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Synthesis of 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione Derivatives as Potential Anticancer Agents

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ABSTRACT

Background and Objective: In light of recent research on thiazole derivatives and their demonstrated biological activities, this study was undertaken to synthesize 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione derivatives as apoptosis-inducing compounds with potential anticancer effects. Accordingly, the main objective was to prepare and evaluate these derivatives as possible anticancer agents.

Materials and Methods: For the synthesis of compounds (4a–4j), 1 mmol of 4-phenylthiazol-2-amine derivatives was reacted with 198.1 mg (1 mmol) of naphthalic anhydride in a 25 mL round-bottom flask. Then, 101.1 mg (1 mmol) of triethylamine was added, and the mixture was refluxed in toluene for 24 hours. The reaction progress was monitored by TLC, confirming completion. The mixture was filtered, the solvent was removed under reduced pressure, and a 50:50 mixture of water and ethyl acetate was added. The organic phase was discarded, and the final derivatives were isolated by standard work-up.

Results: In this study, derivatives 4a–4j were successfully synthesized and evaluated as apoptosis inducers with potential anticancer activity.

Conclusion: In the search for new molecules with anticancer potential, isoquinoline and thiazole derivatives have been identified as promising scaffolds. In addition to their reported antifungal and antibacterial effects, these compounds display cytotoxic properties, supporting their potential role in anticancer drug discovery.

Key words: Cancer; 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione derivatives; synthesis; anticancer agents

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells, which if not controlled, can lead to death. It may arise from both external factors (such as tobacco, chemicals, radiation, and infectious agents) and internal factors (including inherited mutations, hormones, immune conditions, and metabolic mutations). These factors may act independently or sequentially to initiate or promote cancer progression [1,2].

In all types of cancer, certain body cells continue dividing without stopping and invade surrounding

tissues. Cancer can originate in almost any part of the body, which is composed of trillions of cells. Normally, human cells grow and divide to form new cells as needed. When cells age or become damaged, they die, and new cells replace them. However, in cancer, this orderly process is disrupted. As cells become increasingly abnormal, damaged, or aged cells that should undergo apoptosis instead survive, while unnecessary new cells are produced. These extra cells can divide indefinitely, forming masses known as tumors. Many cancers form solid tumors, whereas blood cancers such as leukemias generally do not [3,4].

Malignant tumors are invasive, meaning they can spread into nearby tissues. In addition, cancer cells can detach and travel through the blood or lymphatic system, forming secondary tumors (metastases) in distant organs. Unlike malignant tumors, benign tumors do not spread to adjacent tissues, though they can sometimes grow quite large. Once surgically removed, benign tumors typically do not recur, whereas malignant tumors frequently do. However, unlike most benign tumors elsewhere in the body, benign brain tumors may still be life-threatening due to their location [3,4].

Systemic symptoms are often shared across many cancers and are not specific to a single type. For example, persistent unexplained fever is common in leukemia as well as liver and kidney cancers. Other symptoms, such as unexplained weight loss, prolonged fatigue, fever, and skin changes, may occur across different cancers, including skin cancer [5,6]. Symptoms caused by metastasis result from the spread of cancer cells to distant sites. These may include lymphadenopathy, detectable as firm and enlarged lymph nodes under the skin, hepatomegaly, and splenomegaly [7].

There is currently no definite cure for cancer. The main therapeutic goals are remission or symptom relief. Remission is defined as the disappearance of all clinical signs of cancer. Effective treatment options include surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy. Each approach has its own advantages and limitations, and a combination is often required for optimal results. Early diagnosis, complete surgical resection, effective radiotherapy, chemotherapy, and other therapeutic interventions are critical determinants of prognosis, with early and accurate detection being the most important factor. Thus, regular screening plays a key role in cancer prevention and management. Although it is difficult to predict who will develop cancer, strong evidence indicates that reducing tobacco and alcohol consumption, controlling obesity, and protecting skin from ultraviolet radiation can reduce the risk [8,9].

Approximately 65% of research projects in organic chemistry focus on heterocyclic compounds [10,11]. Heterocyclic chemistry is one of the most important branches of organic chemistry due to its theoretical significance, wide synthetic diversity, physiological properties, and industrial applications [12]. Aromatic five-membered heterocyclic rings represent a major area of heterocyclic research due to their structural importance and reactive positions. Among them, thiazoles are particularly noteworthy. Since December 1976, thiazole chemistry has attracted increasing interest among chemists. The first systematic studies were conducted by Hansch and Weber [13,14], who classified thiazoles as pyridine-thiophene analogs and introduced a comprehensive list of compounds consistent with this definition [15]. In their nomenclature, α and β positions correspond to those in pyridine, while the μ (meso) position has no equivalent in pyridine.

Popsavin et al. (2006) synthesized a novel thiazofurine analog, 2-(3-amino-3-deoxy-β-D-xylopyranosyl) thiazole-4-carboxamide, which exhibited approximately 100-fold greater antitumor activity against K562 leukemia cells compared to thiazofurine. Notably, this compound showed no significant cytotoxicity toward normal embryonic lung cells (MRC-5) [16]. Holla et al. synthesized a new series of arylidene-5-aryl-2-furfurylidenehydrazinothiazoles, with compounds 1 and 2 demonstrating significant anti-inflammatory activity compared to ibuprofen [17]. In 2007, Bondock et al. reported new thiazole derivatives synthesized from 1-chloro-4,3-hydronaphthalen-2-carboxaldehyde [18]. Similarly, Holla et al. (2003) synthesized a new series of 4-aryl/chloroalkyl-2-(2,3,5-trichlorophenyl)-thiazoles [19].

Wu et al. (2009) synthesized several isoquinoline-1,3(2H)-dione derivatives and evaluated their

antitumor effects on seven cancer cell lines. All compounds demonstrated antitumor activity, although some selectively inhibited specific cell lines more effectively [20]. Al-Salahi et al. (2014) synthesized novel 2-amino-benzo[de]isoquinoline-1,3-dione derivatives and evaluated their anticancer activity against three cancer cell lines, comparing the results with doxorubicin. All synthesized derivatives exhibited significant anticancer effects [21].

He et al. (2016) synthesized a series of 2,4,5-substituted 1,3-thiazole derivatives, including hydrazide-hydrazone and carboxamide compounds, and evaluated their anticancer activity against five cell lines: MCF-7, HepG2, BGC-823, HeLa, and A549. Among the synthesized compounds, T1, T26, and T38 demonstrated the highest activity, with IC50 values of 2.21, 1.67, and 1.11 µg/mL, respectively, against MCF-7, BGC-823, and HepG2. These results indicate that 1,3-thiazole-hydrazide-hydrazone and carboxamide derivatives are promising candidates for anticancer agents [22].

Cai et al. (2016) synthesized a series of 2-phenyl-4-(trifluoromethyl)thiazole-5-carboxamide derivatives and evaluated them against three cancer cell lines. Among these, the 4-chloro-2-methylphenyl amide derivative exhibited the most potent cytotoxic effects [23]. Zhou et al. (2016) synthesized novel 2-(4-pyridinyl)thiazole carboxamide derivatives and investigated their antitumor activity. The study revealed that these compounds disrupted angiogenesis via inhibition of signaling pathways, and some derivatives exhibited superior effects compared to vandetanib [24].

Ulviye Acar Çevik et al. (2019) synthesized a series of 1,3,4-thiadiazole derivatives and evaluated their anticancer activity. Compounds j4, v4, and y4 showed notable anticancer effects against the N1H3T3 cell line [25].

Cancer arises from genetic alterations within cells. A normal cell may transform into a cancerous cell following a series of genetic changes. Under normal conditions, cells grow and divide in a controlled manner according to the body's needs. However, when genetic regulation is disrupted, cells begin to divide uncontrollably, producing excess cells. In the search for novel molecules with anticancer potential, isoquinoline and thiazole derivatives have been identified as cytotoxic compounds in addition to their known antifungal and antibacterial activities. Based on recent studies and the promising biological effects of thiazole derivatives, the present research aimed to synthesize 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione derivatives as apoptosis-inducing agents with potential anticancer activity. Accordingly, the primary objective of this study was the synthesis of 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione derivatives as potential anticancer agents.

Materials and Methods

General Scheme for the Synthesis of 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione Derivatives

As illustrated in Figure 1, various 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione derivatives were synthesized, and the completion of the reactions was confirmed by TLC. The structures of the synthesized compounds were characterized using NMR, IR, and Mass spectrometry techniques.

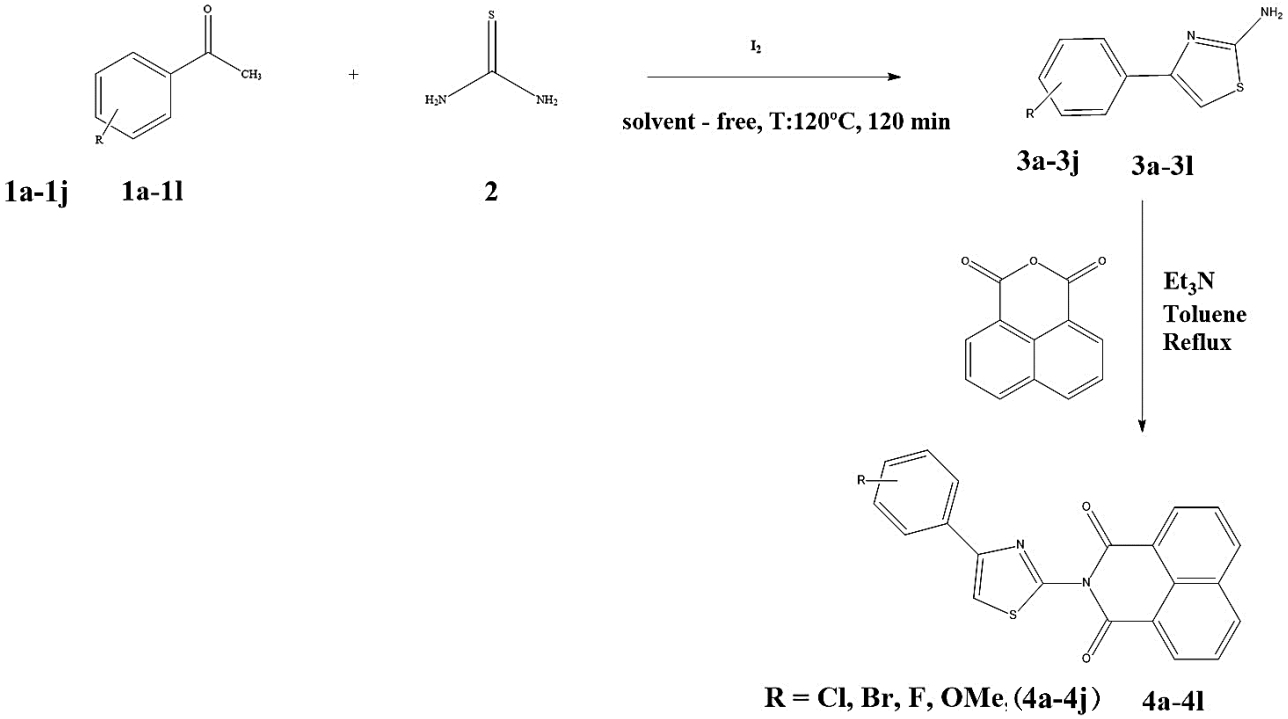

Figure 1. General synthetic scheme for compounds 4a–4j.

General Procedure for the Synthesis of 4-phenylthiazol-2-amine Derivatives (Compounds 3a–3j)

To prepare compounds 3a–3j, 6.8 mmol of the respective acetophenone derivative was combined with 3.1 g (17.2 mmol) of thiourea in a 25 mL round-bottom flask. Subsequently, 2.2 g (8.6 mmol) of iodine was added, and the mixture was stirred at 120 °C for 2 hours under solvent-free conditions. The reaction progress was monitored by thin-layer chromatography (TLC), confirming completion.

Afterward, the reaction temperature was reduced to 70 °C, and diethyl ether was added to wash the precipitate. Once dried, hot water was added, and the pH was adjusted to 11–12 using ammonium hydroxide (NH_4OH). The resulting precipitate was filtered, dried, and then dissolved in a mixture of water and ethanol. The solution was stored in a refrigerator until the final product crystallized.

General Procedure for the Synthesis of 2-(4-phenylthiazol-2-yl)-benzo[de]isoquinoline-3,1-dione Derivatives (Compounds 4a–4j)

To synthesize compounds 4a–4j, 1 mmol of the corresponding 4-phenylthiazol-2-amine derivative and 198.1 mg (1 mmol) of naphthalic anhydride were placed in a 25 mL round-bottom flask. Then, 101.1 mg (1 mmol) of triethylamine was added, and the mixture was refluxed in toluene for 24 hours. Reaction progress was monitored by TLC, confirming completion.

The reaction mixture was filtered, and the solvent was removed under reduced pressure using a rotary evaporator. A 50:50 mixture of water and ethyl acetate was added, and the organic layer was discarded. The target derivatives were then extracted according to standard work-up procedures. A schematic of the synthesis of compounds 4a–4j is shown in Figure 2.

For improved separation during the work-up, a 2% sodium bicarbonate solution was prepared by dissolving 2 g of sodium bicarbonate in 100 mL of distilled water.

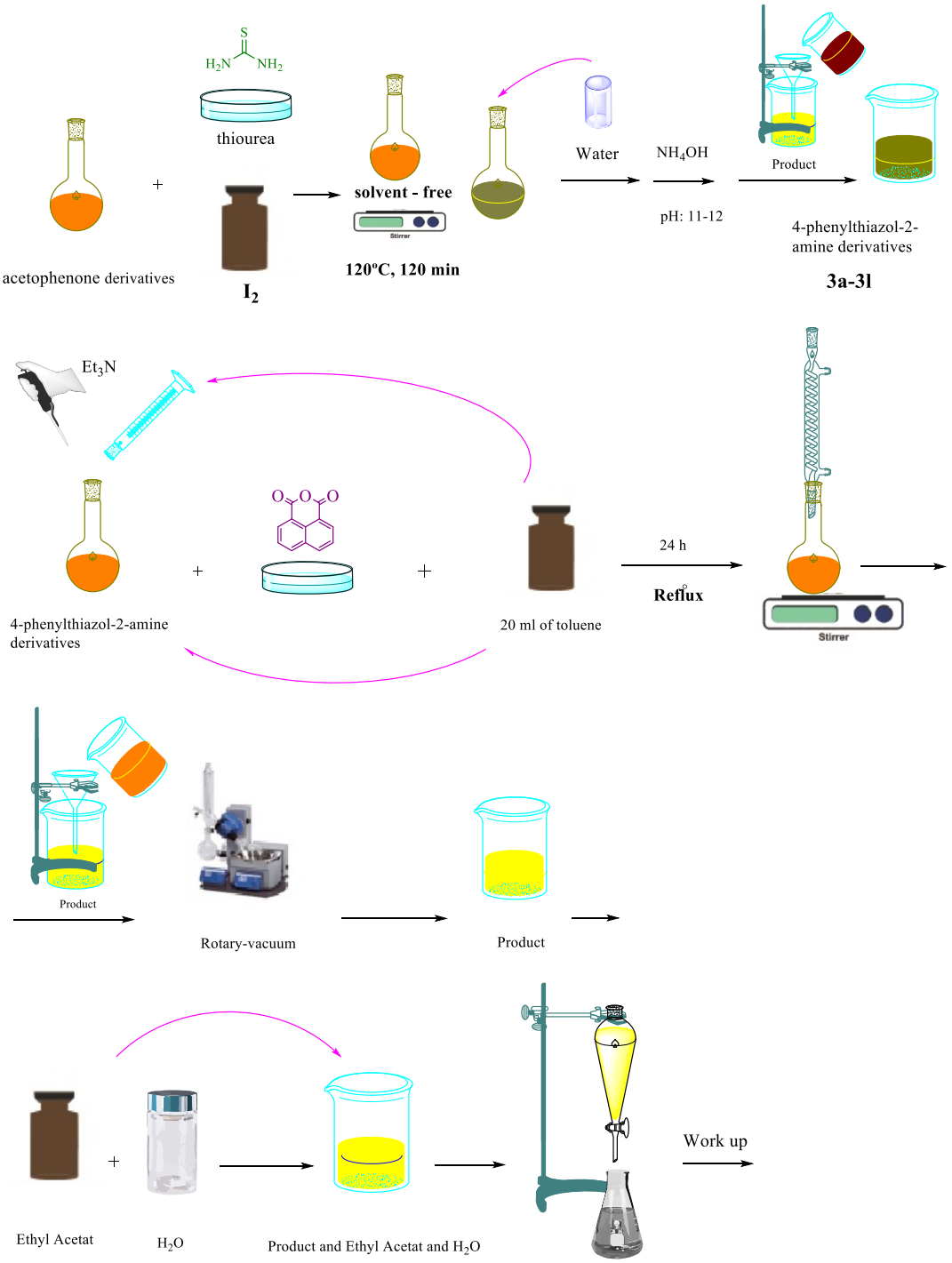

Figure 2: Schematic representation of the synthesis of compounds 4a–4j

Work-Up Procedure:

- To the obtained precipitate, 30 mL of a 1:1 mixture of water and ethyl acetate was added. After thorough stirring, two distinct layers formed.
- For efficient phase separation, the mixture was transferred to a separatory funnel.
- Supersaturated sodium chloride solution (brine) was added in two portions. The brine helps transfer ionized impurities into the aqueous phase.
- A 2% sodium bicarbonate solution was then added in two portions, with stirring, and the upper

organic layer was separated.

- Anhydrous sodium sulfate was added to the organic layer to remove residual water.
- After drying, the solution was filtered into a 100 mL round-bottom flask, and the solvent was removed under reduced pressure using a rotary evaporator.
- Finally, the precipitate was washed with diethyl ether to remove any remaining impurities, and the flask was stored in a refrigerator for 24 hours to complete crystallization.

Important Notes for the Synthesis of Compounds 4a–4j:

1. All reactants were combined in a 1:1 molar ratio.
2. Ethyl acetate, being less dense than water, forms the upper layer in a separatory funnel, whereas halogenated solvents such as chloroform or dichloromethane, being denser than water, form the lower layer.

A schematic representation of the work-up procedure is shown in Figure 3.

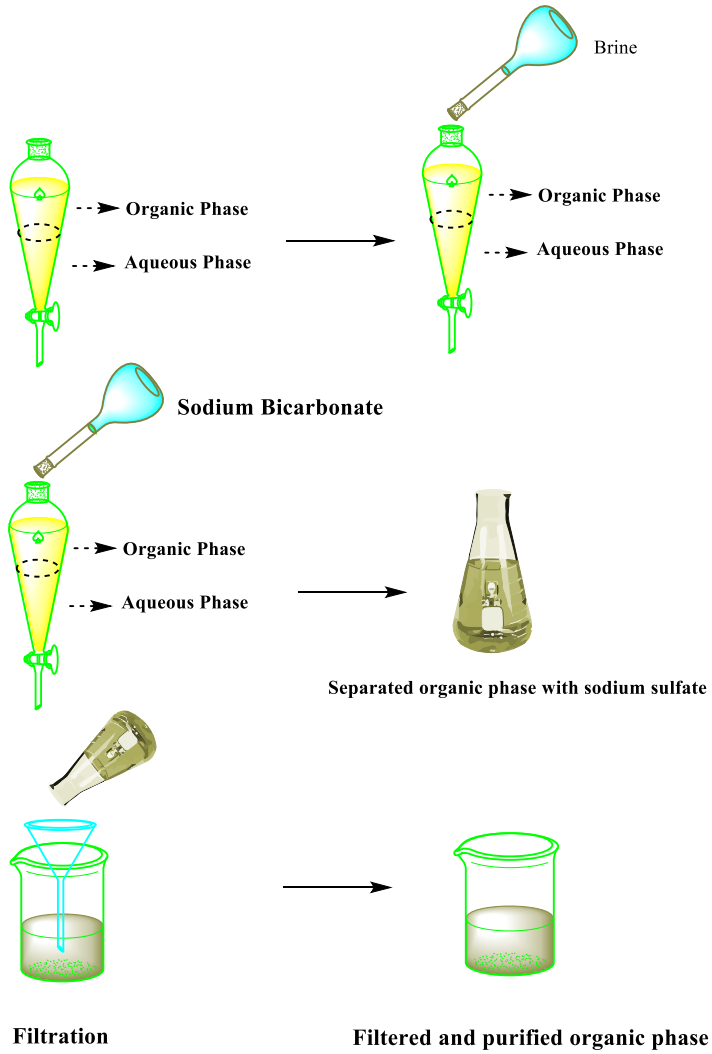

Figure 3: Schematic representation of the work-up procedure

After the work-up, the purity of the obtained product was verified using thin-layer chromatography (TLC). To confirm the structure of the final compound, the precipitate was further analyzed by FT-IR, ^{1}H-NMR, and mass spectrometry. The remaining derivatives were synthesized following the same

procedure.

TLC Analysis:

TLC was performed to monitor the completion of the reaction and to ensure that the synthesized products were ready for subsequent steps, including further synthesis, spectroscopic analyses, or cell-based studies. The analysis used a specific mixture of ethyl acetate and petroleum ether as the mobile phase for each compound. Small samples of the synthesized product and the starting material were applied to TLC plates, which were then placed in a developing tank containing the solvent system. Once the solvent front reached an appropriate height, the plates were removed, dried, and visualized under UV light.

FT-IR Analysis:

The structures of the synthesized compounds were investigated using an FT-IR spectrometer (Shimadzu IR Prestige-21). KBr pellets of each compound were prepared and analyzed in the range of 400–13,900 cm^{-1}, with a resolution of 4 cm^{-1} and 64 scans per sample.

^{1}H-NMR Analysis:

^{1}H-NMR spectra were recorded in DMSO-d_6 to confirm the structures of the synthesized compounds using a Bruker MSI-250 MHz NMR spectrometer.

Mass Spectrometry:

Mass spectrometry was employed to determine the molecular weights of the synthesized compounds. Samples were dissolved in a standard solvent and introduced into the instrument under vacuum and elevated temperature, where they were fragmented. The molecular weights of the resulting fragments were then recorded.

Results

Physicochemical properties of 4-(p-tolyl)thiazol-2-amine (3a)

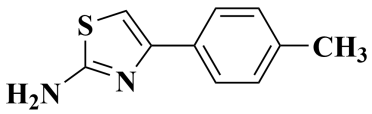

Figure 4: Chemical structure of compound 3a

Table 1: Physicochemical properties of compound 3a

Physicochemical Properties of 4-(p-Tolyl)thiazol-2-amine			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{10}H_{10}N_2S$	190.26	130˚C	**81%**

4-(P-tolyl) thiazol-2-amine

IR (KBr, cm^{-1}) ῡ: 3387, 3305, 3124, 3022, 2918, 2856, 1637, 1539, 1517, 1490, 1336.

^{1}HNMR (250 MHz, DMSO-d_6): 2.43 (s, 3H, -CH_3), 6.98 (s, 2H, NH_2), 7.05 (s, 1H, H_5-thiazole), 7.56 (d, 2H, $H_{3.5}$-phenyl), 7.68 (d, 2H, $H_{2.6}$-phenyl).

Physicochemical Properties of 4-(4-Iodophenyl)thiazol-2-amine (3b)

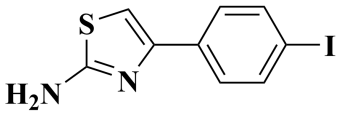

Figure 5: Chemical structure of compound 3b

Table 2: Physicochemical properties of compound 3b

Physicochemical Properties of 4-(4-Iodophenyl)thiazol-2-amine			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_9H_7IN_2S$	302.13	115˚C	**84%**

4-(4-Iodophenyl) thiazol-2-amine

IR (KBr, cm^{-1}) ῡ: 3116, 2922, 2852, 1629, 1531, 1471, 1390.

^{1}HNMR (250 MHz, DMSO-d_6): 6.88 (s, 1H, H_5-thiazole), 6.98 (s, 2H, NH_2), 7.13 (d, 2H, $H_{2.6}$-phenyl), 7.65 (d, 2H, $H_{3.5}$-phenyl).

Physicochemical Properties of 2-(4-phenylthiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4a)

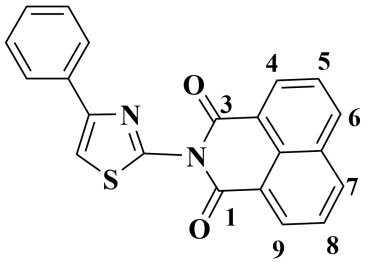

Figure 6: Chemical structure of compound 4a

Table 3: Physicochemical properties of compound 4a

Physicochemical Properties of 2-(4-phenylthiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{12}N_2O_2S$	356.06	149 ˚C	**80%**

2-(4-Phenylthiazol-2-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3107, 3070, 1776, 1735, 1683, 1583.

^{1}HNMR (250 MHz, DMSO-d_6): 6.97 (d, 1H, phenyl), 7.22 (t, 1H, phenyl), 7.33 (t, 1H, phenyl), 7.45 (t, 1H, phenyl), 7.77 (d, 1H, phenyl), 7.90 (m, 2H, $H_{5,8}$-naphthalimide), 8.35 (s,1H, H5-thiazole), 8.52 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 356 (M^+, 60), 180 (100), 154 (20), 134 (45), 126 (45), 77 (10).

Physicochemical Properties of 2-(4-(3-Hydroxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4b)

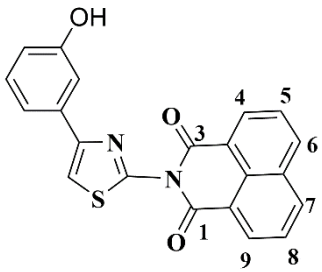

Figure 7: Chemical structure of compound 4b

Table 4: Physicochemical properties of compound 4b

Physicochemical Properties of 2-(4-(3-Hydroxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{12}N_2O_3S$	372.40	191 ˚C	**78%**

2-(4-(3-Hydroxyphenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 2800-3336, 3072, 2926, 2854, 1776, 1735, 1587.

^{1}HNMR (250 MHz, DMSO-d_6): 6.53 (s, 1H, H_2-3-hydroxyphenyl), 7.02-7.51 (m, 3H, 3-hydroxyphenyl), 7.67 (s, 1H, H_5-thiazole), 7.91 (m, 2H, $H_{5,8}$-naphthalimide), 8.25 (brs, 1H, OH), 8.52 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 372 (M^+, 40), 198 (45), 180 (65), 154 (80), 126 (100).

Physicochemical Properties of 2-(4-(3-Methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4c)

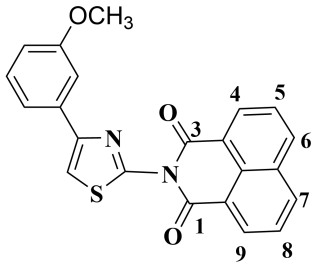

Figure 8: Chemical structure of compound 4c

Table 5: Physicochemical properties of compound 4c

Physicochemical Properties of 2-(4-(3-Methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{22}H_{14}N_2O_3S$	386.43	160 ˚C	**64%**

2-(4-(3-Methoxyphenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3109, 1774, 1735, 1716, 1681, 1614, 1583, 1516.

^{1}HNMR (250 MHz, DMSO-d_6): 3.75 (s, 3H, -OCH_3), 6.78 (d, 1H, J = 7.5 Hz, H_4-3-methoxyphenyl), 6.95 (d, 1H, J = 7.5 Hz, H_6-3-methoxyphenyl), 7.24 (t, 1H, J = 7.5 Hz, H_5-3-methoxyphenyl), 7.33 (s, 1H, H_2-3-methoxyphenyl), 7.90 (t, 2H, $H_{5,8}$-naphthalimide), 8.38 (s, 1H, H_5-thiazole), 8.52 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

Physicochemical Properties of 2-(4-(4-Methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4d)

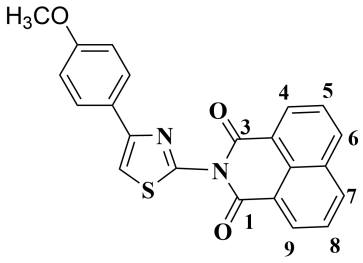

Figure 9: Chemical structure of compound 4d

Table 6: Physicochemical properties of compound 4d

Physicochemical Properties of 2-(4-(4-Methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{22}H_{14}N_2O_2S$	386.43	244 ˚C	**79%**

2-(4-(4-Methoxyphenyl) thiazol-2-yl)-1*H*-benzo [*de*] Iisoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3072, 2924, 2852, 1776, 1735, 1585.

^{1}HNMR (250 MHz, $CDCl_3$): 7.38 (m, 2H, $H_{3,5}$-4-chlorophenyl), 7.89 (m, 2H, $H_{5,8}$-naphthalimide), 7.93 (m, 2H, $H_{2,6}$-4-chlorophenyl), 8.36 (s,1H, H_5-thiazole), 8.51 (t, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 386 (M^+, 90), 180 (100), 149 (50), 126 (50), 77 (15).

Physicochemical Properties of 2-(4-(4-Chlorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4e)

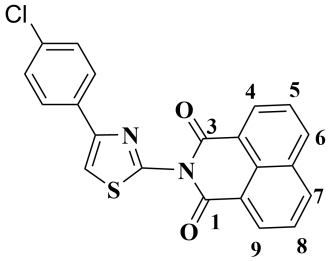

Figure 10: Chemical structure of compound 4e

Table 7: Physicochemical properties of compound 4e

Physicochemical Properties of 2-(4-(4-Chlorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{11}ClN_2O_2S$	390.02	102 ˚C	**86%**

2-(4-(4-Chlorophenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3105, 3070, 2922, 2852, 1774, 1737, 1683, 1583, 1307, 1232.

MS (*m/z*, %): 392 (M^++2, weak), 390 (M^+, weak), 356 (65), 180 (100), 154 (20), 134 (50).

Physicochemical Properties of 2-(4-(4-Bromophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4f)

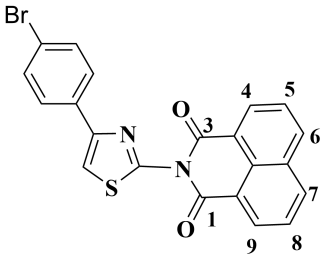

Figure 11: Chemical structure of compound 4f

Table 8: Physicochemical properties of compound 4f

Physicochemical Properties of 2-(4-(4-Bromophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{11}BrN_2O_2S$	435.30	142˚C	**83%**

2-(4-(4-Bromophenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3111, 2956, 2924, 2852, 1772, 1735, 1631, 1533.

^{1}HNMR (250 MHz, DMSO-d_6): 7.05 (s, 1H, H_5-thiazole), 7.52 (d, 2H, *J* = 7.5 Hz, $H_{2,6}$-4-bromophenyl), 7.71 (d, 2H, *J* = 7.5 Hz, $H_{3,5}$-4-bromophenyl), 7.89 (t, 2H, $H_{5,8}$-naphthalimide), 8.52 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 436 (M^++2, 35), 434 (M^+, 35), 254 (20), 213 (20), 180 (100), 154 (25), 126 (55).

Physicochemical Properties of 2-(4-(4-Fluorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4g)

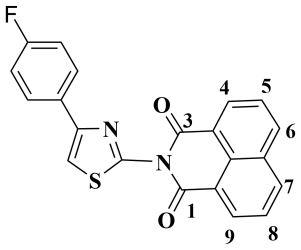

Figure 12: Chemical structure of compound 4g

Table 9: Physicochemical properties of compound 4g

Physicochemical Properties of 2-(4-(4-Fluorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione

Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{11}FN_2O_2S$	374.39	234˚C	**80%**

2-(4-(4-Fluorophenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3113, 2958, 2926, 2854, 1776, 1734, 1718, 1685, 1627, 1593, 1529, 1489.

^{1}HNMR (250 MHz, DMSO-d_6): 8.34 (s, 1H, H_5-thiazole), 7.18 (t, 2H, J = 7.5 Hz, $H_{2,6}$-4-flourophenyl), 7.79 (t, 2H, J = 7.5 Hz, $H_{3,5}$-4-flourophenyl), 7.91 (t, 2H, $H_{5,8}$-naphthalimide), 8.52 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 374 (M^+, 60), 180 (100), 152 (60), 126 (45).

Physicochemical Properties of 2-(4-(4-Iodophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4h)

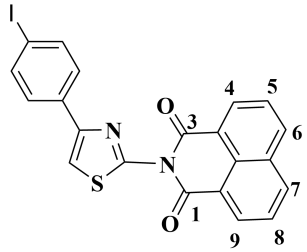

Figure 13: Chemical structure of compound 4h

Table 10: Physicochemical properties of compound 4h

Physicochemical Properties of 2-(4-(4-Iodophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{11}IN_2O_2S$	482.30	240 ˚C	**74%**

2-(4-(4-Iodophenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3115, 3070, 1774, 1735, 1583. (

^{1}HNMR (250 MHz, DMSO-d_6): 7.04 (s, 1H, H_5-thiazole), 7.58 (d, 2H, J = 7.5 Hz, $H_{2,6}$-4-iodophenyl), 7.66 (d, 2H, J = 7.5 Hz, $H_{3,5}$-4-iodophenyl), 7.89 (t, 2H, $H_{5,8}$-naphthalimide), 8.51 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 482 (M^+, weak), 279 (25), 167 (30), 149 (100).

Physicochemical Properties of 2-(4-(p-Tolyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4i)

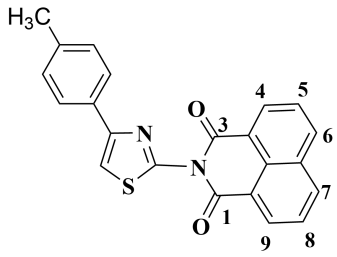

Figure 14: Chemical structure of compound 4i

Table 11: Physicochemical properties of compound 4i

Physicochemical Properties of 2-(4-(p-Tolyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{22}H_{14}N_2O_2S$	370.43	226 ˚C	**82%**

2-(4-(P-tolyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3115, 3070, 2924, 2852, 1774, 1737, 1583.

^{1}HNMR (250 MHz, DMSO-d_6): 2.27 (s, 3H, -CH_3), 7.25 (d, 2H, J = 7.5 Hz, $H_{3,5}$-4-methylphenyl), 7.65 (d, 2H, J = 7.5 Hz, $H_{2,6}$-4-methylphenyl), 7.89 (t, 2H, $H_{5,8}$-naphthalimide), 8.26 (s, 1H, H_5-thiazole), 8.53 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

MS (*m/z*, %): 370 (70), 180 (100), 147 (35), 126 (40), 91 (10).

Physicochemical Properties of 2-(4-(4-Nitrophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4j)

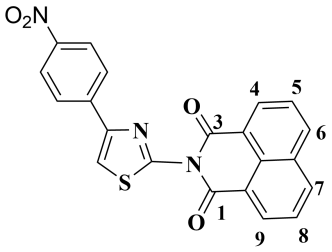

Figure 15: Chemical structure of compound 4j

Table 12: Physicochemical properties of compound 4j

Physicochemical Properties of 2-(4-(4-Nitrophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione			
Chemical Formula	Molecular Weight	Melting Point (°C)	**Yield (%)**
$C_{21}H_{11}N_3O_4S$	401.40	205 ˚C	**77%**

2-(4-(4-Nitrophenyl) thiazol-2-yl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-dione

IR (KBr, cm^{-1}) ῡ: 3161, 3072, 1774, 1735, 1587, 1510, 1313.

^{1}HNMR (250 MHz, DMSO-d_6): 7.88 (m, 2H, $H_{5,8}$-naphthalimide), 8.01 (d, 2H, J = 8.76 Hz, $H_{2,6}$-4-nitrophenyl), 8.20 (d, 2H, J = 8.76 Hz, $H_{3,5}$-4-nitrophenyl), 8.41 (s, 1H, H_5-thiazole), 8.51 (m, 4H, $H_{4,6,7,9}$-naphthalimide).

Discussion

Apoptosis can be triggered via the intrinsic (mitochondrial) pathway. In this pathway, various cellular signals influence mitochondrial membrane permeability, leading to the release of cytochrome C and subsequent activation of caspase-9. The modulation of mitochondrial membrane permeability is primarily regulated by Bcl-2 family proteins. Translocation of these proteins to the outer mitochondrial membrane reduces the mitochondrial membrane potential, thereby promoting apoptotic signaling.

In this study, the physicochemical properties of the following compounds were examined: 4-(p-tolyl)thiazol-2-amine (3a), 4-(4-iodophenyl)thiazol-2-amine (3b), 2-(4-phenylthiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4a), 2-(4-(3-hydroxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4b), 2-(4-(3-methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4c), 2-(4-(4-methoxyphenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4d), 2-(4-(4-chlorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4e), 2-(4-(4-bromophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4f), 2-(4-(4-fluorophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4g), 2-(4-(4-iodophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4h), 2-(4-(p-tolyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4i), and 2-(4-(4-nitrophenyl)thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4j).

The release of intracellular hydrolases contributes to the degradation of cellular macromolecules. Among these hydrolases, cathepsins are particularly notable. Although lysosomes and cathepsins play more prominent roles in autophagy and necrosis, evidence suggests that they can also significantly influence apoptosis. Several mechanisms can enhance lysosomal membrane permeability, with reactive oxygen species (ROS) being a key factor that reduces lysosomal membrane potential.

Based on the evaluation of the pharmacological properties of the synthesized derivatives, such as solubility, stability, and membrane permeability, further synthesis and optimization of novel compounds is recommended to explore their potential bioactivity.

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