Synthesis, Characterization and Anticancer Activity of Some Benzothiazole and Thiazole Derivatives

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ABSTRACT

Objective: This study aimed synthesis of benzothiazole and thiazole derivatives due to the importance of these heterocycles as anticancer. Method: Novel benzothiazole and thiazole derivatives 2-40 were synthesized through different chemical reactions. Results: Structures of these compounds were confirmed by spectral and elemental analyses. The obtained compounds were evaluated for their in vitro antitumor activity against 60 human cancer cell lines by the National Cancer Institute (NCI). Conclusion: Twelve compounds 4, 6, 10, 12, 13, 16, 18, 20, 21, 25, 28b and 40 were selected by NCI for evaluation and have anticancer activity.

Keywords: Anticancer; Benzothiazole; Thiazole

INTRODUCTION

Benzothiazole derivatives represent an important class of biologically active molecules having broad pharmacological activities such as anticancer 1-3, antimicrobial4,5, anti-inflammatory6, antiviral7, antioxidant8, antitubercular9, anticonvulsant10, antimalarial11 and antileishmanial12 activities. Furthermore, many benzothiazole derivatives were reported to be responsible for inhibition of topoisomerase II13-15 and tyrosine kinase histone deacetylase16 enzymes.

Additionally, many compounds containing thiazole system have been investigated because of their broad spectrum of biological activities which include anticancer17,18, antimicrobial19, anti-inflammatory20, antioxidant21, antitubercular22 and antiprotozoal activities23. The aforementioned biological activities together with the industrial importance of these compounds stimulated our interest for the synthesis of several new heterocyclic compounds containing benzothiazole moiety attached to or condensed with each of pyrrole, pyridine, quinoline, tetrazole, triazole, triazine, oxadiazole, thienopyrimidine, quinazoline, benzoxazole and pyrimidine moieties.

Also, such information encouraged us to synthesize thiazole derivatives attached to oxazole, thiazole and chromen rings in addition to, thiazole derivatives condensed with pyrrole ring.

The new condensed heterocyclic derivatives possessing latent functional substituents appear promising to fulfill the objectives of our biological
activity studies and the desired chemical transformations. However, benzothiazol-2-ylacetonitrile and thiazol-2-ylacetonitrile seemed to be excellent candidates for these syntheses.

**MATERIAL AND METHODS**

**Part 1-Chemistry**

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 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 Micro- analytical 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 El III CHN analyzer at the microanalytical unit, Regional center for Mycology and Biotechnology, Al-Azhar University. Reactions were monitored by thin-layer chromatography (TLC) 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. Chemicals were purchased from Alfa Aesar and were used without further purification. All compounds are new except compounds 1 and 27a-c.

*Synthesis of 2-(benzo[d]thiazol-2-yl)acetonitrile; 1.*

An equimolar mixture of 2-aminothiophenol (1.25 g, 1.07 mL, 10 mmol) and malononitrile (0.66 g, 10 mmol) in ethanol (10 mL) in presence of a catalytic amount of acetic acid (1 mL) was stirred for 2 h. The precipitate was filtered, washed with ethanol, dried and recrystallized from ethanol. Shiny yellow crystals; yield 1 g (57%); m.p.103-104°C as reported. IR (KBr, cm$^{-1}$): 3050 (CH- Ar); 2918 (CH–aliph.); 2252 (C–\(\equiv\)N); 1580 (C=N); 1511 (C=C); 1239, 1043 (C–S–C).


To a solution of compound 1 (0.35 g, 2 mmol) in DMF (10 mL), chloroacetyl chloride (0.25 g, 0.17 mL, 2.2 mmol) was added. The reaction mixture was stirred at 56°C for 48 h., concentrated to half its volume and brown powder was separated out. The formed product was filtered, washed with ethanol, left to dry and crystallized from dioxane. Brown powder; yield 0.25 g (58%); m.p.294-296°C. IR (KBr, cm$^{-1}$): 3022 (CH-Ar); 2925 (CH-aliph.); 2233 (C=O); 1649 (C=O; 1580 (C=N); 1511 (C=C); 1239, 1043 (C–S–C).


To a solution of compound 1 (0.35 g, 2 mmol) in DMF (10 mL), chloroacetyl chloride (0.25 g, 0.17 mL, 2.2 mmol) was added. The reaction mixture was stirred at 56°C for 48 h., concentrated to half its volume and brown powder was separated out. The formed product was filtered, washed with ethanol, left to dry and crystallized from dioxane. Brown powder; yield 0.25 g (58%); m.p.294-296°C. IR (KBr, cm$^{-1}$): 3022 (CH-Ar); 2925 (CH-aliph.); 2233 (C=O); 1649 (C=O; 1580 (C=N); 1511 (C=C); 1239, 1043 (C–S–C).

An equimolar mixture of compound 1 (0.35 g, 2 mmol) and cinnamoyl chloride 5 (0.33 g, 2 mmol) in toluene (10 mL) containing a catalytic amount of TEA (3 dps) was refluxed for 22 h. The reaction mixture was allowed to cool and the sticky mass was dissolved in ethanol to afford the desired product that was filtered, washed with ethanol, dried and recrystallized from boiling ethanol, toluene and DMF. Pale brown powder; yield 0.25 g (52%); m.p. >300°C. IR (KBr, cm⁻¹): 3449 (tautomeric OH); 3005 (CHattack); 2222 (C=O); 1718 (ester oxo); 1612 (C=N); 1502 (C=C); 1276, 1039 (C–H). Found (%): C, 60.39; H, 3.38; N, 9.20. Found (%): C, 70.97; H, 4.01; N, 9.28.

Synthesis of 1-phenyl-2,3-dihydro-3-oxo-1H-pyrido[2,1-b]benzo[d]thiazole-4-carbonitrile: 6

An equimolar mixture of compound 1 (0.35 g, 2 mmol) and cinnamoyl chloride 5 (0.33 g, 2 mmol) in toluene (10 mL) containing a catalytic amount of TEA (3 dps) was refluxed for 22 h. The reaction mixture was allowed to cool and the sticky mass was dissolved in ethanol to afford the desired product that was filtered, washed with ethanol, dried and recrystallized from boiling ethanol, toluene and DMF. Pale brown powder; yield 0.25 g (52%); m.p. >300°C. IR (KBr, cm⁻¹): 3449 (tautomeric OH); 3005 (CHattack); 2222 (C=O); 1718 (ester oxo); 1612 (C=N); 1502 (C=C); 1276, 1039 (C–H). Found (%): C, 60.39; H, 3.38; N, 9.20. Found (%): C, 70.97; H, 4.01; N, 9.28.
C3-H), 13C-NMR (DMSO-d6-δppm): 56.30 (C2-OCH3); 56.75 (C2̐-OCH3); 98.82 (pyridobenzothiazole-C6); 101.38 (2.4-(OCH2)2C6H3-C3); 107.45 (2.4-(OCH2)2C6H3-C3); 114.05 (2.4-(OCH2)2C6H3-C1 & pyridobenzothiazole-C2); 117.37 (C=C=N); 122.78 (pyridobenzothiazole-C6); 123.28 (pyridobenzothiazole-C7); 126.29 (pyridobenzothiazole-C5); 127.45 (pyridobenzothiazole-C5); 129.96 (pyridobenzothiazole-C5a); 134.41 (2.4-(OCH2)2C6H3-C6); 141.44 (pyridobenzothiazole-C9a); 153.51 (C=O); 161.07 (2.4-(OCH2)2C6H3-C3); 164.24 (pyridobenzothiazole-C4a); 165.36 (pyridobenzothiazole-C3). Molecular Formula: C6H3N2O.S. Analysis, Calcd. (%): C, 65.11; H, 3.38; N, 10.85. Found (%): C, 65.23; H, 3.41; N, 11.02.

To a solution of compound 1 (0.35 g, 2 mmol) in toluene (10 mL) containing few drops of triethylamine, 2,4-dimethoxybenzyl chloride (0.6 g, 3 mmol) was added and the reaction mixture was refluxed for 29 h. The resulting product was concentrated, cooled and the obtained powder was filtered, washed with toluene, dried and crystallized from ethanol. Brownish black powder; yield 0.2 g (48%); m.p. 283-285°C. IR (KBr, cm-1): 3242, 3151, 3122 (NH); 2856 (CH-aliph.); 1600 (C=N); 1456 (C=C); 1292, 1070 (C-S-C). 1H-NMR (DMSO-d6-δppm): 1.24 (s, 2H, CH2); 6.30 (s, 2H, NH, D2O exchangeable); 6.99 (t, 1H, J = 7.5 Hz, benzothiazole-C6-H); 7.42 (t, 1H, J = 7.5 Hz, benzothiazole-C1-H); 7.68 (d, 1H, J = 7.5 Hz, benzothiazole-C2-H); 7.80 (d, 1H, J = 7.5 Hz, benzothiazole-C3-H); 10.88 (s, 1H, NH, D2O exchangeable); 12.60 (s, 1H, imino NH, D2O exchangeable). MS: m/z (%): 207(M+1, 1.03); 206(M+, 4.50); 189(100). Molecular Formula: C17H10N3S. Analysis, Calcd. (%): C, 52.41; H, 4.89; N, 27.16. Found (%): C, 52.74; H, 4.96; N, 27.42.

Synthesis of 5-(benzo[d]thiazol-2-ylmethyl)-1H-1,2,4-triazole-3(2H)-thione; 12
To a stirred suspension of compound 1 (0.21 g, 1 mmol) in absolute ethanol (10 mL), potassium hydroxide (0.03 g, 0.5 mmol) and carbon disulfide (0.46 g, 0.037 mL, 6 mmol) were added gradually and the reaction mixture was then heated under reflux for 15 h. After cooling and evaporation of the solvent, the obtained potassium salt was dissolved in water and acidified with 10% HCl to afford the desired product. The obtained product was filtered, washed with excessive amount of water, dried and washed from boiling ethanol, benzene, dioxane and DMF. Reddish brown powder; yield 0.15 g (59%); m.p. >300°C. IR (KBr, cm-1): 3421 (NH); 3050 (CH-Ar); 2920 (CH-aliph.); 1620 (C≡N); 1545 (C=C); 1255 (C=S); 1049 (C-S-C). MS: m/z (%): 248(M+, 19.44); 91(100). Molecular Formula: C17H10N3S. Analysis, Calcd. (%): C, 48.37; H, 3.25; N, 22.56. Found (%): C, 48.61; H, 3.32; N, 22.81.

To a solution of hydroxylamine hydrochloride (0.17 g, 2.5 mmol) in absolute ethanol (15 mL), (0.26 g, 0.06 mL, 2.6 mmol) of TEA was added. After the addition was completed, the solution was stirred at 50°C for 30 min. Then compound 1 (0.35 g, 2 mmol) was added and the reaction mixture was heated under reflux for 52 h. The reaction mixture was concentrated, cooled and the obtained precipitate was filtered, washed with ethanol, dried and crystallized from ethanol to provide two products; the insoluble part in ethanol was filtered to give compound 14, while the filtrate was concentrated to afford compound 13.
Reagents and conditions: (i) chloroacetyl chloride, DMF / reflux; (ii) diethyl ethoxymethylene malonate, absolute ethanol / reflux; (iii) dimethyl acetylenedicarboxylate, NaOCl / reflux; (iv) cinnamoyl chloride 5 toluene / TEA / reflux; (v) ethyl 2-cyano-3-(2,4-dimethoxyphenyl)acrylate 7, absolute ethanol / Pip / reflux; (vi) 2,4-dimethoxybenzoyl chloride, dry toluene / TEA / reflux.

Scheme 1

Reagents and conditions: (i) sodium azide, NH₄Cl / DMF / reflux; (ii) hydroxylamine hydroxide 95%, absolute ethanol / reflux; (iii) carbon disulfide, KOH / absolute ethanol / reflux; (iv) hydroxylamine hydrochloride, absolute ethanol / TEA / reflux; (v) methyl orthoformate, fusion at 170-180°C; (vi) diacyanamide, KOH / methoxy ethanol / reflux.

Scheme 2
Reagents and conditions: (i) 2-aminophenol, 10% HCl / reflux; (ii) 5-bromoanthranilic acid, fusion at 170-180°C; (iii) ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate 19, gl. AcOH / reflux; (iv) naphthalene-1,8-diamine, fusion at 175-180°C.

Scheme 3

Reagents and conditions: (i) dimedone, 2,4-dichlorobenzaldehyde, p-TSA / absolute ethanol / reflux; (ii) 1-(4-Chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one 23, 4-chloroaniline, DMF-AcOH 1:4 / reflux; (iii) 1-tetralone, dimethyl acetylenedicarboxylate, hydrazine hydrate 99% / absolute ethanol / reflux.

Scheme 4

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Reagents and conditions: (i) absolute ethanol / reflux; (ii) 2-aminothiophenol, absolute ethanol / reflux; (iii) phenyl isothiocyanate, NaOC₂H₅ / reflux; (iv) 4-chlorophenacyl bromide, NaOC₂H₅ / reflux; (v) dimethylformamide dimethylacetal, xylene / Pip. / reflux; (vi) hydroxylamine hydrochloride, NaOC₂H₅ / reflux; (vii) 5-bromoaldehyde, absolute ethanol /gl. AcOH / reflux.

Scheme 5
2-(Benzo[d]thiazol-2-yl)-N'-hydroxyacetimidamide; 13.

Yellowish brown powder; crystallized from ethanol; yield 0.18 g (43%); m.p. 178-180°C. IR (KBr, cm⁻¹): 3420 (broad OH); 3327, 3277 (NH₂); 3057 (CH-Aliph.); 2922, 2850 (CH-Aliph.); 1610 (C=N); 1508 (C=C); 1242, 1015 (C–S–C).

1H-NMR (DMSO-d₆, δ ppm): 2.63 (s, 2H, CH₂); 7.33-7.74 (m, 1H, benzothiazole-C₆–H); 8.11-8.26 (m, 1H, benzothiazole-C₅–H); 8.65 (d, 1H, J = 7.2 Hz, benzothiazole-C₄–H); 8.97 (d, 1H, J = 7.2 Hz, benzothiazole-C₇–H); 11.96 (s, 2H, NH₂, D₂O exchangeable); 14.95 (s, 1H, OH, D₂O exchangeable).

Molecular Formula: C₉H₉N₃OS. Analysis, Calcd. (%): C, 52.16; H, 4.38; N, 20.27. Found (%): C, 52.34; H, 4.45; N, 20.52.


Brown powder; washed from boiling ethanol, toluene and dioxane; yield 0.1 g (26%); m.p. >300°C. IR (KBr, cm⁻¹): 3327, 3244 (NH₂); 3055 (CH-Ar); 1620 (C=N); 1539 (C=C); 1295, 1065 (C–S–C). MS: m/z(%): 189(M⁺, 6.41); 40(100). Molecular Formula: C₉H₉N₃S. Analysis, Calcd. (%): C, 57.12; H, 3.73; N, 22.21. Found (%): C, 57.38; H, 3.71; N, 22.49.

Reagents and conditions: (i) thiaacetamide, c.HCl / DMF / oil bath at 90-100°C; (ii) ethyl bromoacetate, absolute ethanol / reflux; (iii) 4-chlorophenyl bromide, benzene / reflux; (iv) ethyl 2-chloro-3-oxobutanoate, absolute ethanol / NH₄OAc / reflux.

Scheme 6

2-(Benzo[d]thiazol-2-yl)-N'-hydroxyacetimidamide; 13.

Brown powder; washed from boiling ethanol, toluene and dioxane; yield 0.1 g (26%); m.p. >300°C. IR (KBr, cm⁻¹): 3327, 3244 (NH₂); 3055 (CH-Ar); 1620 (C=N); 1539 (C=C); 1295, 1065 (C–S–C). MS: m/z(%): 189(M⁺, 6.41); 40(100). Molecular Formula: C₉H₉N₃S. Analysis, Calcd. (%): C, 57.12; H, 3.73; N, 22.21. Found (%): C, 57.38; H, 3.71; N, 22.49.


Brown powder; washed from boiling ethanol, toluene and dioxane; yield 0.1 g (26%); m.p. >300°C. IR (KBr, cm⁻¹): 3327, 3244 (NH₂); 3055 (CH-Ar); 1620 (C=N); 1539 (C=C); 1295, 1065 (C–S–C). MS: m/z(%): 189(M⁺, 6.41); 40(100). Molecular Formula: C₉H₉N₃S. Analysis, Calcd. (%): C, 57.12; H, 3.73; N, 22.21. Found (%): C, 57.38; H, 3.71; N, 22.49.

Synthesis of 3-(benzo[d]thiazol-2-ylmethyl)-1,2,4-oxadiazone; 15.

An equimolar mixture of compound 13 (0.41 g, 2 mmol) and triethyl orthoformate (0.3 g, 0.34 mL, 2 mmol) was fused at 170-180°C for 20 h. The reaction mixture was cooled, triturated with ethanol and the obtained product was filtered, washed with ethanol, dried and crystallized from dioxane.

Black powder; yield 0.13 g (30%); m.p. >300°C. IR (KBr, cm⁻¹): 3059 (CH-Ar); 2873 (CH-Aliph.); 1600 (C=N); 1435 (C=C); 1212, 1091 (C–S–C). MS: m/z(%): 217(M⁺, 2.01); 57(100). Molecular Formula: C₁₀H₉N₃O₂S. Analysis, Calcd. (%): C, 55.29; H, 3.25; N, 19.34. Found (%): C, 55.53; H, 3.34; N, 19.60.
Synthesis of 6-(benzo[d]thiazol-2-ylmethyl)-1,3,5-triazine-2,4-diamine; 16.

The solution of compound 1 (0.35 g, 2 mmol) in methoxy ethanol (10 mL) was treated with dicyandiamide (0.17 g, 2 mmol) and potassium hydroxide (0.11 g, 2 mmol). The resultant mixture was heated at 100°C for 20 h. and poured into cold water providing solid precipitate. The obtained precipitate was collected, filtered, washed with ethanol, dried and recrystallized by boiling benzene. Reddish crystals; yield 0.3 g (58%); m.p. >300°C. IR (KBr, cm⁻¹); 3351 (NH₂); 3061 (CH-Ar); 2900 (CH-aliph.); 1627 (C=O); 1515 (C=C); 1270, 1050 (C=S–C). 1H-NMR (DMSO-d6-δppm): 2.67, 2.78 (CH₂); 3.53 (s, 2H, CH₂); 3.45 (s, 2H, NH); 4.79 (s, 1H, NH, D₂O exchangeable); 6.36-6.40 (m, 2H, benzothiazole–C₃–C₄); 9.05 (s, 1H, J = 7.5 Hz, benzothiazole–C₅–C₆); 8.44 (d, 1H, J = 7.8 Hz, benzothiazole–C₇–C₈). Molecular Formula: C₁₁H₁₀BrN₂O₂S₂. Analysis, Calcul. (%): C, 48.31; H, 3.39; N, 22.31. Found (%): C, 48.27; H, 3.41; N, 22.14.


Compound 1 (0.35 g, 2 mmol) was refluxed with 2-aminothanol (0.22 g, 2 mmol) in presence of 10% HCl (10 mL) for 60 h. The reaction mixture was concentrated, cooled and the obtained precipitate was filtered, washed with ethanol, dried and recrystallized from ethanol. Yellowish brown powder; yield 0.2 g (35%); m.p. >300°C. IR (KBr, cm⁻¹); 3375, 3304 (NH, NH); 3051, 3020 (CH-Ar); 2900, 2852 (CH-aliph.); 1604 (C≡N); 1512 (C=C); 1282, 1085 (C–S–C); 1267, 1074(C–O–C). 1H-NMR (DMSO-d6-δppm): 2.67, 2.72 (s, 2H, CH₂); 3.35 (s, 2H, NH, D₂O exchangeable); 3.37-3.40 (m, 2H, benzoxazole–C₃–C₄); 4.56-4.60 (s, 2H, NH, D₂O exchangeable); 6.36-6.40 (m, 2H, benzoxazole–C₅–C₆); 2.47 (s, 1H, J = 7.5 Hz, benzoxazole–C₇–C₈); 8.05 (d, 1H, J = 7.8 Hz, benzothiazole–C₉–C₁₀). Molecular Formula: C₁₂H₁₀BrN₂O₂S₂. Analysis, Calcul. (%): C, 51.32; H, 3.97; N, 32.79. Found (%): C, 51.32; H, 3.97; N, 32.79.


An equimolar mixture of compound 1 (0.35 g, 2 mmol) and 7-bromotriazalene (0.43 g, 2 mmol) were thoroughly ground together in a mortar and taken in a sealed tube. The reaction mixture was fused at 180-190°C for 1 h. The obtained mixture was cooled, triturated with ethanol and the resultant product was filtered, washed with ethanol, left to dry and crystallized from DMF. Dark green powder; yield 0.2 g (27%); m.p. >300°C. IR (KBr, cm⁻¹); 3311 (NH); 3057 (CH-Ar); 2924, 2852 (CH-aliph.); 1680 (C≡O); 1612 (C≡N); 1550 (C≡C); 1278, 1070 (C=S–C). MS: m/z(%): 374(M⁺+ 6.11); 372(M⁺, 1.57); 174(100). Molecular Formula: C₁₆H₁₀BrN₂O₂S₂. Analysis, Calcul. (%): C, 48.31; H, 2.71; N, 21.47. Found (%): C, 51.81; H, 2.78; N, 21.49.

Synthesis of ethyl 2-amino-4,5-dimethylthioephene-3-carboxylate; 19.

An equimolar mixture of ethyl cyanoacetate (1.13 g, 10 mL, 10 mmol), ethyl methyl ketone (0.72 g, 0.90 mL, 10 mmol) was added to elemental sulphur (0.35 g, 11 mmol) in absolute ethanol (30 mL). The reaction mixture was stirred at 45°C in water bath for 24 h. and 3 drops of morpholine were added while stirring. Then, the mixture was cooled and poured onto crushed ice to yield crystalline precipitate that was filtered, washed with ethanol, dried and recrystallized from ethanol. Brown crystals; yield 0.98 g (49%); m.p. 91-92°C as reported 20.


A mixture of compound 1 (0.35 g, 2 mmol) and ethyl 2-amino-4,5-dimethylthioephene-3-carboxylate 19 (0.8 g, 4 mmol) in glacial acetic acid (10 mL) was heated under reflux for 60 h. The reaction mixture was concentrated, cooled and the obtained precipitate was collected, filtered, washed with ethanol, dried and recrystallized from methanol. Brown powder; yield 0.22 g (33%); m.p. 276-278°C. IR (KBr, cm⁻¹); 3414 (broad OH); 3059 (CH-Ar); 2926, 2854 (CH-aliph.); 1640 (C≡N); 1597 (C=C); 1298, 1093 (C–S–C). 1H-NMR (DMSO-d6-δppm): 2.06 (s, 3H, thiophene–C₃–C₄); 2.17 (s, 3H, thiophene–C₂–C₃); 2.05 (s, 2H, CH₂); 3.03 (s, 2H, CH₂); 6.36-6.40 (m, 2H, benzothiazole–C₃–C₄); 9.05 (s, 1H, J = 7.5 Hz, benzothiazole–C₅–C₆); 8.05 (d, 1H, J = 7.8 Hz, benzothiazole–C₇–C₈). Molecular Formula: C₁₆H₁₆N₄O₂S₂. Analysis, Calcul. (%): C, 58.69; H, 4.00; N, 12.83. Found (%): C, 58.81; H, 4.06; N, 12.97.


An equimolar mixture of compound 1 (0.35 g, 2 mmol) and naphthalene-1,8-diamine (0.32 g, 2 mmol) was taken in a sealed tube and fused at 175-190°C for 1 h. The reaction mixture was cooled, triturated with ethanol and the obtained product was filtered, washed with ethanol, dried and recrystallized from ethanol. Brown powder; yield 0.2 g (32%); m.p. 198-200°C. IR (KBr, cm⁻¹); 3385, 3336 (NH); 3057 (CH-Ar); 2924, 2852 (CH-aliph.); 1630 (C≡N); 1560 (C=C); 1263, 1065 (C–S–C). 1H-NMR (DMSO-d6-δppm): 2.89 (s, 2H, CH₂); 4.74 (s, 1H, NH, D₂O exchangeable); 6.56 (d, 1H, J = 7.8 Hz, perimidin–C₃–H); 6.96 (d, 1H, J = 7.8 Hz, perimidin–C₄–H); 7.04 (t, 2H, J = 7.8 Hz, perimidin–C₅–C₆–H); 7.48-7.55 (m, 5H, perimidin–C₅–C₆–H); 8.05 (d, 1H, J = 8.1 Hz, 

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benzothiazole–C$_2$H–H); 8.12 (d, 1H, J = 8.1 Hz, benzothiazole–C$_2$–H). Molecular Formula: C$_9$H$_7$N$_2$S.

Analysis, Calcd. (%): C, 72.36; H, 4.15; N, 13.32. Found (%): C, 72.51; H, 4.18; N, 13.57.

Synthesis of 5-(2,4-dichlorophenyl)-2,2-dimethyl-4-oxo-1,2,3,4-tetrahydro-5H-benzo[d]thiazolo[3,2-a]quinoline-6-carbonitrile; 22.

An equimolar mixture of compound 1 (0.35 g, 2 mmol), dimedone (0.28 g, 2 mmol) and 2,4-dichlorobenzaldehyde (0.35 g, 2 mmol) in absolute ethanol (15 mL) containing catalytic amount of p-TSA was refluxed for 2 h. The reaction mixture was concentrated, cooled and the desired product was filtered, washed with ethanol, dried and recrystallized from ethanol. Orange crystals; yield 0.4 g (44%); m.p. 272-274°C. IR (KBr, cm$^{-1}$): 3427 (tautomeric OH); 3101 (CH=Ar); 2910 (CH=Ph); 2218 (C≡N); 1650 (C=O); 1577 (C=C); 1250, 1045 (C–S–C). 1H-NMR (DMSO-d$_6$, 0 ppm): 2.10 (s, 6H, 2 CH$_3$); 3.19 (s, 2H, CH$_2$); 4.06 (s, 2H, CH$_2$CO); 7.55-7.64 (m, 2H, benzothiazole–C$_5$–H); 7.70 (d, 2H, J = 8.4 Hz, 2,4-(Cl)$_2$C$_6$H$_4$-C$_5$–H); 7.89 (s, 1H, quinoline–C$_3$–H); 8.12-8.22 (m, 2H, benzothiazole–C$_4$–H); 8.47 (s, 1H, 2,4-(Cl)$_2$C$_6$H$_4$-C$_5$–H). MS: m/z (%): 453(M$^+$), 293(100). Molecular Formula: C$_{25}$H$_{19}$N$_5$O$_5$. Analysis, Calcd. (%): C, 63.58; H, 4.00; N, 6.18. Found (%): C, 63.72; H, 4.07; N, 6.25.

Synthesis of 1-(4-chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one; 23.

An equimolar mixture of 4-chloroacetophenone (0.31 g, 0.26 mL, 2 mmol) and thiophene-2-carboxaldehyde (0.22 g, 0.19 mL, 2 mmol) in absolute ethanol (25 mL) was stirred at room temperature for 10 min., then a solution of 60% NaOH was added dropwise during the first 20 min. of the reaction until the first precipitate appeared. The reaction mixture was further stirred for additional 2 h then the precipitate was filtered, washed with water, dried and crystallized from ethanol. Yellow powder; yield 0.43 g (86%); m.p.123-125°C as reported 20.

Synthesis of 3-(benzo[d]thiazol-2-yl)-N,6-bis(4-chlorophenyl)-4-(thiophen-2-yl) pyridin-2-amine; 24.

An equimolar mixture of compound 1 (0.35 g, 2 mmol), compound 23 (0.5 g, 2 mmol) and 4-chloroaniline (0.26 g, 2 mmol) in a mixture of DMF-AcOH (1:4) (10 mL) was refluxed at 100°C for 39 h. during which brown crystals were formed. The desired product was filtered, washed with ethanol, dried and recrystallized from DMF. Yellowish brown crystals; yield 0.5 g (47%); m.p. >300°C. IR (KBr, cm$^{-1}$): 3383 (NH); 3080 (CH=Ar); 1618 (C≡N); 1508 (C≡C); 1285, 1080 (C–S–C). 1H-NMR (DMSO-d$_6$, 0 ppm): 7.05 (s, 1H, pyridine-C$_5$–H); 7.45-7.56 (m, 5H, thiophene-C$_3$–H & benzothiazole–C$_5$–H); 7.60 (d, 2H, J = 8.1 Hz, NH-4-Cl-C$_6$H$_4$-C$_5$–H); 7.91 (d, 2H, J = 7.8 Hz, 4-Cl-C$_6$H$_4$-C$_5$–H); 7.96-7.99 (m, 4H, two 4-Cl-C$_6$H$_4$-C$_5$–H); 8.13 (d, 2H, J = 7.5 Hz, benzothiazole–C$_4$–H); 12.13 (s, 1H, NH, D$_2$O exchangeable). Molecular Formula: C$_{25}$H$_{17}$ClN$_5$S$_2$. Analysis, Calcd. (%): C, 63.39; H, 3.23; N, 7.92. Found (%): C, 63.51; H, 3.28; N, 8.04.

Synthesis of methyl 4-[(benzo[d]thiazol-2-yl)(cyano)methyl]-1,2,3,4-tetrahydro napthalen-1-yl)-3-hydroxy-1H-pyrazole-5-carboxylate; 25.

A mixture of compound 1 (0.35 g, 2 mmol), tetralone (0.29g, 0.27 mL, 2 mmol) and triethylamine (0.2 g, 0.28 mL, 2 mmol) in 10 mL ethanol was stirred at room temperature for 30 min. then solution of hydrazine hydrate 99% (0.11 g, 0.11 mL, 2.2 mmol) and dimethyl acetylenedicarboxylate (0.31g, 0.27 mL, 2.2 mmol) in 6 mL ethanol was added and the whole mixture was heated under reflux for 40 h. The reaction mixture was cooled, filtered, washed with ethanol, dried and crystallized from ethyl acetate. Reddish brown powder; yield 0.55 g (62%); m.p. 288-290°C. IR (KBr, cm$^{-1}$): 3394, 3367, 3275, 3194 (broad OH & NH); 3062 (CH=Ar); 2924, 2854 (CH=Aliph.); 2210 (C≡N); 1720 (C=O); 1577 (C≡N); 1454 (C=C); 1246, 1095 (C–S–C); 1200, 1033 (C–O–C). MS: m/z (%): 444(M$^+$), 276; 52(100).

Molecular Formula: C$_{25}$H$_{23}$N$_5$O$_7$. Analysis, Calcd. (%): C, 64.85; H, 4.54; N, 12.60. Found (%): C, 65.02; H, 4.58; N, 12.87.

Synthesis of 2-cyanothiocetamide; 26.

The Erlemeyer flask (0.5 L) was charged with malononitrile (100 g, 1.51 mole) and absolute ethanol (100 mL). Malononitrile was dissolved by stirring at room temperature. Then, triethylamine (1.0-1.5 mL) was added, the flask was closed with a two-holed rubber stopper fitted with two glass tubes, one of which should be immersed in a solution of malononitrile. The stream of hydrogen sulfide generated from sodium sulfide was passed through the tube system. After a short induction period, an exothermic reaction begins, which is accompanied by strong absorption of hydrogen sulfide by reaction mass. It is important to keep the temperature in the range 15-20 °C (cooling with ice or snow), to avoid the crystallization of malononitrile on the one hand, and overheating of the reaction mixture on the other. After ~30-40 min, cyanothiocetamide begins to crystallize. The reaction mixture should be stirred or shaken periodically to avoid clogging of gas supply pipe by product. Hydrogen sulfide must be passed through a cold solution for at least 2 h. to attain a good yield of cyanothiocetamide. At the end of the reaction, the mixture was cooled and the crystals were filtered, washed several times with cold ethanol then washed with cold diethylether and petroleum ether. Sand-yellow
needle crystals, recrystallized from ethanol, yield %; 125 g (83%), m.p.; 118-120 °C as reported 30.31.

Synthesis of 2-(4-(4-substitutedphenyl)thiazol-2-yl)acetanilide; 27a-c.

An equimolar mixture of 2-cyanothioacetamide (0.5 g, 5 mmol) and phenacyl bromide derivatives (5 mmol) in absolute ethanol (20 mL) was refluxed for 4-12 h. The resultant mixture was allowed to cool and treated with aqueous ammonia to afford the desired product. The precipitate was filtered, washed with ethanol, dried and recrystallized from methanol.

2-(4-Phenylthiazol-2-yl)acetanilide; 27a.

Brown powder; yield 0.7 g (70%); m.p. 63-65°C as reported 32. IR (KBr, cm⁻¹): 3058, 2916, 2884 (CH-aliph.); 2252 (C≡N); 1650 (C–N); 1525 (C=C); 1288, 1054 (C–O).

1H-NMR (DMSO-d₆, ppm): 6.46 (d, 2H, J = 8.5 Hz, NH); 7.88 (s, 1H, thiazole–S); 8.21 (s, 1H, thiazole–C–H).


2-(4-(4-Chlorophenyl)thiazol-2-yl)acetanilide; 27b.

Yellowish amber crystals; yield 0.85 g (73%); m.p. 125-126°C (reported m.p. 69-71°C) 30. IR (KBr, cm⁻¹): 3058, 2884 (CH-aliph.); 1650 (C≡N); 1525 (C=C); 1288, 1054 (C–O).

1H-NMR (DMSO-d₆, ppm): 6.46 (d, 2H, J = 8.5 Hz, 4-Cl-C₆H₄–C₂-H–S); 7.98 (d, 2H, J = 8.5 Hz, 4-Cl-C₆H₄–C₃–H–S). 8.21 (s, 1H, thiazole–C–H).

Molecular Formula: C₁₉H₁₃ClN₂S₂. Analysis, Calcd. (%): C, 62.85; H, 4.72; N, 12.91. Found (%): C, 62.85; H, 4.72; N, 13.08.

2-(4-Aminophenyl) 2-(4-(4-chlorophenyl)thiazol-2-yl)ethanimidothioate; 28b. Brown powder; yield 0.42 g (58%); m.p. 178-180°C. IR (KBr, cm⁻¹): 3379, 3298, 3113 (NH₂ & NH); 3062, 3012 (CH–Ar); 2920, 2850 (CH-aliph.); 1612 (C≡N); 1469 (C≡C); 1246, 1072 (C–S–C). MS: m/z (%): 362(M+2, 3.42); 361(M+1, 6.17); 360(M⁺, 2.95); 133(100).


Synthesis of 2-(4-(4-substitutedphenyl)thiazol-2-yl)-2-cyano-N-phenylethanethioamide; 29a,b.

A mixture of compounds 27a,b (2 mmol), finely divided sodium metal (0.05 g, 2 mmol) and phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol) was refluxed for 12 h. in absolute ethanol (15 mL). The reaction mixture was allowed to cool and poured onto ice-cooled water followed by addition of 10% HCl dropwise until formation of a precipitate. The formed product was filtered, washed with excess amount of water, dried and crystallized from suitable solvent.

2-(4-(4-Chlorophenyl)thiazol-2-yl)-2-cyano-N-phenylethanethioamide; 29a.

Brownish powder; yield 0.42 g (61%); m.p. 186-188°C. IR (KBr, cm⁻¹): 3263 (NH); 3055 (CH–Ar); 2924, 2850 (CH-aliph.); 2183 (C≡N); 1589 (C≡N); 1530 (C≡C); 1508, 1338, 1192, 1029 (N–C=S); 1261, 1095 (C–S–C). MS: m/z (%): 336(M+1, 6.15); 335(M⁺, 27.42); 93(100).

Molecular Formula: C₁₉H₁₃N₃S₂. Analysis, Calcd. (%): C, 64.45; H, 3.91; N, 12.53. Found (%): C, 64.62; H, 3.97; N, 12.68.

2-(4-(4-MethylPhenyl)thiazol-2-yl)-2-cyano-N-phenylethanethioamide; 29b.

Yellowish brown powder; yield 0.42 g (60%); m.p. 193-195°C. IR (KBr, cm⁻¹): 3388, 3246 (NH); 3024 (CH–Ar); 2922, 2852 (CH-aliph.); 2183 (C≡N); 1597 (C≡C); 1498 (C≡C); 1573, 1323, 1182, 1076 (N–C=S); 1261, 1076 (C–S–C).

1H-NMR (DMSO-d₆, ppm): 2.35 (s, 3H, CH₃); 3.94 (s, 1H, CH-CN); 7.28-7.41 (m, 3H, NH–C₆H₄–C₂,8,6–H); 7.52 (t, 2H, J = 7.8 Hz, NH–C₆H₄–C₃,5–H); 7.61 (d, 2H, J = 6.9 Hz, 4-CH₃–C₆H₄–C₃,5–H); 7.88 (s, 1H, thiazole–C₅–H); 7.91 (d, 2H, J = 6.9 Hz, 4-CH₃–C₆H₄–C₂,6,8–H); 11.65 (s, 1H, NH, D₂O exchangeable).


Synthesis of 2-(4-(4-chlorophenyl)-3-phenylthiazol-2(3H)-yldene)-2-(4-phenylthiazol-2-yl)acetanitride; 30.

A solution of compound 29a (0.34 g, 1 mmol) in absolute ethanol (20 mL) containing sodium ethoxide [prepared from 0.01 g, 0.5 mmol atom sodium] was treated with 2-bromo-4-chloroacetophenone (0.23 g, 1

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mmol). The reaction mixture was heated under reflux for 28 h, the solid obtained was filtered, washed with large amount of water, dried and crystallized from methanol to give the target compound. Brown powder; yield 0.24 g (50%); m.p. 251-253°C. IR (KBr, cm⁻¹): 3074 (CH=Ar); 2717 (C≡N); 1590, 1570 (C≡N); 1490 (C≡C); 1260, 1080 (C–S–C). ¹H-NMR (DMSO-d₆-ppm): 7.15-7.29 (m, 5H, N-C₆H₅); 7.30-7.56 (m, 7H, thiazole-C₆-C₆H₅ & 4-Cl-C₆H₃-C₆H₅-H); 7.52 (s, 2H, two thiazole-C₅-H); 8.08 (d, 2H, J = 8.1 Hz, 4-Cl-C₆H₃-C₅-). **Molecular Formula:** C₅H₆ClN₃S₂. Analysis, Calcld. (%): C, 66.44; H, 3.43; N, 8.94. **Found** (%): C, 66.72; H, 3.49; N, 9.02.

**Synthesis of 3-(dimethylamino)-2-(4-phenylthiazol-2-yl)acrylonitrile; 31.**
A mixture of compound 27a (0.4 g, 2 mmol) and DMF DMA (0.24 g, 0.27 mL, 2 mmol) was refluxed in several solvents including dioxane (10 mL) or xylene (10 mL) either alone or in the presence of catalytic amount of piperidine (2 dps). The most suitable method that afford the highest yield and the puriest product is the final method. The reaction mixture was refluxed for 6 h. then cooled and the crystallized product was filtered, washed with ethanol, dried and recrystallized from ethanol. Umber brown crystals; yield 0.4 g (78%); m.p. 172-174°C. IR (KBr, cm⁻¹): 3057, 3024 (CH–Ar); 2924 (CH-aliph.); 2194 (C≡N); 1610 (C≡C); 1473 (C≡C); 1288, 1060 (C–S–C). ¹H-NMR (DMSO-d₆-ppm): 3.22 (s, 6H, O(CH₃)₂); 4.62 (s, 1H, CH=C-CN); 7.32 (t, 1H, J = 6.8 Hz, C₆H₅–C₅=); 7.42 (t, 2H, J = 6.8 Hz, C₆H₅–C₅=); 7.72 (s, 1H, thiazole–C₅=); 7.95 (d, 2H, J = 6.8 Hz, C₆H₅–C₆=–H). **Molecular Formula:** C₁₅H₁₅N₃S₃. Analysis, Calcld. (%): C, 65.85; H, 5.13. **Found** (%): C, 66.02; H, 5.17.

**Synthesis of 3-(hydroxyamino)-2-(4-phenylthiazol-2-yl)acrylonitrile; 32 and 4-(4-phenylthiazol-2-yl)isoxazol-5-amine; 33.**
To 50 mL rounded bottom flask equipped with a magnetic stirrer, (0.05 g, 2 mmol) of sodium atom, (0.28 g, 4 mmol) of hydroxylamine hydrochloride and (15 mL) of absolute ethanol were added and stirred for 10 min. compound 27a (0.26 g, 1 mmol) was added to the mixture and allowed to stir at R.T. overnight. The collected precipitate was filtered, washed with ethanol, dried and crystallized from ethanol to afford two products, one was insoluble in boiling ethanol 33 and the another one was crystallized from ethanol 32.

3-(Hydroxyamino)-2-(4-phenylthiazol-2-yl)acrylonitrile; 32.
Brownish black powder; crystallized from ethanol; yield 0.07 g (28%); m.p. 95-97°C. IR (KBr, cm⁻¹): 3379 (broad OH); 3153, 3111 (NH); 3055, 3026 (CH– Ar); 2926 (CH-aliph.); 2185 (C≡N); 1622 (C≡N); 1480 (C=C); 1294, 1072 (C–S–C). MS: m/z(%) #: 244(M+1, 5.50); 243(M⁺, 7.76); 134(100). **Molecular Formula:** C₁₂H₁₃N₃O₂S. Analysis, Calcld. (%): C, 59.24; H, 3.73; N, 17.27. **Found** (%): C, 59.37; H, 3.81; N, 17.49.

4-(4-Phenylthiazol-2-yl)isoxazol-5-amine; 33.
Brownish black powder; washed from boiling ethanol, benzene, dioxane and DMF; yield 0.05 g (20%); m.p. >300°C. IR (KBr, cm⁻¹): 3387 (NH₂); 3090 (CH– Ar); 1604 (C≡N); 1560 (C≡C); 1294, 1074 (C–S–C). ¹H-NMR (DMSO-d₆-ppm): 3.99 (s, 2H, NH₂, D₂O exchangeable); 7.30-7.56 (m, 5H, thiazole–C₆-C₆H₅); 8.15 (s, 2H, thiazole–C₅–H & oxazole–C₅–H). **Molecular Formula:** C₁₂H₁₃N₃O₂S. Analysis, Calcld. (%): C, 59.24; H, 3.73; N, 17.27. **Found** (%): C, 59.43; H, 3.76; N, 17.42.

**Synthesis of 6-bromo-3-(4-(4-chlorophenyl)thiazol-2-yl)-2H-chromen-2-imine; 34.**
An equimolar mixture of compound 27b (0.47 g, 2 mmol) and 5-bromosalicylaldehyde (0.4 g, 2 mmol) in absolute ethanol (15 mL) containing a catalytic amount of piperidine (5 drops) was refluxed for 1 h. where upon yellow precipitate separated out, filtered, washed with ethanol, left to dry and crystallized from toluene.

Yellow powder; yield 0.6 g (72%); m.p. 254-255°C. IR (KBr, cm⁻¹): 3306 (ε-NH); 3095 (CH–Ar); 2927 (CH-aliph.); 1659 (C≡N); 1470 (C≡C); 1287, 1073 (C–S–C & C–O–C). ¹H-NMR (DMSO-d₆-ppm): 7.21 (d, 1H, J = 8.9 Hz, chromen–C₆–H); 7.56 (d, 2H, J = 8.6 Hz, 4-Cl-C₆H₅-C₆=H); 7.65 (d, 1H, J = 8.9 Hz, chromen–C₅–H); 8.09 (d, 2H, J = 8.6 Hz, 4-Cl-C₆H₅-C₆=H); 8.13 (s, 1H, chromen–C₅–H); 8.32 (s, 1H, chromen–C₅–H); 8.65 (s, 1H, thiazole–C₅–H); 9.17 (s, 1H, imino NH, D₂O exchangeable). **Molecular Formula:** C₁₄H₁₀BrClN₃O₂S. Analysis, Calcld. (%): C, 51.76; H, 2.41; N, 6.71. **Found** (%): C, 51.93; H, 2.46; N, 6.79.

**Synthesis of 2-(4-(4-substitutedphenyl)thiazol-2-yl)ethanethioamide; 35a.**
A solution of compounds 27a, b (2 mmol) and thioacetamide (0.05 g, 0.67 mmol) in DMF (10 mL) was heated in oil bath at 90-100°C for 16 h. while cHCl (0.5 mL) was added to the reaction mixture. The residue was triturated with acetone to yield the desired product that was filtered, washed with acetone, dried and crystallized from the proper solvent.

2-(4-Phenylthiazol-2-yl)ethanethioamide; 35a.
Brown powder; crystallized from acetone; yield 0.34 g (73%); m.p. 291-293°C. IR (KBr, cm⁻¹): 3394, 3251 (NH₂); 3059 (CH–Ar); 2924, 2854 (CH-aliph.); 1624 (C≡N); 1539 (C≡C); 1269 (C≡S); 1269, 1072 (C–S–C). MS: m/z(%) #: 235(M+1, 8.09); 234(M⁺, 9.51); 55(100). **Molecular Formula:** C₁₅H₁₀N₃S₂. Analysis,
Calcd. (%) : C, 56.38; H, 4.30; N, 11.95. Found (%) : C, 56.53; H, 4.28; N, 12.19.

2-(4-(4-Chlorophenyl)thiazol-2-yl)ethanethioamide; 35b.

Brownish black powder; crystallized from ethanol; yield 0.4 g (74%); m.p. 213-215°C. IR (KBr, cm⁻¹): 3329, 3190 (NH₂); 3101 (CH₃OH); 2925 (CH₃-aliph.); 1622 (C=C); 1530 (C=C); 1265 (C=S); 1265, 1087 (C=S–C). ¹H-NMR (DMSO-d₆-δppm): 2.29 (s, 2H, CH₂); 7.49 (d, 2H, J = 8.4 Hz, 4-Cl-C₆H₄–C₆–H); 7.87 (s, 1H, thiazole–C₅–H); 7.96 (d, 2H, J = 8.4 Hz, 4-Cl–C₆H₄–C₆–H); 9.54 (s, 2H, NH₂, D₂O exchangeable). Molecular Formula: C₁₁H₇ClN₂S₂. Analysis, Calcd. (%) : C, 49.15; H, 3.37; N, 10.42. Found (%) : C, 49.38; H, 3.34; N, 10.57.

Synthesis of ethyl 2-(1-amino-2-(4-phenylthiazol-2-yl)vinylthio)acetate; 36 and 2-((4-phenylthiazol-2-yl)methyl)thiazol-4(5H)-one; 37.

An equimolar mixture of compound 35a (0.23 g, 1 mmol) and ethyl bromoacetate (0.17 g, 0.11 mL, 1 mmol) in absolute ethanol (10 mL) was refluxed for 23 h, during which a precipitate was formed. The precipitate was filtered, washed with ethanol, dried and crystallized from dioxane where two products were separated, one was insoluble in hot dioxane 37 and the other was crystallized from dioxane 36.

Ethyl 2-(1-amino-2-(4-phenylthiazol-2-yl)vinylthio)acetate; 36.

Brownish black powder; crystallized from dioxane; yield 0.11 g (35%); m.p. 231-233°C. IR (KBr, cm⁻¹): 3390 (NH₂); 3061 (CH=Ar); 2926, 2854 (CH₃-aliph.); 1728 (C=O); 1600 (C=N); 1470 (C=C); 1294, 1074 (C=S–C); 1269, 1060 (C=O–C). MS: m/z(%) : 321(M⁺+1, 1.52); 320(M⁺, 1.71); 44(100). Molecular Formula: C₈H₁₀N₂O₂S₂. Analysis, Calcd. (%) : C, 56.22; H, 5.03; N, 8.74. Found (%) : C, 56.34; H, 5.09; N, 8.89.

2-((4-Phenylthiazol-2-yl)methyl)thiazol-4(5H)-one; 37.

Black powder; washed from boiling dioxane, toluene, acetone and DMF; yield 0.13 g (48%); m.p. >300°C. IR (KBr, cm⁻¹): 3429, 3417 (broad tautomeric OH); 3055, 3024 (CH=Ar); 2924 (CH₃-aliph.); 1726 (C=O); 1635 (C=N); 1469 (C=C); 1294, 1060 (C=S–C); 1269, 1026 (C=O–C). MS: m/z(%) : 273(M⁺–1, 0.80); 257 (M–OH, 17.21); 73(100). Molecular Formula: C₁₃H₁₀N₂O₂S₂. Analysis, Calcd. (%) : C, 56.91; H, 3.67; N, 10.21. Found (%) : C, 57.08; H, 3.72; N, 10.42.

Synthesis of 2-(1-amino-2-(4-chlorophenyl)thiazol-2-yl)vinylthio)-1-(4-chlorophenylethanone; 38 and bis(4(4-chlorophenyl)thiazol-2-yl)methane; 39.

Compound 35b (0.27 g, 1 mmol) was refluxed with α-bromo-4-chloroacetophenone (0.23 g, 1 mmol) in dry benzene (10 mL) as solvent. Reflux was carried out for 7 h. then the reaction mixture was filtered while hot to yield compound 38, while the filtrate was cooled and triturated with diethyl ether to afford compound 39. Both compounds were filtered, washed with ethanol, dried and crystallized from the suitable solvent.

2-(1-Amino-2-(4-(4-chlorophenyl)thiazol-2-yl)vinylthio)-1-(4-chlorophenylethanone; 38.

Brown powder; crystallized from methanol; yield 0.21 g (50%); m.p. 99-101°C. IR (KBr, cm⁻¹): 3370 (NH₂); 3010 (CH–Ar); 2910 (CH₃-aliph.); 1695 (C=O); 1589 (C=N); 1570 (C=C); 1282, 1091 (C=S–C). ¹H-NMR (DMSO-d₆-δppm): 4.76 (s, 1/2H, CH₂=CH-NH tautomer); 5.47 (s, 1/2H, OH tautomer, D₂O exchangeable); 5.62 (s, 1H, CH₂CO); 6.62 (br.s, 1H, NH₂, D₂O exchangeable); 7.36 (s, 1/2H, CH=CH-NH); 7.59 (d, 2H, J = 8.4 Hz, thiazole–C₄–4–Cl–C₆H₄–C₆–H); 7.65 (d, 2H, J = 6.3 Hz, CO–4–Cl–C₆H₄–C₆–H); 7.74 (s, 1/2H, S=CH=CH=O–OH tautomer); 7.93 (d, 2H, J = 6.3 Hz, CO–4–Cl–C₆H₄–C₆–H); 7.97 (s, 1H, thiazole–C₅–S); 8.08-8.09 (m, 2H, thiazole–C₄–4–Cl–C₆H₄–C₆–H); 9.47 (s, 1H, imino NH tautomer, D₂O exchangeable). Molecular Formula: C₁₉H₁₂Cl₂N₂O₂S. Analysis, Calcd. (%) : C, 54.16; H, 3.35; N, 6.65. Found (%) : C, 54.37; H, 3.39; N, 6.73.

Bis(4-(4-chlorophenyl)thiazol-2-yl)methane; 39.

Black powder; crystallized from dioxane; yield 0.12 g (30%); m.p. >300°C. IR (KBr, cm⁻¹): 3086, 3064, 3055 (CH=Ar); 2926, 2852 (CH₃-aliph.); 1589 (C=N); 1469 (C=C); 1286, 1089 (C=S–C). MS: m/z(%) : 405(M⁺+2, 1.22); 403(M⁺, 2); 43(100). Molecular Formula: C₁₉H₁₂Cl₂N₂S₂. Analysis, Calcd. (%) : C, 56.58; H, 3.00; N, 6.95. Found (%) : C, 56.74; H, 3.03; N, 7.08.

Synthesis of ethyl 3-(4-chlorophenyl)-7-cyano-6-methylpyrrolol[2,1-b]thiazole-5-carboxylate; 40.

A solution of compound 27b (0.47 g, 2 mmol) in absolute ethanol (10 mL), ethyl 2-chloro-3-oxobutanoate (0.33 g, 0.28 mL, 2 mmol) and piperidine (3 dps) was refluxed for 12 h. The reaction mixture was left to cool at R.T. and the separated product was filtered, washed with ethanol, dried and crystallized from ethanol. Brown powder; yield 0.46 g (67%); m.p. 248-250°C. IR (KBr, cm⁻¹): 3045 (CH=Ar); 2949, 2841 (CH₃-aliph.); 2214 (C≡N); 1724 (C=O); 1639 (C≡N); 1556 (C=C); 1298, 1091 (C=S–C); 1249, 1051 (C=O–C). ¹H-NMR (DMSO-d₆-δppm): 1.00-1.20 (m, 3H, CH₃CH₂); 3.34 (s, 3H, CH₃ under DMSO); 4.20-4.60 (m, 2H, CH₂CH₃); 7.59 (d, 2H, J = 8.4 Hz, 4–Cl–C₆H₄–C₆–H); 8.12 (d, 2H, J = 8.4 Hz, 4–Cl–C₆H₄–C₆–H); 8.76 (s, 1H, thiazole–C₅–H). Molecular Formula: C₁₇H₁₂ClN₂O₂S. Analysis,
RESULTS AND DISCUSSION

Part 1-Chemistry

Literature survey is enriched with various methods to synthesize acetonitrile derivatives. Adopting the reported method, stirring equimolar mixture of 2-mercaptoaniline and malononitrile at room temperature in absolute ethanol/glacial acetic acid mixture afforded 2-(benzo[d]thiazol-2-yl)acetonitrile 1.

Furthermore, the reaction of compound 1 with chloroacetyl chloride in dimethylformamide afforded the corresponding pyrrolobenzothiazole derivatives 2. The structure of the prepared compound was confirmed by spectral data and elemental analysis. IR spectrum of compound 2 displayed absorption band at 1649 cm$^{-1}$ corresponding to carbonyl group. Also, $^1$H-NMR spectrum of compound 2 revealed a singlet at $\delta$ 3.76 ppm attributed to CH$_2$-CO protons.

It should be noted that, the preparation of pyridobenzothiazole derivatives 3, 4, 6 and 8 were achieved via refluxing compound 1 with either diethyl ethoxy methylenemalonate, dimethyl acetylenedicarboxylate, cinnamoyl chloride 5 and ethyl 2-cyano-3-(2,4-dimethoxyphenyl)acrylate 7; respectively.

From our findings, the reaction of 2-(benzo[d]thiazol-2-yl)acetonitrile 1 with diethyl ethoxy methylenemalonate was indicated to proceed through nucleophilic substitution of ethoxy group by the active methylene proton followed by intramolecular cyclization with subsequent elimination of an ethanol molecule to furnish the target compound.

On the other hand, the reaction of compound 1 with dimethyl acetylenedicarboxylate was suggested to proceed via nucleophilic addition of activated methylene group on the acetylenic carbon of dimethyl acetylenedicarboxylate followed by nucleophilic attack of endocyclic NH function on the ester carbonyl group with the subsequent elimination of a methanol moiety.

Moreover, the reaction of compound 1 with cinnamoyl chloride was indicated to proceed through the initial acylation of the active methylene with cinnamoyl chloride followed by the cycloaddition of endocyclic NH on the cinnamoyl double bond to yield the target compound analogous to the reported mechanism.

In addition, the reaction of compound 1 with $\alpha,\beta$-unsaturated nitriles was reported to proceed via Michael addition followed by cycloaddition of endocyclic NH to ester carbonyl function to yield their corresponding fused pyridine derivatives.

The structures of the prepared compounds 3, 4, 6 and 8 were confirmed by spectral data and elemental analyses. IR spectra of these compounds showed absorption bands characteristic to C=O at 1650-1718 cm$^{-1}$. $^1$H-NMR spectra of compounds 3 and 4 revealed singlet at $\delta$ 6.83-8.50 ppm characteristic for pyridinone proton as well as triplet and quartet in compound 3 at $\delta$ 1.32 and 4.28 ppm attributed to ester methyl and methylene protons; respectively. Also, $^1$H-NMR spectrum of compound 6 revealed two multiplets at $\delta$ 2.88-2.97 and 3.11-3.19 ppm assigned for CH$_2$CO and CH-Ph protons; respectively.

It is to be mentioned that, benzothiazoloquinoline derivatives 9 was prepared through refluxing compound 1 with 2,4-dimethoxybenzoyl chloride where its structure was supported by absorption band at 1668 cm$^{-1}$ corresponding to carbonyl function.

Furthermore, cyanomethyl derivatives were also indicated to react with sodium azide in dimethylformamide containing ammonium chloride to afford the corresponding tetrazole derivatives 10. It is to be noted that, the reaction of compound 1 with hydrazine hydrate 99% gave the corresponding imidrazene derivative 11 that upon refluxing with carbon disulfide yielded the corresponding 1,2,4-triazole-3-thione derivative 12.

However, refluxing of compound 1 with hydroxylamine hydrochloride yielded both the open chain amidoxime derivative 13 in addition to the fused pyrazolobenzothiazole derivative 14. In addition, 1,2,4-oxadiazole derivative 15 was prepared via fusion of the amidoxime analogue 13 with triethyl orthoformate at 170-180°C. Also, reaction of compound 1 with dicyandiamide yielded the corresponding triazine diamine derivative 16.

The structures of the prepared compounds were confirmed by spectral data and elemental analyses. IR spectra of compounds 10-16 lacked absorption band characteristic for cyano function of their precursors and revealed absorption band at 3380-3122 cm$^{-1}$ corresponding to NH$_2$ and NH groups in compounds 10-14 and 16.

$^1$H-NMR spectra of compounds 10, 11, 13 and 16 showed deuterium oxide exchangeable singlets at $\delta$ 5.02-12.60 ppm and 6.30-11.96 ppm attributed to NH and NH$_2$ protons, respectively as well as another D$_2$O exchangeable singlet at 14.95 ppm in compound 13 due to OH proton (Scheme 2).

In this investigation, reaction of 2-(benzo[d]thiazol-2-yl)acetonitrile 1 with 2-aminophenol produced the corresponding 2-aminobenzoxazole derivative 17. Also, the condensation of compound 1 with 5-bromoanthranilic acid yielded the corresponding quinazolinone heterocycle 18. The reaction was assumed to proceed through addition of amino group to the cyano function followed by intramolecular cyclization via nucleophilic attack to the acidic carbonyl function with the subsequent elimination of a water molecule.

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<th>Delta</th>
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<th>Subpanel cell lines (Growth inhibition percent)</th>
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Furthermore, the target thienopyrimidine analogue 20 was obtained by refluxing 2-(benzo[d]thiazol-2-yl)acetanilide 1 with ethyl 2-aminoo-4,5-dimethylthiophene-3-carboxylate 19 in glacial acetic acid. The reaction was suggested to proceed through nucleophilic addition of amino function followed by intramolecular cyclization via the elimination of an ethanol moiety to produce the target compound 20. Moreover, fusion of compound 1 with naphthalene-1,8-diamine at 175-190°C provided the corresponding perimidine derivatives 21.

The structures of these compounds were evidenced via spectral and elemental data. IR spectra of compounds 17, 18, 20 and 21 lacked absorption band due to cyano group in their precursor and revealed absorption bands at 3385-3304 cm⁻¹ attributed to NH functions in compounds 17, 18 and 21 as well as broad absorption band at 3414 cm⁻¹ due to OH group in compound 20. ¹H-NMR spectra of these compounds displayed deuterium oxide exchangeable singlets at δ 4.44-8.85 ppm assigned for NH protons in compounds 17, 18 and 21 as well as another D₂O exchangeable singlet at δ 12.26 ppm attributed to OH proton in compounds 20 (Scheme 3).

The scope of our survey was extended to record the one-pot three-component reaction of aromatic aldehyde, activated nitrile and dimedone 39, 40 to provide the corresponding heterocyclic derivatives. Consequently, a one-pot three-component reaction of 2-(benzo[d]thiazol-2-yl)acetanilide 1, dimedone and 2,4-dichlorobenzaldehyde in ethanol in the presence of p-toluene sulfonic acid as a catalyst afforded the corresponding benzothiazoloquinoline derivative 22. The reaction was suggested to proceed through two steps which involve the initial condensation of the aromatic aldehyde with activated nitrile derivative via standard Knoevenagel reaction to produce the corresponding benzylidene derivative. Then dimedone C-H reacted with benzylidene derivative through Michael addition followed by intramolecular cyclization with removal of a water molecule. IR spectrum of compound 22 displayed absorption band at 1650 cm⁻¹ corresponding to carbonyl function and ¹H-NMR spectrum revealed four singlets at δ 2.10, 3.19, 4.06 and 7.89 ppm attributed to two CH₃, CH₃, CH₂-CO and quinoline-C₃-H protons; respectively.

Moreover, the target compound 24 was prepared by refluxing a mixture of compound 1, 1-(4-(chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one 23 and 4-chloroaniline in a mixture of dimethylformamide/ acetic acid (1:4). IR spectrum of compound 24 lacked absorption band characteristic to cyano group of its precursor and displayed absorption band at 3383 cm⁻¹ corresponding to NH function where ¹H-NMR spectrum showed a singlet at δ 7.05 ppm attributed to pyidine-C₅ proton and a deuterium oxide exchangeable singlet at δ 12.13 ppm assigned for NH proton.

In addition, a one-pot four-component reaction of compound 1, tetralone, dimethyl acetylenedicarboxylate and hydrazine hydrate in refluxing ethanol containing triethylamine as a base produced the corresponding spiro compound 25. It is worth mentioning that, stirring at room temperature as the reported procedure 41 did not allow the reaction to proceed even after 48 hours of stirring.

The reaction mechanism is postulated to proceed through Knoevenagel condensation of activated nitrile 1 and tetralone followed by reaction of dimethyl acetylenedicarboxylate with hydrazine hydrate to give the pyrazole carboxylate derivative. Then pyrazole
The carboxylate intermediate underwent Michael addition followed by enolization affording the target compound 25. IR spectrum of compound 25 showed broad absorption bands at 3394, 3367, 3275 and 3194 cm\(^{-1}\) corresponding to OH and NH functions, in addition to absorption band at 1720 cm\(^{-1}\) attributed to ester carbonyl functionality (Scheme 4).

It is worth mentioning that, thiazol-2-y lacetonitriles 27a,b were refluxed with 2-aminothiophenol in ethanol in order to afford the cyclized benzo thiazole analogues, however the noncyclized ethanamidothioiioate derivatives 28a,b were obtained. Furthermore, cyanothioamide derivatives 29a,b were synthesized via refluxing thiazol-2-y lacetonitrile derivatives 27a,b with phenyl isothiocyanate in sodium ethoxide solution. The cyclocondensation of thiocarbamoyl derivatives 29a with 4-chlorophenacyl bromide yielded the corresponding thiazole-ylidene derivative 30. Moreover, refluxing of compound 27a with dimethylformamide dimethyle thiole in xylene containing a catalytic amount of piperidine provided the corresponding dimethylamino acrylonitrile derivative 31 that upon treatment with hydroxylamine hydrochloride in sodium ethoxide solution afforded both the open chain hydroxyl aminoacrylonitrile derivative 32 and the cyclic amino isoxazole derivative 33. It is to be noted that, cyclocondensation of 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile 27b with 5-bromosaclylaldehyde in ethanol in the presence of a catalytic amount of glacial acetic acid provided the corresponding chromen-2-imine derivative 34.

The structures of the target compounds were confirmed by spectral and elemental analyses. IR spectra of compounds 28a,b , 29, 32 and 34 revealed absorption bands at 3388-3113 cm\(^{-1}\) corresponding to NH group whereas IR spectra of compounds 28a,b and 33 displayed absorption bands at 3387-3113 cm\(^{-1}\) corresponding to NH\(_2\) functionality. Additionally, there is broad absorption band at 3379 cm\(^{-1}\) assigned for OH group in compound 32. \(^1\)H NMR spectra of compounds 28a, 29 and 34 showed deuterium oxide exchangeable singlets at \(\delta\) 9.17-12.22 ppm attributed to NH protons. Also, \(^1\)H NMR spectra of compounds 28a and 33 revealed deuterium oxide exchangeable singlets at \(\delta\) 3.99-5.41 ppm due to NH\(_2\) protons (Scheme 5).

It is worth mentioning that, heating thiazol-2-y lacetonitrile derivatives 27a,b with thioacetamide in dimethylformamide in an oil bath at 90-100°C accompanied with addition of 0.5 mL of concentrated hydrochloric acid formed the corresponding thioamide derivatives 35a,b. The thioamide derivative 35a was treated with ethyl bromoacetate to give the S-alkylated ethyl thioacetate derivative 36 and the corresponding thiazole derivative 37. Similarly, the thioamide derivative 35b was reacted with 4-chlorophenacyl bromide to yield also the open chain ethanamidothioiioate derivative 38 as well as the cyclic thiazole derivative 39.

The structures of the target compounds were confirmed by spectral and elemental analyses. IR spectra of compounds 35a,b lacked absorption band characteristic for cyano functions of their precursors and displayed absorption bands at 3394-3190 cm\(^{-1}\) corresponding to NH\(_2\) group in addition to, another absorption bands at 1269-1265 cm\(^{-1}\) attributed to C=S functions. \(^1\)H NMR spectrum of compound 35b revealed a deuterium oxide exchangeable singlet at \(\delta\) 9.54 ppm corresponding to NH\(_2\) protons.

Besides, IR spectrum of compound 36 showed absorption bands at 3390 and 1728 cm\(^{-1}\) corresponding to NH\(_2\) and ester carbonyl functions; respectively. While, IR spectrum of compound 37 revealed broad absorption band at 3429 and 3417 cm\(^{-1}\) due to tautomeric OH group, in addition to absorption band at 1726 cm\(^{-1}\) attributed to carbonyl functionality. Also, IR spectrum of compound 38 showed absorption bands at 3370 and 1695 cm\(^{-1}\) corresponding to NH\(_2\) and carbonyl groups; respectively. As well as IR spectrum of compound 39 lacked absorption band due to amino function of its precursor.

\(^1\)H NMR spectrum of compound 38 revealed three singlets, two of them integrated for half proton at \(\delta\) 4.76 and 7.36 ppm corresponding to CH\(_3\)=C=NH and CH\(_2\)=C=NH tautomers and the other singlet integrated for one proton at \(\delta\) 5.62 ppm attributed to CH\(_2\)CO proton. In addition to, three deuterium oxide exchangeable singlets at \(\delta\) 5.47 ppm integrated for half proton corresponding to OH tautomer and at \(\delta\) 6.62 and 9.47 ppm both integrated for one proton attributed to NH\(_2\) and imino NH tautomer protons, respectively.

Finally, refluxing 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile 27b with ethyl 2-chloro-3-oxobutanoate in ethanol containing ammonium acetate as a base yielded the corresponding pyrrolothiazole derivatives 40. IR spectrum of compound 40 showed absorption band at 1724 cm\(^{-1}\) due to ester carbonyl function. \(^1\)H NMR spectrum revealed two multiplets at \(\delta\) 1.00-1.20 and 4.20-4.60 ppm attributed to methyl and methylene protons of ester ethyl moiety; respectively, in addition to a singlet at \(\delta\) 3.34 ppm assigned for CH\(_3\) protons (Scheme 6).

**Part 2-Biological results**

**Anticancer screening**

Developmental Therapeutic Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, Maryland, USA has adopted an in-vitro model consisting of 60 human tumor cell lines for primary anticancer screening. Twelve of the newly synthesized compounds were selected by the NCI for screening in a two stage process, beginning with evaluation of all compounds against 60 human tumor cell lines in a one dose (10 \(\mu\)mol) screening
Panel. The output from the single 60 cell panel screen is reported as a mean graph and is available for analysis by the COMPARE program. The one dose screening results of the selected compounds are presented in tables 1-2.

Discussion of the anticancer results of selected compounds of schemes 1-6 (Tables 1 and 2):

Twelve compounds 4, 6, 10, 12, 13, 16, 18, 20, 21, 25, 28b and 40 were selected by NCI for evaluation. As revealed from one dose screen results presented in tables 1 and 2 and in a trial to shed more light on the SAR of compounds bearing benzothiazole, it is evident that, the fusion of pyridine ring to the benzothiazole nucleus as in compounds 4 and 6 diminished the anticancer activity against all of the cell lines except moderate growth inhibition activity towards Melanoma UACC-62 by 30.93% in compound 6.

Furthermore, the introduction of different substituted rings at active methylene in C2 of benzothiazole backbone resulted in variable activities in which compound 10 possessing tetrazole ring exhibited moderate activity against CNS Cancer SNB-75 cell line by 23.80%, Ovarian Cancer IGROV1 cell line by 32.46% and Breast Cancer MCF7 cell line by 23.78%.

While, compound 12 bearing triazole ring exerted reasonable activity against Melanoma UACC-62 cell line by 24.96%. Furthermore, introduction of hydroxyacetimidamide moiety to the benzothiazole skeleton as in compound 13 resulted in increasing growth inhibition activity against most of cell lines. Compound 13 showed promising growth inhibition activity against Leukemia CCRF-CEM, MOLT-4, RPMI-8226 and SR cell lines by 79.87%, 68.11%, 35.95% and 32.75%; respectively.

It also showed inhibitory activity against Non-Small Cell Lung Cancer NCI-H522 (76.93%), Melanoma UACC-62 (32.44%) and Ovarian Cancer IGROV1 (33.26%) and OVCA-R-8 (31.15%) cell lines. Furthermore, it exerted potent anticancer activity towards Prostate Cancer PC-3 (43.44%) and Breast Cancer MCF7 (41.65%) and T-47D cell lines (63.23%).

It is to be noted that, compound 16 having triazine ring attached to benzothiazole nucleus via a methylene bridge, exhibited moderate anticancer activity against Non-Small Cell Lung Cancer EKVX cell line by 32.95% and Renal Cancer UO-31 cell line by 25.90 %. While, compound 18 bearing quinazolinone ring exerted powerful growth inhibition activity against most of the cell lines including Leukemia CCRF-CEM, K-562 and MOLT-4 cell lines by 43.81%, 76.81% and 41.01%; respectively.

Also, it exerted potent anticancer activity against Non-Small Cell Lung Cancer A549/ATCC (39.03%), HOP-62 (62.41%), NCI-H460 (46.69) and NCI-H522 cell lines (41.30%). In addition, it showed remarkable activity against Colon Cancer HCT-116, HT29 and KM12 cell lines by 49.36%, 56.27% and 58.56%; respectively.

Furthermore, compound 18 exhibited good anticancer activity against CNS Cancer SF-268 (39.00%) and Melanoma LOX IMVI (72.16%), M14 (64.75%), MDA-MB-435 (54.36%), SK-MEL-2 (42.52%), SK-MEL-28 (44.90%) and UACC-62 (97.19%), in addition to Ovarian Cancer OVCA-R-5 (33.50%).

It is worth mentioning that, compound 18 showed activity against Renal Cancer ACHN, CAKI-1 and UO-31 cell lines by 64.08%, 41.30% and 62.74%; respectively together with Prostate Cancer PC-3 (39.08%) as well as Breast Cancer MDA-MB-231/ATCC (34.42%) and T47D (45.79%) cell lines.

Moreover, the introduction of thienopyrimidine ring to active methylene attached to C-2 of benzothiazole skeleton as in compound 20 exhibited mild anticancer activity against Ovarian Cancer IGROV1 by 25.92%. While, introduction of perimidine nucleus to the same backbone as in compound 21 exerted good inhibitory activity against Non-Small Cell Lung Cancer NCI-H522, Ovarian Cancer IGROV1, Renal Cancer UO-31 and Breast Cancer MDA-MB-231/ATCC cell lines by 24.04%, 29.61%, 30.50% and 26.44%; respectively.

However, attachment of tetrahydronaphthyl and pyrazole ring to the active methylene in benzothiazole acetonitrile backbone as in compound 25 showed mild growth inhibitory activity against Non-Small Cell Lung Cancer HOP-92 (27.12%) and Renal Cancer UO-31 cell lines (27.58%).

On the other hand, in a trial to investigate the anticancer activity of thiazol-2-ylacetonitrile pharmaphore bearing ethanimidothioate side chain as in compound 28b, it was observed that, compound 28b exhibited reasonable growth inhibition activity against Non-Small Cell Lung Cancer HOP-92 by 26.31%, Ovarian Cancer IGROV1 by 25.27%, Renal Cancer UO-31 by 35.87% and Prostate Cancer PC-3 cell lines by 40.70%. In addition to, its activity against Breast Cancer cell lines MDA-MB-231/ATCC (27.52%) and T-47D (26.00%).

It is worth mentioning that, fusion of pyrrole ring to the thiazole nucleus as in compound 40 resulted in a marked decrease in the anticancer activity against all of the cell lines.

CONCLUSION

It could be concluded that the tested compound 18 exhibited good anticancer activity and introduction of pyrimidine nucleus to the benzothiazole skeleton in compound 21 exerted good inhibitory activity against Non-Small Cell Lung Cancer. It is worth mentioning that, fusion of pyrrole ring to the thiazole nucleus as in compound 40 resulted in a marked decrease in the anticancer activity against all of the cell lines.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES


