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Synthesis and anticancer activity of benzoselenophene and heteroaromatic derivatives of 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI)†

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The current study reports the synthesis of different derivatives of benzoselenophene analogs as well as a diverse series of compounds (**14a–p**, **15** and **16**) from 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI) and benzoselenophene or heteroaromatic acids. The overall yield of scaffold **12** was improved by an one-pot reaction, which helps in large-scale synthesis of CBI, a duocarmycin alkylation subunit analog. The series of compounds were evaluated for their cytotoxicity against SK-OV3 ovarian cancer cell lines, which revealed that benzoselenophene can enhance or maintain the anticancer activity of the duocarmycin analog upon replacing the indole moiety. CBI-benzoselenophenes with *N*-amido substituents at the C-5 position, **14g**, **14f** and **16** (IC_{50} = 0.5, 1.2 and 1.6 nM, respectively), were found to be more potent than the CBI-TMI and other benzoselenophene analogs. The CBI-benzoselenophene analogs, **14f** and **14g** (containing *N*-acetamido and *N*-butyramido substituents, respectively), were found to be 8 and 120 times more potent than the corresponding indole analogs of CBI, **14q** and **14r**, respectively.

Introduction

Despite substantial work being done towards the development of efficient anticancer therapies, cancers are still delineated as a major cause of death, accounting for approximately 13% of all deaths worldwide.[1] While some cancer types can be treated effectively, most clinically approved drugs show a poor response owing to their high toxicity and lack of selectivity. Antibody–drug conjugates (ADCs) have been attracting growing interest in current cancer therapy due to their potential targeted delivery of cytotoxic drugs, and less toxicity toward normal cells.[2] Around 50 distinct ADCs are currently in clinical trials among that 35 ADCs are investigated for solid tumors.[3] In recent years, duocarmycin analogs are used as potent payloads in the development of ADCs with the main aim of improving the therapeutic index by their effective mechanism of action.[4–6] The potency of the conjugated cytotoxic agent should be sufficiently high so that it can kill tumor cells at the amounts delivered by antibody retention in the tumor. Thus the selection of a potent candidate for ADCs has become crucial in current preclinical and clinical research.

CC-1065, duocarmycin SA and yatakemycin are cyclopropylpyrrolo[*e*]indolone (CPI) containing alkaloids belonging to a class of naturally occurring antitumor agents (Fig. 1).[7–11] Initial studies have explained the highly potent antitumor activity of these natural products by their characteristic duplex DNA alkylation and DNA binding affinity.[12,13] For example, CC-1065 binds to double stranded B-DNA within the minor groove with a sequence preference for 5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′ and alkylates the N3 position of 3′-adenine with the CPI segment.[14–16] In CC-1065, duocarmycin SA and duo-

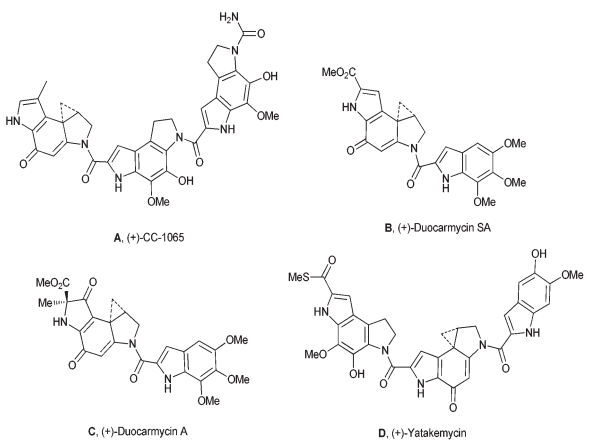

Fig. 1 Natural products (DNA alkylating agents).

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carmycin A (Fig. 1), the substituted indole is a common structural unit on the right hand side of the DNA alkylating unit, which plays a crucial role in enhancing binding affinity and selectivity.[13,17,18] Benzoselenophene is expected to have a similar or an even better effect than the indole in enhancing anticancer activity of duocarmycin and CC-1065 analogs due to the biological significance of the selenium element[19] and its structural features. The larger size of the selenium atom changes the bond length and bond angle with the adjacent carbon and ultimately affects the structural unit, which makes it different from indole. Selenophene-containing compounds have diverse biological effects[20] including antioxidant,[21] antinociceptive,[22] and anti-inflammatory properties[23] as well as being efficacious maturation-inducing agents.[24] They also exhibit potent *in vitro* and *in vivo* antitumor activities which involve DNA damage and nuclear protein kinase activation.[25] It would be interesting to study the effect of introduction of selenophene compounds into the duocarmycin family.

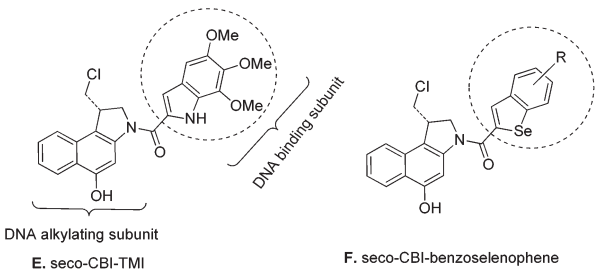


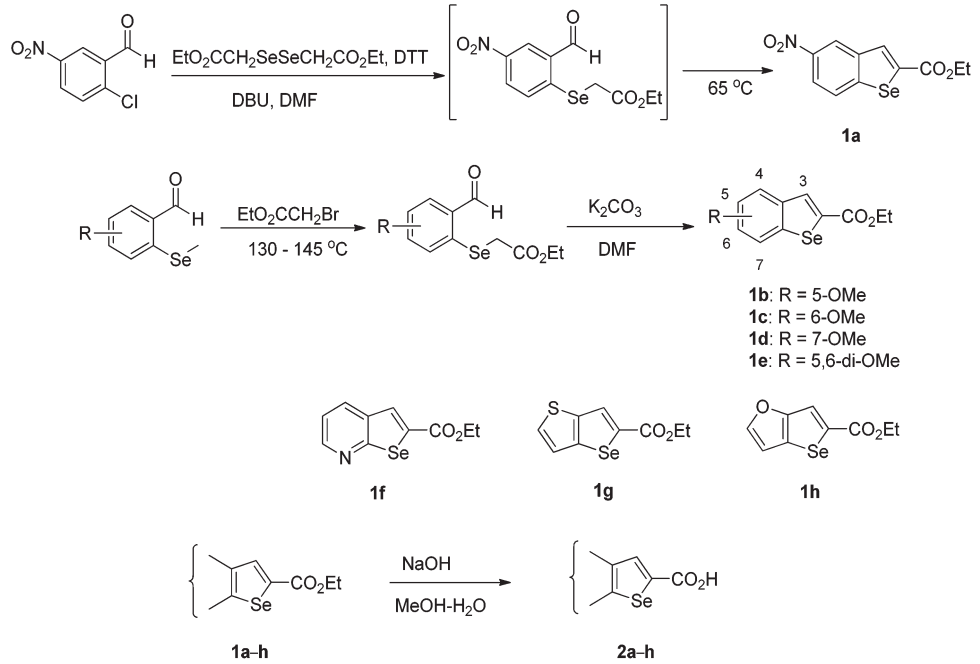
Fig. 2 Structural comparison between seco-CBI-TMI and seco-CBI-benzoselenophene.

Taking these facts into consideration and our expectation to achieve improved anticancer activity, the indole moiety of the duocarmycin subunit was replaced with the benzoselenophene analog (Fig. 2). 1,2,9,9a tetrahydrocyclopropa[*c*]benzo[*e*] indol-4-one (CBI)[26–28] was selected as the DNA alkylating agent, which is one of the most extensively studied alkylation subunits of duocarmycin. It has the advantage of being easily synthesized, more stable, and highly cytotoxic than CPI.[29] This study describes the syntheses and anticancer activities of substituted benzoselenophenes and different heteroaromatic derivatives of CBI. The results from the structure–activity relationship (SAR) study of the highly potent anticancer agents are also provided.

Results and discussion

Chemistry

The SAR study of duocarmycin analogs revealed that substitution at the C-5 position of the DNA binding unit is crucial for inducing cytotoxicity against cancer cell lines,[30,31] so we mostly focused on the synthesis of C-5 substituted benzoselenophene analogs. According to this, first we synthesized various selenophene fused aromatic compounds by two methods (Scheme 1). In the first method, the aryl selenide was the intermediate formed from 2-chloro-5-nitro-benzaldehyde and diethyl 2,2′-diselanediyldiacetate using dithiothreitol (DTT) and 8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the reducing agent and base, respectively. The resulting intermediate undergoes cyclization under heating conditions to afford the desired 5-nitro benzoselenophene ester **1a**. For the synthesis

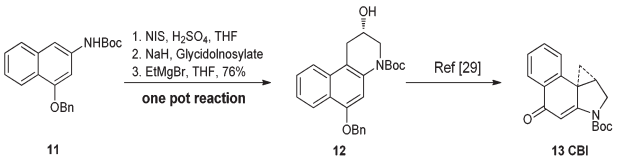


Scheme 1 Synthesis of selenophene carboxylic acids.

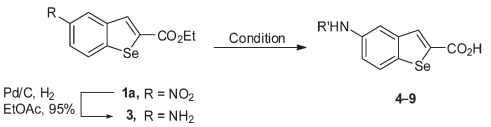
of electron-rich benzoselenophene analogs, the aryl methyl selenides[32,33] were first treated with ethyl bromoacetate and then cyclized with the base to obtain the desired products **1b–e**. The heteroaryl-fused selenophenes, **1f–h**, were also prepared by a similar procedure to that described for **1b–e**. The esters, **1a–h**, were then hydrolyzed to prepare the corresponding carboxylic acids **2a–h** (Scheme 1).

To prepare more benzoselenophene analogs, the nitro group of **1a** was modified to produce diverse amide and urea analogs. First, palladium-catalyzed nitro reduction of **1a** was performed to obtain the amine **3**. Then the product **3** was converted into different amide and urea esters, which hydrolyzed to provide their corresponding acids (**4–9**) with excellent overall yields (Scheme 2). Demethylation of 5-methoxy benzoselenophene ester **1b** was performed by using BCl_3 and tetra (*n*-butyl)ammonium iodide, and then alkylation of the phenolic (OH) intermediate was carried out with 2-chloro-*N*,*N*-dimethylethanamine under the basic conditions to obtain the *N*,*N*-dimethylethoxy derivative of the benzoselenophene ester, which was hydrolyzed to obtain benzoselenophene carboxylic acid **10** (Scheme 3).

In order to synthesize CBI, first we synthesized scaffold **11** from benzaldehyde by a previously reported procedure,[34] and then synthesized scaffold **12** from **11** with three different reactions as described previously.[35] To avoid separate purification after each step, we performed a one-pot synthesis of compound **12** from **11** with iodination, alkylation and cyclization reactions, which provided the desired product in 76% yield (Scheme 4). Then the desired CBI compound **13** was synthesized from **12** as reported previously.[35] Finally, a potent library of analogs, **14a–r**, were synthesized by Boc deprotection of **13** with 4 N HCl/ethyl acetate, followed by coupling with different carboxylic acids using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (Scheme 5). The spirocyclized derivatives of **14d** and **14g** were also prepared by treatment with a solution of 15% aq. $NaHCO_3$ in DMF (1 : 1) at 0 to 20 °C for 3 h which resulted in **15** and **16**, respectively (Scheme 6).

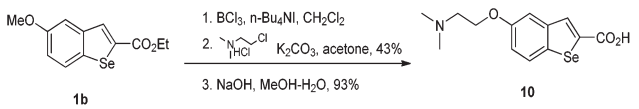


Scheme 4 One-pot reaction of scaffold **12**.



Condition	R′	Product
a. Ac_2O, pyridine, CH_2Cl_2, 96% b. 3N NaOH, MeOH, 92%	Ac	4
a. Butyric anhydride, pyridine, CH_2Cl_2, 90% b. 3N NaOH, MeOH, 99%	$-COC_3H_7$	5
a. Hexanoic acid, DCC, pyridine, 65% b. 3N NaOH, MeOH, 95%	$-COC_5H_{11}$	6
a. n-BuNCO, CH_2Cl_2, 81% b. LiOH, MeOH-H_2O, 97%	$-CONHC_4H_9$	7
a. 4-F-PhNCO, CH_2Cl_2, 96% b. LiOH, MeOH-H_2O, 78%	- CONH-4-FC_6H_4	8
a. Fmoc-L-Lys(Boc)-OH, DMTMM, MeOH-H_2O, 88% b. 50% diethyl amine in CH_2Cl_2, 20% TFA in CH_2Cl_2, Ac_2O, pyridine, 3N NaOH, H_2O-MeOH, 5%	$-COCH(C_4H_8NHAc)NHAc$	9

Scheme 2 Synthesis of amide and urea analogs.



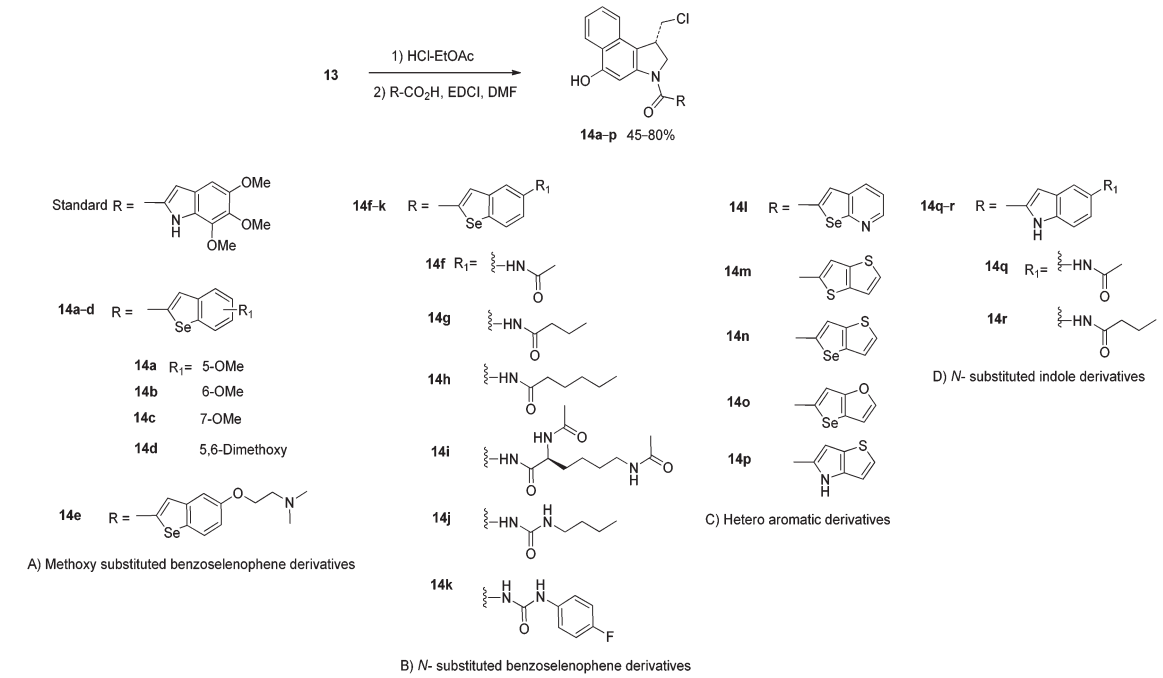
Scheme 3 Synthesis of *N*,*N*-dimethylaminoethoxy benzoselenophene acid.

Biological activity

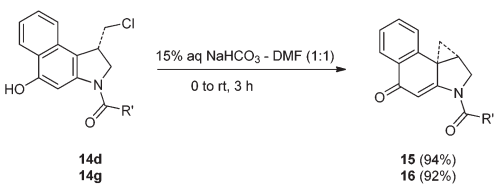
A diverse series of compounds (**14a–r**, **15** and **16**) along with CBI-TMI[36,37] were assayed for cytotoxic potential against the human ovarian cancer cell line (SK-OV-3). The cells growing on McCoy's 5A Medium, which contained 10% fetal bovine serum (FBS) and 1% P/S, were treated with different concentrations of **14a–r**, **15** and **16** as well as CBI-TMI, which is one of the most potent analogs of the class of duocarmycin compounds.[31]

The IC_{50} values in nM for the screened compounds against the SK-OV-3 cell line are shown in Table 1. The CBI-benzoselenophene analog with 5,6-dimethoxy substituents *i.e.* compound **14d** (IC_{50} = 7.4 nM) was found only 3 times less potent than CBI-TMI (IC_{50} = 2.5 nM). The analog **14e** with a longer, flexible *N*,*N*′-dimethylethoxy substituent was equipotent (IC_{50} = 7.4 nM) to the 5,6-dimethoxy substituted analog **14d**. The amide analogs **14f** and **14g** (containing *N*-acetamido and *N*-butyramido substituents, respectively) exhibit higher anticancer activities (IC_{50} = 1.6 and 0.5 nM respectively) than CBI-TMI (IC_{50} = 2.5 nM) and the analogs **14d–e**. Comparatively, the indole analogs of *N*-acetamido and *N*-butyramido substituents **14q–r** (IC_{50} = 11.9 and 58 nM, respectively) were found much less active than CBI-TMI. This trend is clearly different from that of the same compounds which are found equally potent against L1210 leukemia cell lines.[31] For the comparison of benzoselenophene and indole with the same substituents, the benzoselenophene analogs **14f** and **14g** were found 8 and 120 times more potent than the corresponding indole analogs **14q** and **14r**, respectively.

This increased potency may be due to the hydrophobicity of benzoselenophene and attractive van der Waals interactions imposed by the increased curvature of benzoselenophene. Compound **14h** with an *N*-hexanamide substituent was less



Scheme 5 Syntheses of CBI analogs of substituted benzoselenophenes, indole and heteroaromatic compounds (**14a–r**).



Scheme 6 Spirocyclization of **14d** and **14g**.

Table 1 IC_{50} (nM) of screened compounds against the SK-OV3 cell line

Compound	IC_{50}(nM) SK-OV-3	Compound	IC_{50}(nM) SK-OV-3
CBI-TMI	2.5	**14k**	7.5
14a	ND[a]	**14l**	110
14b	ND	**14m**	6.8
14c	ND	**14n**	3.4
14d	7.4	**14o**	ND
14e	7.4	**14p**	1.8
14f	1.6	**14q**	11.9
14g	0.5	**14r**	58
14h	4.3	**15**	4.0
14i	49	**16**	1.2
14j	8.2	—	—

[a] 23% inhibition at 10 nM.

active (IC_{50} = 4.3 nM) than **14f–g**, but had comparable potency over the series of compounds tested. We also observed that the analog of branched and longer substituents at the amide position, **14i**, exhibits less cytotoxicity (IC_{50} = 49 nM). This fact implies that the C-5 substituent of benzoselenophene can locate more inside of the DNA minor groove than the corresponding indole analog. *N*-Substituted urea analogs **14j–k** (IC_{50} = 8.2 and 7.5 nM, respectively) were less active than amide substituted analogs **14f–h**, but equipotent to dimethoxy substituted analogs **14d**. There were no significant differences in biological activity after spirocyclization of *seco*-CBI analogs, for example, compound **14g** compared to **16** (IC_{50} = 0.5 *versus* 1.2 nM) and **14d** compared to **15** (IC_{50} = 7.4 *versus* 4.0 nM). In the CBI-heteroaromatic analogs, compound **14l** with the selenofused-pyridine moiety was found to be least cytotoxic among all the other compounds examined (IC_{50} = 110 nM). Compound **14p** with the pyrrolo-thiophene moiety was 3.5- and 2-fold more potent than the selenofused-thiophene analog **14m** and the thieno-thiophene analog **14n**, respectively. After the biological study we selected *N*-amido benzoselenophene derivatives of duocarmycin as starting payloads in our current ADC study.

Conclusions

In summary, we synthesized various benzoselenophene esters, *N*-substituted amido and urea derivatives from the nitro benzoselenophene ester. We also improved the overall yield of scaffold **12** from **11** by an one-pot reaction.

In addition, we synthesized a diverse series of CBI-benzoselenophene, heteroaromatic and indole analogs (**14a–r**). Moreover, the *in vitro* cytotoxicity study and SAR showed that the benzoselenophene compounds **14f** and **14g** were more potent than CBI-TMI, as well superior to the rest of the synthesized benzoselenophene series of compounds. In compari-

son with indole analogs with the acetamido and butyramido substituents, **14q** and **14r**, the activities of benzoselenophene analogs **14f** and **14g** are 8 and 120 times more potent, respectively. Overall, these results show that the benzoselenophene derivative can play an important role as a DNA binding unit and can enhance or maintain the cytotoxicity of the duocarmycin analog after replacing the indole moiety. Notably *N*-amido substituents at the C-5 position are crucial for their improved anticancer activity, and such candidates can be used to develop effective therapeutics for advanced chemotherapy.

Experimental section

General experimental

All reagents were obtained from commercial suppliers and used without further purification, unless specified. The starting carboxylic acids of the analogs **14m** and **14p**, *i.e.* thieno[3,2-*b*]thiophene-2-carboxylic acid and 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid, respectively, were purchased from Aldrich. Dry DMF and ethyl acetate were purchased from Sigma Aldrich (>99.9%). Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were distilled over sodium and benzophenone. A saturated solution of HCl in ethyl acetate was prepared by purging pure HCl gas (99.99%, manufactured by RIGAS, Korea) in dry ethyl acetate at 0 to −5 °C for 1 h and stored in a deep freezer. ^{1}H and ^{13}C NMR spectra were collected at resonance frequencies of 500.1 and 125.7 MHz, respectively. The solvents used for NMR were DMSO-d_6, acetone-d_6, $CDCl_3$ and MeOH-d_4 as indicated. The chemical shifts for ^{1}H NMR are reported in ppm from tetramethylsilane (0 ppm) or referenced to the solvent (DMSO-d_6 2.50; acetone-d_6 2.05; MeOH-d_4 3.31 and $CDCl_3$ 7.26 ppm) on the δ scale. Chemical shifts (δ) for ^{13}C NMR spectra are referenced to the signals for residual deuterated solvents (DMSO-d_6 39.5; acetone-d_6 29.84, 206.26; MeOH-d_4 49.00 and $CDCl_3$ 77.16 ppm) Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet), *J* (coupling constants in hertz). Analytical reverse-phase high performance liquid chromatography (RP-HPLC) was carried out using a C18 (4.6 × 150 mm) reverse-phase column at a flow rate of 1 mL min^{-1} with UV detection at 214 and 254 nm. Linear gradients of CH_3CN/H_2O solvents, each containing 0.1% TFA were used as follows: condition A (10 to 80% CH_3CN gradient over 20 min), condition B (30 to 100% CH_3CN gradient over 20 min). For preparative HPLC, a C18 column (5 μM, 10 × 150 mm) was employed at a flow rate of 4 mL min^{-1} using the gradient condition B. High resolution mass spectra (HRMS) were recorded using two different instruments: (i) fast atom bombardment ionization using a double-focusing magnetic sector mass analyzer (ii) electrospray ionization using an ion trap analyzer (for all other compounds). Only the strongest and/or structurally important absorptions of IR spectra were reported in wavenumbers (cm^{-1}). All reactions were monitored by thin-layer chromatography (TLC) performed on glass packed silica gel plates (60F-254) with UV light and visualized with ninhydrin, *p*-anisaldehyde, phosphomolybdic acid or $KMnO_4$ solution stains. Column chromatography was performed with silica gel (100–200 mesh) with the indicated solvent system.

Synthetic procedure for amide and urea derivatives of benzoselenophene

Ethyl 5-aminobenzo[*b*]selenophene-2-carboxylate (3). To a solution of ethyl 5-nitrobenzo (b) selenophene-2-carboxylate **1a**[38] (1.3 g, 4.36 mmol) in dry ethyl acetate, was added 10% Pd/C under a N_2 atmosphere. The reaction mixture was stirred under a H_2 atmosphere for 8 h. On completion of the reaction, the mixture was filtered through a Celite pad followed by washing with ethyl acetate (3 × 20 mL). The filtrate was concentrated under reduced pressure to provide a crude residue, which was purified by silica column chromatography using ethyl acetate/hexane (1 : 3) as an eluent to obtain the desired pure benzoselenophene amine intermediate **3** (1.11 g, 95%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 6.82 (dd, J = 8.5, 2.2 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.72 (brs, NH, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 163.0, 143.4, 141.2, 135.7, 132.8, 132.3, 125.1, 116.3, 110.7, 60.5, 13.3; HRMS (ESI); *m*/*z* calcd for $C_{11}H_{11}NO_2Se$ $[M]^+$: 269.0017, found 270.0017 $[M + H]^+$.

5-Acetamidobenzo[*b*]selenophene-2-carboxylic acid (4). Compound **3** (0.691 g, 2.58 mmol) was dissolved in 10 mL dry CH_2Cl_2 and then pyridine (0.62 mL, 7.74 mmol) was added. The reaction mixture was stirred for 15 min at room temperature, after that acetic anhydride (0.37 mL, 3.87 mmol) was added slowly under a N_2 atmosphere. The reaction mixture was stirred continuously at room temperature until complete conversion was observed by TLC. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine and dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica column chromatography, and ethyl acetate/hexane (1 : 1) was used as an eluent to afford the desired ethyl 5-acetamidobenzo[*b*]selenophene-2-carboxylate as a pale yellow solid (0.765 g, 96%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.18–8.17 (m, 2H), 7.77 (d, J = 8.7 Hz, 1H), 7.69 (brs, 1H, NH), 7.40 (dd, J = 8.7, 1.6 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.5, 163.9, 141.9, 139.4, 137.9, 135.6, 134.2, 126.2, 120.0, 118.2, 61.8, 24.7, 14.4; HRMS (ESI); *m*/*z* calcd for $C_{13}H_{13}NO_3Se$ $[M]^+$: 311.0061, found 312.0114 $[M + H]^+$. The obtained ethyl 5-butyramidobenzo[*b*]selenophene-2-carboxylate (0.765 g, 2.47 mmol) was dissolved in 10 mL MeOH and then 10 mL of aqueous 3 N NaOH solution was added. The mixture was stirred at room temperature for 24 h. After complete hydrolysis, the reaction mixture was concentrated under reduced pressure to afford a crude residue which was acidified with 2 N HCl solution. The required product was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was concentrated to obtain a crude product which was purified by silica column chromatography by using ethyl acetate/hexane

(1 : 1) as an eluent to provide the desired product **4** as a yellow solid (0.63 g, 92%). ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.39 (dd, J = 2.1, 8.6 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 168.5, 166.8, 151.8, 142.9, 136.6, 136.5, 127.9, 125.9, 117.8, 116.1, 24.1; LCMS (ESI); m/z calcd for $C_{11}H_9NO_3Se$ $[M]^+$: 282.97, found 284.1 $[M + H]^+$.

5-Butyramidobenzo[*b*]selenophene-2-carboxylic acid (5). The intermediate amide ester was synthesized by a similar method used for the synthesis of an amide intermediate of compound **4** from starting amine **3**, *i.e.* compound **3** (200 mg, 0.75 mmol) was treated with butyric anhydride (0.182 mL, 1.13 mmol) and pyridine (0.18 mL, 2.25 mmol) in CH_2Cl_2. The crude product was purified *via* silica column chromatography with ethyl acetate/hexane (1 : 1) as an eluent to provide the desired ethyl 5-butyramidobenzo[*b*]selenophene-2-carboxylate as a brown solid (227 mg, 90%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.40 (brs, 1H, NH), 8.15 (s, 1H), 8.04 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 4.34 (q, J = 6.7 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 1.73 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.4, 162.1, 139.8, 137.4, 135.6, 134.0, 132.3, 124.1, 118.7, 116.7, 59.9, 37.6, 17.3, 12.5, 11.9 LCMS (ESI); m/z calcd for $C_{15}H_{17}NO_3Se$ $[M]^+$: 339.04, found 340.0 $[M + H]^+$. The obtained ester, ethyl 5-butyramidobenzo[*b*]selenophene-2-carboxylate (166 mg, 0.49 mmol) was hydrolyzed by a similar method used for the synthesis of compound **4**, and the desired acid (**5**) was obtained as a pale yellow solid (150 mg, 99%). ^{1}H NMR (500.1 MHz, MeOH-d_4) δ 8.25 (s, 1H), 8.17 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 2.38 (t, J = 7.1 Hz, 2H), 1.74 (q, J = 7.2 Hz, 2H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.7 MHz, MeOH-d_4) δ 174.7, 167.7, 143.4, 140.9, 140.4, 137.6, 134.9, 127.2, 121.2, 119.1, 39.9, 20.4, 14.1; LCMS (ESI); m/z calcd for $C_{13}H_{13}NO_3Se$ $[M]^+$: 311.01, found 312.0 $[M + H]^+$.

5-Hexanamidobenzo[*b*]selenophene-2-carboxylic acid (6). Compound **3** (300 mg, 1.12 mmol) was dissolved in 10 mL pyridine, and then hexanoic acid (0.42 mL, 3.36 mmol) and DCC (346 mg, 1.68 mmol) were added under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h until complete conversion was observed by TLC. The reaction mixture was quenched with 10 mL water and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography using ethyl acetate/hexane (1 : 1) as an eluent to provide desired ethyl 5-hexanamidobenzo[*b*]selenophene-2-carboxylate (264 mg, 65%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.12 (s, 1H), 7.95 (brs, 1H, NH), 7.72 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 4.36 (q, J = 6.9 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.72 (s, 2H), 1.40–1.32 (m, 7H), 0.87 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.1, 163.9, 141.7, 139.2, 137.6, 135.8, 134.14, 126.0, 120.3, 118.3, 61.7, 37.7, 31.5, 25.4, 22.5, 14.3, 13.9; LCMS (ESI); m/z calcd for $C_{17}H_{21}NO_3Se$ $[M]^+$: 367.07, observed 368.1 $[M + H]^+$. The obtained ethyl 5-pentanamidobenzo[*b*]selenophene-2-carboxylate (264 mg, 0.72 mmol) was hydrolyzed by the above mentioned same procedure for the synthesis of **4**, and the desired product **6** was obtained as a brown solid (232 mg, 95%). ^{1}H NMR (500.1 MHz, MeOH-d_4) δ 8.17 (s, 1H), 8.05 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.46 (dd, J = 8.6, 1.5 Hz, 1H), 2.39 (t, J = 7.4 Hz, 2H), 1.72 (t, J = 7.1 Hz, 2H), 1.40–1.38 (m, 4H), 0.94 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 171.3, 167.6, 150.3, 142.7, 136.5 (2C), 128.6, 125.9, 117.9, 116.1, 36.3, 30.9, 24.8, 21.9, 13.9; LCMS (ESI); m/z calcd for $C_{15}H_{17}NO_3Se$ $[M]^+$: 339.04, found 340.0 $[M + H]^+$.

5-(3-Butyl-ureido)-benzo[*b*]selenophene-2-carboxylic acid (7). The compound **3** (50 mg, 0.19 mmol) was partially dissolved in anhydrous CH_2Cl_2 (10 mL) under a nitrogen atmosphere, and then reaction vessel was submerged in an ice bath. A solution of butyl isocyanate (56 mg, 0.57 mmol) in anhydrous CH_2Cl_2 (60 mL) was slowly added to the cooled reaction vessel over a course of 20 min stirring. Once the addition completed, the ice bath was removed, and then reaction continued with stirring at room temperature for 12 h until disappearance of starting compound observed on TLC. The reaction mixture was concentrated under vacuum to obtain a yellow solid product which was washed with ether/pentane (1 : 4) solution, and the solid product was filtered and dried under vacuum to provide the pure desired 5-(3-butyl-ureido)-benzo[*b*]selenophene-2-carboxylic acid ethyl ester as a brown solid (55 mg, 81%). IR (KBr cm^{-1}) 3316, 3079, 2969, 2960, 2932, 2859, 1716, 1626, 1573, 1555, 1446, 1295, 1240, 1162, 1024, 1002, 908, 827, 748; ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.28 (s, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.44 (dd, J = 8.8, 2.1 Hz, 1H), 6.19 (t, J = 5.4 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 6.7 Hz, 2H), 1.43 (m, 2H), 1.35–1.31 (m, 5H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.2, 155.2, 141.4, 138.5, 136.1, 135.2, 134.4, 126.1, 119.1, 115.3, 61.3, 38.7, 31.8, 19.4, 14.1, 13.6; HRMS Calcd for ($C_{16}H_{20}N_2O_3Se$) 369.0717 $[M + H]^+$, found 369.0716. The resulting 5-(3-butyl-ureido)-benzo[*b*]selenophene-2-carboxylic acid ethyl ester (55 mg, 0.15 mmol) was dissolved in THF–MeOH–H_2O (4 : 1 : 1, 1.5 mL) and then treated with LiOH (19 mg, 0.45 mmol). The suspension was stirred at 23 °C for 18 h and quenched with 6 mL H_2O. The solution was acidified with 10 mL of 10% aqueous HCl solution and then the precipitate was extracted in CH_2Cl_2 (2 × 10 mL), washed with brine, dried over Mg_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford a crude product which was purified by silica column chromatography with 5% MeOH in CH_2Cl_2 as an eluent to provide a faint yellow solid product **7** (49 mg, 97%). IR (KBr cm^{-1}) 3217, 2960, 2931, 2861, 2561, 1674, 1626, 1577, 1560, 1452, 1296, 1224, 1160, 1055, 882, 749, 666; ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.21 (s, 1H), 8.11 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 6.18 (brs, 1H), 3.08 (m, 2H), 1.41–1.28 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 164.7, 155.3, 141.8, 138.4, 138.2, 135.3, 133.9, 126.1, 118.9, 115.3, 38.6, 31.9, 19.5, 13.6; HRMS Calcd for ($C_{14}H_{16}N_2O_3Se$) 341.0404 $[M + H]^+$, found 341.0406.

5-[3-(4-Fluoro-phenyl)-ureido]-benzo[*b*]selenophene-2-carboxylic acid (8). The intermediate 5-[3-(4-fluoro-phenyl)-

ureido]-benzo[*b*]selenophene-2-carboxylic acid ethyl ester was synthesized by using compound **3** (100 mg, 0.37 mmol) and 1-fluoro-4-isocyanato-benzene (152 mg, 1.11 mmol). The reaction method was similar to that described for the synthesis of the intermediate ester of compound **7** from the corresponding amine **3**. The crude product was washed with ether/pentane (1 : 4) solution to obtain a brown solid (145 mg, 96%). IR (KBr cm^{-1}) 2970, 2327, 2141, 1704, 1655, 1510, 1418, 1365, 1280, 1217, 953, 897, 831, 736, 731; ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.91 (s, 1H), 8.32 (s, 1H), 8.19 (d, J = 1.3 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.53–7.48 (m, 3H), 7.11 (t, J = 8.8 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.2, 158.3, 156.4, 152.8, 141.5, 137.7, 136.5, 136.2, 136.1, 134.4, 126.3, 120.0, 119.6, 116.2, 115.3, 115.1, 61.4, 14.2; HRMS Calcd for ($C_{18}H_{15}FN_2O_3Se$) 407.0310 $[M + H]^+$, found 407.0312. Then, the obtained intermediate (145 mg, 0.36 mmol) was hydrolyzed by a similar procedure used for the synthesis of compound **7**. Compound **8** was obtained as an off-white solid after purification by silica column chromatography using 5% MeOH in CH_2Cl_2 as an eluent (105 mg, 78%). IR (KBr cm^{-1}) 3365, 3089, 2584, 1657, 1611, 1504, 1313, 1200, 1157, 1047, 901, 876, 830, 706; ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.73 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.49–7.45 (m, 3H), 7.12 (t, J = 8.7 Hz, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 164.7, 158.3, 156.4, 152.7, 141.8, 138.5, 137.4, 136.3, 136.0, 133.9, 126.4, 120.0, 119.3, 116.1, 115.3, 115.2; HRMS Calcd for ($C_{16}H_{11}FN_2O_3Se$) 378.9997 $[M + H]^+$, found 378.9996.

5-(2,6-Diacetamidohexanamido)benzo[*b*]selenophene-2-carboxylic acid (9). The mixture of Fmoc-Lys(Boc)-OH (436 mg, 0.93 mmol) and compound **3** (300 mg, 1.12 mmol) was dissolved in MeOH (18 mL) and water (2 mL) and the solution was stirred for 15 min. After that 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMT-MM) (386 mg, 1.39 mmol) was added slowly to the reaction mixture and stirred continuously for 8 h. The reaction mixture was diluted with 25 mL water and then the reaction product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine and dried over Mg_2SO_4, filtered and concentrated under reduced pressure to obtain a crude residue. The crude residue was purified by silica column chromatography with ethyl acetate/hexane (1 : 1) to afford the desired ethyl 5-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6-((*tert*-butoxycarbonyl)amino)hexanamido)benzo[*b*]selenophene-2-carboxylate as a brown solid (586 mg, 88%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.74–7.72 (m, 3H), 7.57–7.54 (m, 2H), 7.41–7.35 (m, 3H), 7.27 (s, 2H), 5.73 (s, 1H), 4.68 (s, 1H), 4.42–4.36 (m, 4H), 4.21–4.18 (m, 1H), 3.85–3.83 (m, 1H), 3.73–3.71 (m, 2H), 3.17–310 (m, 2H), 1.55–1.39 (m, 14H); ^{13}C NMR (125.7 MHz, MeOH-d_4) δ 171.5, 169.6, 163.0, 155.7, 142.8, 140.8 (2C), 140.5 (2C), 138.6, 136.9, 134.6, 133.3, 126.9 (2C), 126.2 (2C), 125.1 (2C), 124.1, 119.2, 119.1 (2C), 117.3, 79.5, 66.4, 65.8, 60.8, 53.7, 46.3, 43.2, 28.1, 27.6 (3C), 21.4, 13.5 LCMS (ESI); m/z calcd for $C_{37}H_{41}N_3O_7Se$ $[M]^+$: 719.21, found 720.1 $[M + H]^+$.

The ethyl 5-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6-((*tert*-butoxycarbonyl)amino)hexanamido)benzo[*b*]-selenophene-2-carboxylate (586 mg, 0.82 mmol) was dissolved in dry CH_2Cl_2 and 20% TFA in CH_2Cl_2 was added to the reaction solution at 0 °C and the mixture was stirred for 2 h. The reaction mixture was concentrated and dissolved in 50 mL of diethylamine–CH_2Cl_2 (1 : 1) solution with stirring for 2 h. After this the solvent was evaporated to obtain a crude residue. The crude residue was dissolved in 10 mL of pyridine and acetic anhydride (0.23 mL, 2.46 mmol) and stirred continuously at room temperature for 3 h. The reaction mixture was concentrated and dissolved in MeOH–H_2O (9 : 1), and then NaOH (163 mg, 4.07 mmol) was added. The mixture was stirred at room temperature for 24 h. The reaction solution was acidified with 20% HCl solution and concentrated by using a lyophilizer. The crude product was purified by silica column chromatography by using MeOH–CH_2Cl_2 (1 : 4) as an eluent to afford the desired product **9** (20 mg, 5%). ^{1}H NMR (500.1 MHz, MeOH-d_4) δ 8.07 (s, 1H), 7.92 (s, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 4.42 (dd, J = 5.5, 2.5 Hz, 1H), 3.13 (t, J = 7.0 Hz, 2H), 1.99 (s, 3H), 1.86 (s, 3H), 1.75–1.68 (m, 1H), 1.54–1.38 (m, 5H); ^{13}C NMR (125.7 MHz, MeOH-d_4) δ 171.8, 171.6, 171.2, 169.8, 142.5, 138.7, 135.0, 129.5, 129.3, 125.3, 118.6, 117.3, 53.9, 38.5, 31.3, 28.4, 22.6, 20.9, 20.8 LCMS (ESI); m/z calcd for $C_{19}H_{23}N_3O_5Se$ $[M]^+$: 453.08; found 454.1 $[M + H]^+$.

Synthesis of 5-(2-(dimethylamino)ethoxy)benzo[*b*]selenophene-2-carboxylic acid (10). To a solution of 5-methoxy benzoselenophene derivative (770 mg, 2.72 mmol) in 10 mL anhydrous CH_2Cl_2, tetra *n*-butylammonium iodide (2.51 g, 6.80 mmol) was added under a N_2 atmosphere at −78 °C. After 2 min stirring, 6.8 mL of BCl_3 (1M CH_2Cl_2 solution, 6.80 mmol) was slowly added, and then the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with 20 mL ice water and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated under vacuum to obtain a crude phenolic product. The crude product was dissolved in 50 mL acetone. 2-Chloro-*N*,*N*-dimethylethanamine hydrochloride (1.17 g, 8.16 mmol) and potassium carbonate (1.88 g, 13.6 mmol) were added to this solution with stirring at 65 °C for 7 h. The reaction mixture was extracted with 200 mL of CH_2Cl_2 and then concentrated under reduced pressure to afford a crude residue which was purified by silica gel column chromatography with ethyl acetate/hexane (1 : 1) as an eluent to provide the intermediate, ethyl 5-(2-(dimethylamino)ethoxy) benzo[*b*]selenophene-2-carboxylate (397 mg, 43%). ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 2.35 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.0, 157.3, 142.2, 137.5, 136.0, 134.1, 126.5, 117.8, 110.2, 66.4, 61.6, 58.3, 45.9 (2C), 14.3.

The ethyl 5-(2-(dimethylamino)ethoxy)benzo[*b*]selenophene-2-carboxylate (160 mg), (0.47 mmol) was hydrolyzed by a similar procedure used for the synthesis of compound **4**. The desired product was obtained as a brown solid (136 mg, 93%).

^{1}H NMR (500.1 MHz, DMSO-d$_6$) δ 8.21 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.14 (dd, J = 8.7, 1.8 Hz, 1H), 4.43 (t, J = 4.2 Hz, 2H), 3.50 (t, J = 4.3 Hz, 2H), 2.82 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d$_6$) δ 165.0, 155.9, 142.4, 140.7, 135.7, 133.1, 127.2, 117.1, 110.9, 62.9, 55.2, 42.9 (2C); LCMS (ESI); m/z calcd for $C_{13}H_{15}NO_3Se$ $[M]^+$: 313.02, found 314.0 $[M + H]^+$.

General procedures for the synthesis of CBI derivatives (14a–r). To compound **13** (50 mg, 0.15 mmol) in a round bottomed flask was added 4 mL saturated solution of HCl in ethyl acetate at −78 °C, then the reaction mixture was stirred at the same temperature for 30 min and then at room temperature for 1 h. After salt formation was observed by TLC, ethyl acetate was evaporated under nitrogen flow and then completely dried under high vacuum for 1 h. The resulting residue was dissolved in anhydrous DMF (0.5 mL) and added to the reaction mixture of acid (1.1 eq.) and EDCI (86 mg, 0.45 mmol) in anhydrous DMF at 0 °C after 45 min stirring. The reaction mixture was stirred at 0 °C to room temperature for 8 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated under vacuum to provide a crude product which was purified by column chromatography to provide the desired product.

Spectral characteristics of 14a–p. (*S*)-(1-Chloromethyl-5-hydroxy-1,2-dihydro-benzo[*e*]indol-3-yl)-(5-methoxy-benzo[*b*]selenophen-2-yl)-methanone (**14a**), yellow solid, 62%; IR (KBr cm^{-1}) 3292, 2340, 1623, 1593, 1398, 1332, 1225, 1152, 1136, 1058, 890, 861, 806, 756; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.40 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.90 (brs, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 2.6 Hz, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.08 (dd, J = 8.8, 2.5 Hz, 1H), 4.78 (t, J = 10.1 Hz, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.23 (t, J = 8.4 Hz, 1H), 4.03–4.02 (m, 1H), 3.88 (s, 3H), 3.83 (dd, J = 11.0, 8.6 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d$_6$) δ 162.2, 157.6, 154.1, 144.1, 142.9, 141.8, 133.4, 129.8, 127.3, 126.5, 123.2, 123.1, 122.8, 122.6, 122.3, 116.3, 115.4, 109.5, 100.1, 55.5, 55.3, 47.5, 41.0; HRMS Calcd for ($C_{23}H_{18}ClNO_3Se$) 472.0219 $[M + H]^+$, found 472.0220.

(*S*)-(1-Chloromethyl-5-hydroxy-1,2-dihydro-benzo[*e*]indol-3-yl)-(6-methoxy-benzo[*b*]selenophen-2-yl)-methanone (**14b**), yellow solid, 58%; IR (KBr cm^{-1}) 3304, 2938, 1626, 1592, 1516, 1390, 1341, 1230, 1153, 1047, 875, 860, 806, 753; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.49 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 7.91 (d, J = 5.8 Hz, 1H), 7.88 (d, J = 4.7 Hz, 1H), 7.86 (s, 1H), 7.67 (s, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 4.79 (t, J = 10.0 Hz, 1H), 4.67 (d, J = 10.8 Hz, 1H), 4.23 (t, J = 8.4 Hz, 1H), 4.05–4.03 (m, 1H), 3.91 (s, 3H), 3.84–3.80 (m, 1H); ^{13}C NMR (125.7 MHz, DMSO-d$_6$) δ 162.0, 158.4, 154.1, 143.7, 141.9, 140.2, 135.7, 129.8 (2C), 128.0, 127.2, 123.1 (2C), 122.7, 122.2, 115.2, 114.7, 108.6, 100.1, 55.5, 54.7, 47.4, 41.0; HRMS Calcd for ($C_{23}H_{18}ClNO_3Se$) 472.0219 $[M + H]^+$, found 472.0220.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl)-(7-methoxybenzo[*b*]selenophen-2-yl)methanone (**14c**), yellow solid, 68%; IR (KBr cm^{-1}) 3328, 2942, 1621, 1593, 1514, 1470, 1380, 1335, 1225, 1133, 1085, 963, 867, 770, 715; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.50 (s, 1H), 8.26–8.24 (m, 2H), 7.90 (brs, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 4.78 (t, J = 10.0 Hz, 1H), 4.65 (d, J = 10.9 Hz, 1H), 4.23 (t, J = 8.1 Hz, 1H), 4.05–4.03 (m, 4H), 3.85–3.81 (m, 1H); ^{13}C NMR (125.7 MHz, DMSO-d$_6$) δ 162.0, 155.6, 154.2, 143.2, 141.8, 130.3, 130.0, 129.8 (2C), 127.4, 127.0, 123.3, 123.1, 122.9, 122.3, 119.8, 115.4, 106.6, 100.1, 55.9, 55.5, 47.5, 41.0; HRMS Calcd for ($C_{23}H_{18}ClNO_3Se$) 472.0219 $[M + H]^+$, found 472.0217.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl)(5,6-dimethoxybenzo[*b*]selenophen-2-yl)methanone (**14d**), yellow solid, 49%; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.27 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 7.91 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.56–7.52 (m, 2H), 7.41–7.38 (m, 1H), 4.78 (t, J = 10.7 Hz, 1H), 4.68 (dd, J = 10.8, 2.0 Hz, 1H), 4.25–4.21 (m, 1H), 4.05 (dd, J = 11.2, 3.2 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.81 (dd, J = 11.2, 8.7 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d$_6$) δ 160.6, 160.5, 152.5, 147.9, 146.6, 140.4, 139.3, 133.5, 133.3, 128.5, 128.2, 125.6, 121.5, 121.1, 120.6, 113.5, 107.1, 105.9, 98.6, 54.1, 53.9, 53.8, 45.8, 39.5; HRMS Calcd for ($C_{24}H_{20}ClNO_4Se$) 502.0324 $[M + H]^+$, found 502.0322.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl)(5-(2-(dimethylamino)ethoxy)benzo[*b*]selenophen-2-yl)methanone (**14e**), yellow solid, 52%; IR (KBr cm^{-1}) 3050, 2910, 1630, 1550, 1430, 1380, 1360, 1210, 1080, 821, 680; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.42 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 2.4 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.8, 3.0 Hz, 1H), 4.76 (t, J = 9.9 Hz, 1H), 4.65 (dd, J = 10.9, 1.8 Hz, 1H), 4.58 (t, J = 5.0 Hz, 2H), 4.25–4.21 (m, 1H), 4.04 (dd, J = 11.2, 3.1 Hz, 1H), 3.83 (dd, J = 11.1, 8.6 Hz, 1H), 3.69 (t, J = 5.0 Hz, 2H), 3.03 (s, 6H); ^{13}C NMR (125.7 MHz, MeOH-d$_4$) δ 165.0, 157.6, 155.9, 144.2, 142.6, 136.9, 131.5, 131.2, 128.7, 127.6, 124.7, 124.6, 124.5, 123.8, 123.5, 123.3, 117.8, 111.6, 101.2, 63.4, 57.7, 57.4, 47.5, 43.9 (2C), 43.3; HRMS Calcd for ($C_{26}H_{25}ClN_2O_3Se$) 527.0641 $[M]^+$, found 527.0639.

(*S*)-*N*-(2-(1-(Chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-benzo[*e*]indole-3-carbonyl)benzo[*b*]selenophen-5-yl)acetamide (**14f**), yellow solid, 60%; IR (KBr cm^{-1}) 3454, 3129, 2957, 2931, 2831, 1648, 1621, 1589, 1519, 1465, 1391, 1334, 1224, 1157, 1025, 905, 857, 818, 717, 695; ^{1}H NMR (500.1 MHz, acetone-d$_6$) δ 9.31 (s, 1H), 9.28 (s, 1H), 8.50 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.57–7.52 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 4.81 (t, J = 10.5 Hz, 1H), 4.68 (d, J = 10.8 Hz, 1H), 4.24 (t, J = 8.0 Hz, 1H), 4.05 (dd, J = 11.2, 3.2 Hz, 1H), 3.84 (dd, J = 10.2, 8.5 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (125.7 MHz, acetone-d$_6$) δ 169.0, 163.4, 155.1, 145.3, 143.6, 143.2, 138.3, 137.4, 131.3, 130.8, 128.3, 126.5, 124.3, 124.2, 123.6 (2C), 119.9, 117.8, 117.0, 101.5, 56.7, 47.6, 43.0, 24.3; HRMS Calcd for ($C_{24}H_{19}ClN_2O_3Se$) 499.0328 $[M + H]^+$, found 499.0326.

(*S*)-*N*-[2-(1-Chloromethyl-5-hydroxy-1,2-dihydro-benzo[*e*] indole-3-carbonyl)-benzo[*b*]selenophen-5-yl]butyramide (**14g**), yellow solid, 71%; IR (KBr cm^{-1}) 3283, 2927, 2859, 1737, 1659, 1606, 1579, 1519, 1448, 1390, 1362, 1333, 1226, 1135, 1078, 856, 738, 690; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 9.38 (s, 1H), 9.30 (s, 1H), 8.54 (s, 1H), 8.26–8.24 (m, 2H), 7.98 (d, J = 8.6 Hz, 1H), 7.90 (brs, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.57–7.53 (m, 2H), 7.40 (t, J = 7.8 Hz, 1H), 4.82 (t, J = 9.6 Hz, 1H), 4.68 (d, J = 11.1 Hz, 1H), 4.24 (m, 1H), 4.05 (d, J = 10.9 Hz, 1H), 3.84 (t, J = 10.5 Hz, 1H), 2.37 (t, J = 7.3 Hz, 2H), 1.72 (q, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 172.0, 163.4, 155.1, 145.2, 143.6, 143.1, 138.2, 137.3, 131.2, 130.8, 128.3, 126.4, 124.2 (2C), 123.6, 123.5, 119.9, 117.9, 116.9, 101.5, 56.6, 47.6, 42.9, 39.6, 19.6, 14.0; HRMS Calcd for ($C_{26}H_{23}ClN_2O_3Se$) 527.0641 $[M + H]^+$, found 527.0639.

(*S*)-*N*-(2-(1-(Chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-benzo [*e*]indole-3-carbonyl)benzo[*b*]selenophen-5-yl)heaxanamide (**14h**), yellow solid, 64%; IR (KBr cm^{-1}) 3282, 2952, 2928, 2859, 1737, 1660, 1606, 1578, 1519, 1448, 1380, 1218, 1153, 1045, 878, 758, 712, 668; ^{1}H NMR (500.1 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.99 (s, 1H), 8.43 (s, 1H), 8.25 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.82 (brs, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 4.76 (t, J = 10.1 Hz, 1H), 4.45 (d, J = 10.1 Hz, 1H), 4.20 (m, 1H), 4.00 (dd, J = 11.1, 2.9 Hz, 1H), 3.89 (dd, J = 11.1, 7.3 Hz, 1H), 2.34 (t, J = 7.4 Hz, 2H), 1.63 (t, J = 7.2 Hz, 2H), 1.33–1.31 (m, 4H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 172.2, 163.4, 155.1, 145.2, 143.6, 143.1, 138.3, 137.3, 131.3, 130.6, 128.3, 126.5, 124.3, 124.2, 123.6, 123.5, 119.9, 117.9, 117.0, 101.5, 56.7, 47.6, 43.0, 37.8, 32.2, 26.0, 23.1, 14.4; HRMS Calcd for ($C_{28}H_{27}ClN_2O_3Se$) 555.0954 $[M + H]^+$, found 555.0952.

N,*N*′-(6-((2-((*S*)-1-(Chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-benzo[*e*]indole-3-carbonyl)benzo[*b*]selenophen-5-yl)amino)-6-oxohexane-1,5-diyl)diacetamide (**14i**), yellow solid, 45%; IR (KBr cm^{-1}) 3258, 2937, 2864, 1736, 1690, 1616, 1579, 1500, 1448, 1385, 1234, 1131, 878, 808, 760, 710, 668; ^{1}H NMR (500.1 MHz, MeOH-d_4) δ 8.31 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.01 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.73–7.71 (m, 2H), 7.51–7.47 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 4.57 (d, J = 10.4 Hz, 1H), 4.47–4.43 (m, 1H), 4.10–4.06 (m, 1H), 3.94 (dd, J = 11.3, 2.8 Hz, 1H), 3.60 (t, J = 9.4 Hz, 1H), 3.16 (t, J = 7.2 Hz, 3H), 2.02 (s, 3H), 1.91–1.80 (m, 4H), 1.79–1.72 (m, 1H), 1.55 (t, J = 7.1 Hz, 2H), 1.47–1.41 (m, 2H); ^{13}C NMR (125.7 MHz, MeOH-d_4) δ 173.5, 173.3, 173.0, 165.0, 155.9, 143.6, 142.6, 139.3, 137.3, 131.6, 131.4, 130.8, 128.6, 126.8, 124.7, 124.6, 124.5, 123.6, 121.2, 119.4, 117.7, 101.2, 57.4, 55.6, 47.5, 43.2, 40.2, 32.9, 30.1, 24.3, 22.5, 22.4; HRMS Calcd for ($C_{32}H_{33}ClN_4O_5Se$) 669.1383 $[M + H]^+$, found 669.1382.

(*S*)-1-Butyl-3-(2-(1-(chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-benzo[*e*]indole-3-carbonyl)benzo[*b*]selenophen-5-yl)urea (**14j**), pale yellow solid; 58% IR (KBr cm^{-1}) 3285, 2952, 2927, 2859, 1704, 1669, 1652, 1606, 1578, 1516, 1448, 1390, 1369, 1226, 1153, 1104, 878, 856, 838, 759, 712, 669; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 9.32 (s, 1H), 8.30 (s, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.89–7.85 (m, 3H), 7.54 (t, J = 7.1 Hz, 1H), 7.41–7.39 (m, 2H), 5.83 (s, 1H), 4.76 (t, J = 9.3 Hz, 1H), 4.64 (d, J = 10.8 Hz, 1H), 4.20 (m, 1H), 4.03 (d, J = 10.7 Hz, 1H), 3.82 (t, J = 9.7 Hz, 1H), 3.23 (m, 2H), 1.50 (m, 2H), 1.37 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 162.2, 155.3, 154.1, 143.4, 142.4, 141.8, 138.4, 133.7, 130.1, 129.8, 127.3, 125.6, 123.2, 123.1, 122.8, 122.2, 118.2, 115.3, 115.1, 100.1, 55.5, 47.5, 40.9, 38.6, 31.8, 19.4, 13.6; HRMS Calcd for ($C_{27}H_{26}ClN_3O_3Se$) 556.0906 $[M + H]^+$, found 556.0905.

(*S*)-1-(2-(1-(Chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-benzo [*e*]indole-3-carbonyl)benzo[*b*]selenophen-5-yl)-3-(4-fluorophenyl) urea (**14k**), pale yellow solid, 51%; IR (KBr cm^{-1}) 3285, 3068, 2970, 1663, 1606, 1577, 1521, 1500, 1387, 1205, 1153, 1077, 831, 807, 760, 705, 668; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 9.20 (s, 1H), 8.30 (s, 1H), 8.22 (s, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.77–7.75 (m, 2H), 7.47–7.41(m, 3H), 7.35 (dd, J = 8.7, 2.0 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 8.8 Hz, 2H), 4.68 (t, J = 9.9 Hz, 1H), 4.55 (d, J = 10.6 Hz, 1H), 4.11 (t, J = 9.2 Hz, 1H), 3.92 (dd, J = 11.2, 3.2 Hz, 1H), 3.71 (dd, J = 11.1, 8.5 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 162.2, 158.3, 156.4, 154.2, 152.8, 143.8, 142.5, 141.9, 137.5, 136.1, 134.7, 130.1, 129.9, 127.3, 125.9, 123.3, 123.2, 122.8, 122.3, 120.0, 119.9, 118.7, 115.9, 115.3, 115.2, 100.2, 55.6, 47.5, 41.0; HRMS Calcd for ($C_{29}H_{21}ClFN_3O_3Se$) 594.0499 $[M + H]^+$, found 594.0501.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl) (selenopheno[2,3-*b*]pyridin-2-yl)methanone (**14l**), pale yellow solid, 80%; IR (KBr cm^{-1}) 3102, 2975, 2942, 1693, 1634, 1521, 1459, 1400, 1273, 1145, 878, 829, 763, 658; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 9.36 (s, 1H), 8.62 (s, 1H), 8.35 (d, J = 7.9 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.57–7.54 (m, 1H), 7.50 (dd, J = 7.9, 4.6 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 4.78 (m, 1H), 4.66 (d, J = 10.7 Hz, 1H), 4.23 (m, 1H), 4.05 (d, J = 11.5 Hz, 1H), 3.87–3.77 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$ + MeOH-d_4) δ 165.4, 163.1, 155.0, 148.0, 143.2, 141.0, 136.2, 134.7, 130.0, 127.8, 127.3, 124.0, 123.9, 123.4, 122.2, 120.6, 116.1, 100.0, 56.2, 46.0, 42.7; HRMS Calcd for ($C_{21}H_{15}ClN_2O_2Se$) 443.0066 $[M + H]^+$, found 443.0063.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl) (thieno[3,2-*b*]thiophen-2-yl)methanone (**14m**), pale yellow solid, 54%; IR (KBr cm^{-1}) 3079, 2971, 2881, 1708, 1667, 1629, 1588, 1369, 1205, 1184, 1146, 1024, 824, 711, 682; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 8.39 (brs, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 5.3 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 5.3 Hz, 1H), 4.73 (d, J = 10.7 Hz, 1H), 4.67–4.63 (m, 1H), 4.09–4.05 (m, 1H), 3.95 (dd, J = 11.4, 2.9 Hz, 1H), 3.47 (t, J = 10.9 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 160.7, 154.1, 142.0, 141.7, 140.8, 138.8, 132.2, 129.8, 127.3, 123.3, 123.2, 123.1, 122.8, 122.2, 120.2, 115.2, 100.2, 55.4, 47.5, 41.1; HRMS Calcd for ($C_{20}H_{14}ClNO_2S_2$) 400.0233 $[M + H]^+$, found 400.0232.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl) (selenopheno[3,2-*b*]thiophen-5-yl)methanone (**14n**), pale yellow solid, 72%; IR (KBr cm^{-1}) 3075, 2971, 2881, 1657, 1629, 1588, 1369, 1220, 1184, 1082, 1024, 825, 710, 681, 658; ^{1}H NMR (500.1 MHz, MeOH-d_4) δ 8.24 (s, 1H), 8.20 (d, J = 8.1 Hz,

1H), 7.78 (d, J = 7.7 Hz, 1H), 7.71 (brs, 2H), 7.52 (t, J = 7.1 Hz, 1H), 7.46 (brs, 1H), 7.37 (t, J = 7.1 Hz, 1H), 4.71–4.69 (m, 1H), 4.61 (d, J = 10.9 Hz, 1H), 4.14 (m, 1H), 3.98 (d, J = 11.4 Hz, 1H), 3.68 (t, J = 10.1 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 161.7, 154.1, 145.6, 142.0, 141.7, 140.2, 131.1, 129.8, 127.2, 125.4, 123.6, 123.1 (2C), 122.7, 122.2, 115.1, 100.2, 55.4, 47.5, 41.1; HRMS Calcd for ($C_{20}H_{14}ClNO_2SSe$) 447.9677 $[M + H]^+$, found 447.9674.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl)(selenopheno[3,2-*b*]furan-5-yl)methanone (**14o**), yellow solid, 54%; IR (KBr cm^{-1}) 3075, 2971, 2881, 1667, 1629, 1588, 1571, 1471, 1369, 1200, 1194, 1146, 1024, 824, 710, 681, 658; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 9.27 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 7.95 (s, 1H), 7.89–7.87 (m, 2H), 7.56–7.53 (m, 1H), 7.42–7.40 (m, 1H), 7.06 (d, J = 1.8 Hz, 1H), 4.84 (dd, J = 10.6, 9.1 Hz, 1H), 4.69 (dd, J = 10.7, 2.1 Hz, 1H), 4.27 (m, 1H), 4.06 (dd, J = 11.2, 3.2 Hz, 1H), 3.84 (dd, J = 11.2, 8.4 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 161.8, 157.3, 154.1, 148.3, 143.8, 142.1, 129.8, 127.3, 126.5, 123.2, 123.1, 122.8, 122.2, 116.8, 115.1, 110.0, 100.2, 55.3, 47.6, 41.1; HRMS Calcd for ($C_{20}H_{14}ClNO_3Se$) 431.9906 $[M + H]^+$, found 431.9904.

(*S*)-(1-(Chloromethyl)-5-hydroxy-1*H*-benzo[*e*]indol-3(2*H*)-yl)(4*H*-thieno[3,2-*b*]pyrrol-5-yl)methanone (**14p**), yellow solid, 70%; IR (KBr cm^{-1}) 3269, 3028, 2942, 2428, 1720, 1651, 1568, 1498, 1456, 1405, 1319, 1247, 1063, 992, 812, 750, 680; ^{1}H NMR (500.1 MHz, acetone-d_6) δ 10.52 (s, 1H), 9.17 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.04 (s, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.89 (s, 1H), 6.60 (s, 1H), 4.72 (t, J = 10.3 Hz, 1H), 4.66 (d, J = 10.5 Hz, 1H), 4.24 (m, 1H), 4.05 (dd, J = 10.9, 2.6 Hz, 1H), 3.77 (t, J = 10.5 Hz, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 159.1, 154.1, 142.6, 141.0, 130.0, 129.9, 128.6, 127.2, 123.5, 123.1, 122.9, 122.6, 122.0, 114.6, 111.9, 105.3, 100.4, 54.9, 47.6, 41.2; HRMS Calcd for ($C_{20}H_{15}ClN2O_2S$) 382.0543 $[M]^+$, found 382.0541.

Spectral characterization of compounds (**14s–t**) is described in ref. 31.

Cell growth inhibition assay

SK-OV-3 cells floated on McCoy's 5A Medium, into which 10% FBS and 1% P/S were added and inoculated into a 96-well plate at a concentration of 3×10^4/100 μL per well, and cultured at 37 °C for 4 h, and then treated with100 μL of each compound, so that a final concentration of 10 nM was attained. The cells were cultured at 37 °C for 72 h. As a control, the cells were treated with DMSO as a solvent of the compounds to attain a final concentration of 0.1%. Each well was treated with 10 μL of a WST-1 assay reagent and cultured at 37 °C for 2 h. Then, the absorbance was measured with an automatic microplate reader at 450 nm. A cell growth inhibition level was calculated by $\{(A450_{control} - A450_{compound})/A450_{control}\} \times 100$.

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