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ORIGINAL ARTICLE

Structure–activity relationship study of DEL-22379: ERK dimerization inhibitors with increased safety

Yang Yang[1] · Yuanzheng Zhou[1] · Lei Tao[1] · Tao Yang[1,2] · Yinglan Zhao[1] · Youfu Luo[1]

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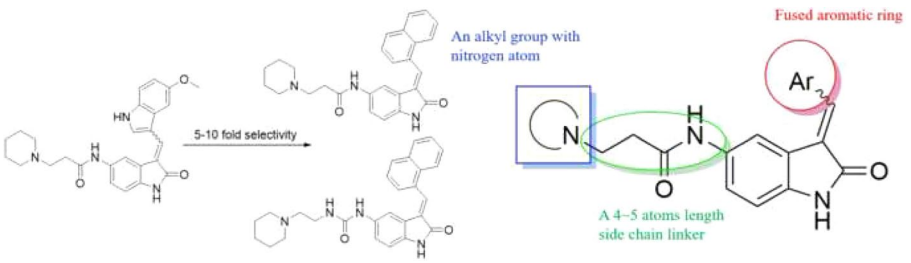
Abstract

Aberrant activation of ERK signaling pathway usually leads to oncogenesis, and small molecular agents targeting this pathway are impeded by the emergence of drug resistance due to reactivation of ERK signaling. Compound DEL-22379 has been reported to inhibit ERK dimerization which was unaffected by drug-resistant mechanism reactivating the ERK signaling. Here, we discussed a structure–activity relationship study of DEL-22379. Forty-seven analogues were designed and synthesized. Each synthesized compound was biologically evaluated for their inhibitory rates on several tumor cell lines and compounds with high inhibitory rates were further evaluated for IC_{50} values. The structure–activity relationship of idolin-2-one scaffold and the impact of *Z*/*E* configuration on potency were discussed. Potential safety of two synthesized analogues was investigated and in silico docking study of five compounds was performed to understand the structural basis of ERK dimerization inhibition.

Graphic abstract



Keywords Indolin-2-one · Synthesis · ERK dimerization inhibitor · Anti-cancer activity · Structure–activity relationship

Yang Yang, Yuanzheng Zhou and Lei Tao have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-020-10088-0) contains supplementary material, which is available to authorized users.

✉ Yinglan Zhao
zhaoyinglan@scu.edu.cn

✉ Youfu Luo
luo_youfu@scu.edu.cn

[1] Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center for Biotherapy, Chengdu, Sichuan, China

[2] Laboratory of Human Diseases and Immunotherapies, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Introduction

The mitogen-activated protein kinase cascade (ERK signaling pathway) plays an essential role in eukaryotic cellular functions ranging from proliferation to differentiation [1–3]. After pathway activation by the extracellular stimulation, the RAS family proteins firstly form a GTP-binding complex, following the sequential phosphorylation of downstream kinase module: RAF, MEK, and ERK [4, 5]. Once phosphorylated, ERK can activate a broad spectrum of nuclear and cytoplasmic substrates [4, 6]. Aberrant activation of this pathway usually leads to various diseases especially oncogenesis [2, 7]. Through the past decades, efforts have been made to exploit small molecular

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inhibitors targeting this pathway for antineoplastic therapy, and some of these agents have already progressed to clinic, such as vemurafenib and dabrafenib [4, 8]. However, the emergence of drug resistance hampered the efficacy of such agents due to diverse mechanism, most of which involve the reactivation of ERK signaling [2, 9]. Thus, novel agents with different mode of action that can circumvent such reactivation are urgently needed.

Upon phosphorylation, ERK monomers form homodimers [10]. The dimerized ERK proteins are able to transport into nucleus or stay in cytoplasm to activate cytoplasmic substrates [11, 12]. It has been demonstrated that interfering ERK dimerization is sufficient to impede tumor progression [2, 8, 12]. A small molecule, DEL-22379 (Fig. 1a), has been reported to inhibit ERK dimerization without alter ERK phosphorylation level [2]. Besides, this molecule is unaffected by drug-resistant mechanism reactivating the ERK signaling [2], suggesting aiming at the inhibition of ERK dimerization a promising solution to cancer therapy.

The inspiring work of DEL-22379 encouraged us to investigate the ERK dimerization inhibitory potency of indolin-2-one scaffold. Our group designed and synthesized three series of indolin-2-one compounds (Fig. 1b) with modification on C-3 position and C-5 position of DEL-22379. MTT experiment was conducted to determine the inhibitory rates of synthesized compounds on several tumor cell lines, and then IC_{50} of selected compounds was evaluated. The structure–activity relationship (SAR) of indolin-2-one scaffold was discussed.

Results and discussion

Analogues synthesis

Three series of DEL-22379 analogues **5a~5k** (series 1), **9a~9q** (series 2) and **16a~16s** (series 3) were prepared in this study. Synthesis of analogues **5a~5k** was carried out by synthetic route depicted in Scheme 1. Compounds **5a** and **5b** were obtained directly by aldol reaction of starting materials indolin-2-one (**3a**) or 5-nitroindolin-2-one (**3b**) with 5-methoxy-1*H*-indole-3-carbaldehyde (**4**), respectively, while **5c** was obtained from reduction of compound **5b**. Analogues **5d~5k** were synthesized by aldol reaction of 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) with intermediates **3d~3k**, which were products of amide condensation of acids **2d~2k** and 5-aminoindolin-2-one (**1**) reduced from 5-nitroindolin-2-one (**3b**).

Synthesis of analogues **9a~9q** follows the similar synthetic route (Scheme 2) of series 1. Amide condensation was firstly performed to couple 5-aminoindolin-2-one (**1**) and 3-(piperidin-1-yl)propanoic acid (**6**) to afford intermediate **7**, followed by aldol reaction of intermediate **7** with aromatic aldehyde **8a~8q** to give analogues **9a~9q**.

The similar strategy (Scheme 3) was also utilized to synthesize analogues **16a~16s**. Compound **16a** was prepared through aldol reaction of starting materials indolin-2-one (**3a**) and 1-naphthaldehyde (**8h**), while compounds **16d~16j** was obtained from aldol reaction of 1-naphthaldehyde (**8h**) and intermediates **3d~3j** used in Scheme 1. Same method in the synthesis of intermediates **3d~3k** was used to condense acid

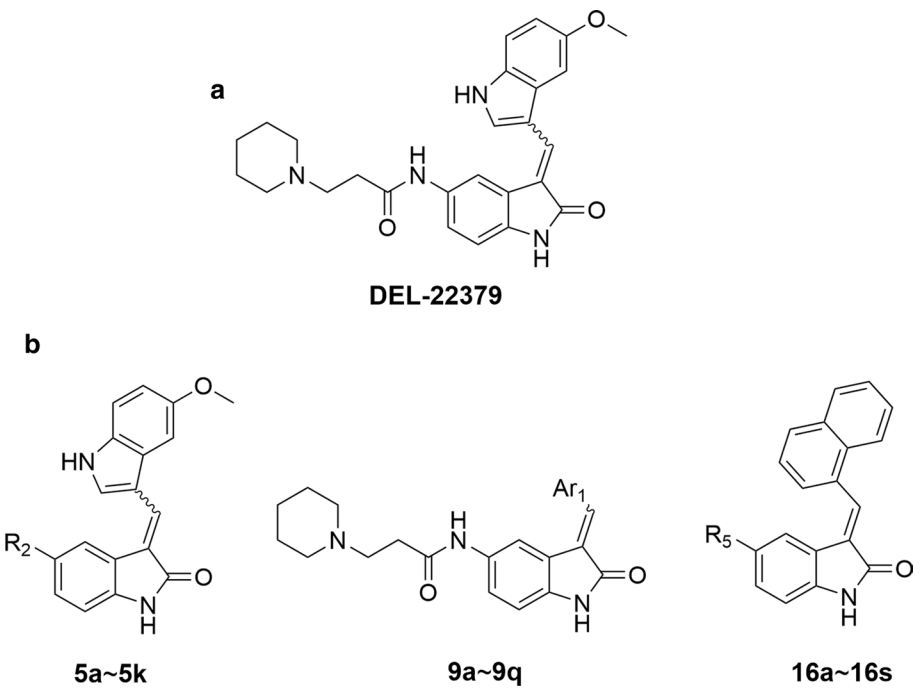
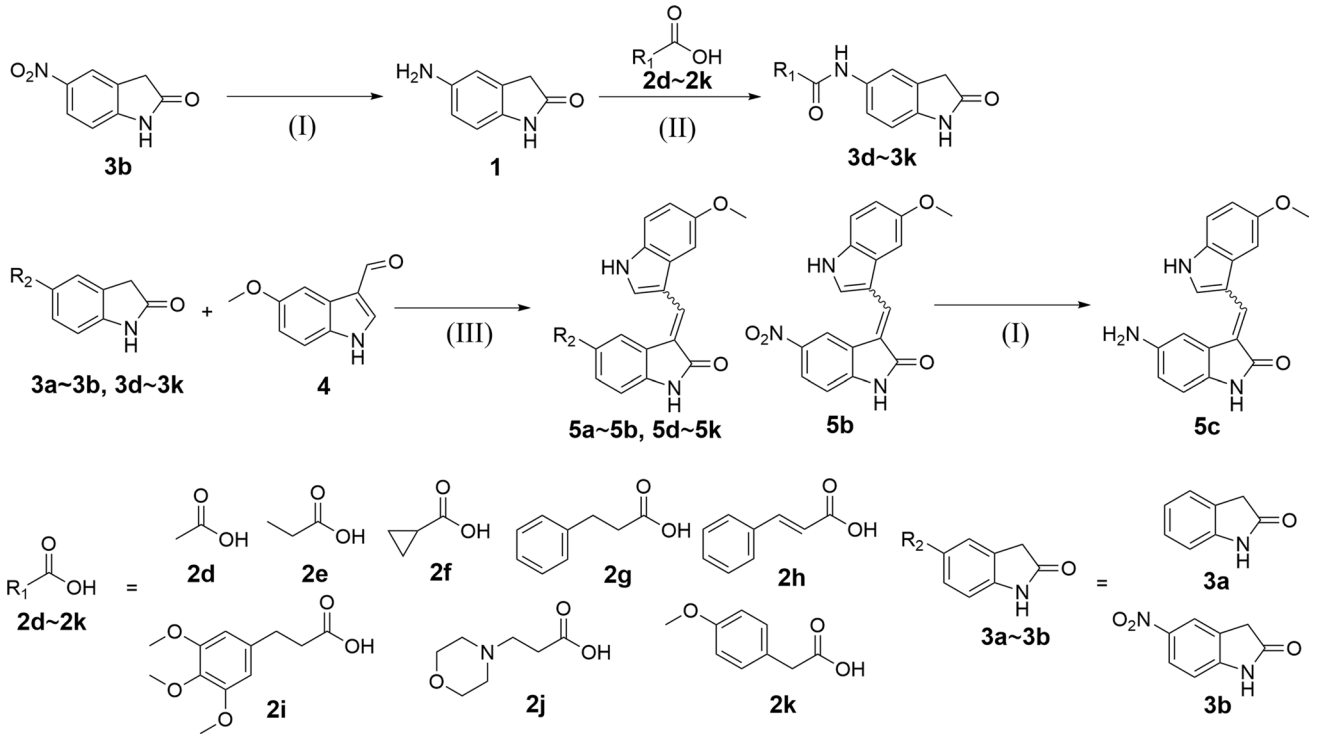
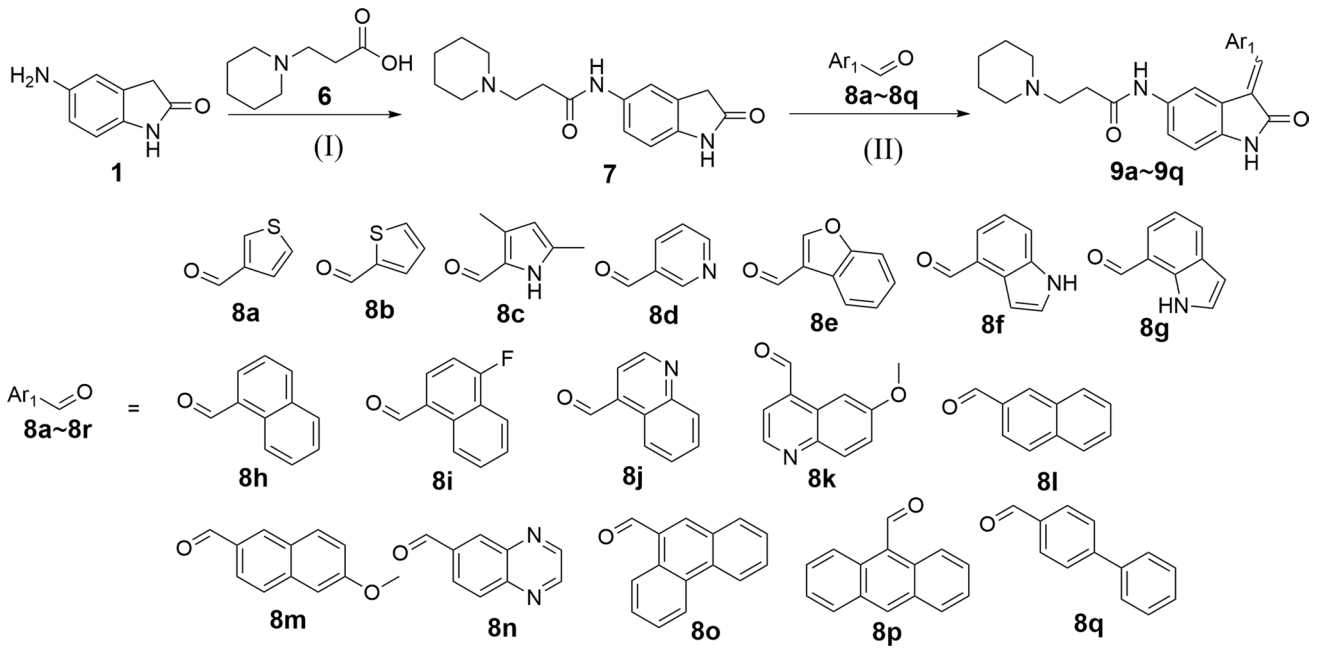


Fig. 1 **a** Structure of DEL-22379. **b** Structure of synthesized compounds **5a~5k**, **9a~9q**, **16a~16s**

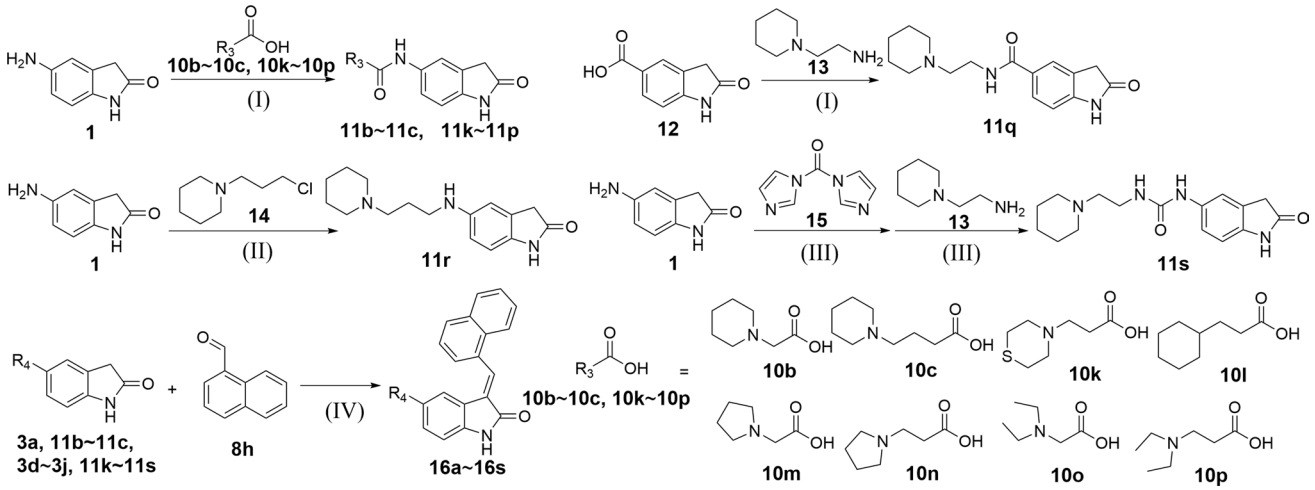


Scheme 1 Synthesis of analogues **5a~5k**. Reagents and conditions: (I). 80% aqueous solution of hydrazine hydrate, $FeCl_3$, activated carbon, EtOH, 78 °C; (II). HATU, Et_3N, DCM, 25 °C; (III). piperidine, MeOH, 64 °C



Scheme 2 Synthesis of analogues **9a~9q**. Reagents and conditions: (I). HATU, Et_3N, DCM, 25 °C; (II). piperidine, MeOH, 64 °C

10b~10c, **10k~10p** with 5-aminoindolin-2-one (**1**) to give intermediates **11b~11c**, **11k~11p**, followed by aldol condensation with 1-naphthaldehyde (**8h**) yielding compounds **16b~16c**, **16k~16p**. Intermediate **11q**, **11r** and **11s** were prepared through different ways. Intermediate **11q** was prepared through amide condensation of 2-oxoindoline-5-carboxylic



Scheme 3 Synthesis of analogues **16a~16s**. Reagents and conditions: (I). HATU, Et_3N, DCM, 25 °C; (II). K_2CO_3, NaI, *N*,*N*'-dimethylformamide (DMF), 90 °C; (III). DMF, 25 °C; (IV). piperidine, MeOH, 64 °C

acid (**12**) and 2-(piperidin-1-yl)ethan-1-amine (**13**); intermediate **11r** was obtained through a nucleophilic substitution reaction by coupling 5-aminoindolin-2-one (**1**) and 1-(3-chloropropyl)piperidine (**14**), intermediate **11s** was prepared by reacting 5-aminoindolin-2-one (**1**) with di(1*H*-imidazol-1-yl) methanone (CDI, **15**) then with 2-(piperidin-1-yl)ethan-1-amine (**13**). Then aldol condensation with 1-naphthaldehyde (**8h**) was conducted to give final product **16q**, **16r** and **16s**.

The *Z*/*E* configuration of all synthesized compounds was determined by 2D ROESY NMR spectrum (Supporting Information 1, only 2D ROESY spectrum of **5g**, **5c**, **5j** and **9a~9q** was showed for the rest of the compounds in series 1 and all compounds in series 3 forming the same configuration, respectively) judging by whether the olefinic hydrogen has a co-signal with hydrogen at C-4 position of indolin-2-one or the C-4 position hydrogen has a co-signal with hydrogen on aromatic ring of aldehyde moiety (Fig. 2). Most analogues of series 1 (**5a~5b**, **5d~5i**, **5k**) with a 5-methoxy-1*H*-indole-3-methylene at the C-3 position formed *Z* isomers except for DEL-22379, **5c** and **5j** (they formed a *Z*/*E* mixture), while all analogues of series 3 (**16a~16s**) with a napthalene-1-methylene at the C-3 position formed *E* isomers. Analogues of series 2 formed different configuration due to different substitution of C-3 position, **9b**, **9c**, **9d**, **9e**, **9g**, **9l~9n**, **9q** were *Z*/*E* mixtures; **9c** was a *Z* isomer; **9h~9k**, **9o**, **9p** formed *E* isomers.

Inhibitory rates, IC_{50} and SAR study

Modification on C-5 position side chain of DEL-22379 (series 1: analogues 5a~5k) and inhibitory rates determination

We started our investigation with modifying the C-5 position side chain on indolin-2-one scaffold of DEL-22379, and 11 analogues **5a~5k** were synthesized. It was documented that tumor cell lines harboring RAS mutant like A549, DLD1, HCT116 or harboring BRAF mutant like A375 were more sensitive to ERK dimerization inhibitors than RAS/BRAF wild-type tumor cell lines [2]. Thus, tumor cell lines A549, A375, DLD1 and HCT116 were chosen and subsequently subjected to 10 μM **5a~5k** and DEL-22379, and the inhibitory rates were determined (Table 1). When 3-(piperidin-1-yl)propanamide side chain of DEL-22379 was replaced by small group like a hydrogen atom (**5a**), a nitro group (**5b**) or an amino group (**5c**), the mean inhibitory rates reduced. A shorter side-chain replacement like acetamide (**5d**), propionamide (**5e**), cyclopropanecarboxamide (**5f**), or oxygen atom subsititution like 3-morpholinopropanamide (**5j**) leads to sharp decreases on inhibitory rates. When using phenylic group on C-5 position side chain (**5g**, **5i** and **5k**), the inhibitory rates also declined a lot. Notably, substituting with a cinnamide (**5h**) making this compound a planar molecule maintained high inhibitory rates on all four tumor cells, this may due to the non-specific binding (off-target) of the Michael acceptor contained by cinnamide moiety.

Modification on C-3 position aromatic ring of DEL-22379 (series 2: analogues 9a~9q), inhibitory rates determination and IC_{50} evaluation of selected compounds

After the exploration on C-5 position side chain of DEL-22379, we wondered how the chemical structure of C-3 position aromatic ring would affect the efficacy of this scaffold. Seventeen analogues **9a~9q** with various aromatic rings on C-3 position were prepared and inhibitory rates (at 10 μM) were determined (Table 2) on four tumor cell lines mentioned above. Single aromatic ring substitutions like thiophene-3-methylene (**9a**), thiophene-2-methylene

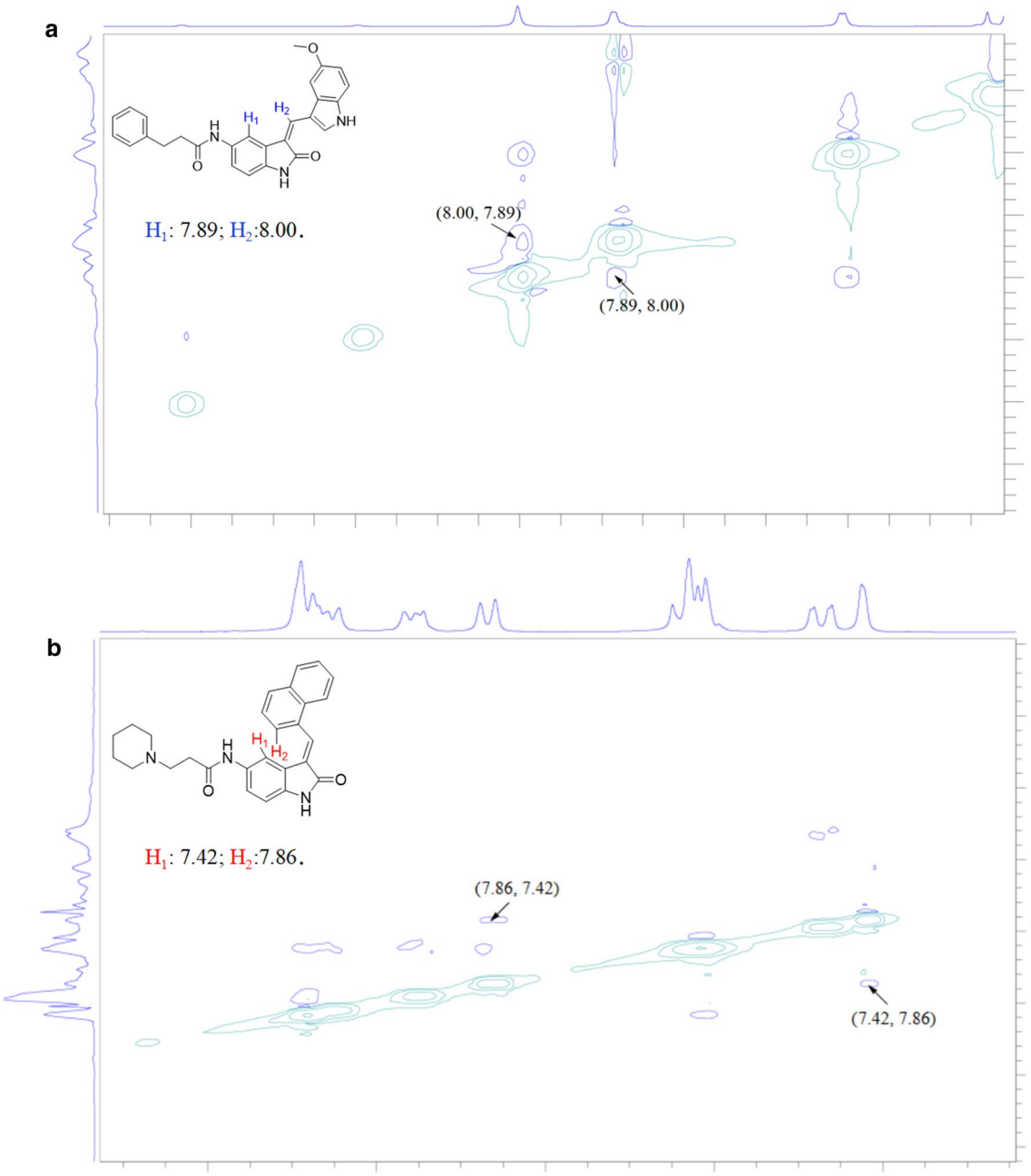
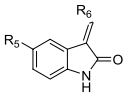
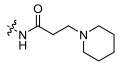
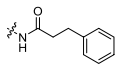
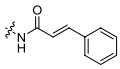
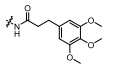
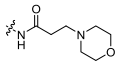
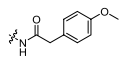


Fig. 2 The 2D ROESY NMR spectrum (part) of compound **5g** (**a**) and compound **9h** (**b**), *Z*/*E* configuration was judging from the existing of co-signal of olefinic hydrogen with hydrogen at C-4 position and C-4 position hydrogen with hydrogens on aromatic ring of aldehyde moiety

(**9b**) and pyridine-2-methylene (**9d**) weakened the efficacy of this scaffold, while 3,5-dimethyl-1-*H*-pyrrole-2-methylene (**9c**), which was designed following the structure of approved anti-cancer drug (sunitinib) that also contain an indolin-2-one scaffold, maintained~60% mean inhibitory rate. Deletion of methoxy group (**9e**) leaded to a slight decrease on inhibitory rates, but substitution with a 1-*H*-indole-5-methylene (**9f**) and a 1-*H*-indole-7-methylene (**9g**) resulted in significant reduction. When using a napthalene-1-methylene (**9h**) and a 4-fluoronapthalene-1-methylene (**9i**), high inhibitory rates were observed. Quinoline-4-methylene (**9j**), napthalene-2-methylene (**9l**) and quinoxaline-2-methylene (**9n**) substitutions also lead to efficacy decline, but adding methoxy groups to **9j** (**9k**) and **9l** (**9m**) enhanced their efficacy (same in DEL-22379 and **9e**). Three benzene rings fusing leaded to lower (**9p**) or higher (**9o**) inhibitory rates, while two benzene rings linking (**9q**) resulted in efficacy attenuation.

Table 1 Inhibitory rates of analogues **5a~5k** (series 1) on four tumor cell lines A549, A375, DLD1 and HCT116



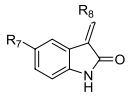
Compounds	R_5	R_6	Configuration	Inhibitory rates (at 10μM)				
				A549 (%),	A375 (%),	DLD1 (%),	HCT 116 (%),	Mean rate (%),
DEL-22379			*Z*/*E* = 3/1	88	91	71	94	86
5a			*Z*	42	56	58	72	57
5b			*Z*	13	38	54	48	38
5c			*Z*/*E* = 4/1	40	37	52	76	51
5d			*Z*	14	30	28	46	30
5e			*Z*	2	11	17	40	18
5f			*Z*	− 7	− 37	5	16	− 6
5g			*Z*	8	42	36	59	36
5h			*Z*	67	74	68	81	72
5i			*Z*	18	31	17	40	26
5j			*Z*/*E* = 4/1	14	15	18	24	18
5k			*Z*	56	19	20	37	33

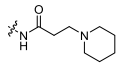
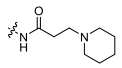
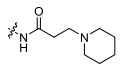
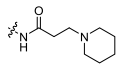
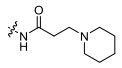
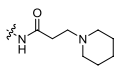
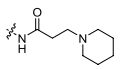
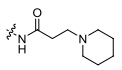
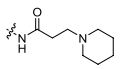
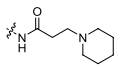
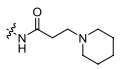
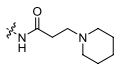
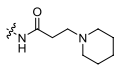
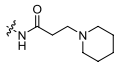
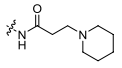
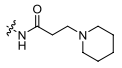
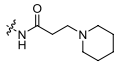
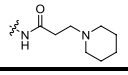
To further investigate the potency of analogues with rather high inhibitory rates, ten analogues (**5h**, **9c**, **9e**, **9h**, **9i**, **9k**, **9m**, **9o**, **9p**, **9q**) and DEL-22379 were selected and IC_{50} values on tumor cell lines A549, A375, DLD1, HCT116 along with human hepatocyte LO_2 were evaluated (Fig. 3,see Table S1 in Supporting Information 1 for IC_{50} values). Compounds **5h**, **9c**, **9e**, **9h** exhibited comparable potency on all tumor cell lines comparing to DEL-22379; compounds **9m**, **9p** and **9q** showed a slight decrease on some tumor cell lines; IC_{50} of compounds **9i** and **9k** on A549 increased to more than 20 μM, while compounds **9o** showed a slightly enhanced tumor inhibitory efficacy. Although the anti-tumor efficacies of analogues of series 1 and 2 did not increase up to any orders of magnitude, but interestingly, compound **9h** with a napthalene-1-methylene on C-3 position exhibited an about fivefold–tenfold selectivity between tumor cell lines and human liver cell LO_2, which encouraged us to make further exploration on this analogue.

Further exploration of C-5 position side chain based on 9h (series 3, analogues 16a~16s), inhibitory rates determination and IC_{50} evaluation of selected compounds

In order to seek more appropriate C-5 position side chain for better analogues with higher selectivity and potency, nineteen analogues **16a~16s** were designed based on **9h** and synthesized, inhibitory rates were determined against the same tumor cells (Table 3). Varying degrees of decreases were observed when substituted with side chain used in series 1 (**16a**, **16d**, **16e**, **16f**, **16g**, **16h**, **16i**, **16j**), and even efficacy of Michael acceptor cinnamide (**16h**) declined to 45% inhibitory rate. Using of a 3-cyclohexylpropanamide (**16l**) also reduced the potency of this scaffold, but using of a 3-thiomorpholinopropanamide (**16k**) kept a rather high inhibitory rate. Replacing the piperidine ring with a pyrrolidine ring (**16n**) or a diethylamine (**16p**) leaded to slight decrease. Attenuation of the side chain length (**16b**, **16m**, **16o**) leaded to markedly decrease in inhibitory rate, while increase in

Table 2 Inhibitory rates of analogues **9a~9q** (series 2) on three tumor cell lines A549, A375, DLD1 and HCT116



Compounds	R_7	R_8	Configuration	Inhibitory rates (at 10μM)				
				A549 (%),	A375 (%),	DLD1 (%),	HCT 116 (%),	Mean rate (%),
DEL – 22379			*Z*/*E* = 3/1	88	91	71	94	86
9a			*Z*/*E* = 1/1	30	16	28	22	24
9b			*Z*/*E* = 3/2	32	57	41	71	50
9c			*Z*	29	64	74	70	59
9d			*Z*/*E* = 1/2	30	20	19	23	23
9e			*Z*/*E* = 2/1	68	84	68	85	76
9f			*E*	34	44	14	26	30
9g			*Z*/*E* = 1/6	23	45	29	32	32
9h			*E*	26	88	66	94	68
9i			*E*	37	96	74	93	75
9j			*E*	40	52	16	35	36
9k			*E*	69	97	56	77	75
9l			*Z*/*E* = 1/5	31	62	42	55	48
9m			*Z*/*E* = 1/4	24	56	81	97	64
9n			*Z*/*E* = 1/3	40	55	16	35	36
9o			*E*	86	94	95	98	93
9p			*E*	13	64	69	90	59
9q			*Z*/*E* = 1/4	15	53	80	94	60

the side chain length (**16c**) maintained comparable potency. Finally, we changed the linker type of the connecting part of side chain to indolin-2-one scaffold (**16q**, **16r**, **16s**), **16r** and **16s** exhibited slightly lower inhibitory rates, while **16q** exhibited a higher inhibitory rate.

IC_{50} of six compounds (**16k**, **16n**, **16p**, **16q**, **16r**, **16s**) along with DEL-22379 and **9h** were evaluated on A549, A375, DLD1, HCT116, and LO_2 (Fig. 4). Compounds **16k**, **16n**, **16p**, **16q** and **16r** exhibited decreased potency and all lost selectivity. Only **16s** showed similar IC_{50} values and selectivity comparing to **9h**. Throughout structure–activity relationship of analogues of all three series, we concluded that some fused aromatic ring substitution at C-3 position, a 4~5 atoms length side chain linker, an alkyl group with

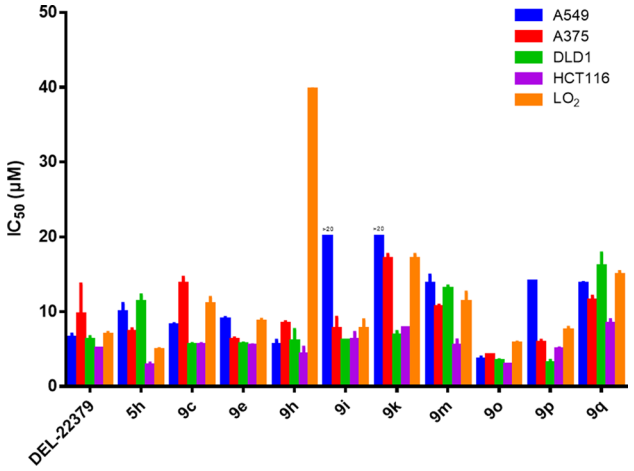


Fig. 3 IC_{50} values of selected compounds. Each tumor cell line was treated with various concentrations (0~20 μM) of selected compounds for 48 h, respectively. Cell viability was detected by CCK-8 assay and IC_{50} values were calculated by Graph-Pad Prism 7 software using XY modeling. Data are expressed as the mean ± S.D. from three experiments

nitrogen at the end of C-5 position side chain of indolin-2-one scaffold are essential for anti-tumor efficacy (Fig. 5).

Relationship between analogue configurations and efficacy

Throughout all three series, we noticed that analogues with high anti-tumor efficacy most come up with an *E* configuration like **9h**, **9i**, **9k**, **9o**, **9p** and analogues of series 3 or a mixture with more *E* isomer like **9m** and **9q**. Only a few compounds with *Z* configuration or mixture with more *Z* isomer exhibited comparable efficacy comparing to DEL-22379, like **5h** (*Z*), **9c** (*Z*), **9e** (*Z*/*E* = 2/1). We presumed that aromatic rings on C-3 position with an *E* configuration make more contribution to increase the anti-tumor potential of this scaffold than *Z*. Compound DEL-22379 obtained from purchasing or synthesized was a *Z*/*E* mixture (*Z*/*E* = 3/1), we wondered whether a pure *E* isomers of DEL-22379 would possess a higher potency. The *Z*/*E* mixed DEL-22379 was heated in dioxane at 110 °C for 8 h to form a > 95% *E* isomer (Fig. 6), then IC_{50} was evaluated (Fig. 7). Only selectivity increase between tumor cells and normal cell were observed but not anti-tumor potency. Consider that compounds with high selectivity were all *E* isomers (**9h**, **16s**, *E*-DEL-22379), we concluded that analogues of this scaffold with *E* configuration were more likely to display selectivity than *Z* isomers.

Acute toxicity study

To further investigate the safety of **9h** and **16s**, we conducted an acute toxicity test and investigated whether **9h** and **16s** could induce hematological changes after two oral administrations of an extreme dose (500 mg/kg) in Balb/c mice. During 15 days observation, the animals showed no abnormality. Meanwhile, we did not observe a loss of body weight in **9h**- or **16s**-treated mice (Fig. 8). The result of hematological evaluation indicated that **9h** and **16s** treatment did not alter the counts of white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB) or hematocrit (HCT) levels, etc. (Fig. 9). In addition, neither biochemical parameters altered after **9h** or **16s** treatment (Fig. 10). Above results suggested that **9h** and **16s** were relative safe agents for oral administration.

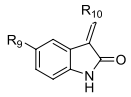
In silico docking

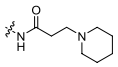
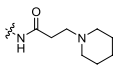
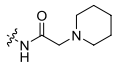
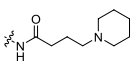
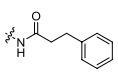
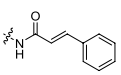
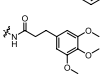
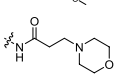
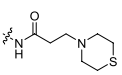
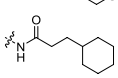
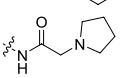
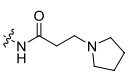
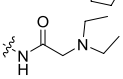
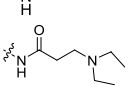
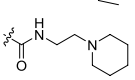
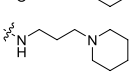
In an attempt to understand the structural basis how our newly synthesized compounds inhibited ERK dimerization, in silico docking of selected compounds with ERK was performed. It has been reported that phosphorylated ERK dimers had a different conformation comparing to unphosphorylated ERK dimers [13, 14], since ERK phosphorylation promote ERK homodimers formation and the fact that DEL-22379 could not disrupt already performed ERK dimers [2], we decided to perform our docking study on phosphorylated ERK monomer. Compounds **9h**, **9o**, **16s**, *E*-DEL-22379 and *Z*-DEL-22379 was selected to dock to available phosphorylated ERK monomer structure (PDB ID: 5V60) [15], the result of **16s** was depicted in Fig. 8 (see Figure S1–S4 in Supporting Information 1 for docking results of **9o**, **16s**, *E*-DEL-22379 and *Z*-DEL-22379). Compound **16s** bounded to the dimer interface of phosphorylated ERK monomer (Fig. 11a) with its indolin-2-one scaffold and the side chain part insert into the cleft of the protein surface of this monomer (Fig. 11b). The benzene ring of indolin-2-one interacted with the benzoyl groups of Phe 181 and Phe 329 through $\pi-\pi$ stacking, the nitrogen atoms of indolin-2-one and urea linkage resembling hydrogen bond interactions with Asp 177 and Asp 335, while nitrogen atom of piperidyl group form an ionic bond interaction with TPO 183, the phosphorylated residue Thr 183 (Fig. 11c, d). The other four compounds adopted similar mode of action with phosphorylated ERK monomer suggesting compounds of this scaffold could interfere ERK dimerization by binding to the interface of phosphorylated ERK.

Conclusion

In summary, three series analogues of DEL-22379 were designed, synthesized and biologically evaluated. The impact of C-3 position aromatic rings and C-5 position side chain of indolin-2-one scaffold on anti-tumor effect was explored. Compounds **9c**, **9e**, **9h**, **9o** in series 2 and compound **16s** in series 3 were found to possess a comparable or increased

Table 3 Inhibitory rates of analogues **16a~16s** (series 3) on four tumor cell lines A549, A375, DLD1 and HCT116



Compounds	R_9	R_{10}	Configuration	Inhibitory rates (at 10μM)				
				A549 ( ),	A375 ( ),	DLD1 ( ),	HCT 116 ( ),	Mean rate ( ),
DEL-22379			*Z*/*E* = 3/1	88	91	71	94	86
9h			*E*	26	88	66	94	68
16a			*E*	18	26	– 1	23	16
16b			*E*	1	18	30	43	23
16c			*E*	25	53	76	95	62
16d			*E*	38	29	5	44	29
16e			*E*	41	10	22	49	30
16f			*E*	19	19	1	32	18
16g			*E*	18	15	9	37	20
16h			*E*	52	35	40	54	45
16i			*E*	5	3	17	36	15
16j			*E*	– 1	39	21	35	24
16k			*E*	8	44	85	97	58
16l			*E*	11	44	47	53	39
16m			*E*	17	23	35	57	33
16n			*E*	26	50	65	81	56
16o			*E*	5	22	51	48	32
16p			*E*	21	41	61	85	52
16q			*E*	48	92	83	97	80
16r			*E*	19	55	60	82	54
16s			*E*	22	89	54	93	64

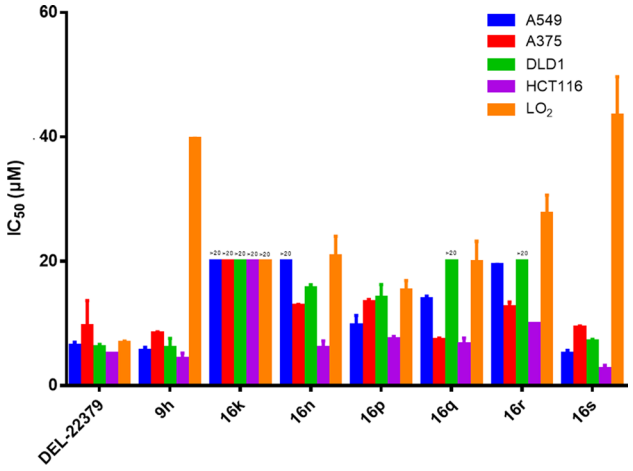


Fig. 4 IC_{50} values of selected compounds. Data are expressed as the mean ± S.D. from three experiments

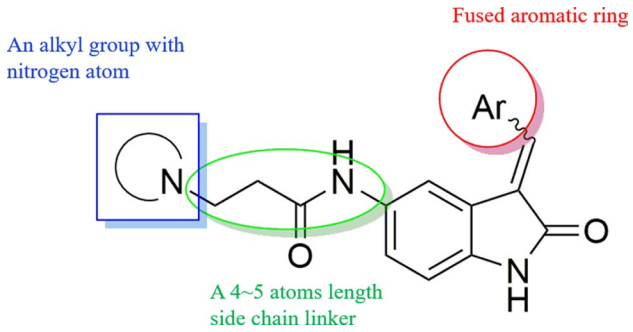


Fig. 5 Structure-activity relationship of indolin-2-one scaffold

potency comparing to DEL-22379. We concluded the SAR that some fused aromatic ring substitution at C-3 position, a 4~5 atoms length side chain linker, an alkyl group with nitrogen at the end of C-5 position side chain are essential for anti-tumor efficacy. Compounds **9h** and **16s** exhibited highly selectivity and further acute toxicity study suggested these two compounds were potential safe agents. In Silico Docking study suggested these analogues of indolin-2-one scaffold inhibited ERK by bound to protein's cleft of dimerization interface. This study presented a preliminary insight into the anti-tumor potency of this chemical structure, and we consider that our future work should consist in the further confirmation of ERK dimerization inhibition mechanism of synthesized compounds and the evaluation of pharmacodynamics and pharmacokinetics of hit compound.

Experimental section

Chemistry

All reagents were directly used as purchased without further purification. All solvents were dried according to standard methods before use, solvents used in optical spectroscopic studies were HPLC grade. All NMR spectrum were recorded on a Bruker Avance (Varian Unity Inova) 500 MHz spectrometer in DMSO-d_6 with tetramethylsilane (TMS) as internal standard. ^{1}H NMR and ^{13}C NMR spectra were recorded respectively at 400 MHz and 100 MHz. ^{1}H NMR and ^{13}C NMR were analyzed by MestReNova Software while 2D ROESY were analyzed by Topspin Software. High resolution mass spectrum (HRMS) was performed on an Agilent LC/MSD TOF system G3250AA. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm) from Qingdao Haiyang Inc., and components were visualized by ultraviolet light (254 nm). Silicycle silica gel 300–400 (particle size 40–63 μm) mesh was used for all flash column chromatography experiments. Melting points of all compounds were determined using SGW X-4 micromelting point apparatus (Shanghai jingke industrial co.,ltd).

Preperation of 5-aminoindolin-2-one (1)

To a suspension of 5-nitroindolin-2-one (5g, 1 eq.) in EtOH (50 mL), activated carbon (1 g) and $FeCl_3$ (1 g) were added. The mixture was heated to 78 °C, and stirred for 10 min. Then 80% aqueous solution of hydrazine hydrate (8 eq.) was added dropwise into the reaction mixture in 5 min, the resulting mixture was allowed to stirred at 78 °C for 8–10 h and then cooled to room temperature. The mixture was filtered to remove residue of activated carbon, the filtrate was concentrated under vacuum to afford crude product, which was purified by recrystallization in EtOH (about 15 mL) to give 5-aminoindolin-2-one as a pale yellow solid (yield 91.9%).

General procedure A for the synthesis of intermediates 3d~3k, 7, 11b~11c, 11k~11p, 11q

To a solution of corresponding acids **2d~2k**, **6**, **10b~10c**, **10k~10p**, **12** (600 mg, 1 eq.) in dichloromethane (DCM) (7 mL), triethylamine (1.4 eq.) and 1-[Bis(dimethylamino) methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (1.3 eq.) were added. The reaction mixture was stirred at room temperature for 20–30 min, then corresponding amines **1**, **13** (1.1 eq.) was added into the

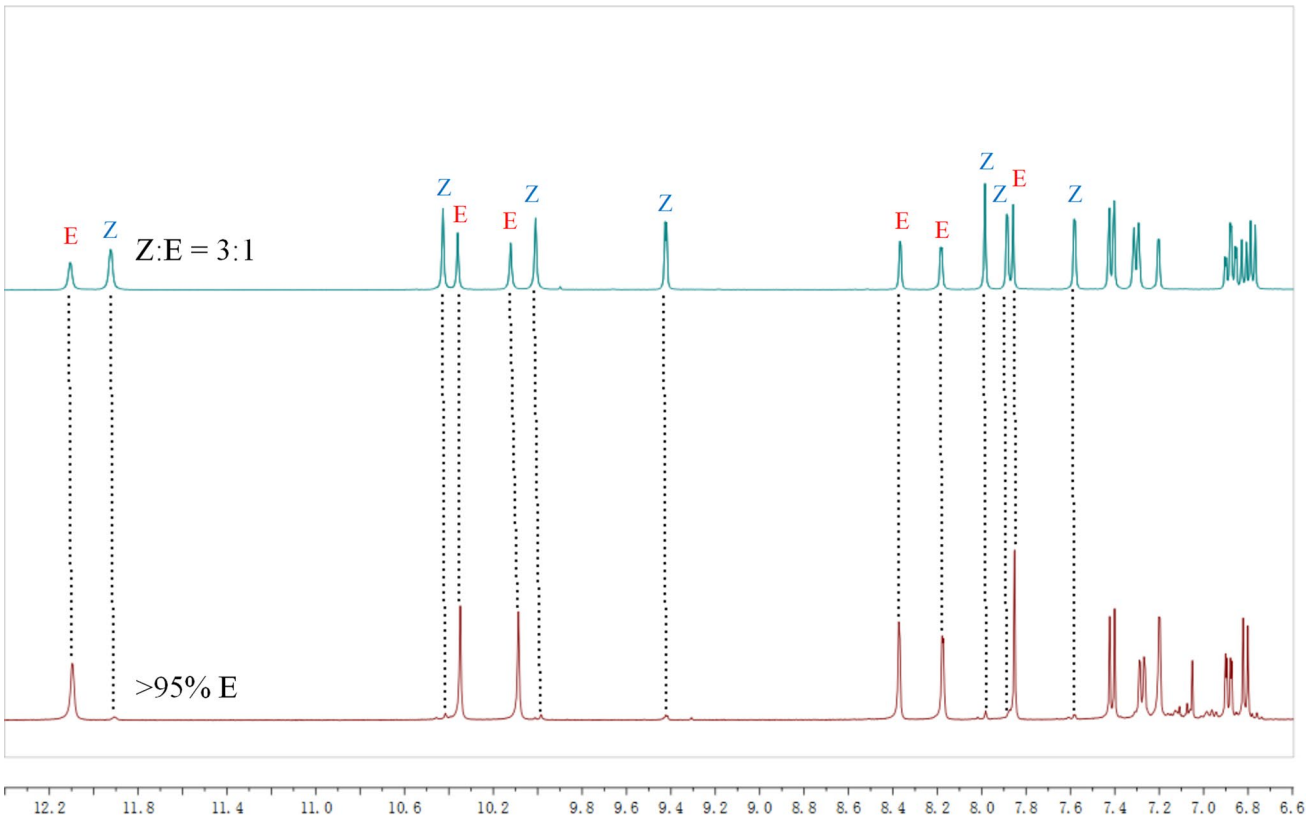


Fig. 6 Comparison of ^{1}H NMR spectrum (part) of purchased or synthesized DEL-22379 (top) and transformed DEL-22379 (below)

reaction mixture. The resulting mixture was stirred at room temperature for 6 h. After the reaction was finished, the solvent was evaporated under vacuum, then purified by column chromatography to give intermediate **3d~3k**, **7**, **11b~11c**, **11k~11p**, **11q** (yield 13.2%~51.4%).

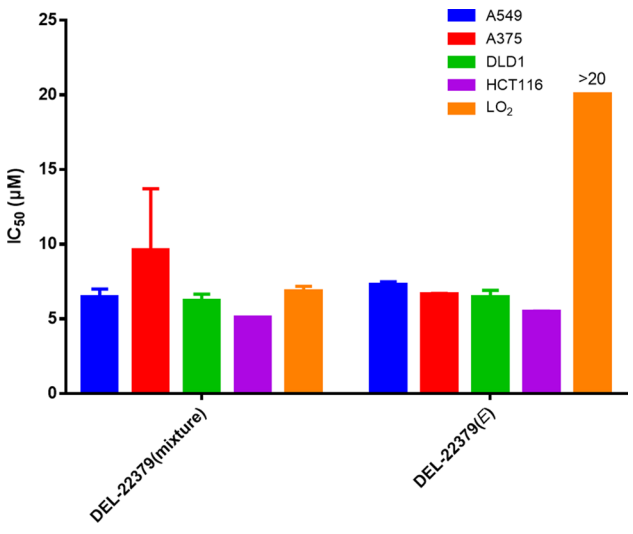


Fig. 7 IC_{50} values of DEL-22379 (*Z*/*E* mixture) and DEL-22379 (*E* isomer). Data are expressed as the mean ± S.D. from three experiments

General procedure B for the synthesis of compounds 5a~5b, 5d~5k, 9a~9q, 16a~16s

To a solution of the corresponding starting materials **3a~3b** or corresponding intermediates **3d~3k**, **7**, **11b~11c**, **11k~11s** (200 mg, 1 eq.) in MeOH (5 mL), piperidine (1.5 eq.) and corresponding aromatic aldehydes **4**, **8a~8q** (1.2 eq.) were added. The reaction mixture was heated to reflux and stirred for 1–8 h, then cooled to room temperature. The mixture was added with water (10 mL) and extracted with DCM (10 mL) for three times, the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Then purified by column chromatography to give products **5a~5b**, **5d~5k**, **9a~9q**, **16a~16s** (yield 17.5%~63.8%).

***N*-(2-oxoindolin-5-yl)acetamide (3d)** Following general procedure A, starting from acetic acid (**2d**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3d** as a white solid (yield 51.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 9.77 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.30 (dd, J = 8.4, 1.6 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.45 (s, 2H), 2.00

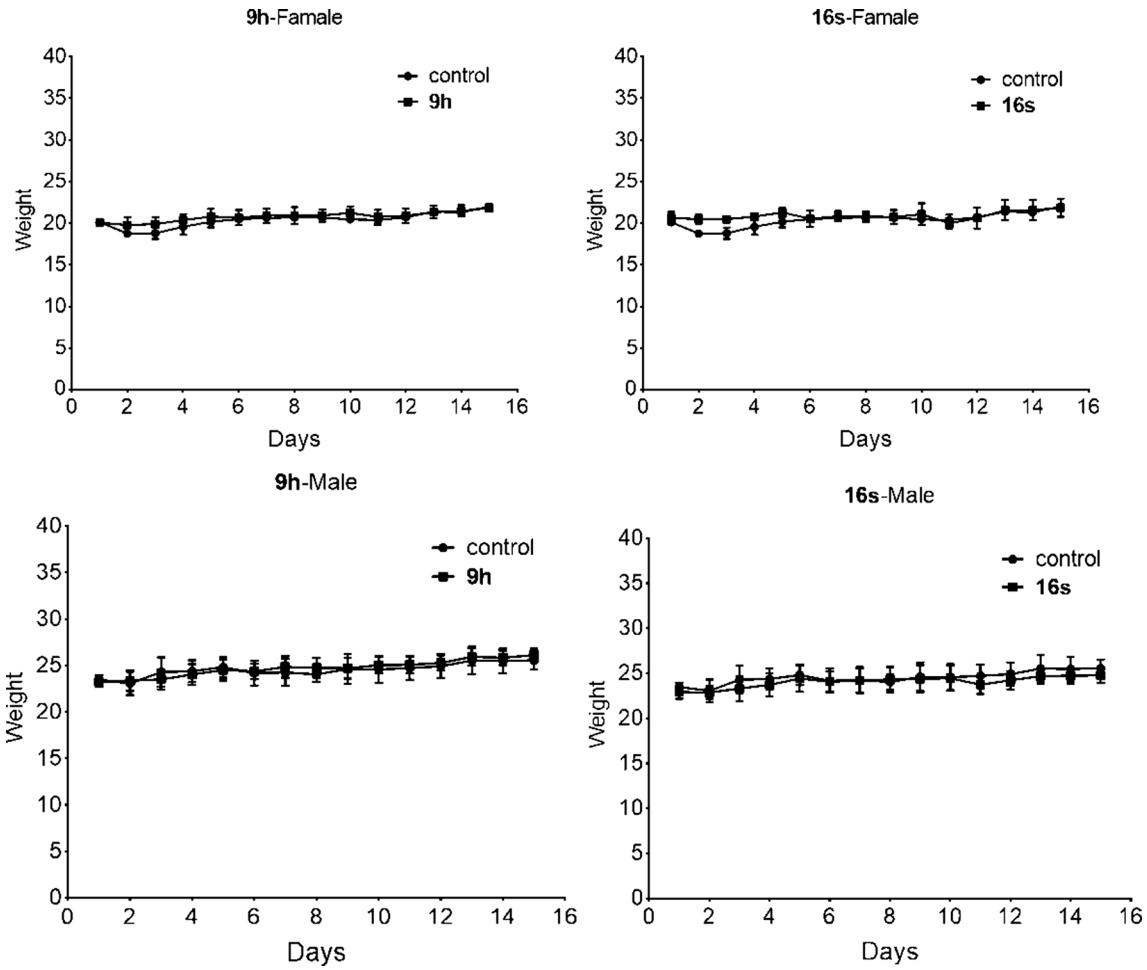


Fig. 8 Body weight of tumor-bearing mice treated with **9h** and **16s**. The data were expressed as the mean ± SD ($n \geqq 6$)

(s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 168.22, 139.58, 133.95, 126.45, 118.84, 116.88, 109.28, 36.52, 24.31.

***N*-(2-oxoindolin-5-yl)propionamide (3e)** Following general procedure A, starting from propionic acid (**2e**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3e** as a white solid (yield 45.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.69 (s, 1H), 7.51 (d, J = 0.8 Hz, 1H), 7.33 (dd, J = 8.0, 1.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 2.28 (q, J = 7.6 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.77, 171.98, 139.51, 133.97, 126.43, 118.89, 116.94, 109.28, 36.51, 29.90, 10.28.

***N*-(2-oxoindolin-5-yl)cyclopropanecarboxamide (3f)** Following general procedure A, starting from cyclopropanecarboxylic acid (**2f**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3f** as a white solid (yield 40.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 10.03 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.33 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.44 (s, 2H), 1.74 (m, 1H), 0.75 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.73, 171.53, 139.51, 134.04, 126.47, 118.80, 116.88, 109.29, 36.52, 14.89, 7.36 (2C).

***N*-(2-oxoindolin-5-yl)-3-phenylpropanamide (3g)** Following general procedure A, starting from 3-phenylpropanoic acid (**2g**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3g** as a white solid (yield 17.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.76 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.30 (m, 2H), 7.25 (m, 3H), 7.18 (m, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.44 (s, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.83, 170.42, 141.67, 139.63, 133.79, 128.76 (2C), 128.69 (2C), 126.47, 126.38, 119.00, 117.02, 109.31, 38.32, 36.49, 31.41.

***N*-(2-oxoindolin-5-yl)cinnamamide (3h)** Following general procedure A, starting from cinnamic acid (**2h**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3h** as a pale yel-

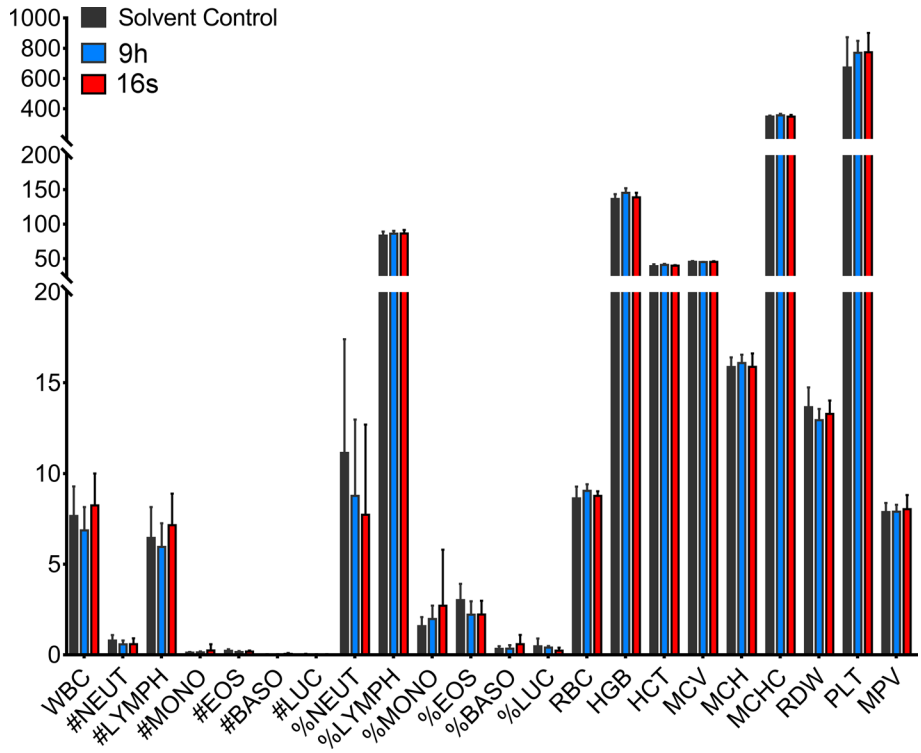


Fig. 9 Effects of oral gavage of **9h** and **16s** on blood routine in Balb/c mice. WBC (white blood cell count), #NEUT (neutrophile granulocyte count), #LYMPH (lymphocyte count), #MONO (monocyte count), #EOS (eosnophils granulocyte count), #BASO (basophilic granulocyte count), #LUC (large unstained cell count), %NEUT (neutrophilic granulocyte percentage), %LYMPH (lymphocyte percentage), %MONO (monocyte percentage), %EOS (eosnophils granulocyte percentage), %BASO (basophilic granulocyte percentage), %LUC (large unstained cell percentage), RBC (red blood cell count), HGB (hemoglobin), HCT (hematocrit), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDW (red cell distribution width), PLT (platelet count), MPV (mean platelet volume)

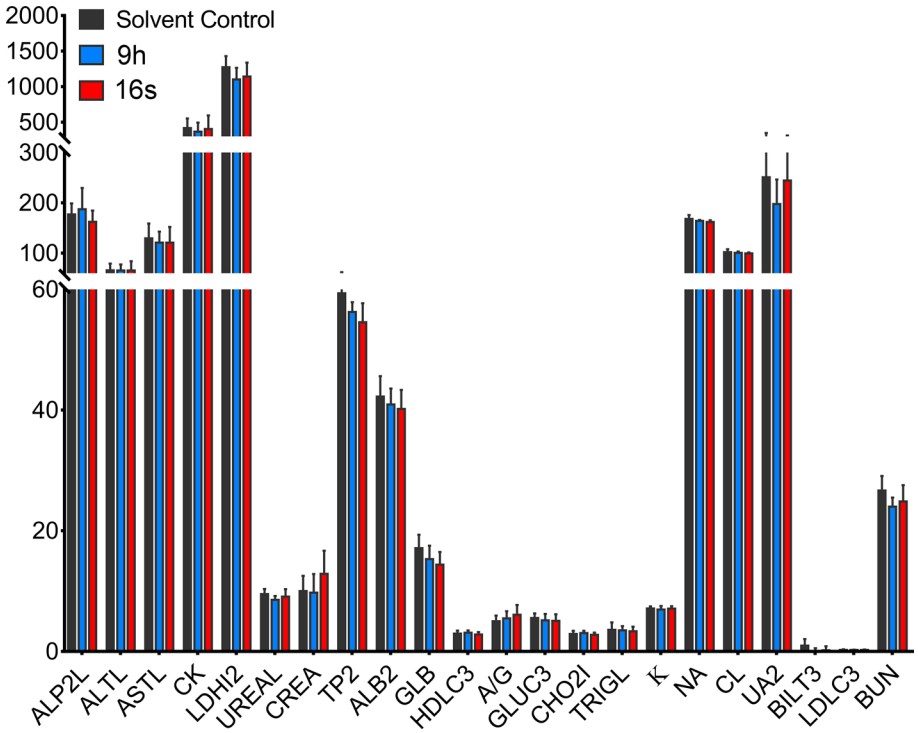


Fig. 10 Effects of oral gavage of **9h** and **16s** on blood biochemistry in Balb/c mice. ALP2L (alkaline phosphatase), ALTL (alanine aminotransferase), ASTL (aspartate aminotransferase), CK (creatine kinase), LDHI2 (lactic dehydrogenase), UREAL (urea), CREA (creatinine), TP2 (total protein), ALB2 (albumin), GLB (globulin), HDLC3 (high-density lipoprotein), A/G (albumin/globulin), GLUC3 (blood glucose), CHO2I (cholesterol), TRIGL (triglyceride), K (K^+), NA (Na^+), CL (Cl^-), UA2 (uric acid), BILT3 (bilirubin), LDLC3 (low density lipoprotein), BUN (blood urea nitrogen)

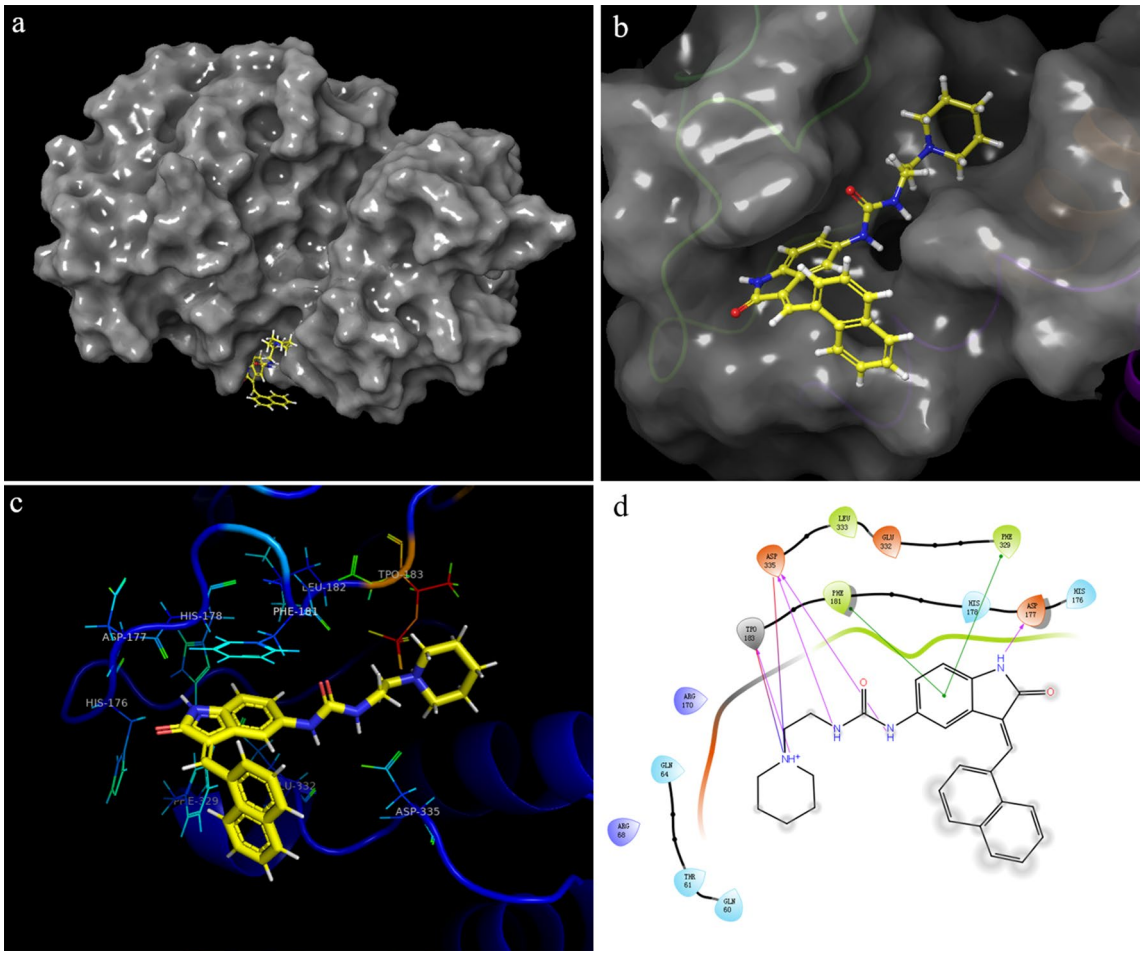


Fig. 11 In silico docking of **16s** with phosphorylated ERK monomer. Compound **16s** bounded to the dimer interface of phosphorylated ERK monomer (**a** and **b**); The amino acid residues involved were His 176, Asp 177, His 178, Phe 181, Leu 182, TPO 183, Phe 329, Leu 332 and Asp 335 (c and d)

low solid (yield 26.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 10.11 (s, 1H), 7.60 (m, 4H), 7.43 (m, 4H), 6.81 (m, 2H), 3.49 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 163.57, 140.02, 139.95, 135.31, 133.90, 130.11, 129.47 (2C), 128.11 (2C), 126.64, 122.99, 119.05, 116.94, 109.45, 36.55.

***N*-(2-oxoindolin-5-yl)-3-(3,4,5-trimethoxyphenyl)propanamide (3i)** Following general procedure A, starting from 3-(3,4,5-trimethoxyphenyl)propanoic acid (**2i**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3i** as a colorless oil (yield, 43.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.77 (s, 1H), 7.53 (s, 1H), 7.35 (dd, J = 8.0, 0.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.56 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.46 (s, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.85, 170.57, 153.20 (2C), 139.69, 137.39, 136.20, 133.80, 126.49, 119.07, 117.08, 109.33, 105.90 (2C), 60.35, 56.13 (2C), 38.43, 36.47, 31.85.

3-morpholino-*N*-(2-oxoindolin-5-yl)propanamide (3j) Following general procedure A, starting from 3-morpholinopropanoic acid (**2j**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3i** as a white solid (yield 26.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.89 (s, 1H), 7.51 (d, J = 0.8 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.57 (m, 4H), 3.45 (s, 2H), 2.60 (t, J = 7.2 Hz, 2H), 2.43 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 170.06, 139.63, 133.85, 126.49, 118.89, 116.92, 109.31, 66.67 (2C), 54.76, 53.50 (2C), 36.52, 34.31.

2-(4-methoxyphenyl)-*N*-(2-oxoindolin-5-yl)acetamide (3k) Following general procedure A, starting from 2-(4-methoxyphenyl)acetic acid (**2k**) and 5-aminoindolin-2-one (**1**) to afford intermediate **3k** as a white solid (yield 33.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.97 (s, 1H), 7.50 (s, 1H), 7.33 (dd, J = 8.4, 1.6 Hz, 1H), 7.24 (m, 2H), 6.88 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 3.72 (s, 3H), 3.52 (s, 2H), 3.44 (s, 2H). ^{13}C NMR (100 MHz, DMSO-

d_6) δ 176.73, 169.43, 158.46, 139.73, 133.84, 130.46 (2C), 128.60, 126.49, 119.00, 116.99, 114.19 (2C), 109.29, 55.50, 42.85, 36.51.

***N*-(2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (7)** Following general procedure A, starting from 3-(piperidin-1-yl)propanoic acid (**6**) and 5-aminoindolin-2-one (**1**) to afford intermediate **7** as a colorless oil (yield 33.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 10.03 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.31 (dd, J = 8.4, 1.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 2.77 (m, 2H), 2.56 (m, 6H), 1.56 (m, 4H), 1.43 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 169.63, 139.70, 133.75, 126.53, 118.90, 116.91, 109.35, 54.34, 53.76 (2C), 36.52, 33.55, 25.28 (2C), 23.81.

***N*-(2-oxoindolin-5-yl)-2-(piperidin-1-yl)acetamide (11b)** Following general procedure A, starting from 2-(piperidin-1-yl)acetic acid (**10b**) and 5-aminoindolin-2-one (**10b**) to afford intermediate **11b** as a colorless oil (yield 24.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 9.50 (s, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.37 (dd, J = 8.0, 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 3.46 (s, 2H), 3.02 (s, 2H), 2.44 (m, 4H), 1.55 (m, 4H), 1.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 168.51, 139.94, 133.10, 126.50, 119.32, 117.28, 109.26, 63.08, 54.55 (2C), 36.49, 25.94 (2C), 24.02.

***N*-(2-oxoindolin-5-yl)-4-(piperidin-1-yl)butanamide (11c)** Following general procedure A, starting from 4-(piperidin-1-yl)butanoic acid (**10c**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11c** as a pale yellow oil (yield 18.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.73 (s, 1H), 7.51 (d, J = 0.8 Hz, 1H), 7.32 (dd, J = 8.4, 1.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.44 (s, 2H), 2.31 (m, 8H), 1.73 (m, 2H), 1.50 (m, 4H), 1.37 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.73, 171.04, 139.52, 133.98, 126.40, 118.87, 116.93, 109.25, 58.30, 54.32 (2C), 36.52, 34.70, 25.78 (2C), 24.39, 22.66.

***N*-(2-oxoindolin-5-yl)-3-thiomorpholinopropanamide (11k)** Following general procedure A, starting from 3-thiomorpholinopropanoic acid (**10k**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11k** as a white solid (yield 22.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.83 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 2.67 (m, 6H), 2.59 (m, 4H), 2.42 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 170.15, 139.64, 133.83, 126.50, 118.91, 116.94, 109.31, 55.37, 54.68 (2C), 36.53, 34.18, 27.70 (2C).

3-cyclohexyl-*N*-(2-oxoindolin-5-yl)propanamide (11l) Following general procedure A, starting from 3-cyclohexylpropanoic acid (**10l**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11l** as a white solid (yield 28.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 9.69 (s, 1H), 7.51 (d, J = 0.8 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.44 (s, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.65 (m, 5H), 1.48 (q, J = 7.2 Hz, 2H), 1.16 (m, 4H), 0.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 171.46, 139.53, 133.99, 126.43, 118.88, 116.94, 109.26, 37.29, 36.52, 34.40, 33.19, 33.09 (2C), 26.59, 26.25 (2C).

***N*-(2-oxoindolin-5-yl)-2-(pyrrolidin-1-yl)acetamide (11m)** Following general procedure A, starting from 2-(pyrrolidin-1-yl)acetic acid (**10m**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11m** as a colorless oil (yield 30.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 9.54 (s, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.37 (dd, J = 8.0, 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 3.20 (s, 2H), 2.57 (m, 4H), 1.74 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.84, 168.83, 139.87, 133.22, 126.44, 119.45, 117.40, 109.27, 59.91, 54.15 (2C), 36.49, 23.92 (2C).

***N*-(2-oxoindolin-5-yl)-3-(pyrrolidin-1-yl)propanamide (11n)** Following general procedure A, starting from 3-(pyrrolidin-1-yl)propanoic acid (**10n**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11n** as a colorless oil (yield 21.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.92 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.45 (m, 6H), 1.68 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 170.09, 139.58, 133.91, 126.48, 118.83, 116.87, 109.30, 53.87 (2C), 52.09, 36.52, 36.45, 23.62 (2C).

2-(diethylamino)-*N*-(2-oxoindolin-5-yl)acetamide (11o) Following general procedure A, starting from diethylglycine (**10o**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11o** as a colorless oil (yield 24.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.47 (s, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 3.45 (s, 2H), 3.10 (s, 2H), 2.58 (q, J = 7.2 Hz, 4H), 1.01 (t, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.75, 169.79, 139.95, 132.98, 126.54, 119.22, 117.19, 109.28, 57.91, 48.37 (2C), 36.49, 12.48 (2C).

3-(diethylamino)-*N*-(2-oxoindolin-5-yl)propanamide (11p) Following general procedure A, starting from 3-(diethylamino)propanoic acid (**10p**) and 5-aminoindolin-2-one (**1**) to afford intermediate **11p** as a colorless oil (yield 18.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.98 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.45 (s, 2H), 2.79 (t, J = 6.8 Hz, 2H), 2.57 (q, J = 6.8 Hz, 4H), 2.42 (t, J = 6.8 Hz, 2H), 1.00 (t, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-

d_6) δ 176.74, 170.12, 139.62, 133.84, 126.51, 118.84, 116.88, 109.33, 48.74, 46.62 (2C), 36.52, 34.06, 11.89 (2C).

2-oxo-*N*-(2-(piperidin-1-yl)ethyl)indoline-5-carboxamide (11q) Following general procedure A, starting from 2-oxoindoline-5-carboxylic acid (**12**) and 2-(piperidin-1-yl) ethan-1-amine (**13**) to afford intermediate **11q** as a white solid (yield 22.6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.21 (m, 1H), 7.71 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 3.53 (s, 2H), 3.30 (m, 2H), 2.40 (m, 6H), 1.49 (m, 4H), 1.37 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.12, 166.34, 146.77, 128.05, 127.80, 126.10, 123.82, 108.90, 58.27, 54.56 (2C), 37.37, 36.07, 26.03 (2C), 24.49.

5-((3-(piperidin-1-yl)propyl)amino)indolin-2-one (11r) To a solution of 5-aminoindolin-2-one (**1**) (300 mg, 1 eq.) in dry DMF (5 mL) was added K_2CO_3 (1.1 eq.), NaI (1.1 eq.) and 1-(3-chloropropyl)piperidine (**14**) (1.1 eq.). The reaction mixture was stirred at 90 °C for 8 h, then cooled to room temperature. 20 mL water was added and the mixture was extracted with DCM (15 mL) for three times, the combined organic layer was washed with brine, dried over sodium sulfate, and concentrated under vacuum to afford crude product, which was purified through silica gel column chromatography to give intermediate **11r** as a colorless oil (yield 25.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 0.8 Hz, 1H), 6.35 (dd, J = 8.4, 2.4 Hz, 1H), 3.33 (s, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.37 (m, 6H), 1.67 (m, 2H), 1.51 (m, 4H), 1.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.27, 144.94, 133.87, 127.14, 110.78, 110.28, 109.87, 56.96, 54.45 (2C), 42.64, 36.68, 26.23, 25.85 (2C), 24.41.

1-(2-oxoindolin-5-yl)-3-(2-(piperidin-1-yl)ethyl)urea (11s) To a solution of di(1*H*-imidazol-1-yl)methanone (CDI, **15**) (300 mg, 1.1 eq.) in dry DMF (5 mL), 5-aminoindolin-2-one (**1**) (1 eq.) was added. The mixture was stirred at room temperature for 3 h. Then 2-(piperidin-1-yl) ethan-1-amine (**13**) (1 eq.) was added dropwise into the reaction mixture and stirred for another 3 h. After the reaction was finished, 20 mL water was added, and the mixture was extracted with DCM (15 mL) for three times, the combined organic layer was washed with brine, dried over sodium sulfate, and concentrated under vacuum to afford crude product, which was purified through silica gel column chromatography to give intermediate 11 s as a white solid (yield 18.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.50 (s, 1H), 7.32 (d, J = 0.8 Hz, 1H), 7.10 (dd, J = 8.0, 1.6 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.01 (m, 1H), 3.41 (s, 2H), 3.18 (q, J = 6.0 Hz, 2H), 2.38 (m, 6H), 1.52 (m, 4H), 1.41 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.65, 155.92, 138.09, 135.22, 126.51, 117.48, 115.91, 109.36, 58.58, 54.41 (2C), 36.80, 36.58, 25.82 (2C), 24.37.

(Z)-3-((5-methoxy-1H-indol-3-yl)methylene)indolin-2-one (5a) Following general procedure B, starting from starting materials (**3a**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5a** as a *Z* isomer, orange solid (yield 58.2%), melting point 257 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 10.48 (s, 1H), 9.43 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.14 (td, J = 7.6, 0.8 Hz, 1H), 6.99 (td, J = 7.2, 0.8 Hz, 1H), 6.86 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.60, 155.50, 139.47, 134.47, 131.22, 129.56, 128.07, 127.00, 126.34, 120.82, 119.18, 118.82, 113.41, 112.85, 111.85, 109.37, 101.21, 56.09. HRMS (Q-TOF): calculated for $C_{18}H_{14}N_2O_2$ [M]: 290.1055. Found $[M+H]^+$: 291.1130.

(Z)-3-((5-methoxy-1H-indol-3-yl)methylene)-5-nitroindolin-2-one (5b) Following general procedure B, starting from starting materials (**3b**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5b** as a *Z* isomer, orange solid (yield 54.9%), decomposed at 370 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.21 (s, 1H), 9.51 (d, J = 3.2 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.51 (s, 1H), 8.10 (dd, J = 8.8, 2.4 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 8.4, 2.0 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.79, 155.91, 144.62, 142.27, 136.04, 132.20, 131.34, 129.83, 127.11, 123.25, 116.10, 114.81, 113.57, 113.02, 112.32, 109.16, 102.02, 56.25. HRMS (Q-TOF): calculated for $C_{18}H_{13}N_3O_4$ [M]: 335.0906. Found $[M+H]^+$: 336.0976.

(*Z*/*E*)-5-amino-3-((5-methoxy-1H-indol-3-yl)methylene) indolin-2-one (5c) To a suspension of **5b** (200 mg, 1 eq.) in EtOH (10 mL), activated carbon (40 mg) and $FeCl_3$ (40 mg) were added. The mixture was heated to 78 °C, and stirred for 10 min. Then 80% aqueous solution of hydrazine hydrate (8 eq.) was added dropwise into the reaction mixture in 5 min, the resulting mixture was allowed to stirred at 78 °C for 8–10 h, then cooled to room temperature. The mixture was filtered to remove residue of activated carbon, the filtrate was concentrated under vacuum to afford crude product, which was purified through silica gel column chromatography to give compound **5c** as a *Z*/*E* mixture (*Z*/*E* = 4:1), red solid (yield 17.5%), melting point 266 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1/5H), 11.79 (s, 4/5H), 10.02 (s, 4/5H), 9.97 (s, 1/5H), 9.38 (d, J = 2.8 Hz, 4/5H), 8.11 (d, J = 1.2 Hz, 1/5H), 7.88 (s, 4/5H), 7.76 (s, 1/5H), 7.58 (d, J = 2.0 Hz, 4/5H), 7.41 (m, 1H), 7.22 (d, J = 1.6 Hz, 1/5H), 7.15 (d, J = 2.0 Hz, 1/5H), 7.12 (d, J = 1.6 Hz, 4/5H), 6.86 (m, 1H), 6.56 (m, 1H), 6.44 (m, 1H), 4.60 (m, 2H), 3.87 (s, 12/5H), 3.81 (s, 3/5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.62, 155.35, 143.49, 143.16, 134.13, 131.17, 130.86, 129.91, 129.40, 127.09, 126.83, 126.52, 120.16, 114.43, 113.64, 113.40,

112.76, 111.57, 110.87, 109.70, 105.77, 100.79, 100.72, 56.00, 55.83. HRMS (Q-TOF): calculated for $C_{18}H_{15}N_3O_2$ [M]: 305.1164. Found $[M+H]^+$: 306.1239.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)acetamide (5d) Following general procedure B, starting from intermediate (**3d**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5d** as a *Z* isomer, yellow solid (yield 35.5%), melting point 325 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.42 (s, 1H), 9.76 (s, 1H), 9.43 (s, 1H), 7.99 (s, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.72, 168.32, 155.50, 135.79, 134.67, 132.98, 131.22, 129.40, 127.87, 126.18, 120.02, 119.01, 113.52, 112.94, 112.15, 111.65, 109.14, 100.76, 56.00, 24.14. HRMS (Q-TOF): calculated for $C_{20}H_{17}N_3O_3$ [M]: 347.1270. Found $[M+H]^+$: 348.1344.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)propionamide (5e) Following general procedure B, starting from intermediate (**3e**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5e** as a *Z* isomer, yellow solid (yield 30.3%), melting point 296 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.42 (s, 1H), 9.69 (s, 1H), 9.44 (d, *J* = 2.4 Hz, 1H), 8.00 (s, 1H), 7.91 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.33 (q, *J* = 7.6 Hz, 2H), 1.12 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.02, 168.73, 155.51, 135.71, 134.69, 133.07, 131.23, 129.41, 127.85, 126.17, 119.96, 119.07, 113.50, 112.92, 112.05, 111.66, 109.14, 100.81, 56.03, 29.79, 10.33. HRMS (Q-TOF): calculated for $C_{21}H_{19}N_3O_3$ [M]: 361.1426. Found $[M+H]^+$: 362.1502.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)cyclopropanecarboxamide (5f) Following general procedure B, starting from intermediate (**3f**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5f** as a *Z* isomer, yellow solid (yield 25.6%), melting point 290 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.42 (s, 1H), 10.01 (s, 1H), 9.44 (d, *J* = 2.4 Hz, 1H), 8.00 (s, 1H), 7.92 (d, *J* = 0.8 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 1.80 (m, 1H), 0.80 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.69, 168.73, 155.51, 135.72, 134.71, 133.11, 131.23, 129.42, 127.90, 126.20, 119.98, 119.07, 113.49, 112.89, 112.06, 111.67, 109.17, 100.88, 56.05, 14.78, 7.25 (2C). HRMS (Q-TOF): calculated for $C_{22}H_{19}N_3O_3$ [M]: 373.1426. Found $[M+H]^+$: 374.1507.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)-3-phenylpropanamide (5g) Following general procedure B, starting from intermediate (**3g**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5g** as a *Z* isomer, yellow solid (yield 28.1%), melting point 255 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 10.43 (s, 1H), 9.77 (s, 1H), 9.44 (d, *J* = 2.0 Hz, 1H), 8.00 (s, 1H), 7.89 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.30 (m, 5H), 7.20 (m, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.44, 168.73, 155.51, 141.79, 135.78, 134.72, 132.96, 131.24, 129.41, 128.81 (2C), 128.75 (2C), 127.89, 126.41, 126.20, 119.93, 119.02, 113.52, 112.92, 111.94, 111.66, 109.17, 100.81, 56.02, 38.30, 31.50. HRMS (Q-TOF): calculated for $C_{27}H_{23}N_3O_3$ [M]: 437.1739. Found $[M+H]^+$: 438.1818.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)cinnamamide (5h) Following general procedure B, starting from intermediate (**3h**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5h** as a *Z* isomer, yellow solid (yield 24.7%), melting point 283 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 10.48 (s, 1H), 10.09 (s, 1H), 9.45 (d, *J* = 2.0 Hz, 1H), 8.05 (s, 2H), 7.62 (m, 4H), 7.45 (m, 5H), 6.87 (m, 3H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.73, 163.73, 155.53, 140.03, 136.01, 135.37, 134.77, 132.98, 131.24, 130.11, 129.50 (2C), 129.42, 128.12 (2C), 128.06, 126.32, 123.02, 119.81, 118.93, 113.54, 112.97, 111.87, 111.69, 109.31, 100.79, 56.01. HRMS (Q-TOF): calculated for $C_{27}H_{21}N_3O_3$ [M]: 435.1583. Found $[M+H]^+$: 436.1658.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)-3-(3,4,5-trimethoxyphenyl)propanamide (5i) Following general procedure B, starting from intermediate (**3i**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5i** as a *Z* isomer, yellow solid (yield 28.4%), melting point 292 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 10.42 (s, 1H), 9.76 (s, 1H), 9.43 (s, 1H), 7.99 (s, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 2H), 3.88 (s, 3H), 3.76 (s, 6H), 3.63 (s, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.54, 168.71, 155.51, 153.22 (2C), 137.46, 136.21, 135.80, 134.72, 132.93, 131.23, 129.40, 127.88, 126.19, 119.93, 119.01, 113.53, 112.92, 111.96, 111.64, 109.19, 106.00 (2C), 100.78, 60.43, 56.25 (2C), 56.01, 38.44, 31.95. HRMS (Q-TOF): calculated for $C_{30}H_{29}N_3O_6$ [M]: 527.2056. Found $[M+H]^+$: 528.2129.

(*Z/E*)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)-3-morpholinopropanamide (5j) Following general procedure B, starting from intermediate (**3j**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5j** as a *Z*/*E* mixture (*Z*/*E* = 4:1), yellow solid (yield 18.8%), melting point 305 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1/5H), 11.90 (s, 4/5H), 10.42 (s, 4/5H), 10.36 (s, 1/5H), 9.95 (s, 1/5H), 9.87 (s, 4/5H), 9.43 (s, 4/5H), 8.38 (d, *J* = 0.8 Hz, 1/5H), 8.18 (s, 1/5H), 8.00 (s, 4/5H), 7.89 (d, *J* = 1.2 Hz, 4/5H), 7.86 (s, 1/5H), 7.59 (d, *J* = 2.0 Hz, 4/5H), 7.41 (m, 1H), 7.31 (m, 1H), 7.21 (d, *J* = 2.0 Hz, 1/5H), 6.88 (m, 1H), 6.80 (m, 1H), 3.88 (s, 12/5H), 3.82 (s, 3/5H), 3.58 (m, 4H), 2.65 (m, 2H), 2.45 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.33, 170.18, 170.12, 168.72, 155.50, 155.37, 137.67, 135.75, 134.71, 133.50, 133.01, 131.53, 131.23, 130.01, 129.40, 128.81, 127.90, 126.20, 121.14, 119.76, 119.01, 114.25, 113.52, 112.92, 111.79, 111.64, 110.86, 109.68, 109.19, 100.79, 100.73, 66.70, 56.00, 55.85, 54.86, 54.80, 53.56, 53.50, 34.41, 34.19. HRMS (Q-TOF): calculated for $C_{25}H_{26}N_4O_4$ [M]: 446.1954. Found $[M+H]^+$: 447.2033.

(Z)-*N*-(3-((5-methoxy-1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)-2-(4-methoxyphenyl)acetamide (5k) Following general procedure B, starting from intermediate (**3k**) and 5-methoxy-1*H*-indole-3-carbaldehyde (**4**) to afford compound **5k** as a *Z* isomer, yellow solid (yield 21.3%), melting point 293 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.43 (s, 1H), 9.95 (s, 1H), 9.44 (d, *J* = 2.4 Hz, 1H), 8.00 (s, 1H), 7.91 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 3H), 6.88 (m, 3H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.50, 168.72, 158.49, 155.51, 135.82, 134.74, 133.01, 131.22, 130.59 (2C), 129.41, 128.64, 128.01, 126.21, 119.80, 119.00, 114.20 (2C), 113.50, 112.93, 111.84, 111.68, 109.18, 100.85, 56.04, 55.52, 42.80. HRMS (Q-TOF): calculated for $C_{27}H_{23}N_3O_4$ [M]: 453.1689. Found $[M+H]^+$: 454.1783.

(*Z/E*)-*N*-(2-oxo-3-(thiophen-3-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9a) Following general procedure B, starting from intermediate (**7**) and thiophene-3-carbaldehyde (**8a**) to afford compound **9a** as a *Z*/*E* mixture (*Z*/*E* = 1:1), orange solid (yield 27.8%), melting point 123 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1/2H), 10.48 (s, 1/2H), 10.09 (s, 1/2H), 10.03 (s, 1/2H), 8.88 (d, *J* = 2.4 Hz, 1/2H), 8.17 (d, *J* = 5.2 Hz, 1/2H), 8.12 (m, 1H), 7.99 (s, 1/2H), 7.75 (dd, *J* = 4.8, 3.2 Hz, 1/2H), 7.71 (s, 1/2H), 7.62 (dd, *J* = 4.8, 2.8 Hz, 1/2H), 7.56 (m, 1H), 7.44 (dd, *J* = 8.4, 1.2 Hz, 1/2H), 7.21 (dd, *J* = 8.4, 1.2 Hz, 1/2H), 6.82 (d, *J* = 8.4 Hz, 1/2H), 6.78 (d, *J* = 8.4 Hz, 1/2H), 2.58 (m, 2H), 2.43 (m, 6H), 1.44 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.42, 169.65, 167.88, 138.80, 136.85, 136.80, 136.19, 134.04, 133.71, 131.84, 130.70, 129.90, 129.38, 129.04, 127.90, 126.53, 126.45, 125.18, 124.88, 121.56, 121.43, 120.80, 115.10, 111.88, 110.26, 109.82, 55.08, 54.98, 54.19, 54.10, 34.46, 26.13, 26.11, 24.51, 24.49. HRMS (Q-TOF): calculated for $C_{21}H_{23}N_3O_2S$ [M]: 381.1511. Found $[M+H]^+$: 382.1556.

(*Z/E*)-*N*-(2-oxo-3-(thiophen-2-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9b) Following general procedure B, starting from intermediate (**7**) and thiophene-2-carbaldehyde (**8b**) to afford compound **9b** as a *Z*/*E* mixture (*Z*/*E* = 3:2), red solid (yield 27.2%), melting point 130 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 10.18 (s, 2/5H), 10.02 (s, 3/5H), 8.60 (d, *J* = 1.6 Hz, 2/5H), 8.01 (m, 11/5H), 7.89 (d, *J* = 5.2 Hz, 3/5H), 7.82 (d, *J* = 3.6 Hz, 2/5H), 7.78 (s, 2/5H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 2/5H), 7.32 (dd, *J* = 5.2, 4.0 Hz, 2/5H), 7.21 (m, 6/5H), 6.85 (d, *J* = 8.4 Hz, 2/5H), 6.80 (d, *J* = 8.0 Hz, 3/5H), 2.60 (m, 2H), 2.45 (m, 2H), 2.38 (m, 4H), 1.51 (m, 4H), 1.39 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.45, 170.40, 169.77, 167.91, 138.74, 138.50, 137.71, 137.63, 136.88, 136.38, 134.95, 133.80, 133.63, 132.51, 129.20, 128.59, 127.88, 127.71 124.72, 124.15, 122.30, 121.41, 121.20, 120.76, 115.53, 111.96, 110.27, 109.90, 55.08, 55.01, 54.19, 54.12, 34.47, 26.15, 26.11, 24.51. HRMS (Q-TOF): calculated for $C_{21}H_{23}N_3O_2S$ [M]: 381.1511. Found $[M+H]^+$: 382.1555.

(Z)-*N*-(3-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9c) Following general procedure B, starting from intermediate (**7**) and 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (**8c**) to afford compound **9c** as a *Z* isomer, yellow solid (yield 26.4%), melting point 299 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 10.71 (s, 1H), 9.97 (s, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.36 (s, 1H), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.01 (d, *J* = 2.0 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.43 (m, 6H), 2.32 (s, 3H), 2.29 (s, 3H), 1.51 (m, 4H), 1.39 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.30, 169.97, 136.22, 134.64, 133.64, 132.01, 126.94, 126.25, 123.31, 118.24, 113.29, 113.08, 110.34, 109.65, 55.09, 54.17 (2C), 34.45, 26.08 (2C), 24.49, 13.99, 11.74. HRMS (Q-TOF): calculated for $C_{23}H_{28}N_4O_2$ [M]: 392.2212. Found $[M+H]^+$: 393.2285.

(*Z/E*)-*N*-(2-oxo-3-(pyridin-3-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9d) Following general procedure B, starting from intermediate (**7**) and nicotinaldehyde (**8d**) to afford compound **9d** as a *Z*/*E* mixture (*Z*/*E* = 1:2), orange solid (yield 23.9%), melting point 149 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1/3H), 10.57 (s, 2/3H), 10.05 (s, 1/3H), 10.04 (s, 2/3H), 9.22 (d, *J* = 1.6 Hz, 1/3H), 8.89 (m, 1H), 8.66 (dd, *J* = 4.8, 1.2 Hz, 2/3H), 8.58 (dd, *J* = 4.8, 1.2 Hz, 1/3H), 8.12 (m, 2/3H), 8.01

(d, J = 1.6 Hz, 1/3H), 7.77 (d, J = 1.6 Hz, 2/3H), 7.68 (s, 1/3H), 7.61 (s, 2/3H), 7.54 (dd, J = 8.0, 4.8 Hz, 2/3H), 7.48 (m, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1/3H), 6.83 (d, J = 8.4 Hz, 2/3H), 6.79 (d, J = 8.4 Hz, 1/3H), 2.61 (t, J = 7.2 Hz, 2/3H), 2.54 (t, J = 6.8 Hz, 4/3H), 2.46 (t, J = 7.2 Hz, 2/3H), 2.37 (m, 16/3H), 1.45 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.45, 170.36, 168.78, 167.60, 152.96, 150.73, 150.60, 150.27, 139.31, 138.43, 137.50, 136.87, 133.88, 133.76, 133.18, 132.62, 130.90, 130.26, 129.95, 129.49, 124.71, 124.16, 123.56, 122.33, 121.79, 121.05, 114.53, 112.71, 110.61, 110.04, 55.04, 54.89, 54.17, 54.06, 34.43, 34.33, 26.08, 26.06, 24.49, 24.45. HRMS (Q-TOF): calculated for $C_{22}H_{24}N_4O_2$ [M]: 376.1899. Found $[M+H]^+$: 377.1865.

(*Z*/*E*)-*N*-(3-((1H-indol-3-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9e) Following general procedure B, starting from intermediate (**7**) and 1*H*-indole-3-carbaldehyde (**8e**) to afford compound **9e** as a *Z*/*E* mixture (*Z*/*E* = 2:1), yellow solid (yield 20.9%), melting point 188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (brs, 1H), 10.45 (s, 2/3H), 10.38 (s, 1/3H), 10.11 (s, 1/3H), 9.99 (s, 2/3H), 9.46 (s, 2/3H), 8.42 (d, J = 2.0 Hz, 1/3H), 8.24 (s, 1/3H), 8.05 (m, 2/3H), 7.98 (m, 4/3H), 7.88 (s, 1/3H), 7.76 (d, J = 7.6 Hz, 1/3H), 7.54 (m, 1H), 7.25 (m, 3H), 6.83 (d, J = 8.4 Hz, 1/3H), 6.79 (d, J = 8.0 Hz, 2/3H), 2.60 (m, 2H), 2.44 (m, 6H), 1.47 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.46, 170.38, 170.26, 168.68, 137.73, 136.68, 136.37, 135.77, 134.19, 133.61, 133.23, 129.61, 128.54, 128.14, 127.82, 127.25, 126.02, 123.31, 122.99, 122.77, 121.81, 121.42, 121.38, 119.74, 119.59, 118.95, 118.46, 114.16, 112.83, 111.49, 111.46, 110.84, 109.77, 109.34, 55.14, 55.07, 54.20, 54.12, 34.57, 34.46, 26.12, 26.10, 24.53, 24.48. HRMS (Q-TOF): calculated for $C_{25}H_{26}N_4O_2$ [M]: 414.2056. Found $[M+H]^+$: 415.2116.

E-*N*-(3-((1H-indol-4-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9f) Following general procedure B, starting from intermediate (**7**) and 1*H*-indole-4-carbaldehyde (**8f**) to afford compound **9f** as an *E* isomer, red solid (yield 17.7%), melting point 150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 10.52 (s, 1H), 9.98 (s, 1H), 7.94 (s, 1H), 7.80 (s, 1H), 7.52 (m, 4H), 7.23 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.47 (m, 1H), 2.61 (s, 2H), 2.40 (m, 6H), 1.47 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.95, 169.57, 138.97, 136.56, 134.80, 133.37, 127.77, 127.39, 127.31, 125.84, 121.89, 121.71, 121.29, 120.41, 115.26, 114.11, 110.09, 100.35, 54.55, 53.85 (2C), 33.77, 25.65 (2C), 24.09. HRMS (Q-TOF): calculated for $C_{25}H_{26}N_4O_2$ [M]: 414.2056. Found $[M+H]^+$: 415.2137.

(*Z*/*E*)-*N*-(3-((1H-indol-7-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9g) Following general procedure B, starting from intermediate (**7**) and 1*H*-indole-7-carbaldehyde (**8g**) to afford compound **9g** as a *Z*/*E* mixture (*Z*/*E* = 1:6), orange solid (yield 25.0%), melting point 151 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1/7H), 11.52 (s, 6/7H), 10.51 (s, 1H), 10.00 (s, 1/7H), 9.95 (s, 6/7H), 8.67 (d, J = 7.6 Hz, 1/7H), 8.14 (s, 1/7H), 8.07 (d, J = 1.2 Hz, 1/7H), 7.98 (s, 6/7H), 7.79 (d, J = 1.2 Hz, 6/7H), 7.69 (m, 1H), 7.57 (d, J = 7.2 Hz, 6/7H), 7.47 (m, 1H), 7.39 (t, J = 2.8 Hz, 6/7H), 7.23 (dd, J = 8.4, 1.6 Hz, 1/7H), 7.13 (t, J = 7.6 Hz, 6/7H), 7.07 (t, J = 8.0 Hz, 1/7H), 6.81 (d, J = 8.4 Hz, 6/7H), 6.77 (d, J = 8.0 Hz, 1/7H), 6.55 (m, 1H), 2.62 (t, J = 6.8 Hz, 2/7H), 2.51 (m, 12/7H), 2.35 (m, 6H), 1.43 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.27, 169.45, 138.99, 134.92, 133.47, 132.67, 128.94, 127.85, 126.66, 123.12, 122.12, 121.90, 119.37, 118.51, 114.84, 110.15, 102.36, 54.89, 54.02, 34.21, 26.05, 24.44. HRMS (Q-TOF): calculated for $C_{25}H_{26}N_4O_2$ [M]: 414.2056. Found $[M+H]^+$: 415.2119.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9h) Following general procedure B, starting from intermediate (**7**) and 1-naphthaldehyde (**8h**) to afford compound **9h** as an *E* isomer, orange solid (yield 39.4%), melting point 157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.90 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.87 (m, 1H), 7.63 (m, 3H), 7.47 (dd, J = 8.4, 1.6 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 2.46 (t, J = 6.8 Hz, 2H), 2.29 (m, 6H), 1.36 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.22, 168.89, 139.20, 133.86, 133.73, 133.54, 131.74, 131.23, 130.41, 130.06, 129.20, 127.55, 127.36, 127.06, 126.05, 124.65, 122.14, 121.48, 114.85, 110.38, 54.83, 53.97 (2C), 34.17, 26.03 (2C), 24.43. HRMS (Q-TOF): calculated for $C_{27}H_{27}N_3O_2$ [M]: 425.2103. Found $[M+H]^+$: 426.2181.

(E)-*N*-(3-((4-fluoronaphthalen-1-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9i) Following general procedure B, starting from intermediate (**7**) and 4-fluoro-1-naphthaldehyde (**8i**) to afford compound **9i** as an *E* isomer, orange solid (yield 26.3%), melting point 136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.90 (s, 1H), 8.18 (m, 1H), 8.00 (m, 2H), 7.86 (dd, J = 8.0, 6.0 Hz, 1H), 7.73 (m, 2H), 7.47 (m, 2H), 7.33 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.47 (t, J = 6.8 Hz, 2H), 2.30 (m, 6H), 1.36 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.21, 168.78, 160.32, 157.80, 139.19, 133.59, 132.94, 132.67 (d, J = 4.9 Hz), 130.39 128.74, 128.38 (d, J = 4.2 Hz), 127.80 (d, J = 8.7 Hz), 125.11 (d, J = 2.1 Hz), 123.52 (d, J = 16.6 Hz), 122.03, 121.39, 121.11 (d, J = 5.0 Hz), 114.67, 110.41, 110.19 (d, J = 20.0 Hz), 54.79, 53.95 (2C), 34.17, 25.99 (2C), 24.38. HRMS (Q-TOF): calculated for $C_{27}H_{26}N_3O_2$ [M]: 443.2009. Found $[M+H]^+$: 444.2076.

(E)-*N*-(2-oxo-3-(quinolin-4-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9j) Following general procedure B, starting from intermediate (**7**) and quinoline-4-carbaldehyde (**8j**) to afford compound **9j** as an *E* isomer, orange solid (yield 26.6%), melting point 264 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.87 (s, 1H), 9.01 (d, J = 4.4 Hz, 1H), 8.15 (m, 1H), 7.97 (m, 2H), 7.85 (m, 1H), 7.75 (m, 1H), 7.66 (m, 1H), 7.51 (dd, J = 8.4, 1.2 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 2.44 (t, J = 7.2 Hz, 2H), 2.27 (m, 6H), 1.35 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.32, 168.22, 150.80, 148.38, 140.84, 139.74, 133.38, 132.24, 130.92, 130.59, 130.21, 127.90, 125.79, 125.16, 122.60, 121.05, 120.92, 115.20, 110.68, 52.98 (2C), 52.71, 31.40, 23.55 (2C), 22.17. HRMS (Q-TOF): calculated for $C_{26}H_{26}N_4O_2$ [M]: 426.2056. Found $[M+H]^+$: 427.2113.

(E)-*N*-(3-((6-methoxyquinolin-4-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9k) Following general procedure B, starting from intermediate (**7**) and 6-methoxyquinoline-4-carbaldehyde (**8k**) to afford compound **9k** as an *E* isomer, orange solid (yield 27.5%), melting point 213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 9.89 (s, 1H), 8.84 (d, J = 4.4 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.97 (s, 1H), 7.71 (d, J = 4.4 Hz, 1H), 7.50 (m, 2H), 7.30 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.46 (t, J = 6.8 Hz, 2H), 2.29 (m, 6H), 1.36 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.25, 168.48, 158.25, 148.00, 144.61, 139.45, 139.24, 133.73, 132.01, 131.81, 131.11, 127.01, 122.95, 122.44, 121.49, 121.00, 115.04, 110.57, 103.00, 56.03, 54.80, 53.99 (2C), 34.24, 26.03 (2C), 24.39. HRMS (Q-TOF): calculated for $C_{27}H_{28}N_4O_3$ [M]: 456.2161. Found $[M+H]^+$: 457.2220.

(*Z*/*E*)-*N*-(3-(naphthalen-2-ylmethylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9l) Following general procedure B, starting from intermediate (**7**) and 2-naphthaldehyde (**8l**) to afford compound **9l** as a *Z*/*E* mixture (*Z*/*E* = 1:5), orange solid (yield 32.2%), melting point 122 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1/6H), 10.56 (s, 5/6H), 10.06 (s, 1/6H), 10.03 (s, 5/6H), 8.85 (s, 1/6H), 8.62 (dd, J = 8.8, 1.2 Hz, 1/6H), 8.32 (s, 5/6H), 8.00 (m, 4H), 7.83 (m, 1H), 7.76 (s, 5/6H), 7.60 (m, 2H), 7.46 (dd, J = 8.4, 1.6 Hz, 5/6H), 7.27 (dd, J = 8.4, 1.6 Hz, 1/6H), 6.85 (d, J = 8.4 Hz, 5/6H), 6.80 (d, J = 8.0 Hz, 1/6H), 2.60 (m, 2H), 2.36 (m, 6H), 1.42 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.30, 169.31, 139.25, 136.31, 133.77, 133.58, 133.19, 132.29, 129.93, 129.15, 128.75, 128.24, 128.15, 127.86, 127.20, 127.05, 122.12, 121.40, 115.10, 110.42, 54.80, 54.14, 53.96, 34.17, 26.02, 25.92, 24.31. HRMS (Q-TOF): calculated for $C_{27}H_{27}N_3O_2$ [M]: 425.2103. Found $[M+H]^+$: 426.2182.

(*Z*/*E*)-*N*-(3-((6-methoxynaphthalen-2-yl)methylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9m) Following general procedure B, starting from intermediate (**7**) and 6-methoxy-2-naphthaldehyde (**8m**) to afford compound **9m** as a *Z*/*E* mixture (*Z*/*E* = 1:4), orange solid (yield 39.6%), melting point 130 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (s, 1/5H), 10.52 (s, 4/5H), 10.04 (s, 1/5H), 10.03 (s, 4/5H), 8.81 (s, 1/5H), 8.66 (dd, J = 8.8, 1.2 Hz, 1/5H), 8.26 (s, 4/5H), 8.09 (d, J = 0.8 Hz, 4/5H), 8.02 (d, J = 0.8 Hz, 1/5H), 7.93 (m, 8/5H), 7.87 (m, 2/5H), 7.80 (m, 4/5H), 7.75 (s, 1/5H), 7.73 (s, 4/5H), 7.42 (m, 8/5H), 7.37 (d, J = 2.0 Hz, 1/5H), 7.24 (m, 6/5H), 6.84 (d, J = 8.4 Hz, 4/5H), 6.79 (d, J = 8.0 Hz, 1/5H), 3.92 (s, 3H), 2.62 (t, J = 6.8 Hz, 2/5H), 2.54 (t, J = 6.8 Hz, 8/5H), 2.47 (t, J = 6.8 Hz, 2/5H), 2.36 (m, 28/5H), 1.42 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.34, 169.46, 159.07, 139.08, 136.72, 135.42, 133.54, 130.81, 130.10, 129.85, 128.58, 127.66, 127.59, 127.31, 121.81, 121.55, 119.77, 115.03, 110.33, 106.61, 55.86, 54.88, 54.17, 54.01, 34.29, 26.07, 26.00, 24.38. HRMS (Q-TOF): calculated for $C_{28}H_{29}N_3O_3$ [M]: 455.2209. Found $[M+H]^+$: 456.2287.

(*Z*/*E*)-*N*-(2-oxo-3-(quinoxalin-6-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9n) Following general procedure B, starting from intermediate (**7**) and quinoxaline-6-carbaldehyde (**8n**) to afford compound **9n** as a *Z*/*E* mixture (*Z*/*E* = 1:3), yellow solid (yield 22.8%), melting point 195 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1/4H), 10.61 (s, 3/4H), 10.07 (s, 1/4H), 10.00 (s, 3/4H), 9.09 (d, J = 1.2 Hz, 1/4H), 9.02 (m, 6/4H), 8.99 (m, 1/4H), 8.97 (m, 1/4H), 8.77 (dd, J = 8.8, 2.0 Hz, 1/4H), 8.38 (s, 3/4H), 8.17 (m, 6/4H), 8.11 (d, J = 8.8 Hz, 1/4H), 8.05 (d, J = 1.6 Hz, 1/4H), 7.93 (s, 1/4H), 7.83 (s, 3/4H), 7.76 (d, J = 1.6 Hz, 3/4H), 7.53 (dd, J = 8.4, 2.0 Hz, 3/4H), 7.30 (dd, J = 8.4, 2.0 Hz, 1/4H), 6.85 (d, J = 8.4 Hz, 3/4H), 6.81 (d, J = 8.4 Hz, 1/4H), 2.62 (t, J = 7.2 Hz, 2/4H), 2.48 (m, 2H), 2.40 (m, 4/4H), 2.31 (m, 18/4H), 1.35 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.48, 170.34, 168.95, 167.55, 146.99, 146.89, 146.86, 146.79, 143.27, 142.93, 142.65, 142.38, 139.47, 137.68, 136.83, 135.97, 135.29, 134.61, 133.87, 133.71, 133.50, 133.06, 131.01, 130.45, 130.09, 129.99, 129.71, 128.89, 124.89, 122.50, 122.03, 121.06, 114.72, 112.93, 110.63, 110.06, 55.06, 54.81, 54.18, 53.95, 34.44, 34.23, 26.09, 25.97, 24.50, 24.35. HRMS (Q-TOF): calculated for $C_{25}H_{25}N_5O_2$ [M]: 427.2008. Found $[M+H]^+$: 428.2036.

(E)-*N*-(2-oxo-3-(phenanthren-9-ylmethylene)indolin-5-yl)-3-(piperidin-1-yl)propanamide (9o) Following general procedure B, starting from intermediate (**7**) and phenanthrene-9-carbaldehyde (**8o**) to afford compound **9o** as an *E* isomer, orange solid (yield 25.3%), melting point 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H),

9.87 (s, 1H), 8.96 (d, J = 8.0 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.05 (m, 3H), 7.74 (m, 4H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 7.39 (d, J = 1.2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 2.37 (t, J = 6.4 Hz, 2H), 2.19 (m, 6H), 1.19 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.22, 168.91, 139.34, 133.98, 133.54, 131.14, 130.88, 130.57 (2C), 130.12, 130.00, 129.93, 128.42, 128.27, 127.94 (2C), 127.70, 125.56, 124.09, 123.41, 122.36, 121.59, 115.33, 110.40, 54.71, 53.83 (2C), 34.02, 25.87 (2C), 24.33. HRMS (Q-TOF): calculated for $C_{31}H_{29}N_3O_2$ [M]: 475.2260. Found $[M+H]^+$: 476.2337.

(E)-*N*-(3-(anthracen-9-ylmethylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9p) Following general procedure B, starting from intermediate (**7**) and anthracene-9-carbaldehyde (**8p**) to afford compound **9p** as an *E* isomer, orange solid (yield 25.2%), melting point 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 9.58 (s, 1H), 8.77 (s, 1H), 8.28 (s, 1H), 8.20 (m, 2H), 7.96 (m, 2H), 7.55 (m, 5H), 6.80 (d, J = 8.4 Hz, 1H), 5.93 (d, J = 2.0 Hz, 1H), 2.28 (t, J = 6.8 Hz, 2H), 2.10 (m, 6H), 1.28 (m, 2H), 1.18 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.98, 168.36, 139.28, 133.50, 132.86, 131.97, 131.32 (2C), 129.57 (2C), 128.83, 128.59 (2C), 128.53, 127.29 (2C), 126.14 (2C), 125.54 (2C), 122.32, 121.64, 115.64, 110.15, 55.38, 53.77 (2C), 33.78, 25.92 (2C), 24.42. HRMS (Q-TOF): calculated for $C_{31}H_{29}N_3O_2$ [M]: 475.2260. Found $[M+H]^+$: 476.2332.

(*Z*/*E*)-*N*-(3-([1,1′-biphenyl]-4-ylmethylene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamide (9q) Following general procedure B, starting from intermediate (**7**) and [1,1′-biphenyl]-4-carbaldehyde (**8q**) to afford compound **9q** as a *Z*/*E* mixture (*Z*/*E* = 1:4), orange solid (yield 31.1%), melting point 212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1/5H), 10.53 (s, 4/5H), 10.03 (s, 1H), 8.52 (m, 2/5H), 8.00 (m, 1H), 7.80 (m, 28/5H), 7.68 (s, 1/5H), 7.65 (s, 4/5H), 7.49 (m, 14/5H), 7.41 (m, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1/5H), 6.83 (d, J = 8.4 Hz, 4/5H), 6.78 (d, J = 8.0 Hz, 1/5H), 2.61 (t, J = 7.2 Hz, 2/5H), 2.54 (m, 8/5H), 2.46 (t, J = 6.8 Hz, 2/5H), 2.36 (m, 28/5H), 1.42 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.37, 169.29, 141.75, 139.74, 139.16, 135.97, 133.83, 133.61, 133.25, 130.68, 129.55, 129.51, 128.50, 128.11, 127.38, 127.23, 127.18, 126.77, 121.99, 121.38, 114.88, 110.41, 55.06, 54.87, 54.18, 54.03, 34.44, 34.33, 26.08, 26.03, 24.49, 24.38. HRMS (Q-TOF): calculated for $C_{29}H_{29}N_3O_2$ [M]: 451.2260. Found $[M+H]^+$: 452.2340.

(E)-3-(naphthalen-1-ylmethylene)indolin-2-one (16a) Following general procedure B, starting from indolin-2-one (**3a**) and 1-naphthaldehyde (**8h**) to afford compound **16a** as an *E* isomer, yellow solid (yield 63.8%), melting point 199 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.11 (s, 1H), 8.07 (t, J = 8.8 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.62 (m, 3H), 7.19 (t, J = 8.2 Hz, 1H), 6.90 (t, J = 6.8 Hz, 2H), 6.69 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.72, 143.50, 133.75, 133.68, 132.20, 131.02, 130.65, 130.24, 130.23, 129.21, 127.54, 127.19, 127.08, 125.95, 124.83, 123.05, 121.51, 121.48, 110.58. HRMS (Q-TOF): calculated for $C_{19}H_{13}NO$ [M]: 271.0997. Found $[M+H]^+$: 272.1077.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-2-(piperidin-1-yl)acetamide (16b) Following general procedure B, starting from intermediate (**11b**) and 1-naphthaldehyde (**8h**) to afford compound **16b** as an *E* isomer, orange solid (yield 36.3%), melting point 120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 9.32 (s, 1H), 8.08 (m, 3H), 7.95 (m, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.62 (m, 3H), 7.41 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 2.89 (s, 2H), 2.34 (m, 4H), 1.48 (m, 4H), 1.37 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.90, 168.37, 139.50, 133.90, 133.72, 132.70, 131.72, 131.21, 130.38, 130.10, 129.21, 127.55, 127.48, 127.04, 126.01, 124.70, 122.59, 121.45, 115.56, 110.29, 62.83, 54.42 (2C), 25.94 (2C), 23.97. HRMS (Q-TOF): calculated for $C_{26}H_{25}N_3O_2$ [M]: 411.1947. Found $[M+H]^+$: 412.2024.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-4-(piperidin-1-yl)butanamide (16c) Following general procedure B, starting from intermediate (**11c**) and 1-naphthaldehyde (**8h**) to afford compound **16c** as an *E* isomer, orange solid (yield 27.2%), melting point 139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 9.54 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.87 (m, 1H), 7.63 (m, 3H), 7.52 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 8.4, 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 2.25 (m, 4H), 2.16 (m, 4H), 1.61 (m, 2H), 1.43 (m, 4H), 1.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.06, 168.93, 139.11, 133.73, 133.72, 133.67, 131.68, 131.31, 130.40, 130.05, 129.20, 127.55, 127.44, 127.06, 126.11, 124.63, 122.20, 121.39, 115.07, 110.28, 58.41, 54.43 (2C), 34.69, 25.98 (2C), 24.58, 22.77. HRMS (Q-TOF): calculated for $C_{28}H_{29}N_3O_2$ [M]: 439.2260. Found $[M+H]^+$: 440.2338.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)acetamide (16d) Following general procedure B, starting from intermediate (**3d**) and 1-naphthaldehyde (**8h**) to afford compound **16d** as an *E* isomer, yellow solid (yield 42.7%), melting point 270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.68 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.63 (m, 3H), 7.56 (d, J = 1.6 Hz, 1H), 7.42 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.92, 168.14, 139.16 133.76, 133.73, 133.69,

131.68, 131.29, 130.38, 130.10, 129.21, 127.54, 127.43, 127.06, 126.15, 124.62, 122.05, 121.40, 114.96, 110.33, 24.17. HRMS (Q-TOF): calculated for $C_{21}H_{16}N_2O_2$ [M]: 328.1212. Found $[M+H]^+$: 329.1299.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl) propionamide (16e) Following general procedure B, starting from intermediate (**3e**) and 1-naphthaldehyde (**8h**) to afford compound **16e** as an *E* isomer, yellow solid (yield 44.0%), melting point 272 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.54 (s, 1H), 8.08 (m, 3H), 7.97 (m, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.64 (m, 3H), 7.55 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.16 (q, J = 7.6 Hz, 2H), 0.98 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.86, 168.93, 139.10, 133.75, 133.73, 133.72, 131.68, 131.32, 130.42, 130.05, 129.20, 127.56, 127.45, 127.07, 126.15, 124.63, 122.13, 121.41, 114.93, 110.32, 29.77, 10.18. HRMS (Q-TOF): calculated for $C_{22}H_{18}N_2O_2$ [M]: 342.1368. Found $[M+H]^+$: 343.1443.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl) cyclopropanecarboxamide (16f) Following general procedure B, starting from intermediate (**3f**) and 1-naphthaldehyde (**8h**) to afford compound **16f** as an *E* isomer, yellow solid (yield 31.8%), melting point 291 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.86 (s, 1H), 8.07 (m, 3H), 7.97 (m, 1H), 7.88 (d, *J* = 6.8 Hz, 1H), 7.64 (m, 3H), 7.48 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 1.61 (m, 1H), 0.69 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.49, 168.95, 139.12, 133.83, 133.73, 133.68, 131.67, 131.30, 130.45, 130.00, 129.20, 127.58, 127.45, 127.09, 126.14, 124.63, 122.22, 121.44, 114.94, 110.36, 14.80, 7.34 (2C). HRMS (Q-TOF): calculated for $C_{23}H_{18}N_2O_2$ [M]: 354.1368. Found $[M+H]^+$: 355.1540.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-phenylpropanamide (16g) Following general procedure B, starting from intermediate (**3g**) and 1-naphthaldehyde (**8h**) to afford compound **16g** as an *E* isomer, orange solid (yield 30.2%), melting point 189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.60 (s, 1H), 8.08 (m, 3H), 7.97 (m, 1H), 7.88 (d, *J* = 6.8 Hz, 1H), 7.64 (m, 3H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.42 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.23 (m, 2H), 7.15 (m, 3H), 6.82 (d, *J* = 8.4 Hz, 1H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.27, 168.93, 141.62, 139.23, 133.83, 133.74, 133.48, 131.68, 131.31, 130.45, 130.02, 129.21, 128.71 (2C), 128.67 (2C), 127.57, 127.43, 127.09, 126.35, 126.13, 124.64, 122.27, 121.42, 115.14, 110.34, 38.24, 31.33. HRMS (Q-TOF): calculated for $C_{28}H_{22}N_2O_2$ [M]: 418.1681. Found $[M+H]^+$: 419.1757.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl) cinnamamide (16h) Following general procedure B, starting from intermediate (**3h**) and 1-naphthaldehyde (**8h**) to afford compound **16h** as an *E* isomer, yellow solid (yield 26.7%), melting point 273 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.92 (s, 1H), 8.09 (m, 3H), 7.98 (m, 1H), 7.92 (d, *J* = 6.8 Hz, 1H), 7.63 (m, 7H), 7.43 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.93, 163.48, 140.08, 139.50, 135.23, 134.00, 133.75, 133.60, 131.71, 131.31, 130.50, 130.10, 129.99, 129.43 (2C), 129.23, 128.08 (2C), 127.58, 127.48, 127.10, 126.18, 124.66, 122.76, 122.24, 121.58, 114.96, 110.51. HRMS (Q-TOF): calculated for $C_{28}H_{20}N_2O_2$ [M]: 416.1525. Found $[M+H]^+$: 417.1598.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-(3,4,5-trimethoxyphenyl)propanamide (16i) Following general procedure B, starting from intermediate (**3i**) and 1-naphthaldehyde (**8h**) to afford compound **16i** as an *E* isomer, orange solid (yield 30.2%), melting point 130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.63 (s, 1H), 8.07 (m, 3H), 7.93 (m, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.63 (m, 3H), 7.57 (d, *J* = 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 2H), 3.67 (s, 6H), 3.59 (s, 3H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.37, 168.92, 153.13 (2C), 139.24, 137.30, 136.13, 133.82, 133.74, 133.53, 131.68, 131.32, 130.43, 130.02, 129.20, 127.57, 127.43, 127.08, 126.11, 124.63, 122.19, 121.44, 115.00, 110.36, 105.87 (2C), 60.39, 56.15 (2C), 38.28, 31.71. HRMS (Q-TOF): calculated for $C_{31}H_{28}N_2O_5$ [M]: 508.1998. Found $[M+H]^+$: 509.2079.

(E)-3-morpholino-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)propanamide (16j) Following general procedure B, starting from intermediate (**11j**) and 1-naphthaldehyde (**8h**) to afford compound **16j** as an *E* isomer, orange solid (yield 32.7%), melting point 137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.73 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.63 (m, 3H), 7.45 (m, 2H), 6.82 (d, *J* = 9.2 Hz, 1H), 3.49 (m, 4H), 2.50 (m, 2H), 2.31 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.99, 168.90, 139.24, 133.86, 133.73, 133.49, 131.72, 131.26, 130.43, 130.06, 129.22, 127.57, 127.40, 127.08, 126.07, 124.65, 122.23, 121.45, 115.00, 110.36, 66.63 (2C), 54.58, 53.39 (2C), 34.09. HRMS (Q-TOF): calculated for $C_{26}H_{25}N_3O_3$ [M]: 427.1896. Found $[M+H]^+$: 428.2076.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-thiomorpholino propanamide (16k) Following general procedure B, starting from intermediate (**11k**) and 1-naphthaldehyde (**8h**) to afford compound **16k** as an *E* isomer, orange solid (yield 34.4%), melting point 140 °C. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.66 (s, 1H), 8.07 (m, 3H), 7.95 (m, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.63 (m, 3H), 7.46 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.60 (m, 4H), 2.54 (m, 6H), 2.29 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.07, 168.90, 139.25, 133.85, 133.72, 133.46, 131.71, 131.26, 130.44, 130.05, 129.21, 127.57, 127.41, 127.08, 126.06, 124.65, 122.29, 121.44, 115.07, 110.35, 54.93, 54.60 (2C), 34.00, 27.68 (2C). HRMS (Q-TOF): calculated for $C_{26}H_{25}N_3O_2S$ [M]: 443.1667. Found $[M+H]^+$: 444.1719.

(E)-3-cyclohexyl-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)propanamide (16l) Following general procedure B, starting from intermediate (**11l**) and 1-naphthaldehyde (**8h**) to afford compound **16l** as an *E* isomer, yellow solid (yield 35.0%), melting point 212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.53 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.63 (m, 3H), 7.53 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 8.4, 1.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.14 (t, J = 7.6 Hz, 2H), 1.61 (m, 5H), 1.37 (q, J = 6.8 Hz, 2H), 1.13 (m, 4H), 0.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.37, 168.93, 139.16, 133.73 (2C), 133.64, 131.69, 131.31, 130.42, 130.05, 129.20, 127.55, 127.44, 127.06, 126.10, 124.63, 122.28, 121.40, 115.13, 110.30, 37.25, 34.28, 33.05, 33.03 (2C), 26.57, 26.22 (2C). HRMS (Q-TOF): calculated for $C_{28}H_{28}N_2O_2$ [M]: 424.2151. Found $[M+H]^+$: 425.2239.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-2-(pyrrolidin-1-yl) acetamide (16m) Following general procedure B, starting from intermediate (**11m**) and 1-naphthaldehyde (**8h**) to afford compound **16m** as an *E* isomer, orange solid (yield 29.1%), melting point 127 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.39 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.88 (d, J = 6.8 Hz, 1H), 7.63 (m, 3H), 7.55 (d, J = 1.2 Hz, 1H), 7.40 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.08 (s, 2H), 2.47 (m, 4H), 1.68 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.94, 168.58, 139.46, 133.80, 133.72, 132.90, 131.67, 131.26, 130.42, 130.04, 129.21, 127.55, 127.52, 127.04, 126.06, 124.67, 122.77, 121.37, 115.69, 110.25, 59.74, 54.05 (2C), 23.85 (2C). HRMS (Q-TOF): calculated for $C_{25}H_{23}N_3O_2$ [M]: 397.1790. Found $[M+H]^+$: 398.1753.

(E)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-(pyrrolidin-1-yl)propanamide (16n) Following general procedure B, starting from intermediate (**11n**) and 1-naphthaldehyde (**8h**) to afford compound **16n** as an *E* isomer, orange solid (yield 22.3%), melting point 140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.81 (s, 1H), 8.07 (m, 3H), 7.96 (m, 1H), 7.87 (d, J = 6.8 Hz, 1H), 7.63 (m, 3H), 7.46 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 2.67 (t, J = 6.8 Hz, 3H), 2.47 (m, 4H), 2.35 (t, J = 6.8 Hz, 2H), 1.64 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.80, 168.90, 139.22, 133.83, 133.73, 133.52, 131.71, 131.27, 130.43, 130.05, 129.21, 127.57, 127.41, 127.08, 126.07, 124.65, 122.14, 121.45, 114.93, 110.36, 53.77 (2C), 51.77, 35.86, 23.55 (2C). HRMS (Q-TOF): calculated for $C_{26}H_{25}N_3O_2$ [M]: 411.1947. Found $[M+H]^+$: 412.2020.

(E)-2-(diethylamino)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)acetamide (16o) Following general procedure B, starting from intermediate (**11o**) and 1-naphthaldehyde (**8h**) to afford compound **16o** as an *E* isomer, orange solid (yield 28.4%), melting point 112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 9.29 (s, 1H), 8.08 (m, 3H), 7.95 (m, 1H), 7.88 (d, J = 6.8 Hz, 1H), 7.62 (m, 3H), 7.46 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.4, 2.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 2.98 (s, 2H) 2.48 (q, J = 6.8 Hz, 4H), 0.92 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.65, 168.91, 139.54, 133.89, 133.72, 132.55, 131.70, 131.22, 130.40, 130.08, 129.21, 127.55, 127.49, 127.04, 125.96, 124.69, 122.70, 121.45, 115.63, 110.29. 57.82, 48.25 (2C), 12.44 (2C). HRMS (Q-TOF): calculated for $C_{25}H_{25}N_3O_2$ [M]: 399.1947. Found $[M+H]^+$: 400.2020.

(E)-3-(diethylamino)-*N*-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)propanamide (16p) Following general procedure B, starting from intermediate (**11p**) and 1-naphthaldehyde (**8h**) to afford compound **16p** as an *E* isomer, orange solid (yield 21.5%), melting point 115 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.93 (s, 1H), 8.07 (m, 3H), 7.95 (m, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.63 (m, 3H), 7.49 (dd, J = 8.4, 2.0 Hz, 1H), 7.36 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 2.59 (t, J = 6.8 Hz, 2H), 2.39 (q, J = 7.2 Hz, 4H), 2.25 (t, J = 6.8 Hz, 2H), 0.86 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.32, 168.87, 139.15, 133.85, 133.74, 133.55, 131.79, 131.20, 130.36, 130.16, 129.20, 127.54, 127.29, 127.06, 126.06, 124.66, 122.04, 121.49, 114.84, 110.36, 48.74, 46.40 (2C), 34.22, 12.22 (2C). HRMS (Q-TOF): calculated for $C_{26}H_{27}N_3O_2$ [M]: 413.2103. Found $[M+H]^+$: 414.2174.

(E)-3-(naphthalen-1-ylmethylene)-2-oxo-*N*-(2-(piperidin-1-yl)ethyl)indoline-5-carboxamide (16q) Following general procedure B, starting from intermediate (**11q**) and 1-naphthaldehyde (**8h**) to afford compound **16q** as an *E* isomer, yellow solid (yield 21.0%), melting point 134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.17 (s, 1H), 8.09 (m, 2H), 8.02 (m, 1H), 7.95 (m, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.65 (m, 5H), 6.92 (d, J = 8.0 Hz, 1H), 3.21 (q, J = 6.4 Hz, 2H), 2.30 (m, 6H), 1.43 (m, 4H), 1.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.04, 166.20, 145.71, 134.80, 133.75, 131.72, 131.25, 130.67, 129.54, 129.37, 129.27, 128.33, 127.64, 127.56, 127.12,

125.92, 124.71, 122.69, 121.34, 109.74, 58.12, 54.48 (2C), 37.30, 26.00 (2C), 24.46. HRMS (Q-TOF): calculated for $C_{27}H_{27}N_3O_2$ [M]: 425.2103. Found $[M+H]^+$: 426.2178.

(E)-3-(naphthalen-1-ylmethylene)-5-((3-(piperidin-1-yl) propyl)amino)indolin-2-one (16r) Following general procedure B, starting from intermediate (**11r**) and 1-naphthaldehyde (**8h**) to afford compound **16r** as an *E* isomer, dark red solid (yield 23.8%), melting point 98 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.05 (m, 2H), 7.98 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.61 (m, 3H), 6.63 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 5.21 (brs, 1H), 2.60 (t, J = 6.0 Hz, 2H), 2.15 (m, 6H), 1.40 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.61, 144.38, 133.79, 133.69, 132.57, 132.40, 131.42, 131.06, 129.93, 129.14, 127.42, 127.05, 126.96, 125.83, 124.87, 122.08, 114.53, 110.88, 107.71, 57.15, 54.42 (2C), 42.66, 25.97 (2C), 25.85, 24.52. HRMS (Q-TOF): calculated for $C_{27}H_{29}N_3O$ [M]: 411.2311. Found $[M+H]^+$: 412.2386.

(E)-1-(3-(naphthalen-1-ylmethylene)-2-oxoindolin-5-yl)-3-(2-(piperidin-1-yl)ethyl)urea (16s) Following general procedure B, starting from intermediate (**11s**) and 1-naphthaldehyde (**8h**) to afford compound **16s** as an *E* isomer, orange solid (yield 26.2%), melting point 207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.23 (s, 1H), 8.07 (m, 3H), 7.95 (m, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.63 (m, 3H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 7.17 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.78 (t, J = 5.2 Hz, 1H), 3.07 (q, J = 6.0 Hz, 2H), 2.27 (m, 6H), 1.46 (m, 4H), 1.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.84, 155.65, 137.86, 134.87, 133.72, 133.40, 131.86, 131.25, 130.33 (2C), 129.20, 127.55, 127.35, 127.08, 126.08, 124.67, 121.51, 121.01, 113.90, 110.38, 58.59, 54.44 (2C), 36.82, 25.96 (2C), 24.54. HRMS (Q-TOF): calculated for $C_{27}H_{28}N_4O_2$ [M]: 440.2212. Found $[M+H]^+$: 441.2271.

Cell culture and reagents

A549 and H1299 (human non-small lung carcinoma cell lines), HCT116 and DLD1 (human colorectal carcinoma cell lines), and LO_2 (human hepatic cell lines) were purchased from American Type Culture Collection (ATCC). Cells were maintained in RPMI-1640 media or DMEM media (Gibco) supplemented with 10% fetal bovine serum (Hyclone), 100 U ml^{-1} penicillin (Sigma-Aldrich, USA) and 100 μg ml^{-1} streptomycin (Sigma-Aldrich, USA) at 37 °C in a humidified atmosphere containing 5% CO_2. All tumor cell lines were maintained according to the ATCC procedures.

Cell proliferation assay

Cell viability assays were performed using the CCK-8 kit according to the manufacturer's instructions. Briefly, A variety of human cell lines were seeded in a 96-well plate at 2000 cells per well, then they were treated with gradient concentrations of compounds for 48 h. Each well was incubated with 10 μL CCK-8 (MedChemExpress, Monmouth Junction, NJ, USA) for 2 h in 37 °C cell culture incubator, then the absorbance was measured at a wavelength of 450 nm by SpectraMAX M5 microplate spectrophotometer (Molecular Devices, Sunnyvale, CA, USA). The inhibition rates of different concentrations of compounds were calculated and the IC_{50} values were calculated by GraphPad Prism 7 software (San Diego, USA) using XY modeling.

Acute toxicity study

Seven-week-old male and female Balb/c mice (4 male and 4 female mice) were orally administered **9h** or **16s** once in a single day at a dose of 500 mg/kg each time, while another panel of control rats (3 male and 3 female mice) received the same volume of vehicle. The condition of the experimental mice was monitored daily for 15 days. Mortality, clinical signs, and gross findings were observed. Then, mice were sacrificed and gross histological examinations of the major organs were performed. The blood of each mice was collected for hematological evaluation. Hematological analysis was performed using ADVIA2120 (Siemens, Germany), while biochemical parameters were measured using COBAS Integra 400 Plus (Roche, Switzerland).

In silico docking

In silico docking was performed through Maestro 1.15 (Schrodinger). Ligands were firstly generated in ChemDraw followed by generation of energy minimized 3D structures using LigPrep module of Maestro 1.15. Protein was prepared by Protein Preparation Wizard of Maestro 1.15 following general procedure. In silico docking was accomplished using Glide XP (extra precision) of Ligand Docking module of Maestro 1.15.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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