Design, Synthesis, and *In Vitro* Anticancer Activities of Diethylene Glycol Tethered Isatin-1,2,3-triazole-coumarin Hybrids

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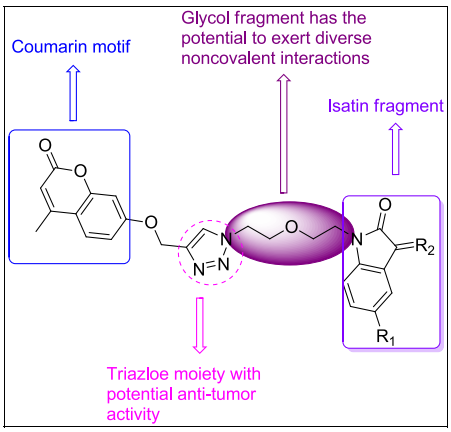


A series of novel diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l** were designed, synthesized, and evaluated for their *in vitro* anticancer activities against HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer), and drug-resistant MCF-7/DOX (doxorubicin-resistant MCF-7) human cancer cell lines. The results showed that most of the synthesized hybrids exhibited considerable *in vitro* activities against the tested seven cancer cell lines, and these hybrids can be acted as starting points for further investigation.

INTRODUCTION

Cancer that is intrinsically complex, comprising both heterogeneous cellular compositions and microenvironmental cues, is a severe health problem that significantly undermines life span and quality [1,2]. The World Health Organization has estimated that cancer was the cause of almost 22% of deaths (8.8 million cancer-related deaths) globally in 2015, and the number is still increasing [3,4]. Chemotherapy is crucial for the treatment of cancer, but the traditional cancer chemotherapy is limited by systemic toxicity, side effects, and the rapid development of resistance [5–7]. Therefore, there is an urgent need to develop new anticancer drugs with low toxicity, high activity, and excellent safety profiles.

Isatin, 1,2,3-triazole, and coumarin possess a variety of biological and 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 the development of new drugs. Several isatin-based or 1,2,3-triazole or coumarin-based compounds such as semaxanib, carboxyamidotriazole, and STX64 (Fig. 1) are under clinical trials or have already been used in clinical practice for the treatment of various cancers [19,20]. Moreover, isatin-1,2,3-triazole-coumarin hybrids demonstrated considerable activity against various cancer cell lines, and the structure–activity relationship (SAR) revealed that the linker between isatin and 1,2,3-triazole has great influence on the activity [21–23].

The previous research results indicated that the noncovalent interactions such as hydrogen bonds are crucial for the compounds to exert their biological activity [24,25], while diethylene glycol fragment has the potential to form hydrogen bonds, so diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids may have potential anticancer activity.

Based on the aforementioned research results and as an ongoing research program to develop new anticancer candidates, a series of novel diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids were designed, synthesized, and evaluated for their *in vitro* anticancer 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

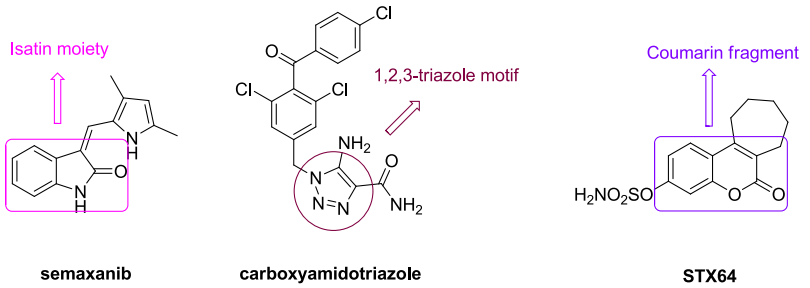


Figure 1. Chemical structures of semaxanib, carboxyamidotriazole, and STX64. [Color figure can be viewed at wileyonlinelibrary.com]

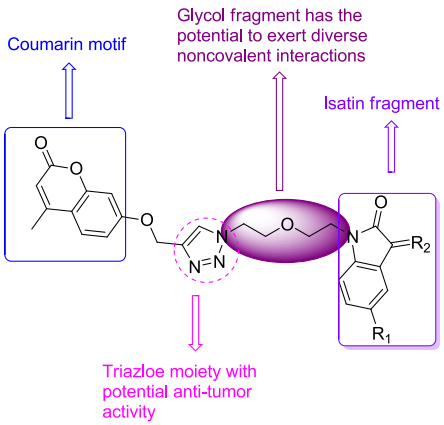


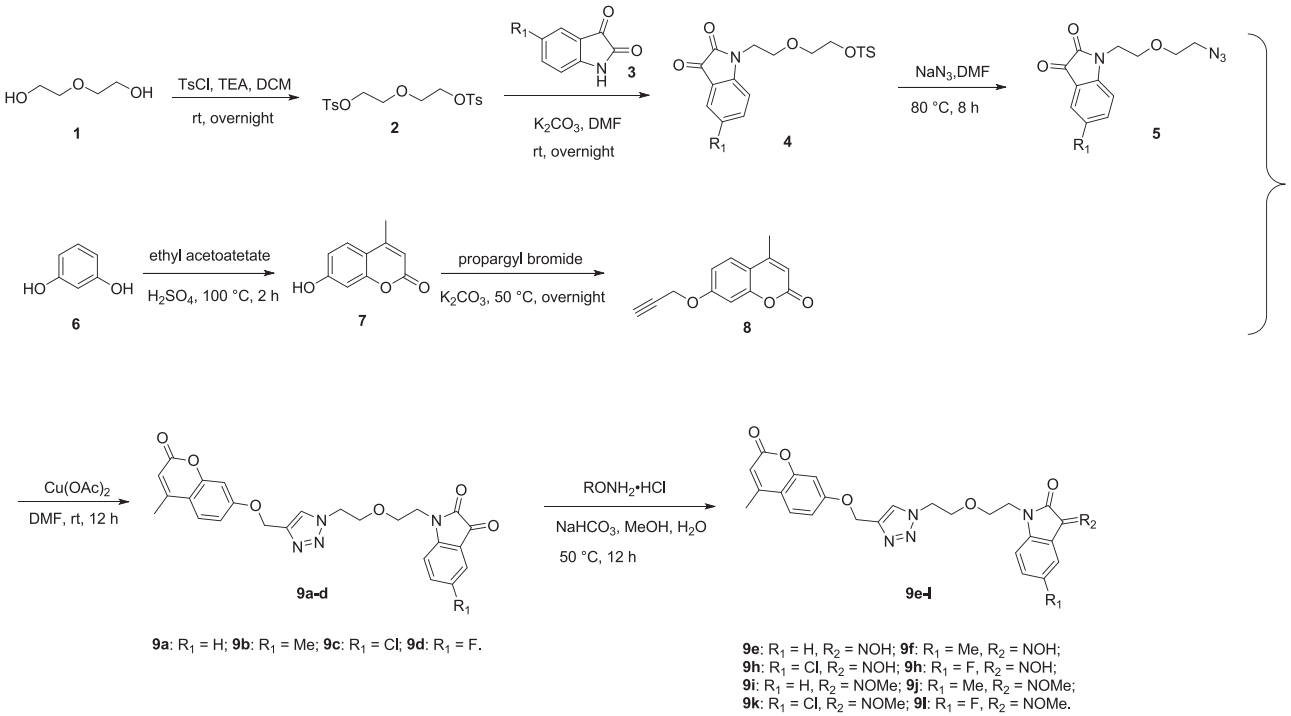
Figure 2. Schematic design strategy on diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

(doxorubicin-resistant MCF-7) human cancer cell lines in this study. The illustration of the design strategy is depicted in Figure 2.

RESULTS AND DISCUSSION

We first designed and synthesized the desired diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l** following the synthetic routes shown in Scheme 1. Treatment of diethylene glycol **1** with tosyl chloride in the presence of triethylamine generated intermediate **2**, which then reacted with isatins **3** and yielded the intermediates **4**. Subsequently, treatment of intermediates **4** with sodium azide provided the desired azido precursors **5**. The 4-methyl-7-(prop-2-ynyloxy)-2*H*-

Scheme 1. Synthesis of diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l**.



9a: R_1 = H; **9b**: R_1 = Me; **9c**: R_1 = Cl; **9d**: R_1 = F.

9e: R_1 = H, R_2 = NOH; **9f**: R_1 = Me, R_2 = NOH; **9h**: R_1 = Cl, R_2 = NOH; **9h**: R_1 = F, R_2 = NOH; **9i**: R_1 = H, R_2 = NOMe; **9j**: R_1 = Me, R_2 = NOMe; **9k**: R_1 = Cl, R_2 = NOMe; **9l**: R_1 = F, R_2 = NOMe.

Table 1

Structures and anticancer activities of isatin-1,2,3-triazole-coumarin hybrids **9a–l**.

Compd.	Structure		IC_{50} (μM)						
	R_1	R_2	HepG2	Hela	A549	DU145	SKOV3	MCF-7	MCF-7/DOX
9a	H	O	39.46	48.57	32.78	>50	28.98	32.56	27.36
9b	Me	O	29.67	36.51	36.04	44.89	24.49	28.74	23.50
9c	Cl	O	>50	>50	>50	>50	44.79	42.17	32.69
9d	F	O	>50	>50	48.76	>50	38.30	39.42	33.88
9e	H	NOH	21.47	44.26	29.27	38.41	23.05	30.24	26.65
9f	Me	NOH	19.89	21.32	18.67	31.50	17.96	29.43	15.46
9g	Cl	NOH	49.42	>50	38.15	45.21	37.85	33.76	27.65
9h	F	NOH	44.79	48.31	35.63	>50	24.40	34.38	20.83
9i	H	NOMe	46.77	>50	37.67	>50	28.20	>50	44.13
9j	Me	NOMe	39.93	49.42	34.58	>50	37.73	48.43	29.74
9k	Cl	NOMe	>50	>50	>50	>50	49.32	>50	43.99
9l	F	NOMe	>50	>50	>50	>50	45.17	>50	41.27
Etoposide	—	—	6.94	>50	>50	18.66	31.79	14.38	>50

chromen-2-one **8** was obtained by treatment of 7-hydroxy-4-methyl-7-2*H*-chromen-2-one **7** with propargyl bromide in the presence of K_2CO_3. The precursors **5** and **8** were utilized for the synthesis of desired diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–d** by Cu-promoted azide-alkyne cycloaddition reaction in the presence of Cu $(OAc)_2$ in dimethylformamide. Finally, condensations of targets **9a–d** with the requested amine hydrochlorides in the presence of sodium bicarbonate produced isatin dimers **9e–l** [25].

The synthesized diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l** were evaluated for their *in vitro* antitumor 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 sulforhodamine B assay [26]. 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.

From Table 1, it can be seen that all of the synthesized diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l** with IC_{50} ranging from 17.96 to >50 μM only showed weak to moderate activities, which were less potent than the reference etoposide against most of the tested cell lines. Preliminary SAR study indicated that substituents at both C-3 and C-5 positions of isatin motif have significantly influence on the anticancer activity: For C-5 position, electron-donating methyl could enhance the activity, while electron-withdrawing chloro and fluoro were detrimental to the activity; for C-3 position, hydrogen-bond donor –NOH could enhance the activity, and the relative contribution order of substituents was –NOH > –O > –NOMe generally. It is worth to notice that the resistance index (RI: $IC_{50(MCF\text{-}7/DOX)}/IC_{50(MCF\text{-}7)}$) of all hybrids was less than 1, suggesting that these hybrids may have novel mechanism of action.

CONCLUSIONS

In toto, the synthesized novel diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids **9a–l** displayed weak to moderate *in vitro* anticancer activities against a panel of cancer cell lines. The enriched SAR may pave the way for further rationale design of this kind of hybrids.

EXPERIMENTAL

The general procedure for preparing targets 9a–l. The precursors **5** and **8** were prepared *via* literature methods [27–30]. A mixture of isatins **5** (1.0 mmol), 4-methyl-7-(prop-2-ynyloxy)-2*H*-chromen-2-one **8** (1.0 mmol), and Cu $(OAc)_2$ (40 mg) in dimethylformamide (20 mL) was stirred for 24 h at room temperature under N_2 atmosphere. After removal of the solvent, 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 **9a–d**.

A mixture of amine hydrochlorides (1.5 mmol), sodium bicarbonate (2 mmol), and **9a–d** (1 mmol) in a mixture of tetrahydrofuran (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 **9e–l**.

1-(2-(2-(4-(((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethyl)indoline-2,3-dione (9a). Yield: 39%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.46 (2H, t, –CH_2–), 3.86 (2H, t, –CH_2–), 4.38 (2H, t, –CH_2–), 5.20 (2H, s, –CH_2O–), 6.24 (1H, s, Ar–H), 6.86 (1H, d, Ar–H), 6.98 (1H, d, Ar–H), 7.04–7.08 (2H, m, Ar–H), 7.50–7.53 (2H, m, Ar–H), 7.68 (1H, d, Ar–H), 8.32 (1H, s, triazole-H). ESI-MS m/z: 475 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{22}N_4O_6$: C, 63.29; H, 4.67; N, 11.81; Found: C, 63.05; H, 4.39; N, 11.63.

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)indoline-2,3-dione (9b). Yield: 42%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (3H, s, –CH_3), 2.40 (3H, s, –CH_3), 3.44 (2H, t, –CH_2–), 3.48 (2H, t, –CH_2–), 3.86 (2H, t, –CH_2–), 4.39 (2H, t, –CH_2–), 5.25 (2H, s, –CH_2O–), 6.25 (1H, s, Ar–H), 6.80 (1H, d, Ar–H), 7.04 (1H, d, Ar–H), 7.15 (1H, s, Ar–H), 7.35–7.39 (2H, m, Ar–H), 7.75 (1H, d, Ar–H), 8.36 (1H, s, triazole-H). ESI-MS m/z: 489 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{26}H_{24}N_4O_6$: C, 63.93; H, 4.95; N, 11.47; Found: C, 63.76; H, 4.82; N, 11.24.

5-Chloro-1-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethyl)indoline-2,3-dione (9c). Yield: 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (3H, s, –CH_3), 3.43 (2H, t, –CH_2–), 3.48 (2H, t, –CH_2–), 3.88 (2H, t, –CH_2–), 4.38 (2H, t, –CH_2–), 5.22 (2H, s, –CH_2O–), 6.27 (1H, s, Ar–H), 6.82 (1H, d, Ar–H), 6.99 (1H, d, Ar–H), 7.10 (1H, s, Ar–H), 7.33 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 7.84 (1H, s, Ar–H), 8.30 (1H, s, triazole-H). ESI-MS m/z: 509 $[M+H]^+$, 511 $[M+2+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{21}ClN_4O_6$: C, 59.00; H, 4.16; N, 11.01; Found: C, 58.74; H, 3.88; N, 10.86.

5-Fluoro-1-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethyl)indoline-2,3-dione (9d). Yield: 33%. ^{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: 493 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{21}FN_4O_6$: C, 60.97; H, 4.30; N, 11.38; Found: C, 60.76; H, 4.12; N, 11.19.

3-(Hydroxyimino)-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 (9e). Yield: 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.48 (2H, t, –CH_2–), 3.86 (2H, t, –CH_2–), 4.36 (2H, t, –CH_2–), 5.21 (2H, s, –CH_2O–), 6.25 (1H, s, Ar–H), 6.84 (1H, d, Ar–H), 6.99 (1H, d, Ar–H), 7.06–7.12 (2H, m, Ar–H), 7.54–7.62 (2H, m, Ar–H), 7.71 (1H, d, Ar–H), 8.33 (1H, s, triazole-H), 12.34 (1H, brs, NOH). ESI-MS m/z: 490 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31; Found: C, 61.16; H, 4.48; N, 14.08.

3-(Hydroxyimino)-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 (9f). Yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (3H, s, –CH_3), 2.41 (3H, s, –CH_3), 3.44 (2H, t, –CH_2–), 3.49 (2H, t, –CH_2–), 3.87 (2H, t, –CH_2–), 4.37 (2H, t, –CH_2–), 5.22 (2H, s, –CH_2O–), 6.26 (1H, s, Ar–H), 6.80 (1H, d, Ar–H), 7.02 (1H, d, Ar–H), 7.16 (1H, s, Ar–H), 7.32–7.36 (2H, m, Ar–H), 7.73 (1H, d, Ar–H), 8.33 (1H, s, triazole-H), 12.46 (1H, brs, NOH). ESI-MS m/z: 504 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91; Found: C, 61.87; H, 4.82; N, 13.76.

5-Chloro-3-(hydroxyimino)-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 (9g). Yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.48 (2H, t, –CH_2–), 3.86 (2H, t, –CH_2–), 4.38 (2H, t, –CH_2–), 5.21 (2H, s, –CH_2O–), 6.26 (1H, s, Ar–H), 6.82 (1H, d, Ar–H), 6.98 (1H, d, Ar–H), 7.08 (1H, s, Ar–H), 7.30 (1H, d, Ar–H), 7.67 (1H, d, Ar–H), 7.82 (1H, s, Ar–H), 8.32 (1H, s, triazole-H), 12.28 (1H, brs, NOH). ESI-MS m/z: 524 $[M+H]^+$, 526 $[M+2+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{22}ClN_5O_6$: C, 57.31; H, 4.23; N, 13.37; Found: C, 57.06; H, 4.01; N, 13.15.

5-Fluoro-3-(hydroxyimino)-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 (9h). Yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.48 (2H, t, –CH_2–), 3.88 (2H, t, –CH_2–), 4.39 (2H, t, –CH_2–), 5.22 (2H, s, –CH_2O–), 6.26 (1H, s, Ar–H), 6.89 (1H, d, Ar–H), 7.04 (1H, d, Ar–H), 7.09 (1H, s, Ar–H), 7.18 (1H, d, Ar–H), 7.65 (1H, d, Ar–H), 7.73 (1H, s, Ar–H), 8.34 (1H, s, triazole-H), 12.38 (1H, brs, NOH). ESI-MS m/z: 508 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{25}H_{22}FN_5O_6$: C, 59.17; H, 4.37; N, 13.80; Found: C, 58.89; H, 4.14; N, 13.63.

3-(Methoxyimino)-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 (9i). Yield: 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.47 (2H, t, –CH_2–), 3.84 (2H, t, –CH_2–), 4.24 (3H, s, $NOCH_3$), 4.36 (2H, t, –CH_2–), 5.24 (2H, s, –CH_2O–), 6.27 (1H, s, Ar–H), 6.92 (1H, d, Ar–H), 7.04 (1H, d, Ar–H), 7.09–7.13 (2H, m, Ar–H), 7.35 (1H, t, Ar–H), 7.72 (1H, d, Ar–H), 7.84 (1H, d, Ar–H), 8.36 (1H, s, triazole-H). ESI-MS m/z: 504 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91; Found: C, 61.76; H, 4.74; N, 13.68.

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 (9j). Yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (3H, s, –CH_3), 2.40 (3H, s, –CH_3), 3.42 (2H, t, –CH_2–), 3.47 (2H, t, –CH_2–), 3.87 (2H, t, –CH_2–),

4.18 (3H, s, $NOCH_3$), 4.36 (2H, t, $–CH_2–$), 5.20 (2H, s, $–CH_2O–$), 6.24 (1H, s, Ar–H), 6.78 (1H, d, Ar–H), 7.00 (1H, d, Ar–H), 7.11–7.13 (2H, m, Ar–H), 7.65–7.69 (2H, m, Ar–H), 8.34 (1H, s, triazole-H). ESI-MS m/z: 518 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{27}H_7N_5O_6$: C, 62.66; H, 5.26; N, 13.53; Found: C, 63.48; H, 5.03; N, 13.28.

5-Chloro-3-(methoxyimino)-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 (9k). Yield: 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (3H, s, $–CH_3$), 3.45 (2H, t, $–CH_2–$), 3.49 (2H, t, $–CH_2–$), 3.87 (2H, t, $–CH_2–$), 4.24 (3H, s, $NOCH_3$), 4.37 (2H, t, $–CH_2–$), 5.20 (2H, s, $–CH_2O–$), 6.22 (1H, s, Ar–H), 6.84 (1H, d, Ar–H), 6.98 (1H, d, Ar–H), 7.07 (1H, s, Ar–H), 7.35 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 7.81 (1H, s, Ar–H), 8.30 (1H, s, triazole-H). ESI-MS m/z: 538 $[M+H]^+$, 540 $[M+2+H]^+$. Elemental *Anal.* Calcd (%) for $C_{26}H_{24}ClN_5O_6$: C, 58.05; H, 4.50; N, 13.02; Found: C, 57.92; H, 4.22; N, 12.86.

5-Fluoro-3-(methoxyimino)-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 (9l). Yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (3H, s, $–CH_3$), 3.42 (2H, t, $–CH_2–$), 3.47 (2H, t, $–CH_2–$), 3.86 (2H, t, $–CH_2–$), 4.20 (3H, s, $NOCH_3$), 4.39 (2H, t, $–CH_2–$), 5.22 (2H, s, $–CH_2O–$), 6.24(1H, s, Ar–H), 6.82 (1H, d, Ar–H), 6.98 (1H, d, Ar–H), 7.07 (1H, s, Ar–H), 7.18 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 7.72 (1H, s, Ar–H), 8.32 (1H, s, triazole-H). ESI-MS m/z: 522 $[M+H]^+$. Elemental *Anal.* Calcd (%) for $C_{26}H_{24}FN_5O_6$: C, 59.88; H, 4.64; N, 13.43; Found: C, 59.64; H, 4.38; N, 13.26.

Anticancer activities. All the synthesized diethylene glycol tethered isatin-1,2,3-triazole-coumarin hybrids were investigated for their *in vitro* anticancer 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 sulforhodamine B assay.[26] IC_{50} values were presented as the concentration of drug inhibition 50% cell growth and determined by at least three separate tests and reported.

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