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One-pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies

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Graphical Abstract

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One-pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies

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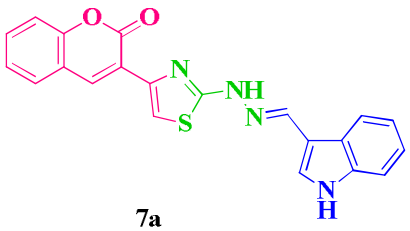
Rajitha Gali,[a] Janardhan Banothu,[a] Ramesh Gondru,[a] Rajitha Bavantula,[a]* Yashodhara Velivela,[b] Peter. A. Crooks[c]



7a

Antibacterial activity:- $ZOI_{[50\ \mu g/mL]}$: *E.coli* - 15 mm and *B.subtilis* - 18 mm
Anticancer activity:- Leukemia: CCRF-CEM (GI_{50} : 0.33 μM); Non-Small Cell Lung Cancer: NCI-H522 (GI_{50}: 1.03 μM); Colon Cancer: HCT-116 (GI_{50}: 1.60 μM); CNS Cancer: SF-539 (GI_{50}: 1.58 μM); Melanoma: MALME-3M (GI_{50}:1.59 μM); Ovarian Cancer: OVCAR-3 (GI_{50}: 1.16 μM); Renal Cancer: UO-31 (GI_{50}: 0.76 μM; Prostate Cancer: PC-3 (GI_{50}: 0.82 μM); Breast Cancer: BT-549 (GI_{50}: 1.13 μM).
DNA Cleavage activity:- Completely cleaved the DNA even at 50 μg/mL

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One-pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies

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ABSTRACT

A series of indole incorporated thiazolylcoumarins (**7a-q**) have been synthesized and evaluated for their antibacterial, anticancer and DNA cleavage studies. Analysis of antibacterial studies indicated that all the synthesized compounds possess promising activity towards the screened bacterial strains. *In vitro* anticancerous action was studied for compound **7a** (NSC: 768621/1) against the full panel of 60 human tumor cell lines. The five dose level activity results revealed that, the compound **7a** was active against all the cell lines among them it has shown potent activity against Leukemia: CCRF-CEM (GI_{50}: 0.33 µM), Non-small cell lung cancer: NCI-H522 (GI_{50}: 1.03 µM), Colon Cancer: HCT-116 (GI_{50}: 1.60 µM), CNS Cancer: SF-539 (GI_{50}: 1.58 µM), Melanoma MALME-3M (GI_{50}: 1.59µM), Ovarian Cancer: OVCAR-3 (GI_{50}: 1.16 µM), Renal Cancer: UO-31 (GI_{50}: 0.76 µM), Prostate Cancer: PC-3 (GI_{50}: 0.82 µM) and Breast Cancer: BT-549 (GI_{50}: 1.13µM). DNA cleavage studies revealed that even at 50 µg/mL concentration complete DNA digestion was observed for all the compounds, except for compound (**7o**) where partial DNA digestion was observed even at 100µg/mL.

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Cancer is a potential life-threatening disease characterized by the uncontrolled growth of abnormal cells. About 12.7 million cancer cases and 7.6 million cancer deaths (13%) are estimated to have occurred in 2008 world-wide.[1] DNA is the primary target molecule for most of the anticancer and antiviral therapies; DNA damage, mutation and altered gene expression are key players in the process of carcinogenesis. Many natural and synthetic anticancer agents having ability to interact with DNA have been discovered.[2] Indole, thiazole and coumarin moieties are endowed with anticancer, anticonvulsant, antitubercular, antimicrobial, antioxidant and anti-inflammatory activities.[3] Some of the widely used anticancer drugs such as Cediranib, Tiazofurin, and Geiparvarin as well as most active thiazolylcoumarin derivatives[4] are shown in (Fig 1).

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry in which three or more different starting materials react to give a final product in a one-pot procedure.[5] Several methods have been reported for the synthesis of thiazolylhydrazones[4,6] in multistep process, for longer reaction times. In the present study and in continuation of our research towards the synthesis of biologically potent heterocyclic compounds,[7] we opted to design a moiety that embodied indole, thiazole and coumarin in a single frame *via* multicomponent approach and their antibacterial, anticancer and DNA cleavage activities were evaluated.

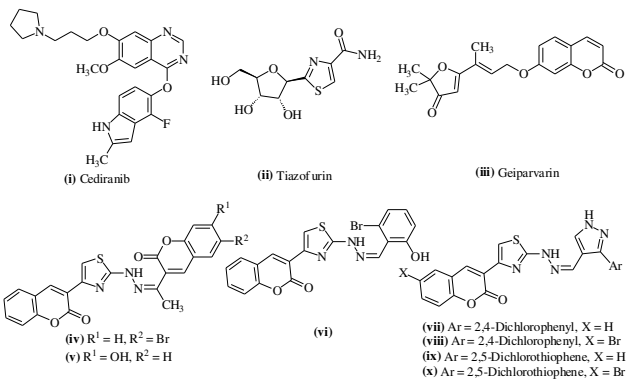

Fig. 1. Some of the widely used anticancer drugs (i, ii & iii) and potent antimicrobial thiazolylcoumarin derivatives (iv to x).

A series of indole incorporated thiazolylcoumarins **(7a-q)** were synthesized *via* multicomponent condensation of 3-(2-bromoacetyl)-2*H*-chromen-2-ones **(4a-d)**/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one **(4e)**, indole-3-carbaldehyde **(5a-e)** and thiosemicarbazide **(6)** in absolute ethanol with catalytic amount of acetic acid under reflux conditions with 84-97% yield.[8] The synthetic pathway was outlined in **Scheme 1**. Indole-3-carbaldehydes **(5a-e)** and 3-(bromoacetyl)-2*H*-chromen-2-ones (**4a-d**)/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one **(4e)** were synthesized according to the literature methods.[9]

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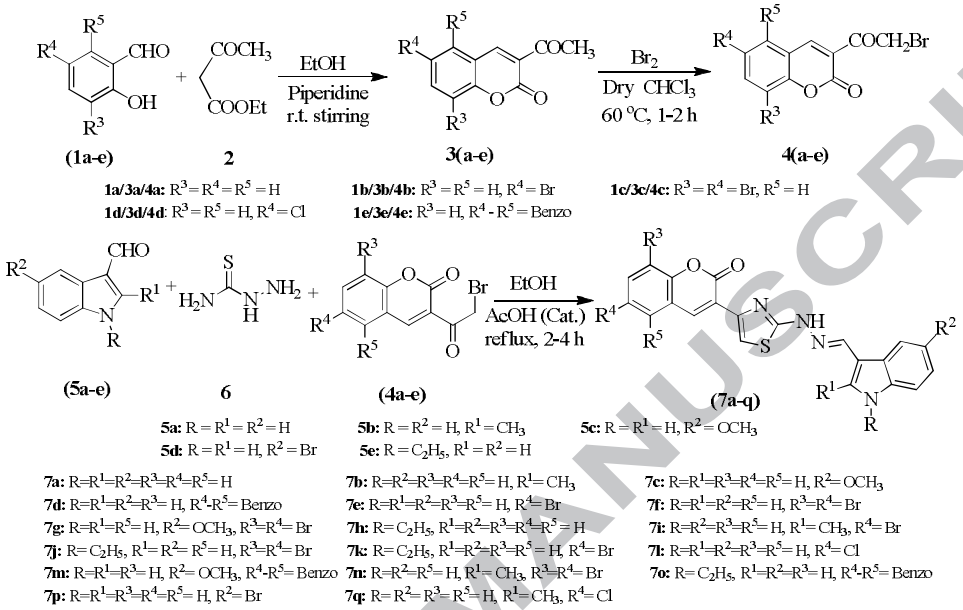
All the newly synthesized compounds were characterized by IR, NMR and mass spectral studies as well as elemental analyses. In the IR spectrum of compound **(7a)**, the appearance of a broad band in the range of 3150-3300 cm^{-1}, sharp bands at 1720, 1623 cm^{-1}, and a medium band at 1105 cm^{-1} corresponds to N-H, C=O, C=N and C-S stretching frequencies respectively. In case of ^{1}H NMR spectrum, the singlets at 8.32 and 8.57 ppm confirm the presence of imine and coumarin 4th protons respectively, whereas the singlets at 11.55 and 11.89 ppm confirm the hydrazinyl and indole NH protons respectively. ^{13}C NMR, spectroscopic analyses also confirmed the structural identity, with resonances observed at 168.55, 159.21, 154.87, 144.29 ppm corresponding to thiazolyl carbon, δ-lactone carbonyl carbon, coumarin 4th carbon, and imine carbons respectively. Molecular ion peak from the mass spectrum as well as elemental analyses further confirmed the product formation**.**



Scheme 1. Synthesis of indole incorporated thiazolylcoumarins.

All the synthesized compounds (**7a-q**) were screened for their *in vitro* antibacterial activity against *Bacillus subtilis* (Gram positive) and *Escherichia coli* (Gram negative) bacterial strains with respect to standard antibiotic drug Streptomycin using cup-plate agar diffusion method.[10] The activity was performed at 50 µg/mL for **7a-q** and 30 µg/mL for Streptomycin, and the resulting zone of inhibition (ZOI) were given in Table 1. The activity results **(Table 1)** revealed that, the compound without having any substitutions (**7a**) on coumarin, thiazole and indole moieties has shown maximum ZOI against *Escherichia coli* (ZOI = 18 mm) and good ZOI against *Bacillus subtilis* (ZOI = 15 mm). Except compound derived from 6,8-dibromo-3-(2-bromoacetyl)-2*H*-chromen-2-one and 1*H*-indole-3-carbaldehyde *i.e.* **7f** and 3-(2-bromoacetyl)-6-chloro-2*H*-chromen-2-one and 2-methyl-1*H*-indole-3-carbaldehyde *i.e.* **7q** against *Escherichia coli,* remaining all the compounds have also shown good ZOI ranging from 10-15 mm against both the tested bacterial strains.

In vitro anticancer activity was carried out at National Cancer Institute, Bethesda, USA.[11] Among all the compounds **7a** was selected by NCI and initially screened at a single high dose of 10^{-5} M concentration on all the 60 human cancer cell lines was organized into nine sub-panels derived from nine different human cancer types: Leukemia, Lung, Colon, CNS, Melanoma, Ovarian, Renal, Prostate and Breast cancer cell lines. Output from the single dose screen is reported as a graph of mean growth percent of the treated cells (supporting file). From the graph both growth inhibition values (between 0 and 100) and cytotoxicity values (less than 0) can be detected. The results were analyzed by COMPARE program.[12] The percentage growth inhibition (GI%) of the treated cells 10^{-5} M concentration with the compound **7a** is given in **Table 2**.

Table 1. Zone of inhibition values for analogs (7a-q) at 50 µg/mL and positive control drug Streptomycin at 30 µg/mL.

Entry	Product	Zone of inhibition in mm	
		Bacillus subtilis	*Escherichia coli*
1	**7a**	18	15
2	**7b**	13	10
3	**7c**	13	10
4	**7d**	15	14
5	**7e**	15	13
6	**7f**	10	7
7	**7g**	10	10
8	**7h**	10	10
9	**7i**	10	12
10	**7j**	10	10
11	**7k**	15	15
12	**7l**	13	15
13	**7m**	15	12
14	**7n**	15	12
15	**7o**	15	12
16	**7p**	15	10
17	**7q**	10	6
18	**Streptomycin**	30	30

Bacillus subtilis:- Resistant: 7a, 7d, 7e, 7k, 7m, 7n, 7o, 7p; Intermediate: 7b, 7c, 7f, 7g, 7h, 7i, 7j, 7l, 7q.
Escherichia coli:- Resistant: 7a, 7d, 7k, 7l; Intermediate: 7b, 7c, 7e, 7g, 7h, 7i, 7j, 7m, 7n, 7o, 7p; Susceptible: 7f, 7q.

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Table 2. Growth percent and growth inhibition (GI%) in single dose assay (10^{-5} M) for compound **7a** (NSC: 768621/1).

Panel/ Cell line	Growth percent	Growth inhibition (GI%)
Leukemia		
CCRF-CEM	-26.91	cytotoxic
HL-60(TB)	-28.24	cytotoxic
K-562 0.99	0.99	99.01
MOLT-4	-32.32	cytotoxic
RPMI-8226	-33.83	cytotoxic
SR	-0.54	cytotoxic
Non-Small Cell Lung Cancer		
A549/ATCC	-30.98	cytotoxic
HOP-62	11.30	88.7
HOP-92	-14.45	cytotoxic
NCI-H226	42.82	57.18
NCI-H23	25.93	74.07
NCI-H322M	15.29	84.71
NCI-H460	5.79	94.21
NCI-H522	-77.80	cytotoxic
Colon Cancer		
COLO 205	28.15	71.85
HCC-2998	8.49	91.51
HCT-116	7.48	92.52
HCT-15	12.32	87.68
HT29	32.14	67.86
KM12	-47.67	cytotoxic
SW-620	17.50	82.50
CNS Cancer		
SF-268	14.73	85.27
SF-295	-25.04	cytotoxic
SF-539	0.41	99.59
SNB-19	39.43	60.57
SNB-75	15.44	84.56
U251	-6.38	cytotoxic
Melanoma		
LOX IMVI	-52.19	cytotoxic
MALME-3M	-10.02	cytotoxic
M14	34.19	65.81
MDA-MB-435	22.44	77.56
SK-MEL-2	-9.49	cytotoxic
SK-MEL-28	54.83	45.17
SK-MEL-5	69.78	30.22
UACC-257	8.34	91.66
UACC-62	42.96	57.04
Ovarian Cancer		
IGROV1	0.26	99.74
OVCAR-3	-80.31	cytotoxic
OVCAR-4	-4.09	cytotoxic
OVCAR-5	55.24	44.76
OVCAR-8	2.99	97.01
NCI/ADR-RES	24.90	75.10
SK-OV-3	62.24	37.76
Renal Cancer		
786-0	-53.65	cytotoxic
A498	6.72	93.28
ACHN	10.07	89.93
CAKI-1	-41.32	cytotoxic
RXF 393	25.19	74.81
SN12C	0.22	99.78
UO-31	-90.51	cytotoxic
Prostate Cancer		
PC-3	-37.33	cytotoxic
DU-145	-36.09	cytotoxic
Breast Cancer		
MCF7	8.91	91.09
MDA-MB-231/ATCC	-37.04	cytotoxic
BT-549	-12.14	cytotoxic
T-47D	4.07	95.93
MDA-MB-468	2.39	97.61

Table 3. GI_{50}, TGI and LC_{50} values of compound **7a** against 60 human cancer cell lines.

Panel/ Cell line	GI_{50} (μM)	MGMID (μM)	TGI (μM)	LC_{50} (μM)
Leukemia				
CCRF-CEM	0.33		1.78	> 100
HL-60(TB)	0.45		7.64	> 100
K-562	3.18	1.18	10.4	> 100
MOLT-4	0.40		3.27	> 100
RPMI-8226	0.90		4.79	> 100
SR	1.83		4.92	> 100
Non-Small Cell Lung Cancer				
A549/ATCC	1.54		5.30	> 100
HOP-62	3.73		20.0	> 100
NCI-H226	2.38		7.70	> 100
NCI-H23	2.44	2.44	5.82	> 100
NCI-H322M	3.16		32.2	> 100
NCI-H460	2.84		9.69	> 100
NCI-H522	1.03		2.26	4.96
Colon Cancer				
COLO 205	1.92		3.55	6.55
HCC-2998	2.82		6.80	> 100
HCT-116	1.60		3.22	6.49
HCT-15	1.61	2.00	3.47	7.46
HT29	2.01		5.55	> 100
KM12	1.86		4.14	9.22
SW-620	2.19		5.24	70.9
CNS Cancer				
SF-268	1.93		8.77	> 100
SF-295	2.23		6.76	> 100
SF-539	1.58	2.14	3.38	7.25
SNB-19	3.39		62.1	> 100
SNB-75	2.00		8.92	> 100
U251	1.75		5.60	77.7
Melanoma				
LOX IMVI	1.93		3.60	6.71
MALME-3M	1.59		4.17	> 100
M14	1.95		4.22	9.13
MDA-MB-435	2.10		5.47	25.2
SK-MEL-2	1.61	2.10	3.62	8.17
SK-MEL-28	3.96		96.9	> 100
SK-MEL-5	2.09		4.97	15.2
UACC-257	2.15		5.63	> 100
UACC-62	1.60		3.38	7.11
Ovarian Cancer				
IGROV1	1.54		4.70	> 100
OVCAR-3	1.16		2.91	7.31
OVCAR-4	1.37		5.87	> 100
OVCAR-5	2.34	2.15	7.80	> 100
OVCAR-8	1.90		4.56	> 100
NCI/ADR-RES	2.82		9.23	> 100
SK-OV-3	3.95		> 100	> 100
Renal Cancer				
786-0	1.35		4.09	> 100
A498	2.21		8.20	> 100
ACHN	1.31		4.36	70.8
CAKI-1	1.61	1.47	4.65	> 100
RXF 393	1.97		4.77	33.9
SN12C	1.08		3.96	> 100
UO-31	0.76		2.23	5.47
Prostate Cancer				
PC-3	0.828	1.31	2.66	7.63
DU-145	1.80		4.27	> 100
Breast Cancer				
MCF7	2.40		15.5	> 100
MDA-MB-231/ATCC	1.39		3.33	7.94
HS 578T	3.20	1.93	58.9	> 100
BT-549	1.13		2.43	5.22
T-47D	1.98		5.90	> 100
MDA-MB-468	1.52		3.92	> 100

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The compound **7a** has shown significant growth inhibition at a single dose of 10^{-5} M concentration and it has been further evaluated for five dose screening at five different minimal concentrations against full 60 cell lines. Dose-response curves of compound **7a** were created by plotting cytotoxic effect against the $\log_{10}$ of the drug concentration for each cell line (Fig. 2). Cytotoxic effects of each compound were determined as GI_{50}, TGI and LC_{50} values. The compound **7a** has exhibited broad spectrum of growth inhibition activity against nine tumor cell lines with average GI_{50} values (MGMID) 1.18-2.44 µM as shown in (Table 3).

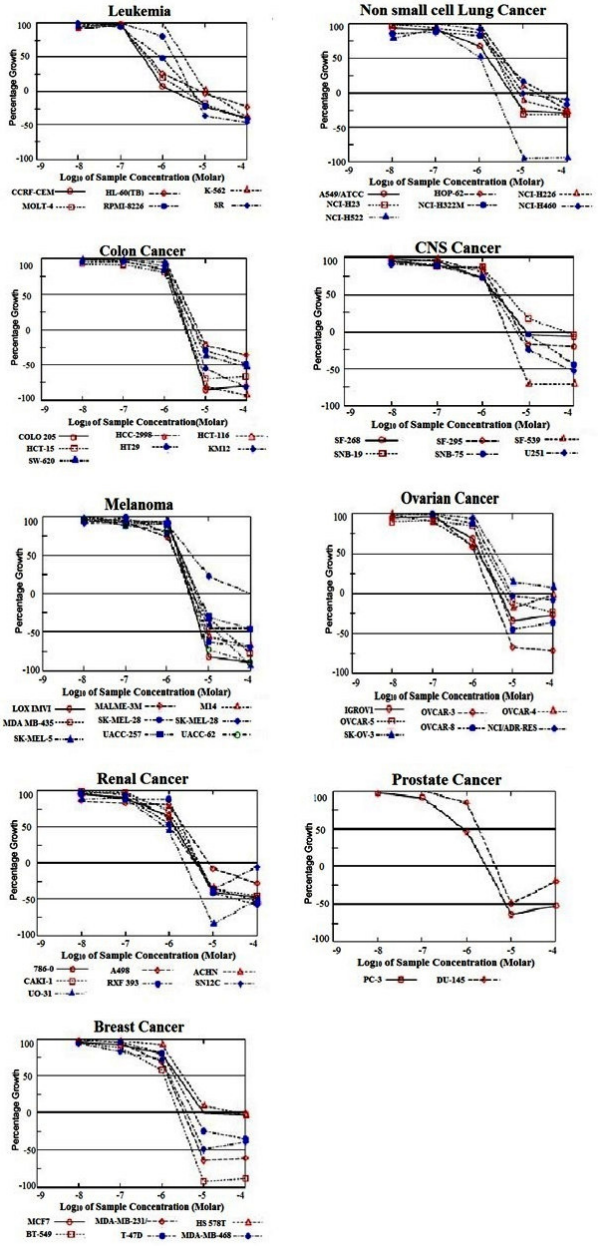

Fig. 2. Dose response curve of nine sub-panel cell lines for compound **7a.**

The DNA cleavage activity on pUC18 was carried out at 50 and 100 µg/mL concentrations using agarose gel electrophoresis method.[13] The pictures of the gels are presented in (Fig. 3). Results have been compared with the standard DNA cleavage agent $FeSO_4$. From these results we noticed that, except compound **7o** and **7h** remaining all the compounds have shown complete DNA cleavage even at 50 µg/mL concentration. Compound **7o** has partially cleaved the DNA at both the concentrations, and compound **7h** has partially cleaved the DNA at 50 µg/mL and completely cleaved at 100 µg/mL. From this, it can be concluded that almost all the compounds (except **7o** and **7h**) inhibit the growth of the pathogenic organism by cleaving the genome.

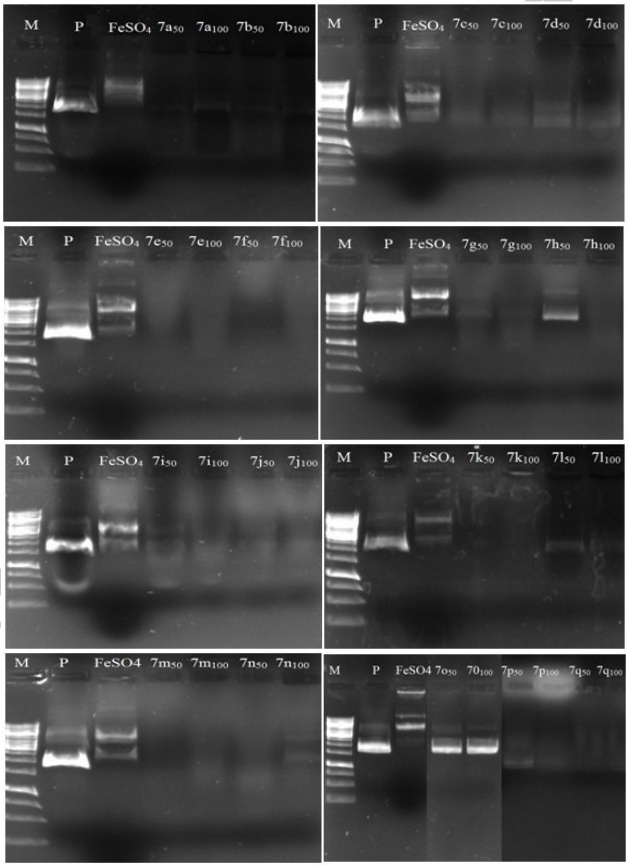

Fig. 3. Agarose gel DNA cleavage analysis of compound **7(a-q)** using pUC18 plasmid; Where, **M**-standard DNA molecular weight marker; **P-**pUC18 plasmid DNA; **$FeSO_4$**-pUC18 plasmid with 5 mM $FeSO_4$; Remaining all lanes: pUC18 plasmid with compound **(7a-q)** at 50 and 100 µg/mL concentrations.

In conclusion, a series of indole incorporated thiazolylcoumarins were synthesized *via* one-pot multicomponent approach with good yields. All the synthesized compounds were screened for their *in vitro* antibacterial and DNA cleavage activities, and anticancer activity of compound **7a** was also evaluated. Antibacterial results revealed that, the compounds **7a, 7d, 7e, 7k, 7l, 7m, 7n** and **7o** exhibited broad spectrum antibiotic activity at 50 µg/mL. DNA cleavage studies have shown that all the compounds exhibit promising DNA cleavage activity at 50 and 100 µg/mL concentration except compound **7o** and **7h**. The primary anticancer screening of compound **7a** was carried at 10^{-5} M concentration and the results have shown 50-99% growth inhibition against all the 60 human tumor cell lines, thus it was further selected for fifth dose level and screened against all the cell lines. Even at fifth dose level, it has exhibited marked anticancer activity in µM concentration

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against all the cell lines. Therefore these studies provide a new lead compound for further development of more potent antibacterial and anticancer agents.

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Supplementary data

Supplementary data (NCI anticancer activity data and characterization data of all compounds) associated with this article can be found, in the online version, at.....

References and notes

1. (a) Bagi, C. M. *J. Musculoskel. Neuron Interact.* **2002**, *2*, 579; (b) Mehlen, P.; Puisieux, A. *Nat. Rev. Cancer* **2006**, *6*, 449; (c) Simpson, C. D.; Anyiwe, K.; Schimmer, A. D. *Cancer Lett.* **2008**, *272*, 177.
2. Riou, J. F.; Fosse, P.; Nguyen, C. H.; Larsen, A. K.; Bissery, M. C.; Grondard, L.; Saucier, J. M.; Bisagni, E.; Lavelle, F. *Cancer Res.* **1993**, *53,* 5987.
3. (a) Weng, J. R.; Tsai, C. H.; Kulp, S. K.; Chen, C. S. *Cancer Lett.* **2008**, *262*, 153; (b) Bialonska, D.; Zjawiony, J. K. *Mar. Drugs* **2009**, *7*, 166; (c) Rosenbaum, C.; Rohrs, S.; Muller, O.; Waldmann, H. *J. Med. Chem.* **2005**, *48,* 1179; (d) Kumar, D.; Sundaree, S.; Johnson, E. O.; Shah, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4492; (e) Kashyap, M.; Kandekar, S.; Baviskar, A. T.; Das, D.; Preet, R.; Mohapatra, P.; Satapathy, S. R.; Siddharth, S.; Guchhait, S. K.; Kundu, C. N.; Banerje, U. C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 934; (f) Reddy, Y. T.; Sekhar, K. R.; Sasi, N.; Reddy, P. N.; Freeman, M. L.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 600; (g) Sonar, V. N.; Thirupathi reddy, Y.; Sekhar, K. R.; Sasi, S.; Freeman, M. L.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6821; (h) Penthala, N. R.; Yerramreddy, T. R.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 591; (i) Vikas, S.; Pradeep, K.; Devender, P. *J. Heterocycl. Chem.* **2010**, *47*, 491; (j) Kashyap, S. J.; Garg, V. K.; Sharma, P. K.; Kumar, N.; Dudhe, R.; Gupta, J. K. *Med. Chem. Res.* **2012**, *21*, 2123; (k) Zhiwei, C.; Jianhao, B.; Weike, S. *Chin. J. Chem.* **2013**, *31*, 507; (l) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887.
4. (a) Arshad, A.; Osman, H.; Bagley, M. C.; Lam, C. K.; Mohamad, S.; Zahariluddin, A. S. *Eur. J. Med. Chem.* **2011**, *46*, 3788; (b) Vijesh, A. M.; Isloor, A. M.; Prabhu, V.; Ahmad, S.; Malladi, S. *Eur. J. Med. Chem.* **2010**, *45*, 5460.
5. Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
6. (a) Franco, C.; Bruna, B.; Adriana, B.; Daniela, S.; Paola, C.; Arianna, G.; Simone, C.; Melissa, D. A.; Maddalena, M. S.; Francesca, S. *J. Heterocycl. Chem.* **2010**, *47*, 1269; (b) Chimenti, P.; Petzer, A.; Carradori, S.; D'Ascenzio, M.; Silvestri, R.; Alcaro, S.; Ortuso, F.; Petzer, J. P.; Secci, D. *Eur. J. Med. Chem.* **2013**, *66*, 221.
7. (a) Kuarm, B. S.; Reddy, Y. T.; Madhav, J. V.; Crooks, P. A.; Rajitha, B. *Bioorg. Med. Chem. Lett.* **2011**, *21,* 524; (b) Laxmi, S. V.; Reddy, Y. T.; Kuarm, B. S.; Reddy, P. N.; Crooks, P. A.; Rajitha, B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4329; (c) Janardhan, B. Rajitha, B. *Chin. Chem. Lett.* **2012**, *23*, 1015; (d) Janardhan, B.; Ravibabu, V.; Rajitha, G.; Rajitha, B.; Crooks, P. A. *Tetrahedron Lett.* **2013**, *54*, 3862.
8. General procedure for the synthesis of indole incorporated thiazolylcoumarins (7a-q): To a mixture of substituted indole-3-carbaldehyde (5a-e, 1 mmol), thiosemicarbazide (6, 1 mmol) and substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (4a-d, 1 mmol)/2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (4e, 1 mmol) in 10 mL ethanol, catalytic amount of acetic acid was added and refluxed for 2-4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid separated out was filtered, washed with hot ethanol, afforded analytically pure product without recrystallization.

Spectral data:

3-(2-(2-((1H-Indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (7a): Yellow solid; Yield: 97%; mp: 248-250 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3229, 3158 (N-H), 1720 (C=O), 1623 (C=N), 1576 (C=C), 1105 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19-7.24 (m, 2H), 7.38-7.47 (m, 3H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 7.2 Hz, 1H), 8.32 (s, 1H), 8.57 (s, 1H), 11.55 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.55, 159.21, 154.87, 152.72, 144.29, 140.32, 138.49, 132.33, 132.04, 130.41, 130.28, 129.27, 125.15, 124.96, 121.06, 119.67, 116.29, 112.88, 111.72, 110.33, 103.81; MS (ESI) *m/z*: 387 [M + H]$^{+}$; HRMS for $C_{21}H_{14}N_4O_2S$: Calcd. 386.0837; Found 386.0835; Anal. calcd. for: C, 65.27; H, 3.65; N, 14.50; Found: C, 65.35; H, 3.62; N, 14.33.

3-(2-(2-((2-Methyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (7b): Yellow solid; Yield: 95%; mp: 264-266 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3416, 3187 (N-H), 1702 (C=O), 1618, 1604 (C=N), 1576 (C=C), 1103 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 7.11-7.14 (m, 2H), 7.32-7.46 (m, 3H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 8.11 (t, *J* = 7.2 Hz, 1H), 8.35 (s, 1H), 8.56 (s, 1H), 11.44 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.88, 158.69, 152.28, 142.80, 140.03, 139.35, 138.27, 135.70, 131.70, 128.79, 125.11, 124.72, 121.75, 120.55, 120.35, 120.08, 119.11, 115.86, 110.93, 109.71, 107.18, 11.50; MS (ESI) *m/z*: 401 [M + H]$^{+}$; Anal. calcd. for $C_{22}H_{16}N_4O_2S$: C, 65.98; H, 4.03; N,13.99; Found: C, 65.87; H, 4.18; N, 14.09.

3-(2-(2-((5-Methoxy-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (7c): Green solid; Yield: 97%; mp: 262-264 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3411, 3273 (N-H), 1698 (C=O), 1619 (C=N), 1577 (C=C), 1098 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H), 6.84-6.87 (m, 1H), 7.34 (d, *J* = 8.8 Hz ,2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 3H), 7.72-7.87 (m, 1H), 8.27 (s, 1H), 8.56 (s, 1H), 11.38 (s, 1H), 11.83 (s, 1H); MS (ESI) *m/z*: 417 [M + H]$^{+}$; Anal. calcd. for $C_{22}H_{16}N_4O_3S$: C, 63.45, H, 3.87; N,13.45; Found: C, 63.55, H, 3.72; N,13.31.

2-(2-(2-((1H-Indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-3H-benzo[f]chromen-3-one (7d): Yellowish green solid; Yield: 90%; mp: 298-300 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3383, 3247 (N-H), 1701 (C=O), 1631, 1604 (C=N), 1574 (C=C), 1100 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18-7.25 (m, 2H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.63-7.69 (m, 2H), 7.81-7.84 (m, 3H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.20-8.39 (m, 4H), 9.31 (s, 1H), 11.56 (s, 1H), 11.91 (s, 1H); MS (ESI) *m/z*: 437 [M + H]$^{+}$; HRMS for $C_{25}H_{16}N_4O_2S$: Calcd. 436.0994; Found 436.0990; Anal. calcd. for: C, 68.79; H, 3.69; N, 12.84; Found: C, 68.81; H, 3.58; N, 12.68.

3-(2-(2-((1H-Indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-6-bromo-2H-chromen-2-one (7e): Green solid; Yield: 89%; mp: 272-274 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3164, 3049 (N-H), 1712 (C=O), 1632, 1603 (C=N), 1575 (C=C), 1067 (C-S), 693 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6, D_2O exchange): δ 7.20 (t, *J* = 8.0 Hz, 2H), 7.40-7.47 (m, 3H), 7.74 (t, *J* = 8.8 Hz, 2H), 8.07 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.29 (s, 1H), 8.48 (s, 1H); MS (ESI) *m/z*: 467 [M + 2]$^{+}$; Anal. calcd. for $C_{21}H_{13}BrN_4O_2S$: C, 54.20; H, 2.82; N, 12.04; Found: C, 54.28; H, 2.74, N, 12.21.

3-(2-(2-((1H-Indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-6,8-dibromo-2H-chromen-2-one (7f): Green solid; Yield: 90%; mp: 285-287 ^{o}C; IR (KBr, υ_{max} cm^{-1}): 3154 (N-H), 1737 (C=O), 1626, 1606 (C=N), 1574 (C=C), 1109 (C-S), 680 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.17-7.24 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 2H), 8.11-8.23 (m, 3H), 8.30 (s, 1H), 8.45 (s, 1H), 11.53 (s, 1H), 11.96 (s, 1H); MS (ESI) *m/z*: 545 [M + H]$^{+}$; HRMS for $C_{21}H_{12}Br_2N_4O_2S$: Calcd. 541.9048; Found 541.9051; Anal. calcd. for: C, 46.35; H, 2.22; N, 10.29; Found: C, 46.48; H, 2.12, N, 10.42.

6,8-Dibromo-3-(2-(2-((5-methoxy-1H-indol-3-yl)methylene)hydrazinyl) thiazol-4-yl)-2H-chromen-2-one (7g): Green solid; Yield: 92%; mp: 266-268 ^{o}C IR (KBr, υ_{max} cm^{-1}): 3417, 3271 (N-H), 1729 (C=O), 1633, 1603 (C=N), 1580 (C=C), 1104 (C-S), 606 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 6.84-6.87 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.73-7.81 (m, 3H), 8.12-8.17(m, 2H), 8.28 (s, 1H), 8.46 (s, 1H), 11.40 (s, 1H), 11.87 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.28, 158.06, 154.84, 148.49, 140.48, 136.59, 136.06, 132.29, 132.05, 130.67, 130.31, 129.00, 124.90, 122.50, 116.75, 113.18, 112.92, 111.76, 111.65, 110.16, 103.83, 55.69; MS (ESI) *m/z*: 575 [M + H]$^{+}$; Anal. calcd. for

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$C_{22}H_{14}Br_2N_4O_3S$: C, 46.01; H, 2.46; N, 9.76; Found: C, 46.20; H, 2.32, N, 9.87.

3-(2-(2-((1-Ethyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7h): Yellow solid; Yield: 85%; mp: 246-248 °C; IR (KBr, υ_{max} cm^{-1}): 3439, 3282 (N-H), 1716 (C=O), 1603 (C=N), 1574 (C=C), 1097 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (t, *J* = 6.8 Hz, 3H), 4.22-4.27 (m, 2H), 7.20-7.29 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.61-7.76 (m, 1H), 7.76 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 8.25 (t, *J* = 8.8 Hz, 2H), 8.56 (s, 1H), 11.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.93, 158.71, 152.26, 143.50, 139.63, 138.09, 136.60, 131.82, 131.61, 128.74, 124.67, 124.54, 122.60, 121.79, 120.68, 120.43, 119.16, 115.84, 110.74, 110.24, 109.80, 40.56, 15.17; MS (ESI) *m/z*: 415 [M + H]$^+$; HRMS for $C_{23}H_{18}N_4O_2S$: Calcd. 414.1150; Found 414.1139; Anal. calcd. for: C, 66.65; H, 4.38; N, 13.52; Found: C, 66.54; H, 4.42, N, 13.39.

6-Bromo-3-(2-(2-((2-methyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7i): Green solid; Yield: 84%; mp: 276-278 °C; IR (KBr, υ_{max} cm^{-1}): 3488, 3234 (N-H), 1738 (C=O), 1638, 1600 (C=N), 1552 (C=C), 1105 (C-S), 664 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.73 (s, 3H), 7.12 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 8.13 (t, *J* = 6.8 Hz, 2H), 8.36 (s, 1H), 8.50 (s, 1H), 11.45 (s, 1H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.00, 158.27, 152.03, 141.18, 141.01, 140.52, 139.59, 136.63, 135.69, 133.78, 130.61, 125.14, 121.36, 121.18, 120.52, 120.29, 118.06, 116.32, 111.09, 110.89, 11.49; MS (ESI) *m/z*: 481 [M + 2]$^+$; Anal. calcd. for $C_{22}H_{15}BrN_4O_2S$: C, 55.12; H, 3.15; N, 11.69; Found: C, 55.23; H, 3.27, N, 11.48.

6,8-Dibromo-3-(2-(2-((1-ethyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7j): Brown solid; Yield: 87%; mp: 260-262 °C IR (KBr, υ_{max} cm^{-1}): 3488, 3234 (N-H), 1738 (C=O), 1638, 1600 (C=N), 1552 (C=C), 1105 (C-S), 664 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (t, *J* = 7.6 Hz, 3H), 4.22-4.27 (m, 2H), 7.20-7.29 (m, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 8.12-8.28 (m, 4H), 8.46 (s, 1H), 11.86 (s, 1H); MS (ESI) *m/z*: 573 [M + H]$^+$; Anal. calcd. for $C_{23}H_{16}Br_2N_4O_2S$: C, 48.27; H, 2.82; N, 9.79; Found: C, 48.07; H, 2.94; N, 9.68.

6-Bromo-3-(2-(2-((1-ethyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7k): Green solid; Yield: 86%; mp: 250-252 °C; IR (KBr, υ_{max} cm^{-1}): 3392, 3025 (N-H), 1726 (C=O), 1634, 1602 (C=N), 1572 (C=C), 1097 (C-S), 694 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (t, *J* = 7.6 Hz, 3H), 4.21-4.25 (m, 2H), 7.22-7.27 (m, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.75-7.79 (m, 2H), 7.85 (s, 1H), 8.14-8.27 (m, 3H), 8.49 (s, 1H), 11.86 (s, 1H); MS (ESI) *m/z*: 494 [M + H]$^+$; Anal. calcd. for $C_{23}H_{17}BrN_4O_2S$: C, 55.99; H, 3.47; N, 11.36; Found: C, 55.90; H, 3.54; N, 11.49.

3-(2-(2-((1H-Indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-6-chloro-2H-chromen-2-one (7l): Yellow solid; Yield: 95%; mp: 258-260 °C; IR (KBr, υ_{max} cm^{-1}): 3429, 3117 (N-H), 1707 (C=O), 1633, 1606 (C=N), 1574 (C=C), 1078 (C-S), 743 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (t, *J* = 7.2 Hz, 2H), 7.45-7.51 (m, 2H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.80 (s, 1H), 8.01 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.30 (s, 1H), 8.51 (s, 1H), 11.53 (s, 1H), 11.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.56, 158.81, 151.31, 144.10, 140.36, 137.53, 137.10, 131.48, 130.15, 128.93, 128.13, 124.45, 123.03, 122.07, 121.18, 120.92, 118.29, 112.34, 111.97, 111.17, 110.00; MS (ESI) *m/z*: 421 [M + H]$^+$; HRMS for $C_{21}H_{13}ClN_4O_2S$: Calcd. 420.0448, Found 420.0452; Anal. calcd. for: C, 59.93; H, 3.11; N, 13.31; Found: C, 59.81; H, 3.20; N, 13.24.

2-(2-(2-((5-Methoxy-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-3H-benzo[f]chromen-3-one (7m): Green solid; Yield: 89%; mp: 281-283 °C; IR (KBr, υ_{max} cm^{-1}): 3176, 3062 (N-H), 1725, 1701 (C=O), 1640, 1602 (C=N), 1577 (C=C), 1104 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.88 (s, 3H), 6.85-6.88 (m, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.66 (t, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.80-7.84 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.30 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 9.32 (s, 1H), 11.41 (s, 1H), 11.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.12, 158.66, 154.45, 151.87, 140.33, 133.54, 132.86, 131.90, 130.06, 130.02, 129.08, 128.67, 128.50, 126.11, 124.52, 121.50, 119.43, 116.41, 113.14, 112.53, 112.44, 111.22, 109.78, 103.48, 55.28; MS (ESI) *m/z*: 467 [M + H]$^+$; HRMS for $C_{26}H_{18}N_4O_3S$: Calcd. 466.1100; Found 466.1091; Anal. calcd. for: C, 66.94; H, 3.89; N, 12.01; Found: C, 66.81; H, 3.75; N, 12.12.

6,8-Dibromo-3-(2-(2-((2-methyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7n): Brown solid; Yield: 85%; mp: 292-294 °C; IR (KBr, υ_{max} cm^{-1}): 3164, 3052 (N-H), 1715 (C=O), 1626, 1607 (C=N), 1574 (C=C), 1104 (C-S), 699 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 7.12-7.14 (m, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.80 (s, 1H), 8.10-8.13 (m, 2H), 8.17 (d, *J* = 6.8 Hz, 1H), 8.35 (s, 1H), 8.46 (s, 1H), 11.45 (s, 1H), 11.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.08, 157.64, 148.04, 143.41, 139.27, 138.92, 136.12, 135.67, 135.58, 130.26, 130.10, 125.14, 122.23, 122.11, 121.66, 120.51, 120.25, 116.31, 111.19, 110.86, 109.70, 11.48; MS (ESI) *m/z*: 559 [M + H]$^+$; Anal. calcd. for $C_{22}H_{14}Br_2N_4O_2S$: C, 47.33; H, 2.53; N, 10.04; Found: C, 47.24; H, 2.59; N, 10.21.

2-(2-(2-((1-Ethyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-3H-benzo[f]chromen-3-one (7o): Green solid; Yield: 88%; mp: 295-297 °C; IR (KBr, υ_{max} cm^{-1}): 3405, 3150 (N-H), 1713 (C=O), 1633, 1603 (C=N), 1570 (C=C), 1099 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (t, *J* = 7.2 Hz, 3H), 4.22-4.28 (m, 2H), 7.22-7.30 (m, 2H), 7.57 (d, *J* = 8 Hz, 1H), 7.66 (t, *J* = 8.8 Hz, 2H), 7.84 (t, *J* = 8.8 Hz, 3H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.21-8.29 (m, 3H), 8.37 (d, *J* = 8.4 Hz, 1H), 9.32(s, 1H), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.99, 158.67, 151.85, 139.57, 136.61, 133.46, 132.81, 131.81, 130.02, 129.08, 128.66, 128.50, 126.09, 124.54, 122.59, 121.79, 121.46, 120.67, 116.42, 113.15, 110.75, 110.24, 109.77, 40.55, 15.16; MS (ESI) *m/z*: 465 [M + H]$^+$; HRMS for $C_{27}H_{20}N_4O_2S$: Calcd. 464.1307; Found 464.1304; Anal. calcd. for: C, 69.81; H, 4.34; N, 12.06; Found: C, 69.74; H, 4.39; N, 12.11.

3-(2-(2-((5-Bromo-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7p): Brown solid; Yield: 90%; mp: 301-303 °C; IR (KBr, υ_{max} cm^{-1}): 3337, 3269 (N-H), 1736, 1698 (C=O), 1621, 1603 (C=N), 1579 (C=C), 1108 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33-7.48 (m, 4H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.79 (s, 1H), 7.85 (t, *J* = 6.8 Hz, 2H) , 8.27 (s, 1H), 8.38 (s, 1H), 8.56 (s, 1H), 11.72 (s, 1H), 11.91 (s, 1H); MS (ESI) *m/z*: 466 [M + H]$^+$; Anal. calcd. for $C_{21}H_{13}BrN_4O_2S$: C, 54.20; H, 2.82; N, 12.04; Found: C, 54.29; H, 2.78; N, 12.18.

6-Chloro-3-(2-(2-((2-methyl-1H-indol-3-yl)methylene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (7q): Green solid; Yield: 93%; mp: 279-281 °C; IR (KBr, υ_{max} cm^{-1}): 3262, 3154 (N-H), 1716 (C=O), 1630, 1604 (C=N), 1579 (C=C), 1101 (C-S), 782 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.63-7.66 (m, 1H),7.79 (s, 1H), 8.03 (s, 1H), 8.11 (t, *J* = 7.2 Hz, 1H), 8.35 (s, 1H), 8.51 (s, 1H), 11.45 (s, 1H), 11.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.02, 158.32, 150.82, 139.30, 138.94, 136.64, 135.67, 130.97, 128.43, 127.66, 125.13, 121.67, 120.50, 120.26, 117.77, 110.87, 110.56, 107.25, 11.46; MS (ESI) *m/z*: 435 [M + H]$^+$; Anal. calcd. for $C_{22}H_{15}ClN_4O_2S$: C, 60.76; H, 3.48; N, 12.88; Found: C, 60.80; H, 3.40; N, 12.79.

9. (a) Smith, G. F. *J. Chem. Soc.* **1954**, 3842; (b) Sahu, S. K.; Mishra, A.; Behera, R. K. *Indian J. Heterocycl. Chem.* **1996**, *6*, 91.
10. Seelay, H. W.; Van Demark, P. J. M*icrobes in action: A laboratory manualin microbiology*, 2nd ed. D. B. Taraporevala Sons & Co. Pvt., Bombay, India. **1975**, 55.
11. (a) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48,* 589; (b) Boyd, M. R.; Paull, K. D. *Drug Dev. Res.* **1995**, *34*, 91; (c) Penthala, N. R.; Yerramreddy, T. R.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1411; (d) Kattimani, P. P.; Kamble, R. R.; Kariduraganavar, M. Y.; Dorababu, A.; Hunnur, R. K. *Eur. J. Med. Chem.* **2013**, *62,* 232.
12. Zaharevitz, D. W.; Holbeck, S. L.; Bowerman, C.; Svetlik, P. A. *J. Mol. Graphics Modell.* **2002**, *20*, 297.
13. (a) Sambrook, J.; Fritsch, E. F.; Maniatis, T. *Molecular cloning, a laboratory manual*, 2nd ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, **1989**; (b) Biradar, J. S.; Sasidhar, B. S.; Parveen, R. *Eur. J. Med. Chem.* **2010**, *45*, 4074; (c) Sasidhar, B. S.; Birdar, J. S.; Med. Chem. Res. **2013**, *22*, 3518; (d) Gopalakrishnan, S.; Vadivel, E.; *Int. Res. J. Pharm.* **2011**, *2*, 153; (e) Janardhan, B.; Manjulatha, K.; Srinivas, B.; Rajitha, B.; Muralikrishna, N.; Sadanandam, A. *R. Soc. Chem. Adv.* **2014**, *4*, 22866.

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