Design, Synthesis, and Evaluation of Tetraethylene Glycol-Tethered Isatin–1,2,3-Triazole–Coumarin Hybrids as Novel Anticancer Agents

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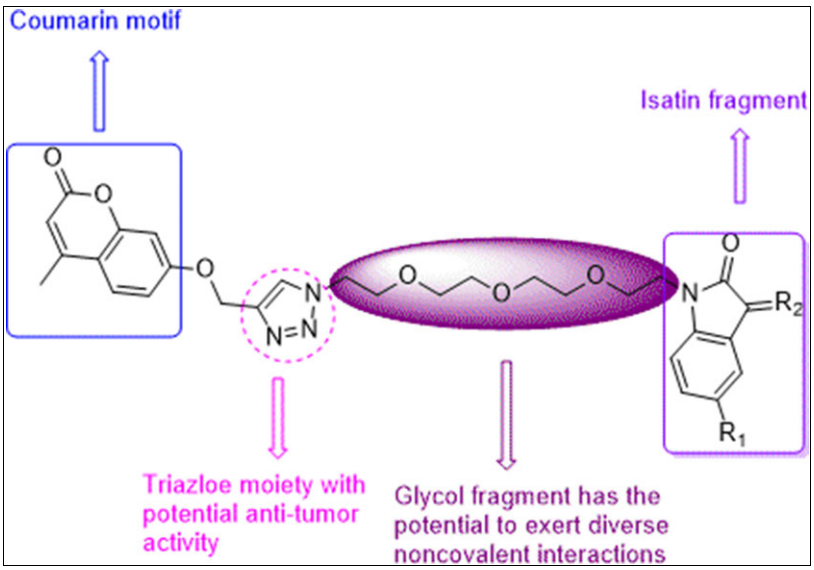
Received July 22, 2018
DOI 10.1002/jhet.3475
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



We report herein the design and synthesis of a series of novel tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids and evaluate their *in vitro* antitumor activities against seven common human cancer cell lines including drug-resistant cell line. Results revealed that all the synthesized hybrids showed weak to moderate activities against the tested seven cancer cell lines. The structure–activity relationship was also discussed, and the enriched structure–activity relationship may pave the way for further rationale design of this kind of hybrids.

INTRODUCTION

Cancer, the uncontrolled growth of cells that can affect almost all parts of the body, is now responsible for almost one in six deaths globally [1,2]. The World Health Organization has estimated that there are around 10.4 million incident cases of cancer globally in the year 2015, accompanied by 8.8 million deaths [3]. It is expected that annual cancer cases will rise to 22 million with 13 million deaths annually within the next two decades [4]. Chemotherapy plays a pivotal role 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]. Moreover, the spiraling costs of the cancer burden on healthcare systems have already caused great concern, because the total annual economic cost of cancer was estimated to reach approximately $1.16 trillion in 2010 [8,9]. Thus, it is imperative to develop new anticancer drugs with low price, high efficacy against both drug-sensitive and drug-resistant cancers, and excellent safety profiles.

Among heterocyclic compounds, isatin-based, 1,2,3-triazole-based, and coumarin-based compounds have broad biological activity spectrum including antitubercular [10–12], antibacterial [13,14], antiviral [15,16], antimalarial [17,18], and anticancer [19,20]

properties. Moreover, some of them such as sunitinib, carboxyamidotriazole, and STX64 (Fig. 1) are under clinical trials or have already been used in clinical practice for the treatment of various cancers [21,22], so isatin, 1,2,3-triazole, and coumarin are important construction motifs for the development of new anticancer drugs.

Hybridization of different pharmacophores into a single molecule may provide new candidates with complimentary activities and/or multiple pharmacological targets and/or one part can counterbalance the side effects caused by another part, so hybridization is emerged as an encouraging strategy in the discovery of new drugs with potential therapeutic application [23–25]. Recently, many isatin–1,2,3-triazole–coumarin hybrids were found to possess promising anticancer potential and have been widely studied [26–29]. The structure–activity relationship (SAR) revealed that for these hybrids, the linker between isatin and 1,2,3-triazole has great influence on the activity [29].

The previous research demonstrated that the noncovalent interactions such as hydrogen bonds play an important role in exertion of their biological activity [30,31], while glycol fragment has the potential to form hydrogen bonds, so glycol-tethered isatin–1,2,3-triazole–coumarin hybrids may have potential anticancer activity.

As a continuous research program, a series of novel tetraethylene glycol-tethered isatin-1,2,3–triazole–coumarin hybrids were designed, synthesized, and screened 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) human cancer cell lines in this study. The illustration of the design strategy is depicted in Figure 2.

RESULTS AND DISCUSSION

The synthetic route for the desired tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–l** was shown in Scheme 1. Treatment of tetraethylene glycol **1** with tosyl chloride in the presence of triethylamine gave intermediate **2**, which was then reacted with isatin **3** generated the intermediate **4**. Subsequently, treatment of intermediate **4** with sodium azide yielded the desired azido precursor **5**. The 4-methyl-7-(prop-2-ynyloxy)-2*H*-

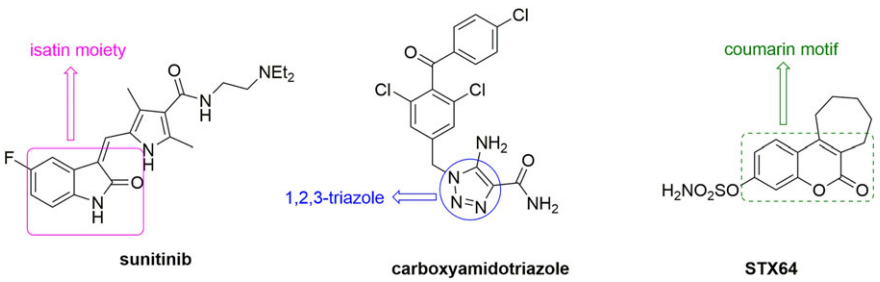


Figure 1. Chemical structures of sunitinib, carboxyamidotriazole, and STX64. [Color figure can be viewed at wileyonlinelibrary.com]

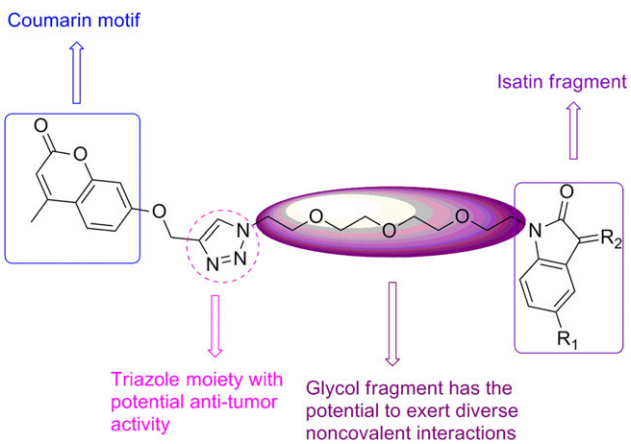


Figure 2. Schematic of design strategy on tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthesis of tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–l**. DCM, dichloromethane; DMF, dimethylformamide; RT, room temperature; TEA, triethylamine.

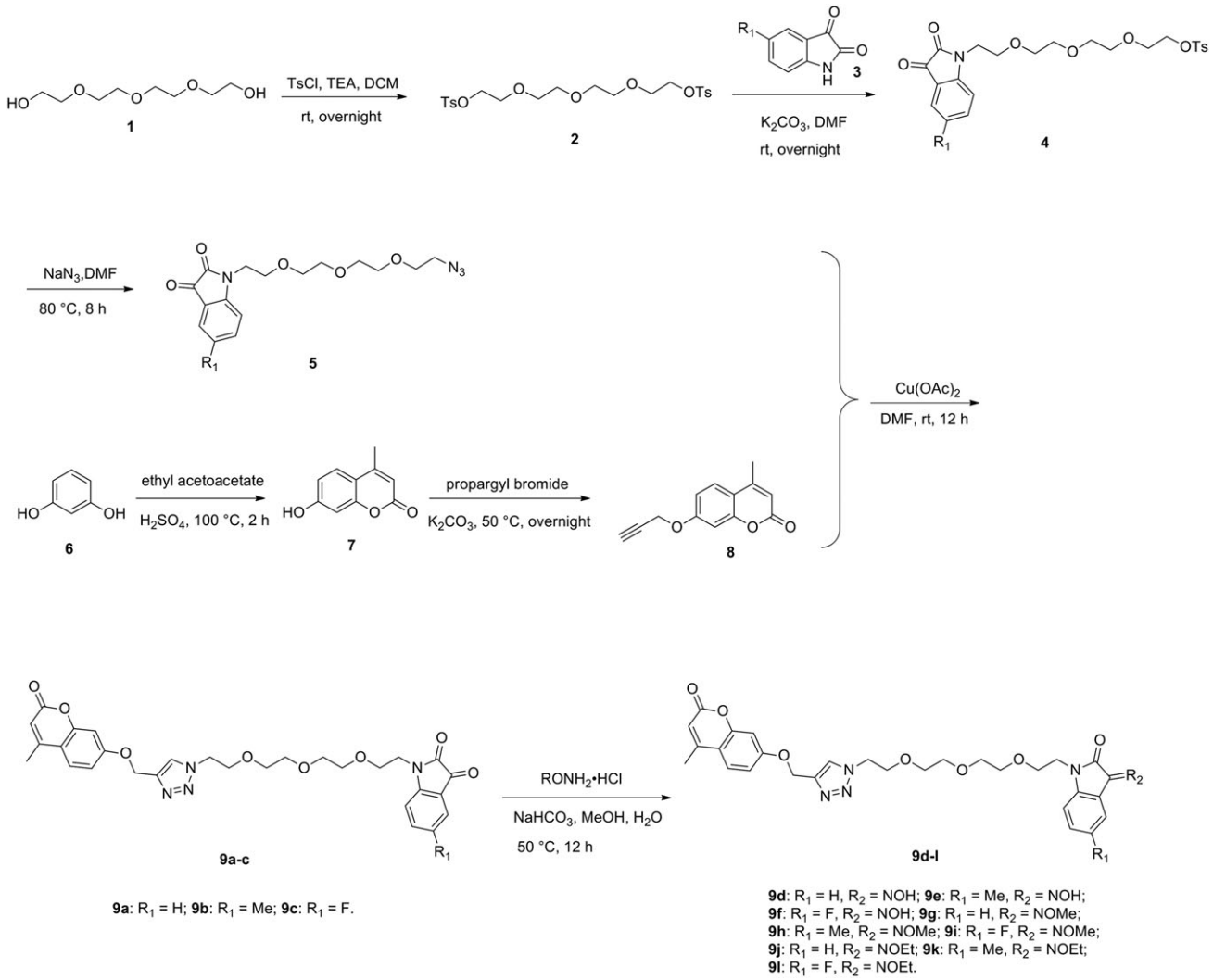


Table 1

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

	Structure		IC_{50} (μM)						
Compound	R_1	R_2	HepG2	Hela	A549	DU145	SKOV3	MCF-7	MCF-7/DOX
9a	H	O	47.67	>50	44.32	>50	39.14	43.26	33.59
9b	Me	O	>50	>50	>50	>50	48.31	>50	41.22
9c	F	O	43.58	45.62	38.17	49.24	29.36	36.89	27.29
9d	H	NOH	>50	>50	>50	>50	36.95	49.23	40.55
9e	Me	NOH	>50	>50	>50	>50	>50	>50	47.85
9f	F	NOH	>50	>50	>50	>50	38.16	45.24	36.20
9g	H	NOMe	30.99	28.63	35.91	41.49	30.28	33.46	27.35
9h	Me	NOMe	>50	42.45	47.33	>50	41.22	46.64	38.53
9i	F	NOMe	26.11	25.49	28.74	33.42	35.28	29.25	20.09
9j	H	NOEt	>50	>50	>50	>50	>50	>50	47.65
9k	Me	NOEt	>50	>50	>50	>50	>50	>50	49.83
9l	F	NOEt	>50	>50	>50	>50	>50	>50	45.32
Sunitinib	—	—	4.9 [33]	2.6 [33]	6.98 [34]	—	25.2 [35]	7.30 [34]	—
Etoposide	—	—	6.94	>50	>50	18.66	31.79	14.38	>50

chromen-2-one **8** was achieved by treatment of 7-hydroxy-4-methyl-7-2*H*-chromen-2-one **7** with propargyl bromide in the presence of K_2CO_3 and was utilized together with precursor **5** for the synthesis of desired tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–c** by Cu-promoted azide–alkyne cycloaddition reaction in the presence of Cu $(OAc)_2$ in dimethylformamide. Finally, condensations of targets **9a–c** with the requested amine hydrochlorides in the presence of sodium bicarbonate produced isatin dimers **9d–l** [31].

The synthesized tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–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 sulforhodamine B assay [32]. 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.

It can be seen from Table 1 that all the synthesized tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–l** with IC_{50} in a range of 25.49 to >50 μ*M* were less potent than the reference etoposide against the majority of the tested cell lines. The SAR indicated that substituents on both C-3 and C-5 positions of isatin motif influenced the anticancer activity greatly: For C-5 position, electron-withdrawing −F could increase the activity, while electron-donating −Me disfavored the activity generally; for C-3 position, the relative contribution of substituents was −NOMe > −O > −NOH > −NOEt. 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 tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids only exhibited weak to moderate *in vitro* anticancer activities against the tested seven cancer cell lines. In spite of that, 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 intermediates **5** and **8** were synthesized according to the well-established procedures. The mixture of intermediates **5** (10 mmol) and **8** (10 mmol) and Cu $(OAc)_2$ (0.5 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 12 h and then removal of the solvent under reduced pressure. The residue was purified by silica gel chromatography eluted with petroleum ether (PE) : ethyl acetate (EA) = 1:1 to give the desired tetraethylene glycol-tethered isatin–1,2,3-triazole–coumarin hybrids **9a–c**. To a mixture of isatin–1,2,3-triazole–coumarin hybrids **9a–c** (1 mmol) and $NaHCO_3$ (6 mmol) in water (10 mL) and MeOH (50 mL), the requested amine hydrochloride (5 mmol) was added. The mixture was stirred at 50°C for 12 h. After cooling to room temperature, the mixture was extracted with EA (20 mL × 2). The combined organic layers were washed with water (50 mL × 2) and brine (50 mL) in sequence and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography eluted with PE : EA = 1:1 to give the desired isatin–1,2,3-triazole–coumarin hybrids **9d–l**.

1-(2-(2-(2-(2-(4-(((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indoline-2,3-dione (9a). Yellow solid, yield: 32%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.40 (3H, s, $-CH_3$), 3.38–3.41 (6H, m, 3 × $-CH_2-$), 3.48 (2H, t, $-CH_2-$), 3.66 (2H, t, $-CH_2-$), 3.74 (2H, t, $-CH_2-$), 3.82 (2H, t, $-CH_2-$), 4.47 (2H, t, $-CH_2-$), 5.20 (2H, s, $-CH_2O-$), 6.24 (1H, s, Ar−H), 6.87 (1H, d, Ar−H), 6.98 (1H, d, Ar−H), 7.04–7.07 (2H, m, Ar−H), 7.48–7.51 (2H, m, Ar−H), 7.66 (1H, d, Ar−H), 8.30 (1H, s, triazole−H). ESI-MS *m/z*: 563 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{30}N_4O_8$: C, 61.91; H, 5.38; N, 9.96. Found: C, 61.74; H, 5.12; N, 9.68.

5-Methyl-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indoline-2,3-dione (9b). Yield: 39%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.28 (3H, s, $-CH_3$), 2.42 (3H, s, $-CH_3$), 3.38–3.42 (6H, m, 3 × $-CH_2-$), 3.49 (2H, t, $-CH_2-$), 3.67 (2H, t, $-CH_2-$), 3.78 (2H, t, $-CH_2-$), 3.84 (2H, t, $-CH_2-$), 4.48 (2H, t, $-CH_2-$), 5.23 (2H, s, $-CH_2O-$), 6.25 (1H, s, Ar−H), 6.82 (1H, d, Ar−H), 7.06 (1H, d, Ar−H), 7.17 (1H, s, Ar−H), 7.32–7.36 (2H, m, Ar−H), 7.71 (1H, d, Ar−H), 8.32 (1H, s, triazole−H). ESI-MS *m/z*: 577 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{20}H_{32}N_4O_8$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.23; H, 5.32; N, 9.48.

5-Fluoro-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indoline-2,3-dione (9c). Yield: 37%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s, $-CH_3$), 3.36–3.39 (6H, m, 3 × $-CH_2-$), 3.47 (2H, t, $-CH_2-$), 3.64 (2H, t, $-CH_2-$), 3.76 (2H, t, $-CH_2-$), 3.84 (2H, t, $-CH_2-$), 4.46 (2H, t, $-CH_2-$), 5.21 (2H, s, $-CH_2O-$), 6.26 (1H, s, Ar−H), 6.88 (1H, d, Ar−H), 7.03 (1H, d, Ar−H), 7.09

(1H, s, Ar—H), 7.18 (1H, d, Ar—H), 7.68 (1H, d, Ar—H), 7.73 (1H, s, Ar—H), 8.33 (1H, s, triazole—H). ESI-MS *m/z*: 581 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{29}FN_4O_8$: C, 60.00; H, 5.03; N, 9.65. Found: C, 59.76; H, 4.82; N, 9.46.

3-(Hydroxyimino)-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)indolin-2-one (9d). Yield: 65%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.40 (3H, s, —CH_3), 3.37–3.40 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.61 (2H, t, —CH_2—), 3.73 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.46 (2H, t, —CH_2—), 5.21 (2H, s, —CH_2O—), 6.25 (1H, s, Ar—H), 6.85 (1H, d, Ar—H), 6.98 (1H, d, Ar—H), 7.06–7.10 (2H, m, Ar—H), 7.57–7.62 (2H, m, Ar—H), 7.69 (1H, d, Ar—H), 8.32 (1H, s, triazole—H), 12.46 (1H, brs, NOH). ESI-MS *m/z*: 578 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{31}N_5O_8$: C, 60.30; H, 5.41; N, 12.13. Found: C, 60.03; H, 5.17; N, 11.95.

3-(Hydroxyimino)-5-methyl-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9e). Yield: 72%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.28 (3H, s, —CH_3), 2.41 (3H, s, —CH_3), 3.34–3.38 (6H, m, 3 × —CH_2—), 3.45 (2H, t, —CH_2—), 3.62 (2H, t, —CH_2—), 3.74 (2H, t, —CH_2—), 3.85 (2H, t, —CH_2—), 4.44 (2H, t, —CH_2—), 5.22 (2H, s, —CH_2O—), 6.26 (1H, s, Ar—H), 6.79 (1H, d, Ar—H), 7.01 (1H, d, Ar—H), 7.15 (1H, s, Ar—H), 7.32–7.35 (2H, m, Ar—H), 7.71 (1H, d, Ar—H), 8.31 (1H, s, triazole—H), 12.38 (1H, brs, NOH). ESI-MS *m/z*: 592 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{33}N_5O_8$: C, 60.90; H, 5.62; N, 11.84. Found: C, 60.62; H, 5.36; N, 11.58.

5-Fluoro-3-(hydroxyimino)-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9f). Yield: 63%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s, —CH_3), 3.37–3.40 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.66 (2H, t, —CH_2—), 3.74 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.47 (2H, t, —CH_2—), 5.24 (2H, s, —CH_2O—), 6.26 (1H, s, Ar—H), 6.88 (1H, d, Ar—H), 7.03 (1H, d, Ar—H), 7.09 (1H, s, Ar—H), 7.17 (1H, d, Ar—H), 7.67 (1H, d, Ar—H), 7.71 (1H, s, Ar—H), 8.32 (1H, s, triazole—H), 12.32 (1H, brs, NOH). ESI-MS *m/z*: 596 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{30}FN_5O_8$: C, 58.48; H, 5.08; N, 11.76. Found: C, 58.21; H, 4.83; N, 11.52.

3-(Methoxyimino)-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)indolin-2-one (9g). Yield: 59%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.46 (3H, s, —CH_3), 3.36–3.40 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.63 (2H, t, —CH_2—), 3.74 (2H, t, —CH_2—), 3.83 (2H, t, —CH_2—), 4.21 (3H, s, NOMe), 4.45 (2H, t, —CH_2—), 5.23 (2H, s, —CH_2O—), 6.26 (1H, s, Ar—H), 6.91 (1H, d, Ar—H), 7.04 (1H, d, Ar—H), 7.10–7.13 (2H, m, Ar—H), 7.34 (1H, t, Ar—H), 7.72 (1H, d, Ar—H), 7.82 (1H, d, Ar—H), 8.31 (1H, s, triazole—H). ESI-MS *m/z*: 592 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{33}N_5O_8$: C, 60.90; H, 5.62; N, 11.84. Found: C, 60.71; H, 5.39; N, 11.63.

3-(Methoxyimino)-5-methyl-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9h). Yield: 70%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.25 (3H, s, —CH_3), 2.40 (3H, s, —CH_3), 3.36–3.40 (6H, m, 3 × —CH_2—), 3.45 (2H, t, —CH_2—), 3.62 (2H, t, —CH_2—), 3.73 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.19 (3H, s, NOMe), 4.44 (2H, t, —CH_2—), 5.20 (2H, s, —CH_2O—), 6.24 (1H, s, Ar—H), 6.79 (1H, d, Ar—H), 7.01 (1H, d, Ar—H), 7.11–7.13 (2H, m, Ar—H), 7.62–7.66 (2H, m, Ar—H), 8.32 (1H, s, triazole—H). ESI-MS *m/z*: 606 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{35}N_5O_8$: C, 61.48; H, 5.82; N, 11.56. Found: C, 61.24; H, 5.56; N, 11.38.

5-Fluoro-3-(methoxyimino)-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9i). Yield: 48%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s, —CH_3), 3.36–3.41 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.64 (2H, t, —CH_2—), 3.75 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.18 (3H, s, NOMe), 4.45 (2H, t, —CH_2—), 5.22 (2H, s, —CH_2O—), 6.24 (1H, s, Ar—H), 6.81 (1H, d, Ar—H), 6.98 (1H, d, Ar—H), 7.04 (1H, s, Ar—H), 7.16 (1H, d, Ar—H), 7.68 (1H, d, Ar—H), 7.74 (1H, s, Ar—H), 8.32 (1H, s, triazole—H). ESI-MS *m/z*: 610 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{32}FN_5O_8$: C, 59.11; H, 5.29; N, 11.49. Found: C, 58.82; H, 5.04; N, 11.20.

3-(Ethoxyimino)-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9j). Yellow solid, yield: 55%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.38 (3H, t, $NOCH_2\underline{CH_3}$), 2.42 (3H, s, —CH_3), 3.35–3.39 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.64 (2H, t, —CH_2—), 3.75 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.42–4.50 (4H, m, —CH_2— and $NO\underline{CH_2}CH_3$), 5.21 (2H, s, —CH_2O—), 6.26 (1H, s, Ar—H), 6.90 (1H, d, Ar—H), 7.03 (1H, d, Ar—H), 7.11–7.13 (2H, m, Ar—H), 7.30 (1H, t, Ar—H), 7.70 (1H, d, Ar—H), 7.81 (1H, d, Ar—H), 8.32 (1H, s, triazole—H). ESI-MS *m/z*: 606 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{35}N_5O_8$: C, 61.48; H, 5.82; N, 11.56. Found: C, 61.29; H, 5.61; N, 11.32.

3-(Ethoxyimino)-5-methyl-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one (9k). Yield: 49%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.36 (3H, t, $NOCH_2\underline{CH_3}$), 2.24 (3H, s, —CH_3), 2.40 (3H, s, —CH_3), 3.36–3.40 (6H, m, 3 × —CH_2—), 3.46 (2H, t, —CH_2—), 3.63 (2H, t, —CH_2—), 3.74 (2H, t, —CH_2—), 3.84 (2H, t, —CH_2—), 4.42–4.48 (4H, m, —CH_2— and $NO\underline{CH_2}CH_3$), 5.20 (2H, s, —CH_2O—), 6.25 (1H, s, Ar—H), 6.80 (1H,

d, Ar—H), 7.00 (1H, d, Ar—H), 7.11–7.13 (2H, m, Ar—H), 7.63–7.66 (2H, m, Ar—H), 8.32 (1H, s, triazole—H). ESI-MS *m/z*: 620 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{37}N_5O_8$: C, 62.02; H, 6.02; N, 11.30. Found: C, 61.86; H, 5.78; N, 11.04.

3-(Ethoxyimino)-5-fluoro-1-(2-(2-(2-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy) ethoxy)ethoxy)ethyl)indolin-2-one (9l). Yield: 56%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.38 (3H, t, $NOCH_2\underline{CH_3}$), 2.42 (3H, s, —CH_3), 3.36–3.40 (6H, m, 3 × —CH_2—), 3.45 (2H, t, —CH_2—), 3.64 (2H, t, —CH_2—), 3.74 (2H, t, —CH_2—), 3.85 (2H, t, —CH_2—), 4.43–4.50 (4H, m, —CH_2— and $NO\underline{CH_2}CH_3$), 5.22 (2H, s, —CH_2O—), 6.25 (1H, s, Ar—H), 6.82 (1H, d, Ar—H), 6.98 (1H, d, Ar—H), 7.03 (1H, s, Ar—H), 7.16 (1H, d, Ar—H), 7.57 (1H, d, Ar—H), 7.73 (1H, s, Ar—H), 8.32 (1H, s, triazole—H). ESI-MS *m/z*: 624 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{34}FN_5O_8$: C, 59.70; H, 5.50; N, 11.23. Found: C, 59.48; H, 5.26; N, 11.05.

Antitumor activities. All the synthesized isatin–1,2,3-triazole–coumarin hybrids were screened 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 sulforhodamine B assay [32]. 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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