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THE ANTI-PROLIFERATIVE ACTIVITIES AND MORPHOLOGICAL STUDIES OF 5,6-DIHYDROBENZO[*d*]THIAZOLE DERIVATIVES SYNTHESIZED FROM CYCLOHEXAN-1,3-DIONE

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ABSTRACT. This study focused on the synthesis of various benzo[*d*]thiazole derivatives with different substituents, exploring their potential as anticancer agents. The key starting material was 2-amino-5,6-dihydrobenzo[d]thiazol-7(4*H*)-one (**4**), which was synthesized through the reaction of 2-bromocyclohexane-1,3-diketone with thiourea. Compound **4** was then used to create azine and azole derivatives based on the benzo[*d*]thiazole core structure. The cytotoxicity of all the synthesized compounds was evaluated against several cancer cell lines, with many demonstrating notable inhibitory activity. The compounds were tested for anti-proliferative effects on six different cancer cell lines, and the results indicated that both the heterocyclic structure and the nature of the substituent groups had a significant impact on their inhibitory potential.

KEY WORDS: Benzo[*d*]thiazole, Fused derivatives, Multi-component reactions, Cytotoxicity, Morphology

INTRODUCTION

In recent years, thiazole derivatives have been widely studied in medicinal chemistry due to their diverse therapeutic applications. They are used in the treatment of pain, allergies, HIV, infections, schizophrenia, hypertension, and inflammation. More recently, they have also been recognized as fibrinogen receptor antagonists with anti-thrombotic properties and as new inhibitors of bacterial DNA gyrase B [1-10]. Thiazole derivatives play an important role in drug discovery and development [11-15]. Furthermore, numerous heterocyclic compounds containing a thiazole moiety have been synthesized in recent years [16-18], many of which have demonstrated pharmacological activities, including anti-inflammatory, anti-hypertensive, anti-bacterial, and anti-HIV properties. Some aminothiazoles are also known to act as ligands for estrogen receptors [19] and as a novel class of adenosine receptor antagonists [20]. In addition, organic compounds with a thiazole nucleus have been found to exhibit high second-order hyperpolarizability [21-24]. Figure 1 shows examples of drugs containing the thiazole moiety in their structure.

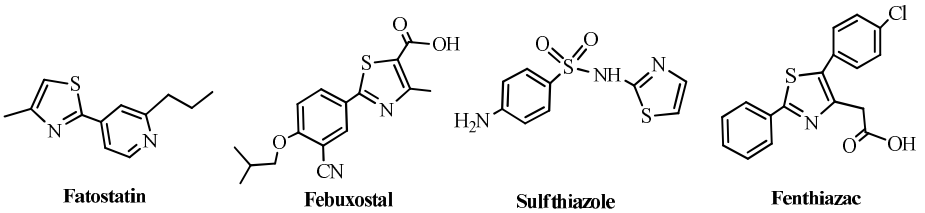

Figure 1. Examples of drugs with thiazole moiety in their molecular structure.

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Several methods have been developed for synthesizing thiazoles and their derivatives due to their biological significance [25, 26]. However, many of these approaches face drawbacks, such as harsh reaction conditions and excessive solvent use. The adoption of solvent-free microwave-assisted synthesis has gained attention because of its simplicity, greater selectivity, and shorter reaction times. Moreover, this method minimizes the use of harmful solvents and facilitates the synthesis of various heterocyclic compounds. A recent focus in thiazole synthesis has been the use of readily available and simple reagents [27-30]. In line with this, the current study focuses on synthesizing new heterocyclic compounds containing thiazole moieties through straightforward synthetic methods. The primary goal is to investigate the anti-cancer activity of these novel compounds against a range of cancer cell lines. The synthetic strategy involves reacting 2-bromocyclohexane-1,3-dione with thiourea to produce a dihydrothiazole derivative, which then undergoes several heterocyclization reactions to form thiazole-based compounds.

RESULTS AND DISCUSSION

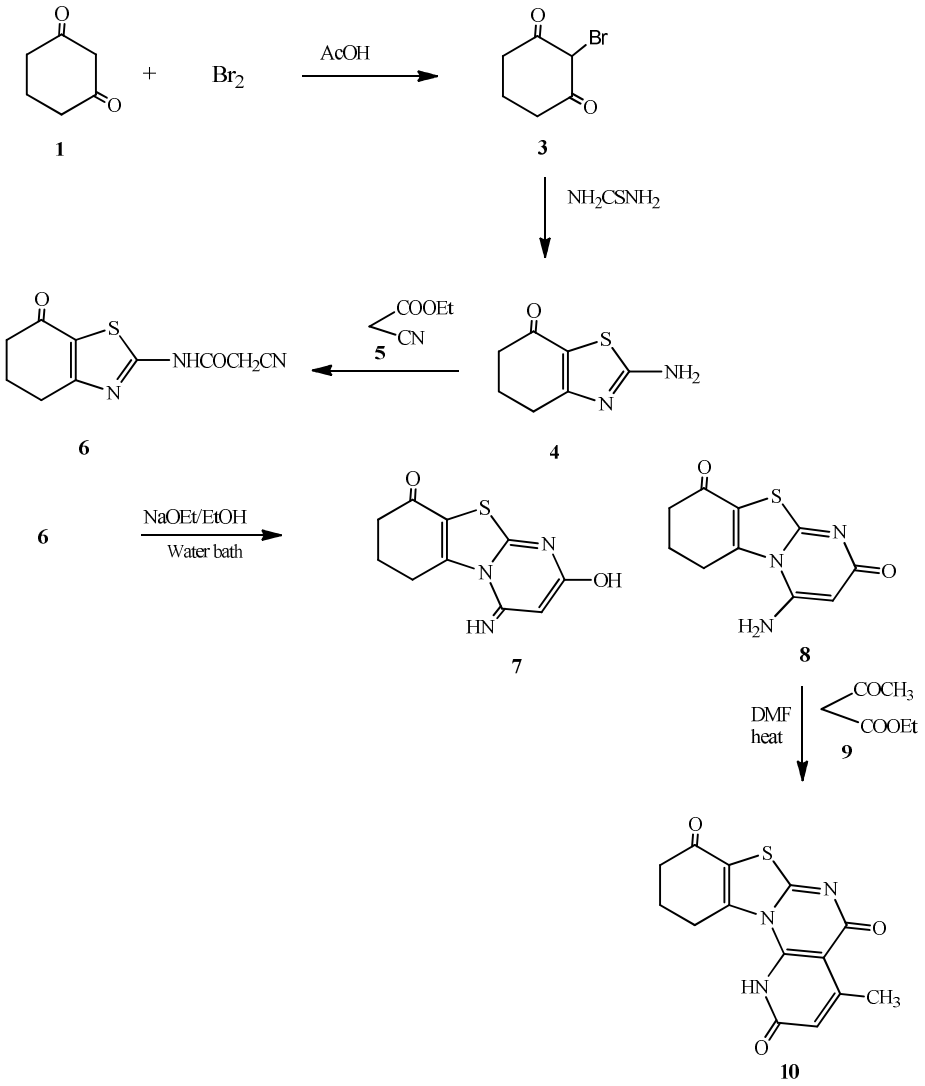
The synthesis and reaction sequences are illustrated in Schemes 1-3. This study focuses on the synthesis of 2-amino-5,6-dihydrobenzo[d]thiazol-7(4*H*)-one, which was produced by reacting 2-bromocyclohexane-1,3-dione with thiourea (NH_2CSNH_2) in absolute ethanol (EtOH) under the reflux conditions. Further heterocyclization of the product was explored to synthesize various heterocyclic compounds based on the dihydrobenzo[*d*]thiazole framework. The synthesized compounds were modified with different substituents on aryl and heterocyclic moieties to study their structure-activity relationships (SAR) through anti-proliferative evaluations.

The reaction of 2-bromocyclohexane-1,3-dione with thiourea in ethanol under reflux conditions yielded the thiazole derivative (compound **4**), whose structure was confirmed by analytical and spectral data (as outlined in the Experimental Section). Compound **4** reacted with ethyl 2-cyanoacetate in dimethylformamide (DMF) under reflux to produce the tetrahydro-benzo[*d*]thiazol-2-yl)acetamido derivative (compound **6**). Compound **6** underwent cyclization when heated in a sodium ethoxide (NaOEt) solution in a boiling water bath, yielding a single product with the molecular formula $C_{10}H_9N_3O_2S$. Two structures were proposed: either 3-iminopyridazine (compound **7**) or 3-aminopyridazine (compound **8**). Based on ^{1}H-NMR and ^{13}C-NMR data, structure **8** was determined to be the correct product.

The ^{1}H-NMR spectrum of compound **8** showed two multiplets beside the expected peaks, a singlet at δ 5.24 ppm for the amino group, and a singlet at δ 6.12 ppm for the pyrimidine proton. The ^{13}C-NMR spectrum displayed beside expected signals, a signal at δ 116.9 ppm for the cyano group, and four signals at δ 129.3, 132.4, 134.8, and 137.9 ppm corresponding to pyrimidine C-4, C-5, and thiazole C-4, C-5. Additionally, signals at δ 167.8, 169.4, and 171.6 ppm were observed, representing two carbonyl groups and one C=N group.

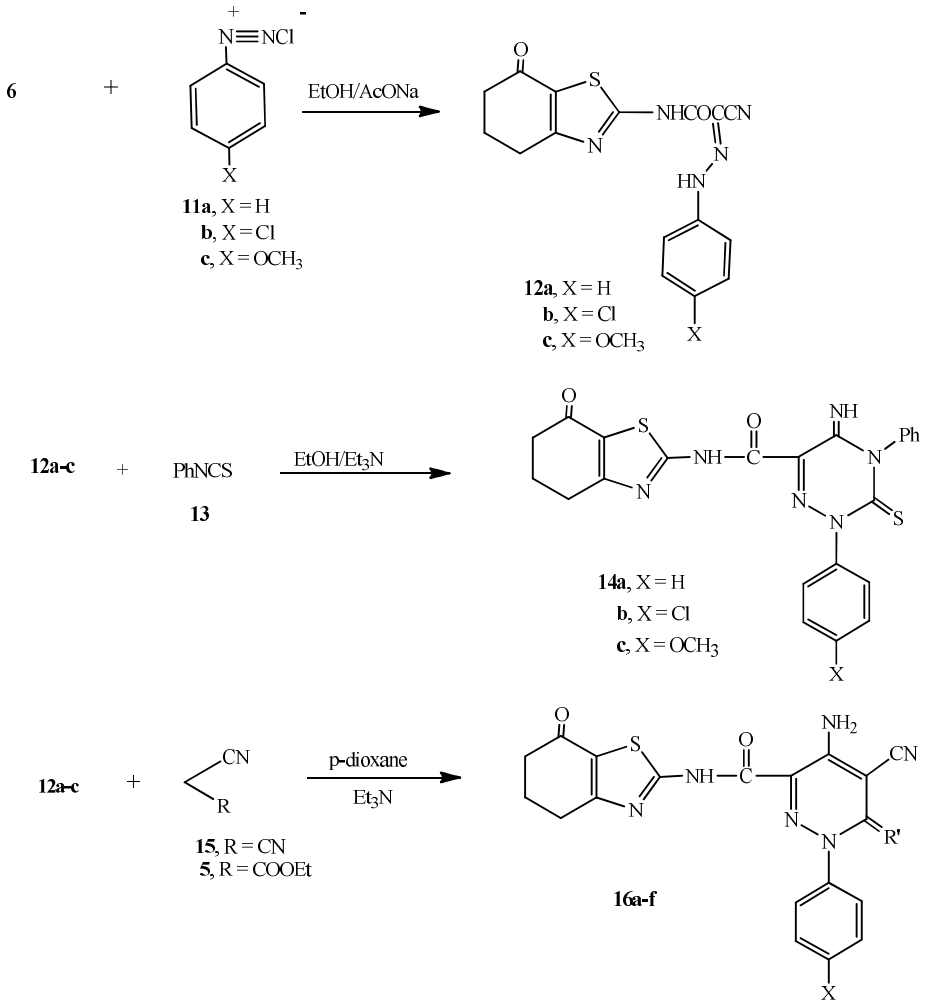
Finally, the reaction of compound **8** with ethyl 2-acetoacetate led to the formation of the benzo[4,5]thiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidine derivative (compound **9**), as confirmed by analytical and spectral data (see Experimental Section). The formation of compound **9** is explained by the initial loss of ethanol followed by the elimination of a water molecule.

Furthermore, the reaction of compound **6** with benzenediazonium chloride (**11a**), 4-chlorobenzenediazonium chloride (**11b**), or 4-methoxybenzenediazonium chloride (**11c**) in an ethanol solution containing sodium acetate (NaOAc) at temperatures between 0-5 °C resulted in the formation of arylhydrazone derivatives **12a-c**. These derivatives were subsequently used to synthesize biologically active 1,2,4-triazine and pyridazine derivatives. Specifically, compounds **12a-c** reacted with phenyl isothiocyanate (PhNCS) to produce the corresponding 1,2,4-triazine derivatives **14a-c**. Additionally, either **12a-c** reacted with dicyanomethane (**15**) or ethyl 2-cyanoacetate (**5**) to yield pyridazine derivatives **16a-f** (Scheme 2). The analytical and spectral data for compounds **14a-c** and **16a-f** provided crucial information for their structural elucidation (details are included in the Experimental Section).



Scheme 1. Synthesis of compounds **3**, **4**, **8** and **10**.

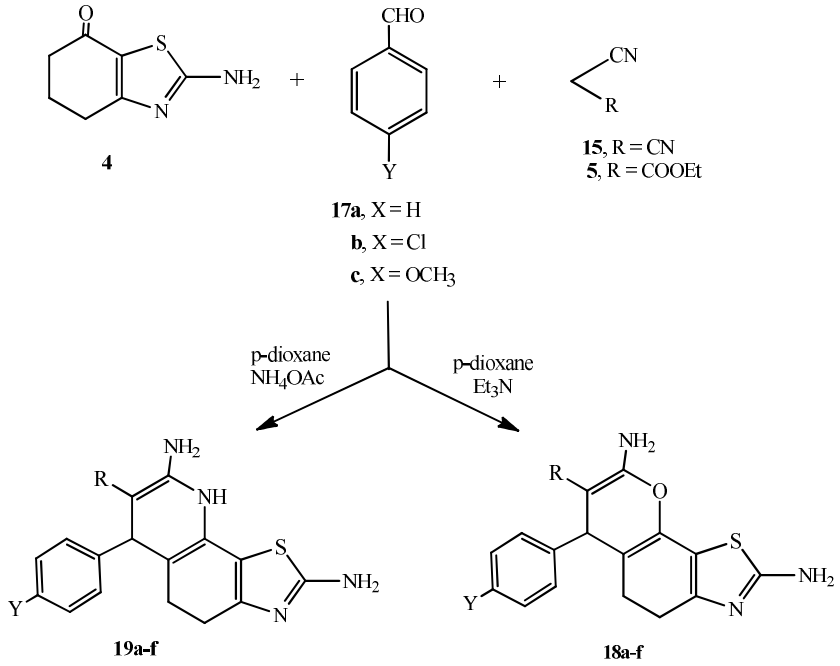
Multi-component reactions are crucial for producing fused pyran and pyridine derivatives, characterized by a hydrogen atom at the C-4 position. These reactions enable simple reagents to combine in a one-pot process, requiring minimal solvent and reducing reaction times [31-34]. As a result, these reactions yield high product quantities and exhibit significant biological and medicinal properties. Compound **4** is well-suited for such reactions. Specifically, the multi-component reactions of compound **4** with phenylmethanal (**17a**), 4-chlorophenylmethanal (**17b**), or 4-methoxyphenylmethanal (**17c**), in combination with either dicyanomethane (**15a**) or ethyl 2-cyanoacetate (**15b**) in a *p*-dioxane solution containing triethylamine (Et_3N) under reflux conditions produced the chromeno[7,8-d]thiazole derivatives **18a-f**.



16	a	b	c	d	e	f
X	H	H	Cl	Cl	OCH_3	OCH_3
R'	NH	O	NH	O	NH	O

Scheme 2. Synthesis of compounds **12a-c**; **14a-c** and **16a-f**.

In contrast, the multi-component reactions of compound **4** with the same aldehydes (**17a-c**) and either dicyanomethane (**15a**) or ethyl 2-cyanoacetate (**15b**) in a p-dioxane solution containing ammonium acetate (NH_4OAc) yielded thiazolo[4,5-h]quinoline derivatives **19a-f** (Scheme 3). The compounds synthesized in this work were obtained in high yields and were subjected to various biological screening assays.



18 &19	a	b	c	d	e	f
Y	H	H	Cl	Cl	OCH_3	OCH_3
R	CN	COOEt	CN	COOEt	CN	COOEt

Scheme 3. Synthesis of compounds **18a-f** and **19a-f**.

Cell proliferation assay

The anti-proliferative activity of the synthesized compounds was assessed by measuring the mean IC_{50} values from three independent experiments, with the results presented in Table 1. Most of the synthesized compounds demonstrated significant anti-proliferative effects, exhibiting IC_{50} values of less than 1.0 μM. It was evident that the substituents on the aryl moiety and the nature of the heterocyclic ring were key factors influencing inhibition against cancer cell lines during the screening process. Foretinib served as the positive control, and the standard MTT assay was employed for the in vitro evaluations [35-37]. The cancer cell lines used in this study included A549, HT-29, MKN-45, U87MG, SMMC-7721, and H460, with the corresponding data shown in Table 1.

Structure activity relationship

Table 1 illustrates that most of the synthesized compounds exhibited strong inhibitory effects against the cancer cell lines tested. The most cytotoxic compounds were identified as **3**, **4**, **8**, **10**, **12b**, **14b**, **16c**, **16d**, **18c**, **18d**, **19a**, and **19d**, all showing inhibitions of less than 0.50 μM. Additionally, compounds **12a**, **16b**, **18a**, **18b**, and **19b** demonstrated inhibitions ranging from 0.50 μM to 3.5 μM.

Table 1. IC_{50}'s of the newly synthesized compounds on six selected cancer cell lines.

Compound No.	IC_{50} ± SEM (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
3	0.39 ± 0.17	0.34 ± 0.19	0.29 ±0.22	0.41± 0.25	0.31 ± 0.14	0.42 ± 0.25
4	0.59 ±0.36	0.37±0.21	0.49±0.22	0.51±0.28	0.47±0.22	0.39± 0.21
8	0.23±0.15	0.25±0.13	0.23±0.16	0.37±0.20	0.42±0.25	0.26±0.15
10	0.25± 0.16	0.36± 0.14	0.19±0.09	0.42± 0.19	0.32± 1.23	0.42± 0.20
12a	2.42± 1.51	2.42± 1.48	1.93± 1.12	2.31±1.12	2.42± 1.31	2.26±1.23
12b	0.20± 0.11	0.24± 0.12	0.30± 0.17	0.21± 0.15	0.32± 0.16	0.25± 0.13
12c	8.36± 2.08	8.29± 2.07	7.35± 2.16	6.38± 3.19	7.48± 1.24	6.26±1.93
14a	4.21± 1.31	3.51± 1.43	5.66± 1.92	6.21± 1.57	5.29± 1.82	3.80±1.63
14b	0.21± 0.17	0.22± 0.19	0.32±0.21	0.22± 0.15	0.26± 0.18	0.31± 0.22
14c	8.42± 2.29	8.39± 2.25	7.52± 1.59	6.61± 1.83	5.58± 1.34	6.36± 2.16
16a	0.85 ± 0.28	0.66 ± 0.63	0.92± 0.28	0.79 ± 0.35	0.88± 0.31	0.68± 0.42
16b	0.49± 0.22	0.85± 0.48	0.63± 0.73	0.82 ± 0.47	0.59 ± 0.31	0.48± 0.28
16c	0.21± 0.12	0.22 ± 0.13	0.25± 0.08	0.21± 0.14	0.25± 0.13	0.19± 0.08
16d	0.18± 0.08	0.19 ± 0.13	0.22 ± 0.19	0.28 ± 0.19	0.25 ± 0.14	0.26± 0.17
16e	8.38± 2.53	7.15 ± 2.16	6.49 ± 1.83	7.25 ± 2.39	6.29 ± 1.82	7.28 ± 2.42
16f	6.52 ± 1.47	5.22 ± 1.24	7.40 ± 1.52	8.22 ± 2.39	6.41 ± 1.04	5.93 ± 2.31
18a	1.83± 0.64	2.37 ± 1.12	2.63 ± 0.83	1.52 ± 0.97	1.49 ± 0.84	1.60 ± 0.78
18b	2.26± 1.25	2.83± 1.07	2.28 ± 1.57	2.26± 1.05	2.81± 1.24	2.53 ± 1.70
18c	0.23± 0.16	0.21± 0.14	0.38± 0.12	0.35 ± 0.19	0.34 ± 0.17	0.27± 0.14
18d	0.15± 0.04	0.27 ± 0.11	0.23 ± 0.12	0.38 ± 0.12	0.32± 0.20	0.26± 0.17
18e	5.60 ± 1.94	6.24 ± 1.87	4.38 ± 1.93	5.42 ± 1.53	6.58 ± 1.62	6.42 ± 2.16
18f	6.38 ± 1.62	7.37± 1.25	5.32 ± 1.13	6.82± 1.27	5.43 ± 2.36	6.38 ± 2.25
19a	4.31± 2.83	5.20± 1.68	4.82 ± 1.62	5.43 ± 1.56	3.82± 1.52	3.71 ± 1.81
19b	3.38 ± 1.14	4.26± 1.49	3.38 ± 1.64	3.52 ± 1.26	2.16± 0.94	4.21± 1.23
19c	0.17 ± 0.03	0.26 ± 0.16	0.27± 0.19	0.27 ± 0.19	0.23± 0.11	0.38± 0.23
19d	0.33 ± 0.16	0.25± 0.18	0.33± 0.18	0.29± 0.15	0.32± 0.17	0.35± 0.23
19e	8.16 ± 2.14	6.29 ± 1.18	7.42 ± 1.47	6.29 ± 2.12	5.38 ± 1.26	3.58± 1.29
19f	8.31 ± 2.29	8.30± 2.13	7.18 ± 1.82	8.52 ± 1.31	7.49 ± 2.81	8.36 ± 2.43
Foretinib	0.08± 0.01	0.18± 0.03	0.15±0.023	0.03±0.0055	0.90 ±0.13	0.44± 0.062

Focusing on the bromo derivative **3**, it showed significant inhibition across all six cancer cell lines, which can be attributed to the presence of the strongly electron-withdrawing bromine (Br) group. When comparing the cytotoxicities of the dihydrobenzo[*d*]thiazole derivative **4** and the benzo[4,5]thiazolo[3,2-*a*]pyrimidine derivative **8**, it is evident that compound **8** exhibited slightly higher inhibitory effects against all tested cancer cell lines. This enhanced activity is likely due to its higher nitrogen content and the additional fused heterocycles. A similar trend was observed with compound **10**, where increased heterocyclization and a higher content of oxygen and nitrogen contributed to its potent inhibitory activity.

Regarding the arylhydrazone derivatives **12a-c** and the 1,2,4-triazine derivatives **14a-c**, compounds **12a** and **14a** (with X = H) displayed moderate inhibition with values less than 2.50 μM. In contrast, compounds **12b** and **14b** (with X = Cl) exhibited the highest levels of inhibition among the six compounds, attributed to the presence of the electronegative chlorine group in their structures. On the other hand, compounds **12c** and **14c** (with X = OCH_3) showed lower inhibitory effects, with IC_{50} values exceeding 6.0 μM.

For the pyridazine derivatives 16a-f, compounds **16a** (X = H, R' = NH), **16b** (X = H, R' = O), **16c** (X = Cl, R' = NH), and **16d** (X = Cl, R' = O) displayed the strongest inhibition among the group. Notably, compounds **16c** and **16d** exhibited the highest inhibitory effects, again due to the presence of the electronegative chlorine group.

Lastly, when examining the chromeno[7,8-d]thiazole derivatives **18a-f** and the

tetrahydrothiazolo[4,5-*h*]quinolines **19a-f**, it is clear from Table 1 that compounds **18c**, **19c** (X = Cl, R' = CN), and **18d**, **19d** (X = Cl, R' = COOEt) showed the most substantial inhibition among these twelve compounds. Conversely, compound **18a** (X = H, R' = CN) exhibited moderate inhibition, with values below 1.50 µM. It is important to note that, in general, compounds **18a-f** demonstrated greater inhibitory effects than compounds **19a-f**, likely due to the presence of the pyran moiety in the structures of **18a-f**.

HTRF kinase assay

In this assay, the experimental procedures and reagents employed were consistent with those outlined in prior studies [38, 39]. Furthermore, the association between c-Met tyrosine kinase and prostate cancer cells has been corroborated by findings from previous research [40-46].

The data presented in Table 2 indicate that the use of different substituents significantly impacts the IC_{50} values.

Table 2. c-Met enzymatic activity and PC-3 inhibition of the newly synthesized compounds.

Compound No.	IC_{50} (nM) c-Met	IC_{50} (µM)) PC-3	VERO[a] (µM)	SI PC-3[b]
3	0.29±0.10	0.21±0.16	60.31±5.26	>100
4	0.39± 0.18	0.41±0.29	58.26±5.82	>100
8	0.32± 0.16	0.24 ± 0.13	56.82±6.59	>100
10	0.28±0.15	0.22±0.18	56.68±3.72	>100
12a	2.30±1.62	1.21±0.82	38.52±4.93	6.89
12b	0.24± 0.06	0.18± 0.07	55.81 ±5.49	>100
12c	4.32±1.85	5.26±2.31	36.27± 6.16	6.89
14a	2.37 ± 1.14	2.81 ± 1.19	32.42 ±6.50	11.54
14b	0.25± 0.12	0.36± 0.25	60.31±6.52	>100
14c	6.31±2.14	7.39±2.58	42.17±3.71	5.71
16a	1.60 ± 1.01	0.92±0.64	32.53±5.20	35.35
16b	0.22±0.16	0.28 ±0.17	59.62±4.58	>100
16c	0.28±0.08	0.33±0.11	55.63 ±5.82	>100
16d	0.35±2.41	0.29 ±0.13	68.27±6.80	>100
16e	4.36± 1.83	6.28± 1.56	38.92 ±5.36	6.20
16f	3.28±1.28	4.28±1.63	35.64±4.27	8.33
18a	3.21 ±1.28	3.72± 1.63	32.93±5.67	10.05
18b	2.61±1.32	4.62±1.57	26.81 ±4.21	5.80
18c	0.32± 0.13	0.25 ± 0.16	59.78±5.53	> 100
18d	0.27 ±0.16	0.35±0.20	60.83±4.23	> 100
18e	7.25± 1.38	6.57± 1.59	58.18±5.42	8.85
18f	3.38±1.41	6.41±1.52	38.42±2.51	5.99
19a	4.28±1.27	5.29±1.41	60.58±5.27	11.45
19b	5.26 ±2.61	4.28±1.84	29.38±4.31	6.86
19c	0.19±0.07	0.24±0.15	62.79±5.82	>100
19d	0.20 ±0.12	0.25 ±0.07	55.17±4.82	>100
19e	8.29 ±2.47	7.95±2.41	30.38±4.53	3.82
19f	6.52 ±1.84	7.82±2.41	35.82±3.94	4.58
	Foretinib 1.16 ± 0.17	**Anibamine** 3.26 ± 0.35	-	-

[a]VERO, is the Monkey Kidney cell line. [b]SI which is the Selectivity index obtained through dividing the IC_{50} on normal cell line to the IC_{50}'s in PC-3 prostate cancer cell line.

The findings summarized in Table 2 demonstrate significant results for c-Met enzymatic activity, with IC_{50} values ranging from 0.19 to 9.29 nM. In contrast, the inhibition of the prostate cancer cell line PC-3 showed IC_{50} values between 0.18 and 7.82 µM. When compared to Foretinib (IC_{50} = 1.16 nM), compounds **3**, **4**, **8**, **10**, **12b**, **14b**, **16b**, **16c**, **16d**, **18c**, **18d**, **19c**, and **19d** exhibited the highest potency, each demonstrating IC_{50} values below 1.00 nM. Remarkably, the synthesized compounds **3**, **4**, **8**, **10**, **12a**, **12b**, **14a**, **14b**, **16a**, **16b**, **16c**, **16d**, **18c**, **18d**, **19c**, and **19d** displayed superior anti-proliferative activities compared to the standard Anibamine (IC_{50} = 3.26 µM). An analysis of the data in Table 2 reveals that the 4,5,6,9-tetrahydrothiazolo[4,5-*h*]quinoline derivative **19c** exhibited the most significant inhibition against both c-Met kinase and the PC-3 cell line, with IC_{50} values of 0.19 and 0.15 µM, respectively.

In conclusion, all synthesized compounds were tested against the VERO monkey kidney normal cell line, where they exhibited minimal activity. Notably, compounds **14a**, **16a**, **16f**, **18a**, **18e**, and **19a** displayed selectivity indices (SIs) greater than 8.00, while compounds **3**, **4**, **8**, **10**, **12b**, **14b**, **16b**, **16c**, **16d**, **18c**, **18d**, **19a**, **19c**, and **19d** showed SIs exceeding 100. Other compounds had SIs below 20, except for compound **16a**, which exhibited an SI of 35.35.

Determination of morphological changes of A549 cell line

In the present study, we examined the morphological alterations in the A549 lung cancer cell line upon exposure to compounds **18d** and **19d** separately. Numerous reports have addressed similar investigations involving other cell lines [47-50]. Both compounds were tested at various concentrations and exposure durations.

Figure 2 shows the morphological changes observed through phase-contrast microscopy, indicated in the gray area A. The green area B illustrates the effects of compound **18d** on A549 cells at concentrations of 1.25, 2.50, and 5.0 µM, with images acquired using a fluorescent microscope following acridine orange staining. The blue area C highlights the effects of compound **18d** on the same cell line at the indicated concentrations, with nuclear alterations detected through DAPI staining and captured via a fluorescent microscope. The red arrows point to areas where cell shrinkage occurred as a result of compound exposure. The impact of compound **19d** on the A549 cell line is depicted in Figure 3.

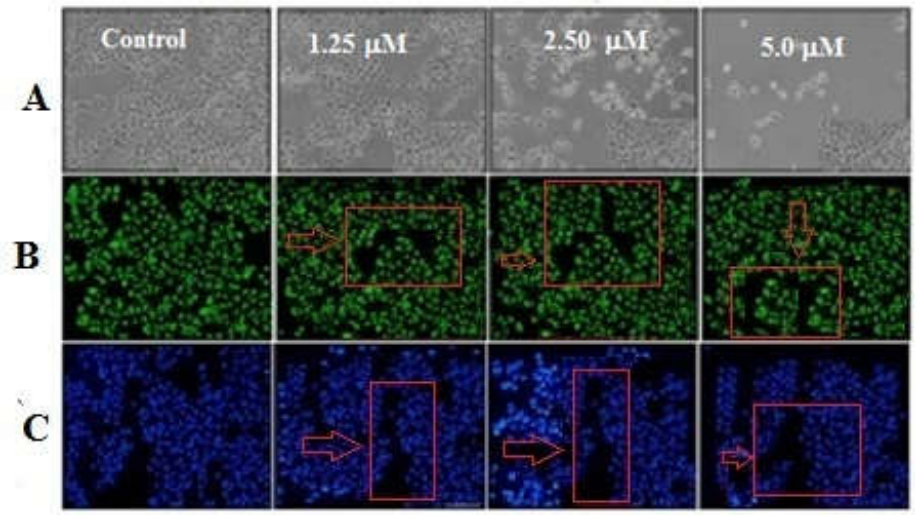


Figure 2. Effect of compound **18d** against A459 cell line.

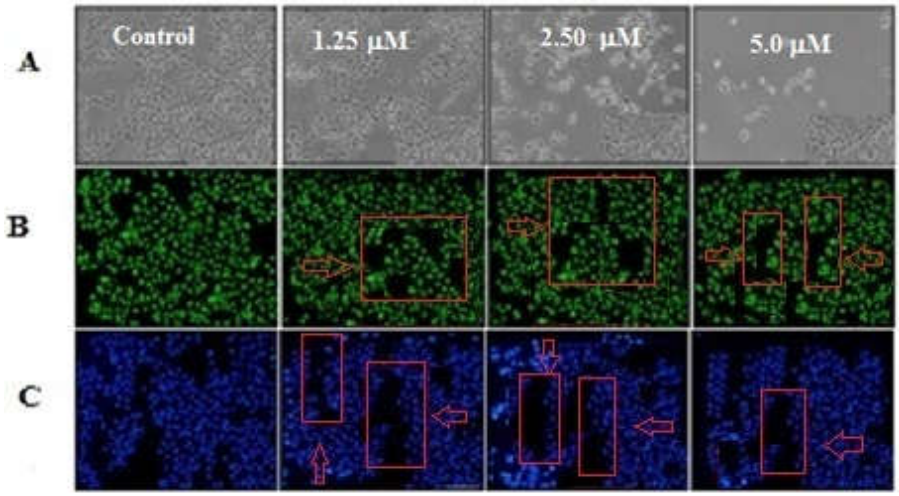


Figure 3. Effect of compound **19c** against A459 cell line.

In summary, the shrinkage of the A549 cell line induced by compound **18d** was found to be more significant compared to the effects of compound **19d**.

EXPERIMENTAL

Chemistry

For the synthesized compounds, the melting points were measured in addition; the IR spectra (KBr discs) were recorded on a FITR plus 460 or Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra were recorded using the Varian Gemini-300 (300 MHZ) (Cairo University) in DMSO-d_6 as solvent using TMS as internal standard and chemical shifts are demonstrated as δ ppm. The molecular weights were determined using the Ex shimadzu instruments for recording m/z values. Elemental analyses CHNS were measured using the Vario El III Elemental CHNS analyzer.

*2-Amino-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**4**)*

Thiourea (0.77 g, 001 mol) was added to a solution of either 2-bromocyclohexan-1,3-dione (1.91 g, 0.01 mol) in absolute ethanol (40 mL). The reaction mixture was heated under the reflux conditions for 1 h and the formed solid product obtained upon leaving the reaction mixture for cooling to room temperature was collected by filtration. Yellow crystals from AcOH, m.p. 186-188 °C, yield: 1.00 g (60%). IR (υ, cm^{-1}): 3468, 3326 (amino), 2896 (methylene), 1689 (carbonyl), 1564 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.48-1.59 (m, 4H, two methylene), 2.36-2.48 (m, 2H, methylene), 5.21(s, 2H, amino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.8, 46.2 (three methylene), 134.2, 137.1 (thiazole two carbons), 168.7 (carbonyl), 172.8 (C=N). Calculated for $C_7H_8N_2OS$ (168.21): C, 49.98; H, 4.79; N, 16.65; S, 19.06%. Found: C, 49.72; H, 4.62; N, 16.80; S, 19.29%. MS: *m/z* = 168 M^+ (59%).

*2-Cyano-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)acetamide (**6**)*

Ethyl 2-cyanoacetate (1.07 g, 0.01 mol) was added to a solution of compound **4** (1.68 g, 0.01 mol) in dimethylformamide (40 mL). The reaction was then proceeded in a similar manner as the synthesis of compound **4** previously described. Yellow crystals from *p*-dioxane, m.p. 194-196 °C, yield: 1.00 g (60%). IR (υ, cm^{-1}): 3488-3342 (imino), 2895 (methylene), 2220 (cyano), 1688, 1889 (two carbonyl), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.45-1.62 (m, 4H, two methylene), 2.39-2.52 (m, 2H, methylene), 5.32(s, 2H, methylene), 8.59 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.4, 39.9, 46.8 (three methylene), 50.1 (methylene), 116.9 (cyano), 134.6, 137.8 (thiazole two carbons), 168.2, 169.0 (two carbonyl), 172.7 (C=N). Calculated for $C_{10}H_9N_3O_2S$ (235.26): C, 51.05; H, 3.86; N, 17.86; S, 13.63%. Found: C, 50.87; H, 3.79; N, 17.96; S, 13.80%. MS: *m/z* = 235 M^+ (68%).

*4-Amino-7,8-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine-2,9(6H)-dione (**8**)*

A suspension of compound **6** (2.53 g, 0.01 mol) in sodium ethoxide solution [prepared by the addition of metallic sodium (0.46 g, 0.02 mol) to absolute ethanol (50 mL) till complete disappearance of sodium]. The reaction was heated under the reflux conditions for 2 h in a boiling water bath then was poured onto ice/water containing a few drops of hydrochloric acid to produce the solid product. Pale yellow crystals from *p*-dioxane, m.p. 225-227 °C, yield: 1.00 g (60%). IR (υ, cm^{-1}): 3474, 3363 (amino), 2895 (methylene), 1687, 1702 (two carbonyl), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.46-1.65 (m, 4H, two methylene), 2.37-2.58 (m, 2H, methylene), 5.24 (s, 2H, amino), 6.12 (s, 1H, pyrimidine carbon). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.7, 46.6 three methylene), 116.9 (cyano), 129.3, 132.4 (pyrimidine two carbons), 134.8, 137.9 (thiazole two carbons), 167.8, 169.4 (two carbonyl), 171.6 (C=N). Calculated for $C_{10}H_9N_3O_2S$ (235.26): C, 51.05; H, 3.86; N, 17.86; S, 13.63%. Found: C, 50.96; H, 3.65; N, 17.69; S, 13.70%. MS: *m/z* = 235 M^+ (40%).

*4-Methyl-10,11-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrido[3,2-e]pyrimidine-2,5,8(1H,9H)-trione (**10**)*

The same reaction conditions previously described for the synthesis of compound **6** was carried out but using the respective reagents. Pale yellow crystals from *p*-dioxane, m.p. 196-196 °C, yield: 1.92 g (64%). IR (υ, cm^{-1}): 3486-3353 (imino), 2895 (methylene), 1688-1703 (three carbonyl), 1563 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.44-1.68 (m, 4H, two methylene), 2.35-2.62 (m, 2H, methylene), 2.80 (s, 3H, methyl), 6.16 (s, 1H, pyridine CH), 8.60 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 26.8 (methyl), 38.5, 39.5, 46.8 (three methylene), 130.5, 134.6, 138.6, 140.3 (pyridine two carbons, pyrimidine one carbon), 134.8, 137.9 (thiazole two carbons), 168.6, 168.8, 169.8 (three carbonyl), 170.8 (C=N). Calculated for $C_{14}H_{11}N_3O_2S$ (301.32): C, 55.81; H, 3.68; N, 13.95; S, 10.64%. Found: C, 55.60; H, 3.48; N, 14.15; S, 10.78%. MS: *m/z* = 301 M^+ (80%).

*General procedure for the synthesis of the arylhydrazone derivatives **12a-c***

The diazonium salts **11a**, **11b** or **11c** (0.01 mol) [prepared by the addition of sodium nitrite solution (0.70 g, 0.01 mol, in 10 mL water) to a cold solution 0-5 °C of either phenylamine (0.93 g, 0.01 mol), 4-chlorophenylamine (1.30 g, 0.01 mol), 4-methoxyphenylamine (1.23 g, 0.01 mol) dissolved in concentrated HCl (8.0 mL, 18 mol) with continuous stirring] was added to a cold solution of **6** (2.35 g, 0.01 mol) in EtOH (50 mL) containing NaOAc (4.0 g) with continuous stirring. The whole reaction mixture was stirred at room temperature for 1 h and the produced solid product solid product was collected by filtration and crystallized from the proper solvent.

*2-Oxo-2-((7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)amino)-N-phenyl-acetohydrazonoyl cyanide (**12a**)*. Orange-red crystals of EtOH, m.p. 158-160 ºC, yield: 1.96 g (58%). IR (υ, cm^{-1}): 3464-3342 (imino), 2893 (methylene), 1689, 1701 (two carbonyl), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.46-1.69 (m, 4H, two methylene), 2.36-2.65 (m, 2H, methylene), 7.28-7.38 (m, 5H, phenyl), 8.56, 8.73 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.4, 39.8, 46.7 (three methylene), 122.3, 122.6, 123.4, 124.8 (phenyl), 134.5, 137.9 (thiazole two carbons), 168.4, 169.5 (two carbonyl), 171.6 (C=N). Calculated for $C_{16}H_{13}N_5O_2S$ (339.37): C, 56.63; H, 3.86; N, 20.64; S, 9.45%. Found: C, 56.75; H, 3.77; N, 20.83; S, 9.62%. MS: *m/z* = 339 M^+ (58%).

*N-(4-Chlorophenyl)-2-oxo-2-((7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)amino)-acetohydrazonoyl cyanide(**12b**)*. Orange crystals of EtOH, m.p. 158-160 ºC, yield: 2.46 g (66%). IR (υ, cm^{-1}): 3480-3335 (imino), 2892 (methylene), 1686, 1703 (two carbonyl), 1568 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.68-1.72 (m, 4H, two methylene), 2.35-2.68 (m, 2H, methylene), 7.26-7.54 (m, 4H, phenyl), 8.53, 8.77 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.5, 46.9 (three methylene), 123.6, 124.2, 125.4, 126.7 (phenyl), 134.7, 137.8 (thiazole two carbons), 168.2, 169.4 (two carbonyl), 171.8 (C=N). Calculated for $C_{16}H_{12}ClN_5O_2S$ (373.81): C, 51.41; H, 3.24; N, 18.74; S, 8.58%. Found: C, 51.29; H, 3.41; N, 18.83; S, 8.73%. MS: *m/z* = 373 M^+ (80%).

*N-(4-Methoxyphenyl)-2-oxo-2-((7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)amino)acetohydrazonoyl cyanide (**12c**)*. Orange crystals of EtOH, m.p. 210-212 ºC, yield: 2.12 g (60%). IR (υ, cm^{-1}): 3494-3355 (imino), 2892 (methylene), 1688, 1701 (two carbonyl), 1563 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.65-1.76 (m, 4H, two methylene), 2.33-2.69 (m, 2H, methylene), 3.68 (s, 3H, methoxy), 7.28-7.58 (m, 4H, phenyl), 8.51, 8.79 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.8, 39.2, 46.9 (three methylene), 50.6 (methoxy), 122.2, 123.8, 125.1, 126.9 (phenyl), 134.4, 137.7 (thiazole two carbons), 168.6, 169.7 (two carbonyl), 171.4 (C=N). Calculated for $C_{17}H_{15}N_5O_3S$ (369.40): C, 55.28; H, 4.09; N, 18.96; S, 8.68%. Found: C, 55.31; H, 3.93; N, 18.81; S, 8.82%. MS: *m/z* = 369 M^+ (77%).

*General procedure for the synthesis of the 1,2,4-triazine derivatives **14a-c***

To a solution of either **12a** (3.73 g, 0.01 mol), **12b** (3.37 g, 0.01 mol) or **12c** (3.69 g, 0.01 mol) in absolute EtOH (50 mL) containing Et_3N (2.0 mL) PhNCS (1.30 g, 0.01 mol) was added. The working up of the reaction was carried in a similar manner like that was previously described used for the synthesis of compound **10**.

*5-Imino-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-2,4-diphenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**14a**)*. Yellow crystals of EtOH, m.p. 173-175 ºC, yield: 2.77 g (62%). Infrared (υ, cm^{-1}): 3459-3331 (imino), 2891 (methylene), 1688, 1703 (two carbonyl), 1560 (vinyl bonding), 1205 (thiocarbonyl). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.48-1.65 (m, 4H, two methyelene), 2.41-2.68 (m, 2H, methylene), 7.25-7.49 (m, 10H, two phenyl), 8.31, 8.78 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.8, 39.4, 46.2 (three methylene), 120.4, 121.6, 122.3, 122.6, 123.4, 123.8, 124.4, 125.3 (two phenyl), 134.3, 137.7 (thiazole two carbons), 168.7, 169.3 (two carbonyl), 171.8, 172.1, 172.5(3 C=N), 180.2 (thiocarbonyl). Calculated for $C_{23}H_{18}N_6O_2S_2$ (474.56): C, 58.21; H, 3.82; N, 17.71; S, 13.51%. Found: C, 58.39; H, 3.69; N, 17.58; S, 13.80%. MS: *m/z* = 474 M^+ (82%).

*2-(4-Chlorophenyl)-5-imino-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**14b**)*. Yellow crystals of *p*-dioxane, m.p. 158-160 ºC, yield: 3.30 g (65%). IR (υ, cm^{-1}): 3483-3341 (imino), 2893 (methylene), 1689, 1702

(two carbonyl), 1562 (vinyl bonding), 1208 (thiocarbonyl). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.45-1.68 (m, 4H, two methylene), 2.46-2.72 (m, 2H, methylene), 7.25-7.49 (m, 9H, two phenyl), 8.33, 8.74 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.5, 46.8 (three methylene), 120.2, 121.8, 122.1, 122.4, 123.2, 124.3, 124.8, 125.6 (two phenyl), 134.6, 137.9 (thiazole two carbons), 168.4, 169.6 (two carbonyl), 171.2, 171.8, 173.4 (3 C=N), 180.6 (thiocarbonyl). Calculated for $C_{23}H_{17}ClN_6O_2S_2$ (509.00): C, 54.27; H, 3.37; N, 16.51; S, 12.60%. Found: C, 54.38; H, 3.46; N, 16.49; S, 12.79%. MS: *m/z* = 509 M^+ (58%).

*5-Imino-2-(4-methoxyphenyl)-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**14c**)*. Yellow crystals of *p*-dioxane, m.p. 203-205 ºC, yield: 2.77 g (55%). IR (υ, cm^{-1}): 3461-3356 (imino), 2893 (methylene), 1689, 1701 (two carbonyl), 1563 (vinyl bonding), 1202 (thiocarbonyl). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.43-1.68 (m, 4H, two methylene), 2.43-2.67 (m, 2H, methylene), 3.67 (s, 3H, methoxy), 7.26-7.58 (m, 9H, two phenyl), 8.35, 8.76 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.5, 39.3, 46.6 (three methylene), 50.7 (methoxy), 120.8, 121.5, 122.3, 122.9, 123.2, 123.5, 124.1, 124.7 (two phenyl), 134.1, 137.4 (thiazole two carbons), 168.8, 169.6 (two carbonyl), 171.4, 171.6, 172.4 (3C=N), 180.6 (thiocarbonyl). Calculated for $C_{24}H_{20}N_6O_3S_2$ (504.58): C, 57.13; H, 4.00; N, 16.66; S, 12.71%. Found: C, 57.26; H, 3.93; N, 16.82; S, 12.93%. MS: *m/z* = 504 M^+ (65%).

*General procedure for the synthesis of the pyridazine derivatives **16a-f***

The same reaction conditions previously described for the synthesis of **14a-c** was carried out but using the respective reagents.

*4-Amino-5-cyano-6-imino-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**16a**)*. Pale yellow crystals of EtOH, m.p. 175-177 ºC, yield: 2.71 g (67%). IR (υ, cm^{-1}): 3479-3327 (imino), 3053 (CH aromatic), 2891 (methylene), 2220 (cyano), 1688, 1702 (two carbonyl), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.47-1.70 (m, 4H, two methylene), 2.36-2.68 (m, 2H, methylene), 5.26 (s, 2H, amino), 7.24-7.43 (m, 5H, phenyl), 8.53, 8.56 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.4, 46.9 (three methylene), 116.9 (cyano), 121.2, 122.8, 124.7, 124.9 (phenyl), 132.5, 134.3, 137.8, 139.6 (pyridazine two carbons), thiazole two carbons), 168.3, 169.8 (two carbonyl), 170.6, 171.2, 174.2 (2C=N). Calculated for $C_{19}H_{15}N_7O_2S$ (405.44): C, 56.29; H, 3.73; N, 24.18; S, 7.91%. Found: C, 56.36; H, 3.83; N, 24.25; S, 8.14%. MS: *m/z* = 405 M^+ (48%).

*4-Amino-5-cyano-6-oxo-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**16b**)*. Yellow crystals from *p*-dioxane, m.p. 194-196 ºC, yield: 2.43 g (60 %). IR (υ, cm^{-1}): 3454-3339 (imino), 3054 (CH aromatic), 2891 (methylene), 2220 (cyano), 1689-1703 (three carbonyl), 1560 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.44-1.73 (m, 4H, two methylene), 2.34-2.69 (m, 2H, methylene), 5.28 (s, 2H, amino), 7.22-7.46 (m, 5H, phenyl), 8.51 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.5, 39.8, 46.7 (three methylene), 116.8 (cyano), 121.6, 122.4, 123.8, 124.5 (phenyl), 132.7, 134.1, 137.4, 139.4 (pyridazine two carbons, thiazole two carbons), 168.1, 169.6, 169.6 (three carbonyl), 170.5, 171.6, (2C=N). Calculated for $C_{19}H_{14}N_6O_3S$ (406.42): C, 56.16; H, 3.47; N, 20.68; S, 7.89%. Found: C, 56.34; H, 3.80; N, 20.74; S, 8.06%. MS: *m/z* = 406 M^+ (64%).

*4-Amino-1-(4-chlorophenyl)-5-cyano-6-imino-N-(7-oxo-4,5,6,7-tetrahydrobenzo-[d]thiazol-2-yl)-1,6-dihydropyridazine-3-carboxamide (**16c**)*. Pale yellow crystals from *p*-dioxane, m.p. 215-217 ºC, yield: 2.19 g (50%). IR (υ, cm^{-1}): 3448-3352 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1689, 1703 (two carbonyl), 1561 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.52-1.75 (m, 4H, two methylene), 2.38-2.69 (m, 2H, methylene), 5.38 (s, 2H,

amino), 7.22-7.56 (m, 4H, phenyl), 8.56, 8.44 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.9, 39.6, 47.3 (three methylene), 116.8 (cyano), 121.1, 123.6, 124.9, 125.4 (phenyl), 132.8, 134.6, 137.5, 139.8 (pyridazine two carbons, thiazole two carbons), 168.6, 169.9 (two carbonyl), 170.4, 171.2, 174.7 (3C=N). Calculated for $C_{19}H_{14}ClN_7O_2S$ (439.88): C, 51.88; H, 3.21; N, 22.29; S, 7.29%. Found: C, 51.96; H, 3.41; N, 22.35; S, 7.38%. MS: *m/z* = 439 M^+ (35%).

*4-Amino-1-(4-chlorophenyl)-5-cyano-6-oxo-N-(7-oxo-4,5,6,7-tetrahydrobenzo-[d]thiazol-2-yl)-1,6-dihydropyridazine-3-carboxamide (**16d**)*. Pale brown crystals from *p*-dioxane, m.p. 155-157 °C, yield: 2.72 g (62%). IR (υ, cm^{-1}): 3484-3341 (imino), 3054 (CH aromatic), 2893 (methylene), 2220 (cyano), 1689-1702 (three carbonyl), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.46-1.75 (m, 4H, two methylene), 2.35-2.68 (m, 2H, methylene), 5.32 (s, 2H, amino), 7.21-7.56 (m, 4H, phenyl), 8.53 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.5, 46.9 (three methylene), 117.3 (cyano), 121.8, 122.5, 124.6, 125.8 (phenyl), 132.5, 134.3, 137.6, 139.8 (pyridazine two carbons, thiazole two carbons), 168.3, 169.4, 169.8 (three carbonyl), 170.52, 171.7 (2C=N). Calculated for $C_{19}H_{13}ClN_6O_3S$ (440.86): C, 51.76; H, 2.97; N, 19.06; S, 7.27%. Found: C, 51.92; H, 3.16; N, 18.84; S, 7.41%. MS: *m/z* = 440 M^+ (60%).

*4-Amino-5-cyano-6-imino-1-(4-methoxyphenyl)-N-(7-oxo-4,5,6,7-tetrahydro-benzo[d]thiazol-2-yl)-1,6-dihydropyridazine-3-carboxamide (**16e**)*. Pale yellow crystals from *p*-dioxane, m.p. 188-190 °C, yield: 2.51 g (58%). IR (υ, cm^{-1}): 3457-3326 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1689, 1702 (two carbonyl), 1561 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.50-1.77 (m, 4H, two methylene), 2.34-2.71 (m, 2H, methylene), 3.72 (s, 3H, methyl), 5.42 (s, 2H, amino), 7.21-7.54 (m, 4H, phenyl), 8.38, 8.48 (2s, 2H, two imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.6, 39.3, 47.7 (three methylene), 116.9 (cyano), 121.3, 122.8, 124.5, 125.2 (phenyl), 132.5, 134.8, 137.2, 139.3 (pyridazine two carbons, thiazole two carbons), 168.4, 169.8 (two carbonyl), 170.2, 171.5, 174.4 (2C=N). Calculated for $C_{20}H_{17}N_7O_3S$ (435.46): C, 55.16; H, 3.94; N, 22.52; S, 7.36%. Found: C, 55.27; H, 3.86; N, 22.62; S, 7.42%. MS: *m/z* = 435 M^+ (66%).

*4-Amino-5-cyano-1-(4-methoxyphenyl)-6-oxo-N-(7-oxo-4,5,6,7-tetrahydrobenzo-[d]thiazol-2-yl)-1,6-dihydropyridazine-3-carboxamide (**16f**)*. Pale brown crystals from *p*-dioxane, m.p. 213-215 °C, yield: 2.61 g (60%). IR (υ, cm^{-1}): 3472-3353 (imino), 3054 (CH aromatic), 2891 (methylene), 2220 (cyano), 1688-1703 (three carbonyl), 1563 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.43-1.78 (m, 4H, two methylene), 2.32-2.65 (m, 2H, methylene), 3.71 (s, 3H, methoxy), 5.36 (s, 2H, amino), 7.24-7.53 (m, 4H, phenyl), 8.56 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 38.8, 39.3, 46.6 (three methylene), 50.6 (methoxy), 117.1 (cyano), 121.5, 123.7, 124.4, 125.9 (phenyl), 132.2, 134.1, 137.7, 139.2 (pyridazine two carbons, thiazole two carbons), 168.1, 169.6, 169.5 (three carbonyl), 170.3, 171.5 (2C=N). Calculated for $C_{20}H_{16}N_6O_4S$ (436.45): C, 55.04; H, 3.70; N, 19.26; S, 7.35%. Found: C, 54.92; H, 3.84; N, 19.39; S, 7.46%. MS: *m/z* = 436 M^+ (50%).

*General procedure for the synthesis of the chromeno[7,8-d]thiazole derivatives **18a-f***

Each of phenylmethanal (1.06 g, 0.01 mol), 4-chloro phenylmethanal (1.40 g, 0.01 mol) or 4-methoxy phenylmethanal (1.36 g, 0.01 mol) and dicyanomethane (0.66 g, 0.01 mol) or ethyl 2-cyanoacetate (1.07 g, 0.01 mol) were added to a solution of compound **4** (1.68 g, 0.01 mol) in *p*-dioxane (50 mL) containing Et_3N (1.0 mL, 0.01 mol). The reaction was proceeded in a similar way for the synthesis of **14a-c**, previously described.

*2,8-Diamino-6-phenyl-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carbonitrile (**18a**)*. Pale brown crystals of AcOH, m.p. 204-206 °C, yield: 2.00 g (62%). IR (υ, cm^{-1}): 3462-3321 (imino), 3055 (CH aromatic), 2890 (methylene), 2221 (cyano), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-

d$_6$, 300 MHz): δ = 1.82-2.16 (m, 4H, two methylene), 4.85, 5.29 (2s, 4H, two amino), 6.42 (s, 1H, pyran H-4), 7.24-7.51 (m, 5H, phenyl). ^{13}C-NMR (DMSO-*d*$_6$, 75 MHz): 39.6, 41.2 (two methylene), 116.9 (cyano), 120.3, 121.6, 123.9, 124.7 (phenyl), 134.6, 135.5, 137.6, 139.2, 140.3, 142.5 (pyran four carbons, thiazole two carbons), 172.5 (C=N). Calculated for $C_{17}H_{14}N_4OS$ (322.39): C, 63.33; H, 4.38; N, 17.38; S, 9.95%. Found: C, 63.17; H, 4.52; N, 17.40; S, 9.74%. MS: *m/z* = 322 M^+ (70%).

Ethyl 2,8-diamino-6-phenyl-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carboxylate ***(18b)***. Pale brown crystals of AcOH, m.p. 164-166 °C, yield: 2.36 g (64%). IR (υ, cm^{-1}): 3491-3353 (imino), 3055 (CH aromatic), 2890 (methylene), 1560 (vinyl bonding). ^{1}H-NMR (DMSO-*d*$_6$, 300 MHz): δ = 1.13 (t, 3H, *J* = 7.05 Hz, ester methyl), 1.82-2.16 (m, 4H, two methylene), 4.22 (q, 2H, *J* = 7.05 Hz, ester methylene), 4.82, 5.31 (2s, 4H, two amino), 6.46 (s, 1H, pyran H-4), 7.26-7.49 (m, 5H, phenyl). ^{13}C-NMR (DMSO-*d*$_6$, 75 MHz): 16.5 (ester methyl), 39.8, 41.5 (two methylene), 50.2 (ester methylene), 120.6, 121.8, 122.4, 124.9 (phenyl), 134.4, 135.3, 137.5, 139.6, 140.1, 142.2 (pyran four carbons, thiazole two carbons), 172.6 (C=N). Calculated for $C_{19}H_{19}N_3O_3S$ (369.44): C, 61.77; H, 5.18; N, 11.37; S, 8.68%. Found: C, 61.84; H, 5.27; N, 11.42; S, 8.79%. MS: *m/z* = 369 M^+ (58%).

2,8-Diamino-6-(4-chlorophenyl)-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carbonitrile ***(18c)***. Pale brown crystals of AcOH, m.p. 188-191 °C, yield: 1.78 g (50%). IR (υ, cm^{-1}): 3472-3347 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1563 (vinyl bonding). ^{1}H-NMR (DMSO-*d*$_6$, 300 MHz): δ = 1.84-2.29 (m, 4H, two methylene), 4.83, 5.35 (2s, 4H, two amino), 6.45 (s, 1H, pyran H-4), 7.21-7.58 (m, 4H, phenyl). ^{13}C-NMR (DMSO-*d*$_6$, 75 MHz): 39.6, 41.2 (two methylene), 116.9 (cyano), 120.5, 121.2, 123.7, 124.5 (phenyl), 134.4, 135.3, 137.2, 139.6, 140.5, 142.8 (pyran four carbons, thiazole two carbons), 172.8 (C=N). Calculated for $C_{17}H_{13}ClN_4OS$ (356.83): C, 57.22; H, 3.67; N, 15.70; S, 8.99%. Found: C, 57.32; H, 3.78; N, 15.58; S, 9.13%. MS: *m/z* = 356 M^+ (78%).

Ethyl-2,8-diamino-6-(4-chlorophenyl)-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carboxylate ***(18d)***. Pale brown crystals of AcOH, m.p. 182-184 °C, yield: 2.41g (60%). IR (υ, cm^{-1}): 3458-3341 (imino), 3055 (CH aromatic), 2893 (methylene), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-*d*$_6$, 300 MHz): δ = 1.12 (t, 3H, *J* = 6.85 Hz, ester methyl), 1.82-2.16 (m, 4H, two methylene), 4.22 (q, 2H, *J* = 6.85 Hz, ester methylene), 4.80, 5.34 (2s, 4H, two amino), 6.44 (s, 1H, pyran H-4), 7.24-7.57 (m, 4H, phenyl). ^{13}C-NMR (DMSO-*d*$_6$, 75 MHz): 16.3 (ester methyl), 39.6, 41.9 (two methylene), 50.1 (ester methylene), 120.8, 122.4, 122.8, 125.3 (phenyl), 134.2, 135.6, 137.2, 139.8, 140.3, 142.1 (pyran four carbons, thiazole two carbons), 172.8 (C=N). Calculated for $C_{19}H_{18}ClN_3O_3S$ (403.88): C, 56.50; H, 4.49; N, 10.40; S, 7.94%. Found: C, 56.37; H, 4.52; N, 10.69; S, 8.15%. MS: *m/z* = 403 M^+ (60%).

2,8-Diamino-6-(4-methoxyphenyl)-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carbonitrile ***(18e)***. Yellow crystals of *p*-dioxane, m.p. 211-213 °C, yield: 2.18 g (62%). IR (υ, cm^{-1}): 3491-3336 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1561 (vinyl bonding). ^{1}H-NMR (DMSO-*d*$_6$, 300 MHz): δ = 1.82-2.32 (m, 4H, two methylene), 3.66 (s, 3H, methoxy), 4.84, 5.38 (2s, 4H, two amino), 6.46 (s, 1H, pyran H-4), 7.23-7.55 (m, 4H, phenyl). ^{13}C-NMR (DMSO-*d*$_6$, 75 MHz): 39.8, 41.6 (two methylene), 50.6 (methoxy), 116.7 (cyano), 120.3, 121.5, 123.2, 124.8 (phenyl), 134.6, 135.1, 138.6, 139.9, 140.3, 142.7 (pyran four carbons, thiazole two carbons), 172.5 (C=N). Calculated for $C_{18}H_{16}N_4O_2S$ (352.41): C, 61.35; H, 4.58; N, 15.90; S, 9.10%. Found: C, 61.29; H, 4.68; N, 15.71; S, 9.23%. MS: *m/z* = 352 M^+ (62%).

Ethyl-2,8-diamino-6-(4-methoxyphenyl)-4,6-dihydro-5H-chromeno[7,8-d]thiazole-7-carboxylate ***(18f)***. Yellowcrystals of *p*-dioxane, m.p. 182-184 °C, yield: 2.59 g (65%). IR (υ, cm^{-1}): 3472-3350

(imino), 3055 (CH aromatic), 2892 (methylene), 1561 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.13 (t, 3H, *J* = 6.46 Hz, ester methyl), 1.85-2.18 (m, 4H, two methylene), 3.68 (s, 3H, methoxy), 4.21 (q, 2H, *J* = 6.46 Hz, ester methylene), 4.83, 5.36 (2s, 4H, two amino), 6.45 (s, 1H, pyran H-4), 7.26-7.59 (m, 4H, phenyl). ^{13}C-NMR (DMSO-d_6, 75 MHz): 16.2 (ester methyl), 39.65, 42.3(two methylene), 50.2 (ester methylene), 50.8 (methoxy), 120.6, 123.6, 124.2, 125.6 (phenyl), 134.4, 135.6, 137.6, 139.6, 141.6, 142.7 (pyran four carbons, thiazole two carbons), 172.9 (C=N). Calculated for $C_{20}H_{21}N_3O_4S$ (399.47): C, 60.13; H, 5.30; N, 10.52; S, 8.03%. Found: C, 60.25; H, 5.28; N, 10.71; S, 8.24%. MS: *m/z* = 399 M^+ (72%).

General procedure for the synthesis of the thiazolo[4,5-h]quinoline derivatives ***19a-f***

The same reaction procedure previously described for the synthesis of compounds **18a-f** was carried out but using NH_4OAc (2.0 g) instead of Et_3N.

2,8-Diamino-6-phenyl-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carbonitrile ***(19a)***. Yellow crystals of AcOH, m.p. 187-189 °C, yield: 1.92 g (60%). IR (υ, cm^{-1}): 3479-3341 (imino), 3055 (CH aromatic), 2890 (methylene), 2221 (cyano), 1558 (vinyl bonding). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.85-2.45 (m, 4H, two methylene), 4.83, 5.40 (2s, 4H, two amino), 6.39 (s, 1H, pyridine H-4), 7.28-7.57 (m, 5H, phenyl), 8.44 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 39.8, 41.4 (two methylene), 116.9 (cyano), 120.1, 121.2, 123.4, 124.9 (phenyl), 134.4, 135.2, 137.6, 139.4, 140.1, 142.6 (pyridine four carbons, thiazole two carbons), 172.56 (C=N). Calculated for $C_{17}H_{15}N_5S$ (321.40): C, 63.53; H, 4.70; N, 21.79; S, 9.98%. Found: C, 63.49; H, 4.63; N, 21.82; S, 9.69%. MS: *m/z* = 321 M^+ (70%).

Ethyl 2,8-diamino-6-phenyl-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carboxylate ***(19b)***. Pale brown crystals of *p*-dioxane m.p. 144-146 °C, yield: 2.02 g (55%). IR (υ, cm^{-1}): 3467-3323 (imino), 3055 (CH aromatic), 2890 (methylene), 1560 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.13 (t, 3H, *J* = 6.85 Hz, ester methyl), 1.78-2.18 (m, 4H, two methylene), 4.22 (q, 2H, J = 6.85 Hz, ester methylene), 4.81, 5.36 (2s, 4H, two amino), 6.48 (s, 1H, pyridine H-4), 7.28-7.52 (m, 5H, phenyl), 8.43 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 16.2 (ester methyl), 39.8, 41.8 (two methylene), 50.2 (ester methylene), 120.8, 121.3, 123.5, 124.6 (phenyl), 134.2, 135.1, 137.2, 139.3, 140.6, 142.4 (pyridine four carbons, thiazole two carbons), 172.7 (C=N). Calculated for $C_{19}H_{20}N_4O_2S$ (368.46): C, 61.94; H, 5.47; N, 15.21; S, 8.70%. Found: C, 61.75; H, 5.52; N, 15.36; S, 8.82%. MS: *m/z* = 368 M^+ (58%).

2,8-Diamino-6-(4-chlorophenyl)-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carbonitrile ***(19c)***. Pale yellow crystals of EtOH, m.p. 161-163 °C, yield: 2.23 g (63%). IR (υ, cm^{-1}): 3482-3343 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1561 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.88-2.46 (m, 4H, two methylene), 4.86, 5.42 (2s, 4H, two amino), 6.48 (s, 1H, pyridine H-4), 7.24-7.56 (m, 4H, phenyl), 8.40 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 39.3, 41.6 (two methylene), 117.2 (cyano), 120.2, 121.6, 123.8, 125.8 (phenyl), 134.6, 135.1, 137.3, 139.8, 140.5, 142.7 (pyridine four carbons, thiazole two carbons), 172.4 (C=N). Calculated for $C_{17}H_{14}ClN_5S$ (355.84): C, 57.38; H, 3.97; N, 19.68; S, 9.01%. Found: C, 57.41; H, 3.83; N, 19.73; S, 9.23%. MS: *m/z* = 355 M^+ (60%).

Ethyl-2,8-diamino-6-(4-chlorophenyl)-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carboxylate ***(19d)***. Pale brown crystals of AcOH, m.p. 159-161°C, yield: 2.33 g (58%). IR (υ, cm^{-1}): 3472-3358 (imino), 3055 (CH aromatic), 2891 (methylene), 1565 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.14 (t, 3H, *J* = 5.82 Hz, ester methyl), 1.86-2.29 (m, 4H, two methylene), 4.22 (q, 2H, *J* = 5.82 Hz, ester methylene), 4.83, 5.42 (2s, 4H, two amino), 6.44 (s, 1H, pyridine H-4), 7.22-7.62 (m, 4H, phenyl), 8.51 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 16.5 (ester methyl), 39.4, 41.8 (two methylene), 50.3 (ester methylene), 120.3, 122.6, 123.5, 125.7 (phenyl),

134.4, 135.9, 137.6, 139.8, 141.2, 142.6 (pyridine four carbons, thiazole two carbons), 172.8 (C=N). Calculated for $C_{19}H_{19}ClN_4O_2S$ (402.90): C, 56.64; H, 4.75; N, 13.91; S, 7.96%. Found: C, 56.52; H, 4.58; N, 14.25; S, 8.16%. MS: *m/z* = 402 M^+ (78%).

2,8-Diamino-6-(4-methoxyphenyl)-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carbonitrile ***(19e)***. Yellow crystals from *p*-dioxane, m.p. 211-213 ºC, yield: 2.31 g (66%). IR (υ, cm^{-1}): 3457-3370 (imino), 3055 (CH aromatic), 2890 (methylene), 2220 (cyano), 1562 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.86-2.36 (m, 4H, two methylene), 3.64 (s, 3H, methoxy), 4.86, 5.41 (2s, 4H, two amino), 6.48 (s, 1H, pyridine H-4), 7.25-7.64 (m, 4H, phenyl), 8.49 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 39.5, 41.8 (two methylene), 50.5 (methoxy), 116.8 (cyano), 120.1, 121.3, 123.6, 124.9 (phenyl), 134.3, 135.5, 138.6, 139.9, 141.8, 142.9 (pyridine four carbons, thiazole two carbons), 172.7 (C=N). Calculated for $C_{18}H_{17}N_5OS$ (351.43): C, 61.52; H, 4.88; N, 19.93; S, 9.12%. Found: C, 61.68; H, 4.74; N, 20.17; S, 9.45%. MS: *m/z* = 351 M^+ (74%).

Ethyl-2,8-diamino-6-(4-methoxyphenyl)-4,5,6,9-tetrahydrothiazolo[4,5-h]quinoline-7-carboxylate ***(19f)***. Yellow crystals of p-dioxane, m.p. 216-218 ºC, yield: 1.94 g (50%). IR (υ, cm^{-1}): 3469-3353 (imino), 3055 (CH aromatic), 2891 (methylene), 1564 (vinyl bonding). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.12 (t, 3H, *J* = 6.80 Hz, ester methyl), 1.85-2.18 (m, 4H, two methylene), 3.71 (s, 3H, methoxy), 4.22 (q, 2H, *J* = 6.80 Hz, ester methylene), 4.88, 5.38 (2s, 4H, two amino), 6.46 (s, 1H, pyridine H-4), 7.25-7.63 (m, 4H, phenyl), 8.52 (s, 1H, imino). ^{13}C-NMR (DMSO-d_6, 75 MHz): 16.3 (ester methyl), 39.8, 42.6 ($2CH_2$), 50.2 (ester methylene), 50.8 (methoxy), 121.3, 123.8, 124.7, 125.6 (phenyl), 134.7, 136.7, 138.6, 139.9, 141.3, 142.9 (pyridine four carbons, thiazole two carbons), 172.6 (C=N). Calculated for $C_{20}H_{22}N_4O_3S$ (398.48): C, 60.28; H, 5.57; N, 14.06; S, 8.05%. Found: C, 60.47; H, 5.63; N, 14.24; S, 8.18%. MS: *m/z* = 398 M^+ (58%).

CONCLUSION

The present work was described for the synthesis of 5,6-dihydrobenzo[*d*]thiazol-7(4*H*)-one derivatives with varieties of substituent's and finding the possibility of their uses as anticancer agents. The basic starting compound was obtained from the reaction of 2-bromocyclohexan-1,3-diketone and thiourea. Compound **4** was utilized for the synthesis of azine and azole derivatives based on the benzo[*d*]thiazole. Cytotoxicity of all compounds on cancer cell lines was measured and the results revealed that many compounds exhibited high inhibitions. The results obtained from this work encourage future investigations to be done in the aim of drug designing and elucidations of new anti-cancer agents.

List of abbreviations

Abbreviation	Meaning
A549	human non-small cell lung cancer cell lines
HT-29	female colorectal adenocarcinoma
MKN-45	gastric adenocarcinoma
U87MG	a human glioblastoma cell line
SMMC-7721	Cellosaurus cell line
H460	non-small cell lung carcinoma
HepG2	Hepatocellular carcinoma
MTT	is a colorimetric assay for assessing cell metabolic activity

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