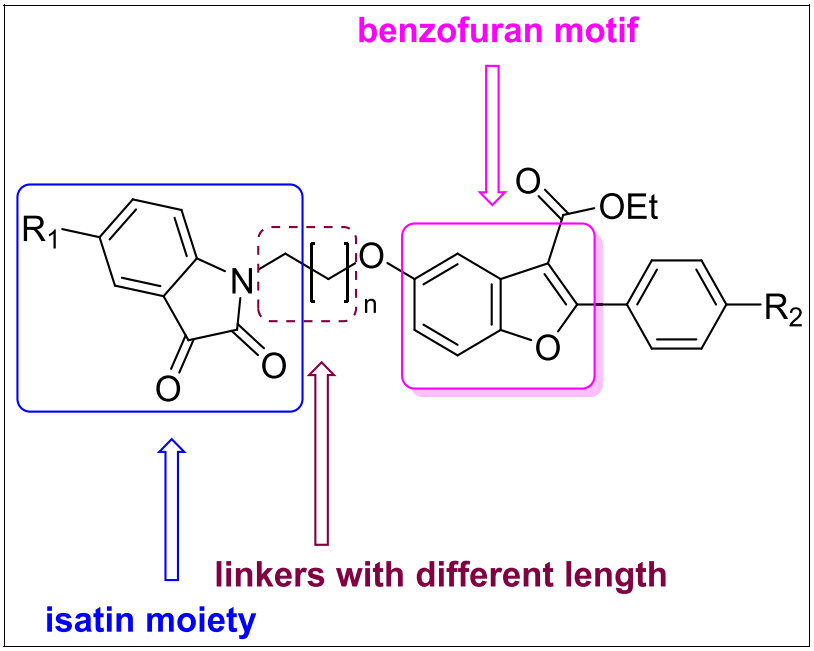
Benzofuran–isatin Hybrids: Design, Synthesis, and *In Vitro* Anti-cancer Activities

Quan-Ping Diao,[a] Hua Guo,[a] and Gang-Qiang Wang[b]*

[a]School of Chemistry and Life Science, Anshan Normal University, Liaoning, Anshan, People's Republic of China
[b]Non-power Nuclear Technology Collaborative Innovation Center, School of Nuclear Technology and Chemistry & Biology, Hubei University of Science and Technology, Xianning, People's Republic of China
*E-mail: wanggq@hbust.edu.cn

Received October 25, 2018
DOI 10.1002/jhet.3554
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel benzofuran–isatin hybrids **6a–s** tethered through propylene and butylene were designed, synthesized, and evaluated for their *in vitro* anti-cancer 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 majority of the synthesized hybrids displayed weak to moderate *in vitro* activities against the tested seven cancer cell lines, but the enriched structure–activity relationship may pave the way for further optimization.

J. Heterocyclic Chem., **00,** 00 (2019).

INTRODUCTION

Cancer, a severe health problem that significantly undermines life span and quality, has been threatened form ancient time [1,2]. Cancer is the second leading cause of death globally, and 9.6 million people worldwide are estimated to die from cancer in 2018 [3]. The most common types of cancer are lung, prostate, colorectal, stomach, and liver cancer in men, while breast, colorectal, lung, cervix, and thyroid cancer are the most common among women [4]. Chemotherapy plays an important role in the treatment of cancer, but the traditional cancer chemotherapy develops resistance rapidly [5–7]. Thus, it is imperative to develop new anti-cancer drugs.

Benzofuran and isatin (indoline-2,3-dione) derivatives possess a variety of biological properties such as anti-bacterial [5,6], anti-tubercular [7–11], and anti-malarial [12] activities, which occupy an important position in the development of new drugs. Benzofuran and isatin derivatives also exhibit promising anti-cancer activities [13–15], and some of them such as semaxanib (Fig. 1) are under clinical trials or have already been used in clinics for the treatment of various cancers [16,17]. Moreover, benzofuran and isatin derivatives also demonstrate excellent physiochemical, toxicological, and pharmacological properties *in vivo*, indicating its potential for the treatment of cancers [7,18,19]. Therefore, incorporation of benzofuran and isatin into one hybrid may provide more effective anti-cancer candidates.

Based on the aforementioned considerations and as a continuous ongoing project, a series of novel benzofuran–isatin hybrids tethered through propylene and butylene were designed, synthesized, and evaluated for their *in vitro* anti-cancer activities against HepG2

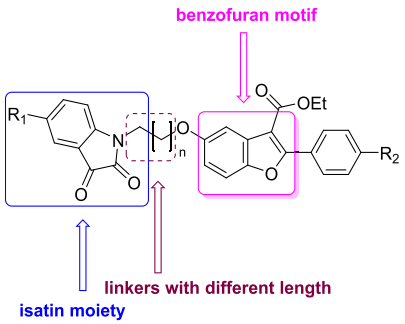


Figure 1. Design strategy for benzofuran–isatin hybrids tethered *via* different linkers. [Color figure can be viewed at wileyonlinelibrary.com]

(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. Preliminary studies on structure–activity relationship study are also taken to facilitate the further development of these hybrids.

RESULTS AND DISCUSSION

All of the desired benzofuran–isatin hybrids **6a–s** can be achieved by the synthetic route depicted in Scheme 1. 5-

Scheme 1. Synthesis of benzofuran–isatin hybrids **6a-s**.

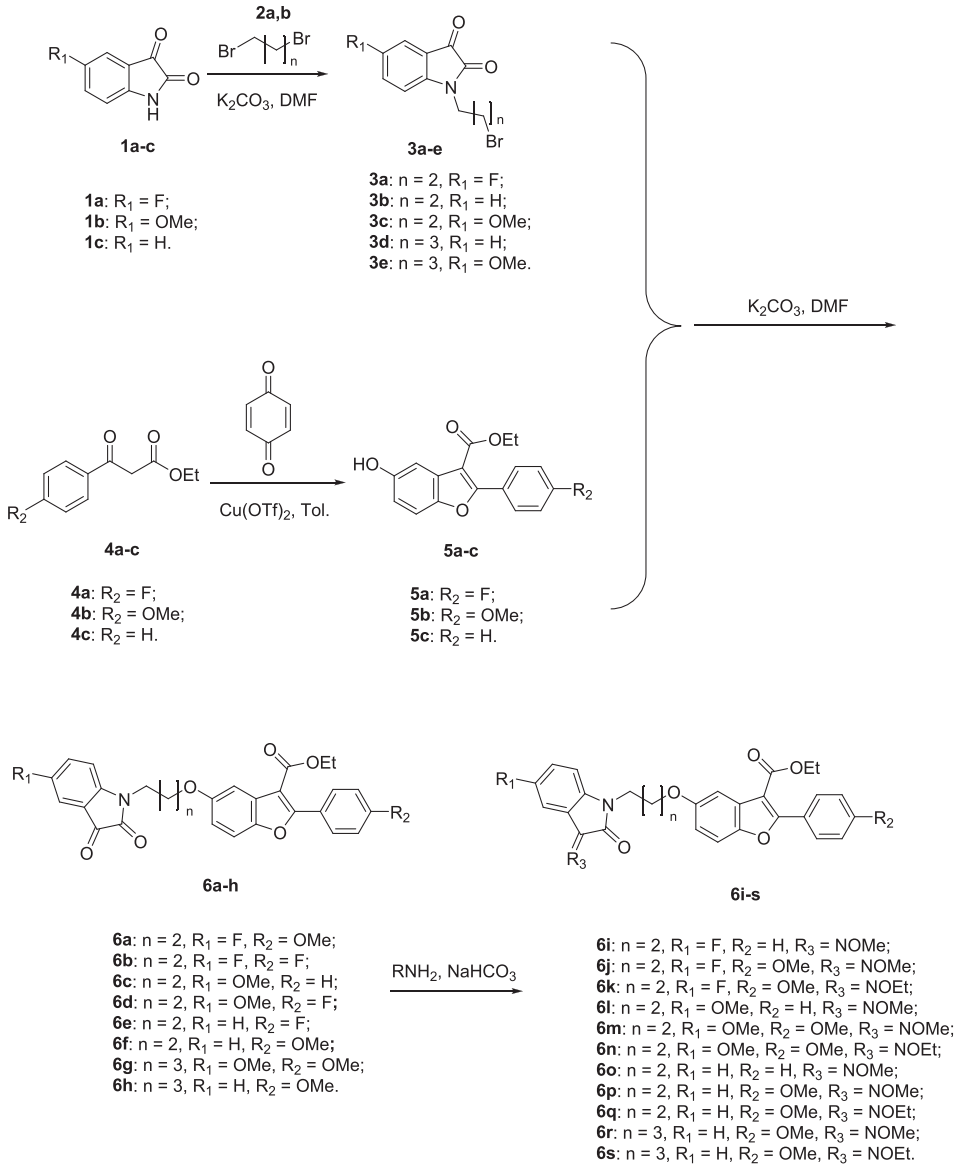


Table 1

Structures and anti-cancer activities of benzofuran–isatin hybrids **6a–s**.

Compound	IC_{50} (μM)						
	HepG2	Hela	A549	DU145	SKOV3	MCF-7	MCF-7/DOX
6a	>50	>50	>50	>50	>50	46.32	41.27
6b	>50	>50	>50	>50	>50	43.46	44.15
6c	>50	>50	>50	>50	>50	49.12	>50
6d	>50	>50	>50	>50	>50	42.84	48.63
6e	>50	>50	>50	>50	>50	47.39	43.86
6f	>50	>50	>50	>50	>50	49.41	>50
6g	>50	>50	>50	>50	>50	41.56	44.76
6h	>50	>50	>50	>50	>50	43.15	48.71
6i	>50	>50	>50	>50	>50	41.60	47.53
6j	>50	>50	>50	>50	>50	39.74	42.65
6k	>50	>50	>50	>50	>50	47.26	41.39
6l	>50	>50	>50	>50	>50	42.72	46.68
6m	>50	>50	>50	>50	>50	32.54	49.62
6n	>50	>50	>50	>50	>50	39.87	45.95
6o	>50	>50	>50	>50	>50	40.29	41.67
6p	>50	>50	>50	>50	>50	42.44	45.32
6q	>50	>50	>50	>50	>50	48.52	43.68
6r	>50	>50	>50	>50	>50	36.18	41.29
6s	>50	>50	>50	>50	>50	38.43	42.36
Etoposide	6.94	>50	>50	18.66	31.79	14.38	>50

Methoxyisatin/5-fluoroisatin/isatin **1a–c** were alkylated with 1,3-dibromopropane and 1,4-dibromobutane in the presence of potassium carbonate to give *N*-(3-bromopropyl/4-bromobutyl)isatin derivatives **3a–e** (yield: 63–87%) [19]. The benzofuran intermediates **5a–c** were obtained by cyclization of ethyl 3-(4-substituted phenyl)-3-oxopropanoates **4a–c** and benzoquinone with copper (II) triflate (Cu $(OTf)_2$) as catalyst [18]. Treatment of isatin derivatives **3a–e** and benzofuran intermediates **5a–c** with potassium carbonate as base generated the desired benzofuran–isatin hybrids **6a–h** (58–83%). Finally, condensations of **6a–h** with the corresponding amine hydrochlorides in the presence of sodium bicarbonate generated the rest benzofuran–isatin hybrids **6i–s** (18–73%).

The synthesized benzofuran–isatin hybrids **6a–s** were evaluated for their *in vitro* anti-cancer activities against HepG2, Hela, A549, DU145, SKOV3, MCF-7, and drug-resistant MCF-7/DOX by SRB assay [20]. IC_{50} values were presented as the concentration of drug inhibition 50% cell growth and determined by at least three separate tests and reported, and the results were presented in Table 1.

It can be concluded from Table 1 that benzofuran–isatin hybrids **6a–s** only exhibited weak to moderate anti-cancer activities against breast cancer cell lines MCF-7 and drug-resistant MCF-7/DOX with IC_{50} ranging from 32.54 to >50 μM and were inactive against HepG2 (liver carcinoma), Hela (cervical cancer), A549 (lung adenocarcinoma), DU145 (prostatic cancer), and SKOV3 (ovarian carcinoma). All hybrids were less potent than the reference etoposide (IC_{50}: 6.94–31.79 μM) against HepG2, DU145, SKOV3, and MCF-7.

The structure–activity relationship results suggested that substituents at R_1 and R_3 positions at isatin moiety and R_2 position at benzofuran motif as well as the length of the linker have great influence on the activity against breast cancer cell lines MCF-7 and MCF-7/DOX: for R_1 position, electron-withdrawing -F could improve the activity, while electron-donating -OMe was detrimental to the activity, and the relative contribution order was -F > -H > -OMe; for R_2 position, introduction of -F and -OMe could increase the activity when compared with the unsubstituted ones, and the relative contribution order of the substituents was -F ≥ -OMe ≥ -H; for R_3 position, -NOMe > -O > -NOEt; for the linker, the longer butylene linker was more favorable than the shorter propylene linker.

Among the synthesized benzofuran–isatin hybrids, hybrids **6m** (IC_{50}: 32.54 μM) and **6a** (IC_{50}: 41.27 μM) were found to be the most active against MCF-7 and drug-resistant MCF-7/DOX, respectively. It is worth to notice that the resistance index values ($IC_{50(MCF\text{-}7/DOX)}$/$IC_{50(MCF\text{-}7)}$) for the majority of the synthesized benzofuran–isatin hybrids **6a–s** were around 1, indicating that these hybrids may have novel action mechanism.

CONCLUSIONS

In conclusion, 19 novel benzofuran–isatin hybrids **6a–s** tethered *via* propylene and butylene were designed,

synthesized, and evaluated for their *in vitro* anti-cancer activities against a panel of human cancer cell lines. In spite of all hybrids were inactive against HepG2, Hela, A549, DU145, and SKOV3, some of them exhibited moderate activities against breast cancer cell lines MCF-7 and drug-resistant MCF-7/DOX. The resistance index values for the majority of benzofuran–isatin hybrids were around 1, indicating that these hybrids may have novel action mechanism.

EXPERIMENTAL

Synthesis. *N*-(3-bromopropyl/4-bromobutyl)isatin derivatives **3a**–**e** (yield: 63–87%) [21] and ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5a**–**c** were prepared *via* literature methods [18,19].

A mixture of *N*-(3-bromopropyl/4-bromobutyl)isatin derivatives **3a**–**e** (1.0 mmol), ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5a**–**c** (1.0 mmol), and K_2CO_3 (3.0 mmol) in DMF (50 mL) was stirred at room temperature for 48 h. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with PE:EA = 1:1 to give the desired benzofuran–isatin hybrids **6a**–**h**.

The mixture of hybrids **6a**–**h** (1 mmol), sodium bicarbonate (2 mmol), and the corresponding amine hydrochlorides (1.5 mmol) dissolving in water (10 mL) and tetrahydrofuran (30 mL) was stirred at 60°C for 12 h. After cooling to room temperature, the mixture was extracted with EA (20 mL × 3). The combined organic layers were washed with water (50 mL × 2) and brine (50 mL) and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a residue, which was further purified by silica gel chromatography eluted with PE: EA = 1:8 to give the rest desired benzofuran–isatin hybrids **6i**–**s** (18–73%).

Ethyl 5-(3-(5-fluoro-2,3-dioxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6a). Yellow solid, yield: 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (3H, t, J = 4.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, J = 4.0 Hz, $-CH_2-$), 3.85 (3H, s, OCH_3), 3.89 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.33 (2H, q, J = 4.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.09 (2H, d, J = 4.0 Hz, Ar—H), 7.25–7.28 (1H, m, Ar—H), 7.39 (1H, d, J = 4.0 Hz, Ar—H), 7.45–7.50 (2H, m, Ar—H), 7.57 (1H, d, J = 8.0 Hz, Ar—H), 7.94–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 540 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{24}FNO_7$: C, 67.31; H, 4.67; N, 2.71. Found: C, 67.08; H, 4.39; N, 2.55.

Ethyl 5-(3-(5-fluoro-2,3-dioxoindolin-1-yl)propoxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6b). Yellow solid, yield: 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.12 (2H, t, J = 4.0 Hz, $-CH_2-$), 3.89 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.24–7.28 (1H, m, Ar—H), 7.36–7.41 (2H, m, Ar—H), 7.44–7.42 (2H, m, Ar—H), 7.60 (1H, d, J = 12.0 Hz, Ar—H), 8.01–8.04 (2H, m, Ar—H). ESI–MS *m/z*: 528 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{28}H_{21}F_2NO_6$: C, 66.53; H, 4.19; N, 2.77. Found: C, 66.31; H, 4.05; N, 2.53.

Ethyl 5-(3-(5-methoxy-2,3-dioxoindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (6c). Yellow solid, yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.24–2.27 (2H, m, $-CH_2-$), 3.85 (3H, s, OCH_3), 4.00 (2H, t, J = 8.0 Hz, $-CH_2-$), 4.13 (2H, t, J = 8.0 Hz, $-CH_2-$), 4.42 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.90 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 6.99–7.02 (3H, m, Ar—H), 7.07–7.11 (1H, m, Ar—H), 7.38 (1H, d, J = 12.0 Hz, Ar—H), 7.50–7.55 (2H, m, Ar—H), 7.59–7.61 (1H, m, Ar—H), 8.00–8.02 (2H, m, Ar—H). ESI–MS *m/z*: 522 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{25}NO_7$: C, 69.73; H, 5.04; N, 2.80. Found: C, 69.71; H, 4.87; N, 2.65.

Ethyl 2-(4-fluorophenyl)-5-(3-(5-methoxy-2,3-dioxoindolin-1-yl)propoxy)benzofuran-3-carboxylate (6d). Yellow solid, yield: 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.12 (2H, t, J = 4.0 Hz, $-CH_2-$), 3.76 (3H, s, OCH_3), 3.87 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, J = 2.0 Hz, $-CH_2-$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.14–7.20 (3H, m, Ar—H), 7.37–7.42 (3H, m, Ar—H), 7.60 (1H, d, J = 12.0 Hz, Ar—H), 8.01–8.05 (2H, m, Ar—H). ESI–MS *m/z*: 540 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{24}FNO_7$: C, 67.31; H, 4.67; N, 2.71. Found: C, 67.09; H, 4.51; N, 2.62.

Ethyl 5-(3-(2,3-dioxoindolin-1-yl)propoxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6e). Yellow solid, yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.13 (2H, t, J = 8.0 Hz, $-CH_2-$), 3.89 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.33 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.11 (1H, t, J = 4.0 Hz, Ar—H), 7.24 (1H, d, J = 8.0 Hz, Ar—H), 7.37–7.42 (3H, m, Ar—H), 7.54–7.64 (3H, m, Ar—H), 8.01–8.05 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 510 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{28}H_{22}FNO_6$: C, 68.99; H, 4.55; N, 2.87. Found: C, 68.76; H, 4.39; N, 2.69.

Ethyl 5-(3-(2,3-dioxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6f). Yellow solid, yield: 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (3H, t, J = 4.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.13 (2H, t, J = 4.0 Hz, $-CH_2-$), 3.86 (3H, s, OCH_3), 3.88 (2H, t, J = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, J = 4.0 Hz, $-CH_2-$),

4.34 (2H, q, J = 4.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.96 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.08–7.13 (3H, m, Ar—H), 7.24 (1H, d, J = 8.0 Hz, Ar—H), 7.40 (1H, d, J = 8.0 Hz, Ar—H), 7.54–7.63 (3H, m, Ar—H), 7.96 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 522 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{25}NO_7$: C, 69.73; H, 5.04; N, 2.80. Found: C, 69.53; H, 4.87; N, 2.60.

Ethyl 5-(4-(5-methoxy-2,3-dioxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6g). Yellow solid, yield: 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.80–1.84 (4H, m, 2× —CH_2—), 3.71–3.76 (5H, m, —CH_2— and OCH_3), 3.85 (3H, s, OCH_3), 4.06 (2H, t, J = 8.0 Hz, —CH_2—), 4.33 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.96 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.08–7.16 (4H, m, Ar—H), 7.22–7.25 (1H, m, Ar—H), 7.42 (1H, d, J = 4.0 Hz, Ar—H), 7.55 (1H, d, J = 8.0 Hz, Ar—H), 7.94–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 566 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{29}NO_8$: C, 68.50; H, 5.38; N, 2.58. Found: C, 68.27; H, 5.19; N, 2.33.

Ethyl 5-(4-(2,3-dioxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6h). Yellow solid, yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.86–1.94 (4H, m, 2× —CH_2—), 3.78 (2H, t, J = 8.0 Hz, —CH_2—), 3.84 (3H, s, OCH_3), 4.04 (2H, t, J = 4.0 Hz, —CH_2—), 4.38 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.85–6.91 (2H, m, Ar—H), 6.94–6.89 (2H, m, Ar—H), 7.06 (1H, t, J = 8.0 Hz, Ar—H), 7.34 (1H, d, J = 12.0 Hz, Ar—H), 7.48 (1H, d, J = 4.0 Hz, Ar—H), 7.50–7.53 (1H, m, Ar—H), 7.95–7.99 (2H, m, Ar—H). ESI–MS *m/z*: 536 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{27}NO_7$: C, 70.17; H, 5.30; N, 2.73. Found: C, 70.02; H, 5.11; N, 2.59.

Ethyl 5-(4-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl) propoxy)-2-phenylbenzofuran-3-carboxylate (6i). Yellow solid, yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, —CH_2—), 3.92 (2H, t, J = 4.0 Hz, —CH_2—), 4.08 (2H, t, J = 4.0 Hz, —CH_2—), 4.21 (3H, s, $NOCH_3$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.18–7.21 (1H, m, Ar—H), 7.30–7.32 (1H, m, Ar—H), 7.38 (1H, d, J = 4.0 Hz, Ar—H), 7.53–7.61 (4H, m, Ar—H), 7.68 (1H, d, J = 4.0 Hz, Ar—H), 7.93–7.96 (2H, m, Ar—H). ESI–MS *m/z*: 539 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{25}FN_2O_6$: C, 67.44; H, 4.88; N, 5.42. Found: C, 67.19; H, 4.67; N, 5.25.

Ethyl 5-(4-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl) propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6j). Yellow solid, yield: 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, —CH_2—), 3.86 (3H, s, OCH_3), 3.92 (2H, t, J = 4.0 Hz, —CH_2—), 4.08 (2H, t, J = 4.0 Hz, —CH_2—), 4.22 (3H, s, $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.91 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.10 (2H, d, J = 4.0 Hz, Ar—H), 7.20–7.23 (1H, m, Ar—H), 7.32–7.37 (2H, m, Ar—H), 7.58 (1H, d, J = 8.0 Hz, Ar—H), 7.70 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.95–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 569 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{27}FN_2O_7$: C, 65.93; H, 4.98; N, 5.13. Found: C, 65.77; H, 4.72; N, 5.06.

Ethyl 5-(4-(5-fluoro-3-(ethoxyimino)-2-oxoindolin-1-yl) propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6k). Yellow solid, yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29–1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, —CH_2—), 3.85 (3H, s, OCH_3), 3.92 (2H, t, J = 4.0 Hz, —CH_2—), 4.08 (2H, t, J = 4.0 Hz, —CH_2—), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.48 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.91 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.10 (2H, d, J = 4.0 Hz, Ar—H), 7.20–7.23 (1H, m, Ar—H), 7.32–7.37 (2H, m, Ar—H), 7.58 (1H, d, J = 8.0 Hz, Ar—H), 7.70 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.95–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 583 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{29}FN_2O_7$: C, 66.42; H, 5.21; N, 5.00. Found: C, 66.19; H, 5.03; N, 4.87.

Ethyl 5-(3-(5-methoxy-3-(methoxyimino)-2-oxoindolin-1-yl) propoxy)-2-phenylbenzofuran-3-carboxylate (6l). Yellow solid, yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, dd, J = 4.0, 8.0 Hz, —CH_2—), 3.74 (3H, s, OCH_3), 3.90 (2H, t, J = 8.0 Hz, —CH_2—), 4.08 (2H, t, J = 4.0 Hz, —CH_2—), 4.20 (3H, s, $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 6.99–7.13 (2H, m, Ar—H), 7.39 (1H, d, J = 4.0 Hz, Ar—H), 7.48 (1H, d, J = 4.0 Hz, Ar—H), 7.54–7.58 (3H, m, Ar—H), 7.62 (1H, d, J = 8.0 Hz, Ar—H), 7.94–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 551 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{28}N_2O_7$: C, 68.17; H, 5.34; N, 5.30. Found: C, 67.96; H, 5.09; N, 5.11.

Ethyl 5-(3-(5-methoxy-3-(methoxyimino)-2-oxoindolin-1-yl) propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6m). Yellow solid, yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.09 (2H, dd, J = 4.0, 8.0 Hz, —CH_2—), 3.75 (3H, s, OCH_3), 3.86–3.91 (5H, m, —CH_2— and OCH_3), 4.05–4.20 (5H, m, —CH_2— and $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.01–7.11 (4H, m, Ar—H), 7.48 (1H, d, J = 4.0 Hz, Ar—H), 7.56 (1H, d, J = 4.0 Hz, Ar—H), 7.62 (1H, d, J = 8.0 Hz, Ar—H), 7.95–7.97 (2H, m, Ar—H). ESI–MS *m/z*: 581 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{30}N_2O_8$: C, 66.66; H, 5.41; N, 5.02. Found: C, 66.51; H, 5.27; N, 4.86.

Ethyl 5-(3-(5-methoxy-3-(ethoxyimino)-2-oxoindolin-1-yl) propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6n). Yellow solid, yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, J = 4.0 Hz, —CH_2—), 3.93 (2H, t, J = 4.0 Hz, —CH_2—), 4.03 (2H, t, J = 4.0 Hz, —CH_2—), 4.34 (2H, q,

J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.45 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.90–7.09 (5H, m, Ar—H), 7.36–7.56 (3H, m, Ar—H), 7.93–7.96 (2H, m, Ar—H). ESI–MS *m/z*: 595 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{32}H_{32}N_2O_8$: C, 67.12; H, 5.63; N, 4.89. Found: C, 66.97; H, 5.52; N, 4.67.

Ethyl 5-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (6o). Yellow solid, yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29–1.38 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.08 (2H, dd, J = 4.0, 8.0 Hz, —CH_2—), 3.75 (3H, s, OCH_3), 3.83–3.89 (5H, m, —CH_2— and OCH_3), 4.06 (2H, t, J = 4.0 Hz, —CH_2—), 4.20 (3H, s, $NOCH_3$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.45 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.98–7.20 (3H, m, Ar—H), 7.40–7.62 (4H, m, Ar—H), 7.89–7.97 (3H, m, Ar—H). ESI–MS *m/z*: 521 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.71; H, 5.06; N, 5.44.

Ethyl 5-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6p). Yellow solid, yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.25 (2H, t, J = 4.0 Hz, —CH_2—), 3.90 (3H, s, OCH_3), 4.02 (2H, t, J = 4.0 Hz, —CH_2—), 4.12 (2H, t, J = 4.0 Hz, —CH_2—), 4.31 (3H, s, $NOCH_3$), 4.43 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.92–6.97 (2H, m, Ar—H), 7.01–7.07 (3H, m, Ar—H), 7.28–7.33 (1H, m, Ar—H), 7.42 (1H, d, J = 8.0 Hz, Ar—H), 7.52 (1H, d, J = 4.0 Hz, Ar—H), 7.96 (1H, d, J = 8.0 Hz, Ar—H), 8.02 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 551 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{28}N_2O_7$: C, 68.17; H, 5.34; N, 5.30. Found: C, 67.95; H, 5.12; N, 5.09.

Ethyl 5-(3-(3-(ethoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6q). Yellow solid, yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, J = 8.0 Hz, —CH_2—), 3.86 (3H, s, OCH_3), 3.93 (2H, t, J = 8.0 Hz, —CH_2—), 4.08 (2H, t, J = 4.0 Hz, —CH_2—), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.46 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.92 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.07–7.11 (3H, m, Ar—H), 7.18 (1H, d, J = 8.0 Hz, Ar—H), 7.38–7.43 (2H, m, Ar—H), 7.56 (1H, d, J = 8.0 Hz, Ar—H), 7.92 (1H, d, J = 8.0 Hz, Ar—H), 7.97 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 565 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{30}N_2O_7$: C, 68.62; H, 5.57; N, 5.16. Found: C, 68.51; H, 5.39; N, 4.95.

Ethyl 5-(4-(3-(methoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6r). Yellow solid, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.74–1.78 (4H, m, 2× —CH_2—), 3.78 (2H, t, J = 4.0 Hz, —CH_2—), 3.85 (3H, s, OCH_3), 4.04 (2H, t, J = 4.0 Hz, —CH_2—), 4.19 (3H, s, $NOCH_3$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.93 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.06–7.09 (3H, m, Ar—H), 7.16 (1H, d, J = 8.0 Hz, Ar—H), 7.37–7.42 (2H, m, Ar—H), 7.52 (1H, d, J = 12.0 Hz, Ar—H), 7.86 (1H, d, J = 8.0 Hz, Ar—H), 7.96 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 565 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{30}N_2O_7$: C, 68.62; H, 5.57; N, 5.16. Found: C, 68.43; H, 5.31; N, 5.02.

Ethyl 5-(4-(3-(ethoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6s). Yellow solid, yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 1.78–1.81 (4H, m, 2× —CH_2—), 3.79 (2H, t, J = 8.0 Hz, —CH_2—), 3.85 (3H, s, OCH_3), 4.06 (2H, t, J = 4.0 Hz, —CH_2—), 4.33 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.46 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.95 (1H, dd, J = 4.0, 8.0 Hz, Ar—H), 7.08–7.11 (3H, m, Ar—H), 7.18 (1H, d, J = 8.0 Hz, Ar—H), 7.38–7.41 (2H, m, Ar—H), 7.56 (1H, d, J = 8.0 Hz, Ar—H), 7.90 (1H, d, J = 8.0 Hz, Ar—H), 7.97 (2H, d, J = 8.0 Hz, Ar—H). ESI–MS *m/z*: 579 $[M + Na]^+$. Elemental *Anal*. Calcd (%) for $C_{32}H_{32}N_2O_7$: C, 69.05; H, 5.80; N, 5.03. Found: C, 68.77; H, 5.61; N, 4.96.

Anti-cancer activities. All the synthesized hybrids **6a–s** were investigated for their *in vitro* anti-cancer 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 [20]. 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.;. L.; Ellisen, 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] World Health Organization. Global Health Observatory (GHO). http://www.who.int/gho/en/

[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] Xu, Z.; Zhao, S. J.; Lv, Z. S.; Feng, L. S.; Wang, Y. L.; Zhang, F.; Bai, L. Y.; Deng, J. L. Eur J Med Chem 2019, 162, 266.

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

[8] 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.

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

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

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

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

[13] Baldisserotto, A.; Demurtas, M.; Lampronti, I.; Moi, D.; Balboni, G.; Vertuani, S.; Manfredini, S.; Onnis, V. Eur J Med Chem 2018, 156, 118.

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

[15] Coskun, D.; Erkisa, M.; Ulukaya, E.; Coskun, M. F.; Ari, F. Eur J Med Chem 2017, 136, 212.

[16] 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.

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

[18] Aggarwal, A.; Parai, M. K.; Shetty, N.; Wallis, D.; Woolhiser, L.; Hastings, C.; Dutta, N. K.; Galaviz, S.; Dhakal, R. C.; Shrestha, R.; Wakabayashi, S.; Walpole, C.; Matthews, D.; Floyd, D.; Scullion, P.; Riley, J.; Epemolu, O.; Norval, S.; Snavely, T.; Robertson, G. T.; Rubin, E. J.; Loerger, T. R.; Sirgel, F. A.; Merwe, R.; Helden, P. D.; Keller, P.; Böttger, E. C.; Karakousis, P. C.; Lenaerts, A. J.; Sacchettini, J. C. Cell 2017, 170, 249.

[19] Gao, F.; Yang, H.; Lu, T. Y.; Chen, Z. J.; Ma, L.; Xu, Z.; Lu, G. M. Eur J Med Chem 2018, 159, 277.

[20] 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.

[21] Xu, Z.; Song, X. F.; Hu, Y. Q.; Qiang, M.; Lv, Z. S. Eur J Med Chem 2017, 138, 66.