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Synthesis and Antitumor Activity of 3-(2-Phenyl-1,3-thiazol-4-yl)-1*H*-indoles and 3-(2-Phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles

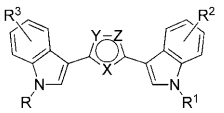
Patrizia Diana,*[a] Anna Carbone,[a] Paola Barraja,[a] Alessandra Montalbano,[a] Barbara Parrino,[a] Alessia Lopergolo,[b] Marzia Pennati,[b] Nadia Zaffaroni,[b] and Girolamo Cirrincione[a]

Given the potent antimicrobial, antiviral, and antitumor activities of many natural products, there is an increasing interest in the synthesis of new molecules based on natural compound scaffolds. Based on a 2,4-bis(3′-indolyl)imidazole skeleton, two new series of phenylthiazolylindoles and phenylthiazolyl-7-azaindoles were obtained by Hantzsch reaction between substituted phenylthioamides and the α-bromoacetyl derivatives. Some azaindole derivatives, tested at the National Cancer Institute against a panel of ~60 tumor cell lines derived from nine human cancer cell types, showed inhibitory effects against all cell lines investigated at micromolar to nanomolar concentrations. Two of them exhibited a high affinity for CDK1, with IC_{50} values of 0.41 and 0.85 μM. These promising results will set the foundation for future investigations into the development of anticancer therapies.

Introduction

Over the last 50 years, the marine environment has been explored in the search for new bioactive compounds. In particular the indole alkaloids class has received a lot of attention because of their potent biological activities, such as, antimicrobial, antiviral, and antitumor activities.[1–4] Nortopsentins A–C having a characteristic 2,4-bis(3′-indolyl)imidazole skeleton, isolated from *Spongosorites ruetzleri*, exhibited in vitro cytotoxicity against P388 cells (IC_{50} values: 4.5–20.7 μM). Their N-methylated derivatives showed a significant improvement in P388 activity relative to that of the parent compounds (IC_{50} values 0.8–2.1 μM).[5] However, a great limitation in the use of marine organisms for therapy is that only very small amounts of the biologically active substances can be isolated from the natural source.

Because of their interesting biological activities, nortopsentins have been considered important lead compounds for the discovery of new biologically active derivatives.[6] We recently reported the synthesis and antitumor activity of a different series of bis-indolyl-5-membered heterocycles **1**–**4**, in which the imidazole moiety of nortopsentin was replaced by thiophene, pyrazole, isoxazole, and furan rings. Some of these compounds showed antiproliferative activity against a wide range of human tumor cell lines with GI_{50} values ranging from micromolar to sub-micromolar concentrations.[7–9] Many other analogues of marine nortopsentins such as 2,4-bis(3′-indolyl)-thiazoles **5**, in which the heterocyclic core of the system is constituted by thiazole have been synthesized. These derivatives showed strong inhibitory activity against a wide range of human tumor cell lines.[10] Also 3,5-bis(2-indolyl)pyridine showed cytotoxic activity against leukemia cells and inhibited CDK1 at micromolar concentrations. A marked cytotoxic effect was observed when one indolyl ring was replaced by a phenyl moiety.[11]



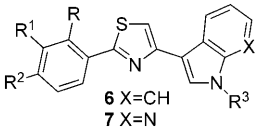
Nortopsentins X=N; Y=CH; Z=NH, NMe; R=H, Me; R^1=H, Me; R^2=H, Br; R^3=H, Br
1 X=S; Y=Z=CH; R=H, Me; R^1=H, Me, SO_2Ph; R^2=R^3=H, Me, OMe, Cl, Br
2 X=CH; Y=N; Z=NH, NMe; R=R^1=Me; R^2=R^3=H, Me, OMe, Cl, Br
3 X=CH; Y=N; Z=O, R=R^1=Me; R^2=R^3=H, Me, OMe, Cl, Br
4 X=O; Y=Z=CH; R=R^1=Me; R^2=R^3=H, Me, OMe
5 X=N; Y=CH; Z=S; R=H, Me; R^1=H, Me; R^2=H, OMe, Br; R^3=H, OMe, Br

Considering the antitumor activity exhibited by bis-indolylthiazoles and that several compounds containing the thiazole ring have shown marked antineoplastic activity,[12] we synthesized new thiazole analogues in which one indole ring was replaced by a phenyl or an azaindole nucleus to verify whether the phenyl or the aza substitution to the indole system increases the antineoplastic activity. Herein we report the synthesis of 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indole of type **6** and 3-(2-

[a] *Prof. P. Diana, Dr. A. Carbone, Prof. P. Barraja, Dr. A. Montalbano, Dr. B. Parrino, Prof. G. Cirrincione*
Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari
Sezione Chimica Farmaceutica e Biologica
Università degli Studi di Palermo
Via Archirafi 32, 90123 Palermo (Italy)
Fax: (+39) 091-238-60-854
E-mail: diana@unipa.it

[b] *Dr. A. Lopergolo, Dr. M. Pennati, Dr. N. Zaffaroni*
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1, 20133 Milano (Italy)

Table 1. 3-(2-Phenyl-1,3-thiazol-4-yl)-1*H*-indoles **6a–l** and 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles **7a–t**.



Compd	R	R^1	R^2	R^3	Compd	R	R^1	R^2	R^3
6a	H	H	H	H	**7e**	H	Me	H	H
6b	H	H	H	Me	**7f**	H	Me	H	Me
6c	H	H	Me	H	**7g**	H	F	H	H
6d	H	H	Me	Me	**7h**	H	F	H	Me
6e	H	H	OMe	H	**7i**	H	H	H	H
6f	H	H	OMe	Me	**7j**	H	H	H	Me
6g	H	H	Cl	H	**7k**	H	H	Me	H
6h	H	H	Cl	Me	**7l**	H	H	Me	Me
6i	H	H	Br	H	**7m**	H	H	OMe	H
6j	H	H	Br	Me	**7n**	H	H	OMe	Me
6k	H	H	F	H	**7o**	H	H	Cl	H
6l	H	H	F	Me	**7p**	H	H	Cl	Me
7a	Cl	H	H	H	**7q**	H	H	Br	H
7b	Cl	H	H	Me	**7r**	H	H	Br	Me
7c	F	H	H	H	**7s**	H	H	F	H
7d	F	H	H	Me	**7t**	H	H	F	Me

phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles of type **7**, their antitumor activity, and kinase activity of the most active compounds in these series (Table 1).

Results and Discussion

Synthesis of compound series 6 and 7

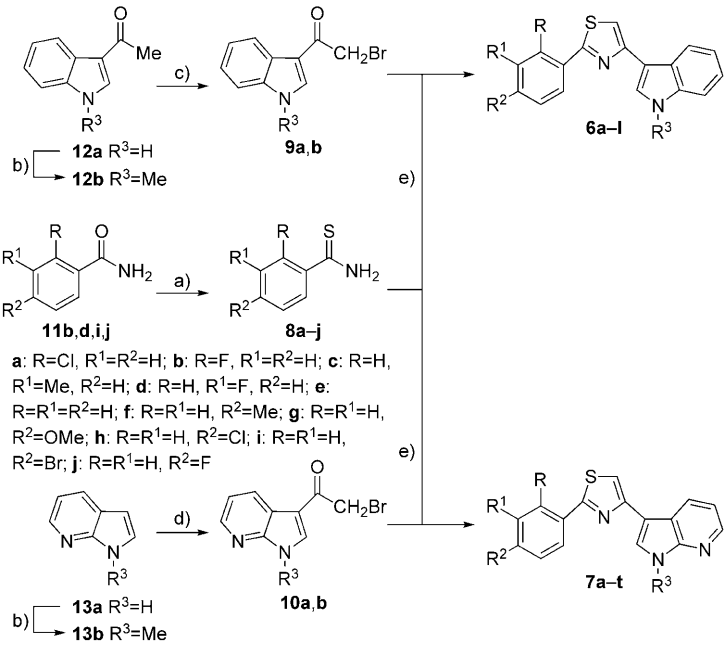
The synthesis of 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indoles of type **6** and 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles of type **7** is based on the Hantzsch reaction between the thioamides **8** and the α-bromoacetyl compounds of type **9** and **10**. The key thioamides **8b**, **8d**, **8i**, and **8j**, which are not commercially available, were prepared in excellent yield (95–98%) by holding the corresponding amides **11b**, **11d**, **11i**, and **11j** at reflux in benzene with Lawesson's reagent (Scheme 1). This method is faster and more efficient than the reaction of aryl nitriles with sulfides in pyridine previously reported.[13]

The 3-acetylindole **12a** and the 7-azaindole **13a** were converted into the corresponding *N*-methyl derivatives **12b** (90%) and **13b** (96%), respectively, using potassium *tert*-butoxide, tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a catalyst, and methyl iodide in anhydrous benzene. The 3-indole derivatives **12a** and **12b** were converted into the 3-bromoacetylindoles **9a** and **9b** in good yield (70%) by treatment with bromine in methanol at reflux.

3-Bromoacetyl-7-azaindoles **10a** and **10b** were efficiently prepared by acylation of 7-azaindoles **13a** and **13b** with bromoacetyl bromide (80–92% yields). Reaction of thioamides of type **8** and α-bromoacetyl compounds **9a**,**b** and **10a**,**b** in ethanol at reflux gave the 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indole **6a–l** (60–82% yields) and 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles **7a–t** (70–87% yields), respectively.

Biology

All of the isolated phenylthiazolylindoles **6a–l** and phenylthiazolyl-7-azaindoles **7a–t** were submitted to the National Cancer Institute (NCI, Bethesda, MD, USA) for testing against a panel of ~60 tumor cell lines grouped into disease subpanels: leukemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast cancer. Among these compounds submitted, eight indoles (**6a**, **6b**, **6e**, **6f**, **6g**, **6h**, **6k**, and **6l**) and 12 azaindoles (**7a**, **7g**, **7h**, **7i**, **7j**, **7k**, **7l**, **7m**, **7n**, **7o**, **7p**, and **7s**) were prescreened at a single concentration (10^{-5} M). Compounds of type **6** were devoid of any significant antiproliferative activity. Instead, compounds **7g**, **7h**, **7l**, **7j**, **7n**, **7o**, and **7p** were further selected for full evaluation at five different concentrations (10^{-4}–10^{-8} M), as they satisfied the threshold inhibition criteria established by the NCI. The antitumor activity of compounds is determined by the pGI_{50} value (GI_{50} is the molar concentration of compound that inhibits 50% net cell growth).



Scheme 1. Synthesis of 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indoles **6a–l** and 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles **7a–t**. *Reagents and conditions*: a) Lawesson's reagent, benzene, reflux, 15 min; b) *t*BuOK, benzene, TDA-1, RT, 3–8 h, then CH_3I, RT, 1–2 h; c) Br_2, MeOH, reflux, 2 h; d) $AlCl_3$, CH_2Cl_2, $BrCH_2COBr$, reflux, 40 min; e) EtOH, RT, 24 h or reflux, 30 min.

The data listed in Table 2 reveal that *N*-methyl-7-azaindoles are more active than the corresponding N-unsubstituted compounds [compare mean graph midpoint of the couples **7p**/**7o**, **7j**/**7i**, **7h**/**7g**, and **7l**/**7k** (**7i** and **7k** were not tested at five different concentrations)]. Among the *N*-methyl derivatives, the most active was the 4-methylphenyl compound **7l**. Replacement of the methyl group with chloro (compound **7p**) or with

Table 2. Overview of the in vitro antitumor screening[a] results for compounds **7g**, **7h**, **7j**, **7l**, **7n**, **7o**, and **7p**.

Compd	N_{cl}[c]	N[d]	pGI_{50}[b] Range	MG_MID[e]
7g	58	29	4.11–6.89	4.43
7h	59	59	4.45–5.98	4.77
7j	59	59	4.63–5.28	4.86
7l	60	60	4.87–7.50	5.54
7n	60	42	4.03–6.11	4.46
7o	59	9	4.01–7.56	4.16
7p	59	59	4.64–5.59	4.88

[a] Data obtained from the NCI in vitro disease-oriented human tumor cell line screen. [b] pGI_{50}: $-\log c$, for which c = concentration (molar) that inhibits 50% net cell growth. [c] Number of cell lines investigated. [d] Number of cell lines giving positive pGI_{50} values. [e] MG_MID: mean graph midpoint; this is the arithmetic mean value for all tested cancer cell lines. If the indicated effect was not attainable under the concentration range used, the highest tested concentration was used for the calculation.

hydrogen (compound **7j**), or the introduction of a fluoro group at position 3 (compound **7h**) of the phenyl ring, significantly decreases biological activity. The introduction of a methoxy moiety at the same position (compound **7n**) produced a compound that is one order of magnitude less active than the most active compounds tested. The most active *N*-methyl derivatives, **7h**, **7j**, **7l**, and **7p**, showed inhibitory effects against all cell lines tested in the micromolar to sub-micromolar range and in two cases reached nanomolar concentrations. Table 3 shows that the *N*-methyl compound **7l** is slightly selective for the leukemia (pGI_{50} 4.90–6.59), colon (pGI_{50} 5.17–6.18), and renal cancer (pGI_{50} 5.16–7.50) subpanels as the calculated pGI_{50} MG_MID values of such panels are higher than the overall cell line MG_MID values (ΔMG_MID 0.16–0.17). The most sensitive cell lines were SR (pGI_{50} 6.59) and K-562 (pGI_{50} 6.12) of the leukemia sub panel, KM12 (pGI_{50} 6.18) and SW-620 (pGI_{50} 5.92) of the colon subpanel, and A498 (pGI_{50} 7.50) of renal subpanel. Compound **7l** also showed good selectivity with respect to the MDA-MB-435 (pGI_{50} 6.50) of the melanoma subpanel and NCI/ADR-RES (pGI_{50} 5.93), of the ovarian subpanel. Derivative **7j** showed good selectivity with respect to EKVX (pGI_{50} 5.28) of the non-small-cell lung subpanel. Derivatives **7g**, **7o**, and **7p** were selectively active with respect to the non-small-cell lung cancer and especially active against HOP-92 (pGI_{50} 6.89, 7.56, and 5.59 respectively) and EKVX (pGI_{50} 5.61, 6.23, and 5.55 respectively). Compound **7n** showed good selectivity with respect to the A498 (pGI_{50} 6.11) of the renal subpanel.

Considering that **7h**, **7j**, **7l**, and **7p** were the most potent compounds of the series, they were also assayed against pancreatic carcinoma (MiaPaCa-2) and malignant peritoneal mesothelioma (STO) cell lines. Cells were exposed to increasing concentrations (from 0.05 to 50 μM) of the phenylthiazolyl-7-azaindoles for 72 h, and their effect on cell proliferation was determined by the SRB assay. Assessment of IC_{50} values showed that all compounds inhibited cell growth in a concentration-dependent manner in both cellular models (Table 4). Nevertheless, compounds **7j** and **7l** were more active than compounds **7p** and **7h** for pancreatic carcinoma cells, and also exhibited a higher cytotoxic profile against malignant peritoneal mesothelioma cells (Table 4), suggesting that the substitution at position 4 with a methyl group (compound **7l**) slightly increases the antiproliferative activity of the unsubstituted derivative **7j**. In contrast, halogen substitution at either positions 4 or 3 of the phenyl moiety produces a substantial decrease in activity.

To better characterize the mechanism of action by which the phenylthiazolyl-7-azaindoles exert their antiproliferative effect, increasing amounts of **7j**, **7p**, **7h**, and **7l** were incubated with purified recombinant CDK1/cyclin B, CDK5/p25, or GSK3β, and their potential kinase inhibitory effect was measured using a fluorimetric assay. As summarized in Table 5, no compound exhibited activity toward both CDK5 and GSK3β, as indicated by IC_{50} values considerably higher than 50 μM. As far as CDK1 is concerned, **7j** and **7l** exhibited a higher affinity for the kinase, with IC_{50} values of 0.41 ± 0.08 μM and 0.85 ± 0.13 μM, respectively, whereas **7p** and **7h** showed activity toward CDK1 only at very high concentrations (Table 5). Notably, the IC_{50} values observed for both **7j** and **7l** are very similar to those obtained using the same assay with roscovitine and purvalanol A (0.73 ± 0.06 μM and 0.59 ± 0.08 μM, respectively), in agreement with previous reports for inhibition of CDK1 by these compounds.[14]

Detailed studies of the cellular pharmacology of **7j** and **7l** in comparison with roscovitine and purvalanol A are currently ongoing. However, preliminary experiments have shown that, consistent with the inhibition of CDK1, the exposure of asynchronously growing STO cells to both compounds caused changes in cell-cycle phase distribution (Figure 1). Specifically, flow cytometric analysis of propidium iodide-stained cells show that 72 h treatment with sub-cytotoxic, IC_{50}, and IC_{80} con-

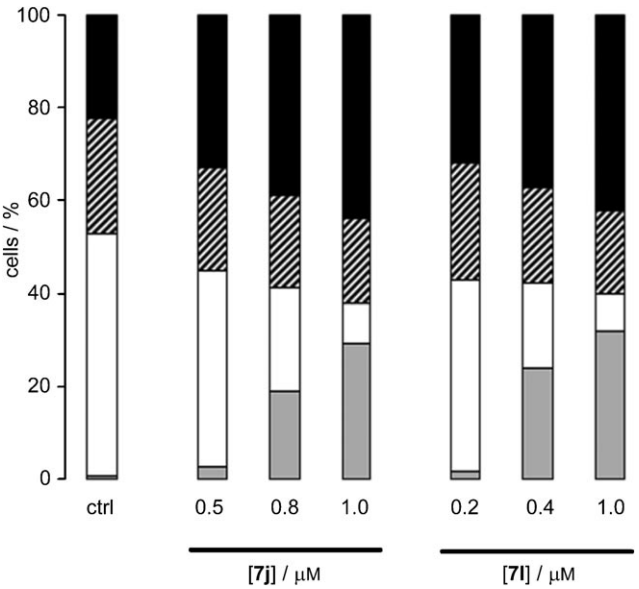


Figure 1. Cell-cycle effects of **7j** and **7l** on asynchronously growing STO cells. Cells were exposed to 1% DMSO (*v/v*) (control cells; ctrl), **7j** (0.5, 0.8, and 1 μM), or **7l** (0.2, 0.4, and 1 μM) and cell-cycle phase distribution was assessed at 72 h after treatment by flow cytometric analyses. The percentage of cells in sub-G_1 (grey), G_1 (white), S (hashed), and G_2/M (black) phases are shown. Columns represent the mean of three independent experiments; SDs always within ±5%.

Table 3. In vitro inhibition of cancer cell line growth by compounds **7g**, **7h**, **7j**, **7l**, **7n**, **7o**, and **7p**.

Cell line	pGI_{50}[a] 7g	7h	7j	7l	7n	7o	7p	Cell line	pGI_{50}[a] 7g	7h	7j	7l	7n	7o	7p
Leukemia								*Melanoma*							
CCRF-CEM	<4.00	4.45	4.64	4.90	<4.00	<4.00	4.74	LOX IMVI	<4.00	4.85	4.89	5.44	4.27	<4.00	4.91
HL-60(TB)	<4.00	4.84	5.03	5.88	5.04	<4.00	4.99	MALME-3 M	5.25	4.75	4.79	5.61	4.65	<4.00	4.83
K-562	<4.00	4.63	4.86	6.12	5.30	<4.00	4.89	M14	5.25	4.81	4.86	5.78	4.55	<4.00	4.92
MOLT-4	<4.00	4.93	4.99	5.47	4.72	<4.00	4.91	MDA-MB-435	<4.00	4.84	4.95	6.50	5.55	<4.00	4.89
RPMI-8226	<4.00	4.60	4.84	5.15	4.43	<4.00	4.91	SK-MEL-2	<4.00	4.63	4.73	5.48	4.26	<4.00	4.76
SR	<4.00	4.87	5.03	6.59	5.01		4.88	SK-MEL-28	<4.00	4.75	4.80	4.99	4.10	<4.00	4.82
								SK-MEL-5	<4.00	4.81	4.86	5.53	4.77	<4.00	4.86
Non-Small-Cell Lung Cancer								UACC-257	<4.00	4.66	4.68	4.93	<4.00	<4.00	4.70
A549/ATCC	4.75	4.68	4.77	5.39	4.12	<4.00	4.76	UACC-62	<4.00	4.86	4.91	5.56	4.89	<4.00	4.98
EKVX	5.61	4.90	5.28	5.37	4.76	6.23	5.55								
HOP-62	4.59	4.72	4.81	5.29	<4.00	<4.00	4.76	*Ovarian Cancer*							
HOP-92	6.89	5.98	4.74	5.82	5.70	7.56	5.59	IGROV1	5.09	4.67	4.78	5.29	<4.00	5.32	4.65
NCI-H226	<4.00	4.71	4.78	5.07	<4.00	<4.00	4.83	OVCAR-3	4.22	4.72	4.79	5.64	4.38	<4.00	4.77
NCI-H23	4.15	4.76	4.79	5.25	<4.00	4.01	4.86	OVCAR-4		4.56	4.63	4.87	<4.00	4.18	4.66
NCI-H322 M	4.11	4.77	4.82	5.21	<4.00	<4.00	4.88	OVCAR-5	<4.00	4.83	4.85	5.37	<4.00	<4.00	4.85
NCI-H460	5.18	4.77	4.80	5.54	4.48	<4.00	4.79	OVCAR-8	4.37	4.58	4.69	5.23	<4.00	<4.00	4.64
NCI-H522	<4.00	4.80	4.85	5.85	4.83	<4.00	4.87	NCI/ADR-RES	<4.00	4.69	4.71	5.93	4.92	<4.00	4.80
								SK-OV-3	4.92	4.60	4.73	5.45	<4.00	<4.00	4.80
Colon Cancer															
COLO 205	<4.00	4.80	4.86	5.70	4.54	<4.00	4.86	*Renal Cancer*							
HCC-2998	<4.00	4.72	4.78	5.17	4.09	<4.00	4.84	786-0	<4.00	4.79	4.84	5.36	4.29	<4.00	4.79
HCT-116	5.10	4.85	4.86	5.57	4.42	4.28	4.89	A498				7.50	6.11	<4.00	
HCT-15	<4.00	4.85	4.89	5.66	4.60	<4.00	4.91	ACHN	5.01	4.74	4.77	5.28	4.04	<4.00	4.85
HT29	<4.00	4.85	4.85	5.72	4.76	<4.00	4.88	CAKI-1	<4.00	4.79	5.15	5.69	4.74	<4.00	5.16
KM12	<4.00	4.80	4.90	6.18	5.10	<4.00	4.89	RXF 393	4.64	4.80	4.83	5.80	4.26	<4.00	4.86
SW-620	<4.00	4.78	4.83	5.92	4.71	4.44	4.82	SN12C	<4.00	4.81	4.82	5.40	<4.00	<4.00	4.83
								TK-10	4.59	4.75	4.75	5.36	<4.00	<4.00	4.91
CNS Cancer								UO-31	4.48	4.80	4.96	5.16	<4.00	<4.00	4.87
SF-268	4.42	4.76	4.77	5.37	4.08	<4.00	4.81								
SF-295	4.43	4.83	4.82	5.60	4.69	<4.00	4.81	*Breast Cancer*							
SF-539	4.16	4.81	4.85	5.50	4.03	4.45	4.83	MCF7	5.28	4.75	4.90	5.73	4.90	<4.00	4.93
SNB-19	4.65	4.70	4.80	5.40	<4.00	<4.00	4.86	MDA-MB-231/ATCC	4.42	4.77	4.87	5.33	4.12	<4.00	4.88
SNB-75	5.08	4.45	4.63	5.33	<4.00	<4.00	4.70	HS 578T	5.53	4.71	4.93	5.51	<4.00	<4.00	4.92
U251	4.60	4.81	4.87	5.45	4.11	<4.00	4.84	BT-549	4.35	4.68	4.77	5.15	4.17	<4.00	4.73
								T-47D	5.63	4.84	5.22	5.78	4.90	5.03	5.29
Prostate Cancer								MDA-MB-468	<4.00	4.70	4.85	5.47	5.42	<4.00	4.98
PC-3	<4.00	4.79	4.84	5.46	4.74	<4.00	4.94								
DU-145	<4.00	4.74	4.82	5.33	<4.00	<4.00	4.82								

[a] Data obtained from the NCI in vitro disease-oriented human tumor cell screen.

centrations of **7j** and **7l** resulted in a concentration-dependent accumulation of cells in the G_2/M phase, with a concomitant increase in the sub-G_1 apoptotic cell population (Figure 1).

Table 4. Cytotoxic activity of **7h**, **7l**, **7j**, and **7p** in MiaPaCA-2 and STO cell lines.

Compd	IC_{50} [μM][a] MiaPaCa-2	STO
7j	5.7 ± 0.8	0.83 ± 0.04
7p	39.6 ± 3.9	5.7 ± 0.8
7h	41.6 ± 2.4	17.2 ± 2.9
7l	4.3 ± 0.6	0.41 ± 0.06

[a] Concentration of drug required to inhibit growth by 50% as determined by SRB assay after 72 h continuous exposure to each compound; data represent the mean ± SD of at least three independent experiments.

Table 5. Kinase inhibition by compounds **7h**, **7j**, **7l**, and **7p**.

Compd	IC_{50} [μM][a] CDK1	CDK5	GSK3β
7h	33.27 ± 2.97	>50.0	>50.0
7j	0.41 ± 0.08	>50.0	>50.0
7l	0.85 ± 0.13	>50.0	>50.0
7p	45.93 ± 4.19	>50.0	>50.0
Roscovitine	0.73 ± 0.06	>50.0	>50.0
Purvalanol A	0.59 ± 0.08	>50.0	>50.0

[a] Inhibitor concentration at which enzyme activity is decreased by 50%, as determined graphically from the curve for each compound; data represent the mean ± SD of at least three independent experiments.

Conclusions

Phenylthiazolylindoles **6** and phenylthiazolyl-7-azaindoles **7** were conveniently synthesized by a Hantzsch reaction between aryl thioamides and α-bromoacetyl derivatives. None of

the thiazolylindoles **6**, tested at a single concentration (10^{-5} M), showed significant antiproliferative activity. Instead, seven derivatives belonging to the 7-azaindole series **7** were tested at five concentrations (10^{-4}–10^{-8} M) and were active having GI_{50} values in the micromolar to sub-micromolar range and in two cases reaching nanomolar levels. The most active compounds were the *N*-methyl derivatives and four of them, **7h**, **7j**, **7l**, and **7p**, were tested further against the pancreatic carcinoma (MiaPaCa-2) and malignant peritoneal mesothelioma (STO) with IC_{50} values in the range 4.3–41.6 μM and 0.41-17.2 μM, respectively.

To gain insight into the mechanism of action of this series of compounds, **7h**, **7j**, **7l**, and **7p** were incubated with CDK1/cyclin, CDK5/p25, or GSK3β. Interestingly, only the compounds with the highest antiproliferative activity (**7j** and **7l**) exhibited affinity for CDK1, with IC_{50} values of 0.41 and 0.85 μM, respectively. Such values were similar to those obtained in the same assay with roscovitine and purvalanol A used as reference drugs. Moreover, exposure of asynchronously growing STO cells to both compounds caused changes in cell-cycle phase distribution. In particular, a concentration-dependent accumulation of cells in the G_2/M phase was observed, with a concomitant increase in the sub-G_1 apoptotic cell population.

Experimental Section

Chemistry

General: All melting points were taken on a Büchi–Tottoli capillary apparatus and are uncorrected. IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz, respectively, in [D_6]DMSO or $CDCl_3$ solution, using a Bruker Avance II series 200 MHz spectrometer [$(CH_3)_4Si$ as internal reference]. Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with Büchi Sepacore chromatography module (prepacked cartridge system). Elemental analyses (C, H, N) were within ±0.4% of the theoretical values.

General procedure for the preparation of benzenecarbothioamides (8b,d,i,j): Lawesson's reagent (0.81 g, 2 mmol) was added to a stirred solution of the proper amide **11b,d,i,j** (4 mmol) in anhydrous benzene (10 mL). The mixture was heated at reflux for 15 min. After cooling the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using CH_2Cl_2 as eluent. Melting point, IR, and NMR data for the synthesized compounds are in agreement with those reported previously.[13]

Synthesis of 3-acetyl-1-methylindole (12b): *t*BuOK (1.0 g, 8.6 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (1–2 drops) were added to a cold solution of 3-acetylindole **12a** (1.0 g, 6.3 mmol) in anhydrous benzene (50 mL). The reaction mixture was stirred at RT for 8 h and then CH_3I (0.4 mL, d = 2.28 g mL^{-1}, 6.3 mmol) was added. TLC analysis (CH_2Cl_2/EtOAc 9:1) revealed that methylation was complete after 2 h. The solvent was evaporated under reduced pressure. The residue was treated with H_2O (50 mL), extracted with CH_2Cl_2 (3×50 mL), dried, evaporated, and purified by column chromatography using CH_2Cl_2/EtOAc (9:1) as eluent.

3-Acetyl-1-methylindole (12b): White solid (0.87 g, 80%): R_f = 0.50 (CH_2Cl_2/EtOAc 9:1); mp: 108–109 °C; ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 2.44 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.19–7.32 (m, 2H, H-5 and H-6), 7.52 (dd, 1H, J = 6.4, 1.8 Hz, H-7), 8.23 (dd, 1H, J = 6.4, 1.8 Hz, H-4), 8.29 ppm (s,1H, H-2); ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 27.2 (q), 33.0 (q), 110.5 (d), 115.6 (s), 121.4 (d), 121.9 (d), 122.7 (d), 125.7 (s), 137.2 (s), 137.9 (d), 192.0 ppm (s); IR (KBr): $\tilde{\nu}$ = 1643 cm^{-1} (CO); Elemental analysis: calcd (%) for $C_{11}H_{11}NO$: C 76.28, H 6.40, N 8.09, found: C 76.41, H 6.29, N 7.87.

General procedure for the preparation of 3-bromoacetylindoles (9a,b): Bromine (0.1 mL, d = 3.12 g mL^{-1}, 1.9 mmol) was added dropwise to a cold suspension of the appropriate 3-acetylindole **12a,b** (1.9 mmol) in anhydrous MeOH (3 mL). The mixture was heated at reflux for 2 h. After cooling the solvent was evaporated under reduced pressure. The residue was treated with H_2O (20 mL), made alkaline by adding $NaHCO_3$, (150 mg) and extracted with EtOAc (3×50 mL). The organic phase was dried, evaporated under reduced pressure, and purified by column chromatography using CH_2Cl_2 as eluent.

3-Bromoacetylindole (9a): Brown solid (0.32 g, 70%): R_f = 0.43 (CH_2Cl_2/EtOAc 98:2); mp: 113–114 °C; ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 4.66 (s, 2H, CH_2), 7.19–7.29 (m, 2H, H-5 and H-6), 7.49–7.54 (m, 1H, H-7), 8.17 (t, 1H, J = 5.9 Hz, H-4), 8.50 (d, 1H, J = 3.2 Hz, H-2), 12.2 (bs, 1H, NH); ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 33.5 (t), 112.3 (d), 113.5 (s), 121.2 (d), 122.1 (d), 123.2 (d), 125.4 (s), 135.2 (d), 136.7 (s), 186.3 (s); IR (KBr): $\tilde{\nu}$ = 3190 (NH), 1639 cm^{-1} (CO); Elemental analysis: calcd (%) for $C_{10}H_8BrNO$: C 50.45, H 3.39, N 5.88, found: C 50.23, H 3.44, N 6.01.

3-Bromoacetyl-1-methylindole (9b): Brown solid (0.33 g, 70%): R_f = 0.44 (CH_2Cl_2); mp: 205–206 °C; ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.37 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 7.27–7.33 (m, 2H, H-5 and H-6), 7.59 (dd, 1H, J = 6.0, 1.9 Hz, H-7), 8.18 (dd, 1H, J = 6.0, 1.9 Hz, H-4), 8.50 ppm (s, 1H, H-2); ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 33.3 (q), 33.4 (t), 110.9 (d), 112.3 (s), 121.3 (d), 122.5 (d), 123.3 (d), 125.9 (s), 137.4 (s), 138.7 (d), 185.8 ppm (s); IR (KBr): $\tilde{\nu}$ = 1643 (CO) cm^{-1}; Elemental analysis: calcd (%) for $C_{11}H_{10}BrNO$: C 52.41, H 4.00, N 5.56, found: C 52.57, H 4.11, N 5.39.

Synthesis of 1-methyl-7-azaindole (13b): *t*BuOK (0.38 g, 3.4 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (1–2 drops) were added at 0 °C to a cold solution of derivative **13a** (0.30 g, 2.5 mmol) in anhydrous benzene (25 mL). The reaction mixture was stirred at RT for 3 h, and then CH_3I (0.2 mL, 2.5 mmol, d = 2.28 g mL^{-1}) was added at 0 °C. TLC analysis (EtOAc) revealed that methylation was complete after 1 h. The solvent was evaporated under reduced pressure. The residue was treated with H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4), evaporated, and purified by column chromatography using CH_2Cl_2/EtOAc (9:1) as eluent.

1-Methyl-7-azaindole (13b): Oil (0.31 g, 96%): R_f = 0.40 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.87 (s, 3H, CH_3), 6.43 (d, 1H, J = 3.4 Hz, H-3), 7.03 (dd, 1H, J = 7.8, 4.8 Hz, H-5), 7.15 (d, 1H, J = 3.4 Hz, H-2), 7.88 (dd, 1H, J = 7.8, 1.5 Hz, H-4), 8.33 ppm (d, 1H, J = 4.8 Hz, H-6); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1 (q), 99.1 (d), 115.3 (d), 120.4 (s), 128.6 (d), 128.9 (d + s), 142.6 ppm (d); Elemental analysis: calcd (%) for $C_8H_8N_2$: C 72.70, H 6.10, N, 21.20, found: C 72.55, H 6.03, N 21.38.

General procedure for the preparation of 3-bromoacetyl-7-azaindoles (10a,b): Anhydrous $AlCl_3$ (1.2 g, 8.8 mmol) was slowly added to a solution of 2.5 mmol of the proper derivative **13a,b** in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was heated under reflux and a solution of bromoacetyl bromide (0.2 mL, d =

2.317 g mL^{-1}, 2.5 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise. The resulting solution was allowed to stir under reflux for 40 min. After cooling, H_2O and ice were slowly added and the obtained precipitate (for derivative **10a**) was filtered off or the oil residue (for derivative **10b**) was extracted with CH_2Cl_2 and purified by column chromatography using CH_2Cl_2/EtOAc 9:1 as eluent.

3-Bromoacetyl-7-azaindole (10a): White solid (0.55 g, 92%): R_f = 0.36 (CH_2Cl_2/MeOH 9:1); mp: 280–282 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 4.71 (s, 2H, CH_2), 7.30 (dd, 1H, J = 7.8, 4.7 Hz, H-5), 8.37 (d, 1H, J = 4.7 Hz, H-6), 8.47 (d, 1H, J = 7.8 Hz, H-4), 8.65 (bs, 1H, H-2), 12.7 ppm (bs, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 46.3 (t), 112.3 (s), 117.7 (s), 118.4 (d), 129.5 (d), 135.1 (d), 144.6 (d), 149.0 (s), 186.4 ppm (s); IR (KBr): $\tilde{\nu}$ = 3556 (NH), 1678 cm^{-1} (CO); Elemental analysis: calcd (%) for $C_9H_7BrN_2O$: C 45.22, H 2.95, N 11.72, found: C 45.40, H 2.82, N 11.54.

3-Bromoacetyl-1-methyl-7-azaindole (10b): White solid (0.50 g, 80%): R_f = 0.62 (CH_2Cl_2/MeOH 9:1); mp: 116–117 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 3.91 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 7.34 (dd, 1H, J = 7.6, 4.7, Hz, H-5), 8.40–8.48 (m, 2H, H-4 and H-6), 8.70 ppm (s, 1H, H-2); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 31.7 (q), 32.9 (t), 110.8 (s), 118.1 (d), 118.7 (s), 129.8 (d), 138.7 (d), 144.4 (d), 148.1 (s), 186.1 ppm (s); IR (KBr): $\tilde{\nu}$ = 1650 cm^{-1} (CO); Elemental analysis: calcd (%) for $C_{10}H_9BrN_2O$: C 47.46, H 3.58, N 11.07, found: C 47.22, H 3.63, N 11.25.

General procedure for the preparation of 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indoles (6a–l): A suspension of the proper thioamide **8a–f** (5 mmol) and 3-bromoacetylindole **9a,b** (5 mmol) in anhydrous EtOH (20 mL) was stirred at RT for 24 h. The solid formed was filtered, dried, and purified by column chromatography using CH_2Cl_2 as eluent.

3-(2-Phenyl-1,3-thiazol-4-yl)-1*H*-indole (6a): Orange solid (0.94 g, 68%): R_f = 0.40 (CH_2Cl_2); mp: 210–211 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.15 (t, 1H, J = 7.1 Hz, H-5), 7.20 (t, 1H, J = 7.1 Hz, H-6), 7.44–7.61 (m, 4H, H-7, H-3′, H-4′ and H-5′), 7.84 (s, 1H, H-5″), 8.00 (d, 1H, J = 2.7 Hz, H-2), 8.07 (dd, 2H, J = 7.9, 2.2 Hz, H-2′ and H-6′), 8.21 (d, 1H, J = 7.1 Hz, H-4), 11.5 ppm (bs, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 109.9 (d), 110.8 (s), 111.9 (d), 119.8 (d), 120.2 (d), 121.6 (d), 124.6 (s), 124.9 (d), 126.1 (2×d), 129.2 (2×d), 130.1 (d), 133.3 (s), 136.6 (s), 152.0 (s), 165.8 ppm (s); IR (KBr): $\tilde{\nu}$ = 3118 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{12}N_2S$: C 73.88, H 4.38, N 10.14, found: C 73.71, H 4.43, N 10.24.

1-Methyl-3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-indole (6b): Yellow solid (0.95 g, 65%): R_f = 0.87 (CH_2Cl_2); mp: 196–197 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.88 (s, 3H, CH_3), 7.20 (t, 1H, J = 7.0 Hz, H-5), 7.27 (t, 1H, J = 7.0 Hz, H-6), 7.50–7.56 (m, 3H, H-3′, H-4′ and H-5′), 7.83 (s, 1H, H-2), 7.99 (s, 1H, H-5″), 8.04–8.08 ppm (m, 3H, H-2′, H-7, H-6′), 8.22 (d, 1H, J = 7.0 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.2 (q), 99.5 (s), 110.0 (d), 110.2 (d), 120.0 (d), 120.3 (d), 121.7 (d), 124.9 (s), 126.1 (2×d), 129.1 (d), 129.2 (2×d), 130.1 (d), 133.2 (s), 137.0 (s), 151.5 (s), 165.9 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{14}N_2S$: C 74.45, H 4.86, N 9.65, found: C 74.53, H 4.96, N 9.48.

3-[2-(4-Methylphenyl)-1,3-thiazol-4-yl]-1*H*-indole (6c): Yellow solid (0.87 g, 60%): R_f = 0.50 (CH_2Cl_2); mp: 235–236 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3H, CH_3), 7.14–7.19 (m, 2H, H-5 and H-6), 7.36 (d, 2H, J = 8.0 Hz, H-3′ and H-5′), 7.44–7.48 (m, 1H, H-7), 7.79 (s, 1H, H-2), 7.93–7.98 (m, 3H, H-2′, H-6′ and H-5″), 8.18–8.22 (m, 1H, H-4), 11.4 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.0 (q), 109.5 (d), 110.7 (s), 111.9 (d), 119.7 (d), 120.2 (d), 121.6 (d), 124.6 (s), 124.9 (d), 126.0 (2×d), 129.7 (2×d), 130.6 (s), 136.5 (s), 139.9 (s), 151.6 (s), 166.0 ppm (s). IR (KBr): $\tilde{\nu}$ = 3020 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{18}H_{14}N_2S$: C 74.45, H 4.86, N 9.65, found: C 74.67, H 4.92, N 9.45.

1-Methyl-3-[2-(4-methylphenyl)-1,3-thiazol-4-yl]-1*H*-indole (6d): Cream solid (0.99 g, 65%): R_f = 0.89 (CH_2Cl_2); mp: 141–142 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.38 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.16–7.30 (m, 2H, H-5 and H-6), 7.35 (d, 2H, J = 8.0 Hz, H-3′ and H-5′), 7.52 (dd, 1H, J = 6.8, 1.7 Hz, H-7), 7.77 (s, 1H, H-2), 7.94 (d, 2H, J = 8.0 Hz, H2′ and H-6′), 7.98 (s, 1H, H-5″), 8.21 ppm (dd, 1H, J = 6.8, 1.7 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.9 (q), 32.6 (q), 109.4 (d), 110.0 (s), 110.1 (d), 119.9 (d), 120.3 (d), 121.7 (d), 124.9 (s), 126.0 (2×d), 129.1 (d), 129.7 (2×d), 130.7 (s), 137.0 (s), 139.9 (s), 151.3 (s), 166.0 ppm (s); Elemental analysis: calcd (%) for $C_{19}H_{16}N_2S$: C 74.97, H 5.30, N 9.20, found: C 75.11, H 5.45, N 8.91.

3-[2-(4-Methoxyphenyl)-1,3-thiazol-4-yl]-1*H*-indole (6e): Cream solid (0.93 g, 60%): R_f = 0.30 (CH_2Cl_2); mp: 213–214 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.85 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.8 Hz, H-3′ and H-5′), 7.13–7.23 (m, 2H, H-5 and H-6), 7.44–7.52 (m,1H, H-7), 7.74 (s,1H, H-2), 7.98 (s, 1H, H-5″), 8.0 (d, 2H, J = 8.8 Hz, H-2′ and H-6′), 8.19–8.23 (m, 1H, H-4), 11.4 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 55.4 (q), 108.8 (d), 110.9 (s), 111.8 (d), 114.5 (2×d), 119.7 (d), 120.2 (d), 121.6 (d), 124.6 (s), 124.8 (d), 126.1 (s), 127.6 (2×d), 136.6 (s), 151.6 (s), 160.7 (s), 165.7 ppm (s); IR (KBr): $\tilde{\nu}$ = 3126 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{18}H_{14}N_2OS$: C 70.56, H 4.61, N 9.14, found: C 74.70, H 5.42, N 8.96.

1-Methyl-3-[2-(4-methoxyphenyl)-1,3-thiazol-4-yl]-1*H*-indole (6f): Cream solid (0.96 g, 60%): R_f = 0.67 (CH_2Cl_2); mp: 154 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.84 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.8 Hz, H-3′ and H5′), 7.19–7.30 (m, 2H, H-5 and H-6), 7.51 (dd, 1H, J = 6.9, 1.5 Hz, H-7), 7.71 (s,1H, H-2), 7.97 (s, 1H, H-5″), 7.99 (d, 2H, J = 8.8 Hz, H-2′ and H-6′), 8.21 ppm (dd, 1H, J = 6.9, 1.5 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.6 (q), 55.4 (q), 108.9 (d), 110.1 (s), 110.2 (d), 114.5 (2×d), 119.9 (d), 120.3 (d), 121.7 (d), 125.0 (s), 126.1 (s), 127.6 (2×d), 129.0 (d), 137.0 (s), 151.2 (s), 160.8 (s), 165.8 ppm (s); Elemental analysis: calcd (%) for $C_{19}H_{16}N_2OS$: C 71.22, H 5.03, N 8.74, found: C 71.38, H 5.10, N 8.66.

3-[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-1*H*-indole (6g): Brown solid (1.09 g, 70%): R_f = 0.58 (CH_2Cl_2); mp: 215–216 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.12 (t, 1H, J = 7.0 Hz, H-5), 7.19 (t, 1H, J = 7.0 Hz, H-6), 7.47 (d,1H, J = 7.0 Hz, H-7), 7.62 (d, 2H, J = 8.7 Hz, H-3′ and H-5′), 7.88 (s, 1H, H-5″), 8.00 (d, 1H, J = 2.6 Hz, H-2), 8.08 (d, 2H, J = 8.7 Hz, H-2′ and H-6′), 8.21 (d, 1H, J = 7.0 Hz, H-4), 11.5 ppm (d, 1H, J = 2.6 Hz, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.4 (d), 110.6 (s), 111.9 (d), 119.8 (d), 120.2 (d), 121.6 (d), 124.6 (s), 125.0 (d), 127.7 (2×d), 129.3 (2×d), 132.1 (s), 134.5 (s), 136.5 (s), 152.1 (s), 164.4 ppm (s); IR (KBr): $\tilde{\nu}$ = 3213 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{11}ClN_2S$: C 65.70, H 3.57, N 9.01, found: C, 65.55; H, 3.43; N, 9.27.

3-[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-indole (6h): White solid (1.24 g, 74%): R_f = 0.84 (CH_2Cl_2); mp: 174–175 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.87 (s, 3H, CH_3), 7.17–7.30 (m, 2H, H-5 and H-6), 7.53 (dd, 1H, J = 6.9, 1.6 Hz, H-7), 7.61 (d, 1H, J = 8.5 Hz, H-3′ and H-5′), 7.85 (s, 1H, H-2), 8.00 (s, 1H, H-5″), 8.07 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 8.22 ppm (dd, 1H, J = 6.9, 1.6 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.6 (q), 109.8 (s), 110.2 (d), 110.4 (d), 120.0 (d), 120.3 (d), 121.7 (d), 124.9 (s), 127.2 (2×d), 129.2 (d), 129.3 (2×d), 132.0 (s), 134.6 (s), 137.0 (s), 151.7 (s), 164.5 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{13}ClN_2S$: C, 66.56; H, 4.03; N, 8.62, found: C 66.77, H 4.15, N 8.43.

3-[2-(4-Bromophenyl)-1,3-thiazol-4-yl]-1*H*-indole (6i): Brown solid (1.25 g, 70%): R_f = 0.54 (CH_2Cl_2); mp 220–221 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.12–7.22 (m, 2H, H-5 and H-6), 7.48 (d, 1H, J = 6.9 Hz, H-7), 7.75 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.87 (s,1H, H-2), 7.99 (s, 1H, H-5″), 8.01 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 8.21 (d, 1H, J = 6.9 Hz, H-4), 11.5 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.4 (d), 110.6 (s), 111.9 (d), 119.8 (d), 120.2 (d), 121.6 (d), 123.3 (s), 124.6 (s), 125.0 (d), 127.9 (2×d), 132.2 (2×d), 132.4 (s), 136.6 (s), 152.2 (s), 164.5 ppm (s); IR (KBr): $\tilde{\nu}$ = 3122 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{11}BrN_2S$: C 57.48, H 3.12, N 7.89, found: C 57.71, H 3.26, N 7.68.

3-[2-(4-Bromophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-indole (6j): White solid (1.43 g, 82%): R_f = 0.84 (CH_2Cl_2); mp: 185–186 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.87 (s, 3H, CH_3), 7.16–7.30 (m, 2H, H-5 and H-6), 7.52 (dd, 1H, J = 6.9, 1.5 Hz, H-7), 7.75 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.86 (s, 1H, H-2), 8.00 (s, 1H, H-5″), 8.01 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 8.21 ppm (dd, 1H, J = 6.7, 1.6 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.6 (q), 109.8 (s), 110.2 (d), 110.4 (d), 120.0 (d), 120.3 (d), 121.7 (d), 124.9 (s), 127.9 (2×d), 129.2 (d), 132.2 (2×d), 132.4 (s), 137.0 (s), 151.7 (s), 164.6 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{13}BrN_2S$: C 58.54, H 3.55, N 7.59, found: C 58.75, H 3.64, N 7.38.

3-[2-(4-Fluorophenyl)-1,3-thiazol-4-yl]-1*H*-indole (6k): White solid (1.04 g, 70%): R_f = 0.48 (CH_2Cl_2); mp: 209–210 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO) δ: 7.12 (t, 1H, J = 7.2 Hz, H-5), 7.17 (t, 1H, J = 7.2 Hz, H-6), 7.35–7.50 (m, 3H, H-3′, H-5′ and H-7), 7.83 (s, 1H, H-5″), 8.00 (d, 1H, J = 2.6 Hz, H-2), 8.08–8.15 (m, 2H, H-2′ and H-6′), 8.22 (d, 1H, J = 7.2 Hz, H-4), 11.5 (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.0 (d), 110.7 (s), 111.9 (d), 116.3 (2×dd, $^2J_{CF}$ = 22 Hz), 119.8 (d), 120.2 (d), 121.6 (d), 124.6 (s), 124.9 (d), 128.3 (2×dd, $^3J_{CF}$ = 8.6 Hz), 129.9 (d, $^4J_{CF}$ = 3.1 Hz), 136.6 (s), 152.0 (s), 163.0 (d, $^1J_{CF}$ = 247 Hz), 164.6 (s); IR (KBr): $\tilde{\nu}$ = 3118 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{11}FN_2S$: C 69.37, H 3.77, N 9.52, found: C 69.11, H 3.86, N 9.76.

3-[2-(4-Fluorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-indole (6l): White solid (1.01 g, 66%): R_f = 0.70 (CH_2Cl_2); mp 151–152 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.87 (s, 3H, CH_3), 7.20 (dt, 1H, J = 9.4, 1.3 Hz, H-5), 7.25 (dt, 1H, J = 9.4, 1.3 Hz, H-6), 7.34–7.43 (m, 2H, H-3′ and H5′), 7.52 (dd, 1H, J = 9.4, 1.3 Hz, H-4), 7.81 (s, 1H, H-2), 7.99 (s, 1H, H-5″), 8.07–8.14 (m, 2H, H-2′ and H-6′), 8.22 ppm (dd 1H, J = 9.4, 1.3 Hz, H-7); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.6 (q), 109.9 (s), 110.0 (d), 110.1 (d), 116.2 (2×dd, $^2J_{CF}$ = 22 Hz), 120.0 (d), 120.3 (d), 121.7 (d), 124.9 (s), 128.3 (2×dd, $^3J_{CF}$ = 8.6 Hz), 129.1 (d), 129.9 (d, $^4J_{CF}$ = 3.1 Hz), 137.0 (s), 151.5 (s), 163.1 (d, $^1J_{CF}$ = 248 Hz), 165.6 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{13}FN_2S$: C 70.11, H 4.25, N 9.08, found: C 70.32, H 4.12, N 8.88.

General procedure for the preparation of 3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindoles (7a–t): A suspension of the proper thioamide **8a–j** (5 mmol) and **10a,b** (5 mmol) in anhydrous EtOH (20 mL) was heated under reflux for 30 min. The precipitate, obtained after cooling, was filtered off, dried, and crystallized with EtOH.

3-[2-(2-Chlorophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7a): Yellow solid (1.13 g, 72%): R_f = 0.58 (EtOAc); mp: 247–248 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.53–7.72 (m, 4H, H-5, H-4′, H-5′ and H-6′), 8.30 (s, 1H, H-2), 8.37–8.43 (m, 2H, H-3′ and H.5″), 8.54 (dd, 1H, J = 5.4, 1.1 Hz, H-6), 9.11 (dd, 1H, J = 7.9, 1.1 Hz, H-4), 12.9 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.7 (s), 114.5 (s), 116.3 (s), 120.7 (s), 126.9 (d), 127.8 (d), 130.7 (2×d), 130.8 (d), 131.0 (d), 131.2 (d), 134.7 (d), 137.6 (d), 142.2 (s), 148.7 (s), 161.9 ppm (s); IR (KBr): $\tilde{\nu}$ = 3087 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{10}ClN_3S$: C 61.64, H 3.23, N 13.48, found: C 61.44, H 3.30, N 13.60.

3-[2-(2-Chlorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7b): Yellow solid (1.19 g, 73%): R_f = 0.64 (EtOAc); mp 258–259 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.97 (s, 3H, CH_3), 7.42 (dd, 1H, J = 7.9, 5.1 Hz, H-5), 7.53–7.71 (m, 3H, H-4′, H-5′ and H-6′), 8.16 (s, 1H, H-2), 8.30 (s, 1H, H-5″), 8.35–8.40 (m, 1H, H-3′), 8.48 (dd, 1H, J = 5.1, 1.3 Hz, H-6), 8.86 ppm (dd, 1H, J = 7.9, 1.3 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 31.9 (q), 109.2 (s), 113.7 (d), 116.3 (d), 119.2 (s), 127.8 (d), 129.9 (d), 130.6 (d), 130.7 (s), 130.8 (d), 131.1 (d), 131.2 (s), 131.9 (d), 140.0 (d), 144.5 (s), 148.9 (s), 161.8 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{12}ClN_3S$: C 62.67, H 3.71, N 12.90, found: C 62.46, H 3.85, N 13.09.

3-[2-(2-Fluorophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7c): Yellow solid (1.03 g, 70%): R_f = 0.55 (EtOAc); mp: 256 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.42–7.63 (m, 4H, H-3′, H-4′, H-5′ and H-6′), 8.28 (s, 1H, H-5″), 8.39 (s, 1H, H-2), 8.47 (dt, 1H, J = 7.1, 4.5 Hz, H-5), 8.56 (d, 1H, J = 4.5 Hz, H-6), 9.17 ppm (d, 1H, J = 7.1 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.9 (s), 114.1 (dd, $^3J_{CF}$ = 8.6 Hz), 116.4 (dd, $^2J_{CF}$ = 21 Hz), 116.3 (d), 120.4 (d, $^2J_{CF}$ = 20 Hz), 121.0 (s), 125.2 (dd, $^4J_{CF}$ = 3.2 Hz), 127.0 (d), 128.4 (d), 131.8 (dd, $^3J_{CF}$ = 8.6 Hz), 135.5 (d), 136.9 (d), 141.5 (s), 148.7 (s), 158.8 (s), 159.3 ppm (d, $^1J_{CF}$ = 251 Hz); IR (KBr): $\tilde{\nu}$ = 3456 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{10}FN_3S$: C 65.07, H 3.41, N 14.23, found: C 65.15, H 3.49, N 14.13.

3-[2-(2-Fluorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7d): Yellow solid (1.18 g, 76%): R_f = 0.65 (EtOAc); mp: 257–258 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.98 (s, 3H, CH_3), 7.40–7.65 (m, 4H, H-3′, H-4′, H-5′ and H-6′), 8.13 (s, 1H, H-5″), 8.31 (s, 1H, H-2), 8.47 (dt, 1H, J = 7.9, 5.3 Hz, H-5), 8.49 (dd, 1H, J = 5.3, 1.3 Hz, H-6), 8.90 ppm (dd, 1H, J = 7.9, 1.3 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 18.5 (q), 109.3 (s), 113.1 (d), 113.2 (d), 116.2 (d), 116.4 (dd, $^2J_{CF}$ = 19 Hz), 119.3 (s), 128.6 (dd, $^4J_{CF}$ = 3.1 Hz), 120.4 (d, $^2J_{CF}$ = 19 Hz), 128.9 (d), 125.2 (dd, $^3J_{CF}$ 8.7 Hz), 132.3 (d), 139.7 (dd, $^3J_{CF}$ = 8.7 Hz), 146.6 (d, $^1J_{CF}$ = 238 Hz), 156.8 (s), 158.7 (s), 158.8 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{12}FN_3S$: C 66.00, H 3.91, N 13.58, found: C 66.21, H 4.06, N 13.37.

3-[2-(3-Methylphenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7e): Yellow solid 0.97 g, 70%): R_f = 0.61 (EtOAc); mp: 258–259 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.44 (s, 3H, CH_3), 7.32–7.49 (m, 2H, H-4′ and H-6′),7.57 (dd, 1H, J = 8.0, 5.4, Hz, H-5), 7.87–7.91 (m, 2H, H-2′ and H-5′), 8.12 (s,1H, H-2), 8.34 (s, 1H, H-5″), 8.54 (dd, 1H, J = 5.4, 1.1 Hz, H-6), 9.11 (dd, 1H, J = 6.8, 1.1 Hz, H-4), 12.9 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.9 (q), 111.1 (s), 112.5 (d), 116.3 (d), 120.9 (s), 123.4 (d), 126.5 (d), 126.8 (d), 129.1 (d), 131.0 (d), 132.8 (s), 135.1 (d), 137.1 (d), 138.6 (s), 141.8 (s), 149.5 (s), 166.8 ppm (s); IR (KBr): $\tilde{\nu}$ = 3089 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{13}N_3S$: C 70.08, H 4.50, N 14.42, found: C 70.29, H 4.62, N 14.21.

1-Methyl-3-[2-(3-methylphenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7f): Yellow solid (1.15 g, 75%): R_f = 0.70 (EtOAc); mp: 221–222 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.43 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 7.31–7.48 (m, 3H, H-5, H-4′ and H-6′), 7.84–7.87 (m, 2H, H-2′ and H-5′), 7.99 (s,1H, H-2), 8.29 (s, 1H, H-5″), 8.50 (dd, 1H, J = 5.1, 1.2, Hz, H-6), 8.90 ppm (dd, 1H, J = 7.9, 1.2 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.9 (q), 21.1 (q), 109.5 (s), 111.7 (d), 116.2 (d), 119.5 (s), 123.4 (d), 126.5 (d), 129.1 (d), 129.9 (s), 130.0 (d), 131.0 (d), 132.5 (d), 132.9 (s), 138.6 (s), 139.4 (d), 149.7 (s), 166.7 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{15}N_3S$: C 70.79, H 4.95, N 13.76, found: C 70.55, H 4.87, N 13.93.

3-[2-(3-Fluorophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7g): Yellow solid (1.04 g, 70%): R_f = 0.56 (EtOAc); mp: 272–273 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.34–7.94 (m, 5H, H-2′, H-4′, H-5, H-5′ and H-6′), 8.20 (s, 1H, H-5″), 8.38 (s, 1H, H-2), 8.56 (d, 1H, J = 4.6 Hz, H-6), 9.15 (d, 1H, J = 7.0 Hz, H-4), 12.94 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.9 (s), 112.5 (dd, $^2J_{CF}$ = 21 Hz), 113.4 (d), 116.4 (d), 117.0 (dd, $^2J_{CF}$ = 21 Hz), 120.9 (s), 122.4 (dd, $^4J_{CF}$ = 2.7 Hz), 127.4 (d), 131.4 (dd, $^3J_{CF}$ = 8.4 Hz), 135.0 (d, $^3J_{CF}$ = 8.4 Hz), 135.4 (d), 136.7 (d), 141.6 (s), 149.7 (s), 162.5 ppm (d, $^1J_{CF}$ = 244 Hz), 165.1 (s); IR (KBr): $\tilde{\nu}$ = 3089 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{10}FN_3S$: C 65.07, H 3.41, N 14.23, found: C 65.29, H 3.52, N 13.96.

3-[2-(3-Fluorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7h): Yellow solid (1.20 g, 78%): R_f = 0.63 (EtOAc); mp: 274 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.97 (s, 3H, CH$_3$), 7.33–7.91 (m, 5H, H-2′, H-4′, H-5, H-5′ and H-6′), 8.06 (s, 1H, H-5″), 8.31 (s, 1H, H-2), 8.56 (dd, 1H, J = 5.1, 1.2 Hz, H-6), 9.15 ppm (dd, 1H, J = 7.9, 1.2 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 31.7 (q), 99.5 (s), 112.2 (dd, $^2J_{CF}$ = 20 Hz), 112.4 (dd, $^4J_{CF}$ = 2.6 Hz), 112.5 (dd, $^2J_{CF}$ = 20 Hz), 116.3 (d), 116.8 (d), 118.6 (s), 122.4 (d), 129.7 (d), 131.4 (dd, $^3J_{CF}$ = 7.5 Hz), 135.1 (d, $^3J_{CF}$ = 7.5 Hz), 138.6 (s), 140.7 (d), 145.3 (s), 150.3 (s), 162.5 ppm (d, $^1J_{CF}$ = 242 Hz); Elemental analysis: calcd (%) for $C_{17}H_{12}FN_3S$: C 66.00, H 3.91, N 13.58, found C 66.26, H 4.04, N 13.41.

3-(2-Phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7i): Yellow solid (1.75 g, 70%): R_f = 0.50 (EtOAc); mp: 254 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.55–8.13 (m, 6H, H-2′, H-3′, H-4′, H-5, H-5′ and H-6′), 8.15 (s, 1H, H-2), 8.37 (s, 1H, H-5″), 8.56 (d, 1H, J = 4.5 Hz, H-6), 9.15 (d, 1H, J = 7.0 Hz, H-4), 12.9 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 111.0 (s), 112.6 (d), 116.3 (d), 120.9 (s), 126.2 (2×d), 126.8 (d), 129.3 (2×d), 130.4 (d), 132.9 (s), 135.2 (d), 137.3 (d), 141.9 (s), 149.6 (s), 166.7 ppm (s); IR (KBr): $\tilde{\nu}$ = 3089 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{11}N_3S$: C 69.29, H 4.00, N 15.15, found: C 69.40, H 4.09, N 14.98.

1-Methyl-3-(2-phenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7j): Yellow solid (1.06 g, 73%): R_f = 0.63 (EtOAc); mp: 231–232 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.99 (s, 3H, CH$_3$), 7.46 (dd, 1H, J = 7.9, 5.2 Hz, H-5), 7.54–7.59 (m, 3H, H-3′, H-4′ and H-5′), 8.01 (s, 1H, H-2), 8.04–8.09 (m, 2H, H-2′ and H-6′), 8.30 (s, 1H, H-5″), 8.50 (dd, 1H, J = 5.2, 1.1 Hz, H-6), 8.92 ppm (dd, 1H, J = 7.9, 1.1 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 32.2 (q), 109.6 (s), 116.2 (d), 111.9 (d), 119.6 (s), 126.1 (2×d), 129.2 (2×d), 130.0 (d), 130.3 (d), 132.8 (s), 132.9 (d), 139.3 (d), 143.9 (s), 149.7 (s), 166.5 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{13}N_3S$: C 70.08, H 4.50, N 14.42, found: C 70.33, H 4.62, N 14.18.

3-[2-(4-Methylphenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7k): Yellow solid (1.03 g, 71%): R_f = 0.54 (EtOAc); mp: 267–268 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3H, CH$_3$), 7.36 (d, 2H, J = 8.0 Hz, H-3′ and H-5′), 7.56 (dd, 1H, J = 8.0, 5.5 Hz, H-5), 7.97 (d, 2H, J = 8.0 Hz, H-2′ and H-6′), 8.08 (s, 1H, H-2), 8.33 (s, 1H, H-5″), 8.53 (d, 1H, J = 5.5 Hz, H-6), 9.11 (d, 1H, J = 8.0 Hz, H-4), 12.80 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.0 (q), 111.0 (s), 112.0 (d), 116.3 (d), 120.7 (s), 126.1 (2×d), 126.7 (d), 129.8 (2×d), 130.3 (s), 134.5 (d), 137.4 (d), 140.2 (s), 142.1 (s), 149.5 (s), 166.8 ppm (s); IR (KBr): $\tilde{\nu}$ = 3062 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{13}N_3S$: C 70.08, H 4.50, N 14.42, found: C 70.29, H 4.64, N 14.19.

1-Methyl-3-[2-(4-methylphenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7l): Yellow solid (1.18 g, 77%): R_f = 0.67 (EtOAc); mp: 278–279 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3H, CH$_3$), 3.97 (s, 3H, CH$_3$), 7.36 (d, 2H, J = 8.1 Hz, H-3′ and H-5′), 7.43 (dd, 1H, J = 7.9, 5.1 Hz, H-5), 7.95 (d, 2H, J = 8.1 Hz, H-2′ and H-6′), 7.95 (s,1H, H-2), 8.28 (s, 1H, H-5″), 8.48 (d, 1H, J = 5.1 Hz, H-6), 8.88 ppm (d, 1H, J = 7.9 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.0 (q), 32.0 (q), 109.5 (s), 111.2 (d), 116.2 (d), 119.3 (s), 126.0 (2×d), 129.8 (2×d), 129.9 (d), 130.3 (s), 132.3 (d), 139.6 (d), 140.1 (s), 140.8 (s), 144.4 (s), 149.7 ppm (s) Elemental analysis: calcd (%) for $C_{18}H_{15}N_3S$: C 70.79, H 4.95, N 13.76, found: C 70.65, H 5.04, N 13.97.

3-[2-(4-Methoxyphenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7m): Yellow solid (1.10 g, 72%): R_f = 0.56 (EtOAc); mp: 233 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.85 (s, 3H, CH$_3$), 7.11 (d, 2H, J = 8.8 Hz, H-3′ and H-5′), 7.52 (dd, 1H, J = 7.9, 5.4 Hz, H-5), 8.01 (s, 1H, H-2), 8.03 (d, 2H, J = 8.8 Hz, H-2′ and H-6′), 8.29 (s, 1H, H-5″), 8.50 (d, 1H, J = 5.4 Hz, H-6), 9.06 (d, 1H, J = 7.9 Hz, H-4), 12.70 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 55.4 (q), 110.9 (s), 111.3 (d), 114.6 (2×d), 116.3 (d), 120.5 (s), 125.8 (s), 126.4 (d), 127.8 (2×d), 134.9 (d), 137.9 (d), 142.9 (s), 149.5 (s), 160.9 (s), 166.6 ppm (s); IR (KBr): $\tilde{\nu}$ = 3062 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{17}H_{13}N_3OS$: C 66.43, H 4.26, N 13.67, found: C 66.51, H 4.33, N 13.59.

3-[2-(4-Methoxyphenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7n): Yellow solid (1.31 g, 82%): R_f = 0.62 (EtOAc); mp: 251 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.85 (s, 3H, CH$_3$), 3.98 (s, 3H, CH$_3$), 7.10 (d, 2H, J = 8.8 Hz, H-3′ and H-5′), 7.45 (dd, 1H, J = 7.9, 5.2 Hz, H-5), 7.91 (s, 1H, H-2), 7.99 (d, 2H, J = 8.8 Hz, H-2′ and H-6′), 8.28 (s, 1H, H-5″), 8.51 (dd, 1H, J = 5.2, 1.0, H-6), 8.91 ppm (dd, 1H, J = 7.9, 1.0 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 31.9 (q), 55.4 (q), 109.4 (s), 110.6 (d), 114.6 (2×d), 116.2 (d), 119.1 (s), 125.8 (s), 127.7 (2×d), 129.7 (d), 132.0 (d), 140.0 (d), 144.6 (s), 149.6 (s), 160.9 (s), 166.4 ppm (s); Elemental analysis: calcd (%) for $C_{18}H_{15}N_3OS$: C 67.27, H 4.70, N 13.07, found: C 67.34, H 4.79, N 12.91.

3-[2-(4-Chlorophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7o): Yellow solid (1.21 g, 78%): R_f = 0.53 (EtOAc); mp: 273 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.53 (dd, 1H, J = 7.9, 5.4 Hz, H-5), 7.64 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 8.10 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 8.14 (s, 1H, H-2), 8.33 (s, 1H, H-5″), 8.52 (d, 1H, J = 5.4 Hz, H-6), 9.07 (d, 1H, J = 7.9 Hz, H-4); 12.8 ppm (s,1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.7 (s), 112.8 (d), 116.3 (d), 120.4 (s), 123.2 (s), 126.7 (d), 127.8 (2×d), 129.3 (2×d), 131.7 (s), 134.8 (d), 137.9 (d), 142.6 (s), 150.0 (s), 165.3 ppm (s); IR (KBr): $\tilde{\nu}$ = 3062 cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{10}ClN_3S$: C 61.64, H 3.23, N 13.48, found: C 61.70, H 3.27, N 13.42.

3-[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7p): Yellow solid (1.41 g, 87%): R_f = 0.66 (EtOAc); mp: 265–266 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.96 (s, 3H, CH$_3$), 7.41 (dd, 1H, J = 7.9, 5.0 Hz, H-5), 7.61 (d, 2H, J = 8.6 Hz, H-3′ and H-5′), 8.01 (s, 1H, H-2), 8.10 (d, 2H, J = 8.6 Hz, H-2′ and H-6′), 8.27 (s, 1H, H-5″), 8.47 (dd, 1H, J = 5.0, 1.2 Hz, H-6), 8.84 ppm (dd, 1H, J = 7.9, 1.2 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 31.7 (q), 109.0 (s), 111.9 (d), 116.3 (d), 118.7 (s), 127.8 (2×d), 129.3 (2×d), 129.7 (d), 131.2 (d), 131.8 (s), 134.8 (s), 140.8 (d), 145.3 (s), 150.3 (s), 165.1 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{12}ClN_3S$: C 62.67, H 3.71, N 12.90, found: C 62.38, H 3.83, N 12.67.

3-[2-(4-Bromophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7q): Yellow solid (1.48 g, 83%): R_f = 0.59 (EtOAc); mp: 278–279 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.55 (dd, 1H, J = 7.9, 5.4 Hz, H-5), 7.75 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 8.03 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 8.15 (s, 1H, H-2), 8.33 (s, 1H, H-5″), 8.53 (d, 1H, J = 5.4 Hz, H-6), 9.08 (d, 1H, J = 7.9 Hz, H-4), 12.8 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.8 (s), 112.9 (d), 126.3 (d), 120.6 (s), 123.6 (s), 126.8 (d), 128.0 (2×d), 132.0 (s), 132.2 (2×d), 134.6 (d), 137.7 (d), 142.4 (s), 149.9 (s), 165.4 ppm (s); IR (KBr): $\tilde{\nu}$ = 2948 cm^{-1}

(NH); Elemental analysis: calcd (%) for $C_{16}H_{10}BrN_3S$: C 53.95, H 2.83, N 11.80, found: C 53.63, H 2.97, N 12.02.

3-[2-(4-Bromophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7r): Yellow solid (1.59 g, 86%): $R_f = 0.69$ (EtOAc); mp: 282–283 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): $\delta = 3.96$ (s, 3H, CH_3), 7.41 (dd, 1H, $J = 7.9$, 5.1 Hz, H-5), 7.74 (d, 2H, $J = 8.6$ Hz, H-3′ and H-5′), 8.00 (d, 2H, $J = 8.6$ Hz, H-2′ and H-6′), 8.02 (s, 1H, H-2), 8.27 (s, 1H, H-5″), 8.47 (dd, 1H, $J = 5.1$, 1.3 Hz, H-6), 8.84 ppm (dd, 1H, $J = 7.9$, 1.3 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 31.9$ (q), 109.2 (s), 112.1 (d), 116.2 (d), 119.1 (s), 123.5 (s), 128.0 (2×d), 129.9 (d), 131.9 (s), 132.1 (d), 132.2 (2×d), 140.1 (d), 144.6 (s), 150.1 (s), 165.2 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{12}BrN_3S$: C 55.15, H 3.27, N 11.35, found: C 55.34, H 3.33, N 11.07.

3-[2-(4-Fluorophenyl-1,3-thiazol-4-yl)-1*H*-7-azaindole (7s): Yellow solid (1.19 g, 80%): $R_f = 0.57$ (EtOAc); mp: 258–259 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): $\delta = 7.36$–7.45 (m, 2H, H-3′ and H-5′), 7.54 (dd, 1H, $J = 8.0$, 5.4 Hz, H-5), 8.11 (s, 1H, H-2), 8.15–8.18 (m, 2H, H-2′ and H-6′), 8.33 (s,1H, H-5″), 8.52 (dd, 1H, $J = 5.4$, 1.1 Hz, H-6), 9.10 (dd, 1H, $J = 8.0$, 1.1 Hz, H-4) 12.82 ppm (s, 1H, NH); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 110.8$ (s), 112.5 (d), 116.2 (2×dd, $^2J_{CF} = 22$ Hz), 116.3 (d), 120.6 (s), 122.4 (d, $^4J_{CF} = 3.0$ Hz), 126.7 (d), 128.5 (2×dd, $^3J_{CF} = 8.4$ Hz), 134.7 (d), 137.6 (d), 141.3 (s), 149.7 (s), 163.2 (d, $^1J_{CF} = 248$ Hz), 165.1 ppm (s); IR (KBr): $\tilde{\nu} = 3099$ cm^{-1} (NH); Elemental analysis: calcd (%) for $C_{16}H_{10}FN_3S$: C 65.05, H 3.41, N 14.23, found: C 65.22, H 3.26, N 13.87.

3-[2-(4-Fluorophenyl)-1,3-thiazol-4-yl]-1-methyl-1*H*-7-azaindole (7t): Yellow solid (1.31 g, 85%): $R_f = 0.60$ (EtOAc); mp: 261 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): $\delta = 3.98$ (s, 3H, CH_3), 7.35–7.48 (m, 3H, H-3′, H-5 and H-5′), 7.99 (s, 1H, H-2), 8.10–8.14 (m, 2H, H-2′ and H-6′), 8.29 (s, 1H, H-5″), 8.49 (dd, 1H, $J = 4.9$, 1.1 Hz, H-6), 9.10 ppm (dd, 1H, $J = 8.0$, 1.1 Hz, H-4); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 32.2$ (q), 107.8 (s), 112.0 (d), 116.2 (d), 116.3 (dd, $^2J_{CF} = 22$ Hz), 117.9 (s), 127.8 (d, $^4J_{CF} = 2.1$ Hz), 128.3 (dd, $^3J_{CF} = 8.7$ Hz), 130.1 (d), 133.0 (d), 139.0 (d), 161.8 (d, $^1J_{CF} = 248$ Hz), 141.9 (s), 148.0 (s), 163.6 ppm (s); Elemental analysis: calcd (%) for $C_{17}H_{12}FN_3S$: C 66.00, H 3.91, N 13.58, found: C 66.09, H 3.82, N 13.43.

Biological studies

Drugs: The phenylthiazolyl-7-azaindoles derivatives were prepared as described above. Roscovitine was purchased from Calbiochem (San Diego, CA, USA) and purvalanol A from Tocris (Bristol, UK). To obtain a 1 mM stock solution of phenylthiazolyl-7-azaindoles, a variable amount of a solution of 1% dimethyl sulfoxide (DMSO) made in sterile water was added to each compound powdered stock and the compound was completely dissolved, stored at −20 °C, and diluted in complete culture medium immediately before use.

Cell culture conditions: The *Mycoplasma*-free human pancreatic carcinoma (MiaPaCa-2) cell line was obtained from American Type Culture Collection (Rockville, MD, USA). The *Mycoplasma*-free human malignant peritoneal mesothelioma cell line (STO) was established in our laboratory.[15] Cells were maintained in culture as a monolayer in DMEM/F12 medium (Lonza Milano s.r.l, Treviglio, Italy) supplemented with 10% heat-inactivated fetal bovine serum in a humidified incubator at 37 °C under an atmosphere of 5% CO_2, 95% air.

*Evaluation of the antiproliferative potential of 3-(2-phenyl-1,3-thiazol-4-yl)-1H-7-azaindoles **7h**, **7l**, **7j**, and **7p***: After harvesting in the logarithmic growth phase, 2×10^3 cells were plated in 96-well flat-bottomed microtiter plates (EuroClone, Milan, Italy) for 24 h and then treated with various concentrations of test derivatives (0.05–50 μM) for 72 h. Control cells received vehicle alone (1% DMSO). All studies were performed in eight replicates and repeated at least three times independently. At the end of drug exposure, the antiproliferative potential was determined with the sulforhodamine B (SRB) protein staining method as previously reported.[16] Briefly, cells were fixed with cold 50% trichloroacetic acid solution (Sigma Aldrich) and stained with 0.4% SRB (Sigma Aldrich) dissolved in 1% acetic acid (Sigma Aldrich) for 30 min. The plates were then washed four times with 1% acetic acid to remove unbound stain, air dried, and bound dye was dissolved by 10 mM Tris base (pH 10.5). Optical density was read at 550 nm on a microplate reader and the results were expressed as a percentage, relative to DMSO-treated cells. Dose–response curves were created and IC_{50} values (that is, concentrations able to inhibit cell growth by 50%) were determined graphically from the curve for each compound.

In vitro kinase assays: CDK1, CDK5, and GSK3β kinase activity was performed using the Omnia™ Ser/Thr Recombinant Kit (Invitrogen, Carlsbad, CA) according to the manufacturer's protocols. Briefly, increasing concentrations of phenylthiazolyl-7-azaindoles **7l** and **7j** (0.05–50 μM) were mixed to recombinant CDK1/cyclin B, or CDK5/p25, or GSK3β (Invitrogen) in 1× kinase buffer containing S/T peptide substrate, ATP, and dithiothreitol, and the kinase reaction was performed at 30 °C for 60 min. The samples were transferred to a 96-well plate and incubated at RT for 20 min. Fluorescence progress curves were measured upon excitation at 360 nm and emission at 485 nm. IC_{50} values (inhibitor concentration at which enzyme activity is reduced by 50%) were determined graphically from the curve for each compound.

Cell-cycle phase distribution: Both adherent and floating cells were fixed in 70% EtOH and incubated on ice for 30 min in staining solution containing 50 μg mL^{-1} of propidium iodide, 50 mg mL^{-1} of RNase, and 0.05% Nonidet P40 in PBS. Samples were analyzed with a FACScan flow cytometer (Becton Dickinson, Sunnyvale, CA, USA) with an excitation wavelength of 488 nm and an emission wavelength of 585 nm. At least 30000 events were read and histograms were analyzed using the CellQuest software according to the Modfit model (Becton Dickinson).

Statistical analysis: Statistical evaluation of data was performed with a two-tailed Student's *t*-test; p values < 0.05 were considered statistically significant.

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