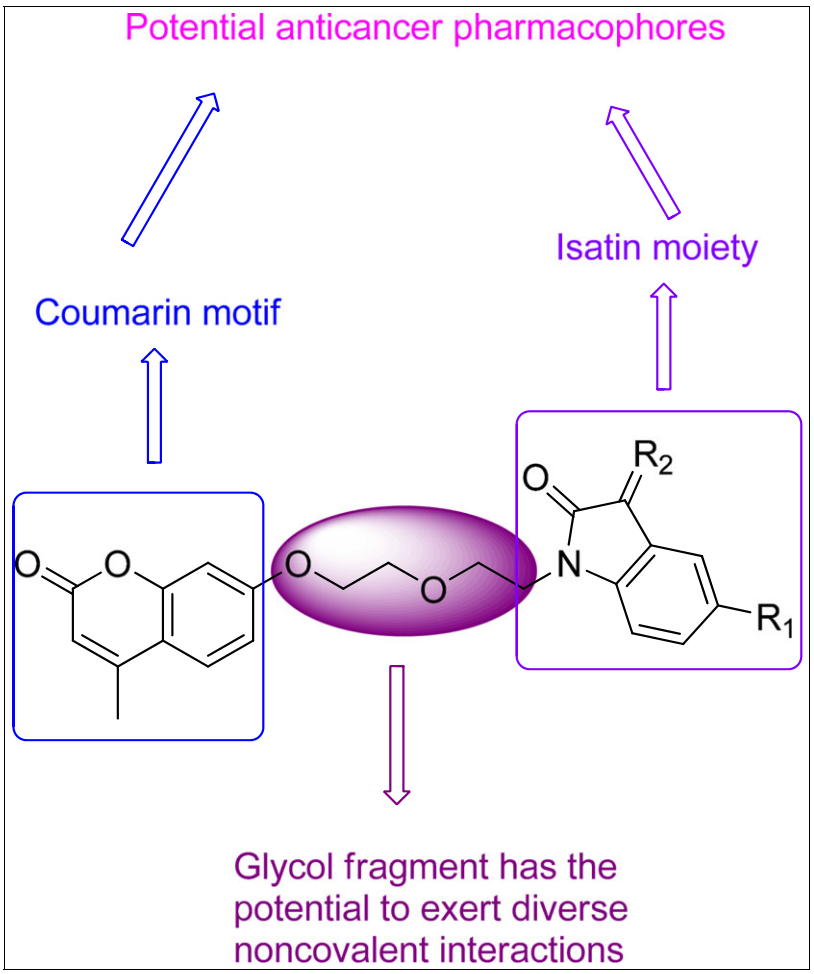
Isatin–Coumarin Hybrids Tethered *via* Diethylene Glycol: Design, Synthesis, and Their *In Vitro* Antitumor Activities

Yi-Lei Fan,[a]* Zhong-Ping Huang,[b] and Min Liu[c]

[a]Key Laboratory of Drug Prevention and Control Technology of Zhejiang Province, Zhejiang Police College, Hangzhou, People's Republic of China
[b]College of Chemical Engineering, Zhejiang University of Technology, Hangzhou, People's Republic of China
[c]College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, People's Republic of China
*E-mail: fanyilei@zjjcxy.cn

Received July 24, 2018
DOI 10.1002/jhet.3329
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel isatin–coumarin hybrids was designed, synthesized, and assessed for their *in vitro* antitumor activities against drug-sensitive HepG2, Hela, A549, DU145 (prostatic cancer), SKOV3, and MCF-7 as well as drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) human cancer cell lines. Results revealed that the synthesized hybrids displayed considerable activities against the tested seven cancer cell lines.

INTRODUCTION

Cancer, the second leading cause of death globally, puts a heavy burden on the health care systems all over the world [1,2]. The World Health Organization has estimated that roughly 10.4 million incident cases of cancer in the year 2015 led to 8.8 million deaths [3]. What is worse, cancer cases will rise to 22 million with 13 million deaths annually within the next two decades [4]. The traditional cancer chemotherapy is limited by systemic toxicity, side effects as well as the rapid development of resistance [5–7]. Therefore, there is an urgent need to develop newer, safer, and higher effective anticancer drugs.

Isatin and coumarin which act as structural subunits of more complex natural products and drugs are ubiquitous in nature. Their derivatives exhibit diverse pharmacological properties such as antitubercular [8–10], antibacterial [11,12], antiviral [13,14], antimalarial [15,16], and anticancer [17,18] activities, occupying an important position in drug discovery. In addition to this, isatin or coumarin pharmacophore unit containing derivatives which are exemplified by sunitinb, nintedanib, semaxanib, and STX64 (Fig. 1) is under clinical trials or has already been used in clinical practice for the treatment of various cancers, suggesting that isatin and coumarin moieties are useful pharmacophores for searching new anticancer agents. [19,20]. Moreover, some isatin–coumarin hybrids demonstrated considerable *in vitro* activity against cancer cell lines, and the structure–activity relationship (SAR) revealed that the linker between isatin and coumarin influenced the activity greatly [21–23].

To optimize the linker between isatin and coumarin moieties and facilitate the further development of isatin–coumarin hybrids, a series of novel isatin–coumarin hybrids tethered *via* diethylene glycol were designed, synthesized, and screened for their *in vitro* anticancer activity against drug-sensitive HepG2, Hela, A549, DU145 (prostatic cancer), SKOV3, and MCF-7 as well as drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) human cancer cell lines in this study. The illustration of the design strategy is depicted in Figure 2.

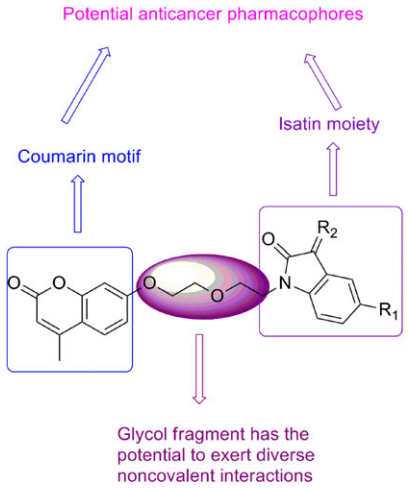


Figure 2. Schematic of design strategy on diethylene glycol tethered isatin–coumarin hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

RESULTS AND DISCUSSION

We first designed and synthesized the desired diethylene glycol tethered isatin–coumarin hybrids **7a–l** following the synthetic routes shown in Scheme 1. Treatment of diethylene glycol **1** with tosyl chloride in presence of triethylamine generated intermediate **2**, which was subsequently reacted with isatins **3** yielded the intermediates **4**. The 7-hydroxy-4-methyl-7-2*H*-chromen-2-one **6** was obtained by treatment of resorcinol **5** with ethyl acetoacetate in the presence of conc. H_2SO4. The precursors **4** and **6** were utilized for the synthesis of desired diethylene glycol tethered isatin–coumarin hybrids **7a–d** by substituted reaction in the presence of K_2CO_3 in DMF. Finally, condensations of targets **7a–d** with the requested amine hydrochlorides in the presence of sodium bicarbonate produced isatin–coumarin hybrids **7e–l** [23].

The diethylene glycol tethered isatin–coumarin hybrids **7a–l** were evaluated for their *in vitro* anticancer activities against HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer), and drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) by SRB assay [24]. IC_{50} values were presented as the concentration of drug inhibition 50% cell growth and determined by at least three separate tests and reported. The IC_{50} values of the synthesized isatin-1,2,3-triazole-coumarin hybrids along with etoposide were measured, and the results were presented in Table 1.

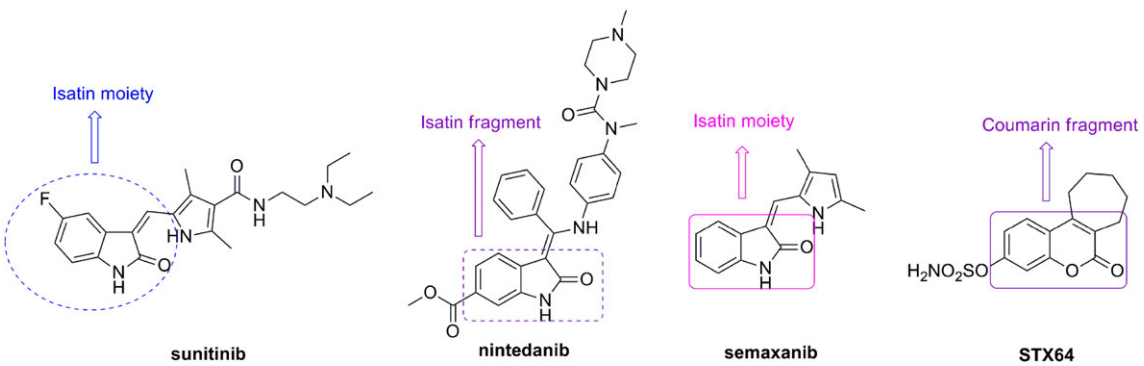
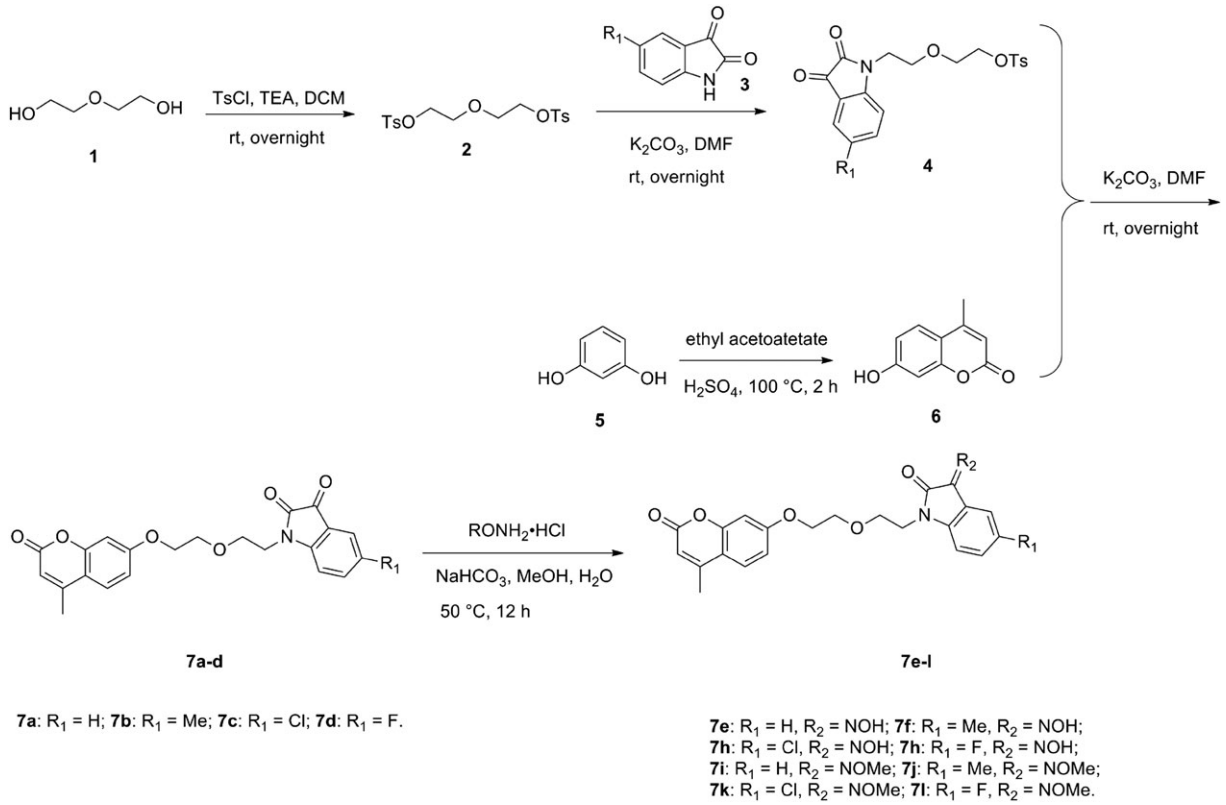


Figure 1. Chemical structures of sunitinb, nintedanib, semaxanib, and STX64. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthesis of diethylene glycol tethered isatin–coumarin hybrids **7a–l**.



7a: R_1 = H; **7b**: R_1 = Me; **7c**: R_1 = Cl; **7d**: R_1 = F.

7e: R_1 = H, R_2 = NOH; **7f**: R_1 = Me, R_2 = NOH;
7h: R_1 = Cl, R_2 = NOH; **7h**: R_1 = F, R_2 = NOH;
7i: R_1 = H, R_2 = NOMe; **7j**: R_1 = Me, R_2 = NOMe;
7k: R_1 = Cl, R_2 = NOMe; **7l**: R_1 = F, R_2 = NOMe.

Table 1

Structures and anticancer activities of isatin–coumarin hybrids **7a–l**.

	Structure		IC_{50} (μM)						
Compd.	R_1	R_2	HepG2	Hela	A549	DU145	SKOV3	MCF-7	MCF-7/DOX
7a	H	O	17.35	26.22	19.67	39.86	33.54	39.27	44.38
7b	Me	O	28.74	32.21	29.90	48.99	47.35	44.28	46.93
7c	Cl	O	15.40	29.17	14.28	33.16	36.53	29.31	19.42
7d	F	O	12.37	11.54	14.25	21.66	29.15	14.46	17.10
7e	H	NOH	15.66	29.38	14.52	24.39	18.63	26.72	15.59
7f	Me	NOH	39.71	23.64	20.09	33.97	48.32	34.78	22.16
7g	Cl	NOH	13.33	19.86	11.71	36.58	32.19	19.44	18.73
7h	F	NOH	10.28	17.39	10.92	20.80	27.36	11.29	14.45
7i	H	NOMe	33.54	29.97	36.18	27.15	39.62	44.19	48.76
7j	Me	NOMe	19.27	49.22	41.90	36.64	42.13	>50	49.97
7k	Cl	NOMe	27.53	38.41	26.92	40.34	32.55	36.53	>50
7l	F	NOMe	20.37	19.01	22.76	30.07	29.98	33.17	41.19
etoposide	-	-	6.94	>50	>50	18.66	31.79	14.38	>50

Obviously, all of the synthesized diethylene glycol tethered isatin–coumarin hybrids **7a–l** (IC_{50}: 10.28 to >50 μM) only showed weak to moderate activities against all tested seven cancer cell lines, which were less potent than the reference etoposide against most of the tested cell lines. The SAR revealed that substituents on both C-3 and C-5 positions of isatin motif affected the anticancer activity greatly: for C-5 position, electron-withdrawing -Cl and -F preferred, while electron-donating -Me disfavored; For C-3 position, hydrogen-bond donor -NOH could boost up the activity, and the relative contributions of substituents was -NOH > -O > -NOMe generally.

CONCLUSIONS

In conclusion, all of the synthesized novel diethylene glycol tethered isatin–coumarin hybrids displayed weak to moderate anticancer activities against HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer), and drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7). In spite of that, the SAR was enriched, and the enriched SAR may pave the way for further rationale design of this kind of hybrids.

EXPERIMENTAL SECTION

The general procedure for preparing targets 7a–l. The precursors **4** and **6** were prepared *via* literature methods [25–28]. A mixture of isatins **4** (1.0 mmol), coumarin **6** (1.0 mmol), and K_2CO_3 (3.0 mmol) in DMF (20 mL) was stirred at room temperature overnight. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with petroleum ether (PE) to *v* (PE):*v* (ethyl acetate/EA) = 1:1 to give the targets **7a–d**.

A mixture of amine hydrochlorides (1.5 mmol), sodium bicarbonate (2 mmol), and **7a–d** (1 mmol) in a mixture of in methanol (10 mL) and water (2 mL) was stirred at 60°C for 12 h. After cooling to room temperature, the mixture was extracted with EA (10 mL × 3). The combined organic layers were concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel) eluted with PE to *v* (PE):*v* (EA) = 1:1 to give the title hybrids **7e–l**.

1-(2-(2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl) indoline-2,3-dione (7a). Yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s, -CH_3), 3.64 (2H, t, -CH_2-), 3.69 (2H, t, -CH_2-), 3.87 (2H, t, -CH_2-), 4.36 (2H, t, -CH_2-), 6.25 (1H, s, Ar-H), 6.86 (1H, d, Ar-H), 6.99 (1H, d, Ar-H), 7.05 (1H, dt, Ar-H), 7.12 (1H, dt, Ar-H), 7.47–7.51 (2H, m, Ar-H), 7.69 (1H, d, Ar-H). ESI-MS m/z: 416 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56; Found: C, 66.89; H, 4.63; N, 3.28.

5-Methyl-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy) ethoxy)ethyl)indoline-2,3-dione (7b). Yield: 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (3H, s, -CH_3), 2.40 (3H, s, -CH_3), 3.65 (2H, t, -CH_2-), 3.68 (2H, t, -CH_2-), 3.88 (2H, t, -CH_2-), 4.39 (2H, t, -CH_2-), 6.25 (1H, s, Ar-H), 6.80 (1H, d, Ar-H), 7.05 (1H, d, Ar-H), 7.17 (1H, s, Ar-H), 7.42–7.46 (2H, m, Ar-H), 7.73 (1H, d, Ar-H). ESI-MS m/z: 430 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.20; N, 3.44; Found: C, 67.64; H, 4.99; N, 3.27.

5-Chloro-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy) ethoxy)ethyl)indoline-2,3-dione (7c). Yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (3H, s, -CH_3), 3.64 (2H, t, -CH_2-), 3.71 (2H, t, -CH_2-), 3.90 (2H, t, -CH_2-), 4.39 (2H, t, -CH_2-), 6.26 (1H, s, Ar-H), 6.81 (1H, d, Ar-H), 6.99 (1H, d, Ar-H), 7.09 (1H, s, Ar-H), 7.35 (1H, d, Ar-H), 7.59 (1H, d, Ar-H), 7.82 (1H, s, Ar-H). ESI-MS m/z: 450 $[M + H]^+$, 452 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{18}ClNO_6$: C, 61.76; H, 4.24; N, 3.27; Found: C, 61.58; H, 4.12; N, 3.11.

5-Fluoro-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy) ethoxy)ethyl)indoline-2,3-dione (7d). Yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (3H, s, -CH_3), 3.44 (2H, t, -CH_2-), 3.48 (2H, t, -CH_2-), 3.87 (2H, t, -CH_2-), 4.39 (2H, t, -CH_2-), 5.21 (2H, s, -CH_2O-), 6.26 (1H, s, Ar-H), 6.88 (1H, d, Ar-H), 7.01 (1H, d, Ar-H), 7.07 (1H, s, Ar-H), 7.16 (1H, d, Ar-H), 7.66 (1H, d, Ar-H), 7.72 (1H, s, Ar-H), 8.33 (1H, s, triazole-H). ESI-MS m/z: 434 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{18}FNO_6$: C, 64.23; H, 4.41; N, 3.40; Found: C, 64.08; H, 4.19; N, 3.26.

3-(Hydroxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7e). Yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s, -CH_3), 3.64 (2H, t, -CH_2-), 3.69 (2H, t, -CH_2-), 3.87 (2H, t, -CH_2-), 4.36 (2H, t, -CH_2-), 6.25 (1H, s, Ar-H), 6.86 (1H, d, Ar-H), 6.99 (1H, d, Ar-H), 7.06–7.10 (2H, m, Ar-H), 7.54–7.59 (2H, m, Ar-H), 7.73 (1H, d, Ar-H), 13.28 (1H, brs, NOH). ESI-MS m/z: 431 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86; Found: C, 64.49; H, 4.73; N, 6.80.

3-(Hydroxyimino)-5-methyl-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7f). Yield: 55%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (3H, s, -CH_3), 2.41 (3H, s, -CH_3), 3.65 (2H, t, -CH_2-), 3.68 (2H, t, -CH_2-), 3.88 (2H, t, -CH_2-), 4.35 (2H, t, -CH_2-), 6.26 (1H, s, Ar-H), 6.83 (1H, d, Ar-H), 7.04 (1H, d, Ar-H), 7.12 (1H, s, Ar-H), 7.32–7.35 (2H, m, Ar-H), 7.71 (1H, d, Ar-H), 13.10 (1H, brs, NOH). ESI-MS m/z: 445 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63; Found: C, 65.17; H, 5.04; N, 6.38.

5-Chloro-3-(hydroxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7g). Yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (3H, s, -CH_3), 3.63 (2H, t, -CH_2-), 3.68 (2H, t, -CH_2-), 3.89 (2H, t, -CH_2-), 4.34 (2H, t, -CH_2-), 6.26 (1H, s, Ar-H), 6.88 (1H, d, Ar-H), 6.99 (1H, d, Ar-H), 7.06 (1H, s, Ar-H), 7.32 (1H, d, Ar-H), 7.69 (1H, d, Ar-H), 7.88 (1H, s, Ar-H), 13.44 (1H, brs, NOH). ESI-MS m/z: 465 $[M + H]^+$, 467 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{19}ClN_2O_6$: C, 59.67; H, 4.32; N, 6.33; Found: C, 59.55; H, 4.03; N, 6.21.

5-Fluoro-3-(hydroxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7h). Yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (3H, s, -CH_3), 3.64 (2H, t, -CH_2-), 3.69 (2H, t, -CH_2-), 3.92 (2H,

t, -CH_2-), 4.38 (2H, t, -CH_2-), 6.28 (1H, s, Ar-H), 6.99 (1H, d, Ar-H), 7.06 (1H, d, Ar-H), 7.12(1H, s, Ar-H), 7.23 (1H, d, Ar-H), 7.65 (1H, d, Ar-H), 7.74 (1H, s, Ar-H), 13.38 (1H, brs, NOH). ESI-MS m/z: 449 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{19}FN_2O_6$: C, 61.97; H, 4.49; N, 6.57; Found: C, 61.69; H, 4.28; N, 6.31.

3-(Methoxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7i). Yield: 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (3H, s, -CH_3), 3.62 (2H, t, -CH_2-), 3.68 (2H, t, -CH_2-), 3.88 (2H, t, -CH_2-), 4.19 (3H, s, $NOCH_3$), 4.34 (2H, t, -CH_2-), 6.27 (1H, s, Ar-H), 6.94 (1H, d, Ar-H), 7.06 (1H, d, Ar-H), 7.12–7.16 (2H, m, Ar-H), 7.34 (1H, t, Ar-H), 7.72 (1H, d, Ar-H), 7.83 (1H, d, Ar-H). ESI-MS m/z: 445 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63; Found: C, 65.23; H, 5.14; N, 6.43.

3-(Methoxyimino)-5-methyl-1-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy) ethyl)indolin-2-one (7j). Yield: 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (3H, s, -CH_3), 2.40 (3H, s, -CH_3), 3.64 (2H, t, -CH_2-), 3.68 (2H, t, -CH_2-), 3.89 (2H, t, -CH_2-), 4.18 (3H, s, $NOCH_3$), 4.38 (2H, t, -CH_2-), 6.24 (1H, s, Ar-H), 6.77 (1H, d, Ar-H), 7.01 (1H, d, Ar-H), 7.14–7.16 (2H, m, Ar-H), 7.62–7.65 (2H, m, Ar-H). ESI-MS m/z: 459 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{22}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42; Found: C, 65.79; H, 5.27; N, 6.18.

5-Chloro-3-(methoxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7k). Yield: 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s, -CH_3), 3.66 (2H, t, -CH_2-), 3.71 (2H, t, -CH_2-), 3.89 (2H, t, -CH_2-), 4.24 (3H, s, $NOCH_3$), 4.40 (2H, t, -CH_2-), 6.27 (1H, s, Ar-H), 6.81 (1H, d, Ar-H), 6.98 (1H, d, Ar-H), 7.05 (1H, s, Ar-H), 7.32 (1H, d, Ar-H), 7.64 (1H, d, Ar-H), 7.81 (1H, s, Ar-H). ESI-MS m/z: 479 $[M + Na]^+$, 481 $[M + 2 + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{23}H_{21}ClN_2O_6$: C, 60.46; H, 4.63; N, 6.13; Found: C, 60.25; H, 4.44; N, 5.87.

5-Fluoro-3-(methoxyimino)-1-(2-(2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)ethoxy)ethyl)indolin-2-one (7l). Yield: 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (3H, s, -CH_3), 33.66 (2H, t, -CH_2-), 3.71 (2H, t, -CH_2-), 3.89 (2H, t, -CH_2-), 4.24 (3H, s, $NOCH_3$), 6.28(1H, s, Ar-H), 6.89 (1H, d, Ar-H), 6.99 (1H, d, Ar-H), 7.07 (1H, s, Ar-H), 7.21 (1H, d, Ar-H), 7.69 (1H, d, Ar-H), 7.74 (1H, s, Ar-H). ESI-MS m/z: 463 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{23}H_{21}FN_2O_6$: C, 62.72; H, 4.81; N, 6.36; Found: C, 62.67; H, 4.72; N, 6.14.

Antitumor activities. All the synthesized diethylene glycol tethered isatin–coumarin hybrids were investigated for their *in vitro* activity against HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer), and drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) by SRB assay [24]. IC_{50} values were presented as the concentration of drug inhibition 50% cell growth and determined by at least three separate tests and reported.

REFERENCES AND NOTES

[1] Zhang, Y. S.; Duchamp, M.; Oklu, R.; Ellisen, L. W.; Langer, R.; Khademhosseini, A. ACS Biomater Sci Eng 2016, 2, 1710.

[2] Chen, H. Y.; Liu, R. H. J Agric Food Chem 2018, 66, 3260.

[3] Comparetti, E. J.; Pedrosa, V. A.; Kaneno, R. Bioconjug Chem 2018, 29, 709.

[4] World Health Organization. Cancer control: knowledge into action. http://www.who.int/cancer/modules/en/

[5] Shah, K. N.; Ditto, A. J.; Crowder, D. C.; Overmeyer, J. H.; Tavana, H.; Maltese, W. A.; Yun, Y. H. Mol Pharm 2017, 14, 3968.

[6] Casi, G.; Neri, D. Mol Pharm 2015, 12, 1880.

[7] Ren, Q. C.; Gao, C.; Xu, Z.; Feng, L. S.; Liu, M. L.; Wu, X.; Zhao, F. Curr Top Med Chem 2018, 18, 101.

[8] Xu, Z.; Zhang, S.; Gao, C.; Zhao, F.; Lv, Z. S.; Feng, L. S. Chin Chem Lett 2017, 28, 159.

[9] Zhang, S.; Xu, Z.; Gao, C.; Ren, Q. C.; Le, C.; Lv, Z. S.; Feng, L. S. Eur J Med Chem 2017, 138, 501.

[10] Hu, Y. Q.; Xu, Z.; Zhang, S.; Wu, X.; Ding, J. W.; Lv, Z. S.; Feng, L. S. Eur J Med Chem 2017, 136, 122.

[11] Tehrani, K. H. M. E.; Hashemi, M.; Hassan, M.; Kobarfard, F.; Mohebbi, S. Chin Chem Lett 2016, 27, 221.

[12] Song, G. Q.; Zhang, W. M.; Li, Z. S.; Wang, Y.; Wang, J. G. Chin Chem Lett 2018, 29, 899.

[13] Xu, Z.; Lv, Z. S.; Gao, C.; Xu, L.; Ren, Q. C.; Feng, L. S. World Notes Antibiot 2017, 38, S63.

[14] Devale, T. L.; Parikh, J.; Miniyar, P.; Sharma, P.; Birendra, P. Bioorg Chem 2017, 70, 256.

[15] Feng, L. S.; Wang, S. H.; Song, X. F.; Xu, Z.; Qiang, M. World Notes Antibiot 2017, 38, S41.

[16] Gao, C.; Xu, Z.; Huang, L.; Ding, J. W.; Xu, Z. World Notes Antibiot 2017, 38, S58.

[17] El-Sherief, H. A. M.; Youssif, B. G. M.; Bukhari, S. N. A.; Abdel-Aziz, M. Bioorg Med 2018, 76, 314.

[18] Wang, J. B.; Yun, D.; Yao, J. L.; Fu, W. T.; Huang, F. Y.; Chen, L. P.; Wei, T. Eur J Med Chem 2018, 144, 493.

[19] Yu, B.; Qi, P. P.; Shi, X. J.; Huang, R. L.; Gao, H.; Zheng, Y. C.; Yu, D. Q.; Liu, H. M. Eur J Med Chem 2016, 117, 241.

[20] Yu, H. N.; Hou, Z.; Tian, Y.; Mou, Y. H.; Guo, C. Eur J Med Chem 2018, 151, 434.

[21] Kajita, D.; Nakamura, M.; Mastumoto, Y.; Makishima, M.; Hashimoto, Y. Bioorg Med Chem 2014, 22, 2244.

[22] Singh, H.; Singh, J. V.; Gupta, M. K.; Saxena, A. K.; Sharma, S.; Nepali, K.; Bedi, P. M. S. Bioorg Med Chem Lett 2017, 27, 3974.

[23] Singh, H.; Kumar, M.; Nepali, K.; Gupta, M. K.; Saxena, A. K.; Sharma, S.; Bedi, P. M. Eur J Med Chem 2016, 116, 102.

[24] Jia, X. D.; Wang, S.; Wang, M. H.; Liu, M. L.; Xia, G. M.; Liu, X. J.; Chai, Y.; He, H. W. Chin Chem Lett 2017, 28, 235.

[25] Huang, G. C.; Xu, Y.; Xu, Z.; Lv, Z. S.; Zhang, J.; Guo, H. Y.; Hu, Y. Q.; Liu, M. L.; Guan, J. G.; Lu, Y. J Heterocyclic Chem 2018, 55, 830.

[26] Zhao, S. Q.; Xu, Y.; Guan, J. G.; Zhao, S. J.; Zhang, G. D.; Xu, Z. J Heterocyclic Chem 2018, 55, 2172 https://doi.org/10.1002/jhet.3255.

[27] Xu, Z.; Song, X. F.; Hu, Y. Q.; Qiang, M.; Lv, Z. S. J Heterocyclic Chem 2018, 55, 192.

[28] Fan, Y. L.; Ke, X.; Liu, M. J Heterocyclic Chem 2018, 55, 791.