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Original article

Design, synthesis and biological evaluation of novel 4-thiazolidinones containing indolin-2-one moiety as potential antitumor agent

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ABSTRACT

A series of novel 4-thiazolidinone and indolin-2-one hybrid derivatives **5a**–**5s** and **10a**–**10s** have been designed and synthesized and their cytotoxic activities were evaluated *in vitro* against three human cancer cell lines including HT-29 (human colon cancer), H460 (human lung cancer), MDA-MB-231 (human breast cancer) by MTT assay. Several potent target compounds (**5m**, **5p**, **5s**, **10a**, **10c**–**10g**, **10m**, **10p**) were further evaluated against one cancer cell line SMMC-7721 (human liver cancer) and one normal cell line WI-38 (human fetal lung fibroblasts). Most of the prepared compounds exhibited significant antitumor activities against different human cancer cell lines. Compound **10c** (IC_{50} = 0.025 μM, 0.075 μM, 0.77 μM, 1.95 μM) was 52, 36, 4.8 and 3.3 times more active than Sunitinib (IC_{50} = 1.3 μM, 2.7 μM, 3.7 μM, 6.47 μM) against HT-29, H460, MDA-MB-231 and SMMC-7721 cancer cell line, respectively.

1. Introduction

4-Thiazolidinone derivatives are an important group of heterocyclic compounds possessing a variety of biological effects [1], including antitumor [2–4], anti-inflammatory [5], antimicrobial [6], antiviral [7], anticonvulsant [8], antifungal [9], antibacterial [10] activities and so on. Among them, 5-benzylidene-4-thiazolidinone derivatives have been reported to show marked antitumor activities with different biotargets and mechanism, such as phosphatase of a regenerating liver (PRL-3) [11], Sphingosine Kinase (SK) [12], JNK-stimulating phosphatase-1 (JSP-1) [13] and nonmembrane protein tyrosine phosphatase (SHP-2) [14]. Moreover, 5-benzylidene-4-thiazolidinone derivatives exhibited potent antitumor activities against non-small cell lung cancer cell line H460, paclitaxel-resistant $H460_{taxR}$, human colon cancer cell line HT-29 and human breast cancer cell line MDA-MB-231 (Fig. 1) [15–17].

The indolin-2-one ring system belongs to the privileged structure in modern medicinal chemistry, particularly in discovery of new antitumor and antiangiogenic agents. Various kinase inhibitors containing indolin-2-one moiety have been intensively studied for the inhibition of VEGFR, c-Kit, FLT3, PDGFR-α/β, and CSF-1-R [18]. Sunitinib, a multitargeted receptor tyrosine kinase inhibitor, interfering with tumor blood vessel formation, is approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST) (Fig. 1) [19]. BIBF 1120, a triple angiokinase inhibitor reported by Boehringer, is currently in phase III clinical trials in non-small cell lung cancer (Fig. 1) [20]. Indirubin, an active ingredient of a traditional Chinese medicine recipe, has been applied to treat chronic myelocytic leukemia (Fig. 1) [21].

The aforementioned compounds have inspired us to attach substituted indolin-2-one to the 5-benzylidene-4-thiazolidinone scafford, and the combination of two privileged structures in one molecule leads to drug-like molecules. To our knowledge there are hardly any studies about introduction of indolin-2-one group at the 2-position of the 4-thiazolidinone ring so far. Thus, indolin-2-one group was introduced at the 2-position of the 4-thiazolidinone ring and a basic side chain was introduced at the 3-position of the 4-thiazolidinone ring, in order to improve the solubility and bioavailability of these structures.

Here, we report the newly synthesized target compounds (Fig. 1) and their cytotoxic activities against HT-29, H460, MDA-MB-231 and SMMC-7721 human cancer cell lines.

2. Chemistry

The preparation of target compounds **5a**–**5s** and **10a**–**10s** was described in Scheme 1. The indolin-2-ones **11a**–**11f** were synthesized from appropriate anilines according to the reported procedures [22,23].

The 5-benzylidene-3-substitutedrhodanine intermediates **3a**–**3h** and **8a**–**8f** were synthesized by reaction of the primary amine **1** or **6** and carbon disulfide under basic conditions followed by ring closure

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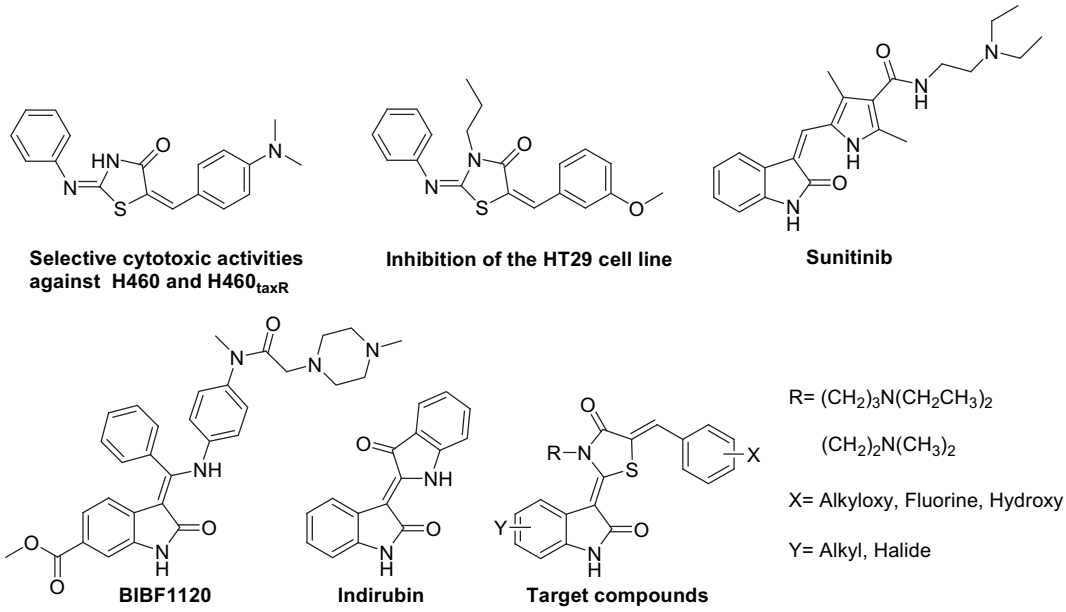
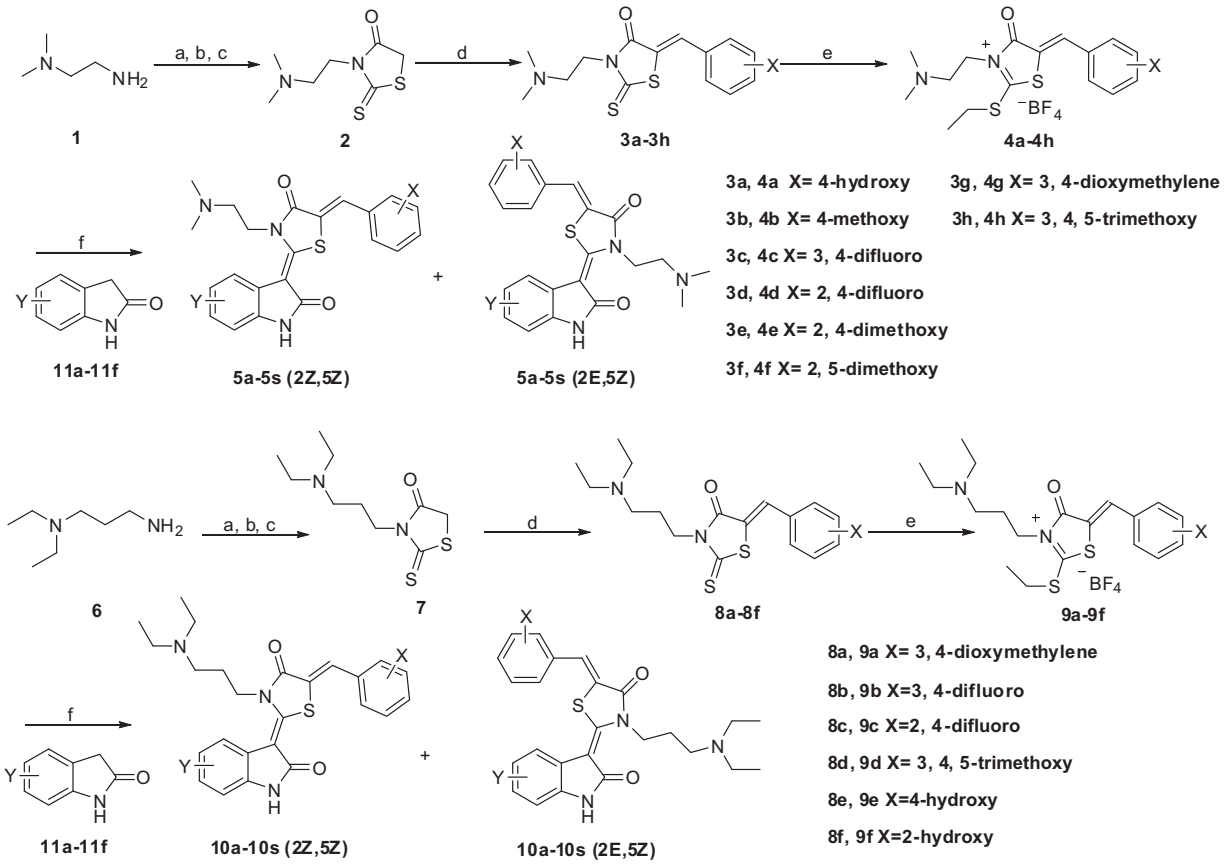


Fig. 1. Structures of 4-thiazolidinones, indolin-2-ones and target compounds.

with chloroacetic acid and subsequent the intermediate **2** or **7** was subjected to Knoevenagel condensation with suitable benzaldehydes in refluxing ethanol (Scheme 1).

The Knoevenagel condensation reaction of **2** or **7** with benzaldehydes provided only the Z isomer, as determined by the chemical shift of the methine proton in **3a**–**3h** and **8a**–**8f** ranging from 7.70 to 8.00 ppm as a singlet. The exclusive formation of the thermodynamically stable Z-isomers is in agreement with which was reported for similar structures in literature [24,25]. This downfield movement of methine proton in **3a**–**3h** and **8a**–**8f** was due to the deshielding effect of the adjacent carbonyl group at the 4-position. The *S*-Ethylation of **3a**–**3h** and **8a**–**8f** with boron trifluoride diethyl



Scheme 1. Reagents and conditions: (a) CS_2, Et_3N, Et_2O, 25 °C, 0.5 h; (b) $ClCH_2COOH$, K_2CO_3, MeOH, H_2O, 25 °C, 7–8 h; (c) concd.H_2SO_4, pH = 4.0, 35–40 °C,12 h; (d) Benzaldehyde, piperidine, EtOH, reflux 3–4 h; (e) $BF_3.Et_2O$, $HC(OEt)_3$, 1,4-dioxane, 80 °C; (f) Et_3N, CH_3CN, 25 °C, 4 h.

etherate and triethyl orthoformate produced thiazolinium salts **4a**–**4h** and **9a**–**9f**, which were condensed with indolin-2-ones **11a**–**11f** in the presence of triethylamine to form target compounds **5a**–**5s** and **10a**–**10s**.

Due to the exocyclic double bond at 2-position of 4-thiazolidinone ring, **5a**–**5s** and **10a**–**10s** existed as inseparable mixture of 2Z, 5Z and 2E, 5Z isomers. The tow isomers were assigned on the basis of NOESY experiment. For the representative compound **5g** or **10c**, the NOESY effect was observed between the proton of a-methylene and the proton in 4-position of the indolin-2-one ring in 2Z, 5Z isomer (see Supplementary information), whereas the 2E, 5Z isomer didn't show this effect (Fig. 2). The downfield shift of a-methylene proton in 2E, 5Z isomer was presumably due to the deshielding effect of the carbonyl group at the 2-position of the indolin-2-one ring (Fig. 2). 2Z, 5Z/2E, 5Z ratios were determined using the corresponding integrals of a-methylene proton in the ^{1}H NMR spectra as shown in Table 1.

3. Biological evaluation

Compounds **5a**–**5s** and **10a**–**10s** were evaluated as mixtures of both isomers for their cytotoxic activities against HT-29 (human colon cancer), H460 (human lung cancer) and MDA-MB-231 (human breast cancer) cancer cell lines together with reference Sunitinib by MTT assay. In addition, several potent target compounds (**5m**, **5p**, **5s**, **10a**, **10c**–**10g**, **10m**, **10p**) were further evaluated against one cancer cell line SMMC-7721 (human liver cancer) and one normal cell line WI-38 (human fetal lung fibroblasts). The results expressed as IC_{50} were summarized in Table 1. The IC_{50} values are the average of at least three independent experiments.

As illustrated in Table 1, most of the synthesized compounds showed moderate to excellent cytotoxic activities against different cancer cell lines in submicromolar range. Compound **10c** possessed the highest potency against all four cancer cell lines, while compounds **5j**, **5m**, **5q**, **10d** and **10g**, indicated significant selectivity toward HT-29 cancer cell line. Compounds **10h**, **10j** and **10l**–**10o** exhibited selectivity on H460 cancer cell line.

The initial structure-activity relationships could be drawn from the pharmacological data: (a) Compound (**5a**–**5f**) bearing different substituted indolin-2-one showed greater cytotoxic activities than the parent intermediate **3a** against all the cancer cell lines, therefore a substituted indolin-2-one ring is a necessary moiety for these compounds to possess potent cytotoxic activities. (b) Smaller electron-withdrawing fluorine atom at 5-position of the indolin-2-one ring was more favorable, as compound **10c** was more potent than **10a**, **10b**, **10d**, **10e** against all the cancer cell lines.

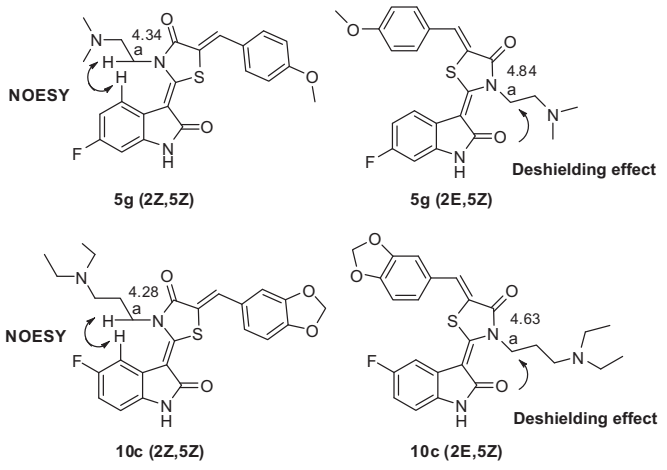


Fig. 2. Key NOESY of **5g** (2Z,5Z) and **10c** (2Z,5Z) and deshielding effect of carbonyl group in **5g** (2E,5Z) and **10c** (2E,5Z).

(c) The 3-(diethylamino)propyl group at the 3-position of 4-thiazolidinone ring was favorable for increasing antitumor potency (**10f** vs **5h**, **10g** vs **5i**, **10i** vs **5k**). (d) The position of substituents in the phenyl ring appears to have significant effect on cytotoxic activity. When comparing compounds with different electron-donating group in the phenyl ring, it could clearly be seen that 4-OH, 4-OMe or 3,4-dioxymethylene group in the phenyl ring (**5a**–**5g**, **5p**–**5r**) were favorable for a good antitumor potency, whereas a drop of potency could be observed for compounds with 2,5-dimethoxybenzylidene group (**5n**–**5o**) or 2-hydroxybenzylidene group (**10q**–**10s**). Furthermore, compounds with fluorine in the phenyl ring were less active, confirming that the electron-withdrawing group in the phenyl ring may be unfavorable. Compounds **10f** and **10g** possessed good potency may be due to the longer basic side chain and fluoroindolin-2-one group. (e) Compounds with 3,4-dioxymethylene group in the phenyl ring displayed less toxicity against normal cell line WI-38 (**10c** vs **10f**, **10c** vs **10m**, **10d** vs **10g**). Moreover, compound **10c** was less toxic for normal cell line WI-38, when compared to HT-29 and H460 cancer cell lines. The selective index (IC_{50} normal cell/IC_{50} cancer cell) for HT-29 and H460 cancer cell lines was 279 and 93, respectively. These data demonstrated that the tumor cells were more sensitive than the normal cells.

4. Conclusion

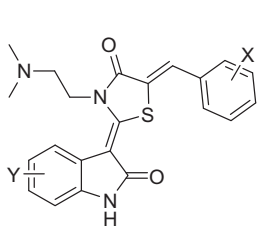
In summary, a series of 4-thiazolidinones with indolin-2-one fragment were designed and synthesized. The cytotoxic activities of synthesized compounds were evaluated against four human cancer cell lines (HT-29, H460, MDA-MB-231 and SMMC-7721). Most of the prepared compounds displayed moderate to excellent cytotoxic activities against one or more cancer cell lines. In particular, compound **10c** showed potent antitumor activity against all four cancer cell lines. In addition, compound **10c** exerted markedly weaker effects on WI-38 normal cell line than on HT-29 and H460 cancer cell lines. From the preliminary SAR studies, it revealed that introduction of 5-fluoroindolinone or 6-fluoroindolinone group at 2-position of the 4-thiazolidinone scaffold could enhance their antitumor activities. Compound **10c** exhibited interesting antitumor activity and selective index in comparison to the other investigated compounds. This compound appeared as promising and interesting lead, endowed of potential antitumor activity. Further studies are in progress in our laboratories and will be reported upon in the future.

5. Experimental protocols

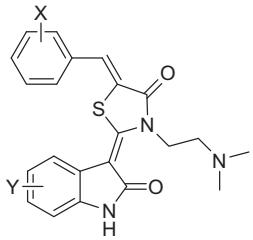
5.1. Chemistry

Melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-300, 300 MHz or Bruker ARX-600, 600 MHz spectrometers (Bruker Bioscience, Billerica, MA USA) with TMS as an internal standard. (2Z, 5Z)/(2E, 5Z) ratios were determined by integration of the corresponding peaks in the ^{1}H NMR spectra. IR spectra (KBr disks) were recorded on a Bruker IFS55 instrument (Bruker). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All chemicals were obtained from commercial suppliers and used without purification. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Indolin-2-ones **11a**–**11f** were synthesized in accordance with literature procedures [22,23]. The detailed experimental data of precursors (**2**, **7**, **3a**–**3h and 8a**–**8f**) are presented in Supplementary information.

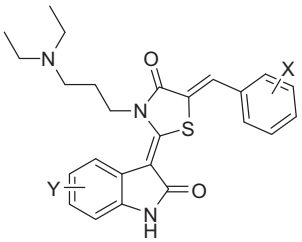
Table 1
Structure and cytotoxic activities of target compounds against HT-29, H460, MDA-MB-231, SMMC-7721 cancer cell lines and WI-38 normal cell line *in vitro*.



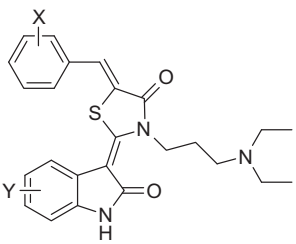
5a-5s (2Z,5Z)



5a-5s (2E,5Z)



10a-10s (2Z,5Z)



10a-10s (2E,5Z)

Compd.	Ratio[a]	X	Y	IC_{50} (μM)[b]± SD				
				HT−29[c]	H460[c]	MDA-MB−231[c]	SMMC−7721[c]	WI−38[c]
3a	–	4-hydroxy	–	59.67 ± 4.21	46.13 ± 3.12	84.2 ± 4.51	ND	ND
5a	67/33	4-hydroxy	H	1.39 ± 0.14	0.98 ± 0.15	4.28 ± 0.26	ND	ND
5b	86/14	4-hydroxy	5-CH_3	2.29 ± 0.06	1.77 ± 0.075	1.32 ± 0.11	ND	ND
5c	72/28	4-hydroxy	5-F	1.48 ± 0.29	1.27 ± 0.38	4.20 ± 0.98	ND	ND
5d	69/31	4-hydroxy	6-F	2.27 ± 0.25	1.43 ± 0.18	3.45 ± 0.25	ND	ND
5e	74/26	4-hydroxy	5-Cl	2.46 ± 0.35	2.03 ± 0.32	3.25 ± 0.41	ND	ND
5f	78/22	4-hydroxy	5-Br	1.92 ± 0.11	1.11 ± 0.19	2.52 ± 0.26	ND	ND
5g	69/31	4-methoxy	6-F	2.30 ± 0.30	2.2 ± 0.36	2.09 ± 0.13	ND	ND
5h	76/24	3,4-difluoro	5-F	3.09 ± 0.25	44.7 ± 5.03	9.48 ± 0.54	ND	ND
5i	64/36	3,4-difluoro	6-F	12.06 ± 0.9	6.4 ± 0.53	25 ± 3	ND	ND
5j	80/20	3,4-difluoro	5-CH_3	7.43 ± 0.78	59.67 ± 4.51	NA	ND	ND
5k	54/46	2,4-difluoro	6-F	6.46 ± 0.27	3.20 ± 0.11	8.44 ± 0.29	ND	ND
5l	80/20	2,4-dimethoxy	5-Cl	1.53 ± 0.24	10.6 ± 1.61	3.83 ± 0.76	ND	ND
5m	71/29	2,4-dimethoxy	6-F	0.868 ± 0.41	20.53 ± 3.16	4.83 ± 0.98	6.81 ± 0.27	3.01 ± 0.28
5n	74/26	2,5-dimethoxy	6-F	4.45 ± 0.14	7.15 ± 0.41	14.53 ± 0.41	ND	ND
5o	88/12	2,5-dimethoxy	H	96 ± 6	63.7 ± 5.51	21 ± 5.57	ND	ND
5p	60/40	3,4-dioxymethylene	H	0.70 ± 0.17	0.82 ± 0.095	3.23 ± 0.35	2.74 ± 0.27	1.77 ± 0.20
5q	52/48	3,4-dioxymethylene	5-CH_3	1.03 ± 0.18	4.03 ± 0.10	8.10 ± 0.16	ND	ND
5r	92/8	3,4-dioxymethylene	6-F	1.36 ± 0.08	2.81 ± 0.12	2.42 ± 0.14	ND	ND
5s	72/28	3,4,5-trimethoxy	5-F	2.53 ± 0.31	1.70 ± 0.26	1.90 ± 0.61	6.06 ± 0.40	8.10 ± 0.39
10a	65/35	3,4-dioxymethylene	H	0.91 ± 0.27	1.02 ± 0.20	1.12 ± 0.18	3.41 ± 0.20	3.93 ± 0.29
10b	60/40	3,4-dioxymethylene	5-CH_3	2.11 ± 0.28	1.86 ± 0.22	3.1 ± 0.26	ND	ND
10c	77/23	3,4-dioxymethylene	5-F	0.025 ± 0.008	0.075 ± 0.025	0.77 ± 0.21	1.95 ± 0.23	6.98 ± 0.26
10d	24/76	3,4-dioxymethylene	6-F	0.19 ± 0.04	1.91 ± 0.54	4.13 ± 0.61	4.02 ± 0.18	8.30 ± 0.32
10e	81/19	3,4-dioxymethylene	5-Cl	0.437 ± 0.10	1.00 ± 0.10	3.13 ± 0.61	3.12 ± 0.27	3.32 ± 0.15
10f	47/53	3,4-difluoro	5-F	0.64 ± 0.12	1.30 ± 0.26	1.22 ± 0.33	3.07 ± 0.51	4.30 ± 0.35
10g	12/88	3,4-difluoro	6-F	0.028 ± 0.009	1.12 ± 0.15	2.9 ± 1.39	5.33 ± 0.42	4.45 ± 0.30
10h	80/20	2,4-difluoro	H	NA	5.47 ± 0.76	NA	ND	ND
10i	80/20	2,4-difluoro	6-F	1.52 ± 0.17	2.33 ± 0.42	2.10 ± 0.12	ND	ND
10j	82/18	2,4-difluoro	5-Cl	NA	6.10 ± 0.36	NA	ND	ND
10k	67/33	3,4,5-trimethoxy	H	1.97 ± 0.31	1.67 ± 0.34	2.39 ± 0.26	ND	ND
10l	37/63	3,4,5-trimethoxy	5-CH_3	NA	2.67 ± 0.50	NA	ND	ND
10m	77/23	3,4,5-trimethoxy	5-F	NA	0.78 ± 0.11	NA	2.21 ± 0.18	2.02 ± 0.13
10n	75/25	3,4,5-trimethoxy	6-F	NA	1.41 ± 0.29	NA	ND	ND
10o	70/30	3,4,5-trimethoxy	5-Cl	NA	2.99 ± 0.36	NA	ND	ND
10p	47/53	4-hydroxy	5-CH_3	0.77 ± 0.40	0.26 ± 0.13	1.81 ± 0.46	5.09 ± 0.33	5.75 ± 0.52
10q	40/60	2-hydroxy	H	NA	NA	NA	ND	ND
10r	44/56	2-hydroxy	5-CH_3	8.07 ± 0.83	11.33 ± 2.31	15.93 ± 2.00	ND	ND
10s	45/55	2-hydroxy	5-Br	18.07 ± 0.90	51.67 ± 5.69	19.93 ± 1.79	ND	ND
Sunitinib[d]				1.30 ± 0.12	2.70 ± 0.26	3.70 ± 0.33	6.47 ± 0.25	8.56 ± 0.35

NA: Compound showing IC_{50} value >200 μM.
ND: not determined.
[a] Ratio = (2Z, 5Z):(2E, 5Z).
[b] IC_{50}: concentration of the compound (μM) producing 50% cell growth inhibition after 72 h of drug exposure, as determined by the MTT assay. Each experiment was run at least three times, and the results are presented as average values ± standard deviation.
[c] HT-29, human colon cancer cell line; H460, non-small-cell lung cancer cell line; MDA-MB-231, human breast cancer cell line; SMMC-7721, human liver cancer cell line; WI-38, human fetal lung fibroblasts.
[d] Used as a positive control.

*5.2. General procedure for the synthesis of 3-substituted-2-thioxo-4-thiazolidinone (**2**, **7**)*

The corresponding primary amine (**1** or **6**) (0.1 mol) was dissolved in dry diethylether (200 ml). After addition of triethylamine (10.2 g, 0.1 mol), a solution of CS_2 (7.7 g, 0.1 mol) in diethylether (50 ml) was added dropwise with stirring. After a short time, the exothermic reactions resulted in the dithiocarbamates salt of a white or slightly yellow crystalline solid. The precipitate was separated, dried and immediately used, without any additional purification, as starting material for the following reactions. The appropriate dithiocarbamates salt was dissolved in water (200 ml) and methanol (50 ml). A prepared solution of chloroacetic acid (9.4 g, 0.1 mol) and K_2CO_3 (6.9 g, 0.05 mol) in water (40 ml) was

added and stirring was continued at 25 °C for 7–8 h. Then the reaction mixture was acidified with dilute H_2SO_4 until pH 4.0 and stirred at 35–40 °C for 12 h. The cyclized product (**2**, **7**) was extracted with ethyl acetate, dried over anhydrous sodium sulfate and evaporated under vacuum and the residue was purified by recrystallization with ethanol to obtain intermediate (**2**, **7**).

5.3. General procedure for the synthesis of 3-substituted-5-benzylidene-2-thioxo-4-thiazolidinones (*3a–3h*, *8a–8f*)

A mixture of intermediate (**2** or **7**) (0.01 mol), appropriate benzaldehyde (0.011 mol) and piperidine (0.01 mol) was refluxed for 3–4 h in ethanol (10 ml) and cooled to room temperature to give in a crystalline product. The solid was filtered under suction. The crude products were then purified by recrystallization with ethanol to obtain intermediate (**3a–3h**, **8a–8f**).

5.4. General procedure for the synthesis of final compounds *5a–5s* and *10a–10s*

To a solution of 3-substituted-5-benzylidene-2-thioxo-4-thiazolidinone (**3a–3h**, **8a–8f**) (0.003 mol) in 1,4-dioxane (15 ml) was added $HC(OEt)_3$ (2 ml) and $BF_3 \cdot Et_2O$ (2 ml). The reaction mixture was heated to 80 °C and stirring was continued at the same temperature for 4 h. The resulting 2-ethylthio-3-substituted-5-benzylidene-4-thiazolium fluoroborate (**4a–4h**, **9a–9f**) was precipitated, filtered off, and dried without any additional purification, as starting material for the following reactions. To a mixture of thiazolium fluoroborate (**4a–4h**, **9a–9f**) (0.003 mol) and indolin-2-one (**11a–11f**) (0.003 mol) in acetonitrile (15 ml) was added triethylamine (0.91 g, 0.009 mol) dropwise at 25 °C, and the mixture was stirred for 4 h at the same temperature. The orange precipitate was collected and washed with ethyl acetate (8 ml). The crude product thus obtained was recrystallized from methanol or acetone to give compound (**5a–5s**, **10a–10s**).

5.4.1. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)indolin-2-one (*5a*)

Yield: 55%. ESI-MS: *m*/*z*, 408.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3444.3, 1696.2, 1671.2, 1612.9, 1582.8, 1514.1, 1464.2, 1364.7, 1348.3, 1315.2, 1290.6, 1229.7, 1208.7, 1173.7, 1137.9. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.98 (s, 0.67 × 6H, 2 × CH_3), 2.07 (s, 0.33 × 6H, 2 × CH_3), 2.41–2.49 (m, 2H, CH_2), 4.36 (t, 0.67 × 2H, J = 6.6 Hz, CH_2), 4.87 (t, 0.33 × 2H, J = 6.6 Hz, CH_2), 6.98–7.76 (m, 9H, CH and arom), 10.36 (s, 1H, OH), 10.65 (s, 0.33 × 1H, NH), 10.85 (s, 0.67 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 67:33. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.6, 159.8, 149.6, 139.3, 132.8, 131.7, 126.8, 125.0, 123.2, 121.0, 120.6, 118.2, 116.5, 109.8, 101.5, 55.7, 45.4, 45.3. Anal. Calcd for $C_{22}H_{21}N_3O_3S$ (%): C, 64.85; H, 5.19; N, 10.31. Found (%): C, 65.89; H, 5.21; N, 10.35.

5.4.2. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (*5b*)

Yield: 52%. ESI-MS: *m*/*z*, 422.2 $[M + H]^+$. IR (KBr) cm^{-1}: 3330.5, 2947.2, 2826.7, 1682.6, 1644.2, 1584.8, 1516.1, 1484.1, 1448.5, 1384.9, 1357.4, 1329.8, 1315.3, 1286.1, 1252.2, 1208.6, 1171.8, 1150.3, 1130.8, 1100.2, 1044.1. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.04 (s, 0.86 × 6H, 2 × CH_3), 2.17 (s, 0.14 × 6H, 2 × CH_3), 2.32 (s, 0.86 × 3H, CH_3), 2.40 (s, 0.14 × 3H, CH_3), 2.42–2.48 (m, 2H, CH_2), 4.37 (t, 0.86 × 2H, J = 6.6 Hz, CH_2), 4.86 (t, 0.14 × 2H, J = 6.9 Hz, CH_2), 6.82–7.78 (m, 8H, CH and arom), 10.35 (s, 1H, OH), 10.55 (s, 0.14 × 1H, NH), 10.75 (s, 0.86 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 86:14. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.6, 159.7, 149.2, 137.1, 132.8, 131.5, 129.8, 127.3, 125.0, 123.7, 120.7, 118.4, 116.5, 109.5, 101.6, 55.8, 45.3, 45.0, 21.1. Anal. Calcd for $C_{23}H_{23}N_3O_3S$ (%):C, 65.54; H, 5.50; N, 9.97. Found (%): C, 65.60; H, 5.52; N, 10.01.

5.4.3. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (*5c*)

Yield: 50%. ESI-MS: *m*/*z*, 426.4 $[M + H]^+$. IR (KBr) cm^{-1}: 3427.9, 1671.6, 1580.3, 1511.6, 1478.7, 1386.0, 1334.7, 1290.1, 1208.3, 1172.7, 1153.1, 1136.6, 1013.4. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.04 (s, 0.72 × 6H, 2 × CH_3), 2.07 (s, 0.28 × 6H, 2 × CH_3), 2.40–2.49 (m, 2H, CH_2), 4.34 (t, 0.72 × 2H, J = 6.6 Hz, CH_2), 4.87 (t, 0.28 × 2H, J = 6.9 Hz, CH_2), 6.83–7.66 (m, 7H, arom), 7.69 (s, 0.72 × 1H, CH), 7.81 (s, 0.28 × 1H, CH), 10.36 (s, 1H, OH), 10.65 (s, 0.28 × 1H, NH), 10.87 (s, 0.72 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 72:28. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.3, 159.9, 151.6, 135.4, 133.2, 133.0, 132.4, 124.9, 121.6, 117.9, 116.7, 116.6, 110.5, 110.1, 100.9, 55.7, 45.3, 45.0. Anal. Calcd for $C_{22}H_{20}FN_3O_3S$ (%):C, 62.10; H, 4.74; N, 9.88. Found (%): C, 62.15; H, 4.78; N, 9.93.

5.4.4. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (*5d*)

Yield: 53%. ESI-MS: *m*/*z*, 426.4 $[M + H]^+$. IR (KBr) cm^{-1}: 3145.0, 1687.5, 1660.9, 1629.0, 1582.5, 1525.4, 1512.8, 1464.3, 1435.7, 1360.1, 1320.4, 1282.1, 1206.3, 1168.3, 1131.0, 1098.7, 1015.5. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.01 (s, 0.69 × 6H, 2 × CH_3), 2.09 (s, 0.31 × 6H, 2 × CH_3), 2.42–2.49 (m, 2H, CH_2), 4.34 (t, 0.69 × 2H, J = 6.6 Hz, CH_2), 4.85 (t, 0.31 × 2H, J = 7.2 Hz, CH_2), 6.72–7.78 (m, 8H, CH and arom), 10.36 (s, 1H, OH), 10.80 (s, 0.31 × 1H, NH), 11.01 (s, 0.69 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 69:31. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.9, 168.4, 159.7, 149.5, 140.8, 132.8, 131.8, 124.9, 124.4, 124.3, 118.0, 117.1, 116.5, 114.7, 107.3, 107.0, 100.5, 55.6, 45.3, 45.2. Anal. Calcd for $C_{22}H_{20}FN_3O_3S$ (%):C, 62.10; H, 4.74; N, 9.88. Found (%): C, 62.17; H, 4.80; N, 9.96.

5.4.5. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-chloroindolin-2-one (*5e*)

Yield: 55%. ESI-MS: *m*/*z*, 442.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3423.5, 3116.2, 2827.9, 1703.6, 1664.9, 1591.7, 1526.8, 1465.4, 1444.6, 1384.2, 1344.3, 1315.3, 1284.7, 1251.7, 1206.0, 1167.0, 1138.7, 1099.8, 1030.4. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.07 (s, 6H, 2 × CH_3), 2.39–2.49 (m, 2H, CH_2), 4.31 (t, 0.74 × 2H, J = 6.9 Hz, CH_2), 4.84 (t, 0.26 × 2H, J = 6.9 Hz, CH_2), 6.90–7.66 (m, 7H, arom), 7.68 (s, 0.74 × 1H, CH), 7.82 (s, 0.26 × 1H, CH), 10.38 (s, 1H, OH), 10.78 (s, 0.26 × 1H, NH), 10.98 (s, 0.74 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 74:26. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.3, 168.2, 159.9, 151.8, 137.7, 132.9, 132.5, 126.0, 125.1, 124.8, 122.4, 122.1, 117.7, 116.5, 110.8, 100.0, 55.7, 45.3, 45.0. Anal. Calcd for $C_{22}H_{20}ClN_3O_3S$ (%):C, 59.79; H, 4.56; N, 9.51. Found (%): C, 59.83; H, 4.70; N, 9.56.

5.4.6. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-bromoindolin-2-one (*5f*)

Yield: 57%. ESI-MS: *m*/*z*, 486.0 $[M + H]^+$. IR (KBr) cm^{-1}: 3416.5, 3114.8, 2825.8, 1701.7, 1663.4, 1591.1, 1518.7, 1465.0, 1444.3, 1384.2, 1343.4, 1314.4, 1283.6, 1247.3, 1204.9, 1165.8, 1137.2, 1099.1, 1027.4. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.08 (s, 6H, 2 × CH_3), 2.40–2.49 (m, 2H, CH_2), 4.30 (t, 0.78 × 2H, J = 6.6 Hz, CH_2), 4.83 (t, 0.22 × 2H, J = 7.2 Hz, CH_2), 6.86–7.82 (m, 8H, CH and arom), 10.38 (s, 1H, OH), 10.79 (s, 0.22 × 1H, NH), 10.99 (s, 0.78 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 78:22. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.3, 168.3, 160.0, 151.9, 138.1, 133.0, 132.6, 129.0, 125.1, 124.9, 122.7, 117.8, 116.6, 112.9, 111.4, 100.0, 55.8, 45.4, 45.2. Anal. Calcd for $C_{22}H_{20}BrN_3O_3S$ (%):C, 54.33; H, 4.14; N, 8.64. Found (%): C, 54.40; H, 4.20; N, 8.70.

5.4.7. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(4-methoxybenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (*5g*)

Yield: 62%. ESI-MS: *m*/*z*, 440.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3426.9, 3127.4, 2978.4, 2825.2, 2775.0, 1705.0, 1675.7, 1623.6, 1593.8, 1566.9, 1524.1, 1510.1, 1464.3, 1419.1, 1393.7, 1363.2, 1320.2, 1259.9, 1232.0, 1211.1, 1163.6, 1135.5, 1099.4, 1060.1, 1033.3. ^1H NMR (600 MHz, DMSO-d_6) δ: 2.02 (s, 0.69 × 6H, 2 × CH_3), 2.12 (s, 0.31 × 6H, 2 × CH_3), 2.43 (t,

0.69 × 2H, J = 6.6 Hz, CH_2), 2.48 (t, 0.31 × 2H, J = 6.0 Hz, CH_2), 3.85 (s, 0.69 × 3H, CH_3), 3.86 (s, 0.31 × 3H, CH_3), 4.35 (t, 0.69 × 2H, J = 6.6 Hz, CH_2), 4.85 (t, 0.31 × 2H, J = 6.0 Hz, CH_2), 6.70 (dd, 0.31 × 1H, J = 9.0, 2.4 Hz, arom), 6.72 (dd, 0.69 × 1H, J = 9.0, 2.4 Hz, arom), 6.79–6.82 (m, 0.69 × 1H, arom), 6.85–6.88 (m, 0.31 × 1H, arom), 7.15–7.17 (m, 2H, arom), 7.51 (dd, 0.69 × 1H, J = 8.4, 6.4 Hz, arom), 7.66 (d, 0.69 × 2H, J = 12.0 Hz, arom), 7.70 (s, 0.69 × 1H, CH), 7.73 (d, 0.31 × 2H, J = 12.0 Hz, arom), 7.78 (dd, 0.31 × 1H, J = 9.0, 5.4 Hz, arom), 7.82 (s, 0.31 × 1H, CH), 10.79 (s, 0.31 × 1H, NH), 11.00 (s, 0.69 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 69:31. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.9, 168.4, 160.9, 149.3, 140.9, 132.5, 131.3, 126.5, 124.7, 124.6, 119.4, 117.2, 116.0, 115.1, 107.5, 107.2, 100.8, 55.7, 55.6, 45.2, 44.8. Anal. Calcd for $C_{23}H_{22}FN_3O_3S$ (%):C, 62.85; H, 5.05; N, 9.56. Found (%): C, 62.90; H, 5.02; N, 9.46.

*5.4.8. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(3,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (**5h**)*

Yield: 53%. ESI-MS: m/z, 446.4 $[M + H]^+$. IR (KBr) cm^{-1}: 3442.7, 3157.6, 3046.9, 2868.5, 2831.2, 1670.9, 1592.3, 1518.9, 1478.5, 1459.0, 1371.5, 1324.1, 1300.2, 1211.8, 1192.2, 1168.3, 1137.7, 1116.2, 1030.5, 1016.0. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.05 (s, 0.76 × 6H, 2 × CH_3), 2.08 (s, 0.24 × 6H, 2 × CH_3), 2.39–2.49 (m, 2H, CH_2), 4.33 (t, 0.76 × 2H, J = 6.3 Hz, CH_2), 4.86 (t, 0.24 × 2H, J = 5.7 Hz, CH_2), 6.83–6.91 (m, 1H, arom), 7.01–7.07 (m, 1H, arom), 7.42–7.94 (m, 5H, CH and arom), 10.71 (s, 0.24 × 1H, NH), 10.92 (s, 0.76 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 76:24. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 167.8, 158.4, 156.9, 150.1, 135.8, 129.2, 123.8, 121.2, 121.1, 119.6, 119.5, 118.9, 118.7, 113.5, 113.3, 110.7, 110.5, 110.4, 110.3, 102.0, 55.5, 45.2, 45.1. Anal. Calcd for $C_{22}H_{18}F_3N_3O_2S$ (%):C, 59.32; H, 4.07; N, 9.43. Found (%): C, 59.38; H, 4.03; N, 9.40.

*5.4.9. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(3,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**5i**)*

Yield: 50%. ESI-MS: m/z, 446.4 $[M + H]^+$. IR (KBr) cm^{-1}: 3443.8, 3132.4, 2829.7, 2778.1, 1697.4, 1677.8, 1627.9, 1603.2, 1516.5, 1457.4, 1327.3, 1299.7, 1281.3, 1207.6, 1168.5, 1135.4, 1112.1, 1057.9. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.01 (s, 0.64 × 6H, 2 × CH_3), 2.07 (s, 0.36 × 6H, 2 × CH_3), 2.39–2.49 (m, 2H, CH_2), 4.35 (t, 0.64 × 2H, J = 6.0 Hz, CH_2), 4.84 (t, 0.36 × 2H, J = 6.0 Hz, CH_2), 6.69–6.87 (m, 2H, arom), 7.55–7.86 (m, 5H, CH and arom), 10.85 (s, 0.36 × 1H, NH), 11.07 (s, 0.64 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 64:36. Anal. Calcd for $C_{22}H_{18}F_3N_3O_2S$ (%):C, 59.32; H, 4.07; N, 9.43. Found (%): C, 59.40; H, 4.10; N, 9.36.

*5.4.10. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(3,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**5j**)*

Yield: 52%. ESI-MS: m/z, 442.5 $[M + H]^+$. IR (KBr) cm^{-1}: 3421.1, 2920.9, 2823.9, 1700.0, 1675.1, 1605.9, 1535.4, 1518.4, 1484.5, 1432.0, 1384.7, 1329.5, 1300.8, 1279.3, 1251.7, 1208.7, 1168.4, 1146.8, 1040.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.05 (s, 0.80 × 6H, 2 × CH_3), 2.08 (s, 0.20 × 6H, 2 × CH_3), 2.32 (s, 0.80 × 3H, CH_3), 2.38 (s, 0.20 × 3H, CH_3), 2.45–2.49 (m, 2H, CH_2), 4.36 (t, 0.80 × 2H, J = 6.3 Hz, CH_2), 4.86 (t, 0.20 × 2H, J = 6.0 Hz, CH_2), 6.74–6.82 (m, 1H, arom), 6.98–7.02 (m, 1H, arom), 7.52–7.90 (m, 5H, CH and arom), 10.58 (s, 0.20 × 1H, NH), 10.79 (s, 0.80 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 80:20. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.1, 147.8, 137.4, 130.0, 128.4, 127.9, 127.2, 124.2, 124.1, 120.4, 119.5, 119.4, 118.9, 118.7, 109.7, 102.8, 55.6, 45.2, 45.0, 21.0. Anal. Calcd for $C_{23}H_{21}F_2N_3O_2S$ (%):C, 62.57; H, 4.79; N, 9.52. Found (%): C, 62.51; H, 4.83; N, 9.56.

*5.4.11. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(2,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**5k**)*

Yield: 56%. ESI-MS: m/z, 446.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3134.7, 2824.6, 2775.7, 1708.3, 1682.1, 1606.1, 1537.3, 1498.7, 1459.8, 1433.2, 1340.1, 1313.5, 1276.1, 1189.6, 1137.6, 1105.1, 1083.0, 1001.9. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.02 (s, 0.54 × 6H, 2 × CH_3), 2.08 (s, 0.46 × 6H, 2 × CH_3), 2.41–2.48 (m, 2H, CH_2), 4.34 (t, 0.54 × 2H, J = 6.0 Hz, CH_2), 4.83 (t, 0.46 × 2H, J = 6.0 Hz, CH_2), 6.69–6.88 (m, 2H, arom), 7.34–7.88 (m, 5H, CH and arom), 10.86 (s, 0.46 × 1H, NH), 11.07 (s, 0.54 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 54:46. Anal. Calcd for $C_{22}H_{18}F_3N_3O_2S$ (%):C, 59.32; H, 4.07; N, 9.43. Found (%): C, 59.36; H, 4.11; N, 9.32.

*5.4.12. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(2,4-dimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-chloroindolin-2-one (**5l**)*

Yield: 52%. ESI-MS: m/z, 486.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3428.8, 2938.4, 2830.2, 1702.1, 1670.5, 1615.1, 1585.0, 1523.3, 1492.8, 1465.7, 1418.7, 1385.7, 1360.5, 1317.1, 1298.6, 1263.5, 1222.9, 1178.2, 1154.3, 1137.9, 1044.0. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.01 (s, 0.80 × 6H, 2 × CH_3), 2.08 (s, 0.20 × 6H, 2 × CH_3), 2.43 (t, 2H, J = 6.3 Hz, CH_2), 3.80 (s, 0.80 × 3H, CH_3), 3.81 (s, 0.20 × 3H, CH_3), 3.87 (s, 0.80 × 3H, CH_3), 3.89 (s, 0.20 × 3H, CH_3), 4.38 (t, 0.80 × 2H, J = 6.3 Hz, CH_2), 4.87 (t, 0.20 × 2H, J = 6.3 Hz, CH_2), 6.88–7.22 (m, 5H, arom), 7.51 (d, 0.80 × 1H, J = 6.0 Hz, arom), 7.68 (d, 0.20 × 1H, J = 6.0 Hz, arom), 7.91 (s, 0.80 × 1H, CH), 7.98 (s, 0.20 × 1H, CH), 10.66 (s, 0.20 × 1H, NH), 10.84 (s, 0.80 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 80:20. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.3, 153.2, 152.6, 149.0, 139.5, 127.1, 125.0, 123.4, 123.1, 122.9, 121.1, 120.5, 116.5, 114.7, 113.0, 109.9, 102.1, 56.4, 55.7, 55.6, 45.3, 44.9. Anal. Calcd for $C_{24}H_{24}ClN_3O_4S$ (%):C, 59.31; H, 4.98; N, 8.65. Found (%): C, 59.35; H, 4.52; N, 8.55.

*5.4.13. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(2,4-dimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**5m**)*

Yield: 50%. ESI-MS: m/z, 470.2 $[M + H]^+$. IR (KBr) cm^{-1}: 3430.3, 2944.4, 2832.3, 1701.3, 1676.3, 1610.9, 1586.2, 1531.1, 1493.8, 1466.6, 1430.5, 1384.6, 1370.9, 1330.8, 1284.8, 1264.6, 1224.9, 1203.4, 1169.0, 1143.0, 1043.9, 1009.5. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.09 (s, 0.71 × 6H, 2 × CH_3), 2.13 (s, 0.29 × 6H, 2 × CH_3), 2.43–2.49 (m, 2H, CH_2), 3.80 (s, 0.71 × 3H, CH_3), 3.85 (s, 0.29 × 3H, CH_3), 3.86 (s, 0.71 × 3H, CH_3), 3.91 (s, 0.29 × 3H, CH_3), 4.30 (t, 0.71 × 2H, J = 6.6 Hz, CH_2), 4.86 (t, 0.29 × 2H, J = 6.9 Hz, CH_2), 6.83–7.36 (m, 5H, arom), 7.73 (s, 0.71 × 1H, arom), 7.80 (s, 0.29 × 1H, arom), 7.92 (s, 0.71 × 1H, CH), 7.98 (s, 0.29 × 1H, CH), 10.80 (s, 0.29 × 1H, NH), 10.98 (s, 0.71 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 71:29. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.3, 168.1, 153.2, 152.7, 151.2, 138.4, 129.3, 125.9, 125.3, 122.9, 122.5, 122.4, 116.8, 114.7, 113.8, 113.5, 113.1, 111.5, 100.6, 56.4, 55.8, 55.7, 45.2, 44.6. Anal. Calcd for $C_{24}H_{24}FN_3O_4S$ (%):C, 61.39; H, 5.15; N, 8.95. Found (%): C, 61.35; H, 5.02; N, 8.82.

*5.4.14. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(2,5-dimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**5n**)*

Yield: 46%. ESI-MS: m/z, 470.2 $[M + H]^+$. IR (KBr) cm^{-1}: 3421.1, 3124.4, 2960.6, 2831.3, 2773.5, 1699.3, 1673.9, 1626.2, 1599.1, 1524.1, 1495.5, 1462.2, 1385.7, 1359.8, 1322.2, 1294.0, 1265.4, 1225.0, 1176.1, 1139.4, 1097.8, 1045.0, 1025.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.00 (s, 0.74 × 6H, 2 × CH_3), 2.09 (s, 0.26 × 6H, 2 × CH_3), 2.34–2.49 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.33 (t, 0.74 × 2H, J = 6.3 Hz, CH_2), 4.83 (t, 0.26 × 2H, J = 6.6 Hz, CH_2), 6.74–7.66 (m, 6H, arom), 7.90 (s, 0.74 × 1H, CH), 7.96 (s, 0.26 × 1H, CH), 10.82 (s, 0.26 × 1H, NH), 11.00 (s, 0.74 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 74:26. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.9, 168.2, 153.3, 153.2, 152.6, 148.9, 125.2, 124.8, 123.0, 122.7, 122.4, 117.1, 116.6, 114.7, 113.1, 107.5, 107.2, 101.2, 56.4, 55.8, 55.6, 45.2, 44.8. Anal. Calcd for $C_{24}H_{24}FN_3O_4S$ (%):C, 61.39; H, 5.15; N, 8.95. Found (%): C, 61.34; H, 5.08; N, 8.89.

*5.4.15. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(2,5-dimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)indolin-2-one (**5o**)*

Yield: 44%. ESI-MS: m/z, 452.2 $[M + H]^+$. IR (KBr) cm^{-1}: 3427.8, 2940.8, 2831.0, 1677.6, 1614.7, 1584.8, 1526.9, 1493.0, 1465.2, 1386.0, 1361.2, 1317.8, 1295.9, 1265.4, 1223.8, 1179.7, 1154.9, 1139.5, 1098.9,

1044.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.07 (s, 6H, 2 × CH_3), 2.34–2.49 (m, 2H, CH_2), 3.80 (s, 0.88 × 3H, CH_3), 3.81 (s, 0.12 × 3H, CH_3), 3.87 (s, 0.88 × 3H, CH_3), 3.89 (s, 0.12 × 3H, CH_3), 4.40 (t, 0.88 × 2H, J = 6.0 Hz, CH_2), 4.87 (t, 0.12 × 2H, J = 6.0 Hz, CH_2), 6.88–7.72 (m, 7H, arom), 7.91 (s, 0.88 × 1H, CH), 7.98 (s, 0.12 × 1H, CH), 10.70 (s, 0.12 × 1H, NH), 10.85 (s, 0.88 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 88:12. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.3, 153.2, 152.6, 149.0, 139.5, 127.1, 125.0, 123.4, 123.1, 122.9, 121.1, 120.5, 116.5, 114.7, 113.0, 109.9, 102.1, 56.4, 55.8, 55.7, 45.4, 45.3. Anal. Calcd for $C_{24}H_{25}N_3O_4S$ (%):C, 63.84; H, 5.58; N, 9.31. Found (%): C, 63.74; H, 5.50; N, 9.35.

*5.4.16. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)indolin-2-one (**5p**)*

Yield: 70%. ESI-MS: m/z, 436.1 [M + H]$^+$. IR (KBr) cm^{-1}: 3428.8, 3147.5, 3027.1, 2893.2, 2824.6, 1714.8, 1676.4, 1618.2, 1585.8, 1526.5, 1501.3, 1487.8, 1467.6, 1447.4, 1370.0, 1340.8, 1313.2, 1287.0, 1263.8, 1209.0, 1148.8, 1103.5, 1039.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.02 (s, 0.60 × 6H, 2 × CH_3), 2.10 (s, 0.40 × 6H, 2 × CH_3), 2.41–2.49 (m, 2H, CH_2), 4.37 (t, 0.60 × 2H, J = 6.0 Hz, CH_2), 4.87 (t, 0.40 × 2H, J = 6.0 Hz, CH_2), 6.15 (s, 2H, CH_2), 6.88–7.79 (m, 8H, CH and arom), 10.66 (s, 0.40 × 1H, NH), 10.87 (s, 0.60 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 60:40. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.3, 149.1, 148.3, 139.4, 131.2, 128.2, 127.0, 126.5, 126.2, 123.3, 121.0, 120.5, 120.2, 109.9, 109.6, 109.3, 102.2, 101.8, 55.7, 45.3, 44.8. Anal. Calcd for $C_{23}H_{21}N_3O_4S$ (%): C, 63.43; H, 4.86; N, 9.65. Found (%): C, 63.54; H, 4.92; N, 9.70.

*5.4.17. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**5q**)*

Yield: 74%. ESI-MS: m/z, 450.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3420.1, 2920.7, 2823.2, 1689.9, 1672.9, 1620.0, 1586.8, 1527.3, 1502.5, 1487.4, 1447.6, 1385.9, 1357.4, 1312.2, 1261.7, 1211.7, 1154.1, 1125.2, 1104.0, 1037.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.05 (s, 0.52 × 6H, 2 × CH_3), 2.06 (s, 0.48 × 6H, 2 × CH_3), 2.32 (s, 0.52 × 3H, CH_3), 2.38 (s, 0.48 × 3H, CH_3), 2.41–2.46 (m, 2H, CH_2), 4.36 (t, 0.52 × 2H, J = 6.0 Hz, CH_2), 4.86 (t, 0.48 × 2H, J = 6.0 Hz, CH_2), 6.15 (s, 0.52 × 2H, CH_2), 6.16 (s, 0.48 × 2H, CH_2), 6.76–7.55 (m, 6H, arom), 7.74 (s, 0.52 × 1H, CH), 7.78 (s, 0.48 × 1H, CH), 10.54 (s, 0.48 × 1H, NH), 10.74 (s, 0.52 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 52:48. Anal. Calcd for $C_{24}H_{23}N_3O_4S$ (%):C, 64.13; H, 5.16; N, 9.35. Found (%): C, 64.19; H, 5.20; N, 9.29.

*5.4.18. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**5r**)*

Yield: 68%. ESI-MS: m/z, 454.5 [M + H]$^+$. IR (KBr) cm^{-1}: 3422.2, 3131.3, 2973.3, 2826.0, 2773.5, 1694.2, 1625.5, 1600.7, 1526.4, 1502.2, 1448.7, 1384.8, 1359.8, 1319.3, 1288.5, 1262.1, 1213.6, 1165.6, 1141.2, 1126.9, 1101.2, 1038.0. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.02 (s, 6H, 2 × CH_3), 2.39–2.48 (m, 2H, CH_2), 4.35 (t, 0.92 × 2H, J = 6.0 Hz, CH_2), 4.84 (t, 0.08 × 2H, J = 6.0 Hz, CH_2), 6.16 (s, 2H, CH_2), 6.72–7.56 (m, 6H, arom), 7.68 (s, 0.92 × 1H, CH), 7.79 (s, 0.08 × 1H, CH), 10.81 (s, 0.08 × 1H, NH), 11.03 (s, 0.92 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 92:8. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.9, 168.3, 149.6, 149.1, 148.3, 141.0, 131.4, 128.2, 126.3, 124.7, 120.0, 117.1, 116.6, 109.7, 109.4, 107.5, 107.2, 102.2, 100.9, 55.6, 45.2, 44.9. Anal. Calcd for $C_{23}H_{20}FN_3O_4S$ (%): C, 60.92; H, 4.45; N, 9.27. Found (%): C, 61.02; H, 4.39; N, 9.32.

*5.4.19. (2(Z/E), 5Z)-3-(3-(2-(dimethylamino)ethyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (**5s**)*

Yield: 55%. ESI-MS: m/z, 500.2 [M + H]$^+$. IR (KBr) cm^{-1}: 2939.2, 2826.4, 2769.3, 1701.7, 1601.6, 1575.0, 1527.5, 1502.9, 1479.1, 1463.0, 1431.9, 1321.5, 1243.0, 1214.0, 1188.4, 1134.2, 1015.9. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.06 (s, 0.72 × 6H, 2 × CH_3), 2.10 (s, 0.28 × 6H, 2 × CH_3), 2.41–2.49 (m, 2H, CH_2), 3.76 (s, 6H, CH_3), 3.87 (s, 0.72 × 3H, CH_3), 3.90 (s, 0.28 × 3H, CH_3), 4.33 (t, 0.72 × 2H, J = 6.0 Hz, CH_2), 4.88 (t, 0.28 × 2H, J = 6.0 Hz, CH_2), 6.83–7.03 (m, 2H, arom), 7.05 (s, 0.72 × 2H, arom), 7.07 (s, 0.28 × 2H, arom), 7.41 (d, 0.72 × 1H, J = 10.5 Hz, arom), 7.50 (d, 0.28 × 1H, J = 9.9 Hz, arom), 7.69 (s, 0.72 × 1H, CH), 7.83 (s, 0.28 × 1H, CH), 10.68 (s, 0.28 × 1H, NH), 10.79 (s, 0.72 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 72:28. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.0, 153.5, 153.4, 139.9, 139.6, 136.0, 135.7, 133.1, 132.1, 129.4, 128.8, 121.6, 118.0, 110.6, 110.4, 108.4, 108.1, 60.5, 56.3, 56.2, 55.5, 44.9, 44.2. Anal. Calcd for $C_{25}H_{26}FN_3O_5S$ (%):C, 60.11; H, 5.25; N, 8.41. Found (%): C, 60.16; H, 5.32; N, 8.49.

*5.4.20. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene) indolin-2-one (**10a**)*

Yield: 65%. ESI-MS: m/z, 478.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3430.1, 2966.4, 1688.5, 1615.4, 1586.1, 1527.0, 1501.2, 1488.0, 1466.9, 1447.0, 1383.2, 1340.5, 1317.1, 1262.9, 1196.2, 1148.9, 1102.5, 1036.6. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.75 (t, 0.65 × 6H, J = 7.2 Hz, 2 × CH_3), 0.85 (t, 0.35 × 6H, J = 7.2 Hz, 2 × CH_3), 1.67–1.78 (m, 2H, CH_2), 2.19–2.42 (m, 6H, 3 × CH_2), 4.32 (t, 0.65 × 2H, J = 7.2 Hz, CH_2), 4.66 (t, 0.35 × 2H, J = 6.9 Hz, CH_2), 6.15 (s, 0.65 × 2H, CH_2), 6.16 (s, 0.35 × 2H, CH_2), 6.86–7.35 (m, 6H, arom), 7.47 (d, 0.65 × 1H, J = 7.2 Hz, arom), 7.68 (s, 0.65 × 1H, CH), 7.78 (s, 0.35 × 1H, CH), 7.80 (d, 0.35 × 1H, J = 6.6 Hz, arom),10.63 (s, 0.35 × 1H, NH), 10.84 (s, 0.65 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 65:35. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.1, 149.0, 148.6, 148.2, 139.3, 131.0, 128.2, 126.8, 126.1, 123.2, 120.8, 120.6, 120.2, 109.7, 109.5, 109.3, 102.1, 101.9, 49.2, 46.1, 45.9, 24.6, 11.2. Anal. Calcd for $C_{26}H_{27}N_3O_4S$ (%):C, 65.39; H, 5.70; N, 8.80. Found (%): C, 65.26; H, 5.56; N, 8.72.

*5.4.21. (2(Z/E),5Z)-3-(3-(3-(diethylamino)propyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**10b**)*

Yield: 63%. ESI-MS: m/z, 492.3[M + H]$^+$. IR (KBr) cm^{-1}: 3422.5, 3152.5, 3029.6, 2966.9, 1697.7, 1674.1, 1620.9, 1587.0, 1521.6, 1500.3, 1485.4, 1447.3, 1430.7, 1363.8, 1333.7, 1313.6, 1248.5, 1205.9, 1153.4, 1092.4, 1037.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.77 (t, 0.60 × 6H, J = 7.2 Hz, 2 × CH_3), 0.85 (t, 0.40 × 6H, J = 7.2 Hz, 2 × CH_3), 1.68–1.77 (m, 2H, CH_2), 2.22–2.42 (m, 9H, 3 × CH_2 and CH_3), 4.32 (t, 0.60 × 2H, J = 7.2 Hz, CH_2), 4.65 (t, 0.40 × 2H, J = 7.2 Hz, CH_2), 6.15 (s, 0.60 × 2H, CH_2), 6.16 (s, 0.40 × 2H, CH_2), 6.75–7.55 (m, 6H, arom), 7.67 (s, 0.60 × 1H, CH), 7.77 (s, 0.40 × 1H, CH), 10.51 (s, 0.40 × 1H, NH), 10.73 (s, 0.60 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 60:40. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.1, 148.9, 148.2, 148.1, 137.1, 130.8, 129.4, 128.2, 127.3, 126.1, 123.6, 120.7, 120.3, 109.5, 109.4, 109.2, 102.0, 49.3, 46.0, 45.4, 24.8, 21.1, 11.4.

Anal. Calcd for $C_{27}H_{29}N_3O_4S$ (%):C, 65.97; H, 5.95; N, 8.55. Found (%): C, 65.86; H, 5.83; N, 8.47.

*5.4.22. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (**10c**)*

Yield: 56%. ESI-MS: m/z, 496.5 [M + H]$^+$. IR (KBr) cm^{-1}: 3421.2, 3179.4, 2967.6, 1679.8, 1586.1, 1525.2, 1503.6, 1476.9, 1448.4, 1382.4, 1361.5, 1312.1, 1261.3, 1188.6, 1156.7, 1121.5, 1102.0, 1038.3. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.76 (t, 0.77 × 6H, J = 7.2 Hz, 2 × CH_3), 0.87 (t, 0.23 × 6H, J = 7.2 Hz, 2 × CH_3), 1.73–1.75 (m, 2H, CH_2), 2.19–2.46 (m, 6H, 3 × CH_2), 4.29 (t, 0.77 × 2H, J = 7.2 Hz, CH_2), 4.64 (t, 0.23 × 2H, J = 7.2 Hz, CH_2), 6.15 (s, 0.77 × 2H, CH_2), 6.16 (s, 0.23 × 2H, CH_2), 6.83 (dd, 0.23 × 1H, J = 8.4, 4.8 Hz, arom), 6.87 (dd, 0.77 × 1H, J = 8.4, 4.8 Hz, arom), 6.97–7.03 (m, 1H, arom), 7.15–7.60

(m, 4H, arom), 7.70 (s, 0.77 × 1H, CH), 7.80 (s, 0.23 × 1H, CH), 10.62 (s, 0.23 × 1H, NH), 10.85 (s, 0.77 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 77:23. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.0, 150.5, 149.1, 148.2, 135.4, 131.7, 128.0, 126.2, 119.9, 112.9, 112.7, 110.3, 110.1, 110.0, 109.6, 109.3, 102.1, 101.3, 49.3, 46.0, 45.9, 24.7, 11.3. Anal. Calcd for $C_{26}H_{26}FN_3O_4S$ (%):C, 63.01; H, 5.29; N, 8.48. Found (%): C, 63.08; H, 5.38; N, 8.52.

*5.4.23. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**10d**)*

Yield: 60%. ESI-MS: *m*/*z*, 496.5 [M + H]$^+$. IR (KBr) cm^{-1}: 3353.6, 3074.8, 1697.3, 1676.3, 1629.1, 1604.0, 1585.4, 1538.5, 1492.2, 1435.7, 1385.2, 1365.9, 1338.0, 1316.9, 1288.8, 1257.0, 1134.1, 1106.6, 1034.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.08 (t, 0.24 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.19 (t, 0.76 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.93–2.18 (m, 2H, CH_2), 2.88–3.23 (m, 6H, 3 × CH_2), 4.31 (t, 0.24 × 2H, *J* = 7.2 Hz, CH_2), 4.47 (t, 0.76 × 2H, *J* = 7.2 Hz, CH_2), 6.17 (s, 0.24 × 2H, CH_2), 6.18 (s, 0.76 × 2H, CH_2), 6.69–7.87 (m, 7H, CH and arom), 10.85 (s, 0.76 × 1H, NH), 11.09 (s, 0.24 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 24:76. Anal. Calcd for $C_{26}H_{26}FN_3O_4S$ (%):C, 63.01; H, 5.29; N, 8.48. Found (%): C, 63.06; H, 5.40; N, 8.55.

*5.4.24. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-((benzo[d][1,3]dioxol-5-yl)methylene)-4-oxo-2-thiazolidinylidene)-5-chloroindolin-2-one (**10e**)*

Yield: 63%. ESI-MS: *m*/*z*, 512.1[M + H]$^+$. IR (KBr) cm^{-1}: 3430.7, 2967.5, 1677.3, 1617.1, 1585.2, 1529.3, 1503.1, 1488.7, 1468.6, 1447.8, 1382.9, 1361.3, 1311.2, 1261.2, 1195.8, 1164.7, 1147.6, 1125.4, 1104.9, 1039.2. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, 0.81 × 6H, *J* = 6.9 Hz, 2 × CH_3), 0.85 (t, 0.19 × 6H, *J* = 6.9 Hz, 2 × CH_3), 1.69–1.82 (m, 2H, CH_2), 2.20–2.42 (m, 6H, 3 × CH_2), 4.27 (t, 0.81 × 2H, *J* = 7.2 Hz, CH_2), 4.62 (t, 0.19 × 2H, *J* = 7.2 Hz, CH_2), 6.16 (s, 0.81 × 2H, CH_2), 6.17 (s, 0.19 × 2H, CH_2), 6.85 (d, 0.19 × 1H, *J* = 8.4 Hz, arom), 6.89 (d, 0.81 × 1H, *J* = 8.1 Hz, arom), 7.14–7.34 (m, 4H, arom), 7.42 (d, 0.81 × 1H, *J* = 1.5 Hz, arom), 7.68 (d, 0.19 × 1H, *J* = 1.8 Hz, arom), 7.70 (s, 0.81 × 1H, CH), 7.82 (s, 0.19 × 1H, CH), 10.75 (s, 0.19 × 1H, NH), 10.97 (s, 0.81 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 81:19. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.4, 168.0, 150.9, 149.2, 148.2, 137.8, 131.9, 128.0, 126.3, 126.1, 124.9, 122.5, 122.2, 119.8, 110.8, 109.6, 109.3, 102.1, 100.5, 49.2, 46.0, 45.3, 24.6, 11.2. Anal. Calcd for $C_{26}H_{26}ClN_3O_4S$ (%):C, 60.99; H, 5.12; N, 8.21. Found (%): C, 61.05; H, 5.16; N, 8.26.

*5.4.25. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (**10f**)*

Yield: 55%. ESI-MS: *m*/*z*, 488.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3432.4, 2925.4, 1692.2, 1630.7, 1606.8, 1540.7, 1516.7, 1479.7, 1436.6, 1384.7, 1337.5, 1301.4, 1281.7, 1254.2, 1188.9, 1131.9. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.04 (t, 0.47 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.18 (t, 0.53 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.90–2.21 (m, 2H, CH_2), 2.80–3.24 (m, 6H, 3 × CH_2), 4.31 (t, 0.47 × 2H, *J* = 6.9 Hz, CH_2), 4.48 (t, 0.53 × 2H, *J* = 6.9 Hz, CH_2), 6.85–7.98 (m, 7H, CH and arom), 10.75 (s, 0.53 × 1H, NH), 10.97 (s, 0.47 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 47:53. Anal. Calcd for $C_{25}H_{24}F_3N_3O_2S$ (%):C, 61.59; H, 4.96; N, 8.62. Found (%): C, 61.64; H, 5.02; N, 8.68.

*5.4.26. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**10g**)*

Yield: 60%. ESI-MS: *m*/*z*, 488.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3433.8, 1706.0, 1628.4, 1605.1, 1545.0, 1515.9, 1436.0, 1384.6, 1342.9, 1301.2, 1281.7, 1180.8, 1133.9, 1109.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.09 (t, 0.12 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.24 (t, 0.88 × 6H, *J* = 7.2 Hz, 2 × CH_3), 2.01–2.21 (m, 2H, CH_2), 2.82–3.24 (m, 6H, 3 × CH_2), 4.32 (t, 0.12 × 2H, *J* = 6.9 Hz, CH_2), 4.48 (t, 0.88 × 2H, *J* = 6.9 Hz, CH_2), 6.71–7.94 (m, 7H, CH and arom), 10.89 (s, 0.88 × 1H, NH), 10.98 (s, 0.12 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 12:88. Anal. Calcd for $C_{25}H_{24}F_3N_3O_2S$ (%):C, 61.59; H, 4.96; N, 8.62. Found (%): C, 61.67; H, 5.05; N, 8.66.

*5.4.27. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)indolin-2-one (**10h**)*

Yield: 56%. ESI-MS: *m*/*z*, 470.1[M + H]$^+$. IR (KBr) cm^{-1}: 3429.6, 3160.9, 2967.5, 2817.5, 1706.7, 1681.5, 1607.7, 1586.4, 1533.2, 1499.0, 1468.8, 1432.4, 1382.1, 1341.7, 1276.5, 1235.6, 1195.4, 1138.5, 1104.1, 1086.8. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.76 (t, 0.80 × 6H, *J* = 6.9 Hz, 2 × CH_3), 0.87 (t, 0.20 × 6H, *J* = 6.9 Hz, 2 × CH_3), 1.74 (t, 2H, *J* = 6.0 Hz, CH_2), 2.19–2.44 (m, 6H, 3 × CH_2), 4.32 (t, 0.80 × 2H, *J* = 6.0 Hz, CH_2), 4.65 (t, 0.20 × 2H, *J* = 6.0 Hz, CH_2), 6.86–7.78 (m, 8H, CH and arom), 10.67 (s, 0.80 × 1H, NH), 10.89 (s, 0.20 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 80:20. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 167.7, 147.6, 140.0, 139.8, 139.5, 130.8, 127.2, 125.2, 123.4, 121.0, 120.4, 113.2, 112.9, 109.8, 105.1, 102.8, 49.2, 46.1, 45.9, 24.5, 11.1. Anal. Calcd for $C_{25}H_{25}F_2N_3O_2S$ (%):C, 63.95; H, 5.37; N, 8.95. Found (%): C, 64.01; H, 5.42; N, 8.98.

*5.4.28. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**10i**)*

Yield: 52%. ESI-MS: *m*/*z*, 488.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3442.9, 3174.9, 2969.3, 1705.3, 1683.2, 1605.7, 1536.4, 1499.0, 1461.4, 1432.3, 1381.7, 1341.1, 1275.7, 1194.5, 1136.6, 1104.9, 1086.8. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.76 (t, 0.80 × 6H, *J* = 6.9 Hz, 2 × CH_3), 0.88 (t, 0.20 × 6H, *J* = 6.9 Hz, 2 × CH_3), 1.73 (t, 2H, *J* = 6.0 Hz, CH_2), 2.10–2.46 (m, 6H, 3 × CH_2), 4.29 (t, 0.80 × 2H, *J* = 6.0 Hz, CH_2), 4.60 (t, 0.20 × 2H, *J* = 6.0 Hz, CH_2), 6.71–7.88 (m, 7H, CH and arom), 10.83 (s, 0.80 × 1H, NH), 11.05 (s, 0.20 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 80:20. Anal. Calcd for $C_{25}H_{24}F_3N_3O_2S$ (%):C, 61.59; H, 4.96; N, 8.62. Found (%): C, 61.65; H, 5.03; N, 8.67.

*5.4.29. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2,4-difluorobenzylidene)-4-oxo-2-thiazolidinylidene)-5-chloroindolin-2-one (**10j**)*

Yield: 59%. ESI-MS: *m*/*z*, 504.1 [M + H]$^+$. IR (KBr) cm^{-1}: 3420.7, 3159.3, 3045.4, 2968.7, 1699.9, 1681.9, 1606.9, 1529.1, 1499.7, 1473.3, 1433.9, 1379.7, 1330.2, 1276.8, 1241.9, 1194.9, 1173.8, 1138.2, 1086.3, 1013.8. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, 0.82 × 6H, *J* = 6.9 Hz, 2 × CH_3), 0.88 (t, 0.18 × 6H, *J* = 6.9 Hz, 2 × CH_3), 1.78 (t, 2H, *J* = 6.3 Hz, CH_2), 2.20–2.46 (m, 6H, 3 × CH_2), 4.27 (t, 0.80 × 2H, *J* = 6.3 Hz, CH_2), 4.61 (t, 0.20 × 2H, *J* = 6.3 Hz, CH_2), 6.79–7.86 (m, 7H, CH and arom), 10.83 (s, 0.82 × 1H, NH), 11.02 (s, 0.18 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 82:18. Anal. Calcd for $C_{25}H_{24}ClF_2N_3O_2S$ (%): C, 59.58; H, 4.80; N, 8.34. Found (%): C, 59.63; H, 4.85; N, 8.40.

*5.4.30. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)indolin-2-one (**10k**)*

Yield: 52%. ESI-MS: *m*/*z*, 524.2 [M + H]$^+$. IR (KBr) cm^{-1}: 3169.4, 2966.6, 2831.6, 1698.5, 1676.5, 1602.6, 1575.7, 1531.2, 1502.0, 1466.7, 1420.7, 1381.9, 1333.0, 1310.9, 1238.8, 1193.9, 1133.9, 1103.8, 1032.8, 1007.7. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.75 (t, 0.67 × 6H, *J* = 7.2 Hz, 2 × CH_3), 0.86 (t, 0.33 × 6H, *J* = 7.2 Hz, 2 × CH_3), 1.68–1.78 (m, 2H, CH_2), 2.22–2.40 (m, 6H, 3 × CH_2), 3.75 (s, 3H, CH_3), 3.85 (s, 0.67 × 3H, CH_3), 3.86 (s, 0.67 × 3H, CH_3), 3.88 (s, 0.33 × 3H, CH_3), 3.89 (s, 0.33 × 3H, CH_3), 4.32 (t, 0.67 × 2H, *J* = 6.6 Hz, CH_2), 4.67 (t, 0.33 × 2H, *J* = 6.6 Hz, CH_2), 6.86–7.21 (m, 5H, arom), 7.45 (d, 0.67 × 1H, *J* = 7.8 Hz, arom), 7.68 (s, 0.67 × 1H, CH), 7.71 (d, 0.33 × 1H, *J* = 7.8 Hz, arom), 7.80 (s, 0.33 × 1H, CH), 10.63 (s, 0.33 × 1H, NH), 10.75 (s, 0.67 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 67:33. Anal. Calcd for $C_{28}H_{33}N_3O_5S$ (%):C, 64.22; H, 6.35; N, 8.02. Found (%): C, 64.26; H, 6.45; N, 8.09.

*5.4.31. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**10l**)*

Yield: 46%. ESI-MS: *m*/*z*, 538.7 $[M + H]^+$. IR (KBr) cm^{-1}: 3160.9, 2965.9, 1697.9, 1602.0, 1574.8, 1529.3, 1502.4, 1430.2, 1382.3, 1323.9, 1239.3, 1194.6, 1133.6, 1029.5, 1005.8. ^1H NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, 0.37 × 6H, J = 6.9 Hz, 2 × CH_3), 0.88 (t, 0.63 × 6H, J = 6.9 Hz, 2 × CH_3), 1.71–1.77 (m, 2H, CH_2), 2.18–2.47 (m, 9H, 3 × CH_2 and CH_3), 3.76 (s, 3H, CH_3), 3.85 (s, 0.37 × 3H, CH_3), 3.86 (s, 0.37 × 3H, CH_3), 3.90 (s, 0.63 × 3H, CH_3), 3.91 (s, 0.63 × 3H, CH_3), 4.32 (t, 0.37 × 2H, J = 6.3 Hz, CH_2), 4.67 (t, 0.63 × 2H, J = 6.3 Hz, CH_2), 6.74 (d, 0.63 × 1H, J = 7.8 Hz, arom), 6.80 (d, 0.37 × 1H, J = 7.8 Hz, arom), 6.95–7.01 (m, 1H, arom), 7.04 (s, 0.37 × 2H, arom), 7.08 (s, 0.63 × 2H, arom), 7.25 (s, 0.37 × 1H, arom), 7.56 (s, 0.63 × 1H, arom), 7.67 (s, 0.37 × 1H, CH), 7.77 (s, 0.63 × 1H, CH), 10.52 (s, 0.63 × 1H, NH), 10.64 (s, 0.37 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 37:63. Anal. Calcd for $C_{29}H_{35}N_3O_5S$ (%): C, 64.78; H, 6.56; N, 7.82. Found (%): C, 64.75; H, 6.46; N, 7.76.

*5.4.32. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-fluoroindolin-2-one (**10m**)*

Yield: 55%. ESI-MS: *m*/*z*, 542.3 $[M + H]^+$. IR (KBr) cm^{-1}: 3416.8, 2966.8, 1703.2, 1676.7, 1601.6, 1575.2, 1527.8, 1502.2, 1478.6, 1429.7, 1382.5, 1322.8, 1241.4, 1190.4, 1132.9, 1023.8. ^1H NMR (300 MHz, DMSO-d_6) δ: 0.76 (t, 0.77 × 6H, J = 6.9 Hz, 2 × CH_3), 0.87 (t, 0.23 × 6H, J = 6.9 Hz, 2 × CH_3), 1.72–1.76 (m, 2H, CH_2), 2.24–2.44 (m, 6H, 3 × CH_2), 3.76 (s, 3H, CH_3), 3.85 (s, 0.77 × 3H, CH_3), 3.86 (s, 0.77 × 3H, CH_3), 3.88 (s, 0.23 × 3H, CH_3), 3.89 (s, 0.23 × 3H, CH_3), 4.30 (t, 0.77 × 2H, J = 6.9 Hz, CH_2), 4.66 (t, 0.23 × 2H, J = 6.9 Hz, CH_2), 6.82–7.02 (m, 2H, arom), 7.06 (s, 0.77 × 2H, arom), 7.08 (s, 0.23 × 2H, arom), 7.27 (dd, 0.77 × 1H, J = 10.5, 1.8 Hz, arom), 7.48 (dd, 0.23 × 1H, J = 10.2, 2.1 Hz, arom), 7.71 (s, 0.77 × 1H, CH), 7.83 (s, 0.23 × 1H, CH), 10.65 (s, 0.23 × 1H, NH), 10.76 (s, 0.77 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 77:23. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 167.9, 153.5, 153.2, 150.4, 139.4, 135.6, 131.8, 129.4, 128.8, 121.5, 121.4, 110.5, 110.1, 108.2, 107.9, 101.5, 60.3, 56.1, 49.2, 46.1, 46.0, 24.7, 11.2. Anal. Calcd for $C_{28}H_{32}FN_3O_5S$ (%): C, 62.09; H, 5.95; N, 7.76. Found (%): C, 62.02; H, 5.87; N, 7.72.

*5.4.33. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-6-fluoroindolin-2-one (**10n**)*

Yield: 50%. ESI-MS: *m*/*z*, 542.3 $[M + H]^+$. IR (KBr) cm^{-1}: 3427.6, 2968.3, 1700.0, 1626.8, 1601.6, 1575.4, 1531.2, 1501.8, 1462.6, 1420.2, 1383.6, 1332.8, 1240.0, 1193.5, 1133.4, 1105.3, 1008.6. ^1H NMR (300 MHz, DMSO-d_6) δ: 0.75 (t, 0.75 × 6H, J = 7.2 Hz, 2 × CH_3), 0.86 (t, 0.25 × 6H, J = 7.2 Hz, 2 × CH_3), 1.66–1.76 (m, 2H, CH_2), 2.21–2.40 (m, 6H, 3 × CH_2), 3.75 (s, 3H, CH_3), 3.85 (s, 0.75 × 3H, CH_3), 3.86 (s, 0.75 × 3H, CH_3), 3.88 (s, 0.25 × 3H, CH_3), 3.89 (s, 0.25 × 3H, CH_3), 4.30 (t, 0.75 × 2H, J = 6.6 Hz, CH_2), 4.64 (t, 0.25 × 2H, J = 6.0 Hz, CH_2), 6.68–6.90 (m, 2H, arom), 7.05 (s, 2H, arom), 7.46–7.50 (m, 0.75 × 1H, arom), 7.69 (s, 0.75 × 1H, CH), 7.71–7.73 (m, 0.25 × 1H, arom), 7.80 (s, 0.25 × 1H, CH), 10.78 (s, 0.25 × 1H, NH), 10.91 (s, 0.75 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 75:25. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.9, 167.9, 153.3, 153.2, 148.4, 141.0, 140.8, 139.3, 131.3, 129.4, 124.6, 121.6, 118.4, 117.2, 108.1, 107.0, 101.2, 60.3, 56.1, 49.2, 46.1, 45.9, 24.6, 11.2. Anal. Calcd for $C_{28}H_{32}FN_3O_5S$ (%): C, 62.09; H, 5.95; N, 7.76. Found (%): C, 62.04; H, 5.89; N, 7.74.

*5.4.34. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(3,4,5-trimethoxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-chloroindolin-2-one (**10o**)*

Yield: 45%. ESI-MS: *m*/*z*, 558.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3155.9, 2965.5, 1704.8, 1679.4, 1601.9, 1574.8, 1524.6, 1501.4, 1468.8, 1430.5, 1382.1, 1322.9, 1238.0, 1192.7, 1166.3, 1133.0, 1014.3. ^1H NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, 0.70 × 6H, J = 6.9 Hz, 2 × CH_3), 0.88 (t, 0.30 × 6H, J = 6.9 Hz, 2 × CH_3), 1.71–1.78 (m, 2H, CH_2), 2.23–2.45 (m, 6H, 3 × CH_2), 3.76 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.26 (t, 0.70 × 2H, J = 6.9 Hz, CH_2), 4.64 (t, 0.30 × 2H, J = 6.6 Hz, CH_2), 6.83 (d, 0.30 × 1H, J = 8.1 Hz, arom), 6.90 (d, 0.70 × 1H, J = 8.4 Hz, arom), 7.04 (s, 0.70 × 2H, arom), 7.07 (s, 0.30 × 2H, arom), 7.15 (d, 0.30 × 1H, J = 8.1 Hz, arom), 7.20 (d, 0.70 × 1H, J = 8.4 Hz, arom), 7.42 (s, 0.70 × 1H, arom), 7.68 (s, 0.30 × 1H, arom), 7.70 (s, 0.70 × 1H, CH), 7.79 (s, 0.30 × 1H, CH), 10.75 (s, 0.30 × 1H, NH), 10.87 (s, 0.70 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 70:30. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.4, 167.9, 153.6, 153.4, 153.3, 150.8, 139.5, 138.0, 132.0, 129.4, 126.2, 125.7, 124.9, 122.5, 122.2, 110.9, 108.3, 100.7, 60.4, 56.2, 49.3, 46.2, 46.1, 25.0, 11.5. Anal. Calcd for $C_{28}H_{32}ClN_3O_5S$ (%): C, 60.26; H, 5.78; N, 7.53. Found (%): C, 60.20; H, 5.83; N, 7.61.

*5.4.35. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(4-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**10p**)*

Yield: 38%. ESI-MS: *m*/*z*, 464.6 $[M + H]^+$. IR (KBr) cm^{-1}: 3427.4, 1689.9, 1587.1, 1535.6, 1512.9, 1484.7, 1434.2, 1386.6, 1337.2, 1285.5, 1254.4, 1211.8, 1173.1, 1136.3, 1084.9, 1034.4. ^1H NMR (300 MHz, DMSO-d_6) δ: 0.98 (t, 0.47 × 6H, J = 6.9 Hz, 2 × CH_3), 1.15 (t, 0.53 × 6H, J = 6.9 Hz, 2 × CH_3), 1.91–2.09 (m, 2H, CH_2), 2.33 (s, 0.47 × 3H, CH_3), 2.39 (s, 0.53 × 3H, CH_3), 2.70–3.20 (m, 6H, 3 × CH_2), 4.34 (t, 0.47 × 2H, J = 6.9 Hz, CH_2), 4.49 (t, 0.53 × 2H, J = 6.6 Hz, CH_2), 6.80–7.77 (m, 8H, CH and arom), 8.99 (s, 1H, OH), 10.57 (s, 0.53 × 1H, NH), 10.77 (s, 0.47 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 47:53. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.4, 159.8, 148.5, 137.2, 132.8, 129.7, 127.4, 124.9, 124.3, 123.6, 120.7, 118.1, 116.7, 109.5, 102.7, 48.5, 46.4, 45.8, 21.4, 21.1, 9.0. Anal. Calcd for $C_{26}H_{29}N_3O_3S$ (%): C, 67.36; H, 6.31; N, 9.06. Found (%): C, 67.29; H, 6.26; N, 9.03.

*5.4.36. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)indolin-2-one (**10q**)*

Yield: 35%. ESI-MS: *m*/*z*, 450.2 $[M + H]^+$. IR (KBr) cm^{-1}: 3379.1, 1692.2, 1616.7, 1591.0, 1533.8, 1480.9, 1454.9, 1434.6, 1387.4, 1344.2, 1313.1, 1259.5, 1188.4, 1140.8, 1029.2. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.07 (t, 0.40 × 6H, J = 6.9 Hz, 2 × CH_3), 1.18 (t, 0.60 × 6H, J = 6.9 Hz, 2 × CH_3), 2.00–2.14 (m, 2H, CH_2), 2.90–3.20 (m, 6H, 3 × CH_2), 4.35 (t, 0.40 × 2H, J = 6.3 Hz, CH_2), 4.52 (t, 0.60 × 2H, J = 6.0 Hz, CH_2), 6.89–7.85 (m, 8H, arom), 8.20 (s, 0.60 × 1H, CH), 8.23 (s, 0.40 × 1H, CH), 9.00 (s, 1H, OH), 10.66 (s, 0.60 × 1H, NH), 10.89 (s, 0.40 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 40:60. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.5, 159.1, 149.5, 139.3, 132.3, 129.2, 128.9, 128.2, 126.3, 124.1, 123.0, 121.0, 118.8, 118.5, 115.9, 109.8, 102.1, 48.3, 46.5, 43.9, 23.1, 8.6. Anal. Calcd for $C_{25}H_{27}N_3O_3S$ (%): C, 66.79; H, 6.05; N, 9.35. Found (%): C, 66.69; H, 6.01; N, 9.28.

*5.4.37. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2-hydroxybenzylidene)-4-oxo-2-thiazolidinylidene)-5-methylindolin-2-one (**10r**)*

Yield: 40%. ESI-MS: *m*/*z*, 464.3 $[M + H]^+$. IR (KBr) cm^{-1}: 3377.2, 3031.7, 1689.4, 1592.7, 1532.4, 1483.7, 1433.4, 1387.9, 1337.6, 1260.0, 1206.5, 1169.8, 1140.6, 1028.3. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.07 (t, 0.44 × 6H, J = 6.9 Hz, 2 × CH_3), 1.18 (t, 0.56 × 6H, J = 6.9 Hz, 2 × CH_3), 2.00–2.14 (m, 2H, CH_2), 2.35 (s, 0.44 × 3H, CH_3), 2.36 (s, 0.56 × 3H, CH_3), 2.90–3.19 (m, 6H, 3 × CH_2), 4.37 (t, 0.44 × 2H, J = 7.2 Hz, CH_2), 4.52 (t, 0.56 × 2H, J = 7.2 Hz, CH_2), 6.76 (d, 0.56 × 1H, J = 7.8 Hz, arom), 6.82 (d, 0.44 × 1H, J = 7.8 Hz, arom), 6.89–7.67 (m, 6H, arom), 8.12 (s, 0.56 × 1H, CH), 8.23 (s, 0.44 × 1H, CH), 9.00 (s, 1H, OH), 10.51 (s, 0.56 × 1H, NH), 10.75 (s, 0.44 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 44:56. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 168.1, 158.7, 149.4, 137.1, 132.2, 130.6, 129.7, 128.2, 126.7,

124.2, 122.8, 120.7, 118.7, 118.4, 116.4, 108.9, 102.2, 48.3, 46.5, 45.6, 23.0, 21.1, 8.6. Anal. Calcd for $C_{26}H_{29}N_3O_3S$ (%): C, 67.36; H, 6.31; N, 9.06. Found (%): C, 67.31; H, 6.28; N, 9.02.

*5.4.38. (2(Z/E), 5Z)-3-(3-(3-(diethylamino)propyl)-5-(2-hydroxy benzylidene)-4-oxo-2-thiazolidinylidene)-5-bromoindolin-2-one (**10s**)*

Yield: 33%. ESI-MS: *m*/*z*, 528.1 $[M + H]^+$. IR (KBr) cm^{-1}: 3384.6, 3040.9, 1701.2, 1665.6, 1594.2, 1534.7, 1469.2, 1436.3, 1388.8, 1338.7, 1302.6, 1262.1, 1236.2, 1208.1, 1191.7, 1166.1, 1143.0, 1091.7, 1052.9, 1007.5. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.08 (t, 0.45 × 6H, $J = 6.6$ Hz, 2 × CH_3), 1.18 (t, 0.55 × 6H, $J = 6.6$ Hz, 2 × CH_3), 1.93–2.21 (m, 2H, CH_2), 2.85–3.24 (m, 6H, 3 × CH_2), 4.29 (t, 0.45 × 2H, $J = 7.2$ Hz, CH_2), 4.48 (t, 0.55 × 2H, $J = 7.2$ Hz, CH_2), 6.82–7.86 (m, 7H, arom), 8.19 (s, 0.55 × 1H, CH), 8.25 (s, 0.45 × 1H, CH), 8.99 (s, 1H, OH), 10.77 (s, 0.55 × 1H, NH), 11.01 (s, 0.45 × 1H, NH). (2Z, 5Z)/(2E, 5Z) ratio (%) 45:55. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.3, 168.0, 159.1, 149.2, 138.2, 132.0, 131.4, 129.9, 128.4, 126.2, 123.8, 122.7, 118.8, 118.2, 115.6, 112.6, 111.4, 100.7, 48.3, 46.5, 45.8, 23.0, 8.6. Anal. Calcd for $C_{25}H_{26}BrN_3O_3S$ (%): C, 56.82; H, 4.96; N, 7.95. Found (%): C, 56.87; H, 5.02; N, 7.98.

5.5. Cytotoxicity assay in vitro

The cytotoxic activities of target compounds were evaluated with HT-29, H460, MDA-MB-231, SMMC-7721 cancer cell lines and WI-38 normal cell lines by the standard MTT assay *in vitro*, with sunitinib as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum (FBS). Approximately 4 × 10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The test compounds at indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μL DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested three times in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.05.017.

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