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Original article

Synthesis and biological evaluation of new rhodanine analogues bearing 2-chloroquinoline and benzo[h]quinoline scaffolds as anticancer agents

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ABSTRACT

Several rhodanine derivatives (**9**–**39**) were synthesized for evaluation of their potential as anticancer agents. Villsmeier cyclization to synthesize aza-aromatic aldehydes, rhodanine derivatives preparation and Knoevenagel type of condensation between the rhodanines and aza-aromatic aldehydes are key steps used for the synthesis of 31 compounds. *In vitro* antiproliferative activity of the synthesized rhodanine derivatives (**9**–**39**) was studied on a panel of six human tumor cell lines viz. HGC, MNK-74, MCF-7, MDAMB-231, DU-145 and PC-3 cell lines. Some of the compounds were capable of inhibiting the proliferation of cancer cell lines at a micromolar concentration. Six compounds are found to be potent against HGC cell lines; compound **15** is found to be active against HGC – Gastric, MCF7 – Breast Cancer and DU145 – Prostate Cancer cell lines; compound **39** is potent against MNK-74; four compounds are found to be potent against MCF-7 cell lines; three compounds are active against MDAMB-231; nine compounds are found to be potent against DU-145; three compounds are active against PC-3 cell lines. These compounds constitute a promising starting point for the development of novel and more potent anticancer agents in future.

1. Introduction

Rhodanine is a five-membered heterocyclic ring with diverse applications particularly in biochemistry, medicinal chemistry, photochemistry, industry and coordination chemistry [1]. In a recent review, rhodanine was reported as privileged scaffold in drug discovery whose functionalization and appropriate modifications led to compounds endowed with various biological activities [1a,1c]. Substituted rhodanine compounds have been investigated for a wide range of pharmacologic indications such as fungal protein mannosyl transferase-1 inhibitors [2], PDE4 inhibitors [3], protease inhibitors [4], JNK stimulating phosphatase-1 (JSP-1) inhibitors [5], UDP-N-acetylmuramate/L-alanine ligase [6], antimalarials [7], HIV-1 Integrase inhibitors [8], aldose reductase inhibitors [9], β-lactamase inhibitors [10], antidiabetic agents [11], HCV NS3 protease inhibitor [12], histidine decarboxylase inhibitors [13], ADAMTS-5 inhibitors [14], MurD ligase inhibitors [15] *Trypanosoma brucei* dolicholphosphate mannose synthase (DPMS) inhibitors [16], antibacterials [17], Photosynthesis inhibitor [18], Anthrax lethal factor protease inhibitor [19] etc.. Epalrestat is a rhodanine analogue and marketed drug as aldose reductase inhibitor in Japan, China and India [20]. Recently we have reported aldose reductase inhibitory activity of rhodanine derivatives whose potency is equivalent to marketed drug epalrestat [9a]. The attention of scientists around the globe has focused on anticancer effects of rhodanine compounds [21a–q]. In this context, we have reported the synthesis and anticancer activity of some rhodanine derivatives

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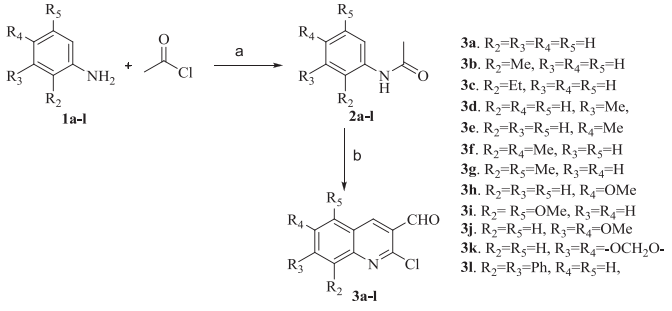
appended with 2-chloropyridine scaffold [21m]. Rhodanine with quinoline derivatives also exhibit various pharmacological activities [22]. In continuation to our work, we present here the synthesis and anticancer activity of newer rhodanine derivatives. These compounds possess 2-chloroquinoline, 2-piperidinequinoline and 2-chlorobenzo[h]quinoline pharmacophore as appendages to rhodanine scaffold. In this work, 31 new compounds were synthesized and screened against six human cancer cell lines. Good number of compounds were found to exhibit potency compared to our previous series of compounds carrying 2-chloropyridine with rhodanine fragment [21m].

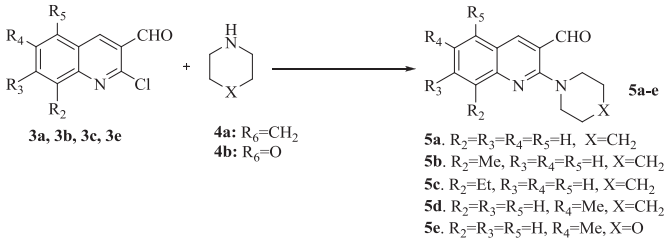
2. Results and discussion

2.1. Chemistry

The synthesis of 31 new quinoline–rhodanine derivatives **9**–**39** was accomplished as outlined in Schemes 1–7. The synthetic strategy involves in making quinoline and rhodanine residues (Schemes 1–3) and taking them for condensation (Schemes 4–7) leading to desired target molecules **9**–**39**. Various anilines (**1a**–**l**) were treated with acetylchloride (Scheme 1) to get corresponding anilides (**2a**–**l**) and subsequent Villsmeier reaction using **3a**–**l** anilides provided chloroquinolinealdehydes **3a**–**l** (Scheme 1) in good yields [23]. Some selected 2-chloroquinoline-3-carbaldehydes **3a**, **3b**, **3c** and **3e** were reacted with piperidine **4a** to make piperidine coupled quinolinecarabaldehydes **5a**–**d** (Scheme 2). 2-Chloroquinoline-3-carbaldehyde **3e** was reacted with morpholine **4b** to get morpholine coupled quinoline-carbaldehyde **5e**, under nucleophilic substitution conditions. Rhodanine compounds **8a**–**c** were prepared as outlined in Scheme 3. Ammonium dithiacarbamates **7a**–**c** were obtained by treating respective amine derivatives **6a**–**c** with carbondisulfide and ammonia [21q,24]. In second step, **7a**–**c** were reacted with sodiumchloroacetate at higher temperature to afford rhodanine derivatives **8a**–**c** in good yield (Scheme 3). Synthesized aldehydes **3a**–**l** were reacted with rhodanine **8a** in the presence of sodium acetate and acetic acid to get target compounds **9**–**20** (Scheme 4) [21q]. Compounds **21**–**31** were synthesized by similar approach of above *i.e.* coupling **3a**–**b** and **3d**–**m** with rhodanine acetic acid (Scheme 5). Rhodanine derivatives **32**–**34** were synthesized by condensation between the requisite phenylrhodanine **8c** and 2-chloroquinoline-3-carboxaldehydes, **3f** and **3g** in the presence of sodium acetate and acetic acid under reflux conditions (Scheme 6). In a similar manner, 2-piperizinequinoline-3-carbaldehydes **5a**–**e** were treated with rhodanine **8a** and rhodanine acetic acid **8b** separately to afford compounds **35**–**39** (Scheme 7). All the synthesized compounds (Table 1) gave satisfactory analytical and spectroscopic data (NMR, Mass and IR etc.), which were in full accordance with their depicted structures.



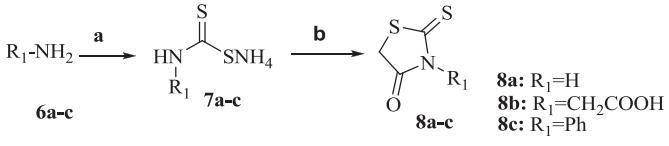
Scheme 1. Synthesis of 2-chloroquinoline-3-carboxaldehyde. *Reagents and conditions*: (a) Et_3N, $CHCl_3$, 0 °C, 1 h; (b) $POCl_3$, DMF, 16 h, reflux.



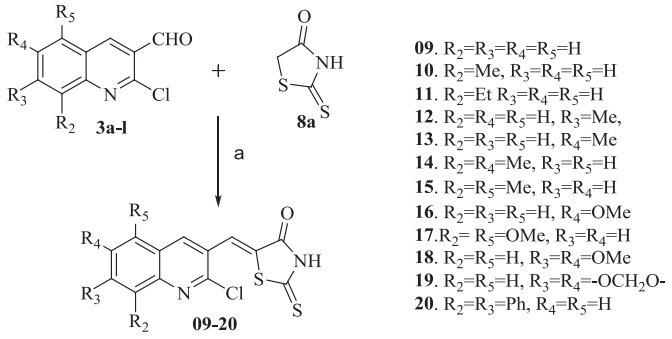
Scheme 2. Synthesis of 2-(piperidin-1-yl)quinoline-3-carboxaldehyde: *Reagents and conditions*: (a) K_2CO_3, (2eq.), reflux, 15 h.

2.2. Biological activity

All the synthesized compounds were screened against six cancer cell lines viz., HGC, MNK-74, MCF-7, MDAMB-231, DU-145 and PC-3 cell lines to test their potential to serve as anticancer agents. The anticancer activities of synthesized compounds (**9**–**39**) were evaluated by MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] method using gastric (HGC, MNK-74), breast (MCF-7, MDAMB-231) and prostate (DU-145 and PC-3) cancer cell lines. The compounds were screened with various cancer cell lines at 100 μM concentration, dose response was done for the compounds exhibiting greater than 50% inhibition and IC_{50} of those compounds only are reported (Table 2). The effect of selected compounds on the cell viability for each cell line after exposure to different concentrations is depicted in Fig. 1. Compounds **14**, **15**, **16**, **18**, **35** and **39** are potent against HGC cell lines. Most of these compounds possess free amine group on rhodanine moiety except compound **11**. Remaining compounds are less active. In case of MNK-74, compound **39** is most active with IC_{50} of 13.9 ± 2.3 μm among the tested compounds. Compounds **14** and **35** are moderately active. Synthesized compounds were screened against MCF-7 cell lines, compounds **9**, **12**, **15** and **20** are active with the inhibition range of 6.3 ± 0.8 to 11.8 ± 2.2 μm. Compound **13** is moderately active and rest of the compounds are inactive. Compounds **15**, **20** and **36** are moderately active against MDAMB-231 cell lines and rest of the molecules are inactive. In case of DU-145, compounds **14**, **15**, **16**, **18**, **19**, **20**, **25**, **35** and **39** are active molecules. Most of these compounds are rhodanine with free amine group. Compounds **10**, **11**, **12**, **13**, **19**, **26**, **36** are moderately active. Compounds **15**, **35** and **39** are active among the screened compounds against PC-3 cell lines and rest of the compounds are inactive. Among the six cell lines, structure–activity relationships (SAR) of two cell lines only (HGC and DU145) in view of dispersion of compounds on observed range of activity. SAR data inferred that rhodanine compounds possessing free –NH– are more active over their counter parts such as –N–CH_2–COOH and –N–Ph derivatives. Substitution on quinoline ring with methyl or ethyl group (**10**–**13**) favored anticancer activity over unsubstituted derivative **9**. Additional methyl substitution either on C-5 (compound **15**) or C-6 (compound **14**) of compound **10** resulted more potency with IC_{50} of 7.2 ± 0.5 or 9.7 ± 1.5 μM respectively. It seems that hydrophobic groups on quinoline favors improved anticancer activity. C-6 methoxy substituted derivative **16** is more potent over compound **9**



Scheme 3. Synthesis of rhodanine, rhodanine acetic acid and phenylrhodanine. *Reagents and conditions*: (a) CS_2, NH_3; (b) $ClCH_2COONa$, 85–90 °C, HCl.

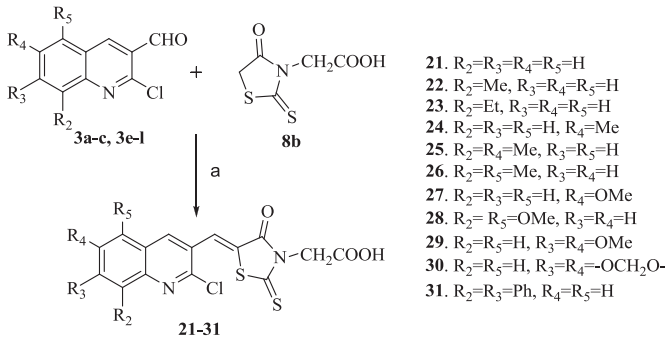


Scheme 4. Synthesis of rhodanine derivatives: *Reagents and conditions*: (a) NaOAc/AcOH, reflux, 4 h.

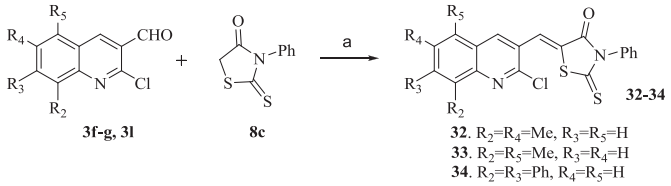
(unsubstituted derivative) and compound **13** (methyl substituted derivative). In case of dimethoxy substitution either at C-6 and C-7 position (compound **18**) or at C-5 and C-8 position (compound **17**), reduced activity is observed. Replacement of chlorine group with piperazine or morpholine indicated improved anticancer activity compared to compound **9**. In case of DU145 cancer cell lines, substitution like methyl, ethyl, dimethyl, methoxy, dimethoxy etc. on quinoline ring enhances the anticancer activity compared to compound **9**. Substitution of piperazine or morpholine in place of 'Cl' (compounds **35** and **36**) improved the activity. Replacement of rhodanine with rhodanine acetic acid (compound **26**) does not change much in the activity but in other cases decreased activity was noticed. Our future work will be focused on synthesis of newer analogues rationally designed based on the SAR data and target oriented molecular mechanistic studies.

3. Conclusion

In this article, several new rhodanine derivatives that may function as anticancer agents have been synthesized using 2-chloroquinoline-3-carbaldehydes. *In vitro* anticancer activity of these compounds was evaluated over six human cancer cell lines. Some of the synthesized compounds displayed potent anticancer activity. Six compounds are found to be potent against HGC cell lines; compound **39** is potent against MNK-74; four compounds are found to be potent against MCF-7 cell lines; three compounds are active against MDAMB-231; nine compounds are found to be potent against DU-145; three compounds are active against PC-3 cell lines. Some of these compounds would serve as potential anticancer agents with modifications on pharmacophore.



Scheme 5. Synthesis of rhodanine derivatives: *Reagents and conditions*: (a) NaOAc/AcOH, reflux, 4 h.



Scheme 6. Synthesis of rhodanine derivatives: *Reagents and conditions*: (a) NaOAc/AcOH, reflux, 4 h.

4. Experimental section

4.1. Chemistry

General: All commercially available chemicals were used without further purification. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded using a Thermo Nicolet Nexus 670 FTIR spectrometer. The NMR spectra were recorded on Bruker Avance 300 magnetic resonance spectrometer at 300 MHz for ^{1}H and 500 MHz for ^{13}C respectively, using TMS as internal standard. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). ESI-MS were obtained on Thermo-Finnigan MAT-1020B instrument. Elemental analyses were carried out with a Perkin Elmer 2400 Series II elemental analyzer. Column chromatography was performed on silica gel (60–120 mesh, Acme, India).

2-Chloroquinoline-3-carbaldehyde derivatives (**3a**–**l**) were prepared as per the literature [24].

4.2. General procedure for the synthesis of substituted 2-(piperidin-1-yl)quinoline-3-carbaldehyde

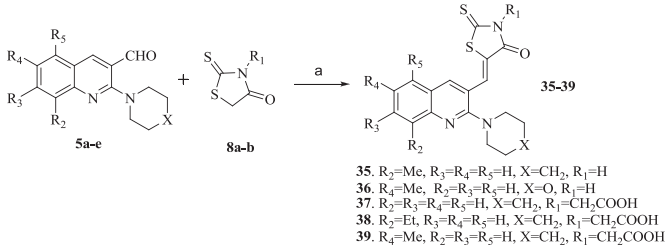
2-Chloro-3-formyl quinoline **3a**, **3b**, **3c** and **3e** (0.001 mol) and potassium carbonate (0.002 mol) was taken in round bottom flask and **4a** or **4b** in excess was added. The mixture was refluxed for 4 h at 200 °C. Reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and poured on to water. It was then filtered through the suction pump, washed with water and dried. The crude product thus obtained was then purified by column chromatography (ethyl acetate–hexane).

4.2.1. 2-(Piperidin-1-yl)quinoline-3-carbaldehyde (**5a**)

Yellow solid; Yield: 75%; mp: 81–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.46 (s, H), 7.80 (d, 1H, J = 8.12 Hz), 7.74 (d, 1H, J = 8.68 Hz), 7.65 (t, 1H, J = 6.98 Hz), 7.34 (t, 3H, J = 6.98 Hz), 3.43 (m, 4H), 1.75 (m, 6H); MS (ESI) m/z (%): 241 $[M+H]^+$.

4.2.2. 8-Methyl-2-(piperidin-1-yl)quinoline-3-carbaldehyde (**5b**)

Yellow solid; Yield: 78%; mp: 83–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.16 (s, 1H), 8.44 (s, H), 7.81 (d, 1H, J = 8.30 Hz), 7.63 (d,



Scheme 7. Synthesis of rhodanine derivatives: *Reagents and conditions*: (a) NaOAc/AcOH, reflux, 4 h.

Table 1
Synthesis of rhodanine analogues (**9**–**39**).

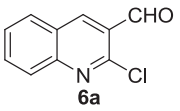
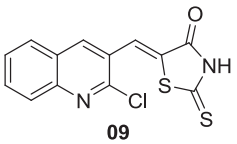
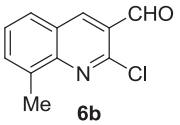
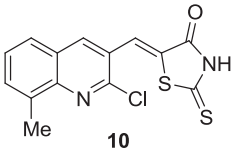
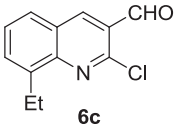
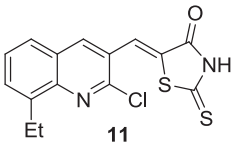
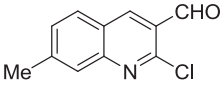
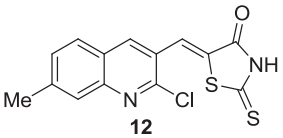
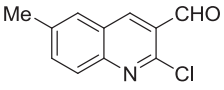
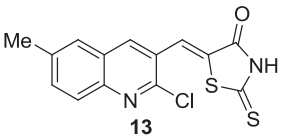
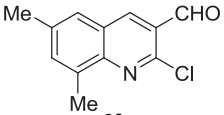
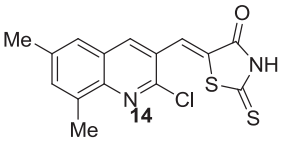
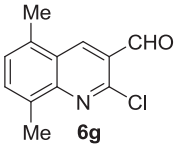
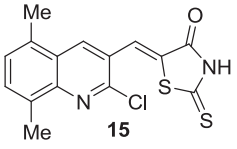
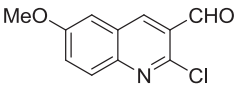
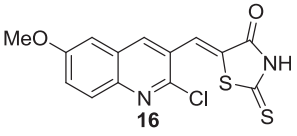
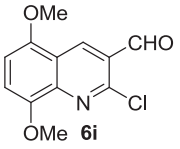
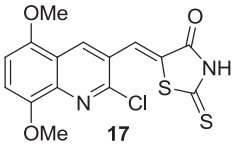
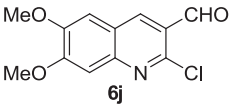
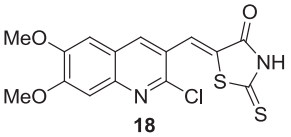
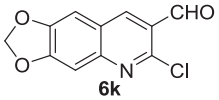
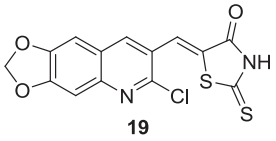
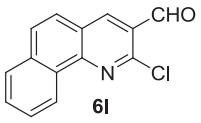
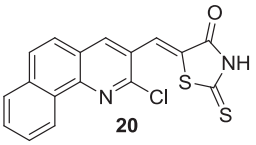
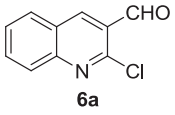
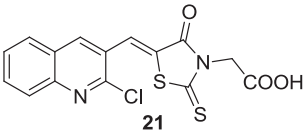
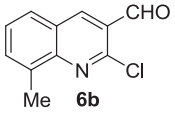
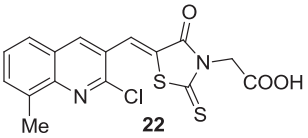
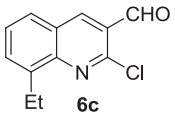
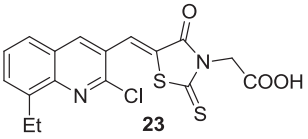
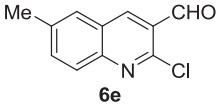
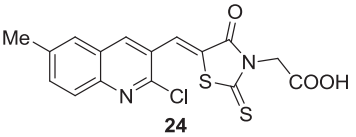
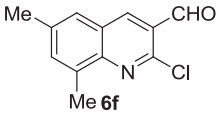
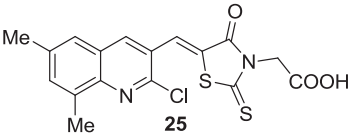
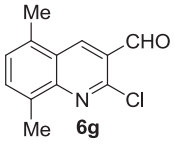
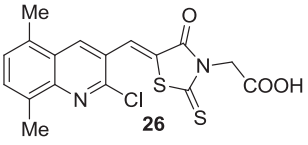
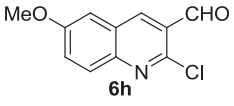
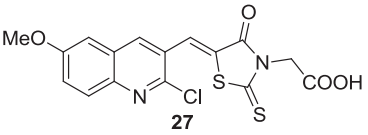
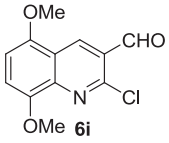
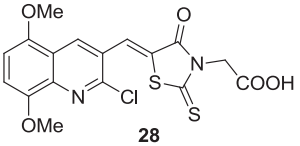
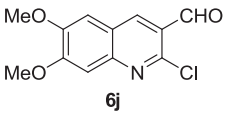
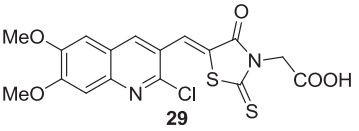
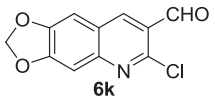
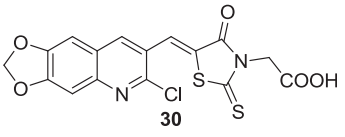
Sl. no	Sub. quinoline	Sub. rhodanine	Product	Yield (%)
01	 **6a**	**3a**	 **09**	66
02	 **6b**	**3a**	 **10**	69
03	 **6c**	**3a**	 **11**	72
04	 **6d**	**3a**	 **12**	69
05	 **6e**	**3a**	 **13**	69
06	 **6f**	**3a**	 **14**	72
07	 **6g**	**3a**	 **15**	72
08	 **6h**	**3a**	 **16**	75
09	 **6i**	**3a**	 **17**	76
10	 **6j**	**3a**	 **18**	76
11	 **6k**	**3a**	 **19**	76

Table 1 (*continued*)

Sl. no	Sub. quinoline	Sub. rhodanine	Product	Yield (%)
12	 **6l**	**3a**	 **20**	66
13	 **6a**	**3b**	 **21**	80
14	 **6b**	**3b**	 **22**	69
15	 **6c**	**3b**	 **23**	70
16	 **6e**	**3b**	 **24**	69
17	 **6f**	**3b**	 **25**	70
18	 **6g**	**3b**	 **26**	70
19	 **6h**	**3b**	 **27**	74
20	 **6i**	**3b**	 **28**	75
21	 **6j**	**3b**	 **29**	75
22	 **6k**	**3b**	 **30**	75

(*continued on next page*)

Table 1 (*continued*)

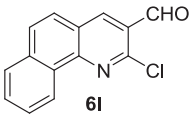
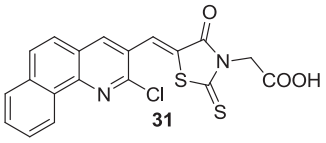
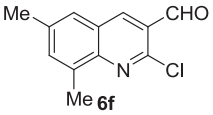
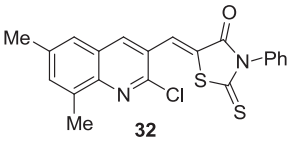
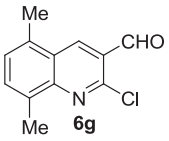
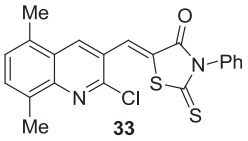
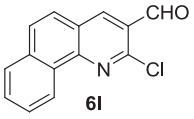
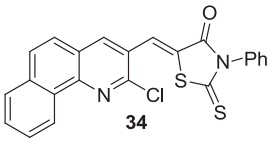
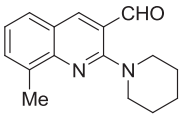
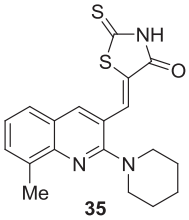
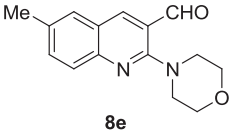
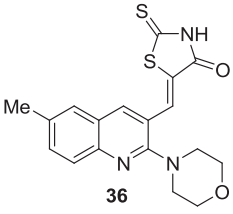
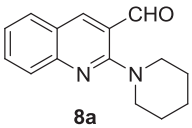
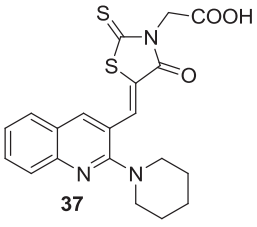
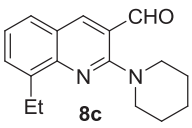
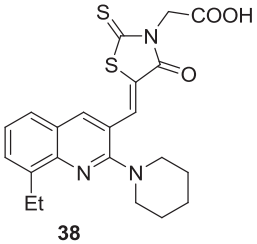
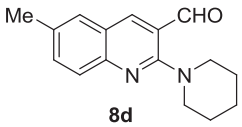
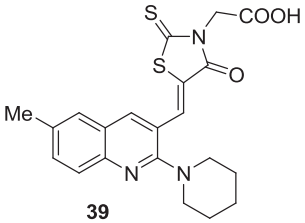
Sl. no	Sub. quinoline	Sub. rhodanine	Product	Yield (%)
23	 **6l**	**3b**	 **31**	85
24	 **6f**	**3c**	 **32**	74
25	 **6g**	**3c**	 **33**	74
26	 **6l**	**3c**	 **34**	80
27	 **8b**	**3a**	 **35**	71
28	 **8e**	**3a**	 **36**	70
29	 **8a**	**3b**	 **37**	70
30	 **8c**	**3b**	 **38**	74

Table 1 (*continued*)

Sl. no	Sub. quinoline	Sub. rhodanine	Product	Yield (%)
31	 **8d**	**3b**	 **39**	72

1H, $J = 8.30$ Hz), 7.24 (t, 1H, $J = 8.30$ Hz) 3.48 (m, 4H), 1.75 (m, 6H), 1.57 (s, 3H); MS (ESI) *m/z* (%): 255 $[M+H]^+$.

4.2.3. 8-Ethyl-2-(piperidin-1-yl)quinoline-3-carbaldehyde (**5c**)

Yellow solid; Yield: 80%; mp: 82–84 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.50 (s, H), 7.80 (d, 1H, $J = 8.12$ Hz), 7.74 (d, 1H, $J = 8.68$ Hz), 7.65 (t, 1H, $J = 8.68$ Hz), 2.54 (q, 2H, $J = 6.98$ Hz), 3.43 (m, 4H), 1.75 (m, 6H), 1.50 (t, 3H, $J = 6.98$ Hz); MS (ESI) *m/z* (%): 269 $[M+H]^+$.

4.2.4. 6-Methyl-2-(piperidin-1-yl)quinoline-3-carbaldehyde (**5d**)

Yellow solid; Yield: 78%; mp: 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.41 (s, H), 7.73 (d, 1H, $J = 8.30$ Hz), 7.54 (s, 1H), 7.51 (d, 1H, $J = 8.30$ Hz), 3.41 (m, 4H), 1.75 (m, 6H), 1.59 (s, 3H); MS (ESI) *m/z* (%): 255 $[M+H]^+$.

4.2.5. 6-Methyl-2-morpholinoquinoline-3-carbaldehyde (**5e**)

Yellow solid; Yield: 79%; mp: 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.15 (s, 1H), 8.42 (s, H), 7.69 (d, 1H, $J = 8.49$ Hz), 7.59 (s, 1H), 7.52 (d, 1H, $J = 8.49$ Hz), 3.86 (t, 3H, $J = 4.34$ Hz) 3.46 (t, 3H, $J = 4.34$ Hz), 2.50 (s, 3H); MS (ESI) *m/z* (%): 257 $[M+H]^+$.

Rhodanine (**8a**), rhodanine acetic acid (**8b**) and N-phenyl-rhodanine (**8c**) were prepared as per the literature [21q,23].

4.3. General procedure for the synthesis of rhodanine derivatives (**9**–**20**)

2-Chloroquinoline-3-carbaldehyde **3a**–**n** (0.0045 mol) was taken in round bottom flask added to 2-thioxothiazolidin-4-one **8a** (0.0045 mol) and to this sodium acetate (0.0135 mol) was added. Acetic acid (20 ml) was added as solvents. The mixture was refluxed for 4 h at 110 °C and cooled to room temperature and poured into water. It was then filtered through the suction pump, washed with water to remove excess of acetic acid and recrystallized from methanol to afford compounds **9**–**20** [21q].

4.3.1. (Z)-5-((2-chloroquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**9**)

Yellow solid; Yield: 66%; mp: 345–347 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.83 (d, 1H, $J = 7.55$ Hz), 7.63 (s, 1H), 7.61 (t, 1H, $J = 7.55$ Hz), 7.34 (d, 1H, $J = 7.55$ Hz), 7.25 (t, 1H, $J = 7.55$ Hz); ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.8, 160.5, 143.8, 139.1, 132.4, 129.2, 127.4, 127.1, 124.5, 122.7, 119.2, 118.5, 115.2. IR (KBr, cm^{-1}): 3434, 3092, 2850, 1712, 1546, 1448, 1212, 748; MS (ESI) *m/z* (%): 307 $[M-H]^+$. Anal. calcd for $C_{13}H_7ClN_2OS_2$: C, 50.89; H, 2.30; N, 9.13; S, 20.90. Found: C, 51.24; H, 2.63; N, 9.45; S, 20.38.

4.3.2. (Z)-5-((2-chloro-8-methylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**10**)

Red solid; Yield: 69%; mp: 334–336 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.70 (d, 1H, $J = 8.12$ Hz), 7.59 (s, 1H), 7.11 (t,

Table 2
Inhibitory effects of selected compounds on the growth of human cancer cell lines Gastric cancer (HGC and MNK 74), Breast cancer (MCF-7 and MDA-MB 231), Prostate cancer (DU145 and PC 3).

Compound no.	Gastric cancer		Breast cancer		Prostate cancer	
	HGC	MNK 74	MCF-7	MDA-MB 231	DU145	PC 3
9	NA	>100	**6.3 ± 0.8**	>100	>100	>100
10	33.9 ± 3.3	>100	>100	>100	64.2 ± 18.7	>100
11	63.0 ± 1.5	>100	>100	>100	51.3 ± 4.6	>100
12	69.1 ± 9.8	>100	**10.5 ± 1.3**	>100	35.3 ± 2.2	>100
13	76.7 ± 5.6	>100	35.7 ± 14.6	>100	74.5 ± 7.4	>100
14	**9.7 ± 1.5**	37.2 ± 7.8	>100	>100	**19.1 ± 1.2**	>100
15	**7.2 ± 0.5**	96.9 ± 11.7	**9.5 ± 0**	55.6 ± 27.9	**15.3 ± 3.7**	39.1 ± 0.2
16	**7.3 ± 0.3**	>100	>100	>100	**19.8 ± 5.6**	>100
18	14.4 ± 5.4	>100	>100	>100	**14.3 ± 5.2**	>100
19	>100	>100	>100	>100	24.05 ± 1	>100
20	28.9 ± 4.2	>100	**11.8 ± 2.2**	74.4 ± 4.7	**12.6 ± 4.1**	>100
23	71.7 ± 1.6	>100	>100	>100	>100	>100
25	40.9 ± 4.3	>100	>100	>100	**19.1 ± 1.1**	>100
26	42.5 ± 0.6	>100	>100	>100	40.2 ± 4.7	>100
31	40.1 ± 2.8	>100	>100	>100	>100	>100
35	**18.9 ± 2**	35.9 ± 1.2	>100	>100	**16.6 ± 2.5**	25.7 ± 7.03
36	105.6 ± 4.4	>100	>100	41.2 ± 15.8	36.9 ± 10.6	>100
39	**11.2 ± 0**	**13.9 ± 2.3**	>100	>100	20.6 ± 1	13.2 ± 6.5
Rosiglitazone[a]	ND	ND	ND	ND	16.0 ± 5.0	20.3 ± 6.2

[a] ND: Not Determined.

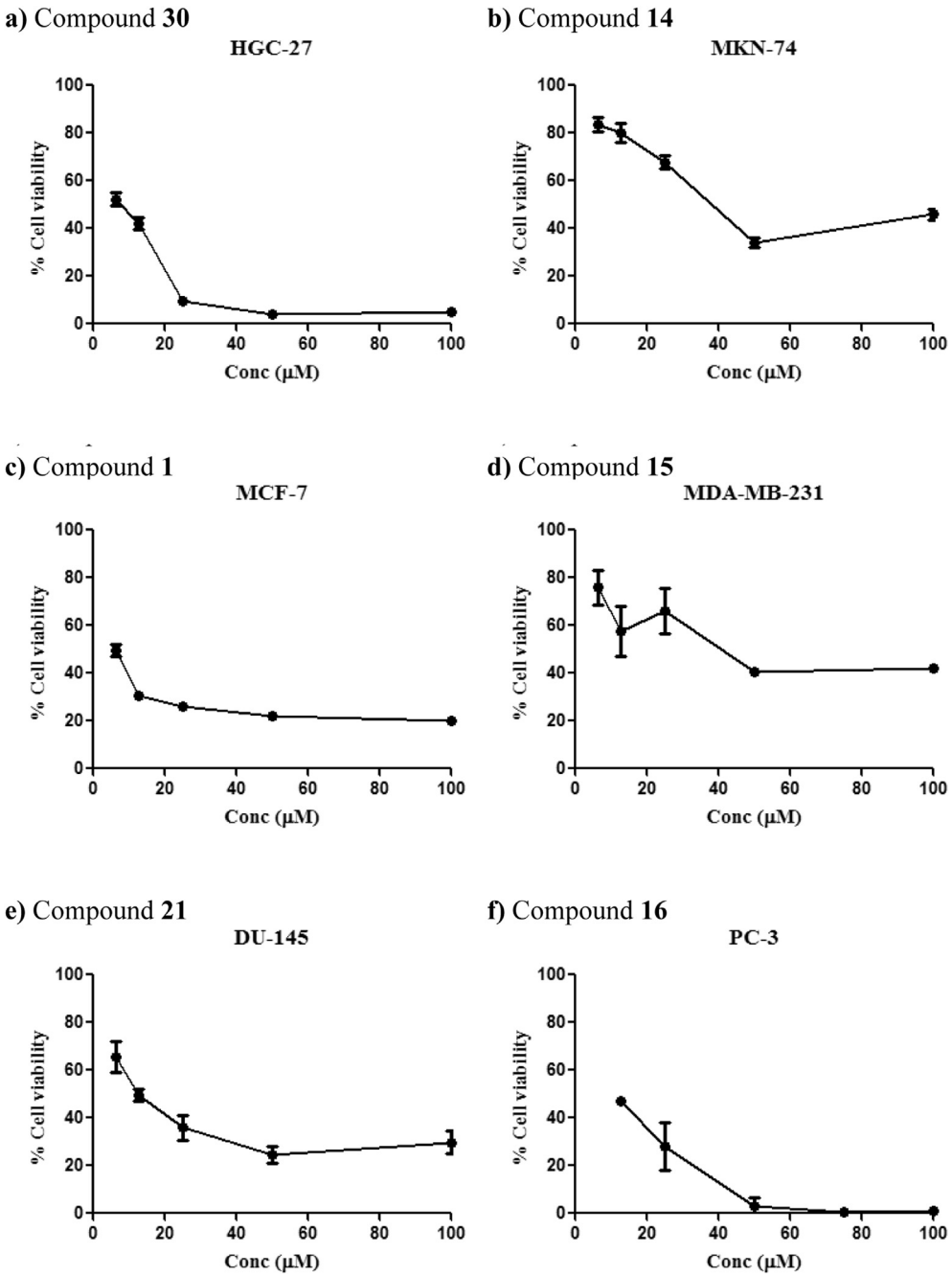


Fig. 1. Dose response curve of rhodanine derivatives on human cancer cell lines determined by MTT assay after 48 h treatment.

1H, J = 5.28 Hz), 7.08 (d, 1H, J = 8.12 Hz), 2.44 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.8, 169.5, 160.9, 144.4, 137.5, 133.5, 127.3 (2), 127.1, 124.1, 123.6, 122.4, 119.2, 17.0; IR (KBr, cm^{-1}): 3150, 3028, 2362, 1719, 1661, 1232, 740. MS (ESI) m/z (%): 319 $[M+H]^+$. Anal. calcd for $C_{14}H_9ClN_2OS_2$: C, 52.41; H, 2.83; N, 8.73; S, 19.99. Found: C, 52.76; H, 3.02; N, 8.34; S, 19.61.

*4.3.3. (Z)-5-((2-chloro-8-ethylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**11**)*

Red solid; Yield: 72%; mp: 340–343 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.64 (s, 1H), 7.56 (d, 1H, J = 7.55 Hz), 7.38 (d, 1H, J = 7.55 Hz), 7.14 (t, 1H, J = 7.55 Hz), 2.89 (q, 2H, J = 7.36 Hz), 1.22 (t, 3H, J = 7.55 Hz). ^{13}C NMR (500 MHz, DMSO-d_6) δ: 189.2, 164.5, 162.4, 156.4, 151.8, 149.9, 149.3, 147.2, 147.2, 143.6, 142.5, 142.3, 139.1, 42.3, 33.8. IR (KBr, cm^{-1}): 3166, 3025, 2362, 1690, 1646, 1440, 1227, 669. MS (ESI) m/z (%): 333 $[M-H]^+$. Anal. calcd for $C_{15}H_{11}ClN_2OS_2$: C, 53.80; H, 3.31; N, 8.37; S, 19.15. Found: C, 54.16; H, 3.54; N, 8.68; S, 19.28.

*4.3.4. (Z)-5-((2-chloro-7-methylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**12**)*

Red solid; Yield: 69%; mp: 358–362 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.64 (s, 1H), 7.54 (d, 1H, J = 7.93 Hz), 7.11 (s, 1H), 6.99 (d, 1H, J = 7.93 Hz), 2,44 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.8, 169.5, 160.6, 143.7, 143.2, 139.3, 129.0, 127.6, 126.4, 124.2, 123.4, 117.2, 114.8, 21.6. IR (KBr, cm^{-1}): 3143, 2851,

2363, 1699, 1658, 1437, 1220, 678; MS (ESI) *m/z* (%): 319 $[M+H]^+$. Anal. calcd for $C_{14}H_9ClN_2OS_2$: C, 52.41; H, 2.83; N, 8.73; S, 19.99. Found: C, 52.68; H, 3.13; N, 8.45; S, 19.64.

*4.3.5. (Z)-5-((2-chloro-6-methylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**13**)*

Yellow solid; Yield: 69%; mp: 345–347 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.15 (s, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.57 (d, 1H, J = 7.17 Hz), 7.37 (d, 1H, J = 7.17 Hz), 2.45 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 198.5, 160.9, 144.3, 142.2, 134.4, 133.9, 132.3, 132.0, 129.0, 128.2, 124.6, 119.7, 115.7, 20.8. IR (KBr, cm^{-1}): 3075, 1643, 1448, 1217, 929. MS (ESI) *m/z* (%): 319 $[M+H]^+$. Anal. calcd for $C_{14}H_9ClN_2OS_2$: C, 52.41; H, 2.83; N, 8.73; S, 19.99. Found: C, 52.69; H, 3.10; N, 8.36; S, 20.07.

*4.3.6. (Z)-5-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**14**)*

Red solid; Yield: 72%; mp: 315–317 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.15 (s, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 2.61 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.9, 169.4, 160.7, 144.2, 137.8, 137.5, 135.1, 134.6, 131.4, 127.5, 126.6, 125.5, 124.6, 21.0, 20.1. IR (neat, cm^{-1}): 3003, 2860, 2358, 2341, 1695, 1651, 1558, 1232, 1215, 1136, 1018, 844, 680; MS (LCMS) *m/z* (%): 335 $[M+H]^+$. Anal. calcd for $C_{15}H_{11}ClN_2OS_2$: C, 53.80; H, 3.31; N, 8.37; S, 19.15. Found: C, 53.56; H, 3.59; N, 8.09; S, 18.78.

*4.3.7. (Z)-5-((2-chloro-5,8-dimethylquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**15**)*

Yellow solid; Yield: 72%; mp: 369–371 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (s, 1H), 7.81 (s, 1H), 7.48 (d, 1H, J = 6.98 Hz), 7.30 (d, 1H, J = 6.98 Hz), 2.69 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 198.2, 169.5, 160.6, 148.1, 145.8, 142.1, 135.3, 133.5, 133.5, 132.3, 128.3, 124.7, 123.6, 17.9, 17.1; IR (neat, cm^{-1}): 3140, 3095, 2854, 2358, 1695, 1685, 1570, 1436, 1357, 1305, 1215, 1186, 798, 675; MS (LCMS) *m/z* (%): 333 $[M-H]^+$. Anal. calcd for $C_{15}H_{11}ClN_2OS_2$: C, 53.80; H, 3.31; N, 8.37; S, 19.15. Found: C, 54.15; H, 3.43; N, 7.99; S, 19.23.

*4.3.8. (Z)-5-((2-chloro-6-methoxyquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**16**)*

Red solid; Yield: 75%; mp: 347–349 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.00 (s, 1H), 7.66 (s, 1H), 7.27 (d, 1H, J = 9.06 Hz), 7.20 (s 1H), 7.12 (d, 1H, J = 9.06 Hz), 3.83 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 198.0, 169.9, 160.6, 155.3, 143.3, 141.8, 134.6, 127.8, 125.6, 122.7, 120.3, 117.4, 110.8, 56.2; IR (KBr, cm^{-1}): 3150, 3074, 2842, 2362, 1696, 1576, 1199, 810; MS (ESI) *m/z* (%): 335 $[M-H]^+$. Anal. calcd for $C_{14}H_9ClN_2O_2S_2$: C, 49.92; H, 2.69; N, 8.32; S, 19.04. Found: C, 50.20; H, 2.42; N, 7.99; S, 18.95.

*4.3.9. (Z)-5-((2-chloro-5,8-dimethoxyquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**17**)*

Red solid; Yield: 76%; mp: 309–312 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.65 (s, 1H), 7.18 (d, 1H, J = 8.87 Hz), 7.71 (d, 1H, J = 8.87 Hz), 3.91 (s, 3H), 3.85 (s, 3H); IR (neat, cm^{-1}): 3161, 3010, 2835, 2358, 2341, 1716, 1647, 1217, 1022, 1002, 823, 667; MS (ESI) *m/z* (%): 365 $[M-H]^+$. Anal. calcd for $C_{15}H_{11}ClN_2O_3S_2$: C, 49.11; H, 3.02; N, 7.64; S, 17.48. Found: C, 49.39; H, 2.82; N, 7.34; S, 17.10.

*4.3.10. (Z)-5-((2-chloro-6,7-dimethoxyquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**18**)*

Red solid; Yield: 76%; mp: 306–310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.38 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 189.8, 160.1, 152.5, 151.0, 149.7, 142.8, 136.8, 132.7, 128.3, 122.7, 116.3, 106.3, 105.1, 55.7, 55.6; IR (neat, cm^{-1}): 3140, 3035, 2846, 1683, 1570, 1496, 1365, 1145, 1001, 798, 675; MS (EI) *m/z* (%): 366 $[M]^+$; HRMS (EI): $[M]^+$ Calcd for $C_{15}H_{11}ClN_2O_3S_2$: 366.99779, Found: 365.98880.

*4.3.11. (Z)-5-((6-chloro-[1,3]dioxolo[4,5-g]quinolin-7-yl) methylene)-2-thioxothiazolidin-4-one (**19**)*

Red solid; Yield: 76%; mp: 385–388 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.55 (s, 1H), 7.29 (s, 1H), 6.81 (s, 1H), 6.14 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.6, 169.4, 160.2, 152.1, 143.9, 143.2, 137.3, 127.9, 125.1, 121.1, 113.8, 105.6, 102.3, 94.8; IR (neat, cm^{-1}): 3153, 3078, 2848, 2358, 2341, 1683, 1645, 1558, 1436, 1209, 1166, 026, 933, 817, 680; MS (ESI) *m/z* (%): 349 $[M-H]^+$. Anal. calcd for $C_{14}H_7ClN_2O_3S_2$: C, 47.93; H, 2.01; N, 7.99; S, 18.28. Found: C, 47.60; H, 1.82; N, 7.40; S, 17.98.

*4.3.12. (Z)-5-((2-chlorobenzo[h]quinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**20**)*

Yellow solid; Yield: 80%; mp: 299–301 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (d, 1H, J = 7.71 Hz), 8.49 (s, 1H), 8.08 (m, 2H), 8.03 (d, 1H J = 7.71 Hz), 7.82 (m, 2H), 7.81 (s, 1H); IR (KBr, cm^{-1}): 3414, 3152, 1697, 1618, 1574, 1213, 899; MS (EI) *m/z* (%): 356 $[M]^+$; HRMS (EI): $[M]^+$ Calcd for $C_{17}H_9ClN_2OS_2$: 355.98448. Found: 355.98440.

*4.4. General procedure for the synthesis of rhodanine derivatives (**21**–**31**)*

2-Chloroquinoline-3-carbaldehyde **3a**–**n** (0.0045 mol) was taken in round bottom flask added to 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid **8b** (0.0045 mol) and to this sodium acetate (0.0135 mol) was added. Acetic acid (20 ml) was added as solvents. The mixture was reflux for 4 h at 110 °C and cooled at rt and poured into water, compound (**21**–**31**) was formed. It was then filtered through the suction pump, washed with water to remove excess of acetic acid and recrystallized from methanol.

*4.4.1. (Z)-5-((2-chloroquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**21**)*

Yellow solid; Yield: 66%; mp: 348–351 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.28 (bs, 1H), 8.43 (s, 1H), 7.81 (d, 1H, J = 8.12 Hz), 7.78 (s, 1H), 7.62 (t, 1H, J = 7.55 Hz), 7.36 (d, 1H, J = 8.12 Hz), 7.26 (t, 1H, J = 7.55 Hz), 4.73 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.2, 167.3, 166.8, 161.3, 145.6, 139.4, 132.7, 130.2, 129.3, 124.3, 123.5, 122.8, 119.3, 115.3, 44.9; IR (KBr, cm^{-1}): 2983, 2841, 2362, 2331, 1697, 1627, 1319, 1199, 1058, 746, 734. MS (ESI) *m/z* (%): 355 $[M-H]^+$. Anal. calcd for $C_{15}H_9ClN_2O_3S_2$: C, 49.38; H, 2.49; N, 7.68; S, 17.58. Found: C, 49.71; H, 2.46; N, 7.33; S, 17.19.

*4.4.2. (Z)-2-(5-((2-chloro-8-methylquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**22**)*

Yellow solid; Yield: 69%; mp: 359–361 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.39 (bs, 1H), 8.18 (s, 1H), 7.81 (s, 1H), 7.54 (d, 1H, J = 8.49 Hz), 7.37 (d, 1H, J = 8.49 Hz), 7.10 (t, 1H, J = 8.49 Hz), 4.72 (s, 2H) 2.47 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.8, 167.9, 167.3, 161.5, 146.9, 138.4, 134.5, 130.7, 128.0, 124.7, 124.4, 124.0, 123.1, 119.9, 45.4, 17.6; IR (neat, cm^{-1}): 3184, 3012, 2970, 2358, 1716, 1701, 1624, 1313, 1197, 1052, 746. MS (ESI) *m/z* (%): 377 $[M-H]^+$. Anal. calcd for $C_{16}H_{11}ClN_2O_3S_2$: C, 50.72; H, 2.93; N, 7.39; S, 16.93. Found: C, 51.08; H, 3.29; N, 7.56; S, 17.20.

*4.4.3. (Z)-2-(5-((2-chloro-8-ethylquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**23**)*

Yellow solid; Yield: 70%; mp: 352–356 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.79 (bs, 1H), 8.72 (s, 1H), 8.07 (s, 1H), 7.96 (d, 1H, J = 7.36 Hz), 7.79 (d, 1H, J = 7.36 Hz), 7.52 (t, 1H, J = 7.36 Hz), 5.04 (s, 2H), 3.20 (qt, 2H, J = 7.36 Hz), 1.48 (t, 3H, J = 7.36 Hz); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.8, 167.9, 167.3, 161.6, 147.0, 137.6, 132.9,

130.7, 130.3, 128.1, 124.3, 124.0, 123.3, 120.1, 45.4, 23.1, 14.7; IR (KBr, cm^{-1}): 3268, 2979, 2360, 1706, 1613, 1327, 1193, 1055, 742. MS (ESI) *m/z* (%): 391 $[M-H]^+$; HRMS(EI): $[M]^+$ Calcd for $C_{17}H_{13}ClN_2O_3S_2$: 392.00561, Found: 392.00462.

4.4.4. (Z)-2-(5-((2-chloro-6-methylquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**24**)

Yellow solid; Yield: 69%; mp: 356–358 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 12.21 (bs, 1H), 8.33 (s, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.45 (d, 1H, $J = 8.49$ Hz), 7.25 (d, 1H, $J = 8.49$ Hz), 4.72 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.8, 167.9, 167.3, 160.9, 146.0, 138.0, 134.7, 132.5, 131.1, 130.9, 129.1, 124.6, 119.8, 115.7, 45.4, 20.8; IR (KBr, cm^{-1}): 3134, 2984, 2742, 2358, 1694, 1340, 1211, 1062, 748; MS (ESI) *m/z* (%): 379 $[M+H]^+$; Anal. calcd for $C_{16}H_{11}ClN_2O_3S_2$: C, 50.72; H, 2.93; N, 7.39; S, 16.93. Found: C, 51.09; H, 3.28; N, 7.72; S, 16.98.

4.4.5. (Z)-2-(5-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**25**)

Yellow solid; Yield: 70%; mp: 346–348 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.49 (bs, 1H), 8.42 (s, 1H), 7.86 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 4.82 (s, 2H), 2.51 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.1, 166.9, 161.0, 146.2, 136.0, 135.7, 135.1, 131.9, 130.5, 126.9, 123.9, 123.4, 119.5, 115.3, 45.2, 20.2, 17.0; IR (KBr, cm^{-1}): 3421, 3179, 2924, 1701, 1632, 1336, 1205, 1061; MS (ESI) *m/z* (%): 391 $[M-H]^+$; HRMS (ESI): $[M-H]^+$ Calcd for $C_{17}H_{13}N_2O_3S_2Cl$: 390.9977, Found: 390.9961.

4.4.6. (Z)-2-(5-((2-chloro-5,8-dimethylquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**26**)

Yellow solid; Yield: 70%; mp: 341–343 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.25 (bs, 1H), 8.47 (s, 1H), 7.78 (s, 1H), 7.30 (d, 1H, $J = 7.36$ Hz), 6.97 (d, 1H, $J = 7.36$ Hz), 4.67 (s, 2H), 2.50 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.1, 166.5, 160.2, 143.3, 137.9, 134.5, 133.5, 130.6, 123.4, 122.8, 122.7, 121.3, 118.2, 117.9, 44.7, 17.8, 16.5; IR (KBr, cm^{-1}): 3422, 2926, 1711, 1624, 1334, 1239, 1205, 1059; MS (ESI) *m/z* (%): 391 $[M-H]^+$; HRMS (ESI): $[M+H]^+$ Calcd for $C_{17}H_{13}N_2O_3S_2Cl$: 392.9977, Found: 392.9978.

4.4.7. (Z)-2-(5-((2-chloro-6-methoxyquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**27**)

Red solid; Yield: 74%; mp: 319–321 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 12.11 (bs, 1H), 8.07 (s, 1H), 7.90 (s, 1H), 7.81 (s, 1H), 7.29 (d, 1H, $J = 9.25$ Hz), 7.12 (d, 1H, $J = 9.25$ Hz), 4.73 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 195.9, 166.7, 160.0, 154.6, 144.5, 134.1, 130, 129.8, 124.5, 123.5, 122.6, 119.8, 116.6, 109.6, 55.4, 45.0; IR (KBr, cm^{-1}): 3145, 3025, 2915, 2360, 1714, 1667, 1336, 1198, 1057, 743; MS (ESI) *m/z* (%): 433 $[M+K]^-$. Anal. calcd for $C_{16}H_{11}ClN_2O_4S_2$: C, 48.67; H, 2.81; N, 7.09; S, 16.24. Found: C, 49.01; H, 2.86; N, 7.33; S, 16.54.

4.4.8. (Z)-2-(5-((2-chloro-5,8-dimethoxyquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid (**28**)

Red solid; Yield: 75%; mp: 339–342 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.52 (bs, 1H), 8.45 (s, 1H), 7.82 (s, 1H), 7.20 (d, 1H, $J = 8.87$ Hz), 6.71 (d, 1H, $J = 8.87$ Hz), 4.72 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 195.3, 166.5, 159.8, 150.1, 139.6, 138.9, 136.6, 128.8, 123.5, 123.2, 115.8, 114.9, 110.5, 102.7, 56.9, 56.6, 44.7. MS (ESI) *m/z* (%): 448 $[M+Na]^+$; Anal. calcd for $C_{17}H_{13}ClN_2O_5S_2$: C, 48.06; H, 3.08; N, 6.59; S, 15.09. Found: C, 48.39; H, 3.45; N, 6.57; S, 15.42.

4.4.9. (Z)-2-(5-((2-chloro-6,7-dimethoxyquinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**29**)

Red solid; Yield: 75%; mp: 334–336 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 12.09 (bs, 1H), 8.20 (s, 1H), 7.74 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.69 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 195.9, 166.7, 160.0, 154.6, 144.5 (2), 134.1, 129.8, 124.5, 123.5, 122.6, 119.8, 116.6, 109.6, 97.4, 55.4, 45.0; IR (neat, cm^{-1}): 2915, 2358, 2330, 1716, 1697, 1508, 1217, 1196, 1001, 846, 738; MS (ESI) *m/z* (%): 425 $[M+H]^+$. Anal. calcd for $C_{17}H_{13}ClN_2O_5S_2$: C, 48.06; H, 3.08; N, 6.59; S, 15.09. Found; C, 48.12; H, 2.81; N, 6.98; S, 15.39.

4.4.10. (Z)-2-(5-((6-chloro-[1,3]dioxolo[4,5-g]quinolin-7-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**30**)

Red solid; Yield: 75%; mp: 371–374 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.00 (bs, 1H), 8.27 (s, 1H), 7.91 (s, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 6.10 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 197.6, 169.5, 160.2, 152.1, 143.9, 143.2, 137.3, 127.9, 125.2, 121.2, 113.9, 105.6, 102.5, 102.2, 94.9, 44.8; IR (neat, cm^{-1}): 3003, 2941, 2358, 2341, 1635, 1541, 1456, 1232, 1029, 829. MS (ESI) *m/z* (%): 407 $[M-H]^+$; Anal. calcd for $C_{16}H_9ClN_2O_5S_2$: C, 47.00; H, 2.22; N, 6.85; S, 15.69. Found: C, 47.37; H, 2.50; N, 6.77; S, 16.01.

4.4.11. (Z)-2-(5-((2-chlorobenzo[h]quinolin-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**31**)

Yellow solid; Yield: 85%; mp: 279–281 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 12.09 (bs, 1H), 8.35 (s, 1H), 7.86 (m, 4H), 7.78 (s, 1H), 7.59 (m, 2H), 4.50 (s, 2H); IR (KBr, cm^{-1}): 3229, 1753, 1701, 1575, 1324, 1188, 1055, 901; MS (ESI) *m/z* (%): 413 $[M-H]^-$; HRMS (ESI): $[M-H]^-$ Calcd for $C_{19}H_{11}N_2O_3S_2Cl$: 412.9821. Found: 412.9806.

4.5. General procedure for the synthesis of rhodanine derivatives (**32**–**34**)

2-Chloroquinoline-3-carbaldehyde **3f**–**g** (0.0045 mol) was taken in round bottom flask added to 3-phenyl-2-thioxothiazolidin-4-one **8c** (0.0045 mol) and to this sodium acetate (0.0135 mol) was added. Acetic acid (20 ml) was added as solvents. The mixture was reflux for 4 h at 110 °C and cooled at rt and poured into water compound (**32**–**34**) was formed. It was then filtered through the suction pump, washed with water to remove excess of acetic acid and recrystallized from methanol.

4.5.1. (Z)-5-((2-chlorobenzo[h]quinolin-3-yl)methylene)-3-phenyl-2-thioxothiazolidin-4-one (**32**)

Yellow solid; Yield: 80%; mp: 288–290 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.20 (d, 1H, $J = 8.82$ Hz), 8.02 (s, 1H), 7.85 (m, 4H), 7.57 (m, 5H), 7.47 (d, 1H, $J = 8.82$ Hz); IR (KBr, cm^{-1}): 3032, 1724, 1639, 1570, 1235, 1143, 902; MS (EI) *m/z* (%): 432 $[M]^+$; Anal. calcd for $C_{23}H_{13}ClN_2OS_2$: C, 63.81; H, 3.03; N, 6.47; S, 14.81. Found: C, 64.16; H, 2.92; N, 6.35; S, 14.80.

4.5.2. (Z)-5-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-3-phenyl-2-thioxothiazolidin-4-one (**33**)

Yellow solid; Yield: 74%; mp: 357–359 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.74 (s, 1H), 7.54 (m, 5H), 7.44 (s, 1H), 7.30 (s, 1H), 2.41 (s, 3H), 2.31 (s, 3H); IR (KBr, cm^{-1}): 3422, 3032, 1721, 1655, 1347, 1243, 1126; MS (EI) *m/z* (%): 392 $[M]^+$. Anal. calcd for $C_{21}H_{15}ClN_2OS_2$: C, 61.38; H, 3.68; N, 6.82; S, 15.61. Found: C, 61.72; H, 3.36; N, 6.60; S, 15.80.

4.5.3. (Z)-5-((2-chloro-5,8-dimethylquinolin-3-yl)methylene)-3-phenyl-2-thioxothiazolidin-4-one (**34**)

Yellow solid; Yield: 74%; mp: 366–368 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 8.52 (s, 1H), 7.81 (s, 1H), 7.52 (m, 5H), 7.36 (d, 1H $J = 7.63$ Hz), 7.32 (d, 1H $J = 7.63$ Hz), 2.52 (s, 3H), 2.38 (s, 3H): ^{13}C

NMR (500 MHz, DMSO-d_6): δ 197.1, 167.4, 160.7, 143.2, 138.2, 135.4, 134.8, 133.7, 130.0 (2), 129.2 (2), 128.6, 125.9, 124.6, 123.7, 123.4, 121.7, 118.3, 18.2, 16.9; IR (KBr, cm^{-1}): 3430, 3162, 3032, 1726, 1654, 1347, 1243, 1126, 746; MS (EI) *m/z* (%): 392 $[M]^+$; Anal. calcd for $C_{21}H_{15}ClN_2OS_2$: C, 61.38; H, 3.68; N, 6.82; S, 15.61. Found: C, 61.68; H, 4.00; N, 6.48; S, 15.96.

4.6. General procedure for the synthesis of rhodanine derivatives (**35**–**39**)

Subtuted-2-(piperidin-1-yl)quinoline-3-carbaldehyde **5a**–**e** (0.0045 mol) was taken and added to **8a**–**b** (0.0045 mol) and to this sodium acetate (0.0135 mol) was added. Acetic acid (20 ml) was added as solvents. The mixture was refluxed for 4 h at 110 °C and cooled at rt and poured into water compound (**35**–**39**) was formed. It was then filtered through the suction pump, washed with water to remove excess of acetic acid and recrystallized from methanol.

4.6.1. (Z)-5-((8-methyl-2-(piperidin-1-yl)quinolin-3-yl) methylene)-2-thioxothiazolidin-4-one (**35**)

Red solid; Yield: 71%; mp: 288–290 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.66 (s, 1H), 7.55 (d, 1H, *J* = 7.36 Hz), 7.46 (d, 1H, *J* = 7.36 Hz), 7.23 (t, 1H, *J* = 7.36 Hz), 3.34 (s, 4H), 2.66 (s, 3H), 1.74 (m, 6H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 196.0, 167.0, 158.1, 144.5 (2), 138.7, 137.5, 133.6, 127.4 (2), 126.3, 124.2, 122.4 (2), 119.3, 51.1, 25.1, 24.0, 17.0; IR (KBr, cm^{-1}): 3165, 3028, 2850, 2363, 1712, 1435, 1218, 1068, 741; MS (EI) *m/z* (%): 369 $[M]^+$; HRMS (EI): $[M]^+$ Calcd for $C_{19}H_{19}N_3OS_2$: 369.09695. Found: 369.09590.

4.6.2. (Z)-5-((6-methyl-2-morpholinoquinolin-3-yl)methylene)-2-thioxothiazolidin-4-one (**36**)

Yellow solid; Yield: 70%; mp: 288–290 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.78 (s, 1H), 7.70 (d, 1H, *J* = 8.49 Hz), 7.60 (d, 1H, *J* = 8.49 Hz), 7.43 (s, 1H), 3.78 (m, 4H), 3.25 (m, 4H), 2.46 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 195.9, 169.3, 158.1, 145.0, 137.7, 134.3, 133.3, 127.6, 127.3, 127.2, 126.8, 124.2, 120.4, 65.8 (2), 50.7 (2), 20.8; IR (KBr, cm^{-1}): 3061, 2864, 2363, 1712, 1470, 1224, 1106, 822; MS (EI) *m/z* (%): 372 $[M+H]^+$. HRMS (EI): $[M]^+$ Calcd for $C_{18}H_{17}N_3O_2S_2$: 371.07622. Found: 371.07522.

4.6.3. (Z)-2-(4-oxo-5-((2-(piperidin-1-yl)quinolin-3-yl) methylene)-2-thioxothiazolidin-3-yl)acetic acid (**37**)

Yellow solid; Yield: 70%; mp: 337–340 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.34 (s, 1H), 7.90 (d, 1H, *J* = 7.16 Hz), 7.85 (s, 1H), 7.74 (d, 1H, *J* = 7.16 Hz), 7.67 (t, 1H, *J* = 7.16 Hz), 7.40 (t, 1H, *J* = 7.16 Hz), 4.75 (s, 2H), 3.40 (s, 4H), 1.71 (m, 6H); IR (KBr, cm^{-1}): 3150, 2939, 2362, 1650, 1337, 1213, 1060, 750; MS (EI) *m/z* (%): 413 $[M]^+$; HRMS (EI): $[M]^+$ Calcd for $C_{20}H_{19}N_3O_3S_2$: 413.08678. Found: 413.08660.

4.6.4. (Z)-2-(5-((8-ethyl-2-(piperidin-1-yl)quinolin-3-yl) methylene)-4-oxo-2-tioxothiazolidin-3-yl)acetic acid (**38**)

Red solid; Yield: 74%; mp: 280–284 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.00 (bs, 1H), 8.17 (s, 1H), 7.86 (s, 1H), 7.60 (d, 1H, *J* = 7.90 Hz), 7.48 (d, 1H, *J* = 6.61 Hz), 7.28 (t, 1H, *J* = 7.90 Hz) 4.76 (s, 2H), 3.36 (s, 4H), 3.15 (q, 2H, *J* = 7.55 Hz), 1.74 (m, 6H), 1.34 (t, 3H, *J* = 7.55 Hz). IR (KBr, cm^{-1}): 2972, 2358, 1715, 1625, 1336, 1200, 1058, 751. MS (ESI) *m/z* (%): 440 $[M-H]^+$. Anal. calcd for $C_{22}H_{23}N_3O_3S_2$: C, 59.84; H, 5.25; N, 9.52; S, 14.52. Found: C, 59.48; H, 4.96; N, 9.14; S, 14.14.

4.6.5. (Z)-2-(5-((6-methyl-2-(piperidin-1-yl)quinolin-3-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**39**)

Red solid; Yield: 72%; mp: 286–289 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 11.00 (bs, 1H), 8.34 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.69 (d, 1H, *J* = 8.40 Hz), 7.58 (d, 1H, *J* = 8.40 Hz), 4.73 (s, 2H), 3.27 (s, 4H), 2.49 (s, 3H), 1.69 (m, 6H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 193.5, 167.1, 166.4, 158.7, 145.4, 138.4, 133.9, 133.4, 130.4, 130.1, 127.3, 126.7, 123.9, 122.8, 120.3, 51.3, 45.4, 30.6, 25.2, 23.9, 20.7; IR (KBr, cm^{-1}): 2919, 2848, 2357, 1712, 1583, 1383, 1201, 825; MS (ESI) *m/z* (%): 426 $[M-H]^+$; HRMS (EI): $[M]^+$ Calcd for $C_{21}H_{21}N_3O_3S_2$: 427.10243. Found: 427.10220.

4.7. Biological activity

4.7.1. Cell culture

MDAMB231 and MCF7 cell lines (Breast cancer) were gifted sample by Dr Radha, CCMB, Hyderabad, India; HGC and MKN74 cell lines (Gastric cancer) and DU-145, PC 3 cell lines (Prostate cancer) were obtained from Cell Bank, RIKEN Bio Resource Centre, Japan. DMEM, MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide], Trypsin, EDTA were purchased from Sigma Chemicals Co (St. Louis, MO), Fetal bovine serum (FBS) was purchased from Gibson, USA and 96 well flat bottom tissue culture plates were purchased from Tarson. HGC, MKN74 cell lines were grown as adherent in MEM, MDAMB231 and MCF 7 cell lines in DMEM and DU-145, PC 3 cell lines in RPMI media respectively supplemented with 10% fetal bovine serum, 100 μg/ml penicillin, 200 μg/ml streptomycin, 2 mM L-glutamine, and culture was maintained in a humidified atmosphere with 5% CO_2.

4.7.2. Cytotoxicity evaluation

Cytotoxicity of the compounds was determined by MTT assay based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly colored blue formazan product. 1×10^4 Cells (counted by Trypan blue exclusion dye method) in 96-well plates were incubated with formulations with series of concentrations for 48 h at 37 °C in DMEM with 10% FBS medium. Then the above media was replaced with 90 μl of fresh serum free media and 10 μl of MTT reagent (5 mg/ml) and plates were incubated at 37 °C for 4 h, there after the above media was replaced with 200 μl of DMSO and the absorbance was measured at 570 nm on a spectrophotometer (spectra max, Molecular devices) and IC_{50} values were determined.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.06.013.

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