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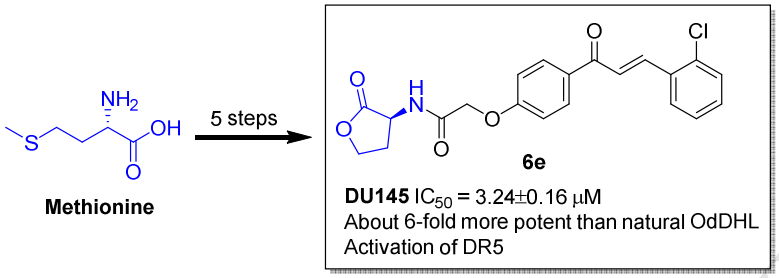
Graphic Abstract



Three series of new homoserine lactones were synthesized from methionine, which exhibited synergistic effects with TRAIL on the growth inhibition and cell apoptosis of DU145 cells possibly *via* activating DR5.

Synthesis of New Chalcone-Based Homoserine Lactones and Their Antiproliferative Activity Evaluation

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Abstract: Three series of new homoserine lactone analogs were efficiently synthesized starting from methionine and further evaluated for their antiproliferative activity against different cancer cell lines. Among these compounds, some of the chalcone containing compounds **6a-n** showed acceptable antiproliferative activity against prostate cancer cells DU145 and PC-3 with the IC_{50} values less than 10 μM. Compounds **6c**, **6e** and **6h** inhibited growth of DU145 and PC-3 cells at low micromolar levels with the IC_{50} values ranging from 3.0 to 5.0 μM, much more potent than natural OdDHL. Compound **6e** concentration-dependently inhibited colony formation and cell migration of DU145 cells. A synergistic effect on the growth inhibition and the apoptosis of DU145 cells was observed when compound **6e** was used in combination with TRAIL. OdDHL or **6e** treatment concentration-dependently activated TRAIL death receptor DR5 which may account for the observed synergistic effect of **6e** or OdDHL with TRAIL on the growth inhibition and cell apoptosis. Compound **6e** also inhibited migration of DU145 cells in a time- and concentration-dependent manner. The data suggest that quorum sensing molecules OdDHL and **6e** may improve the sensitivity of DU145 cells toward TRAIL *via* activating DR5, compound **6e** may be used as a potential lead compound for developing new TRAIL receptor agonists.

Keywords: Homoserine lactones; AHLs; OdDHL; TRAIL; Death Receptor 5

1. Introduction

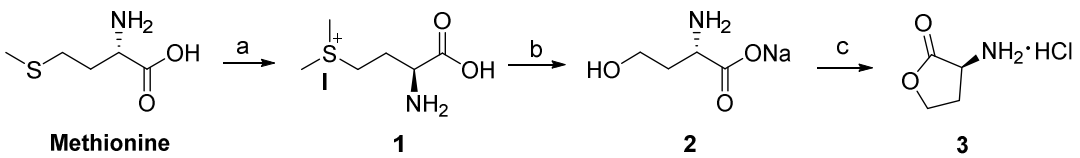
The *tumor necrosis factor* (*TNF*)-related apoptosis-inducing ligand (TRAIL, also known as Apo-2L and TNFSF10), a member of the *TNF* superfamily, was first reported to be an apoptosis-inducing cytokine in 1995 and was subsequently proved to be able to induce apoptosis of diverse cancer cell types in caspase-dependent manner by cross-linking TRAIL death receptors DR4/TRAIL-R1 and DR5/TRAIL-R2 while sparing vital normal cells [1-3]. TRAIL deficiency has been observed in a variety of human cancers and is also associated with carcinogen-induced tumorigenesis and metastasis in mice, and restoration of TRAIL can enhance sensitivity of tumor cells to chemotherapeutic drugs [4-6]. Besides, treatment of recombinant TRAIL or TRAIL receptor agonists effectively eliminates tumor cells *in vivo*. To date, several TRAIL receptor agonistic antibodies (e.g. Dulanermin, MD5-1, etc.) are actively being developed for clinical cancer therapy [7, 8]. However, TRAIL-induced cell death involves complex extrinsic and intrinsic pathways, and some TRAIL receptor agonists have basically failed to induce apoptosis because of the poor agonistic activity. All these render tumor cells resistant to known TRAIL receptor agonists. Therefore, the discovery of new agonists with increased bioactivity targeting TRAIL receptors or novel chemotypes that can increase DR4/TRAIL-R1 and/or DR5/TRAIL-R2 expression has been highly pursued in last decades, aiming to overcome the resistance observed. To date, some synthetic compounds including marketed drugs (e.g. Bortezomib, etc.), natural products and nanoparticles being able to overcome resistance have been identified to treat cancers [9-14]. Recently, Janda and co-workers reported that *N*-acylhomoserine lactone (AHL) OdDHL (also known as C12), a natural quorum sensing signaling molecule produced by *Pseudomonas aeruginosa*, can result in a strong pro-apoptotic response to TNF or TRAIL and also lead to MAPK p38 activation when combined with TRAIL, finally overcoming the TRAIL resistance [15]. Natural products have long been recognized as rich sources to identify new agents, over 100 natural products and analogs are currently being used in clinic [16-18]. Inspired by the interesting biological profiles of OdDHL [19] and in continuation with our previous work on the identification of new anticancer leads [20,

21], we herein report the design and synthesis of a library of AHLs and their underlying mechanisms of inducing cell death.

2. Results and discussion

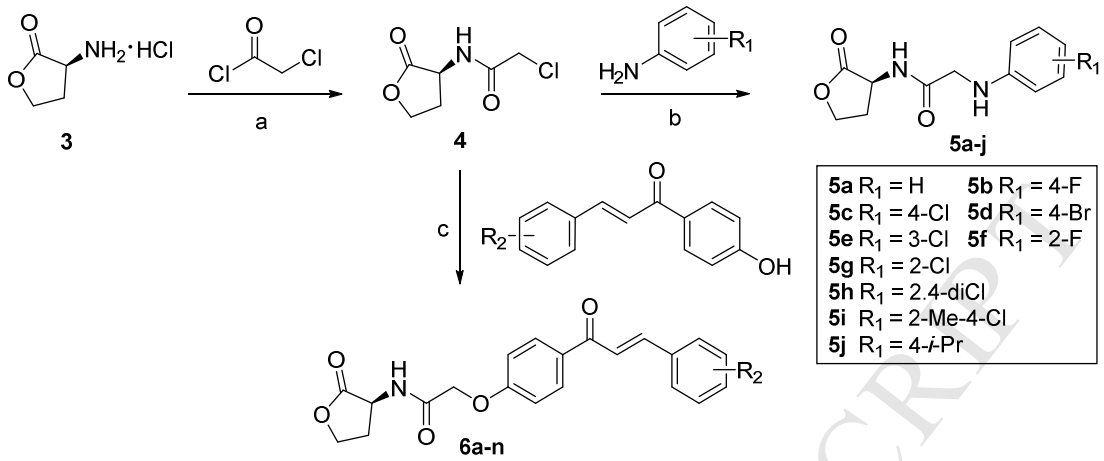
2.1. Chemistry

Homoserine lactone hydrochloride (compound **3**) was efficiently synthesized from methionine following our previously reported methods (Scheme 1) [20, 21]. With this key intermediate in hand, we next synthesized a focused library of AHL analogs by introducing different terminal moieties. In our previous work, we found that the incorporation of chalcone scaffold can improve the antiproliferative activity of the AHL/chalcone hybrids [21-24]. Therefore, in this design, the chalcone scaffold was also introduced to the AHL *via* suitable linker to further explore its effect on the activity. In addition, the dithiocarbamate derivatives have been reported to possess diverse and profound biological activities [25, 26]. The installation of such group may endow the target compounds with improved or new biological profiles. Specifically, treatment of compound **3** with chloroacetyl chloride in the presence of $NaHCO_3$ yielded compound **4**, which then reacted with various anilines to afford compounds **5a-j**. Similarly, compound **4** reacted with hydroxylated chalcones in the presence of K_2CO_3 and catalytic KI in MeCN to give **6a-n** (Scheme 2). Compounds **8a-j** were efficiently synthesized from the corresponding phenols through two steps (Scheme 3). Specifically, substituted phenols reacted with 1,2-dibromoethane in the presence of NaOH in MeOH to give compounds **7a-j**, which then reacted with CS_2 and compound **3** in the presence of Na_3PO_4•$12H_2O$ in acetone to form compounds **8a-j** (Scheme 3). In order to compare the activity of the synthesized compounds with **OdDHL** and explore further SARs, **OdDHL** were synthesized following the previously reported procedures (Scheme 4) [20, 21]. **S12** was also synthesized from compound **3** as described for the synthesis of compounds **8a-j** (Scheme 5).



Scheme 1. Synthesis of homoserine lactone hydrochloride **3**. Reagents and conditions:

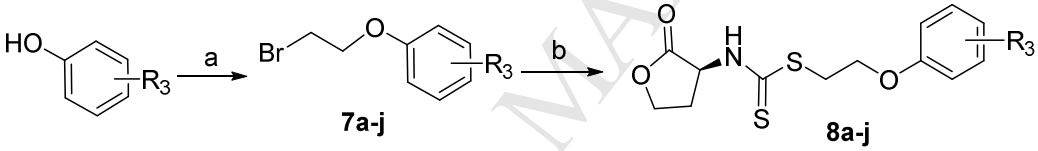
(a) MeOH/H_2O, CH_3I, r.t., 20h; (b) $NaHCO_3$ aq, rt~reflux 12h; (c) 6M HCl, 30% H_2O_2, reflux, 12h.



5a R_1 = H **5b** R_1 = 4-F
5c R_1 = 4-Cl **5d** R_1 = 4-Br
5e R_1 = 3-Cl **5f** R_1 = 2-F
5g R_1 = 2-Cl
5h R_1 = 2.4-diCl
5i R_1 = 2-Me-4-Cl
5j R_1 = 4-*i*-Pr

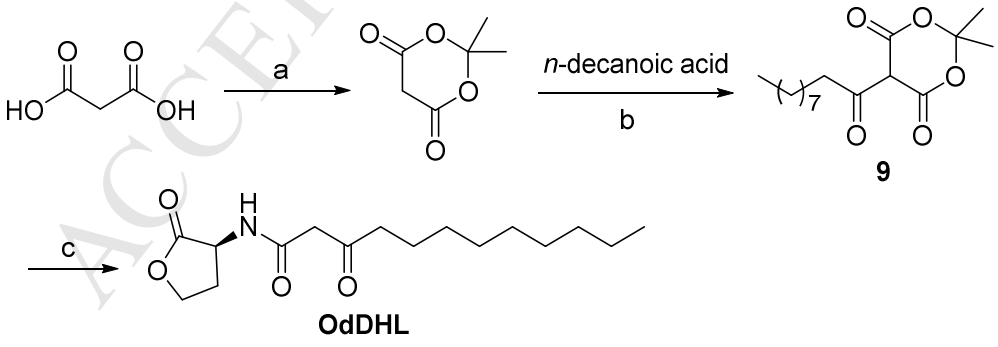
6a R_2 = 4-i-Pr **6b** R_2 = H **6c** R_2 = 3-Cl **6d** R_2 = 2-OMe **6e** R_2 = 2-Cl **6f** R_2 = 2,4-diCl
6g R_2 = 3-NO_2 **6h** R_2 = 2-Br **6i** R_2 = 3,4-diF, **6j** R_2 = 4-Br **6k** = 3-F, **6l** = 4-*t*-Bu **6m** = 3-Br, **6n** = 4-F

Scheme 2. Synthesis of compounds **5a-j** and **6a-n**. Reagents and conditions: (a) $NaHCO_3$, DCM/H_2O; (b) KI, DMF, 60 ^oC~under reflux; (c) K_2CO_3, KI, MeCN, r.t. to under reflux, 6h.

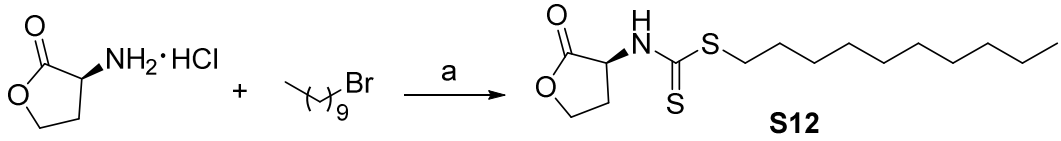


8a R_3 = H, **8b** R_3 = 4-acetyl, **8c** R_3 = 2-Bn, **8d** R_3 = 2-OMe-4-allyl, **8e** R_3 = 2-*i*-Pr-5-Me
8f R_3 = 2-NO_2, **8g** R_3 = 4-NO_2, **8h** R_3 = 4-Cl, **8i** R_3 = naphthyl **8j** R_3 = 2-ethoxyl

Scheme 3. Synthesis of compounds **8a-j**. Reagents and conditions: (a) 1,2-dibromoethane, aq. NaOH, MeOH, r.t.; (b) compound **3**, Na_3PO_4•$12H_2O$, CS_2, acetone.



Scheme 4. Synthesis of natural OdDHL. Reagents and conditions: (a) Ac_2O, H_2SO_4, 0 ^oC-rt. (b) DCC, DMAP, r.t. (c) Compound **3**, Et_3N, CH_3CN, reflux.



Scheme 5. Synthesis of compound **S12**. Reagents and conditions: (a) $Na_3PO_4 \cdot 12H_2O$, CS_2, acetone.

*2.2. The antiproliferative activity of synthesized AHLs, **OdDHL** and **S12***

The synthesized compounds were initially evaluated for their antiproliferative activity against different cancer cell lines including MCF-7, MGC-803, DU145 and PC-3 using the MTT assay [27], OdDHL and **S12** were used as the control. The primary data are summarized in Table 1. Evidently, compounds **5a-j** with the terminal aniline group were inactive against the tested cancer cell lines (IC_{50} > 64 μM) regardless of their substituents attached. The chalcone is a privileged scaffold that exists in a large number of natural products and pharmaceutically relevant small molecules. Chalcone-based hybridization/conjugation has yielded numerous structurally new and biologically important compounds with interesting antiproliferative activity [26]. To our delight, the incorporation of the chalcone scaffold improved the antiproliferative activity. For MCF-7 and MGC-803 cells, compounds **6a-n** exhibited weak to moderate inhibitory activity, no clear SARs were observed. Compound **6h** showed the best potency against MCF-7 cells with an IC_{50} value of 15.25 μM, compounds **6h** also displayed moderate inhibitory activity against MGC-803 cells (IC_{50} =12.17 μM), comparable to that of compound **6m** (IC_{50} = 11.87 μM). Interestingly, some of compounds **6a-n** showed selective and potent growth inhibition toward prostate cancer cells DU145 and PC-3 with the IC_{50} values less than 10 μM. Among these compounds, halogenated compounds **6c**, **6e** and **6h** displayed the best antiproliferative activity with the IC_{50} values less than 5.0 μM, significantly more potent than **OdDHL** and **S12**, unveiling the essential structural elements for the activity against prostate cancer cells. In contrast, the hydroxylated chalcone fragment of compound **6e** inhibited growth of DU145 cells with an IC_{50} value of 23.67±2.52 μM, about 7.3-fold less potent than **6e** (IC_{50} = 3.24±0.16 μM), suggesting the importance of the homoserine lactone/chalcone conjugate for the antiproliferative activity of **6e**. The toxicity of **6e** toward normal cell line GES-1 was also examined, showing relatively weak toxicity of **6e** (IC_{50} = 13.37±1.13 μM). Conceivably, more analogs could be obtained from readily accessible chalcone starting materials, the homoserine

lactone/chalcone hybrid **6e** could be used as a starting point for the development of next-generation small-molecule compounds targeting prostate cancer cells.

The dithiocarbamate group, due to the prevalence in bioactive molecules and synthetic simplicity, has been extensively used in the design of lead compounds or probe molecules. As represented in Table 1, compounds **8a-j** showed significantly decreased activity against the tested cancer cell lines, some of them were much more potent than **S12**, which was found to be devoid of the activity.

Table 1. The antiproliferative activity of synthesized *N*-acyl homoserine lactones (AHLs) against four human cancer cell lines

Compound	IC_{50} (μM) [a]			
	MCF-7	MGC-803	DU145	PC-3
5a-5j	>64	>64	>64	>64
6a	23.35±1.86	16.84±1.43	13.12±1.11	4.66±0.66
6b	>64	>64	48.34±1.56	56.77±1.75
6c	20.85±1.85	29.09±1.69	3.70±0.57	4.99±0.49
6d	>64	39.40±1.84	10.119±1.00	7.24±0.86
6e	17.43±1.51	27.07±1.75	3.24±0.16	4.61±0.33
6f	34.35±1.98	26.47±1.56	8.606±0.93	8.04±0.90
6g	>64	>64	41.794±1.62	56.25±1.71
6h	15.25±1.40	12.17±1.51	3.54±0.21	3.26±0.34
6i	>64	>64	19.82±1.29	21.89±1.34
6j	>64	50.96±1.71	51.67±1.77	>64
6k	>64	>64	17.23±1.23	23.18±1.19
6l	16.44±1.56	17.15±1.23	6.57±0.81	10.58±1.02
6m	28.34±1.45	11.87±1.50	9.80±0.99	7.89±0.86
6n	>64	>64	18.79±1.27	15.56±1.20
8a	>64	53.78±1.78	63.78±1.80	>64
8b	>64	>64	32.61±1.38	46.87±1.67
8c	39.49±1.05	32.31±1.50	>64	>64
8d	>64	27.92±1.44	>64	>64
8e	>64	43.37±1.80	>64	>64
8f	>64	46.98±1.82	33.42±1.52	23.98±1.38
8g	>64	>100	31.01±1.49	32.52±1.51
8h	50.53±1.56	51.12±1.78	>64	>64
8i	>64	>64	>64	>64
8j	>64	>64	28.25±1.45	24.12±1.24

OdDHL	26.24±1.68	29.53±1.29	19.33±0.98	22.51±1.34
S12	>64	>64	>64	>64

[a] Cells were treated with compounds for 72h, the data were presented as IC_{50} ± SD and analyzed with the SPSS16.0 software.

2.3. Colony formation assay

The favorable antiproliferative activity of compound **6e** against DU145 prompted us to investigate the effect on colony formation and cell migration. The clone formation of cancer cells represents an indirect estimation of neoplastic transformation [28]. As shown in Fig. 1A and 1B, both OdDHL and compound **6e** are able to inhibit colony formation of DU145 cells concentration-dependently. Evidently, compound **6e** exhibited stronger inhibitory effect than OdDHL and completely inhibited colony formation at 5.0 μM.

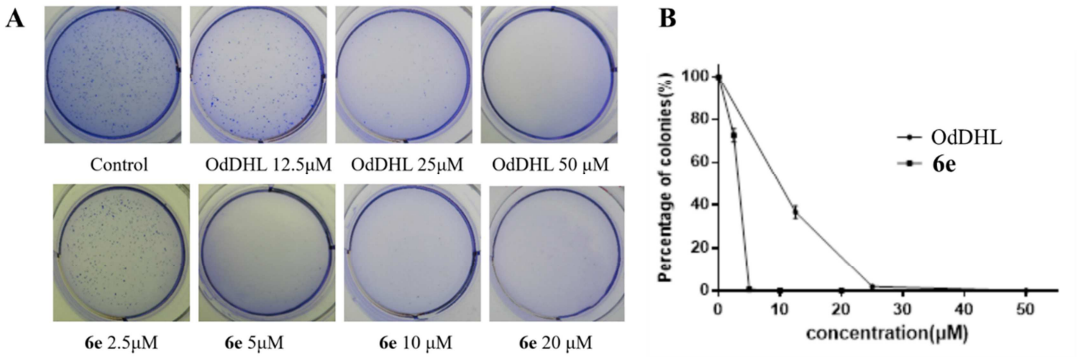


Figure 1. Effect of OdDHL and **6e** on the colony formation of DU145 cells. (A) Representative images of DU145 colonies after treatment at the indicated concentrations for 21 d; (B) The percentage of colonies after treatment with **6e** and OdDHL at the indicated concentrations for 21 days.

*2.4. The synergistic effect of **6e** and TRAIL on the growth inhibition of DU145 cells*

As shown in Fig. 2A, compound **6e** and OdDHL inhibited growth of DU145 cells in a time-dependent manner. After 24 and 48h treatment, these two compounds showed comparable inhibitory effect toward DU145 cells. However, compound **6e** showed higher potency than OdDHL after 72h treatment (IC_{50} = 3.24 *vs*. 19.33 μM). Next, we investigated the effect of the combination of compound **6e** or OdDHL with TRAIL on the growth inhibition of DU145 cells. As shown in Fig. 2B (c-e), OdDHL (5.0 μM)

and TRAIL (100 ng/mL) showed a synergistic effect on the growth inhibition of DU145 cells with around 20% of DU145 cells inhibited. In contrast, the combination of **6e** (2.5 μM) and TRAIL (100 ng/mL) displayed better growth inhibition of DU145 cells even at a lower concentration (2.5 μM) with the growth inhibition rate of about 50% (Fig. 2B-b), higher than that of **6e** and TRAIL treatment alone (Fig. 2B, a & e). Our data clearly suggest that homoserine lactone analogs and TRAIL have synergistic effects on the growth inhibition of cancel cells, and homoserine lactone analogs, e.g. **6e**, could be potentially used to overcome the resistance of tumor cells toward TRAIL.

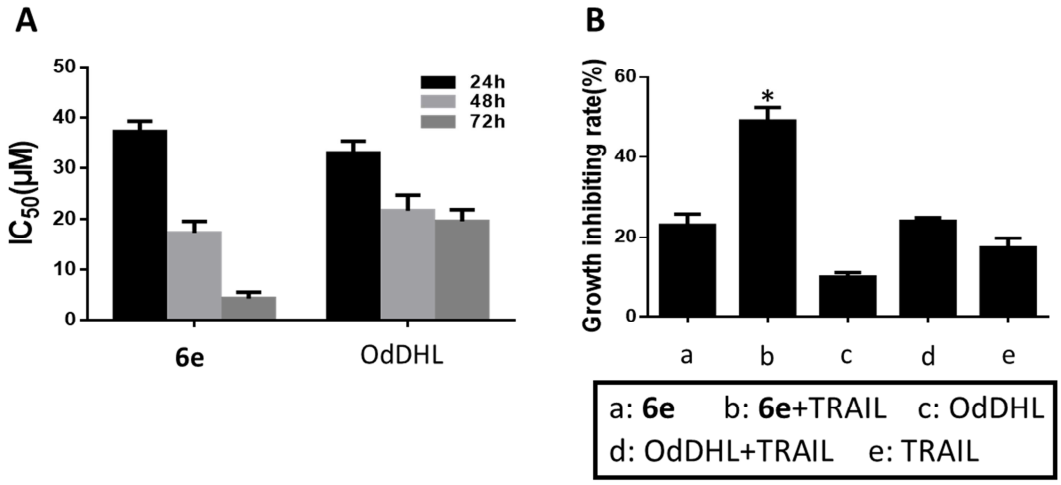


Figure 2. Growth inhibition of compound **6e** and OdDHL alone and in combination with TRAIL toward DU145 cells. (A) IC_{50} value (μM) of **6e** and OdDHL of inducing cell death of DU145 after treatment for 24, 48, and 72 h; (B) Effect of **6e**, OdDHL or their combination with TRAIL on the growth inhibition of DU145 cells (**6e**: 2.5 μM, OdDHL: 5.0 μM, TRAIL: 100 ng/mL). *P < 0.05 was considered statistically significant. Data are the mean ± SD. The experiment was repeated three times (n = 3).

2.5. The effect of homoserine lactone alone or its combination with TRAIL on apoptosis of DU145 cells

In view of the ability of compound **6e**, OdDHL or their combination with TRAIL inhibiting growth of DU145 cells, we next investigated the potential effect on the apoptosis of DU145 cells. As depicted in Fig. 3A, after treatment with OdDHL (10 μM), **6e** (5.0 μM) and TRAIL (100 ng/mL) alone for 24 hours, characteristic

apoptotic morphological changes of DU145 cells were observed, especially for the group treated with the combination of OdDHL or **6e** with TRAIL including cell rounding, chromatin shrinkage and formation of apoptotic bodies. To further explore the effect of the combination of OdDHL or **6e** with TRAIL on cell apoptosis, the apoptotic analysis was also performed with Annexin V-FITC/PI double staining. Clearly, treatment of DU145 cells with the combination of OdDHL or compound **6e** with TRAIL induced apoptosis (Fig. 3B-C), the statistical analysis showed that the corresponding apoptotic rate was higher than that of the group treated with **6e**, OdDHL and TRAIL alone ($P < 0.01$, Fig. 3C). Specifically, the percentage of apoptotic cells treated with OdDHL+TRAIL and **6e**+TRAIL, respectively at the indicated concentrations was up to 21.9% and 15.1%, respectively (Fig. 3B).

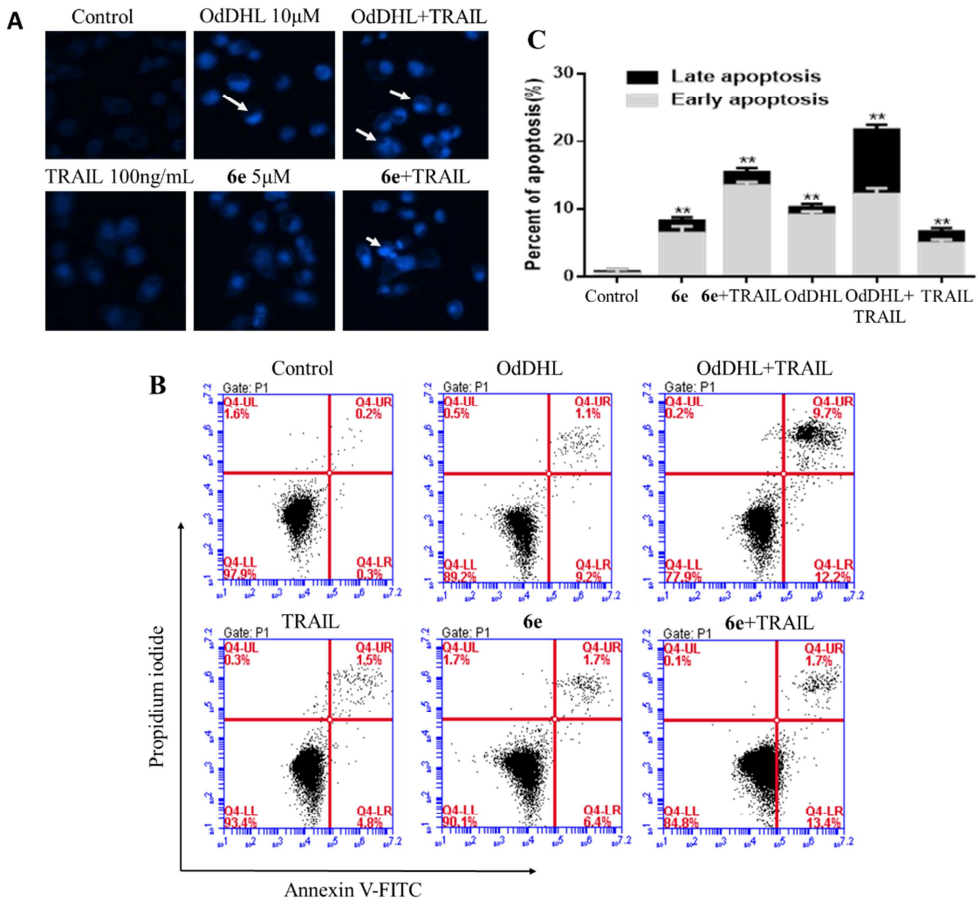


Figure 3. Effect of **6e**, OdDHL or their combination with TRAIL on the apoptosis of DU145 cells. (A) Apoptosis analysis with Hoechst 33258 staining after 24 h treatment; (B-C) Quantitative analysis of apoptotic cells using Annexin V-FITC/PI double

staining and flow-cytometry calculation. $^{**}P < 0.01$ was considered statistically highly significant. Data are the mean ± SD. All experiments were carried out three times (n = 3).

2.6. The effect of homoserine lactone alone or its combination with TRAIL on expression changes of apoptosis-related proteins in DU145 cells

The observed ability of the combination of OdDHL or **6e** with TRAIL in inducing apoptosis of DU145 cells promoted us to further investigate the effect on the apoptosis-related proteins (Fig. 4). Initially, we evaluated the effect of TRAIL, OdDHL and **6e** on the activity of caspase-3/7. Compared to the control group, OdDHL and **6e** marginally activated caspase-3/7 even at extremely high concentrations (50 μM for OdDHL). In contrast, the combination of OdDHL (10 μM) or **6e** (5 μM) with TRAIL (100 ng/mL) led to about 2- and 3-fold activation of caspase-3/7, respectively ($P < 0.05$, Fig. 4). The data indicate that OdDHL or **6e** with TRAIL are synergistic in activating caspase-3/7.

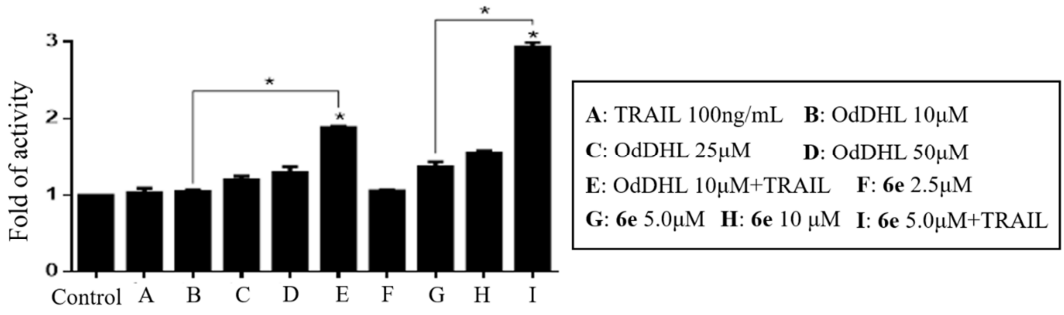


Figure 4. The effect of **6e**, OdDHL or their combination with TRAIL on the activity of caspase-3/7 in DU145 cells after 24 h treatment. All experiments were carried out three times (n = 3). $^{*}P < 0.05$ was considered statistically significant. Data are the mean ± SD.

*2.7. The effect of homoserine lactones OdDHL and **6e** on the cell migration of DU145 cells*

In light of the acceptable potency of **6e** toward DU145 cells (IC_{50} = 3.24 μM), we then examined the effect of **6e** and OdDHL on the cell migration ability of DU145 cells by the wound healing assay. As shown in Fig. 5, both compound **6e** and OdDHL inhibited migration of DU145 cells in a time-and concentration-dependent manner,

and **6e** showed stronger migration inhibition than OdDHL.

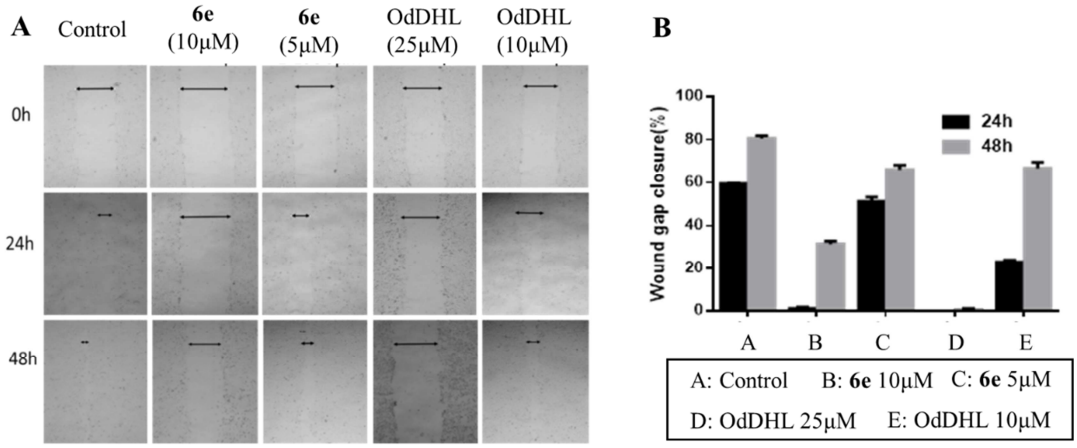


Figure 5. Migration inhibition of DU145 cell upon treated with **6e** and OdDHL. (A) The effect of **6e** and OdDHL on the cell migration of DU145 cells after 24 and 48 h treatment at the indicated concentrations; (B) Statistic analysis of would gap closure after 24 and 48 h treatment at different concentrations.

3. Conclusions

In summary, three series of new homoserine lactone analogs were efficiently synthesized starting from methionine, the key intermediate homoserine lactone hydrochloride (compound **3**) and natural OdDHL were also synthesized following our previously reported methods. The synthesized homoserine lactone analogs structurally feature different terminal motifs, hoping to identify essential structural elements for the activity. SARs studies showed that compounds **6a-n** showed improved antiproliferative activity against the tested cancer cell lines and were particularly effective against prostate cancer cells DU145 and PC-3, underscoring the importance of the chalcone scaffold for the observed activity. Among these compounds, some of them were much more potent than natural OdDHL and S12 with the IC_{50} values less than 10 μM. Especially, compounds **6c**, **6e** and **6h** inhibited growth of DU145 and PC-3 cells at low micromolar levels with the IC_{50} values ranging from 3.0 to 5.0 μM. Compound **6e** concentration-dependently inhibited colony formation and cell migration of DU145 cells, being more potent than natural OdDHL. A synergistic effect on the growth inhibition and the apoptosis of DU145 cells was observed when

compound **6e** was used in combination with TRAIL. OdDHL or **6e** treatment concentration-dependently activated TRAIL death receptor DR5 which may account for the observed synergistic effect of **6e** or OdDHL with TRAIL on the growth inhibition and cell apoptosis. Compound **6e** time and concentration-dependently inhibited migration of DU145 cells. Compound **6e** may be used as a potential lead compound for developing new TRAIL receptor agonists. The development of new small molecules that activate death receptors may be a viable strategy for cancer therapy, especially for those resistant to known TRAIL receptor agonists.

4. Experimental section

4.1. General

Reagents and solvents were purchased from commercial sources and were used without further purification. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Bruker (DPX-400) spectrometer. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-Tof of Micromass spectrometer by electrospray ionizaton (ESI).

*4.2. Synthesis of Homoserine lactone hydrochloride **3** and natural OdDHL*

Homoserine lactone hydrochloride **3** and OdDHL were efficiently synthesized from methionine following our previously reported methods [20, 21]. Therefore, the synthetic details are not discussed here.

(*S*)-3-aminodihydrofuran-2(3*H*)-one hydrochloride (**3**), white solid, m.p. 218-220 □; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.04 (s, 3H, NH_2•HCl), 4.45 (t, J = 8.8 Hz, 1H, -O-CH_2), 4.37-4.21(m, 2H, -O-CH_2, -CH-CO), 2.62-2.51 (m, 1H, -O-CH_2-CH_2-CH), 2.42-2.27 (m, 1H, -O-CH_2-CH_2-CH); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 173.81, 66.71, 48.12, 27.42. HRMS (ESI) Calcd for $C_4H_8ClNO_2$ $[M+H]^+$: 138.0322, found: 138.0325.

(*S*)-3-oxo-*N*-(2-oxotetrahydrofuran-3-yl)dodecanamide (**OdDHL**), white solid, m.p. 84-86 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71 (d, *J* = 5.7 Hz, 1H, -CH-NH), 4.66-4.58 (m, 1H, -O-CH_2), 4.49 (t, *J* = 9.0 Hz, 1H, -CH-NH), 4.34-4.15 (m, 1H, -O-CH_2), 3.49 (s, 2H, -CO-CH_2-CO), 2.82-2.72 (m, 1H, -O-CH_2-CH_2-CH), 2.57-2.52 (m, 2H,

-CO-CH_2-CH_2), 2.34-2.20 (m, 1H, -O-CH_2-CH_2-CH), 1.65-1.55 (m, 2H, -CO-CH_2-CH_2), 1.28 (m, 12H, -CO-CH_2-(CH_2)6), 0.89 (t, *J* = 6.6 Hz, 3H, -CH_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.61, 174.84, 166.38, 65.89, 49.03, 48.11, 43.93, 31.83, 29.80, 29.37, 29.35, 29.24, 28.98, 23.35, 22.65, 14.10. HR-MS (ESI): Calcd. $C_{16}H_{27}NNaO_4$, $[M+Na]^+$m/z: 320.1838, found: 320.1840.

4.3. Synthesis of ***S12***

To a solution of homoserine lactone hydrochloride **3** (153 mg, 1.11 mmol) and $Na_3PO4{\cdot}12H_2O$ (634 mg, 1.66 mmol) in acetone (15 mL) was added CS_2 (141μL, 2.32 mmol) slowly. After 0.5h stirring, 1-bromo decane (219mg, 0.99mmol) was added. Upon completion of the reaction indicated by TLC，acetone was removed under vacuum, the resulting residue was dissolved with dichloromethane (DCM) and washed with brine for 2-3 times, the aqueous layer was extracted with DCM for 2-3 times，the combined organic layers were evacuated to give the residue, which was then subject to column chromatography, affording white solid, decyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (**S12**)，m.p. 66-68 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16.9 Hz, 1H, -CO-N<u>H</u>), 4.52 (t, *J* = 9.0 Hz, 1H, -<u>CH</u>-NH), 4.36 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H, -CO-O-C<u>H_2</u>), 3.36–3.13 (m, 3H, -CO-O-C<u>H_2</u>, -S-C<u>H_2</u>), 2.18 (dd, *J* = 11.8, 9.2 Hz, 1H, -O-CH_2-<u>CH_2</u>-CH), 1.76-1.65 (m, 2H, -O-CH_2-<u>CH_2</u>-CH, -S-CH_2-<u>(CH_2)$_8$</u>), 1.50-1.21 (m, 15H, -S-CH_2-<u>(CH_2)$_8$</u>), 0.90 (t, *J* = 6.8 Hz, 3H, -CH_2-<u>CH_3</u>). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.98, 174.61, 66.29, 54.97, 36.06, 31.89, 30.32, 29.53, 29.48, 29.30, 29.13, 28.89, 28.74, 22.68, 14.11. HRMS (ESI): Calcd. $C_{15}H_{27}NO_2S_2Na$ $[M+Na]^+$ m/z:340.1381,found:340.1380.

4.4. Synthesis of compound ***4***

To a solution of homoserine lactone hydrochloride **3** (4.0 g, 22.52 mmol) in water (60 mL) was added $NaHCO_3$ (5.67 g, 67.58 mmol). 5 min later, DCM (60 mL) was added to the mixture followed by slow addition of chloroacetyl chloride (2.6 mL, 27.02 mmol). Upon completion of the reaction indicated by TLC, the DCM layer was separated and evacuated under vacuum to give the white solid, (*S*)-2-chloro-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (**4**), yield: 72%, m.p.121-122 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, *J* = 8.0 Hz, 1H, -CO-NH), 4.63 (dd, *J* = 20.0 Hz, *J* = 8.0 Hz, 1H, -O-CH_2), 4.35 (t, *J* = 8.0 Hz, 1H, -<u>CH</u>-NH), 4.21 (dd, *J* =

20.0 Hz, *J*= 8.0 Hz, 1H, -O-CH_2), 4.14 (s, 2H, -CH_2-Cl), 2.44-2.36 (m, 1H, -O-CH_2-CH_2-CH), 2.24-2.15 (m, 1H, -O-CH_2-CH_2-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.30, 166.56, 65.80, 48.73, 42.71, 28.41. HRMS (ESI) Calcd for $C_6H_8ClNO_3$ $[M+H]^+$: 178.0271, found: 178.0273.

*4.5. General procedure for the synthesis of compounds **5a-j***

To a solution of compound **4** (150 mg, 0.84 mmol) in DMF (5 mL) was added KI (280 mg, 1.69 mmol). The resulting mixture was stirred at 60 ^oC for 2 h, the corresponding aniline (0.84 mmol) was added, and the mixture was stirred at 120 ^oC for 6 h. When the mixture was cooled to room temperature, the mixture was extracted with EtOAc for several times, the combined EtOAc layers were washed with water for several times and then dried under vacuum to give the residue, which was subject to column chromatography, affording compounds **5a-j**.

(*S*)-*N*-(2-oxotetrahydrofuran-3-yl)-2-(phenylamino)acetamide (compound **5a**), yield: 65%, white solid, m.p.135-137 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 8.1 Hz, 1H, -CO-NH), 7.16-7.00 (m, 2H, Ar-H), 6.66 -6.48 (m, 3H, Ar-H), 6.00 (t, *J* = 5.9 Hz, 1H, Ar-NH), 4.60 (dt, *J* = 10.8, 8.9 Hz, 1H, -O-CH_2), 4.33 (td, *J* = 8.8, 1.7 Hz, 1H, -CH-NH), 4.20 (ddd, *J* = 10.4, 8.7, 6.6 Hz, 1H, -O-CH_2), 3.66 (d, *J*= 5.9 Hz, 2H, -NH-CH_2), 2.41-2.29 (m, 1H, -O-CH_2-CH_2-CH), 2.27-2.07 (m, 1H, -O-CH_2-CH_2-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.64, 171.14, 148.87, 129.30, 117.04, 112.88, 65.71, 48.29, 47.53, 28.45. HR-MS (ESI): Calcd. $C_{12}H_{15}N_2O_3$, $[M+H]^+$m/z: 235.1083, found: 235.1081.

(*S*)-2-((4-fluorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5b**), yield: 55%, white solid, m.p.162-163 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 8.2 Hz, 1H, -CO-NH), 6.94 (t, *J* = 8.9 Hz, 2H, Ar-H), 6.57-6.51(m, 2H, Ar-H), 5.97 (s, 1H, Ar-NH), 4.60 (dt, *J* = 10.7, 8.9 Hz, 1H, -O-CH_2), 4.33 (d, *J* = 1.6 Hz, 1H, -CH-NH), 4.21 (ddd, *J* = 10.3, 8.8, 6.6 Hz, 1H, -O-CH_2), 3.65 (d, *J* = 5.9 Hz, 2H, -NH-CH_2), 2.41-2.27 (m, 1H , -O-CH_2-CH_2-CH), 2.27-2.09 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.65, 171.06, 156.37, 154.07,

145.57, 145.55, 115.78, 115.56, 113.68, 113.61, 65.71, 48.29, 47.96, 28.46. HR-MS (ESI): Calcd. $C_{12}H_{13}FN_2NaO_3$, $[M+Na]^+$m/z: 275.0808, found: 275.0802.

(*S*)-2-((4-chlorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5c**), yield: 63%, light yellow solid, m.p.146-147 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 8.1 Hz, 1H, -CO-NH), 7.12 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.55 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.22 (s, 1H, Ar-NH), 4.60 (d, *J* = 10.4 Hz, 1H, -O-CH_2), 4.33 (d, *J* = 1.6 Hz, 1H, -CH-NH), 4.21 (s, 1H, -O-CH_2), 3.68 (d, *J* = 5.9 Hz, 2H, -NH-CH_2), 2.41-2.30 (m, 1H, -O-CH_2-CH_2-CH), 2.19 (s, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.63, 170.77, 147.79, 128.97, 120.27, 114.22, 65.72, 48.31, 47.29, 28.48. HR-MS (ESI): Calcd. $C_{12}H_{13}ClN_2NaO_3$, [M+Na]+m/z: 291.0512, found: 291.0511.

(*S*)-2-((4-bromophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5d**), yield: 71%, light yellow solid, m.p.156-158 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 8.1 Hz, 1H, -CO-NH), 7.23 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.51 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.25 (s, 1H, Ar-NH), 4.60 (dt, *J* = 10.7, 8.9 Hz, 1H, -O-CH_2), 4.33 (dt, *J* = 8.8, 4.4 Hz, 1H, -CH-NH), 4.21 (ddd, *J* = 15.3, 8.8, 6.6 Hz, 1H,-O-CH_2), 3.67 (d, *J* = 5.9 Hz, 2H, -NH-CH_2), 2.40-2.29 (m, 1H, -O-CH_2-CH_2 -CH), 2.25-2.09 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.63, 170.72, 148.14, 131.78, 114.79, 107.65, 65.72, 48.31, 47.17, 28.48. HR-MS (ESI): Calcd. $C_{12}H_{13}BrN_2NaO_3$, [M+Na]+m/z: 335.0007, found: 335.0004 & 336.9978.

(*S*)-2-((3-chlorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5e**), yield: 64%, white solid, m.p.142-144 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J* = 8.1 Hz, 1H, -CO-NH), 7.09 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.58 (dt, *J* = 3.8, 1.6 Hz, 2H, Ar-H), 6.51 (s, 1H, Ar-H), 6.35 (s, 1H, Ar-NH), 4.59 (ddd, *J* = 34.8, 18.3, 11.2 Hz, 1H, -O-CH_2), 4.34 (d, *J* = 1.7 Hz, 1H, -CH-NH), 4.27-4.14 (m, 1H,-O-CH_2), 3.70 (d, *J* = 5.9 Hz, 2H, -NH-CH_2), 2.42-2.32 (m, 1H, -O-CH_2-CH_2-CH), 2.25-2.07 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.63, 170.66, 150.33, 134.01, 130.80, 116.33, 112.14, 111.44, 65.74, 48.33, 46.90, 28.46. HR-MS (ESI): Calcd. $C_{12}H_{13}ClN_2NaO_3$, [M+Na]+m/z: 291.0512, found: 291.0510.

(*S*)-2-((2-fluorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5f**), yield: 55%, white solid, m.p.148-151 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, *J* = 8.1 Hz, 1H, -CO-NH), 6.97 (s, 2H, Ar-H), 6.55 (s, 2H, Ar-H), 5.82 (s, 1H, Ar-NH), 4.60 (dd, *J* = 19.2, 8.9 Hz, 1H, -O-CH_2), 4.33 (s, 1H, -CH-NH), 4.20 (dd, *J* = 12.8, 6.1 Hz, 1H, -O-CH_2), 3.74 (d, *J* = 5.9 Hz, 2H, -NH-CH_2), 2.36 (dt, *J* = 9.9, 7.6 Hz, 1H, -O-CH_2-CH_2-CH), 2.26-2.07 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.62, 170.71, 152.56, 150.19, 136.90, 136.79, 125.21, 125.18, 116.89, 116.83, 114.88, 114.70, 112.62, 112.59, 65.72, 48.32, 46.92, 28.44. HR-MS (ESI): Calcd. $C_{12}H_{13}FN_2NaO_3$, [M+Na]+m/z: 275.0808, found: 275.0804.

(*S*)-2-((2-chlorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5g**), yield: 80%, white solid, m.p.152-154 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 8.0 Hz, 1H, -CO-NH), 7.28 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar-H), 7.14 (s, 1H, Ar-H), 6.64 (d, *J* = 1.0 Hz, 1H, Ar-H), 6.54-6.48 (m, 1H, Ar-H), 5.75 (s, 1H, Ar-NH), 4.61 (dt, *J* = 10.7, 8.9 Hz, 1H, -O-CH_2), 4.34 (td, *J* = 8.8, 1.5 Hz, 1H, -CH-NH), 4.27-4.15 (m, 1H, -O-CH_2), 3.80 (d, *J* = 5.7 Hz, 2H, -NH-CH_2), 2.44-2.31 (m, 1H, -O-CH_2-CH_2-CH), 2.26-2.11 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.60, 170.35, 144.22, 129.38, 128.49, 118.56, 117.72, 111.95, 65.75, 48.40, 46.83, 28.47. HRMS (ESI): Calcd. $C_{12}H_{13}ClN_2O_3$ $[M+H]^+$ m/z:269.0693, found: 269.0692.

(*S*)-2-((2,4-dichlorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5h**), yield: 77%, white solid, m.p.135-137 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 8.1 Hz, 1H, -CO-NH), 7.40 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-H), 6.50 (d, *J* = 8.8 Hz, 1H, Ar-H), 5.93 (s, 1H, Ar-NH), 4.61 (dt, *J* = 10.7, 8.9 Hz, 1H, -O-CH_2), 4.34 (d, *J* = 1.5 Hz, 1H, -CH-NH), 4.21 (ddd, *J* = 10.3, 8.8, 6.6 Hz, 1H, -O-CH_2), 3.81 (d, *J* = 5.8 Hz, 2H, -NH-CH_2), 2.42-2.33 (m, 1H, -O-CH_2-CH_2-CH), 2.24-2.12 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR(100 MHz, DMSO-d_6) δ 175.60, 170.07, 143.41, 128.62, 128.26, 120.15, 119.02, 112.83, 65.75, 48.39, 46.71, 28.47. HR-MS (ESI): Calcd. $C_{12}H_{12}C_{l2}N_2NaO_3$, $[M+Na]^+$m/z: 325.0123, found: 325.0122.

(*S*)-2-((2-methyl-4-dichlorophenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5i**), yield: 58%, white solid, m.p.131-133 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J* = 8.1 Hz, 1H, -CO-NH), 6.99 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.56 (dd, *J* = 7.8, 1.9 Hz, 1H, Ar-H), 6.30 (d, *J* = 1.8 Hz, 1H, Ar-H), 5.65 (s, 1H, Ar-NH), 4.60 (dd, *J* = 19.2, 8.9 Hz, 1H, -O-CH_2), 4.35 (d, *J* = 1.3 Hz, 1H, -CH-NH), 4.25-4.17 (m, 1H, -O-CH_2), 3.75 (d, *J* = 5.8 Hz, 2H, -NH-CH_2), 2.37 (ddd, *J* = 12.4, 9.9, 7.2 Hz, 1H, -O-CH_2-CH_2-CH), 2.20 (dd, *J* = 20.8, 10.7 Hz, 1H, -O-CH_2-CH_2-CH), 2.11 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.59, 170.71, 147.82, 131.69, 131.31, 121.44, 116.10, 109.27, 65.73, 48.37, 47.08, 28.39, 17.50. HR-MS (ESI): Calcd. $C_{13}H_{15}ClN_2NaO_3$, [M+Na]+m/z: 305.0669, found: 305.0670.

(*S*)-2-((4-isopropylphenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **5j**), yield: 74%, white solid, m.p.128-130 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, *J* = 8.1 Hz, 1H, -CO-NH), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.49 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.80 (s, 1H, Ar-NH), 4.59 (dd, *J* = 19.2, 8.9 Hz, 1H, -O-CH_2), 4.33 (d, *J* = 1.4 Hz, 1H, -CH-NH), 4.25-4.16 (m, 1H, -O-CH_2), 3.63 (d, *J* = 5.8 Hz, 2H, -NH-CH_2), 2.73 (dq, *J* = 13.7, 6.9 Hz, 1H, -O-CH_2-CH_2-CH), 2.35 (ddd, *J* = 12.4, 9.8, 7.2 Hz, 1H, -O-CH_2-CH_2-CH), 2.21 (dt, *J* = 21.6, 10.8 Hz, 1H, Ar-CH), 1.14 (d, *J* = 6.9 Hz, 6H, Ar-CH-(CH_3)$_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.67, 171.39, 146.92, 137.12, 127.04, 112.93, 65.72, 48.29, 47.93, 33.00, 28.39, 24.72. HR-MS (ESI): Calcd. $C_{15}H_{20}N_2NaO_3$, $[M+Na]^+$m/z: 299.1372, found: 299.1376.

*4.6. General procedure for the synthesis of compounds **6a-n***

To a solution of compound **4** (150 mg, 0.85 mmol) and hydroxylated chalcone (0.85 mmol) in MeCN (5 mL) were added K_2CO_3 (350 mg, 3 mmol) and KI (42.3 mg, 0.3 mmol). The mixture was heated under reflux for 6 h and filtered upon completion of the reaction indicated by TLC. The filtrate was evacuated under vacuum to give the residue, which was then subject to column chromatography, affording the corresponding **6a-n**. The corresponding chalcone was prepared following the literature reported methods [21].

(*S,E*)-2-((4-(3-(4-isopropylphenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3

-yl)acetamide (compound **6a**), yield: 52%, light yellow solid, m.p.194-196 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 8.3 Hz, 1H, -CO-NH), 8.19 (d, J = 8.9 Hz, 2H, Ar-H), 7.91 (d, J = 15.6 Hz, 1H, -CO-HC=CH), 7.81 (d, J = 8.2 Hz, 2H, Ar-H), 7.71 (d, J = 15.6 Hz, 1H, -CO-HC=CH), 7.34 (d, J = 8.2 Hz, 2H, Ar-H), 7.14 (d, J = 8.9 Hz, 2H, Ar-H), 4.78-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (td, J = 8.7, 1.5 Hz, 1H, CH-CH_2-CH_2-O), 4.29-4.22 (m, 1H, CH-CH_2-CH_2-O), 2.94 (dt, J = 13.7, 6.9 Hz, 1H, -O-CH_2-CH_2-CH), 2.47-2.38 (m, 1H, -O-CH_2-CH_2-CH), 2.28 (m, 1H, -CH(CH_3)$_2$), 1.23 (d, J = 6.9 Hz, 6H, -CH(CH_3)$_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.88, 175.51, 167.91, 161.84, 151.76, 143.86, 132.98, 131.67, 131.26, 129.44, 127.35, 121.51, 115.29, 67.28, 65.80, 48.17, 33.89, 28.41, 24.09. HR-MS (ESI): Calcd. $C_{24}H_{26}NO_5$, [M+H]+m/z: 408.1811, found: 408.1807.

(*S*)-2-((4-cinnamoylphenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6b**), yield: 60%, light yellow solid, m.p.179-183 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 8.2 Hz, 1H, -CO-NH), 8.21 (d, J = 8.8 Hz, 2H, Ar-H), 7.98 (d, J = 15.6 Hz, 1H, -CO-HC=CH), 7.90 (dd, J = 6.4, 2.8 Hz, 2H, Ar-H), 7.73 (d, J = 15.6 Hz, 1H, -CO-HC=CH), 7.51-7.44 (m, 3H, Ar-H), 7.15 (d, J = 8.9 Hz, 2H, Ar-H), 4.77-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (dd, J = 8.8, 7.4 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, J = 15.3, 8.8, 6.6 Hz, 1H, CH-CH_2-CH_2-O), 2.42 (ddd, J = 12.2, 9.8, 7.1 Hz, 1H, -O-CH_2-CH_2-CH), 2.35-2.22 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.89, 175.51, 167.90, 161.92, 143.79, 135.27, 131.56, 131.33, 130.94, 129.37, 129.29, 122.47, 115.32, 67.28, 65.80, 48.18, 28.41. HR-MS (ESI): Calcd. $C_{21}H_{19}NNaO_5$, [M+Na]+m/z: 388.1161, found: 388.1139.

(*S*,*E*)-2-((4-(3-(3-chlorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6c**), yield: 43%, light yellow solid, m.p.178-181 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 8.2 Hz, 1H, -CO-NH), 8.23 (dd, J = 12.3, 5.4 Hz, 3H, Ar-H), 8.03 (s, 2H, -CO-HC=CH), 7.60-7.56 (m, 1H, Ar-H), 7.52-7.44 (m, 2H, Ar-H), 7.16 (d, J = 8.8 Hz, 2H, Ar-H), 4.77-4.68 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (t, J = 8.3 Hz, 1H, CH-CH_2-CH_2-O), 4.29-4.21 (m, 1H, CH-CH_2-CH_2-O), 2.42 (m, 1H, -O-CH_2-CH_2-CH), 2.30 (m, 1H, -O-CH_2-CH_2-CH).^{13}C NMR (100 MHz, DMSO-d_6) δ

187.66, 175.51, 167.87, 162.11, 138.35, 134.76, 132.87, 132.33, 131.50, 131.26, 130.48, 129.06, 128.13, 125.21, 115.38, 67.29, 65.80, 48.18, 28.41. HR-MS (ESI): Calcd. $C_{21}H_{18}ClNNaO_5$, [M+Na]+m/z: 422.0771, found: 422.0771.

(*S,E*)-2-((4-(3-(2-methoxyphenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6d**), yield: 70%, light yellow solid, m.p.138-142 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.3 Hz, 1H, -CO-NH), 8.16 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.04 (d, *J* = 15.7 Hz, 1H, -CO-HC=CH), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-H), 7.90 (d, *J* = 15.7 Hz, 1H, -CO-HC=CH), 7.49-7.43 (m, 1H, Ar-H), 7.13 (dd, *J* = 8.4, 4.9 Hz, 3H, Ar-H), 7.04 (t, *J* = 7.5 Hz, 1H, Ar-H), 4.76-4.63 (m, 3H, -CH-NH, Ar-O-CH_2), 4.38 (td, *J* = 8.8, 1.4 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 10.4, 8.8, 6.6 Hz, 1H, CH-CH_2-CH_2-O), 3.91 (s, 2H, Ar-O-CH_3), 2.46-2.37 (m, 1H, -O-CH_2-CH_2-CH), 2.34-2.22 (m, 1H, -O-CH_2-CH_2-CH).^{13}C NMR (100 MHz, DMSO-d_6) δ 188.05, 175.53, 167.92, 161.81, 158.66, 138.30, 132.65, 131.68, 131.22, 128.86, 123.50, 122.20, 121.16, 115.31, 112.26, 67.25, 65.81, 56.20, 48.17, 28.38. HR-MS (ESI): Calcd. $C_{22}H_{21}NNaO_6$, [M+Na]+m/z: 418.1267, found: 418.1265.

(*S,E*)-2-((4-(3-(2-chlorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6e**), yield: 59%, light yellow solid,，m.p.166-169 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.27-8.19 (m, 3H, Ar-H), 8.02 (s, 2H, -CO-HC=CH), 7.60-7.55 (m, 1H, Ar-H), 7.47 (ddd, *J* = 6.3, 5.2, 3.5 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.77-4.67 (m, 3H, -CH-NH, Ar-O-CH_2), 4.42-4.35 (td, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 10.4, 8.8, 6.5 Hz, 1H, CH-CH2-CH2-O), 2.43 (m, 1H, -O-CH2-CH2-CH), 2.29 (m, 1H, -O-CH2-CH2-CH).13C NMR (100 MHz, DMSO-d6) δ 187.67, 175.52, 167.88, 162.10, 138.36, 134.76, 132.87, 132.33, 131.50, 131.26, 130.47, 129.04, 128.13, 125.19, 115.38, 67.28, 65.81, 48.18, 28.40. HR-MS (ESI): Calcd. $C_{21}H_{18}ClNNaO_5$, [M+Na]+m/z: 422.0771, found: 422.0770.

(*S,E*)-2-((4-(3-(2,4-dichlorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6f**), yield: 66%, light yellow solid, m.p.193-195 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.29 (d, *J* = 8.6 Hz,

1H, Ar-H), 8.22 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.07 (d, *J* = 15.5 Hz, 1H, -CO-HC=CH), 7.95 (d, *J* = 15.5 Hz, 1H, -CO-HC=CH), 7.77 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.57 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 7.15 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.76-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.38 (dd, *J* = 8.8, 7.3 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 10.4, 8.7, 6.5 Hz, 1H, CH-CH_2-CH_2-O), 2.46-2.37 (m, 1H, -O-CH_2-CH_2-CH), 2.34-2.22 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.51, 175.50, 167.86, 162.17, 137.09, 135.94, 135.54, 131.96, 131.54, 131.17, 130.30, 129.95, 128.39, 125.78, 115.39, 67.29, 65.80, 48.18, 28.40. HR-MS (ESI): Calcd. $C_{21}H_{17}Cl_2NNaO_5$, [M+Na]+m/z: 456.0381, found: 456.0383.

(*S*,*E*)-2-((4-(3-(3-nitrophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6g**), yield: 40%, light yellow solid, m.p.185-188 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H, Ar-H), 8.74 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.35 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.27 (m, 3H, Ar-H), 8.20 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.84 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.76 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.77-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (td, *J* = 8.9, 1.3 Hz, 1H, CH-CH_2-CH_2-O), 4.29-4.21 (m, 1H, CH-CH_2-CH_2-O), 2.42 (m, 1H, -O-CH_2-CH_2-CH), 2.30 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.71, 175.51, 167.87, 162.13, 148.93, 141.26, 137.20, 135.55, 131.58, 131.27, 130.81, 125.24, 125.02, 123.42, 115.35, 67.29, 65.80, 48.18, 28.40. HR-MS (ESI): Calcd. $C_{21}H_{18}N_2NaO_7$, [M+Na]+m/z: 433.1012, found: 433.0972.

(*S*,*E*)-2-((4-(3-(2-bromophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6h**), yield: 48%, light yellow solid, m.p.163-166 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.22 (d, *J* = 8.9 Hz, 3H, Ar-H), 7.99 (s, 2H, -CO-HC=CH), 7.75 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.53-7.47 (m, 1H, Ar-H), 7.40 (td, *J* = 7.8, 1.5 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.78-4.68 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (td, *J* = 8.7, 1.3 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 10.4, 8.8, 6.6 Hz, 1H, CH-CH_2-CH_2-O), 2.42 (m, 1H, -O-CH_2-CH_2-CH), 2.28 (m, 1H, -O-CH_2-CH_2-CH).^{13}C NMR (100 MHz, DMSO-d_6) δ 187.64, 175.51, 167.87, 162.11, 141.10, 134.54, 133.75, 132.52, 131.51, 131.25, 129.24, 128.68,

125.78, 125.35, 115.38, 67.28, 65.80, 48.17, 28.40. HR-MS (ESI): Calcd. $C_{21}H_{18}BrNNaO_5$, [M+Na]+m/z: 466.0266, found: 466.0264 & 468.0244.

(*S*,*E*)-2-((4-(3-(3,4-difluorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6i**), yield: 40%, light yellow solid, m.p.215-217 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.3 Hz, 1H, -CO-NH), 8.28-8.11 (m, 3H, Ar-H), 8.00 (d, *J* = 15.5 Hz, 1H, -CO-HC=CH), 7.74 (d, *J* = 4.3 Hz, 2H, Ar-H), 7.70 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.59-7.47 (m, 1H, Ar-H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.78-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (td, *J* = 8.6, 1.1 Hz, 1H, CH-CH_2-CH_2- O), 4.30-4.20 (m, 1H, CH-CH_2-CH_2-O), 2.47-2.37 (m, 1H, -O-CH_2-CH_2-CH), 2.34-2.23 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.63, 175.52, 167.89, 162.03, 141.48, 133.31, 133.27, 133.25, 133.21, 131.43, 131.36, 127.27, 127.24, 127.21, 127.18, 123.71, 123.69, 118.50, 118.33, 117.48, 117.31, 115.33, 67.27, 65.81, 48.18, 28.39. HR-MS (ESI): Calcd. $C_{21}H_{17}F_2NNaO_5$, [M+Na]+m/z: 424.0972, found: 424.1010.

(*S*,*E*)-2-((4-(3-(4-bromophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6j**), yield: 62%, light yellow solid, m.p.204-208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 8.3 Hz, 1H, -CO-NH), 8.20 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.01 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.87 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.68 (dd, *J* = 11.9, 10.1 Hz, 3H, -CO-HC=CH, Ar-H), 7.14 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.76-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.38 (td, *J* = 8.8, 1.5 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J*=10.3, 8.7, 6.5 Hz, 1H, CH-CH_2-CH_2-O), 2.47-2.37 (m, 1H, -O-CH_2-CH_2-CH), 2.34-2.22 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.77, 175.53, 167.91, 161.97, 142.41, 134.56, 132.33, 131.43, 131.39, 131.21, 124.28, 123.23, 115.32, 67.25, 65.82, 48.18, 28.38. HR-MS (ESI): Calcd. $C_{21}H_{18}BrNNaO_5$, [M+Na]+m/z: 466.0266, found: 466.0263 & 468.0234.

(*S*,*E*)-2-((4-(3-(3-fluorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl) acetamide (compound **6k**), yield: 67%, light yellow solid, m.p.184-188 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.23 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.05 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.87 (d, *J* = 10.2 Hz, 1H, Ar-H),

7.76-7.68 (m, 2H, -CO-HC=CH, Ar-H), 7.51 (dd, *J* = 14.2, 7.9 Hz, 1H, Ar-H), 7.29 (td, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.80-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 ((td, *J* = 9.0, 1.5 Hz, 1H, CH-CH_2-CH_2-O), 4.32-4.21 (m, 1H, CH-CH_2-CH_2-O), 2.48-2.36 (m, 1H, -O-CH_2-CH_2-CH), 2.28 (m, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.75, 175.52, 167.89, 164.20, 162.03, 161.78, 142.32, 142.30, 137.90, 137.82, 131.45, 131.39, 131.33, 131.25, 126.03, 123.89, 117.69, 117.48, 115.33, 115.16, 114.94, 67.28, 65.80, 48.18, 28.40. HR-MS (ESI): Calcd. $C_{21}H_{18}FNNaO_5$, [M+Na]+m/z: 406.1067, found: 406.1065.

(*S*,*E*)-2-((4-(3-(4-*t*-butylphenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6l**), yield: 64%, light yellow solid, m.p.163-166 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.3 Hz, 1H, -CO-NH), 8.19 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.91 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.82 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.71 (d, *J* = 15.5 Hz, 1H, -CO-HC=CH), 7.49 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.78-4.66 (m, 3H, -CH-NH, Ar-O-CH_2), 4.39 (td, *J* = 8.8, 1.6 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 15.4, 8.8, 6.6 Hz, 1H, CH-CH_2-CH_2-O), 2.47-2.38 (m, 1H, -O-CH_2-CH_2-CH), 2.34-2.22 (m, 1H, -O-CH_2-CH_2-CH), 1.32 (s, 9H, -C(CH_3)$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.90, 175.51, 167.91, 161.85, 153.93, 143.75, 132.57, 131.66, 131.26, 129.17, 126.18, 121.63, 115.30, 67.28, 65.80, 48.17, 35.12, 31.39, 28.41. HR-MS (ESI): Calcd. $C_{25}H_{27}NNaO_5$, [M+Na]+m/z: 444.1787, found: 444.1784.

(*S*,*E*)-2-((4-(3-(3-bromophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl)acetamide (compound **6m**), yield: 75%, light yellow solid, m.p.207-211 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 8.3 Hz, 1H, -CO-NH), 8.27-8.20 (m, 3H, Ar-H), 8.06 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.87 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.69 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.64 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.42 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.78-4.66 (m, 3H, -CH-NH ,Ar-O-CH_2), 4.39 (td, *J* = 8.6, 1.3 Hz, 1H, CH-CH_2-CH_2-O), 4.30-4.21 (m, 1H, CH-CH_2-CH_2-O), 2.47-2.38 (m, 1H, -O-CH_2-CH_2-CH), 2.28 (dt, *J* = 22.3, 11.0 Hz, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.21, 175.03, 167.40, 161.53,

141.54, 137.30, 132.88, 130.99, 130.91, 130.87, 130.70, 128.24, 123.43, 122.37, 114.82, 66.76, 65.31, 47.67, 27.89. HR-MS (ESI): Calcd. $C_{21}H_{18}BrNNaO_5$, [M+Na]+m/z: 466.0266, found: 466.0265 & 468.0257.

(*S,E*)-2-((4-(3-(4-fluorophenyl)acryloyl)phenyl)amino)-*N*-(2-oxotetrahydrofuran-3-yl) acetamide (compound **6n**), yield: 77%, light yellow solid, m.p.186-189 □; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 8.2 Hz, 1H, -CO-NH), 8.20 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.02-7.90 (m, 3H, Ar-H, -CO-HC=CH), 7.73 (d, *J* = 15.6 Hz, 1H, -CO-HC=CH), 7.31 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.14 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.78-4.65 (m, 3H, -CH-NH, Ar-O-CH_2), 4.38 (td, *J* = 8.7, 1.3 Hz, 1H, CH-CH_2-CH_2-O), 4.25 (ddd, *J* = 10.4, 8.8, 6.6 Hz, 1H, CH-CH_2-CH_2-O), 2.46-2.38 (m, 1H, -O-CH_2-CH_2-CH), 2.28 (dt, *J* = 22.5, 11.1 Hz, 1H, -O-CH_2-CH_2-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.80, 175.52, 167.91, 165.04, 162.57, 161.92, 142.55, 131.96, 131.93, 131.67, 131.59, 131.52, 131.33, 122.35, 116.48, 116.26, 115.31, 67.27, 65.81, 48.18, 28.39. HRMS (ESI): Calcd. $C_{21}H_{18}FNO_5$ $[M+H]^+$ m/z: 384.1247, found: 384.1248.

*4.7. General procedure for the synthesis of compounds **8a-j***

Compounds **7a-7j** were prepared following the literature reported methods in 54-83% yields [29]. To a solution of compound **3** (102 mg, 0.74 mmol) and $Na_3PO4{\cdot}12H_2O$ (423 mg, 1.11mmol) in acetone (10 mL) was added CS_2 (94 μL, 1.55 mmol). After 0.5 h stirring, the corresponding compounds **7a-7j** were added. About 1-2 h later, the solvent was removed under vacuum, the resulting residue was dissolved with DCM and then washed with brine. The organic layer was dried over $MgSO_4$ and evacuated under vacuum to give the residue, which was then subject to column chromatography, affording the corresponding **8a-j**.

2-Phenoxyethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8a**), yield: 67%, white solid, m.p.89-90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.5 Hz, 1H, -CS-NH), 7.37-7.26 (m, 2H, Ar-H), 7.01-6.88 (m, 3H, Ar-H), 5.16 (m, 1H, -CO-O-CH_2), 4.50 (t, *J* = 9.0 Hz, 1H, -CH-NH), 4.34 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H, -CO-O-CH_2), 4.23 (t, *J* = 6.2 Hz, 2H, Ar-O-CH_2), 3.67 (t, *J* = 6.1 Hz, 2H, -CS-S-CH_2),

3.24-3.08 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.27-2.07 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH);^{13}C NMR (100 MHz, $CDCl_3$) δ 199.70, 174.45, 158.34, 129.65, 121.38, 114.80, 66.39, 55.29, 35.16, 30.22. HR-MS (ESI): Calcd. $C_{13}H_{15}NNaO_3S_2$, [M+Na]+m/z: 320.0391, found: 320.0389.

2-(4-Acetylphenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8b**), yield: 58%, white solid, m.p.107-109 □; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.76 (d, *J* = 2.2 Hz, 1H, -CS-NH), 6.96 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.21 (t, *J* = 12.6 Hz, 1H, -CO-O-CH_2), 4.51 (t, *J* = 9.1 Hz, 1H, -CH-NH), 4.40-4.33 (m, 1H, -CO-O-CH_2), 4.33-4.23 (m, 2H, -S-CH_2), 3.70 (t, *J* = 6.2 Hz, 2H, -Ar-O-CH_2), 3.23-3.07 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.56 (s, 3H, -CO-CH_3), 2.29-2.11 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH);^{13}C NMR (100 MHz, $CDCl_3$) δ 199.37, 196.89, 174.33, 162.24, 130.72, 130.64, 114.33, 66.45, 66.28, 55.27, 34.65, 30.04, 26.37. HR-MS (ESI): Calcd. $C_{15}H_{17}NNaO_4S_2$, [M+Na]+m/z: 362.0497, found: 362.0495.

2-(3-Benzylphenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8c**), yield: 56%, light yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 14.8 Hz, 1H, -CS-NH), 7.29-7.08 (m, 7H, Ar-H), 6.97-6.82 (m, 2H, Ar-H), 5.11 (s, 1H, -CO-O-CH_2), 4.48 (t, *J* = 9.0 Hz, 1H, -CH-NH), 4.32 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H, -CO-O-CH_2), 4.19 (t, *J* = 6.1 Hz, 2H ,Ar-O-CH_2), 3.97 (s, 2H Ar-CH_2-Ar), 3.64 (t, *J* = 5.5 Hz, 2H, -S-CH_2), 3.22-3.08 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.20-2.04 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH).^{13}C NMR (100 MHz, $CDCl_3$) δ 199.88, 174.39, 156.09, 141.04, 130.59, 129.96, 128.98, 128.27, 127.47, 125.79, 121.08, 111.75, 66.38, 66.26, 55.20, 36.14, 35.33, 30.22. HR-MS (ESI): Calcd. $C_{20}H_{21}NNaO_3S_2$, [M+Na]+m/z: 410.0861, found: 410.0860.

2-(4-Allyl-3-methoxyphenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8d**), yield: 39%, light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 5.3 Hz, 1H, -CS-NH), 6.88 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.75-6.68 (m, 2H, Ar-H), 5.95 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H,-Ar-CH_2-$\underline{CH}$=CH_2), 5.20 (dt, *J* = 19.1, 6.5 Hz, 1H, -CO-O-CH_2), 5.14-5.03 (m, 2H, -Ar-CH_2-CH=$\underline{CH_2}$), 4.48 (t, *J* = 8.9 Hz, 1H, -$\underline{CH}$-NH), 4.40-4.22 (m, 3H, -CO-O-CH_2, Ar-O-CH_2), 3.85 (s, 3H, -O-CH_3),

3.74-3.66 (m, 1H, -Ar-$\underline{CH_2}$-CH=CH_2), 3.56 (dt, *J* = 8.3, 5.4 Hz, 1H-Ar-$\underline{CH_2}$-CH=CH_2), 3.33 (d, *J* = 6.6 Hz, 2H, -CS-S-CH_2), 3.12-3.04 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.25 -2.08 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH).^{13}C NMR (100 MHz, $CDCl_3$) δ 199.50, 174.15, 149.47, 145.85, 137.50, 134.11, 120.68, 115.79, 114.44, 112.70, 68.41, 66.14, 56.00, 55.07, 39.82, 35.03, 29.79. HR-MS (ESI): Calcd. $C_{17}H_{21}NNaO_4S_2$, [M+Na]+m/z: 390.0810, found: 390.0812.

2-(2-Isopropyl-6-methylphenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl) carbamodithioate (compound **8e**), yield: 62%, light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 16.7 Hz, 1H, -CS-NH), 7.09 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.76 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 5.25-5.05 (m, 1H, -CO-O-CH_2), 4.50 (t, *J* = 9.0 Hz, 1H, -$\underline{CH}$-NH), 4.34 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H, -CO-O-CH_2), 4.22 (t, *J* = 6.0 Hz, 2H, Ar-O-CH_2), 3.72 (t, *J* = 5.8 Hz, 2H, -CS-S-CH_2), 3.28 (dt, *J* = 13.8, 6.8 Hz, 1H, Ar-$\underline{CH}$-$(CH_3)_2$), 3.17 (dt, *J* = 13.1, 7.4 Hz, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.31 (s, 3H Ar-CH_3), 2.22-2.08 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 1.20 (d, *J* = 6.9 Hz, 6H, Ar-CH-$(\underline{CH_3})_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.93, 174.26, 155.36, 136.39, 134.19, 126.04, 121.72, 112.61, 66.34, 66.25, 55.23, 35.59, 30.32, 26.64, 22.81, 21.28. HR-MS (ESI): Calcd. $C_{17}H_{23}NNaO_3S_2$, [M+Na]+m/z: 376.1017, found: 376.1018.

2-(2-Nitrophenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8f**), yield: 47%, white solid, m.p.92-94 □; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.70 (m, 2H, Ar-H,-CS-NH), 7.61-7.48 (m, 1H, Ar-H), 7.14 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.06 (t, *J* = 7.8 Hz, 1H, Ar-H), 5.30-5.09 (m, 1H, -CO-O-CH_2), 4.52 (t, *J* = 9.1 Hz, 1H, -$\underline{CH}$-NH), 4.37 (pd, *J* = 9.6, 6.4 Hz, 3H,-CO-O-CH_2, Ar-O-CH_2), 3.83-3.64 (m, 2H, -CS-S-CH_2), 3.18-3.01 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.34-2.16 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.28, 151.72, 134.25, 125.70, 120.98, 114.99, 68.14, 66.31, 55.30, 34.49, 29.81. HRMS (ESI): Calcd. $C_{13}H_{14}N_2O_5S_2$ $[M+Na]^+$ m/z: 365.0242, found: 365.0240.

2-(4-Nitrophenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8g**), yield: 53%, white solid, m.p.98-100 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (d, *J* = 7.9 Hz, 1H, -CS-NH), 8.21 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.3 Hz, 2H,

Ar-H), 5.55 (dt, *J* = 11.0, 8.7 Hz, 1H, -CO-O-CH_2), 4.34 (dqd, *J* = 10.5, 8.8, 7.0 Hz, 4H, -CO-O-CH_2, Ar-O-CH_2), 3.77-3.61 (m, 2H, -CS-S-CH_2), 2.64-2.53 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.23 (dt, *J* = 22.8, 11.2 Hz, 1H, -O-CH_2-$\underline{CH_2}$-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.46, 173.53, 163.33, 141.03, 125.88, 115.10, 66.94, 65.49, 54.46, 33.14, 27.80. HR-MS (ESI): Calcd. $C_{13}H_{14}N_2NaO_5S_2$, [M+Na]+m/z: 365.0242, found: 365.0264.

2-(4-Chlorophenoxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8h**), yield: 64%, white solid, m.p.123-125 □; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, -CS-NH), 7.29-7.20 (m, 2H, Ar-H), 6.93-6.81 (m, 2H, Ar-H), 5.17 (t, *J* = 12.5 Hz, 1H,-CO-O-CH_2), 4.51 (t, *J* = 8.9 Hz, 1H, -$\underline{CH}$-NH), 4.35 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H, -CO-O-CH_2), 4.20 (dt, *J* = 12.7, 6.4 Hz, 2H, Ar-O-CH_2), 3.66 (t, *J* = 6.2 Hz, 2H, -CS-S-CH_2), 3.23-3.09 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.25-2.09 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.50, 174.38, 156.91, 129.40, 126.14, 116.00, 66.67, 66.31, 55.25, 34.85, 30.12. HR-MS (ESI): Calcd. $C_{13}H_{14}ClNNaO_3S_2$, [M+Na]+m/z: 354.0001, found: 353.9995.

2-(Naphthalen-1-yloxy)ethyl (*S*)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8i**), yield: 66%, white solid, m.p.58-60 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.5, 4.2 Hz, 1H, Ar-H), 7.82-7.75 (m, 1H, Ar-H), 7.61-7.40 (m, 4H, Ar-H, -CS-NH), 7.35 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.83 (d, *J* = 7.5 Hz, 1H, Ar-H), 5.16 (d, *J* = 3.9 Hz, 1H, -CO-O-CH_2), 4.43 (dt, *J* = 12.2, 7.6 Hz, 3H, -$\underline{CH}$-NH, Ar-O-CH_2), 4.31 (ddd, *J* = 11.3, 9.5, 5.7 Hz, 1H, -CO-O-CH_2), 3.84 (t, *J* = 5.8 Hz, 2H, -CS-S-CH_2), 3.19-3.07 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH), 2.20-2.07 (m, 1H, -O-CH_2-$\underline{CH_2}$-CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.77, 174.63, 154.09, 134.52, 127.51, 126.52, 125.84, 125.55, 125.36, 122.03, 120.78, 105.19, 66.53, 66.34, 60.48, 55.24, 35.24, 29.85, 21.10, 14.23. HRMS (ESI): Calcd. $C_{17}H_{17}NO_3S_2$, $[M+Na]^+$ m/z: 370.0548, found: 370.0547.

2-(4-Ethoxyphenoxy)ethyl (S)-(2-oxotetrahydrofuran-3-yl)carbamodithioate (compound **8j**), yield: 57%, white solid, m.p.94-96 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (d, *J* = 8.0 Hz, 1H, -CS-NH), 7.01 (dd, *J* = 7.5, 1.9 Hz, 1H, Ar-H), 6.96 (dd, *J* = 7.7, 1.9 Hz, 1H, Ar-H), 6.93-6.84 (m, 2H, Ar-H), 5.55 (dt, *J* = 11.1, 8.7 Hz, 1H,

-CO-O-CH_2), 4.40 (dd, *J* = 8.9, 7.6 Hz, 1H，-CO-O-CH_2), 4.30 (ddd, *J* = 10.6, 8.8, 6.3 Hz, 1H, -CH-NH), 4.16 (t, *J* = 6.6 Hz, 2H, Ar-O-CH_2-CH_2-S), 4.05-3.98 (m, J = 7.0 Hz, 2H, Ar-O-CH_2-CH_3), 3.61 (td, J = 6.6, 2.0 Hz, 2H, -CS-S-CH_2), 2.62-2.52 (m, 1H, -O-CH_2-CH_2-CH), 2.29-2.16 (m, J = 11.1, 9.2 Hz, 1H, -O-CH_2-CH_2-CH), 1.32 (t, 3H, -O-CH_2-CH_3). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 197.86, 173.56, 148.39, 147.79, 121.59, 120.87, 114.49, 113.98, 66.98, 65.47, 63.86, 54.40, 33.60, 27.81, 14.78. HRMS (ESI): Calcd. $C_{15}H_{19}NO_4S_2$, $[M+Na]^+$ m/z: 364.0653, found: 364.0653.

4.8. Antiproliferative activity assay [23]

Human breast cancer cell MCF-7, gastric cancer cell MGC-803, prostate cancer cells DU145 and PC-3 were purchased from the Cell Bank of Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, People's Republic of China) and cultured in Dulbecco's modified Eagle medium (DMEM, Gibco Invitrogen Corp., Carlsbad, CA, USA). Cell were seeded into 96-well plates at a concentration of 3,000 cells per well. After 24 h of incubation, the culture medium was removed and fresh medium containing different concentration (64, 32, 16, 8, 4, 2, 1, 0.5 μM) of the candidate compound was added to each well. The cells were then incubated for 72 h, thereafter MTT assays were performed and cell viability was assessed at 570 nm by a microplate reader (Biotech, Shanghai, China).

4.9. Colony formation inhibition assay [30]

DU145 cells (4000 cells/well) were seeded in a 6-well plate and incubated for 4 days, then the media were replaced with fresh media containing different concentrations of compound **6e** and OdDHL. After 21 days of treatment, the cells were washed twice with PBS, fixed with 4% paraformaldehyde, and colonies were visualized using 0.1% crystal violet staining. The cells were imaged, and the number of colonies were quantified by Image J software (Developed by National Institutes of Health). A group of >10 cells was defined as one colony. Inhibition rate = (1-number oftreatment/number of control) * 100%.

4.10. Hoechst 33258 staining [30]

DU145 cells were seeded into a 6-well plate (1×10^5/well) and incubated overnight for adherent and treated with **6e**, OdDHL or its combination with TRAIL at different

concentrations for 24 h, and underwent Hoechst 33258 staining for 30 min in the dark. The cells were observed under a Nikon Eclipse TE 2000-S fluorescence microscope (Nikon, Japan).

4.11. Cell apoptosis assay [30]

DU145 cells were seeded into a 6-well plate (3×10^5/well) and incubated for 24 h. Then the cells were treated with different concentrations of **6e**, OdDHL or its combination with TRAIL for 24 h. Thereafter, the cells were collected and the Annexin-V-FITC/PI apoptosis kit (Biovision) was used according to the manufacturer's protocol. The cells were analyzed by high content screening system (ArrayScan XTI, Thermo Fisher Scientific, MA).

4.12. Western blot analysis [30]

DU145 cells were treated with different concentrations of compound **6e**, OdDHL or its combination with TRAIL for 24 h, the cells were collected, lysed in RIPA buffer contained a protease inhibitor cocktail for 30 min, followed by centrifugation at 14,000 rpm for 15 min at 4 ^{o}C. After the collection of supernatant, the protein concentration was detected using a bicinchonininc acid assay kit (Beyotmie Biotechnology, Haimen, China). After added with loading buffer, cell lyses were boiled for 10 min at 100 ^{o}C for SDS- polyacrylamide gel electrophoresis (PAGE). Proteins were transferred to nitrocellulose (NC) membranes. Then the membranes were blocked with 5% skim milk at room temperature for 2 h, and then incubated overnight at 4 ^{o} C with primary antibodies. After washing the membrane with the secondary antibody (1: 5000) at room temperature for 2 h. Finally, the blots were washed in TBST/TBS. The antibody-reactive were revealed by enhanced chemiluminescence (ECL) and exposed on Kodak radiographic film.

4.13. Caspase-3/7 activity detection

The caspase-3/7 activity of compound **6e**, OdDHL or its combination with TRAIL was detected according to the standard Caspase-Glo® 3/7 assay protocol.

4.14. Wound healing assay [30]

DU145 cells (3×10^5/well) were placed in a 6-well plate and incubated for 24 h, and the cell surface was scratched using a 10 μL pipet tip. Then the cells were treated with compound **6e** or OdDHL at different concentrations, and then incubated for 24 or 48 h

and photographed on an inverted microscope.

4.15. Date analysis

Graphpad prism 6.0 (USA) was used for all calculations. All values are presented as the mean ± SD. The quantitative variables were analyzed by Student's *t* test. $P < 0.05$ and $P < 0.01$ were considered statistically significant for all tests.

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Highlights

- Three series of new homoserine lactone analogs were synthesized from methionine;
- Compounds **6a-n** were particularly sensitive to prostate cancer cells DU145 and PC-3;
- Compound **6e** concentration-dependently inhibited colony formation and cell migration of DU145 cells;
- **6e** and TRAIL showed synergistic effect on the growth inhibition and the apoptosis of DU145 cells;