14** revealed multiplet signals at δ 0.80–1.40 and 2.60–2.77 ppm due to dihydronaphthyl and dihydronapthothiophene protons, respectively, in addition to a triplet signal in compound **13** at δ 4.12 ppm corresponding to dihydronaphthyl–C_2–CH_2 protons. Besides, ^{1}H NMR spectrum of compound **14** showed a deuterium oxide exchangeable singlet signal at δ 7.50 ppm integrated for two protons corresponding to NH_2 protons.

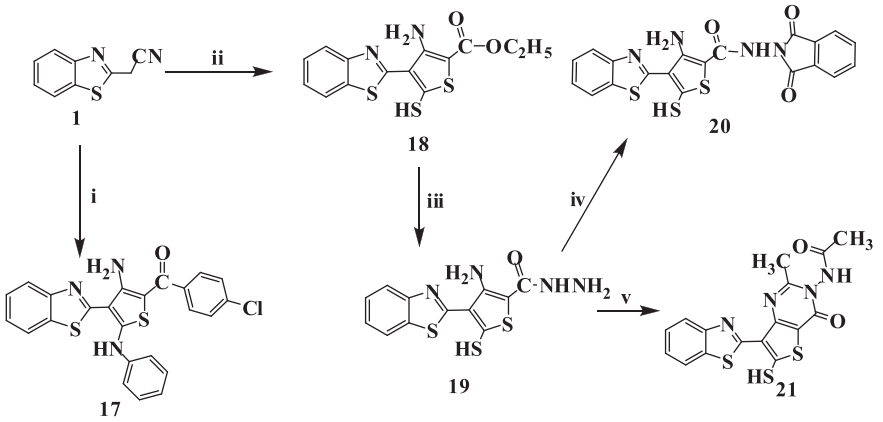
Treatment of activated nitriles with different ketones in basic medium was reported to afford alkylidene Knoevenagel condensation products [36,37] that were cyclized *via* their reaction with malononitrile [36].

Consequently, compound **1** was condensed with 4-nitroacetophenone by fusion in ammonium acetate at 160–170°C to yield the corresponding benzylidene derivative **15** that was cyclized with malononitrile *via* heating under reflux in ethanol in the presence of triethylamine as a base adopting the reported procedure. [36] The electron impact mass spectrum of compound **16** revealed the molecular ion peak at 387 (1.37), while the base peak appeared at 95 (100).

Base-catalyzed reactions of active methylene bearing compounds with phenyl isothiocyanate were reported to afford the corresponding potassium salt of thiocarbamoyl derivative that upon cyclization with phenacyl halide yielded their corresponding thiophene derivative [21,38] (Scheme 3). Compound **1** was stirred with phenyl isothiocyanate in dimethyl formamide containing potassium hydroxide at room temperature followed by treatment with 4-chlorophenacyl bromide to provide the corresponding thiophene derivative **17**. ^{1}H NMR spectrum of compound **17** showed two deuterium oxide exchangeable singlet signals at δ 8.54 and 10.42 ppm assigned for NH_2 and NH protons, respectively.

Furthermore, the reaction of active methylene moiety in cyanomethyl containing compounds with electrophilic reagents such as carbon disulfide yielded ketene-acetal intermediates, which were cyclized with haloesters to afford their corresponding thiophene derivatives [39]. So compound **1** was stirred with carbon disulfide in dimethyl formamide containing potassium hydroxide at 10°C followed by addition of ethyl chloroacetate to form the corresponding 2-aminoester derivative **18** that was subjected to hydrazinolysis *via* refluxing with hydrazine hydrate to yield the acid hydrazide analogue **19**. ^{1}H NMR spectrum of compound **18** showed a triplet signal at δ 1.13 ppm and a quartet signal at δ 4.04 ppm due to ester methyl and methylene protons, respectively, while ^{1}H NMR spectrum of compound **19** lacked the triplet and quartet signals characteristic to ester ethyl protons and revealed three dueterium oxide exchangeable singlet signals at δ 5.01, 5.79, and 11.86 ppm assigned for acid hydrazide NH_2, thiophene–C_3–NH_2, and NH protons, respectively.

Scheme 3. Reagents and conditions: (i) phenyl isothiocyanate/KOH/DMF/0°C/4-chlorophenacyl bromide; (ii) carbon disulfide/KOH/DMF/10°C, ethyl chloroacetate; (iii) hydrazine hydrate 99%/absolute ethanol/reflux; (iv) phthalic anhydride/gl. AcOH/reflux; (v) gl. AcOH/Ac_2O/reflux.



Condensation of acid hydrazide analogue **19** with either phthalic anhydride or glacial acetic acid/acetic anhydride mixture yielded the corresponding carboxamide derivatives **20** and acetamide derivative **21**, respectively. Electron impact mass spectra of compounds **20** and **21** revealed their molecular ion peaks at *m*/*z* (%) 452 (3.73) and 388 (7.71), while their base peaks appeared at *m*/*z* (%) 248 (100) and 91 (100), respectively.

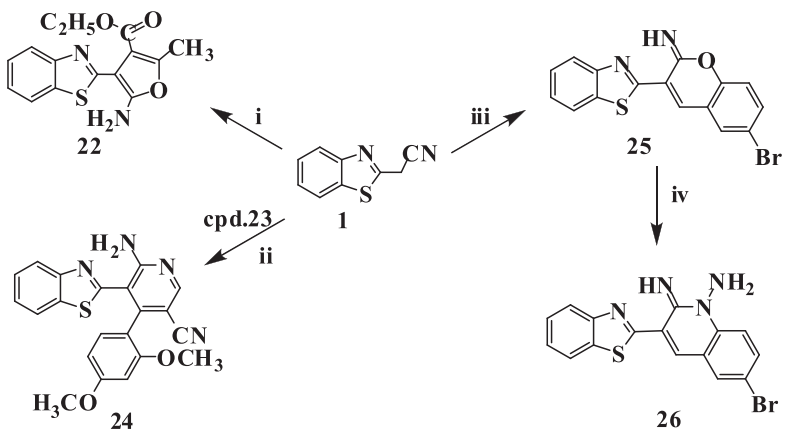
Compound **1** was stirred with ethyl 2-chloro-3-oxobutanoate in sodium ethoxide solution at room temperature to yield the corresponding furan-3-carboxylate derivative **22** (Scheme 4). This reaction is postulated to proceed *via* nucleophilic substitution reaction with removal of hydrogen chloride molecule followed by subsequent addition of tautomeric OH group on the cyano function.

^{1}H NMR spectrum of compound **22** revealed a triplet and a quartet signal at δ 1.35 and 4.34 ppm corresponding to ester methyl and methylene protons, respectively, in addition to a deuterium oxide exchangeable singlet signal at δ 7.83 ppm integrated for two protons assigned for NH_2 protons.

Elzahabi [40] documented that the reaction of 2-(benzo[*d*]thiazol-2-yl)acetonitrile with benzylidene malononitrile afforded the corresponding aminopyridine carbonitrile analogue. Therefore, compound **1** was heated under reflux with 2-(2,4-dimethoxybenzylidene) malononitrile **23** [41] in absolute ethanol containing a catalytic amount of piperidine to provide the aminopyridine carbonitrile derivative **24**. The reaction was suggested to proceed *via* Michael addition of the active methylene to the arylidene double bond followed by the nucleophilic addition of exocyclic NH on the cyano function to yield the target aminopyridine derivative.

^{1}H NMR spectrum of compound **24** revealed two singlet signals at δ 3.91 and 3.97 ppm corresponding to two methoxy protons, in addition to a deuterium oxide exchangeable singlet signal at δ 6.81 ppm due to NH_2 protons.

Scheme 4. Reagents and conditions: (i) ethyl 2-chloro-3-oxobutanoate/NaOEt/RT; (ii) 2-(2,4-dimethoxybenzylidene)malononitrile **23**/absolute ethanol/piperidine/reflux; (iii) 5-bromosalicylaldehyde/absolute ethanol/piperidine/reflux; (iv) hydrazine hydrate 99%/absolute ethanol/reflux.



Moreover, cyclocondensation of compound **1** with 5-bromosalicylaldehyde in absolute ethanol containing a catalytic amount of piperidine yielded the corresponding chromen-2-imine derivative **25**. The reaction was assumed to proceed through condensation of salicylaldehyde with activated nitrile with subsequent intramolecular cyclization through addition of phenolic hydroxyl function on the triple bond of cyano group. Such chromen-2-imine derivative was subjected to hydrazinolysis *via* heating under reflux with hydrazine hydrate in absolute ethanol to afford the corresponding iminoquinolinamine derivative **26**.

However, the 2-iminoquinoline-1-amine derivative **26** was further utilized for the synthesis of different triazine and triazepine derivatives (Scheme 5). In which compound **26** was reacted with ethyl 2-chloro-3-oxobutanoate to yield the target triazin-6-one derivative **27**. ^{1}H NMR spectrum of compound **27** revealed two singlet signals at δ 2.30 and 3.57 ppm assigned for CH_3 and triazine-C_3 protons, respectively, in addition to a deuterium oxide exchangeable singlet signal at δ 8.15 ppm attributed to NH proton.

It is to be noted that multicomponent reaction of compound **26** with compound **1** and 4-chorobenzaldehyde in dioxane afforded the corresponding aminotriazepine analogue **28**. The reaction was suggested to proceed *via* initial reaction of 4-chlorobenzaldehyde with compound **1** to yield the benzylidine derivative, which reacted with compound **26** *via* Michael addition of amino group to the benzylidene double bond followed by intramolecular cyclization through addition of imino NH on the cyano function. ^{1}H NMR spectrum of compound **28** revealed a deuterium oxide exchangeable singlet signal at δ 11.11 ppm integrated for two protons assigned for NH_2 protons.

Also, compound **26** was heated with 1-tetralone and 2,4-dichlorobenzaldehyde in dioxane containing a catalytic amount of p-toluene sulfonic acid to afford the corresponding triazepine derivative **29**. The reaction was suggested to proceed through the reaction of 1-tetralone with the aldehyde to yield the arylidine intermediate that was subjected to Michael addition of imino NH to the arylidene double bond with subsequent cyclocondensation.

^{1}H NMR spectrum of compound **29** revealed two triplet signals at δ 2.03 and 2.59 ppm attributed to tetrahydronaphthyl–C_4 and C_3–CH_2 protons, respectively. Besides, a singlet signal at δ 4.56 ppm integrated for one proton assigned for triazepine–C_5 proton.

Furthermore, the reaction of compound **26** with the reagents of either **23** and **30**[41] was carried out *via* heating under reflux in absolute ethanol containing a catalytic amount of piperidine to yield the target

Scheme 5. Reagents and conditions: (i) ethyl 2-chloro-3-oxobutanoate/fusion at 180–190°C; (ii) 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1**/4-chlorobenzaldehyde/dioxane/ reflux; (iii) 1-tetralone/2,4-dichlorobenzaldehyde/p-toluene sulfonic acid/dioxane/reflux; (iv) 2-(2,4-dimethoxybenzylidene)malononitrile **23** or ethyl 2-cyano-3-(2,4-dimethoxyphenyl)acrylate **30**/absolute ethanol/piperidine/reflux; (v) 2-(bis(methylthio)-methylene) malononitrile **32** or ethyl 2-cyano-3,3-bis(methylthio)acrylate **33**/DMF/TEA/reflux.

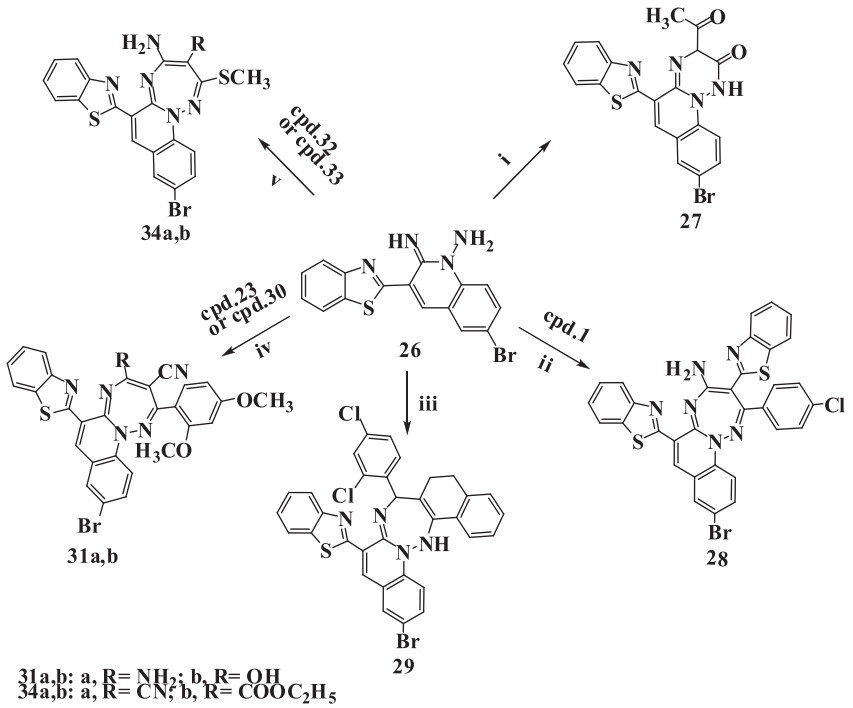


Table 1

The mean growth percent, delta values, the percent growth inhibition, and the lethality percent against some subpanel cell lines of the selected compounds of Scheme 1.

Comp. no. (NSC-number)	Mean growth percent	Panel: Subpanel cell lines (growth inhibition percent)	Subpanel cell lines (lethality percent)
2b (790032)	89.94 (31.26)	Leukemia: MOLT-4 (19.40), SR (16.52). Non-Small Cell Lung Cancer: HOP-92 (24.08), NCI-H226 (27.48), NCI-H23 (16.90), NCI-H522 (41.32). Colon Cancer: HCT-116 (19.25). CNS Cancer: SNB-75 (18.28). Melanoma: UACC-62 (39.54). Ovarian Cancer: IGROV1 (31.48), OVCAR-4 (23.11). Renal Cancer: UO-31 (37.94). Breast Cancer: MDA-MB-231/ATCC (22.45), T-47D (37.20).	
3 (790038)	83.86 (43.20)	Leukemia CCRF-CEM (20.16), K-562 (15.37), MOLT-4 (26.29), RPMI-8226 (34.62), Non-Small Cell Lung Cancer: A549/ATCC (15.04), HOP-62 (18.00), HOP-92 (57.51), NCI-H226 (20.56), NCI-H522 (24.98). Colon Cancer: HCT-116 (40.42), HCT-15 (17.00), HT29 (19.48), KM12 (20.09). CNS Cancer: SNB-19 (16.75), SNB-75 (23.70), U251 (15.56). Melanoma: UACC-62 (50.91). Ovarian Cancer: IGROV1 (29.88), OVCAR-4 (28.67), SK-OV-3 (22.35). Renal Cancer: ACHN (20.13), CAKI-1 (15.31), SN12C (18.34), UO-31 (37.45). Prostate Cancer: PC-3 (27.03). Breast Cancer: MCF7 (34.58), MDA-MB-231/ATCC (29.61), BT-549 (17.63), T-47D (59.34), MDA-MB-468 (31.89).	
4 (790039)	23.76 (102.88)	Leukemia CCRF-CEM (91.55), HL-60 (TB) (83.39), K-562 (95.17), MOLT-4 (95.94), RPMI-8226 (76.03), SR (86.39). Non-Small Cell Lung Cancer A549/ATCC (80.01), EKVX (80.98), HOP-62 (71.35), NCI-H226 (42.68), NCI-H23 (75.84), NCI-H322M (62.38), NCI-H460 (94.06). Colon Cancer Colo 205 (35.78), HCC-2998 (81.72), HCT-116 (96.27), HCT-15 (88.91), HT29 (41.52), KM12 (84.38), SW-620 (84.53). CNS Cancer SF-268 (68.96), SF-295 (71.37), SF-539 (44.88), SNB-19 (65.95), SNB-75 (55.84), U251 (77.97). Melanoma: MALME-3 M (16.62), M14 (93.59), MDA-MB-435 (77.20), SK-MEL-2 (73.22), SK-MEL-28 (64.59), SK-MEL-5 (42.35), UACC-257 (49.36), UACC-62 (72.77). Ovarian Cancer: IGROV1 (71.54), OVCAR-3 (74.66), OVCAR-4 (70.46), OVCAR-5 (65.52), OVCAR-8 (61.61), NCI/ADR-RES (69.96), SK-OV-3 (51.23). Renal Cancer 786–0 (89.83), A498 (53.24), ACHN (84.50), CAKI-1 (74.88), RXF 393 (63.74), SN12C (65.80), TK-10 (77.05), UO-31 (81.24). Prostate Cancer PC-3 (85.06), DU-145 (72.18). Breast Cancer MCF7 (87.57), HS 578 T (57.76), BT-549 (61.86), T-47D (97.10), MDA-MB-468 (82.47).	HOP-92 (15.78), NCI-H522 (44.56). LOX IMVI (79.12). MDA-MB-231/ ATCC (16.96).
5 (790035)	57.78 (70.63)	Leukemia: CCRF-CEM (75.29), HL-60 (TB) (55.41), K-562 (52.57), MOLT-4 (36.37), RPMI-8226 (74.96), SR (18.78). Non-Small Cell Lung Cancer: A549/ATCC (25.24), EKVX (25.75), HOP-62 (27.49), NCI-H226 (41.01), NCI-H23 (41.74), NCI-H322M (20.56), NCI-H460 (42.27), NCI-H522 (93.73). Colon Cancer: HCC-2998 (17.82), HCT-116 (85.75), HCT-15 (38.17), KM12 (41.73), SW-620 (18.47). CNS Cancer: SF-268 (44.93), SF-539 (39.83), SNB-19 (33.10), SNB-75 (25.72), U251 (23.48). Melanoma: LOX IMVI (15.85), MALME-3 M (32.05), M14 (51.92), MDA-MB-435 (23.52), SK-MEL-2 (59.99), SK-MEL-28 (61.21), SK-MEL-5 (72.14), UACC-257 (46.00), UACC-62 (90.56).	HOP-92 (12.85).

(*Continues*)

Table 1

(*Continued*)

Comp. no. (NSC-number)	Mean growth percent	Panel: Subpanel cell lines (growth inhibition percent)	Subpanel cell lines (lethality percent)
		Ovarian Cancer: IGROV1 (50.70), OVCAR-3 (29.99), OVCAR-4 (31.88), OVCAR-5 (27.51), OVCAR-8 (29.84), NCI/ADR-RES (23.34), SK-OV-3 (80.37). Renal Cancer: 786–0 (38.16), A498 (50.08), ACHN (37.55), CAKI-1 (44.20), SN12C (65.05), UO-31 (48.21). Prostate Cancer: PC-3 (69.96). Breast Cancer: MCF7 (52.70), MDA-MB-231/ATCC (47.07), HS 578 T (22.94), BT-549 (86.91), T-47D (66.82), MDA-MB-468 (56.23).	
8 (790023)	99.42 (20.81)	Non-Small Cell Lung Cancer: NCI-H322M (15.38). Melanoma: MALME-3 M (21.39). Ovarian Cancer: IGROV1 (21.24). Renal Cancer: UO-31 (17.70). Breast Cancer: MDA-MB-231/ATCC (15.23).	

Table 2

The mean growth percent, delta values, the percent growth inhibition, and the lethality percent against some subpanel cell lines of the selected compounds of Schemes 2 and 3.

Comp. no. (NSC-number)	Mean growth percent (Delta)	Panel: Subpanel cell lines (growth inhibition percent)	Subpanel cell lines (lethality percent)
12 (790028)	85.16 (37.09)	LEUKEMIA: CCRF-CEM (16.58), MOLT-4 (20.27). NON-SMALL CELL LUNG CANCER: A549/ATCC (21.15), HOP-92 (20.68), NCI-H226 (18.70), NCI-H23 (15.96), NCI-H322M (16.63), NCI-H460 (20.93), NCI-H522 (35.24). COLON CANCER: HCT-116 (15.92), HT29 (17.05), KM12 (18.92), SW-620 (16.66). CNS CANCER: SF-268 (18.35), SNB-19 (22.52), SNB-75 (21.67), U251 (16.35). MELANOMA: SK-MEL-2 (25.67), SK-MEL-28 (15.41), UACC-62 (30.91). Ovarian Cancer: IGROV1 (32.97). RENAL CANCER: A498 (27.15), ACHN (15.03), UO-31 (29.92). Prostate Cancer: PC-3 (23.97). BREAST CANCER: MCF7 (51.93), MDA-MB-231/ATCC (16.22), T-47D (38.14), MDA-MB-468 (31.75).	
17 (790031)	29.23 (53.64)	Leukemia: CCRF-CEM (39.74), HL-60 (TB) (30.41), K-562 (44.79), MOLT-4 (23.53), RPMI-8226 (71.68), SR (66.85). Non-Small Cell Lung Cancer: A549/ATCC (82.20), EKVX (40.09), NCI-H226 (50.11), NCI-H23 (82.96), NCI-H322M (69.47), NCI-H522 (92.62). Colon Cancer: COLO 205 (48.64), HCC-2998 (32.48), HCT-116 (86.05), HCT-15 (60.25), HT29 (82.07), KM12 (83.91), SW-620 (60.70). CNS Cancer: SF-268 (54.53), SF-539 (56.77), SNB-19 (37.93), SNB-75 (81.88), U251 (95.06). Melanoma: LOX IMVI (82.17), MALME-3 M (79.34), M14 (69.40), MDA-MB-435 (83.26), SK-MEL-2 (61.47), SK-MEL-28 (57.40), SK-MEL-5 (44.90), UACC-257 (41.20), UACC-62 (92.12). Ovarian Cancer: IGROV1 (70.92), OVCAR-3 (95.90), OVCAR-5 (53.64), OVCAR-8 (77.00), NCI/ADR-RES (81.21). Renal Cancer: 786–0 (91.90), A498 (53.85), ACHN (73.76), CAKI-1 (74.80), RXF 393 (27.24), SN12C (17.44), UO-31 (80.66). Prostate Cancer: PC-3 (89.72), DU-145 (74.54).	HOP-62 (7.72), HOP-92 (18.74), NCI-H460 (0.30). SF-295 (24.41). OVCAR-4 (9.61), SK-OV-3 (0.59). TK-10 (13.30).

(*Continues*)

Table 2

(*Continued*)

Comp. no. (NSC-number)	Mean growth percent (Delta)	Panel: Subpanel cell lines (growth inhibition percent)	Subpanel cell lines (lethality percent)
		Breast Cancer: MCF7 (56.06), MDA-MB-231/ATCC (81.18), HS 578 T (67.57), BT-549 (44.80), T-47D (88.22), MDA-MB-468 (85.30).	
20 (790059)	95.06 (26.28)	Non-Small Cell Lung Cancer: NCI-H226 (19.48), NCI-H522 (28.63).	
		Melanoma: UACC-62 (23.84).	
		Ovarian Cancer: IGROV1 (25.68), SK-OV-3 (23.08).	
		Renal Cancer: UO-31 (26.80).	
		Prostate Cancer: PC-3 (17.60).	
		Breast Cancer: MCF7 (19.39), MDA-MB-231/ATCC (16.26), T-47D (31.22).	

Table 3

: The mean growth percent, delta values, and the percent growth inhibition against some subpanel cell lines of the selected compounds of Schemes 4 and 5.

Comp. no. (NSC-number)	Mean growth percent (Delta)	Panel: Subpanel cell lines (growth inhibition percent)
24 (790020)	97.94 (24.19)	Leukemia: HL-60(TB) (26.25).
		Renal Cancer: A498 (21.91).
		Breast Cancer: MDA-MB-231/ATCC (21.02).
29 (790050)	62.06 (50.81)	Leukemia: CCRF-CEM (70.09), HL-60 (TB) (44.28), K-562 (83.78), MOLT-4 (76.97), RPMI-8226 (62.21), SR (69.02).
		Non-Small Cell Lung Cancer: A549/ATCC (27.46), EKVX (33.08), HOP-62 (32.44), HOP-92 (56.79), NCI-H226 (31.02), NCI-H23 (40.18), NCI-H460 (22.49), NCI-H522 (57.47).
		Colon Cancer: COLO 205 (18.88), HCC-2998 (37.26), HCT-116 (55.16), HCT-15 (40.11), HT29 (30.54), KM12 (48.75), SW-620 (58.91).
		CNS Cancer: SF-268 (29.97), SF-295 (19.12), SNB-19 (32.90), SNB-75 (27.90), U251 (28.76).
		Melanoma: LOX IMVI (40.81), MALME-3 M (28.73), M14 (33.39), MDA-MB-435 (88.75), SK-MEL-2 (27.93), SK-MEL-28 (22.74), SK-MEL-5 (30.83), UACC-257 (26.99), UACC-62 (57.54).
		Ovarian Cancer: IGROV1 (55.96), OVCAR-3 (35.83), OVCAR-4 (40.90), OVCAR-5 (20.43), OVCAR-8 (26.58), NCI/ADR-RES (29.26), SK-OV-3 (36.27).
		Renal Cancer: A498 (27.04), ACHN (19.71), CAKI-1 (20.70), RXF 393 (16.89), SN12C (36.98), UO-31 (60.30).
		Prostate Cancer: PC-3 (48.25).
		Breast Cancer: MCF7 (76.56), MDA-MB-231/ATCC (42.32), HS 578 T (23.05), T-47D (74.92), MDA-MB-468 (72.01).
31a (790036)	88.68 (40.33)	Leukemia: CCRF-CEM (27.03), RPMI-8226 (17.00).
		Non-Small Cell Lung Cancer: A549/ATCC (17.66), HOP-62 (15.93), HOP-92 (26.64), NCI-H226 (16.10), NCI-H522 (31.06).
		Melanoma: LOX IMVI (15.57), SK-MEL-2 (15.32), SK-MEL-28 (22.91), UACC-257 (16.32), UACC-62 (36.32).
		Ovarian Cancer: OVCAR-5 (15.17), SK-OV-3 (28.25).
		Renal Cancer: A498 (25.70), ACHN (17.98), UO-31 (34.97).
		Prostate Cancer: PC-3 (31.05).
		Breast Cancer: MCF7 (37.76), MDA-MB-231/ATCC (29.21), BT-549 (17.75), T-47D (51.65).
34a (790029)	89.45 (33.62)	Leukemia: CCRF-CEM (23.57), MOLT-4 (17.11), SR (15.56).
		Non-Small Cell Lung Cancer: HOP-62 (22.06), HOP-92 (26.33), NCI-H226 (24.07).
		CNS Cancer: SNB-75 (18.24).
		Melanoma: LOX IMVI (16.02), UACC-62 (21.78).
		Ovarian Cancer: IGROV1 (35.38), OVCAR-5 (18.30), SK-OV-3 (16.77).
		Renal Cancer: ACHN (15.00), UO-31 (44.17).
		Prostate Cancer: PC-3 (31.83).

(*Continues*)

Table 3

(*Continued*)

Comp. no. (NSC-number)	Mean growth percent (Delta)	Panel: Subpanel cell lines (growth inhibition percent)
34b (790030)	92.45 (30.77)	Breast Cancer: MCF7 (27.54), MDA-MB-231/ATCC (27.87), BT-549 (17.10), T-47D (41.02). Leukemia: MOLT-4 (15.86), SR (24.63). Non-Small Cell Lung Cancer: HOP-62 (17.14), HOP-92 (19.41), NCI-H226 (18.22), NCI-H522 (15.34). CNS Cancer: SNB-75 (22.53). Melanoma: UACC-62 (23.34). Ovarian Cancer: IGROV1 (32.35). Renal Cancer: UO-31 (38.32). Prostate Cancer: PC-3 (23.87). Breast Cancer: MCF7 (35.65), MDA-MB-231/ATCC (21.71), T-47D (36.33).

triazepine carbonitrile derivative **31a**,**b**, respectively. ^{1}H NMR spectra of compound **31a**,**b** revealed two singlet signals at δ 2.73–3.90 ppm attributed to two methoxy protons.

Finally, 2-iminoquinoline-1-amine derivative **26** was heated under reflux with either 2-[bis(methylthio) methylene]malononitrile **32**[42] or ethyl 2-cyano-3,3-bis(methylthio)acrylate **33**[42] in dimethyl formamide containing a catalytic amount of triethylamine to give the corresponding 4-amino-2-methylsulfanyl-3-carbonitrile derivative **34a** or 4-amino-2-methylsulfanyl-3-carboxylate analogue **34b**, respectively. ^{1}H NMR spectra of compound **34a**,**b** revealed singlet signals at δ 2.89 ppm assigned for S–CH_3 protons, while ^{1}H NMR spectrum of compound 3**4b** showed a triplet and a multiplet signal at δ 1.06 and δ 3.38–3.50 ppm attributed to ester methyl and methylene protons, respectively.

Anticancer screening. Thirteen of the newly synthesized compounds, **2b**, **3**, **4**, **5**, **8**, **12**, **17**, **20**, **24**, **29**, **31a**, **34a**, and **34b**, were selected by Developmental Therapeutic Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI), Bethesda, Maryland, USA, to be evaluated *in vitro* in a single high dose (10 μmol) against 60 human tumor cell lines for their primary anticancer activity [45]. Among which two compounds **4** and **17** showed strong anticancer activity against various cell lines as they fulfilled the criteria required to be further evaluated by the NCI in the five-dose full panel assay. The one-dose screening results of the selected compounds are represented as the mean growth inhibition percent, delta values, and percent growth inhibition against some subpanel cell lines in (Tables 1, 2, and 3), while the results of the five-dose full panel assay of compounds **4** and **17** are presented in Tables 4 and 5), respectively.

However, Figures 1 and 2 represent the dose–response curves of compounds **4** and **17** against various cancer cell

Table 4

GI_{50}, TGI, and LC_{50} of five-dose screening of compound **4**.

Panel/cell line	GI_{50}	TGI	LC_{50}
Leukemia			
CCRF-CEM	0.911	9.61	>100
HL-60(TB)	2.61	7.00	42.7
K-562	1.88	7.81	>100
MOLT-4	0.683	7.81	84.3
RPMI-8226	2.24	6.65	67.5
SR	1.84	8.02	>100
Non-small cell lung cancer			
A549/ATCC	2.69	11.9	50.0
EKVX	1.26	4.28	22.0
HOP-62	2.08	5.87	28.1
HOP-92	1.40	3.77	10.6
NCI-H226	3.71	17.00	72.7
NCI-H23	1.73	5.04	23.2
NCI-H322M	2.20	11.7	39.6
NCI-H460	1.94	4.17	8.97
NCI-H522	1.58	3.63	8.31
Colon cancer			
Colo 205	1.89	3.92	8.15
HCC-2998	1.88	4.21	9.41
HCT-116	1.29	2.71	5.70
HCT-15	1.18	3.04	7.86
HT29	3.39	11.5	37.9
KM12	1.61	3.60	8.07
SW-620	2.58	7.29	28.3
CNS cancer			
SF-268	2.36	8.83	43.6
SF-295	1.56	3.27	6.84
SF-539	1.68	3.34	6.64
SNB-19	2.08	4.56	10.1
SNB-75	2.39	10.9	43.6
U251	2.26	5.50	20.7
Melanoma			
LOX IMVI	1.59	2.97	5.53
MALME-3M	2.79	8.58	42.8
M14	1.55	3.58	8.29
MDA-MB-435	1.94	4.89	15.9
SK-MEL-2	2.77	8.90	34.1
SK-MEL-28	2.06	4.29	8.93
SK-MEL-5	4.66	15.8	41.4

(*Continues*)

Table 4

(*Continued*)

Panel/cell line	GI_{50}	TGI	LC_{50}
UACC-62	1.40	2.96	6.27
Ovarian cancer			
IGROV1	2.58	8.88	42.3
OVCAR-3	1.70	3.76	8.34
OVCAR-4	2.19	11.8	55.0
OVCAR-5	2.26	8.77	46.6
OVCAR-8	2.36	5.98	31.3
NCI/ADR-RES	2.11	6.64	31.5
SK-OV-3	4.63	15.7	39.6
Renal cancer			
786-0	1.34	3.08	7.11
A498	1.69	4.01	9.51
ACHN	2.08	6.27	23.2
SN12C	1.58	3.25	6.65
TK10	3.02	9.10	32.1
UO-31	1.33	7.16	34.9
Prostate cancer			
PC-3	1.58	3.39	7.27
DU-145	3.02	11.6	39.5
Breast cancer			
MCF7	2.26	8.68	45.8
MDA-MB-231/ATCC	1.59	3.75	8.83
HS 578T	2.53	9.86	60.9
BT-549	1.52	3.34	7.34
T-47D	2.20	11.2	55.0
MDA-MB-468	2.23	5.98	47.6

Table 5

GI_{50}, TGI, and LC_{50} of five-dose screening of compound **17**.

Panel/cell line	GI_{50}	TGI	LC_{50}
Leukemia			
CCRF-CEM	6.69	>100	>100
HL-60(TB)	>100	>100	>100
K-562	2.13	>100	>100
MOLT-4	8.41	80.3	>100
RPMI-8226	1.64	>100	>100
SR	0.523	>100	>100
Non-small cell lung cancer			
A549/ATCC	—	—	>100
EKVX	1.61	>100	>100
HOP-62	0.875	—	>100
HOP-92	1.19	4.72	43.0
NCI-H226	2.29	—	>100
NCI-H23	1.67	—	>100
NCI-H322M	—	>100	>100
NCI-H460	0.402	—	>100
NCI-H522	3.22	>100	>100
Colon cancer			
Colo 205	—	>100	>100
HCC-2998	>100	>100	>100
HCT-116	0.724	—	>100
HCT-15	2.40	>100	>100
HT29	—	>100	>100
KM12	0.615	—	>100
SW-620	0.55	>100	>100
CNS cancer			
SF-268	0.928	>100	>100
SF-295	1.32	3.19	—
SF-539	1.68	—	>100
SNB-19	3.49	>100	>100
SNB-75	1.87	6.92	>100
U251	1.88	—	—
Melanoma			
LOX IMVI	2.22	—	>100
MALME-3M	0.782	—	>100
M14	1.77	>100	>100
MDA-MB-435	—	—	>100
SK-MEL-2	2.48	6.92	>100
SK-MEL-28	—	—	>100
SK-MEL-5	1.66	—	>100
UACC-62	1.29	3.47	—
Ovarian cancer			
IGROV1	1.72	>100	>100
OVCAR-3	1.02	—	—
OVCAR-4	0.217	—	—
OVCAR-5	—	>100	>100
OVCAR-8	1.92	>100	>100
NCI/ADR-RES	4.25	>100	>100
SK-OV-3	2.14	10.8	>100
Renal cancer			
786–0	1.41	3.34	—
A498	1.81	5.17	>100
ACHN	1.41	—	>100
SN 12C	4.08	>100	>100
TK-10	1.91	4.58	>100
UO-31	1.66	—	>100
Prostate cancer			
PC-3	0.759	—	>100
DU-145	—	>100	>100
Breast cancer			
MCF7	1.94	>100	>100
MDA-MB-231/ATCC	1.35	—	>100
HS 578 T	0.561	7.87	>100
BT-549	2.29	19.5	>100
T-47D	1.40	>100	>100
MDA-MB-468	1.37	3.30	—

(*Continues*)

lines, while Table 6 shows the MG-MID and the selectivity ratio of compound **4** toward different cancer cell lines.

As revealed from one-dose screening results presented in Tables 1–3 and in a trial to shed more light on the SAR of compounds bearing benzothiazole, it is evident that the presence of arylidene nitrile at 2-position of benzothiazole as in compounds **2b** and **3** bearing thiazinane and aminophenyl exhibited weak to moderate growth inhibitory activity against several cancer cell lines. However, replacement of arylidene moiety by two *S*-methyl functions as in compound **5** resulted in marked increase in growth inhibitory activity against many cell lines.

It is to be noted that the conversion of arylidene moiety into amino pyrazole nucleus as in compound **4** containing phenylamino side chain resulted in powerful anticancer activity against all cell lines. However, replacement of

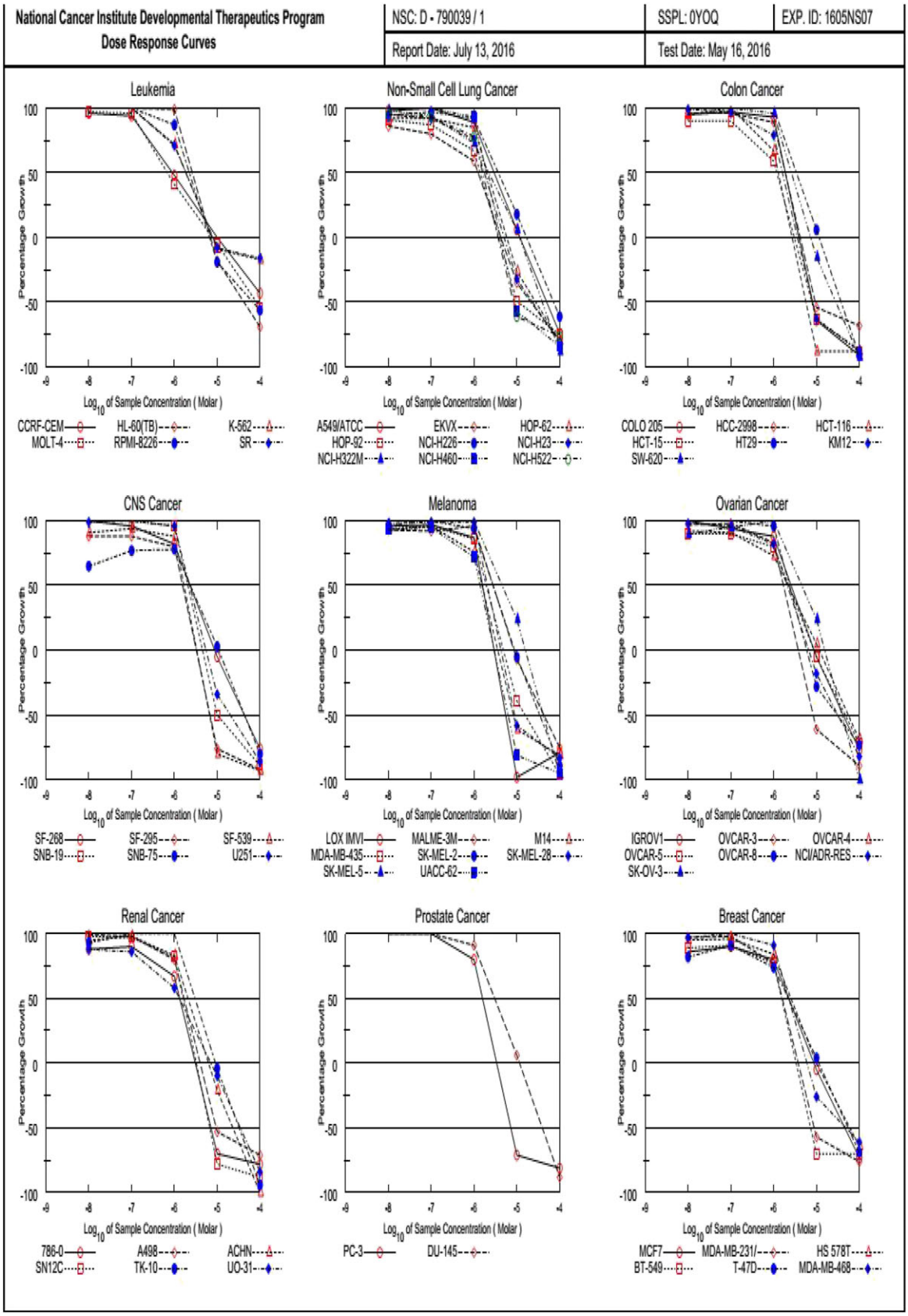


Figure 1. Dose–response curves of compound **4** against variable cancer cell lines. [Color figure can be viewed at wileyonlinelibrary.com]

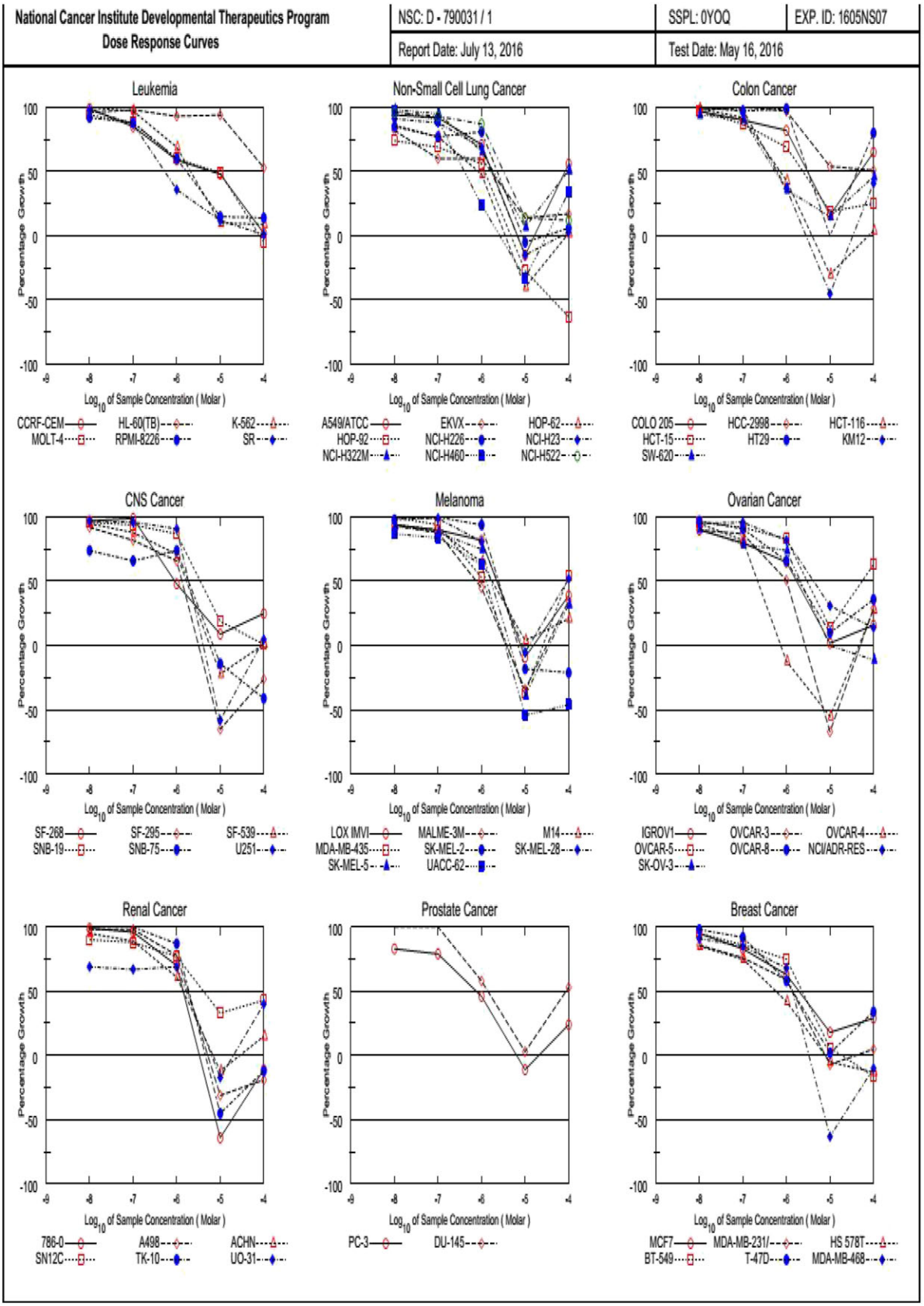


Figure 2. Dose–response curves of compound **17** against variable cell lines. [Color figure can be viewed at wileyonlinelibrary.com]

Table 6

The MG-MID (GI_{50}) μM/L and the selectivity ratio of compound **4**.

Full Panel GI_{50} MG-MID (μM/L)	Subpanel tumor cell lines GI_{50} MG-MID (μM/L) (SI)								
	I	II	III	IV	V	VI	VII	VIII	IX
2.10	1.694 (1.24)	2.095 (1.00)	1.974 (1.06)	2.055 (1.02)	2.345 (0.89)	2.547 (0.82)	1.84 (1.14)	2.3 (0.91)	2.055 (1.02)

I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer. SI, selectivity index.

phenylamino side chain of aminopyrazole ring in compound **4** with 4-bromophenyl moiety in compound **8** diminished the anticancer activity.

In a trial to investigate the effect of linkage of different heterocyclic rings to the benzothiazole backbone, it was found that attachment of aminopyrrolone ring to the benzothiazole nucleus as in compound **12** exhibited weak to moderate anticancer activity against most of the cell lines. However, it showed promising growth inhibition activity against breast cancer MDA-MB-468 cell line.

Also, attachment of 3-amino-5-(phenylamino)thiophen-2-yl-(4-chlorophenyl)methanone to the benzothiazole backbone as in compound **17** resulted in strong growth inhibitory activity and lethal effect toward all of the cancer cell lines.

Furthermore, replacement of 4-chlorophenylmethanone and 5-phenylamino moieties in compound **17** by dioxoisoindolin amide moiety and mercapto function, respectively, as in compound **20** diminished the anticancer activity. Also, attachment of 2-aminopyridine ring to the benzothiazole nucleus as in compound **24** resulted in weak anticancer activity.

Moreover, attachment of triazepinoquinoline to the benzothiazole backbone as in compounds **29**, **31a**, **34a**, and **34b** resulted in variable activities in which only compound **29** bearing 2,4-dichlorophenyl moiety at C5 and fused dihydronaphthyl nucleus at C6 and C7 showed moderate to strong anticancer activity against various cancer cell lines.

The five-dose screen results of compounds **4** and **17** presented in Tables 4 and 5 revealed that compound **4** exhibited powerful growth inhibitory activity against all cell lines exerting GI_{50} ranging from 0.683 to 4.66 μM/L and TGI ranging from 2.97 to 17 μM/L, and it exerted lethal effect against many cell lines. However, it was non-selective showing selectivity index less than 3 as presented in Table 6.

It is to be noted that the five-dose screening results of compound **17** revealed potent growth inhibitory activity with GI_{50} less than 1 μM/L against many cell lines including leukemia SR, non-small cell lung cancer HOP-62 and NCI-H460, colon cancer HCT-116, KM12 and SW-620, CNS cancer SF-268, melanoma MALME-3M, ovarian cancer OVCAR-4, prostate cancer PC-3, and breast cancer HS578T.

CONCLUSION

It can be concluded that attachment of different heterocyclic moieties to the biologically active benzothiazole backbone resulted in variable anticancer activities upon screening in the single-dose 60 cell line panel assay performed by the NCI, Bethesda, Maryland, USA. Among which compounds **4** and **17**, bearing 3-amino-5-phenylaminopyrazole and 3-amino-5-phenylami nothiophen-2-yl-(4-chlorophenyl)methanone, respectively, attached to the 2-position of benzothiazole exhibited powerful anticancer activity in the five-dose full panel screening assay exerting highly potent growth inhibitory activity against all cell lines as well as strong lethal activity against many cell lines.

MATERIALS AND METHODS

All melting points were measured on Electro thermal LA 9000 SERIS, Digital Melting point Apparatus, and are uncorrected. IR spectra were recorded, for potassium bromide discs, on a Perkin-Elmer 1430 Infrared spectrophotometer at IR analytical unit, Faculty of Pharmacy, Cairo University. ^{1}H NMR and ^{13} C NMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard at Microanalytical Research Center, Chemical Warfare Department, Ministry of Defense. Mass spectra were carried out using a Schimadzu GCMS-QP-1000EX mass spectrometer at 70 *ev* at Regional Center for Mycology and Biotechnology, Al-Azhar University. Elemental analyses were performed on Elementar Vario EI III CHN analyzer at the microanalytical unit, Regional center for Mycology and Biotechnology, Al-Azhar University. Reactions were monitored by thin-layer chromatography on silica gel (60 GF 254, Merck), using glass plates. The spots were visualized by exposure to UV-lamp at λ 254 nm for few seconds.

General procedure for the synthesis of compounds (2a–c). To a well-stirred and ice-cooled suspension of compound **1** [17] (0.35 g, 2 mmol) and finely powdered potassium hydroxide (0.22 g, 4 mmol) in dry dimethyl formamide (6 mL), phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol) was added portion wise. After complete addition, stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0°C, treated with equimolar amounts of chloroacetyl chloride (0.22 g, 0.16 mL, 2 mmol), 1,3-dichloropropane (0.23 g, 0.19 mL, 2 mmol), or ethyl bromoacetate (0.33 g, 0.22 mL, 2 mmol), and stirring was continued for additional 6 h at room temperature then poured onto ice-cold water. The obtained precipitate was filtered, washed with water, and dried and crystallized from the appropriate solvent to afford compounds **2a**, **2b**, and **2c**, respectively.

2-(Benzo[d]thiazol-2-yl)-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetonitrile (2a). Bright light brown crystals; crystallized from toluene; yield 0.4 g (57%); mp 214–216°C. IR (KBr, ν cm^{-1}): 3083 (CH–Ar); 2914 (CH–aliph.); 2187 (C≡N); 1720 (C=O); 1589 (C=N); 1520 (C=C); 1245, 1004 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 4.17 (s, 2H, thiazolidinone–CH_2); 7.17–7.22 (m, 1H, C_6H_5–C_4–H); 7.25–7.43 (m, 2H, C_6H_4–$C_{2,6}$–H); 7.51–7.54 (m, 2H, C_6H_4–$C_{3,5}$–H); 7.67 (d, 1H, *J* = 8.1 Hz, benzothiazole–C_4–H); 7.84–7.91 (m, 1H, benzothiazole–C_6–H); 7.92–7.95 (m, 1H, benzothiazole–C_5–H); 8.06 (d, 1H, *J* = 8.1 Hz, benzothiazole–C_7–H). ^{13}C NMR (DMSO-d_6, δ ppm): 79.29 (thiazolidinone–C_4); 114.84 (C–CN); 122.08 (C≡N); 122.58 (C_6H_5–$C_{2,6}$); 125.38 (C_6H_5–C_4); 125.85 (benzothiazole–C_4); 127.23 (benzothiazole–C_6); 128.66 (benzothiazole–C_7); 129.96 (benzothiazole–C_5); 130.13 (C_6H_5–C_3); 131.15 (C_6H_5-C_5); 133.27 (benzothiazole–C_{1a}); 135.30 (C_6H_5–C_1); 153.44 (thiazolidinone–C_2); 164.37 (benzothiazole–C_{3a}); 165.01 (benzothiazole–C_2); 173.65 (C=O). *Anal*. Calcd (%) for $C_{18}H_{11}N_3OS_2$: C, 61.87; H, 3.17; N, 12.03. Found: C, 62.03; H, 3.20; N, 12.17.

2-(Benzo[d]thiazol-2-yl)-2-(3-phenyl-1,3-thiazinan-2-ylidene)acetonitrile (2b). Light orange powder; crystallized from ethanol; yield 0.38 g (54%); mp 208–210°C. IR (KBr, ν cm^{-1}): 3091, 3055 (CH–Ar); 2899, 2866 (CH–aliph.); 2187 (C≡N); 1591 (C=N); 1537 (C=C); 1282, 1070 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 3.22–3.29 (m, 2H, thiazinane–C_5–CH_2); 3.59 (t, 2H, *J* = 6.8 Hz, thiazinane–C_4–CH_2); 3.97 (t, 2H, *J* = 6.8 Hz, thiazinane–C_6–CH_2); 7.18 (t, 1H, *J* = 7.5 Hz, C_6H_5–C_4–H); 7.33–7.39 (m, 2H, C_6H_5–$C_{2,6}$–H); 7.42–7.49 (m, 2H, C_6H_4–$C_{3,5}$–H); 7.67 (d, 1H, *J* = 7.7 Hz, benzothiazole–C_4–H); 7.82–7.96 (m, 2H, benzothiazole–$C_{5,6}$–H); 8.06 (d, 1H, *J* = 7.7 Hz, benzothiazole–C_7–H). ^{13}C NMR (DMSO-d_6, δ ppm): 31.32 (thiazinane–C_5); 32.08 (thiazinane–C_6); 43.74 (thiazinane–C_4); 78.12 (C–CN); 114.06 (C≡N); 122.51 (C_6H_5–C_2); 122.64 (C_6H_5–C_6); 124.59 (C_6H_5–C_4); 125.85 (benzothiazole–C_4); 126.35 (benzothiazole–C_6); 127.11 (benzothiazole–C_7); 127.68 (benzothiazole–C_5); 128.67 (C_6H_5–$C_{3,5}$); 129.74 (benzothiazole–C_{1a}); 138.84 (C_6H_5–C_1); 140.60 (benzothiazole–C_{3a}); 169.06 (benzothiazole–C_2); 187.13 (thiazinane–C_2). *Anal*. Calcd (%) for $C_{19}H_{15}N_3S_2$: C, 65.30; H, 4.33; N, 12.02. Found: C, 65.49; H, 4.41; N, 12.21.

Ethyl 2-(2-(benzo[d]thiazol-2-yl)-2-cyano-1-(phenylamino) vinyl thio)acetate (2c). Dark gray powder; crystallized from ethanol; yield 0.55 g (69%); mp 142–144°C. IR (KBr, ν cm^{-1}): 3313 (NH); 3055, 3028 (CH–Ar); 2900, 2866 (CH–aliph.); 2198 (C≡N); 1725 (ester C=O); 1597 (C=N); 1573 (C=C); 1288, 1068 (C–S–C); 1230, 1053 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.23 (t, 3H, *J* = 7.2 Hz, CH_2CH_3); 2.87 (s, 2H, S-CH_2); 4.18 (q, 2H, *J* = 7.2 Hz, CH_2CH_3); 7.07 (t, 1H, *J* = 7.6 Hz, C_6H_5–C_4–H); 7.21–7.32 (m, 2H, C_6H_5–$C_{2,6}$–H); 7.33–7.40 (m, 2H, C_6H_5–$C_{3,5}$–H); 7.91 (d, 1H, *J* = 8.4 Hz, benzothiazole–C_4–H); 8.05–8.18 (m, 3H, benzothiazole–$C_{5,6,7}$–H); 10.12 (s, 1H, NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{20}H_{17}N_3O_2S_2$: C, 60.74; H, 4.33; N, 10.62. Found: C, 60.98; H, 4.39; N, 10.91.

2-(Benzo[d]thiazol-2-yl)-3-(ethylthio)-3-(phenylamino) acrylonitrile (3). To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethyl formamide (10 mL), compound **1** was added (0.35 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol) was added to the resulting mixture, and stirring was continued for further 6 h at room temperature, then ethyl iodide (0.31 g, 0.16 mL, 2 mmol) was added, and the reaction mixture was stirred overnight, diluted with cold water (5 mL), and the solid precipitate was collected, filtered, washed with water, dried and crystallized from hexane.

Lemon yellow powder; yield 0.5 g (74%); mp 134–135°C. IR (KBr, cm^{-1}): 3394 (NH); 3059 (CH-Ar); 2868, 2854 (CH–aliph.); 2194 (C≡N); 1593 (C=N); 1494 (C=C); 1278, 1085 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.15 (t, 3H, *J* = 7.5 Hz, CH_2CH_3); 2.65 (q, 2H, *J* = 7.5 Hz, CH_2CH_3); 7.32–7.44 (m, 5H, C_6H_5); 7.47–7.50 (m, 2H, benzothiazole–$C_{5,6}$–H); 7.92 (d, 1H, *J* = 8.1 Hz, benzothiazole–C_4–H); 8.07 (d, 1H, *J* = 8.1 Hz, benzothiazole–C_7–H); 12.37 (s, 1H, NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{18}H_{15}N_3S_2$: C, 64.06; H, 4.48; N, 12.45. Found: C, 64.24; H, 4.53; N, 12.69.

4-(Benzo[d]thiazol-2-yl)-N^5-phenyl-1H-pyrazole-3,5-diamine (4). A mixture of compound **3** (0.34 g, 1 mmol) and hydrazine hydrate 99% (0.1 g, 0.1 mL, 2 mmol) in absolute ethanol (10 mL) was heated under reflux for 6 h. The reaction mixture was allowed to cool, and the solid crystals were filtered, washed with ethanol, then dried and recrystallized from ethanol.

Creamy white crystals; yield 0.2 g (65%); mp 181–183°C. IR (KBr, ν cm^{-1}): 3360, 3186, 3136 (NH_2, NH); 3089, 3051 (CH–Ar); 1616, 1593 (C=N); 1550 (C=C); 1290, 1090 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.16 (s, 2H, NH_2, D_2O exchangeable); 6.76 (t, 1H, J = 7.5 Hz, C_6H_5–C_4–H); 7.17–7.29 (m, 4H, C_6H_5–$C_{2,3,5,6}$–H); 7.43 (t, 2H, J = 8.1 Hz, benzothiazole–$C_{5,6}$–H); 7.91 (d, 1H, J = 8.1 Hz, benzothiazole–C_4–H); 7.96 (d, 1H, J = 8.1 Hz, benzothiazole–C_7–H); 8.73 (s, 1H, NH–phenyl, D_2O exchangeable); 11.45 (s, 1H, pyrazole-NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm): 70.03 (pyrazole–C_4); 115.83 (C_6H_5–$C_{2,6}$); 119.17 (benzothiazole–C_4); 121.00 (benzothiazole–C_7); 121.93 (C_6H_5–C_4); 123.73 (benzothiazole–C_6); 126.43 (benzothiazole–C_5); 129.28 (C_6H_5–$C_{3,5}$); 132.24 (benzothiazole–C_{1a}); 144.24 (C_6H_5–C_1); 148.83 (pyrazole–C_3); 149.01 (benzothiazole–C_2); 152.54 (pyrazole–C_5); 161.74 (benzothiazole–C_{3a}). *Anal*. Calcd (%) for $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78. Found: C, 62.67; H, 4.34; N, 22.95.

2-(Benzo[d]thiazol-2-yl)-3,3-bis(methylthio)acrylonitrile (5). To a stirred suspension of finely powdered potassium hydroxide (0.22 g, 4 mmol) in dry DMF (10 mL), compound **1** (0.35 g, 2 mmol) was added, and the reaction mixture was stirred at 10°C in an ice bath, then carbon disulfide (0.15 g, 0.12 mL, 2 mmol) was added slowly, and stirring was continued for 6 h. Then, dimethylsulfate (0.25 g, 0.19 mL, 2 mmol) was added to the reaction mixture, and stirring was continued for additional 3 h. The reaction mixture was poured onto crushed ice and neutralized with 10% HCl, and the obtained precipitate was filtered, washed with water, dried and crystallized from ethanol.

Orange powder; yield 0.51 g (91%); mp 118–120°C as reported [43]. IR (KBr, ν cm^{-1}): 3050 (CH-Ar); 2870 (CH–aliph.); 2220 (C≡N); 1620 (C=N); 1506 (C=C); 1232, 1060 (C–S–C).

4-(Benzo[d]thiazol-2-yl)-5-(methylthio)-1H-pyrazol-3-amine (6). An equimolar mixture of compound **5** (0.56 g, 2 mmol) and hydrazine hydrate 99% (0.1 g, 0.1 mL, 2 mmol) was heated under reflux for 8 h in absolute ethanol (15 mL). The reaction mixture was concentrated and allowed to cool, and the obtained precipitate was filtered, washed with ethanol, left to dry then crystallized from DMF.

Brown powder; yield 0.32 g (61%); mp >300°C. IR (KBr, ν cm^{-1}): 3290, 3163, 3151 (NH_2, NH); 3012 (CH–Ar); 2856 (CH–aliph.); 1620, 1583 (C=N); 1541 (C=C); 1270, 1070 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.55 (s, 3H, SCH_3); 6.86 (s, 2H, NH_2, D_2O exchangeable); 6.87–7.03 (m, 1H, benzothiazole–C_6–H); 7.20–7.60 (m, 1H, benzothiazole–C_5–H); 7.73 (d, 1H, J = 7.5 Hz, benzothiazole–C_4–H); 7.94–8.08 (m, 1H, benzothiazole–C_7–H); 9.36 (s, 1H, pyrazole–N_1H, D_2O exchangeable). *Anal*. Calcd (%) for $C_{11}H_{10}N_4S_2$: C, 50.36; H, 3.84; N, 21.36. Found: C, 50.53; H, 3.88; N, 21.51.

General procedure for the synthesis of 2-(benzo[*d*]thiazol-2-yl)-3-(4-substituted phenyl)acrylonitriles (7a–c). An equimolar mixture of compound **1** (0.35 g, 2 mmol) and the appropriate 4-substituted benzaldehyde (2 mmol), namely, 4-bromobenzaldehyde, 4-chlorobenzaldehde, and 4-dimethylaminobenzaldehde, was heated under reflux for 4–6 h in absolute ethanol (10 mL) containing few drops of triethyl amine The reaction mixture was concentrated, and the obtained solid product was filtered, washed with ethanol, dried and recrystallized from ethanol.

2-(Benzo[d]thiazol-2-yl)-3-(4-bromophenyl)acrylonitrile (7a). Greenish yellow crystals; yield 0.51 g (74%); mp 146–148°C as reported [44].

2-(Benzo[d]thiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (7b). Creamy white crystals; yield 0.5 g (84%); mp 154–156°C as reported [44].

2-(Benzo[d]thiazol-2-yl)-3-(4-(dimethylamino)phenyl) acrylonitrile (7c). Red crystals; yield 0.45 g (73%); mp 237–238°C. IR (KBr, ν cm^{-1}): 3051, 3005 (CH–Ar); 2920, 2854 (CH–aliph.); 2214 (C≡N); 1612 (C=N); 1566 (C=C); 1280, 1060 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 3.09 (s, 6H, two CH_3); 6.87 (d, 2H, J = 9 Hz, 4-N $(CH_3)_2$-C_6H_4–$C_{3,5}$–H); 7.43 (t, 1H, J = 7.5 Hz, benzothiazole–C_6–H); 7.53 (t, 1H, J = 7.5 Hz, benzothiazole–C_5–H); 7.95–8.04 (m, 2H, 4-N $(CH_3)_2$–C_6H_4–$C_{2,6}$–H); 8.10 (d, 2H, J = 7.5 Hz, benzothiazole–$C_{4,7}$–H); 8.14 (s, 1H, arylidene–H). *Anal*. Calcd (%) for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76. Found: C, 71.03; H, 4.99; N, 13.98.

4-(Benzo[d]thiazol-2-yl)-3-(4-bromophenyl)-1H-pyrazol-5-amine (8). Hydrazine hydrate 99% (0.5 g, 0.49 mL, 10 mmol) was added to a solution of compound **7a** (0.34 g, 1 mmol) in absolute ethanol (10 mL). The reaction mixture was heated under reflux for 12 h then concentrated and left to cool. The obtained solid precipitate was filtered, washed with ethanol, dried and recrystallized from ethanol.

Yellow crystals; yield 0.16 g (43%); mp 225–227°C. IR (KBr, ν cm^{-1}): 3262 (broad NH_2, NH); 3056 (CH–Ar); 1616 (C=N); 1576 (C=C); 1250, 1060 (C–S–C). EI-MS: *m/z* (%): 373 (M + 2, 0.76); 371 (M^+, 1.31); 104 (C_7H_6N, 100). *Anal*. Calcd (%) for $C_{16}H_{11}BrN_4S$: C, 51.76; H, 2.99; N, 15.09 Found (%): C, 51.94; H, 3.04; N, 15.32.

2-(Benzo[d]thiazol-2-yl)-3-oxo-3-phenylpropanenitrile (9). To a solution of compound **1** (0.35 g, 2 mmol) in toluene (10 mL), benzoyl chloride (0.42 g, 0.35 mL, 3 mmol) was added, and the reaction mixture was heated under reflux for 12 h in the presence of triethyl amine (three drops). The reaction mixture was then concentrated and left to cool, and the desired product was filtered, washed with toluene, dried and crystallized from acetone.

Reddish brown powder; yield 0.36 g (64%); mp 288–290°C. IR (KBr, ν cm^{-1}): 3412, 3387 (broad tautomeric OH); 3057 (CH–Ar); 2929 (CH–aliph.); 2194 (C≡N); 1685 (C=O); 1624 (C=N); 1545 (C=C); 1274, 1076 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.06 (s, 1H, CH–CN); 7.29–7.34 (m, 2H, benzothiazole–$C_{5,6}$–H); 7.40–7.42 (m, 3H, C_6H_5–$C_{3,4,5}$–H); 7.48 (d, 2H, J = 8.4 Hz, C_6H_5–$C_{2,6}$–H); 7.59 (d, 1H, J = 7.8 Hz, benzothiazole–C_4–H); 7.92 (d, 1H, J = 7.8 Hz, benzothiazole–C_7–H). *Anal*. Calcd (%) for $C_{16}H_{10}N_2OS$: C, 69.04; H, 3.62; N, 10.06. Found: C, 69.31; H, 3.68; N, 10.29.

3-Amino-2-(benzo[d]thiazol-2-yl)-3-hydrazinylacrylonitrile (10). An equimolar mixture of compound **1** (0.35 g, 2 mmol) and thiosemicarbazide (0.18 g, 2 mmol) was heated under reflux for 20 h in glacial acetic acid (10 mL). The reaction mixture was concentrated and cooled, and the desired precipitate was filtered, washed with ethanol, dried and crystallized from toluene.

Pale brown powder; yield 0.26 g (56%); mp 270–272°C. IR (KBr, ν cm^{-1}): 3385, 3278, 3215 (NH_2, NH); 3061 (CH–Ar); 2206 (C≡N); 1618 (C=N); 1533 (C=C); 1255, 1083 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 4.74 (s, 2H, NH_2, D_2O exchangeable); 7.18 (s, 2H, $NHNH_2$, D_2O exchangeable); 7.35–7.60 (m, 1H, benzothiazole–C_6–H); 7.94–8.03 (m, 1H, benzothiazole–C_5–H); 8.08 (d, 1H, J = 8 Hz, benzothiazole–C_4–H); 8.27 (d, 1H, J = 8 Hz, benzothiazole–C_7–H); 9.66 (s, 1H, $NHNH_2$, D_2O exchangeable). *Anal*. Calcd (%) for $C_{10}H_9N_5S$: C, 51.93; H, 3.92; N, 30.28. Found: C, 52.14; H, 3.94; N, 30.45.

3-(Benzo[d]thiazol-2-yl)-3-cyanopropanamide (11) and 5-amino-4-(benzo[d]thiazol-2-yl)-1H-pyrrol-2(3H)-one (12). A mixture of compound **1** (0.35 g, 2 mmol), chloroacetamide (0.19 g, 2 mmol), and finely divided potassium carbonate (0.35 g, 2.5 mmol) in absolute ethanol (10 mL) was heated under reflux for 6 h. The reaction mixture was then cooled, triturated with water, filtered, washed with excessive amount of H_2O, dried, and crystallized from ethanol, in which the insoluble part in boiling ethanol was filtered to give the cyclic compound **12**, while the filtrate was concentrated and allowed to cool to afford the open-chain derivative **11**.

3-(Benzo[d]thiazol-2-yl)-3-cyanopropanamide (11). Green powder; crystallized from ethanol; yield 0.32 g (69%); mp 253–255°C. IR (KBr, ν cm^{-1}): 3383, 3360 (NH_2); 3059 (CH–Ar); 2927 (CH–aliph.); 2198 (C≡N); 1660 (C=O); 1614 (C=N); 1556 (C=C); 1280, 1089 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.88–1.91 (m, 1H, CHCN); 2.69–2.73 (m, 1H, CH_2CO); 2.86–2.89 (m, 1H, CH_2CO); 7.26 (s, 2H, NH_2, D_2O exchangeable); 7.35–7.74 (m, 2H, benzothiazole–$C_{5,6}$–H); 8.03–8.15 (m, 2H, benzothiazole–$C_{4,7}$–H). *Anal*. Calcd (%) for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18.17. Found: C, 57.34; H, 3.90; N, 18.39.

5-Amino-4-(benzo[d]thiazol-2-yl)-1H-pyrrol-2(3H)-one (12). Dark green powder; washed with boiling solvents; yield 0.1 g (22%); mp >300°C. IR (KBr, ν cm^{-1}): 3388, 3305, 3248 (NH_2, NH); 3059 (CH–Ar); 2926 (CH–aliph.); 1678 (C=O); 1645 (C=N); 1543 (C=C); 1282, 1087 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.73 (s, 2H, CH_2); 4.10 (s, 2H, NH_2, D_2O exchangeable); 7.47–7.55 (m, 2H, benzothiazole–$C_{5,6}$–H); 7.68 (s, 1H, NH, D_2O exchangeable); 7.94–8.01 (m, 1H, benzothiazole–C_4–H); 8.05–8.10 (m, 1H, benzothiazole–C_7–H). MS: *m/z* (%): 231 (M^+, 9.60); 83 (C_4H_5NO, 100). *Anal*. Calcd (%) for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18.17. Found: C, 57.28; H, 3.96; N, 18.41.

2-(Benzo[d]thiazol-2-yl)-2-(3,4-dihydronaphthalen-1(2H)-ylidene) acetonitrile (13) and 1-(benzo[d]thiazol-2-yl)-4,5-dihydronaphtho[2,1-b]thiophen-2-amine (14). An equimolar mixture of compound **1** (0.35 g, 2 mmol), elemental sulfur (0.06 g, 2 mmol), and 1-tetralone (0.29 g, 0.27 mL, 2 mmol) in absolute ethanol (10 mL) containing triethyl amine (0.5 mL) was heated under reflux for 12 h. The reaction mixture was filtered while hot, and the obtained solid precipitate was crystallized from toluene to afford two products. The insoluble part in boiling toluene was filtered, dried to give the cyclic compound **14**, while the filtrate was concentrated and allowed to cool to yield the open-chain derivative **13**.

2-(Benzo[d]thiazol-2-yl)-2-(3,4-dihydronaphthalen-1(2H)-ylidene)acetonitrile (13). Green powder; crystallized from toluene; yield 0.2 g (33%); mp 125–127°C. IR (KBr, ν cm^{-1}): 3057, 3032 (CH–Ar); 2926, 2858 (CH–aliph.); 2206 (C≡N); 1577 (C=N); 1533 (C=C); 1271, 1055 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 0.80–0.90 (m, 2H, dihydronaphthyl–C_3–CH_2); 1.20–1.40 (m, 2H, dihydronaphthyl–C_4–CH_2); 4.12 (t, 2H, J = 5.2 Hz, dihydronaphthyl–C_2–CH_2); 7.19–7.36 (m, 1H, dihydronaphthyl–C_6–H); 7.42–7.52 (m, 1H, dihydronaphthyl–C_7–H); 7.55–7.68 (m, 1H, benzothiazole–C_6–H); 7.69–7.70 (m, 1H, benzothiazole–C_5–H); 7.94 (d, 1H, J = 7.6 Hz, dihydronaphthyl–C_5–H); 8.01 (d, 1H, J = 7.6 Hz, dihydronaphthyl–C_8–H); 8.07 (d, 1H, J = 7.6 Hz, benzothiazole–C_4–H); 8.25 (d, 1H, J = 7.6 Hz, benzothiazole–C_7–H). *Anal*. Calcd (%) for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26. Found: C, 75.52; H, 4.70; N, 9.26.

1-(Benzo[d]thiazol-2-yl)-4,5-dihydronaphtho[2,1-b]thiophen-2-amine (14). Dark olive green powder; washed with boiling solvents; yield 0.3 g (45%); mp >300°C. IR (KBr, ν cm^{-1}): 3385, 3107 (NH_2); 3057 (CH–Ar); 2924 (CH–aliph.); 1560 (C=N); 1508 (C=C); 1247, 1093 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.60–2.65 (m, 2H, dihydronaphthothiophene–C_5–CH_2); 2.72–2.77 (m, 2H, dihydronaphthothiophene–C_4–CH_2); 7.32–7.35 (m, 2H, dihydronaphthothiophene–$C_{7,8}$–H); 7.50 (s, 2H, NH_2, D_2O exchangeable); 7.69–7.73 (m, 2H, dihydronaphthothiophene–$C_{6,9}$–H); 7.91–8.23 (m, 2H, benzothiazole–$C_{5,6}$–H); 8.28–8.35 (m, 2H, benzothiazole–$C_{4,7}$–H). *Anal*. Calcd (%) for $C_{19}H_{14}N_2S_2$: C, 68.23; H, 4.22; N, 8.38. Found: C, 68.37; H, 4.29; N, 8.54.

2-(Benzo[d]thiazol-2-yl)-3-(4-nitrophenyl)but-2-enenitrile (15). An equimolar mixture of compound **1** (0.35 g, 2 mmol), 4-nitroacetophenone (0.33 g, 2 mmol), and ammonium acetate (0.15 g, 2 mmol) was fused in an oil bath at 160–170°C for 2 h. The resulted mass was triturated with ethanol, and the obtained precipitate was filtered, washed with ethanol, dried and crystallized from ethanol.

Pale brown powder; yield 0.41 g (64%); mp 153–155°C. IR (KBr, ν cm^{-1}): 3071 (CH–Ar); 2855 (CH–aliph.); 2227 (C≡N); 1583 (C=N); 1516, 1335 (NO_2); 1450 (C=C); 1230, 1013 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.84 (s, 3H, CH_3); 7.42–7.55 (m, 1H, benzothiazole–C_6–H); 7.58–7.67 (m, 1H, benzothiazole–C_5–H); 7.76 (d, 1H, *J* = 7.8 Hz, benzothiazole–C_4–H); 7.95 (d, 1H, *J* = 7.8 Hz, benzothiazole–C_7–H); 8.03 (d, 1H, *J* = 8 Hz, 4–NO_2–C_6H_4–C_2–H); 8.16 (d, 1H, *J* = 8 Hz, 4–NO_2–C_6H_4–C_6–H); 8.25 (d, 1H, *J* = 8 Hz, 4–NO_2–C_6H_4–C_3–H); 8.36 (d, 1H, *J* = 8 Hz, 4–NO_2–C_6H_4–C_5–H). *Anal*. Calcd (%) for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found (%): C, 63.70; H, 3.48; N, 13.21.

3,5-Diamino-2-(benzo[d]thiazol-2-yl)-4′-nitrobiphenyl-4-carbonitrile (16). An equimolar mixture of compound **15** (0.32 g, 1 mmol) and malononitrile (0.07 g, 1 mmol) in absolute ethanol (10 mL) containing three drops of triethyl amine was heated under reflux for 50 h. The reaction mixture was concentrated and cooled, and the resulted precipitate was filtered, washed with ethanol, dried and crystallized from DMF.

Brown powder; yield 0.16 g (41%); mp > 300°C. IR (KBr, ν cm^{-1}): 3385, 3246 (NH_2); 3057 (CH-Ar); 2200 (C≡N); 1597 (C=N); 1516, 1340 (NO_2); 1445 (C=C); 1290, 1090 (C–S–C). EI-MS: *m/z* (%): 387 (M^+, 1.37); 95 ($C_4H_5N_3$, 100). *Anal*. Calcd (%) for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08. Found: C, 62.24; H, 3.36; N, 18.19.

(3-Amino-4-(benzo[d]thiazol-2-yl)-5-(phenylamino)thiophen-2-yl)(4-chlorophenyl)-methanone (17). To a well-stirred, ice-cold suspension of finely powdered potassium hydroxide (0.22 g, 4 mmol) and compound **1** (0.35 g, 2 mmol) in dry dimethyl formamide (10 mL), phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol) was added portion wise. After complete addition, stirring was continued at room temperature for 3 h. Then the reaction mixture was cooled to 0°C and treated with 2-bromo-4′-chloroacetophenone (0.47 g, 2 mmol), and stirring was continued for another 6 h. The reaction mixture was then poured onto ice-cold water, and the obtained precipitate was filtered, washed with water, dried and crystallized from ethanol.

Pale orange powder; yield 0.62 g (67%); mp 225–227°C. IR (KBr, ν cm^{-1}): 3404, 3282, 3267, 3221 (NH_2, NH); 3057, 3026 (CH–Ar); 1665 (C=O); 1645 (C=N); 1571 (C=C); 1265, 1050 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 7.08–7.18 (m, 1H, C_6H_5–C_4–H); 7.36–7.45 (m, 2H, C_6H_5–$C_{2,6}$–H); 7.47–7.51 (m, 2H, C_6H_5–$C_{3,5}$–H); 7.53–7.60 (m, 4H, 4–Cl–C_6H_4–$C_{3,5}$–H & benzothiazole–$C_{5,6}$–H); 7.68 (d, 2H, *J* = 8.4 Hz, 4–Cl–C_6H_4–$C_{2,6}$–H); 8.04–8.18 (m, 2H, benzothiazole–$C_{4,7}$–H); 8.54 (s, 2H, NH_2, D_2O exchangeable); 10.42 (s, 1H, NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{24}H_{16}ClN_3OS_2$: C, 62.40; H, 3.49; N, 9.10. Found (%): C, 62.53; H, 3.57; N, 9.15.

Ethyl 3-amino-4-(benzo[d]thiazol-2-yl)-5-mercaptothiophene-2-carboxylate (18). An equimolar mixture of compound **1** (0.35 g, 2 mmol) and finely powdered potassium hydroxide (0.22 g, 4 mmol) in dry DMF (10 mL) was cooled at 10°C in an ice bath, then carbon disulfide (0.15 g, 0.12 mL, 2 mmol) was added slowly over a period of 10 min, and stirring was continued for 6 h. Ethyl chloroacetate (0.25 g, 0.21 mL, 2 mmol) was added to the reaction mixture, then stirring was continued for another 3 h. The reaction mixture was poured onto crushed ice and neutralized with 10% HCl. The obtained precipitate was filtered, washed with water, dried and crystallized from ethyl acetate.

Shiny orange powder; yield 0.55 g (81%); mp 169–171°C. IR (KBr, ν cm^{-1}): 3446, 3421 (NH_2); 3040 (CH–Ar); 2924 (CH–aliph.); 1735 (C=O); 1600 (C=N); 1510 (C=C); 1292, 1023 (C–S–C); 1232, 1008 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.13 (t, 3H, *J* = 6.6 Hz, CH_2CH_3); 1.99 (s, 1H, SH, D_2O exchangeable); 4.04 (q, 2H, *J* = 6.6 Hz, CH_2CH_3); 4.25 (s, 2H, NH_2, D_2O exchangeable); 7.59 (t, 1H, *J* = 7.7 Hz, benzothiazole–C_6–H); 7.68 (t, 1H, *J* = 7.7 Hz, benzothiazole–C_5–H); 8.13 (d, 1H, *J* = 7.7 Hz, benzothiazole–C_4–H); 8.27 (d, 1H, *J* = 7.7 Hz, benzothiazole–C_7–H). *Anal*. Calcd (%) for $C_{14}H_{12}N_2O_2S_3$: C, 49.98; H, 3.59; N, 8.33. Found: C, 50.16; H, 3.64; N, 8.49.

3-Amino-4-(benzo[d]thiazol-2-yl)-5-mercaptothiophene-2-carbohydrazide (19). To a suspension of compound **18** (0.67 g, 2 mmol) in absolute ethanol (10 mL), hydrazine hydrate 99% (1 g, 0.97 mL, 20 mmol) was added, and the reaction mixture was heated under reflux for 5 h. The reaction mixture was concentrated and cooled, and the obtained precipitate was filtered, washed with ethanol, left to dry then crystallized from dioxane.

Brown powder; yield 0.3 g (47%); mp > 300°C. IR (KBr, ν cm^{-1}): 3304, 3116 (NH_2, NH); 3040 (CH–Ar); 1660 (C=O); 1581 (C=N); 1544 (C=C); 1282, 1095 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 4.48 (s, 1H, SH, D_2O exchangeable); 5.01 (br. s, 2H, $NHNH_2$, D_2O exchangeable); 5.79 (s, 2H, NH_2, D_2O exchangeable); 7.23 (t, 1H, *J* = 7.7 Hz, benzothiazole–C_6–H); 7.39 (t, 1H, *J* = 7.7 Hz, benzothiazole–C_5–H); 7.70 (d, 1H, *J* = 7.7 Hz, benzothiazole–C_4–H); 7.96 (d, 1H,

J = 7.7 Hz, benzothiazole–C_7–H); 11.86 (s, 1H, NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{12}H_{10}N_4OS_3$: C, 44.70; H, 3.13; N, 17.38. Found: C, 44.98; H, 3.17; N, 17.57.

3-Amino-4-(benzo[d]thiazol-2-yl)-N-(1,3-dioxoisoindolin-2-yl)-5-mercaptothiophene-2-carboxamide (20). An equimolar mixture of compound **19** (0.32 g, 1 mmol) and phthalic anhydride (0.15 g, 1 mmol) in glacial acetic acid (10 mL) was heated under reflux for 12 h. The reaction mixture was concentrated and cooled, and the obtained product was filtered, washed with ethanol, dried and crystallized from methanol.

Dark green powder; yield 0.35 g (78%); mp 188–190°C. IR (KBr, ν cm^{-1}): 3383, 3367, 3213 (NH_2, NH); 3095 (CH–Ar); 1732 (cyclic C=O); 1685 (C=O); 1585 (C=N); 1543 (C=C); 1280, 1072 (C–S–C). EI-MS: *m/z* (%): 452 (M^+, 3.73); 248 ($C_{11}H_6NS_3$, 100). *Anal*. Calcd (%) for $C_{20}H_{12}N_4O_3S_3$: C, 53.08; H, 2.67; N, 12.38. Found: C, 53.24; H, 2.69; N, 12.52.

N-*(7-(Benzo[d]thiazol-2-yl)-6-mercapto-2-methyl-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)acetamide (21).* Compound **19** (0.32 g, 1 mmol) was heated under reflux in a mixture of glacial acetic acid (5 mL) and acetic anhydride (5 mL) for 12 h. The reaction mixture was allowed to cool, and the obtained precipitate was filtered, washed with dioxane, dried and crystallized from dioxane.

Dark brown powder; yield 0.28 g (73%); mp >300°C. IR (KBr, ν cm^{-1}): 3410 (tautomeric OH); 2924 (CH–Ar); 2854 (CH–aliph.); 1680 (cyclic C=O); 1660 (amidic C=O); 1600 (C=N); 1543 (C=C); 1246, 1041 (C–S–C). EI-MS: *m/z* (%): 389 (M + H, 1.81); 388 (M^+, 7.17); 91 (C_6H_5N, 100). *Anal*. Calcd (%) for $C_{16}H_{12}N_4O_2S_3$: C, 49.47; H, 3.11; N, 14.42. Found: C, 49.68; H, 3.17; N, 14.60.

Ethyl 5-amino-4-(benzo[d]thiazol-2-yl)-2-methylfuran-3-carboxylate (22). A solution of compound **1** (0.35 g, 2 mmol) and ethyl 2-chloro-3-oxobutanoate (0.33 g, 0.28 mL, 2 mmol) in absolute ethanol (10 mL) was added drop wise at room temperature to a solution of sodium ethoxide [prepared from sodium metal (0.05 g, 2 mmol) in absolute ethanol (10 mL)]. The reaction mixture was stirred at room temperature for 2 h during which a white precipitate separated out. The obtained product was filtered, washed several times with water, dried and crystallized from ethanol.

Pale yellow powder; yield 0.5 g (82%); mp 179–180°C. IR (KBr, ν cm^{-1}): 3392, 3288 (NH_2); 3066 (CH–Ar); 2924, 2900 (CH–aliph.); 1697 (C=O); 1624 (C=N); 1500 (C=C); 1271, 1089 (C–S–C); 1240, 1030 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.35 (t, 3H, J = 7.2 Hz, CH_2CH_3); 2.46 (s, 3H, CH_3); 4.34 (q, 2H, J = 7.2 Hz, CH_2CH_3); 7.25 (t, 1H, J = 7.8 Hz, benzothiazole–C_6–H); 7.40 (t, 1H, J = 7.8 Hz, benzothiazole–C_5–H); 7.83 (s, 2H, NH_2, D_2O exchangeable); 7.84 (d, 1H, J = 7.8 Hz, benzothiazole–C_4–H); 7.94 (d, 1H, J = 7.8 Hz, benzothiazole–C_7–H). ^{13}C NMR (DMSO-d_6, δ ppm): 13.96 (CH_3); 14.59 (CH_2CH_3); 60.82 (CH_2CH_3); 88.92 (furan–C_3); 111.18 (benzothiazole–C_4); 120.79 (benzothiazole–C_7); 121.59 (benzothiazole–C_6); 123.59 (benzothiazole–C_5); 126.19 (furan–C_4); 133.43 (benzothiazole–C_{1a}); 149.29 (furan–C_5); 152.37 (benzothiazole–C_2); 158.79 (benzothiazole–C_{3a}); 162.20 (furan–C_2); 163.82 (C=O). *Anal*. Calcd (%) for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.75; H, 4.74; N, 9.45.

6-Amino-5-(benzo[d]thiazol-2-yl)-4-(2,4-imethoxyphenyl) nicotinonitrile (24). A mixture of compound **1** (0.35 g, 2 mmol), 2-(2,4-dimethoxybenzylidene)malononitrile **23**[41] (0.43 g, 2 mmol), and piperidine (0.1 mL) in absolute ethanol (20 mL) was heated under reflux for 2 h. The formed needle crystals were filtered, washed with ethanol, dried and recrystallized from acetone.

Light orange crystals; yield 0.71 g (91%); mp 175–177°C. IR (KBr, ν cm^{-1}): 3310 (NH_2); 3095 (CH–Ar); 2930 (CH–aliph.); 2217 (C≡N); 1566 (C=N); 1460 (C=C); 1278, 1025 (C–S–C); 1211, 1010 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 3.91 (s, 3H, 2,4–$(OCH_3)_2$–C_6H_3–C_4–OCH_3); 3.97 (s, 3H, 2,4–$(OCH_3)_2$–C_6H_3–C_2–OCH_3); 6.70–6.80 (m, 2H, 2,4–$(OCH_3)_2$–C_6H_3–$C_{3,5}$–H); 6.81 (s, 2H, NH_2, D_2O exchangeable); 7.49 (t, 1H, J = 7.8 Hz, benzothiazole–C_6–H); 7.57 (t, 1H, J = 7.8 Hz, benzothiazole–C_5–H); 8.06 (d, 1H, J = 8.1 Hz, 2,4–$(OCH_3)_2$–C_6H_3–C_6–H); 8.14 (d, 1H, J = 7.8 Hz, benzothiazole–C_4–H); 8.24 (d, 1H, J = 7.8 Hz, benzothiazole–C_7–H); 8.50 (s, 1H, pyridine–C_2–H). ^{13}C NMR (DMSO-d_6, δ ppm): 56.34 (C_4–OCH_3); 56.79 (C_2–OCH_3); 98.89 (pyridine–C_5); 101.49 (2,4–$(OCH_3)_2$–C_6H_3–C_5); 107.50 (C≡N); 114.08 (pyridine–C_3); 117.38 (2,4–$(OCH_3)_2$–C_6H_3–C_1); 122.83 (benzothiazole–C_4); 123.31 (benzothiazole–C_7); 126.34 (benzothiazole–C_6); 127.34 (benzothiazole–C_5); 130.03 (2,4–$(OCH_3)_2$–C_6H_3–C_6); 134.43 (benzothiazole–C_{1a}); 141.56 (pyridine–C_6); 151.92 (benzothiazole–C_2 & pyridine–C_4); 153.52 (benzothiazole–C_{3a}); 161.11 (pyridine–C_2 & 2,4–$(OCH_3)_2$–C_6H_3–C_2); 164.27 (2,4–$(OCH_3)_2$–C_6H_3–C_4); 165.39 (2,4–$(OCH_3)_2$–C_6H_3–C_3). *Anal*. Calcd (%) for $C_{21}H_{16}N_4O_2S$: C, 64.93; H, 4.15; N, 14.42. **Found**: C, 65.12; H, 4.19; N, 14.58.

3-(Benzo[d]thiazol-2-yl)-6-bromo-2H-chromen-2-imine (25). An equimolar mixture of compound **1** (0.35 g, 2 mmol) and 5-bromosalicylaldehyde (0.4 g, 2 mmol) was heated under reflux in absolute ethanol (15 mL) containing a catalytic amount of piperidine (five drops) for 1 h. A yellow precipitate was separated out, which was filtered, washed with ethanol, left to dry and crystallized from methanol.

Yellow powder; yield 0.6 g (84%); mp 250–251°C. IR (KBr, ν cm^{-1}): 3249 (NH); 3048 (CH–Ar); 1659 (C=N); 1544 (C=C); 1225, 1061 (C–S–C); 1210, 1061 (C–O–

C). ^{1}H NMR (DMSO-d_6, δ ppm): 7.21 (d, 1H, J = 8 Hz, chromen–C_8–H); 7.47 (t, 1H, J = 7.7 Hz, benzothiazole–C_6–H); 7.57 (t, 1H, J = 7.7 Hz, benzothiazole–C_5–H); 7.68 (d, 1H, J = 8 Hz, chromen–C_7–H); 8.05–8.18 (m, 2H, benzothiazole–$C_{4,7}$–H); 8.47 (s, 1H, chromen–C_5–H); 8.73 (s, 1H, chromen–C_4–H) 9.23 (s, 1H, imino NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{16}H_9BrN_2OS$: C, 53.80; H, 2.54; N, 7.84. Found: C, 54.03; H, 2.57; N, 7.95.

3-(Benzo[d]thiazol-2-yl)-6-bromo-2-iminoquinolin-1(2H)-amine (26). To a suspension of compound **25** (0.71 g, 2 mmol) in absolute ethanol (20 mL), hydrazine hydrate 99% (0.1 g, 0.09 mL, 2 mmol) was added, and the reaction mixture was heated under reflux for 8 h. It was then left to cool, and the reaction mixture was diluted with water and neutralized with 10% HCl. The obtained product was filtered, washed with water, dried and crystallized from toluene.

Dark yellow powder; yield 0.45 g (61%); mp 295–296°C. IR (KBr, ν cm^{-1}): 3419, 3387 (NH_2, NH); 3068 (CH–Ar); 1625 (C=N); 1564 (C=C); 1267, 1078 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.95 (d, 1H, J = 8.7 Hz, quinoline–C_8–H); 7.52–7.55 (m, 3H, quinoline–C_7–H & benzothiazole–$C_{5,6}$–H); 7.87–7.97 (m, 3H, quinoline–C_5–H & benzothiazole–$C_{4,7}$–H); 8.90–8.95 (m, 2H, quinoline–C_4–H & imino NH); 11.12 (s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd (%) for $C_{16}H_{11}BrN_4S$: C, 51.76; H, 2.99; N, 15.09. Found (%): C, 51.98; H, 3.04; N, 15.34.

3-Acetyl-5-(benzo[d]thiazol-2-yl)-8-bromo-1H-[1,2,4]triazino[2,3-a]quinolin-2(3H)-one (27). Equimolar amounts of compound **26** (0.37 g, 1 mmol) and ethyl 2-chloro-3-oxobutanoate (0.16 g, 0.14 mL, 1 mmol) were fused at 170–180°C for 27 h. The reaction mixture was filtered, and the solid product was washed with ethanol, dried and boiled with ethanol, benzene, dioxane and DMF.

Reddish brown powder; yield 0.37 g (82%); mp >300°C. IR (KBr, ν cm^{-1}): 3437 (tautomeric OH); 3090 (CH–Ar); 2870 (CH–aliph.); 1728 (broad C=O); 1616 (C=N); 1556 (C=C); 1260, 1095 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.30 (s, 3H, CH_3); 3.57 (s, 1H, triazine–C_3–H); 7.15–7.21 (m, 4H, quinoline–$C_{4,5,7,8}$–H); 7.22–7.27 (m, 4H, benzothiazole–$C_{4,5,6,7}$–H); 8.15 (s, 1H, NH, D_2O exchangeable). MS: *m/z* (%): 454 (M + H, 1.16); 105 (C_7H_7N, 100). *Anal*. Calcd (%) for $C_{20}H_{13}BrN_4O_2S$: C, 52.99; H, 2.89; N, 12.36. Found: C, 53.00; H, 2.91; N, 12.37.

3,6-Di(benzo[d]thiazol-2-yl)-9-bromo-2-(4-chlorophenyl)-[1,2,4]triazepino[2,3-a]quinolin-4-amine (28). Compound **26** (0.37 g, 1 mmol) was added to an equimolar mixture of compound **1** (0.17 g, 1 mmol) and 4-chlorobenzaldehyde (0.14 g, 1 mmol) in dioxane (10 mL) as solvent. The reaction mixture was heated under reflux for 54 h, then concentrated and cooled, and the obtained precipitate was filtered, washed with dioxane, dried and crystallized from methanol.

Brown powder; yield 0.42 g (63%); mp 118–120°C. IR (KBr, ν cm^{-1}): 3398, 3385 (NH_2); 3057 (CH–Ar); 1624 (C=N); 1560 (C=C); 1269, 1087 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 6.95 (d, 1H, J = 7.8 Hz, quinolinine–C_8–H); 7.19–7.80 (m, 4H, two benzothiazole–$C_{5,6}$–H); 7.89 (d, 1H, J = 7.8 Hz, quinoline–C_7–H); 8.13–8.22 (m, 2H, 4–Cl–C_6H_4–$C_{2,6}$–H); 8.28–8.39 (m, 2H, 4–Cl–C_6H_4–$C_{3,5}$–H); 8.70 (s, 1H, quinoline–C_5–H); 8.80 (s, 1H, quinoline–C_4–H); 8.90 (d, 4H, J = 11.7 Hz, two benzothiazole–$C_{4,7}$–H); 11.11 (s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd (%) for $C_{32}H_{18}BrClN_6S_2$: C, 57.71; H, 2.72; N, 12.62. Found: C, 57.89; H, 2.70; N, 12.81.

6-(Benzo[d]thiazol-2-yl)-9-bromo-4-(2,4-dichlorophenyl)-1,4-dihydro-3′,4′-dihydronaphthyl[1′,2′:6,7][1,2,4]triazepino[2,3-a]quinoline (29). Equimolar amounts of compound **26** (0.37 g, 1 mmol), 1-tetralone (0.15 g, 0.13 mL, 1 mmol), and 2,4-dichlorobenzaldehyde (0.18 g, 1 mmol) were heated under reflux in dioxane (10 mL) containing a catalytic amount of p-toluene sulfonic acid for 35 h. The reaction mixture was then cooled, and the solid product was filtered, washed with dioxane, dried and crystallized from benzene.

Dark brown powder; yield 0.33 g (50%); mp 88–90°C. IR (KBr, ν cm^{-1}): 3170 (NH); 3066, 3035 (CH–Ar); 2927, 2870 (CH–aliph.); 1597 (C=N); 1477 (C=C); 1284, 1080 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.03 (t, 2H, J = 5.7 Hz, tetrahydronaphthyl–C_4–CH_2); 2.59 (t, 2H, J = 5.7 Hz, tetrahydronaphthyl–C_3–CH_2); 4.56 (s, 1H, triazepine–C_5–H); 6.94 (d, 1H, J = 7.2 Hz, quinoline–C_8–H); 7.10 (d, 2H, J = 6.6 Hz, 2,4–$(Cl)_2$–C_6H_3–$C_{5,6}$–H); 7.24 (s, 1H, 2,4–$(Cl)_2$–C_6H_3–C_3–H); 7.34 (d, 1H, J = 7.2 Hz, quinoline–C_7–H); 7.42–7.63 (m, 4H, tetrahydronaphthyl–$C_{5,6,7,8}$–H); 7.62 (s, 1H, quinoline–C_5–H); 7.68–7.82 (m, 2H, benzothiazole–$C_{5,6}$–H); 7.84–8.00 (m, 2H, benzothiazole–$C_{4,7}$–H); 8.93 (s, 1H, quinoline–C_4–H); 11.12 (s, 1H, NH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{33}H_{21}BrCl_2N_4S$: C, 60.38; H, 3.22; N, 8.54. Found: C, 60.64; H, 3.20; N, 8.70.

4-Amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(2,4-dimethoxyphenyl)[1,2,4]triazepino-[2,3-a]quinoline-3-carbonitrile (31a) and 6-(benzo[d]thiazol-2-yl)-9-bromo-2-(2,4-dimethoxyphenyl)-4-hydroxy-[1,2,4]triazepino[2,3-a]quinoline-3-carbonitrile (31b). An equimolar mixture of compound **26** (0.37 g, 1 mmol) and compound **23** (41) (0.21 g, 1 mmol) or compound **30**[41] (0.26 g, 1 mmol) was heated under reflux in absolute ethanol (20 mL) containing a catalytic amount of piperidine (0.5 mL) for 35 h. The reaction mixture was concentrated and cooled, and the solid product was filtered, washed with ethanol, dried and crystallized from ethanol to yield compounds **31a** and **31b**, respectively.

4-Amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(2,4-dimethoxyphenyl)[1,2,4]triazepino-[2,3-a]quinoline-3-carbonitrile (31a). Light orange crystals; yield 0.24 g (41%); mp 264–266°C. IR (KBr, ν cm^{-1}): 3400 (NH_2); 3005 (CH–Ar); 2927, 2852 (CH–aliph.); 2195 (C≡N); 1616, 1602 (C=N); 1541 (C=C); 1269, 1099 (C–S–C); 1234, 1074 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 3.86, 3.90 (two s, 6H, two OCH_3); 6.61 (s, 1H, 2,4–$(OCH_3)_2$–C_6H_3–C_3–H); 6.66 (d, 1H, J = 8.3 Hz, 2,4–$(OCH_3)_2$–C_6H_3–C_5–H); 6.95 (d, 1H, J = 8.3 Hz, 2,4–$(OCH_3)_2$–C_6H_3–C_6–H); 7.44–7.60 (m, 2H, quinoline–$C_{7,8}$–H); 7.83–7.93 (m, 2H, benzothiazole–$C_{5,6}$–H); 8.81 (s, 1H, quinoline–C_5–H); 8.86 (d, 2H, J = 7.8 Hz, benzothiazole–$C_{4,7}$–H); 8.93 (s, 1H, quinoline–C_4–H); 11.10 (s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd (%) for $C_{28}H_{19}BrN_6O_2S$: C, 57.64; H, 3.28; N, 14.40. Found: C, 57.89; H, 3.25; N, 14.62.

6-(Benzo[d]thiazol-2-yl)-9-bromo-2-(2,4-dimethoxyphenyl)-4-hydroxy-[1,2,4]triazepino[2,3-a]quinoline-3-carbonitrile (31b). Pale brown powder; yield 0.26 g (45%); mp 218–220°C. IR (KBr, ν cm^{-1}): 3446, 3421 (broad OH); 3095 (CH–Ar); 2929, 2854 (CH–aliph.); 2220 (C≡N); 1624 (C=N); 1560 (C=C); 1267, 1074 (C–S–C & C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.73, 2.89 (two s, 6H, two OCH_3); 6.91–7.00 (m, 3H, 2,4–$(OCH_3)_2$–C_6H_3–$C_{3,5,6}$–H); 7.53 (d, 2H, J = 8.4 Hz, quinoline–$C_{7,8}$–H); 7.84–7.91 (m, 2H, benzothiazole–$C_{5,6}$–H); 7.95 (s, 1H, quinoline–C_5–H); 7.98–8.03 (m, 2H, benzothiazole–$C_{4,7}$–H); 8.93 (s, 1H, quinoline–C_4–H); 11.10 (s, 1H, OH, D_2O exchangeable). *Anal*. Calcd (%) for $C_{28}H_{18}BrN_5O_3S$: C, 57.54; H, 3.10; N, 11.98. Found: C, 57.81; H, 3.14; N, 12.17.

4-Amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(methylthio)[1,2,4]triazepino[2,3-a]quinoline-3-carbonitrile (34a) and ethyl 4-amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(methylthio)-[1,2,4]triazepino[2,3-a]quinoline-3-carboxylate (34b). To a solution of compound **26** (0.37 g, 1 mmol) in DMF (10 mL) an equimolar amount of either compound **32** [42] (0.17 g, 1 mmol) or compound **33** [42] (0.22 g, 1 mmol) was added, and the reaction mixture was heated under reflux in the presence of TEA (two drops) for 66–70 h. The solvent was then evaporated, and the solid mass was triturated with ethanol, and the obtained solid was filtered, washed with ethanol, dried and crystallized from ethanol to afford compounds **34a** and **34b**, respectively.

4-Amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(methylthio)[1,2,4]triazepino[2,3-a]quinoline-3-carbonitrile (34a). Brown powder; yield 0.23 g (47%); mp 248–250°C. IR (KBr, ν cm^{-1}): 3427, 3419 (NH_2); 3068 (CH–Ar); 2924 (CH–aliph.); 2210 (C≡N); 1624 (C=N); 1548 (C=C); 1267, 1078 (C–S–C). ^{1}H NMR (DMSO-d_6, δ ppm): 2.89 (s, 3H, S–CH_3); 6.95 (d, 2H, J = 8.4 Hz, quinoline–$C_{7,8}$–H); 7.48–7.60 (m, 4H, benzothiazole–$C_{4,5,6,7}$–H); 7.89 (s, 1H, quinoline–C_5–H); 8.93 (s, 1H, quinoline–C_4–H); 11.10 (s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd (%) for $C_{21}H_{13}BrN_6S_2$: C, 51.12; H, 2.66; N, 17.03. Found (%): C, 51.30; H, 2.63; N, 17.19.

Ethyl 4-amino-6-(benzo[d]thiazol-2-yl)-9-bromo-2-(methylthio)[1,2,4]triazepino[2,3-a]quinoline-3-carboxylate (34b). Brown powder; yield 0.27 g (50%); mp 280–282°C. IR (KBr, ν cm^{-1}): 3421 (NH_2); 3068 (CH–Ar); 2924, 2868 (CH–aliph.); 1710 (C=O); 1624 (C=N); 1475 (C=C); 1267, 1078 (C–S–C); 1234, 1078 (C–O–C). ^{1}H NMR (DMSO-d_6, δ ppm): 1.06 (t, 3H, J = 6.9 Hz, CH_2CH_3); 2.89 (s, 3H, S–CH_3); 3.38–3.50 (m, 2H, CH_2CH_3); 6.95 (d, 2H, J = 9 Hz, quinoline–$C_{7,8}$–H); 7.50–7.60 (m, 4H, benzothiazole–$C_{4,5,6,7}$–H); 7.89 (s, 1H, quinoline–C_5–H); 8.93 (s, 1H, quinoline–C_4–H); 11.10 (s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd (%) for $C_{23}H_{18}BrN_5O_2S_2$: C, 51.11; H, 3.36; N, 12.96. Found: C, 51.23; H, 3.35; N, 13.14.

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