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RESEARCH ARTICLE

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Synthesis, anticancer evaluation and in silico studies of novel N-substituted arylidenethiazolidine-2,4-dione derivatives as adenosine monophosphate-activated protein kinase activators

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Abstract

Design and development of AMP-activated protein kinase (AMPK) activator emerged as a potential therapeutic approach for various types of cancers. In this context, thiazolidine 2,4-dione was invariably found as an important skeleton for the development of new lead compounds. The present study described the synthesis and antitumor evaluation of new hybrids of *N*-substituted arylidenethiazolidine-2,4-diones as AMPK activators. The in vitro results revealed that several of newly prepared compounds exhibited significant anticancer activity against human prostate cancer (PC3) and breast cancer (MDMB-231) cell growths with IC_{50} in the range of 2–10 μM. Particularly, molecular hybridization of thiazolidine 2,4-dione with N-2-(4-(trifluoromethyl) phenyl)ethanol and azaindole (compound **16**) was the most effective among the series against both PC3 and MDMB-231 cell lines with IC_{50} 4.28 and 2.5 μM, respectively. Western blot analysis of these thiazolidine 2,4-dione hybrids showed increased (p)-AMPK level in the PC-3 cells indicating direct activation of AMPK. The docking studies at the interface of activator binding site of the AMPK reinforced the in vitro results of potent compounds **13**, **16**, and **25** having low docking scores −9.0, −9.5, and −9.1 Kcal/mol, respectively.

1 | INTRODUCTION

Adenosine monophosphate-activated protein kinase (AMPK) is serine/threonine protein kinase found in the all-eukaryote species and plays a pivotal role in the regulation of cellular processes such as metabolism, inflammation, and proliferation [1, 2]. Structurally, AMPK is heterotrimeric in nature and consists of three subunits, namely, catalytic α subunit, regulatory β, and γ subunits encoded with distinct genes for activation/deactivation processes [3, 4]. Recent studies showed that activated AMPK functioned as metabolic tumor suppressor that inhibited both PI3K/Akt pathway as well as the cell cycle regulatory proteins p21, p27, and p53 leading to inhibition of cell proliferation and cell cycle arrest [5, 6]. Consequently, a number of natural products, herbal medicines, and synthetic small molecule heterocycles have been reported as AMPK activators against various cancer cell growths [2, 7, 8]. Thus, AMPK emerged as a druggable target for the treatment of various types of cancers.

In the quest of newer and potent anticancer agents, molecular-hybridization approach turned out as an

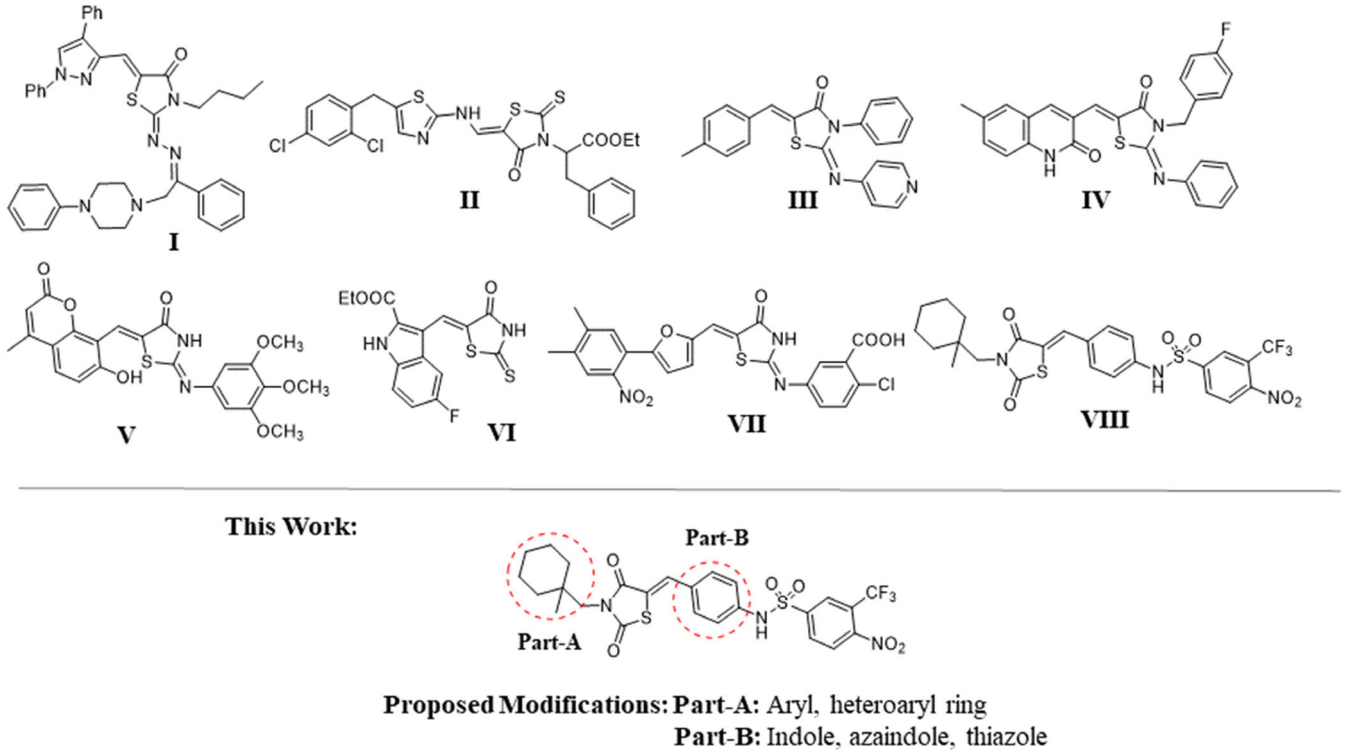


FIGURE 1 Representative examples of 2,4-thiazolidinone based anticancer agents and proposed modifications.

important strategy in the design and development of small molecule-based kinase inhibitors/activators for cancer therapy [9, 10]. For that purpose, thiazolidine 2,4-dione skeleton has been extensively utilized to obtain novel anticancer agents [11–13]. For instance, combination of 2,4-thiazolidinone with privileged scaffolds (Figure 1) such as pyrazole (I) [14], thiazole (II) [15], pyridine (III) [16], quinoline (IV) [17], coumarin (V) [18], and indole (VI) [19] led to potent anticancer activities against numerous cell growths. Further studies toward mechanism of action indicated that most of these privileged scaffolds-thiazolidine 2,4-dione hybrids exerted variety of mechanism such as potent inhibitors of VEGFR2-tyrosine kinases [13], apoptosis inducers through caspase-dependent pathways [16], and inhibition of carbonic anhydrases [17] as well as tubulin polymerization [20]. Moreover, hybrids of *N*-substituted arylidenethiazolidine-2,4-dione with substituted furan (Figure 1, VII) [21, 22] or benzene sulfonamide derivative (VIII) [23] have also been reported as AMPK activator with significant anticancer activity. These reports underline the scope for the design and development of new hybrids of thiazolidine 2,4-dione as AMPK activator and anticancer agents.

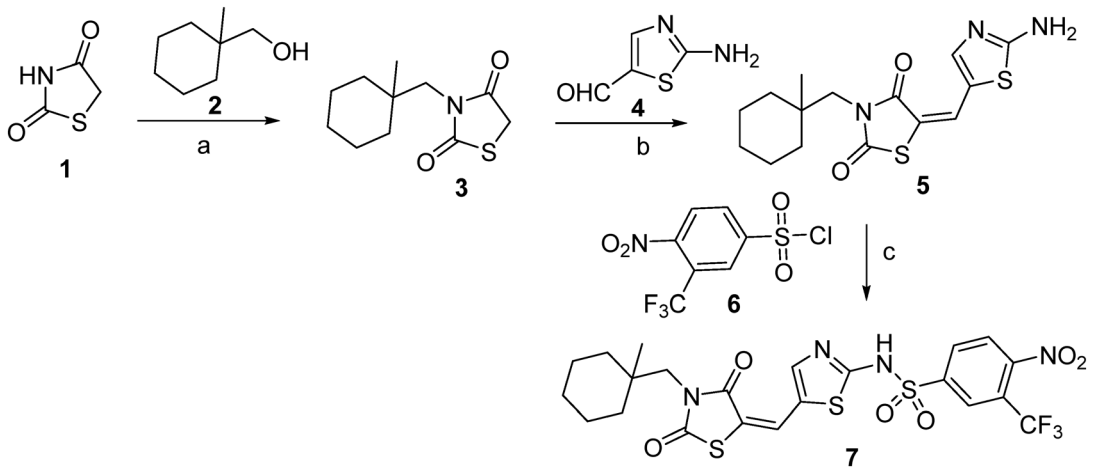
Based on aforementioned findings and continuing our research interest in the discovery of newer and potent bioactive agents [24], it was sought to hybridize thiazolidine-2,4-diones with effective antitumor moieties such as indole, azaindole, and thiazole (Figure 1). Herein, we report synthesis and anticancer evaluation of novel *N*-substituted arylidenethiazolidine-2,4-diones as AMPK activators.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

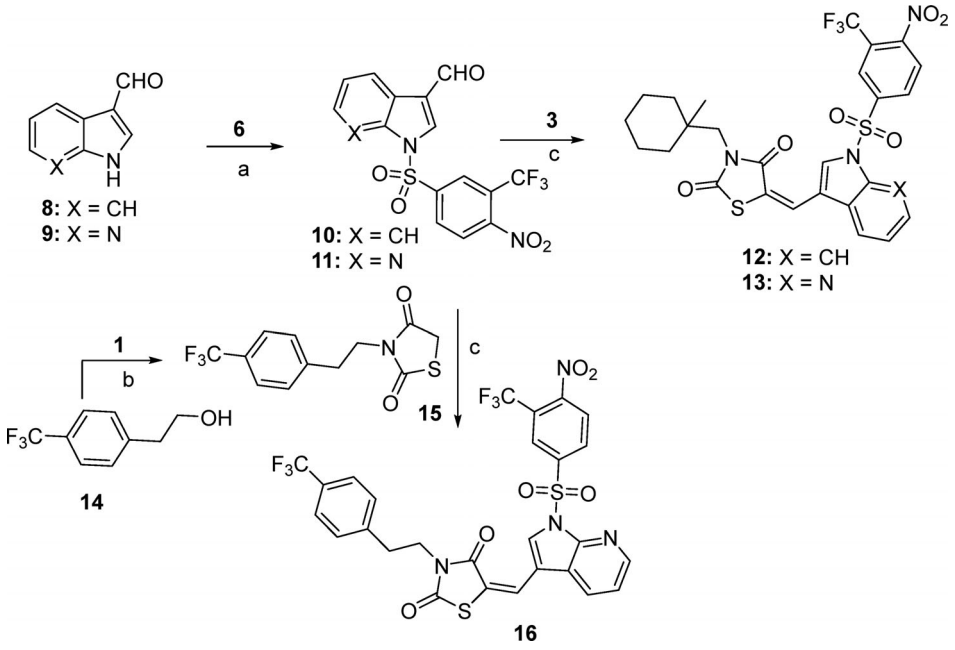
Scheme 1 represented the synthesis of new hybrids of *N*-substituted heteroarylidene of thiazolidine-2,4-diones bearing thiazole heterocycle. Initially, commercially available thiazolidine 2,4-dione (**1**) was reacted with (1-methylcyclohexyl)methanol (**2**) under standard Mitsunobu reaction condition (DIAD/PPh_3) [25] to get *N*-substituted intermediate (**3**) [23] which was further treated with commercially available 2-aminothiazole-5-carbaldehyde (**4**) using catalytical piperidine to prepare corresponding *N*-substituted arylidenethiazolidine-2,4-dione (**5**). The coupling of aminothiazole (**5**) with 4-nitro-3-(trifluoromethyl)benzenesulfonyl chloride (**6**) was carried out by TEA at room temperature to get targeted hybrid of *N*-substituted arylidenethiazolidine-2,4-diones with thiazole- benzenesulfonamide (**7**) in excellent yield (83%).

The synthesis of novel hybrids of *N*-substituted heteroarylidenes of thiazolidine 2,4-diones containing



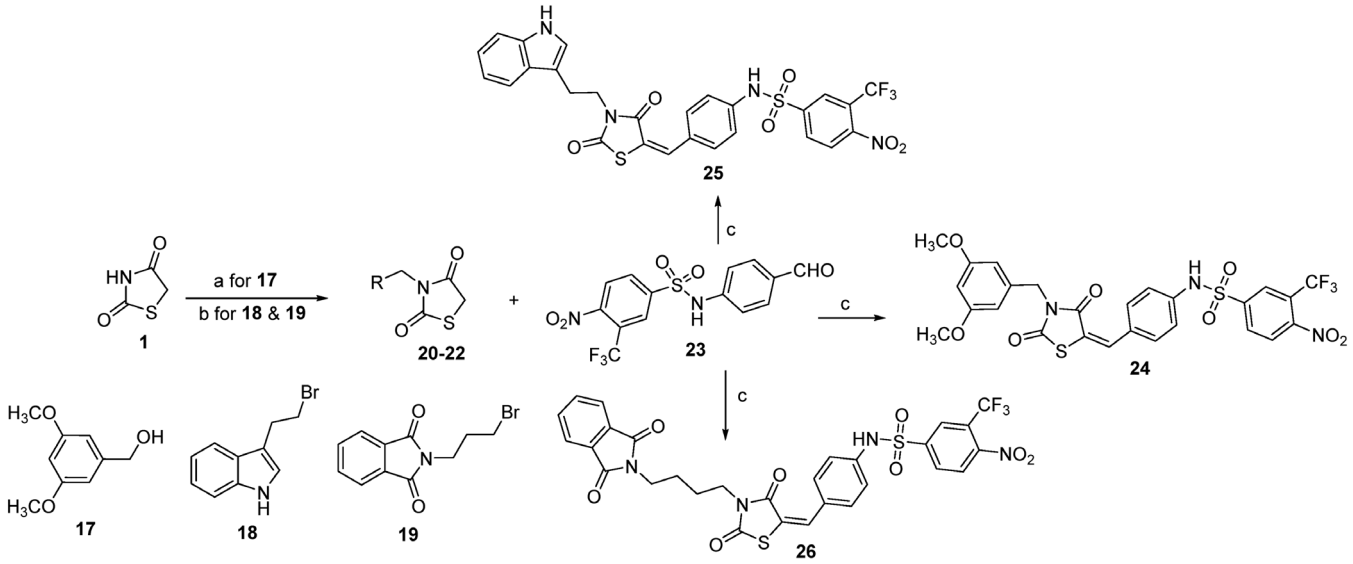
SCHEME 1 Synthesis of novel hybrids of *N*-substituted heteroarylidene of thiazolidine-2,4-diones bearing thiazole. Reaction conditions: (a) DIAD, PPh_3, THF; (b) **4**, Piperidine, EtOH, Reflux; (c) **6**, TEA, DCM, room temperature.

SCHEME 2 Synthesis of novel hybrids of *N*-substituted heteroarylidenes of thiazolidine 2,4-diones containing indole/azaindole scaffolds. Reaction conditions: (a) **6**, TEA, DMAP, DCM; (b) **14**, DIAD, PPh_3, THF; (c) **3 or 15**, Piperidine, EtOH, Reflux.



indole/azaindole scaffolds is depicted in Scheme 2. Commercially available indole 3-carbaldehyde (**8**) or 7-azaindole 3-carbaldehyde (**9**) were reacted with 4-nitro-3-(trifluoromethyl)benzenesulfonyl chloride (**6**) under basic conditions to generated corresponding phenylsulfonyl-indole-3-carbaldehydes (**10** and **11**). Reaction of *N*-cyclohexyl substituted intermediate (**3**) with the aldehydes **10** and **11** in EtOH/piperidine under reflux conditions produced thiazolidine 2,4-dione-indole/azaindole hybrids (**12** and **13**). On the other hand, synthesis thiazolidine-2,-4-dione appended with N-2-(4-(trifluoromethyl)phenyl)ethanol and azaindole nucleus (**16**) was carried out by treating thiazolidine 2,4-dione (**1**) with 2-(4-(trifluoromethyl)phenyl)ethanol (**14**) under Mitsunobu reaction condition followed by reaction with azaindole-3-carbaldehyde (**6**) in EtOH/piperidine under reflux.

Scheme 3 depicted the synthesis of some *N*-heteroarene substituted arylidenes of thiazolidine 2,4-diones hybrids. The requisite *N*-heteroarene substituted thiazolidine 2,4-diones (**20**–**22**) was achieved from corresponding commercially available alcohol and alkyl bromides (**17** to **19**) either through Mitsunobu condition (DIAD/PPh_3) or by K_2CO_3/DMF, respectively. Thus obtained thiazoldine 2,4-diones (**20**–**22**) were treated with N-(4-formylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide (**23**) [23] in the presence of catalytical pieridine in refluxing EtOH to furnish desired *N*-heteroarene substituted arylidenes of thiazolidine 2,4-diones hybrids (**24**–**26**) in excellent yields.



SCHEME 3 Synthesis of some *N*-heteroarene substituted arylidenes of thiazolidine 2,4-diones hybrids. Reaction conditions: (a) **17**, DEAD, PPh_3, THF; (b) **18** or **19**, K_2CO_3, DMF, room temperature; (c) Piperidine, EtOH, Reflux.

The structure establishment of the newly prepared compounds was carried out by ^1H & ^{13}C NMR spectroscopy and elemental analysis.

2.2 | In vitro antitumor activity

The antiproliferative effect of the newly prepared N-substituted arylidenethiazolidine-2,4-dione derivatives (**7, 12, 13, 16, 24, 25**, and **26)** was evaluated against human prostate cancer (PC3) and breast cancer cell line (MDMB-231) using MTT assay and the results are presented in Table 1. As evident, most of the synthesized compounds exhibited potent antitumor activity with $IC_{50} < 10$ μM against both PC3 and MDMB-231 cell growths. Interestingly, PC3 cells were found more susceptible than MDMB-231 cells against these agents. Of these derivatives, thiazolidine 2,4-dione containing indole or azaindole scaffolds (**12, 13**, **16**, **25**) found to be more potent than thiazole-thiazolidine 2,4-dione hybrid (**7**). Particularly, molecular hybridization of thiazolidine 2,4-dione with N-2-(4-(trifluoromethyl)phenyl)ethanol and azaindole (compound **16**) was the most effective among the series resulted in potent antiproliferative activity toward both PC3 and MDMB-231 cell lines with IC_{50} 4.28 μM and 2.5 μM, respectively.

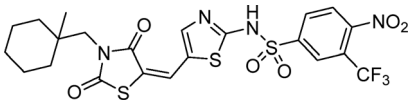
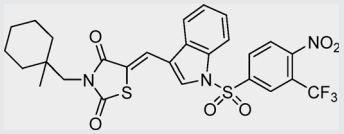
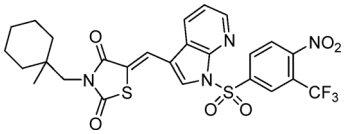
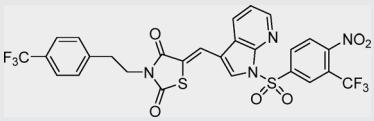
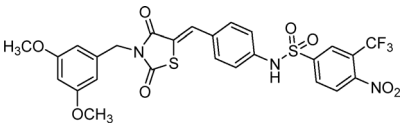
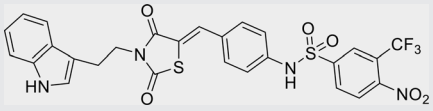
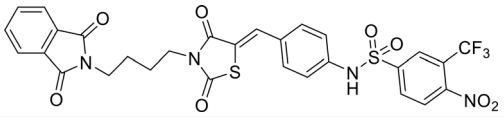
To assess whether the anticancer activity of these agents was associated with AMPK activation, PC-3 cells were treated with 5 μM of synthesized *N*-substituted arylidenethiazolidine-2,4-dione derivatives for 24 h and the lysates were subjected to the western blot analysis (Figure 2). Interestingly, we found that PC-3 cells treated with compound **13**, **16**, **24**, and **25** showed significantly increased phosphorylated (p)-AMPK compared to DMSO and total AMPK protein content. The results indicated that these thiazolidine 2,4-dione hybrids might have exerted antitumor activity through direct activation of AMPK. However, compounds **7** and **26** were less effective for the AMPK activation under the tested condition which might be due to their low potency or possessed different mechanism of action.

3 | MOLECULAR DOCKING ANALYSIS

The molecular docking analysis has been exploited as an important tool to predict the energetically favorable binding mode of a ligand with its receptor [26]. To assess the binding energy and putative binding mode with AMPK, all the synthesized compounds were docked in the activator binding site of AMPK (PDB: 6C9F) using the co-crystallized ligand 5-{[6-chloro-5-(1-methyl-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy}-*N*-hydroxy-2-methylbenzamide (R734) [27]. To ensure accuracy, the docking protocol was first validated by re-docking of R734 with AMPK crystal structure (PDB: 6C9F) and re-reproduced the crystal pose with low RMSD value (Figure 3).

Next, by employing the validated protocol, all the synthesized compounds were docked at the interface of activator binding site of the AMPK. Table 2 outlines the calculated docking scores and the interactions with the protein residues. The study revealed that compounds

TABLE 1 Antitumor activity of newly synthesized *N*-substituted arylidenethiazolidine-2,4-diones against human prostate cancer (PC3) and human breast cancer cell line (MDMB-231).

Compound	Structure	Cell growth inhibition ($IC_{50} \pm SD$)	
		PC3 (μM)	MDMB-231 (μM)
7		>10	>10
12		9.62 ± 0.27	>10
13		5.32 ± 0.18	>10
16		4.28 ± 0.16	2.65 ± 0.09
24		7.23 ± 0.23	>10
25		5.13 ± 0.12	8.47 ± 0.16
26		7.81 ± 0.14	8.28 ± 0.08

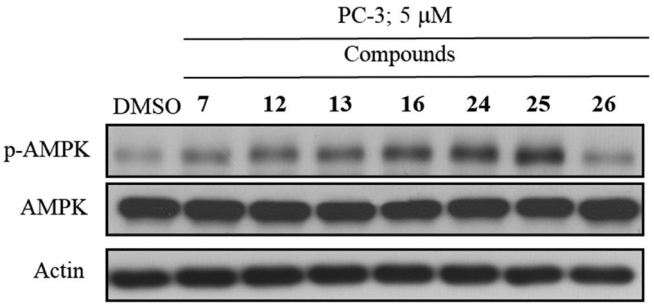


FIGURE 2 Western blot analysis of effect of newly prepared 2,4-thiazolidinone hybrids on activation of AMP-activated protein kinase in PC-3 cell line.

13, **16**, and **25** have higher affinity toward AMPK with low docking scores −9.0, −9.5, and − 9.1 Kcal/mol, respectively, compared to the other derivatives of series. The binding pose (3D) of most active compounds **13**, **16**, and **25** within the binding pocket receptor is represented in Figure 4. As evident, these derivatives possessed several interactions such as H-bond, π-cation, hydrophobic as well as halogen bond interactions with the residues of AMPK protein. For instance, compound **13** incorporated in two H-bond interaction with Asp90 and Arg83 residue as well as π-cation interaction with Lys53 through azaindole nucleus. Compound **16** showed hydrophobic interactions with residues of Ile48, Gln52, and Val113 through Ar-CF_3 substituent. It is also incorporated in favorable H-bonding and π-cation with Lys53 through azaindole nucleus while several halogen bond interactions with Thr106, Asp108, and Glu139 via CF_3 group. Similarly, compound **25** demonstrated two H-bond interaction with Asn50 and Lys53 and seven hydrophobic interactions with Val13, Val26, Lys31, Lys53, Asp108, Asn111, and Val113 via indole-2,4-thiazolidinone moiety within the binding pocket. The comparison of compounds having lower (**7**,**12**, and **24**) and higher (**13**, **16**, and **25**) docking score, it was revealed that a number of binding interactions including H-bonding and π-cation with Lys53, Arg83,

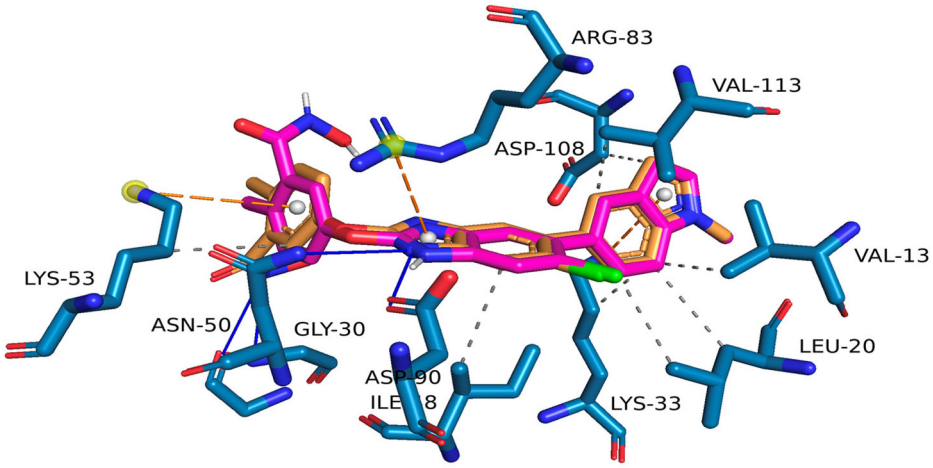


FIGURE 3 Crystal structure pose of R734 reproduced as a part of the validation of the docking process.

TABLE 2 Docking scores and interactions with the amino acids in the activator binding site of AMP-activated protein kinase.

Sr No	Compound	Docking score (kcal/mol)	Interactions with amino acids
1	**R734 (bound)**	−11.2	Hydrophobic: A:Val13, A:Leu20, A:Lys33, A:Ile48, A:Lys53, B:Asp108, B:Val113 H-Bond: A:Gly27, A:Gly30, A:Asn50, B:Arg83, A:Asp90 π-Cation: A:Lys33, A:Lys53, B:Arg83
2	**7**	−8.9	Hydrophobic: A:Lys31, A:Ile48, A:Gln52 H-Bond: A:Lys31, A:Asn50, B:Arg83, B:Asn111 π-Cation: B:Arg83 Halogen Bond: A:Asp90
3	**12**	−7.9	Hydrophobic: A:Val13, A:Leu20, A:Ile48, A:Phe92, B:Val81, B:Val113 H-Bond: A:Asn50, A:Lys53 π-Cation: A:Lys53 Halogen Bond: B:Asp108
4	**13**	−9.0	Hydrophobic: A:Val26, A:Lys31, A:Ile48 H-Bond: A:Asp90, B:Arg83 π-Cation: A:Lys53 Halogen Bond: A:Asp90
5	**16**	−9.5	Hydrophobic: A:Ile48, A:Gln52, B:Val113 H-Bond: A:Asn50, A:Lys53 π-Cation: A:Lys53, B:Arg83 Halogen Bond: B:Thr106, B:Asp108, B:Glu139
6	**24**	−8.7	Hydrophobic: A:Val13, A:Asn50, A:Lys53, B:Thr106, B:Asn111, B:Val113 H-Bond: A:Lys31, A:Lys33, B:Arg83, B:Thr106 Halogen Bond: A:Asp22, A:Thr23
7	**25**	−9.1	Hydrophobic: A:Val13, A:Val26, A:Lys31, A:Lys53, B:Asp108, B:Asn111, B:Val113 H-Bond: A:Asn50, A:Lys53 Halogen Bond: B:Asn111
8	**26**	−8.7	Hydrophobic: A:Lys31, A:Lys33, A:Ile48, A:Lys53, B:Thr106 π-Cation: A:Lys33 Halogen Bond: B:Asn111

hydrophobic interactions with Ile48, Gln52, Val113, and halogen bond interaction with Thr106, Asp108 were crucial for the energetically stable complex formation for later compounds with AMPK. These findings also corroborated with their in vitro antitumor activity.

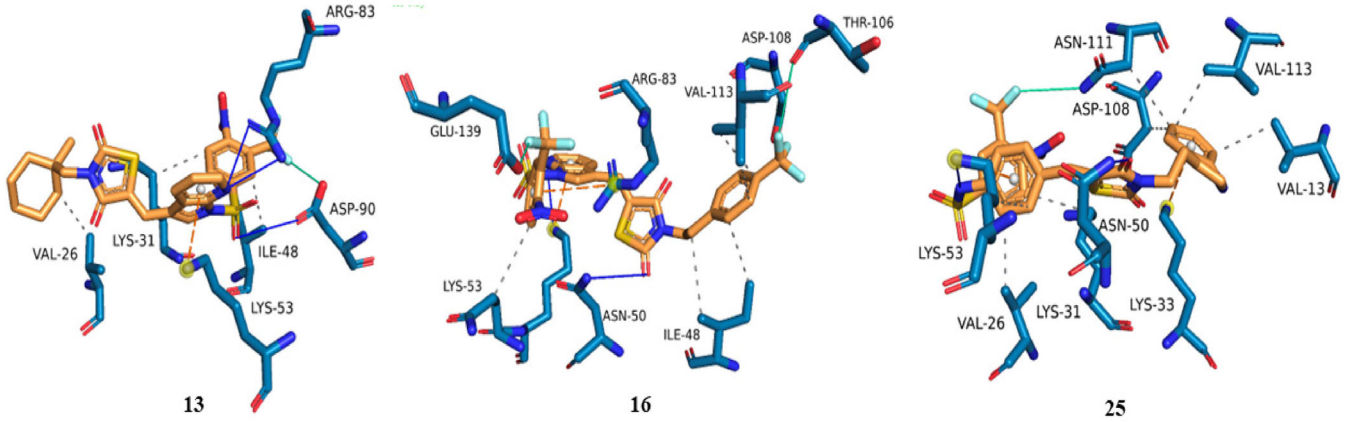


FIGURE 4 3-D pose of binding site interactions of activator compounds **13**, **16**, and **25**, in complex with AMP-activated protein kinase.

4 | CONCLUSION

A series of novel hybrids of *N*-substituted arylidenethiazolidine-2,4-diones designed through molecular-hybridization approach has been synthesized and evaluated for anticancer activity as AMPK activator. The in vitro results revealed that several of the newly prepared compounds (**13**, **16**, and **25**) exhibited significant anticancer activity against human prostate cancer (PC3) and breast cancer (MDMB-231) cell growths with $IC_{50} < 10$ μM. Interestingly, PC-3 cells were found more vulnerable against these hybrids. Of these, molecular hybridization of thiazolidine 2,4-dione with azaindole (compound **16**) was the most effective with IC_{50} 4.28 and 2.5 μM against PC3 and MDMB-231 cell growth respectively. AMPK activation studies in the PC-3 cells employing western blot analysis showed significantly increased (p)-AMPK level indicating direct activation of AMPK. The molecular docking studies of the newly prepared compounds at the interface of activator binding site of the AMPK also reinforced results showing efficient binding ability toward AMPK. In the present study, compound **16** was found to be a potential AMPK activator endowed with potent anticancer potential and warrants further investigation.

5 | EXPERIMENTAL SECTION

5.1 | General methods

All the commercial grade chemicals, reagents, and organic solvents were procured from Loba Chemie or Sigma-Aldrich and were utilized without further purification. The reaction progress was monitored by TLC plate pre-coated with silica gel G. The purification of compound was carried out by column chromatography over silica gel (100–200 mesh) using appropriate solvents. ^{1}H & ^{13}C NMR spectra of the synthesized compounds were recorded on a Bruker 300 MHz spectrometer using TMS as internal standard and $CDCl_3$ or DMSO-*d6* as solvent. The chemical shifts (δ) were reported in parts per million (ppm) relative to the TMS peak. Elemental analysis was carried out in Elementar vario MICRO cube instrument.

5.2 | Synthetic methods for compounds outlined in Schemes 1 to 3

5.2.1 | 3-((1-Methylcyclohexyl)methyl) thiazolidine-2,4-dione(3) [23]

To a mixture of thiazolidine-2,4-dione (**1**) (1.17 g, 10 mmol), (1-methylcyclohexyl)methanol, (1.28 g, 10 mmol), and triphenylphospine (2.62 g, 10 mmol) in dry THF (50 mL), a solution of Diisopropylazodicarboxylate (DIAD) (2.42 g, 12 mmol) in dry THF (15 mL) was added dropwise at room temperature. After completion of addition, the reaction mixture was further stirred at room temperature for 6 h. After completion of the reaction, the mixture was diluted with water (100 mL) and extracted twice with ethyl acetate (50 mL). The combined organic phase was dried over anhy. Na_2SO_4 and filtered. After evaporation of solvent under vacuo, the residue was purified by column chromatography (EA:Hexane, 10:90 v/v) to give 3-((1-methylcyclohexyl) methyl)thiazolidine-2,4-dione (**3**); Yield: 2.02 g (89%). ^{1}H NMR. (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.27–1.54 (m, 10H), 3.51 (s, 2H), 3.92 (s, 2H).

5.2.2 | 5-((2-aminothiazol-5-yl)methylene)-3-((1-methylcyclohexyl)methyl)thiazolidine-2,4-dione (5)

3-((1-Methylcyclohexyl)methyl)thiazolidine-2,4-dione(**3**) (1.135 g, 5 mmol), 2-aminothiazole-5-carbaldehyde

(0.640 g, 5 mmol), piperidine (1–2 drops), EtOH (30 mL) was stirred at reflux temperature for 16 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give 5-((2-aminothiazol-5-yl)methylene)-3-((1-methylcyclohexyl)methyl) thiazolidine-2,4-dione (**5**). Yield; 1.28 g (76%). ^{1}H NMR (300 MHz, DMSO-*d*6) δ 0.84 (s, 3H), 1.23–1.47 (m, 10H), 3.48 (s, 2H), 7.72 (s, 1H), 8.01 (s, 1H), 8.13 (brs, 2H); Anal. Calcd. For $C_{15}H_{19}N_3O_2S_2$: C, 53.39; H, 5.68; N, 12.45; S, 19.00; Found: C, 53.36; H, 5.62; N, 12.44; S, 19.03.

5.2.3 | *N*-(5-((3-((1-Methylcyclohexyl) methyl)-2,4-dioxothiazolidin-5-ylidene)methyl) thiazol-2-yl)-4-nitro-3-(trifluoromethyl) benzenesulfonamide (7)

A solution of 5-((2-aminothiazol-5-yl)methylene)-3-((1-methylcyclohexyl)methyl) thiazolidine-2,4-dione (**5**) (0.34 g, 1 mmol) in dichloromethane (25 mL) containing triethylamine (0.20 g, 2 mmol) cooled to 0°C. To this, a solution of 4-nitro-3-(trifluoromethyl)benzenesulfonyl chloride (**6**) (0.288 g, 1 mmol) was added dropwise and further stirred at room temperature for 3 h. After completion (TLC monitored) of reaction, the organic layer was washed with dilute HCl (1%) followed by water and brine. The organic layer was dried over anhy.Na_2SO_4 and evaporated to dryness. The residue was crystallized from EtOH to give N-(5-((3-((1-methylcyclohexyl) methyl)-2,4-dioxothiazolidin-5-ylidene)methyl)thiazol-2-yl)-4-nitro-3-(trifluoromethyl)benzene sulfonamide (**7**). Yield; 0.49 g (83%). ^{1}H NMR (300 MHz, DMSO-*d*6) δ 0.85 (s, 3H), 1.16–1.47 (m, 10H), 3.49 (s, 2H), 7.97 (s, 1H), 8.03 (s, 1H), 8.27 (s, 1H), 8.34–8.42 (m, 2H), 10.59 (s, 1H); ^{13}C NMR (300 MHz, DMSO) δ 21.28, 22.90, 25.58, 35.51, 35.98, 52.08, 118.75, 119.80, 122.49, 122.67, 123.59, 125.31, 127.13, 132.07, 134.12, 134.19, 145.75, 148.95, 165.74, 166.83, 169.22; Anal. Calcd. For $C_{22}H_{21}F_3N_4O_6S_3$: C, 44.74; H, 3.58; N, 9.49; S, 16.28; Found: C, 44.70; H, 3.61; N, 9.44; S,16.36.

5.2.4 | 1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-indole-3-carbaldehyde (10)

A solution of 1H-indole-3-carbaldehyde (**8**) (0.28 g, 2 mmol), triethylamine (0.22 g, 2.2 mmol) and DMAP (15 mg) in dry DCM (20 mL) was cooled to 0°C. To this, a solution of 4-nitro-3-(trifluoromethyl)benzenesulfonyl chloride (**6**) (0.288 g, 1 mmol) in dry DCM (10 mL) was added dropwise and further stirred at room temperature for 10 h. After completion (TLC monitored) of reaction, the organic layer was washed with dilute HCl (1%) followed by water and brine. The organic layer was dried over anhy.Na_2SO_4 and evaporated to dryness. The residue was crystallized from EtOH to give 1-((4-nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1H-indole-3-carbaldehyde (**10**). Yield: 0.72 g (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.92 (m, 3H), 8.23 (d, $J = 8.7$ Hz, 1H), 8.21–8.240 (m, 1H), 8.73 (s, 1H), 8.82 (d, $J = 8.4$ Hz, 2H), 9.08 (s, 1H), 10.13 (s, 1H); Anal. Calcd. For $C_{16}H_9F_3N_2O_5S$: C, 48.25; H, 2.28; N, 7.03; S, 8.05; Found C, 48.29; H, 2.25; N, 7.05; S, 8.11.

5.2.5 | 1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (11)

A solution of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**9**) (0.29 g, 2 mmol), triethylamine (0.22 g, 2.2 mmol) and DMAP (15 mg) in dry DCM (25 mL) was cooled to 0°C. To this, a solution of 4-nitro-3-(trifluoromethyl)benzenesulfonyl chloride (**6**) (0.29 g, 1 mmol) in dry DCM (10 mL) was added dropwise and further stirred at room temperature for 10 h. After completion (TLC monitored) of reaction, the organic layer was washed with dilute HCl (1%) followed by water and brine. The organic layer was dried over anhy.Na_2SO_4 and evaporated to dryness. The residue was crystallized from EtOH to give 1-((4-nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **(11)**: Yield: 0.65 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.52 (m, 1H), 8.44–8.52 (m, 3H), 8.81–8.83 (m, 2H), 9.00 (s, 1H), 10.08 (s, 1H); Anal. Calcd. For $C_{15}H_8F_3N_3O_5S$: C, 45.12; H, 2.02; N, 10.52; S, 8.03; Found C, 45.08; H, 2.00; N, 10.55; S, 8.16.

5.2.6 | 3-((1-Methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-indol-3-yl)methylene)thiazolidine-2,4-dione (12)

A mixture of 3-((1-methylcyclohexyl)methyl)thiazolidine-2,4-dione (**3**) (0.22 g, 1 mmol) and 1-((4-nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1H-indole-3-carbaldehyde (**10**) (0.39 g, 1 mmol), piperidine (1–2 drops), EtOH (20 mL) was stirred at reflux temperature for 18 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give 3-((1-methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-indol-3-yl)methylene)thiazolidine-2,4-dione (**12**). Yield; 0.46 g (77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.29–1.56 (m, 10H), 3.63 (s, 2H), 7.27–7.33 (m, 2H), 7.69 (s, 1H), 7.92 (d, $J = 6.3$ Hz,

1H), 8.17–8.21 (m, 4H), 8.51–8.53 (m, 1H); ^{13}C NMR (300 MHz, DMSO) δ 21.34, 23.13, 25.65, 35.66, 35.70, 25.99, 51.36, 109.29, 11.69, 112.31, 115.15, 117.25, 119.01, 125.30, 126.68, 127.56, 129.31, 142.93, 148.63, 149.73, 166.40, 167.90; Anal. Calcd. For $C_{27}H_{24}F_3N_3O_6S_2$: C, 53.37; H, 3.98; N, 6.92; S, 10.55; Found C, 53.40; H, 4.02; N, 6.89; S, 10.49.

5.2.7 | 3-((1-Methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) methylene)thiazolidine-2,4-dione (13)

A mixture of 3-((1-methylcyclohexyl)methyl)thiazolidine-2,4-dione (**3**) (0.22 g, 1 mmol) and 1-((4-Nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **(11)** (0.39 g, 1 mmol), piperidine (1–2 drops), EtOH (20 mL) was stirred at reflux temperature for 18 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give 3-((1-Methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-pyrrolo [2,3-b]pyridin-3-yl)methylene)thiazolidine-2,4-dione (**13**). Yield; 0.52 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.28–1.62 (m, 10H), 3.66 (s, 2H), 7.28–7.35 (m, 3H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.56 (d, $J = 2.7$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 8.27 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.95, 23.07, 26.26, 36.29, 36.86, 52.69, 111.90, 112.67, 116.14, 118.98, 121.99, 124.15, 125.66, 126.89, 127.26, 135.96, 167.47, 168.59; Anal. Calcd. For $C_{26}H_{23}F_3N_4O_6S_2$: C, 51.31; H, 3.81; N, 9.21; S, 10.54; Found C, 51.40; H, 3.85; N, 9.22; S, 10.57.

5.2.8 | 3-(4-(trifluoromethyl)phenethyl) thiazolidine-2,4-dione (15)

To a mixture of thiazolidine-2,4-dione (**1**) (0.56 g, 5 mmol), 2-(4-(trifluoromethyl)phenyl)ethan-1-ol (**14**, 0.95 g, 5 mmol) and triphenylphospine (0.66 g, 5 mmol) in dry THF (40 mL), a solution of Diisopropylazodicarboxylate DIAD (1.21 g, 6 mmol) in dry THF (15 mL) was added dropwise at room temperature. After completion of addition, the reaction mixture was further stirred at room temperature for 4 h. After completion of the reaction, the mixture was diluted with water (100 mL) and extracted twice with ethyl acetate (50 mL). The combined organic phase was dried over anhy. Na_2SO_4 and filtered. After evaporation of solvent under vacuo, the residue was purified by column chromatography (EA:Hexane, 30:70 v/v) to give 3-(4-(trifluoromethyl)phenethyl)thiazolidine-2,4-dione (**15**); Yield: 1.19 g (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (t, $J = 7.5$ Hz, 2H), 3.87 (t, $J = 6.0$ Hz, 2H), 3.92 (s, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 8.1$ Hz, 1H); Anal. Calcd. For $C_{12}H_{10}F_3NO_2S$: C, 49.83; H, 3.48; N, 4.84; S, 11.08; Found C, 49.80; H, 3.53; N, 4.80; S, 11.05.

5.2.9 | 5-((1-((4-nitro-3-(trifluoromethyl) phenyl)sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) methylene)-3-(4-(trifluoromethyl)phenethyl) thiazolidine-2,4-dione (16)

A mixture of 3-(4-(trifluoromethyl)phenethyl)thiazolidine-2,4-dione (**15**) (0.29 g, 1 mmol) and 1-((4-Nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **(11)** (0.39 g, 1 mmol), piperidine (1–2 drops), EtOH (25 mL) was stirred at reflux temperature for 18 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give 3-((1-Methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methylene)thiazolidine-2,4-dione (**13**). Yield; 0.52 g (85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.09 (t, $J = 6.6$ Hz, 2H), 3.92 (t, $J = 6.6$ Hz, 2H), 7.21–7.25 (m, 1H), 7.43 (d, $J = 7.6$ Hz, 2H), 7.64 (d, $J = 7.6$ Hz, 2H), 7.86 (s, 1H), 8.05–8.25 (m, 2H), 8.34–8.47 (m, 2H), 8.57–8.64 (m, 1H), 8.94 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 33.42, 113.33, 124.21, 124.85, 125.12, 125.17, 126.16, 126.74, 127.43, 129.53, 132.37, 142,41, 143.02, 143.26, 149.45, 166.88, 166.92. Anal. Calcd. For $C_{27}H_{16}F_6N_4O_6S_2$: C, 48.36; H, 2.41; N, 8.36; S, 9.56; Found C, 48.39; H, 2.40; N, 8.30; S, 9.53.

5.2.10 | 3-(3,5-dimethoxybenzyl) thiazolidine-2,4-dione (20)

To a mixture of thiazolidine-2,4-dione (**1**) (0.56 g, 5 mmol), (3,5-dimethoxyphenyl)methanol (**17**) (0.84 g, 5 mmol), and triphenylphospine (0.66 g, 5 mmol) in dry THF (30 mL), a solution of Diisopropylazodicarboxylate (DIAD) (1.21 g, 6 mmol) in dry THF (15 mL) was added dropwise at room temperature. After completion of addition, the reaction mixture was further stirred at room temperature for 6 h. After completion of the reaction, the mixture was diluted with water (100 mL) and extracted twice with ethyl acetate (50 mL). The combined organic phase was dried over anhy. Na_2SO_4 and filtered. After evaporation of solvent under vacuo, the residue was purified by column chromatography (EA:Hexane, 40:60 v/v) to give 3-(3,5-dimethoxybenzyl)thiazolidine-2,4-dione (**20**); Yield: 1.07 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 6H), 3.95 (s, 2H), 4.70 (s, 2H), 6.39 (d, $J = 2.1$ Hz, 1H), 6.53 (d, $J = 2.1$ Hz, 2H); Anal. Calcd. For

$C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24; S, 11.99; Found C, 53.99; H, 4.89; N, 5.20; S, 12.02.

5.2.11 | 3-(2-(1H-indol-3-yl)ethyl) thiazolidine-2,4-dione (21)

A mixture of thiazolidine-2,4-dione (**1**) (0.56 g, 5 mmol), 3-(2-bromoethyl)-1H-indole (**18**) (0.84 g, 5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in dry DMF (30 mL) was stirred at room temperature for 7 h. After completion of the reaction, the solvent was removed under vacuo. The residue was diluted with water (50 mL) and extracted twice with ethyl acetate (40 mL). The combined organic phase was dried over anhy. Na_2SO_4 and filtered. After evaporation of solvent under vacuo, the residue was purified by crystallization from EA to give 3-(2-(1H-indol-3-yl)ethyl) thiazolidine-2,4-dione (**21**); Yield: 1.17 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, $J = 7.2$ Hz, 2H), 3.82 (s, 2H), 3.92 (t, $J = 8.1$ Hz, 2H), 7.02 (s, 1H), 7.11–7.20 (m, 2H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 8.03 (brs, 1H); Anal. Calcd. For $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32; Found C, 60.07; H, 4.75; N, 10.79; S, 12.43.

5.2.12 | 3-(4-(1,3-dioxoisoindolin-2-yl)butyl) thiazolidine-2,4-dione (22)

A mixture of thiazolidine-2,4-dione (**1**) (0.56 g, 5 mmol), 2-(3-bromopropyl)isoindoline-1,3-dione (1.34 g, 5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in dry DMF (40 mL) was stirred at room temperature for 5 h. After completion of the reaction, the solvent was removed under vacuo. The residue was diluted with water (50 mL) and extracted twice with ethyl acetate (50 mL). The combined organic phase was dried over anhy. Na_2SO_4 and filtered. After evaporation of solvent under vacuo, the residue was purified by crystallization from EtOH to give 3-(4-(1,3-dioxoisoindolin-2-yl)butyl)thiazolidine-2,4-dione (**22**); Yield: 1.40 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67–1.72 (m, 4H), 3.65–3.72 (m, 4H), 3.95 (s, 2H), 7.72 (d, $J = 3.0$ Hz, 2H), 7.84 (t, $J = 4.5$ Hz, 2H); Anal. Calcd. For $C_{15}H_{14}N_2O_4S$: C, 56.51; H, 4.43; N, 8.80; S, 10.07; Found: C, 56.59; H, 4.40; N, 8.78; S, 10.00.

5.2.13 | *N*-(4-((3-(3,5-dimethoxybenzyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-nitro-3-(trifluoromethyl) benzenesulfonamide (24)

A mixture of 3-(3,5-dimethoxybenzyl)thiazolidine-2,4-dione (**20**) (0.28 g, 1 mmol) and N-(4-formylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide **(23)** (0.37 g, 1 mmol) and piperidine (1–2 drops) in EtOH (25 mL) was stirred at reflux temperature for 16 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give 3-((1-Methylcyclohexyl)methyl)-5-((1-((4-nitro-3-(trifluoromethyl)phenyl) sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) methylene)thiazolidine-2,4-dione (**13**). Yield; 0.57 g (92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.68 (s, 6H), 4.71 (s, 2H), 6.39 (s, 3H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.82 (s, 1H), 8.29–8.34 (m, 3H), 11.01 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 44.62, 55.15, 99.15, 105.60, 120.02. 120.28, 122.89, 126.23, 127.26, 129.04, 131.79, 132.57, 137.62, 138.84, 143.41, 149.36, 160.62, 165.49, 167.23. Anal. Calcd. For $C_{26}H_{20}F_3N_3O_8S_2$: C, 50.08; H, 3.23; N, 6.74; S, 10.28; Found C, 50.06; H, 3.20; N, 6.75; S, 10.25.

5.2.14 | *N*-(4-((3-(2-(1H-indol-3-yl)ethyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-nitro-3-(trifluoromethyl) benzenesulfonamide (25)

A mixture of 3-(2-(1H-indol-3-yl)ethyl)thiazolidine-2,-4-dione (**21**) (0.26 g, 1 mmol) and N-(4-formylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide **(23)** (0.37 g, 1 mmol) and piperidine (1–2 drops) in EtOH (20 mL) was stirred at reflux temperature for 16 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give N-(4-((3-(2-(1H-indol-3-yl)ethyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide **(25)**. Yield; 0.52 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (t, $J = 7.2$ Hz, 2H), 3.89 (t, $J = 7.2$ Hz, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 7.18 (s, 1H), 7.29–7.35 (m, 3H), 7.53–7.56 (m, 3H), 7.80 (s, 1H), 8.31–8.35 (m, 3H), 10.97 (s, 1H), 11.20 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.00, 42.22, 110.10, 111.52, 117.95, 118.46, 120.35, 121.07, 123.12, 126.18, 126.25, 127.04, 127.37, 129.16, 131.71, 131.93, 132.90. 136.26, 138.68, 149.37, 165.57, 167.14. Anal. Calcd. For $C_{27}H_{19}F_3N_4O_6S_2$: C, 52.60; H, 9.24; N, 9.09; S, 10.40; Found C, 52.62; H, 9.28; N, 9.01; S, 10.47.

5.2.15 | *N*-(4-((3-(4-(1,3-dioxoisoindolin-2-yl) butyl)-2,4-dioxothiazolidin-5-ylidene)methyl) phenyl)-4-nitro-3-(trifluoromethyl) benzenesulfonamide (26)

A mixture of 3-(4-(1,3-dioxoisoindolin-2-yl)butyl)thiazolidine-2,4-dione (**22**) (0.32 g, 1 mmol) and *N*-(4-formylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide **(23)**

(0.37 g, 1 mmol) and piperidine (1–2 drops) in EtOH (20 mL) was stirred at reflux temperature for 16 h. The reaction was monitored by TLC. After completion, the reaction was cooled to 0°C and separated solid was filtered to give *N*-(4-((3-(4-(1,3-dioxoisoindolin-2-yl) butyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide (**26**). Yield; 0.59 g (88%). ^{1}H NMR (300 MHz, DMSO d_6) δ 1.41–1.70 (m, 4H), 3.35–3.61 (m, 4H), 7.27 (d, $J = 6.9$ Hz, 2H), 7.50 (d, $J = 7.5$ Hz, 2H), 7.27–7.78 (m, 5H), 8.28–8.32 (m, 3H), 11.20 (s, 1H). ^{13}C NMR (300 MHz, DMSO-d_6) δ 24.51, 25.19, 36.89, 41.07, 119.24, 120.30, 121.00, 122.96, 127.35, 129.13, 131.59, 131.67, 131.90, 132.90, 134.29, 138.63, 143.37, 149.36, 165.66, 167.29, 167.94. Anal. Calcd. For $C_{29}H_{21}F_3N_4O_8S_2$: C, 51.63; H, 3.14; N, 8.31; S, 9.50; Found C, 51.65; H, 3.19; N, 8.34; S, 9.42.

5.3 | Cell viability assay

The in vitro antitumor evaluation was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays as reported previously [23]. The human prostate cancer cell lines (PC-3) and human breast cancer cell lines (PC-3) for screening were cultured in RPMI 1640 medium containing 10% fetal bovine serum. The assay was performed in 96-well plates. The cells were seeded with expected target cell density of 5000–10,000 cells per well in the presence of 10% FBS 24 h prior to treatment. The Test compounds were evaluated at different concentrations ranging from 1 to 10 μM for 24 h in the presence of 5% FBS. The anticancer activity was determined by using formazan dye (MTT) solubilized in 100 μL of DMSO and absorbance was measured at 570 nm.

5.4 | Western blot analysis

Immunoblotting was performed using earlier reported method [23]. After Treatment of PC-3 cells with compound at given concentration (5 μM), treated cells were collected, washed with cold phosphate-buffered saline (PBS), and then cells were lysed using 1% sodium dodecyl sulfate (SDS), 10 m EDTA, and 50 mM Tris–HCl (pH 8.1) in the presence of a protease inhibitor cocktail. The Lysates were then centrifuged for 15 min. and Protein concentrations of the supernatants were determined using a colorimetric bicinchoninic acid assay. Further, an equivalent volume of 2 × SDS-polyacrylamide gel electrophoresis sample loading buffer was added to each sample and incubated for 10 min and equal amounts of protein were resolved in SDS-polyacrylamide gels and then transferred to nitrocellulose membranes. After blocking (Tris-buffered saline), the proteins were further incubated with primary antibody of p-AMPK at 1:1000 dilution in 0.1% Tween 20 (TBST) at 4°C for 2 h, further washed with TBST. The membrane was incubated with immunoglobulin and visualized by enhanced chemiluminescence.

5.5 | Computational studies

The structures of the synthesized molecules (**7**, **12**, **13**, **16**, **24**, **25**, and **26**) were generated using Marvin Sketch (v. 21.15) and Open Babel (v 3.1.1) [28]. In addition, the X-ray crystal structure (PDB ID: 6C9F) retrieved from the Protein Data Bank was prepared using MGLTools (v 1.5.7) and subsequently the molecules were docked using Autodock Vina (v. 1.1.2) into the activator binding site of AMPK as defined by the co-crystallized ligand [29, 30]. The binding site interactions were analyzed using Protein Ligand Interaction Profiler (PLIP) Web-Server [31, 32].

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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