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Synthesis of aristolactam analogues and evaluation of their antitumor activity

Young Lok Choi [a,b], Joa Kyum Kim [a], Sang-Un Choi [a], Yong-Ki Min [a], Myung-Ae Bae [a], Bum Tae Kim [a], Jung-Nyoung Heo [a,*]

[a] Bioorganic Science Division, Korea Research Institute of Chemical Technology, Daejeon 305-600, Republic of Korea
[b] Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Republic of Korea

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ABSTRACT

A series of natural aristolactams and their analogues have been prepared and evaluated for antitumor activity against human cancer cells, including multi-drug resistant cell lines. Naturally occurring aristolactams, such as aristolactam BII (cepharanone B), aristolactam BIII, aristolactam FI (piperolactam A), *N*-methyl piperolactam A, and sauristolactam showed moderate antitumor activities in selected cell lines. However, several synthetic aristolactam derivatives exhibited potent antitumor activities against a broad array of cancer cell lines with GI_{50} values in the submicromolar range.

The phenanthrene lactam core is frequently found in biologically interesting natural products. Among them, aristolactams and aporphines (Fig. 1) constitute an important alkaloid family due to their unique structural features and potent biological activities.[1] The aristolactams were isolated from various plant species and were traditionally used as folk medicines.[2] Recently, the aristolactams have received much attention due to an interesting array of biological properties including anti-inflammatory,[3] antiplatelet,[4] antimycobacterial,[5] and neuro-protective[6] activities. In particular, naturally occurring aristolactams such as cepharanone B (aristolactam BII), aristolactam BIII, piperolactam A, and goniothalactam have been discovered that display potent inhibitory activity against human cancer cells.[7]

Although the cytotoxicity of aristolactams is well-known, structure–activity relationship (SAR) studies have been limited mainly

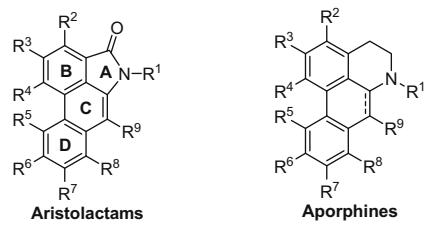
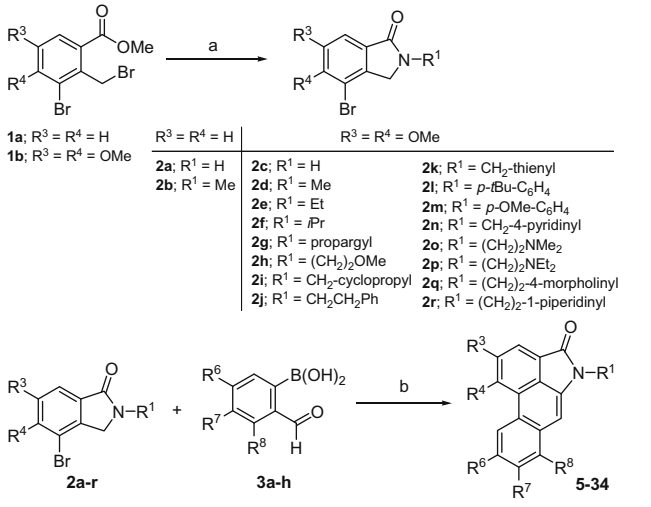


Figure 1. Aristolactam and aporphine analogues.



Scheme 1. Synthesis of phenanthrene lactams **5**–**34**. Reagents and conditions: (a) amine, THF, rt, 66–99%; (b) $Pd(PPh_3)_4$ (4 mol %), Cs_2CO_3 (3 equiv), toluene/EtOH (2:1 v/v), microwave 150 °C, 10 min, 42–99%.

* Corresponding author. Tel.: +82 42 860 7085; fax: +82 42 861 0307.
E-mail address: heojn@krict.re.kr (J.-N. Heo).

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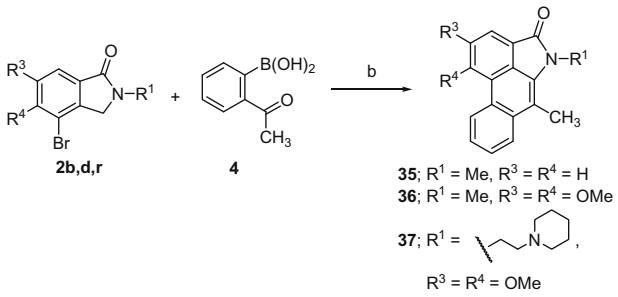


Scheme 2. Synthesis of phenanthrene lactams **35**–**37**. Reagents and conditions: (b) $Pd(PPh_3)_4$ (4 mol %), Cs_2CO_3 (3 equiv), toluene/EtOH (2:1 v/v), microwave 150 °C, 10 min, 23–77%.

as a consequence of synthetic difficulties associated with the preparation of a diverse array of aristolactam analogues.[8–10] Pioneering investigations by the Couture group demonstrated the potent cytotoxic activity of N-substituted aristolactam derivatives using the murine L1210 leukemia cell line.[11]

In an effort to explore the structure–activity relationship, we designed a new library of aristolactam derivatives containing various phenanthrene ring substitutions and different N-substituents.

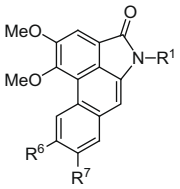
We have previously developed a strategy for the concise and rapid synthesis of aristolactams that employs a Suzuki–Miyaura coupling/aldol condensation cascade sequence.[12] This approach led to the efficient synthesis of natural aristolactams such as aristolactam BII (cepharanone B), aristolactam BIII, aristolactam FI (piperolactam A), *N*-methyl piperolactam A, and sauristolactam. Herein we describe the construction of a wide range of aristolactam analogues and their anti-proliferative effects against different human cancer cells, including multi-drug resistant cell lines.

An efficient synthetic route to aristolactams starts from the preparation of isoindolin-1-ones **2a**–**r** by the reaction of 2-bromomethylbenzoates **1a**–**b** with various aliphatic and aromatic amines (Scheme 1). Accordingly, isoindolin-1-ones **2a**–**r** were prepared in good to excellent yields (66–99%).[13] We next examined the direct one-pot synthesis of aristolactam analogues with a number of 2-formylphenylboronic acids by using the previously developed conditions ($Pd(PPh_3)_4$ (4 mol %), Cs_2CO_3 (3 equiv), toluene/EtOH (2:1 v/v), microwave 150 °C, 10 min). Treatment of isoindolin-1-ones **2a**–**r** with boronic acids **3a**–**h** provided the respective aristolactam analogues in 42–99% yields. In addition, reactions of isoindolin-1-ones **2a**, **2d**, **2r** with 2-acetylphenylboronic acid **4** proceeded less effectively to give the corresponding aristolactams **35**–**37** in 77%, 44%, and 23% yield, respectively (Scheme 2).[14] It is worth mentioning that 2-formylboronic acids, possessing electron-deficient or -rich substituents, are reactive in the cascade process.

Initial investigations were conducted to evaluate aristolactam derivatives for their antiproliferative activity against human cancer cell lines by using the sulforhodamine B (SRB) colorimetric assay.[15] This panel includes the cell lines MES-SA (uterine cancer), HCT-15 (colon cancer), and their multidrug-resistant sublines, MES-SA/DX5 and HCT-15/CLO2. The results, summarized in Table 1, show that the tri-methoxy substituted aristolactam BIII (**6**) has modest activity (GI_{50} = 2.7–3.7 μM) whereas cepharanone B (**5**) and piperolactam A (**7**) are inactive. It is noteworthy that the methoxy-substituted compounds (**6** and **11**–**14**) are more potent than the hydroxyl-substituted compounds (**7** and **9**–**10**). Importantly, the tetra-methoxy substituted phenanthrene lactam **12** has highly potent cytotoxic activity with GI_{50} values in the submicromolar range (0.06–1.05 μM). Furthermore, the results show that aristolactam derivatives are equally potent toward multidrug-resistant cell lines compared to the commercially available drug, etoposide.[16]

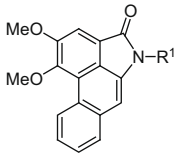
In order to probe the SAR of the N-substituents connected to lactam ring A, we investigated the effect of side chain variation on antiproliferative activity. Table 2 summarizes the SAR with respect to substitution on lactam ring A. In this case, the panel of cell lines includes SK-OV-3 (ovarian), A431 (epidermis), MDA-MB-231 (breast), and BT-474 (breast) cell lines. Compared to the methyl-substituted compound **11**, most compounds are less active except for aminoethyl compounds, **27** and **28**. Thus, the aminoalkyl substituents such as morpholinylethyl and piperidinylethyl are beneficial to the antiproliferative activity.

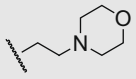
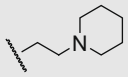
Table 1
Cytotoxic activities of aristolactam analogues



Compound	R^1	R^3	R^4	R^6	R^7	Yield (%)	Cytotoxicity, GI_{50} (μM)			
							MES-SA	MES-SA/DX5	HCT-15	HCT-15/CLO2
Cepharanone B (**5**)	H	OMe	OMe	H	H	81	>30.00	>30.00	>30.00	>30.00
Aristolactam BIII (**6**)	H	OMe	OMe	OMe	H	83	2.70	2.82	3.74	3.35
Piperolactam A (**7**)	H	OMe	OH	H	H	Ref. 12a	>30.00	26.96	>30.00	>30.00
8	Me	H	H	H	H	99	1.81	3.56	4.21	5.72
N-Methyl piperolactam A (**9**)	Me	OMe	OH	H	H	Ref. 12a	14.51	14.47	12.77	10.76
Sauristolactam (**10**)	Me	OH	OMe	H	H	Ref. 12a	23.75	23.11	4.10	4.38
11	Me	OMe	OMe	H	H	86	3.84	9.52	8.47	8.61
12	Me	OMe	OMe	OMe	OMe	86	1.05	1.01	0.06	0.07
13	Me	OMe	OMe	OCH_2O		80	27.11	18.94	5.93	1.64
14	Me	OMe	OMe	H	OMe	89	1.22	0.76	0.30	0.16
15	Me	OMe	OMe	H	Cl	86	>30.00	>30.00	2.94	17.90
16	Me	OMe	OMe	Me	H	82	>30.00	>30.00	1.53	1.46
Etoposide							0.21	9.72	1.25	10.02

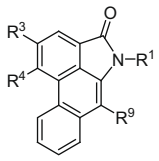
Table 2
Cytotoxic activities of aristolactam analogues

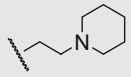


Compound	R^1	Yield (%)	Cytotoxicity, GI_{50} (μM)			
			SK-OV-3	A431	MDA-MB-231	BT-474
11	Me	86	3.42	5.75	nd[a]	nd[a]
17	Et	71	5.45	10.90	9.37	4.16
18	*i*Pr	62	19.42	>30.00	>30.00	20.57
19	Propargyl	53	>30.00	>30.00	>30.00	>30.00
20	$(CH_2)_2OMe$	66	24.29	>30.00	>30.00	22.52
21	CH_2-cyclopropyl	53	24.18	27.12	>30.00	22.96
22	CH_2CH_2Ph	66	13.44	23.67	>30.00	12.76
23	CH_2-thiophenyl	63	23.79	>30.00	>30.00	>30.00
24	*p*-*t*Bu-C_6H_4	70	6.04	3.51	18.22	11.10
25	*p*-OMe–C_6H_4	86	16.25	32.54	>30.00	23.74
26	CH_2-4-pyridinyl	58	9.94	>30.00	nd[a]	nd[a]
27		42	5.49	4.64	nd[a]	nd[a]
28		77	0.95	1.29	nd[a]	nd[a]

[a] nd = not determined.

Table 3
Cytotoxic activities of aristolactam analogues



Compound	R^1	R^3	R^4	R^9	Yield (%)	Cytotoxicity, GI_{50} (μM)			
						A549	SK-OV-3	A431	HCT-15
8	Me	H	H	H	99	1.54	4.26	8.02	5.72
35	Me	H	H	Me	77	1.62	13.05	2.83	3.79
36	Me	OMe	OMe	Me	44	nd[a]	>30.00	>30.00	nd[a]
37		OMe	OMe	Me	23	0.18	0.33	0.18	0.27

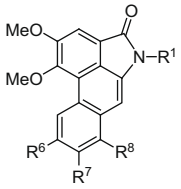
[a] nd = not determined.

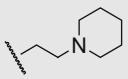
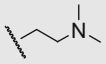
Compounds **35**–**37** possessing a methyl group as a R^9 substituent exhibited only moderate potency, which is similar with that of the corresponding protonated compound **8** (Table 3).

Finally, we optimized the substitution pattern of the D ring. As shown in Table 4, compounds **28**–**34** were highly effective against a wide range of cell lines including the multidrug resistant cell lines MES-SA/DX5 and HCT-15/CLO2, which were resistant to potent cytotoxic agents such as doxorubicin and paclitaxel. The combination of an *N*,*N*-dimethylaminoethyl group on ring A with a [1,3]dioxolyl group on ring D provided compound **34** and resulted in the most potent antiproliferative activity with GI_{50} values in the subnanomolar range (<0.1 nM).

In summary, a natural and synthetic aristolactam library was designed and constructed by using a direct one-pot strategy developed in our laboratories. The cytotoxic evaluation of these compounds revealed that compounds, bearing an aminoethyl group on ring A and multi-methoxy substitutions on ring B and D, showed significantly potent antitumor activities against a broad array of cancer cell lines. Of the compounds tested, **34** is the most active with GI_{50} values in the subnanomolar range (<0.1 nM) against various human cell lines including cell lines resistant to doxorubicin, etoposide, and paclitaxel. We will disclose further biological studies in due course.

Table 4
Cytotoxic activities of aristolactam analogues



Compound	R^1	R^6	R^7	R^8	Yield (%)	Cytotoxicity, GI_{50} (μM)						
						A549	SK-OV-3	A431	MES-SA	MES-SA/DX5	HCT-15	HCT-15/CLO2
28		H	H	H	77	0.95	1.29	0.94	1.46	1.51	1.73	1.58
29		OMe	OMe	H	67	1.54	1.71	1.19	nd[a]	nd[a]	4.22	nd[a]
30		OMe	H	H	40	4.10	6.72	2.95	nd[a]	nd[a]	5.91	nd[a]
31		H	–OCH_2O–		42	<0.1	<0.1	<0.1	<0.1	<0.1	0.10	0.14
32		H	Cl	H	47	0.26	0.91	0.18	0.59	0.61	0.92	0.83
33		OMe	OMe	H	42	0.19	0.33	0.15	0.39	0.51	0.72	0.57
34		H	–OCH_2O–		70	<0.1	<0.1	<0.0001	<0.0001	<0.0001	<0.0001	0.0095
Doxorubicin						0.003	0.021	0.0012	0.0051	0.93	0.19	7.92
Paclitaxel						nd[a]	nd[a]	<0.00001	<0.00001	0.16	0.011	0.83

[a] nd = not determined.

Acknowledgments

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References and notes

1. (a) Kumar, V.; Poonam; Prasad, A. K.; Parmar, V. S. *Nat. Prod. Rep.* **2003**, *20*, 565; (b) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444.
2. Castedo, L.; Tojo, G.. In *The Alkaloid*; Brossi, A., Ed.; Academic: New York, 1990; Vol. 39, pp 99–138.
3. (a) Lan, Y.-H.; Chia, Y.-C.; Chang, F.-R.; Hwang, T.-L.; Liaw, C.-C.; Wu, Y.-C. *Helv. Chim. Acta* **2005**, *88*, 905; (b) Zhang, Y.-N.; Zhong, X.-G.; Zheng, Z.-P.; Hu, X.-D.; Zuo, J.-P.; Hu, L.-H. *Bioorg. Med. Chem.* **2007**, *15*, 988.
4. (a) Chen, Y.-C.; Chen, J.-J.; Chang, Y.-L.; Teng, C.-M.; Lin, W.-Y.; Wu, C.-C.; Chen, I.-S. *Planta Med.* **2004**, *70*, 174; (b) Chia, Y.-C.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. *J. Nat. Prod.* **2000**, *63*, 1160.
5. Mata, R.; Morales, I.; Pérez, O.; Rivero-Cruz, I.; Acevedo, L.; Enriquez-Mendoza, I.; Bye, R.; Franzblau, S.; Timmermann, B. *J. Nat. Prod.* **2004**, *67*, 1961.
6. Kim, S. R.; Sung, S. H.; Kang, S. Y.; Koo, K. A.; Kim, S. H.; Ma, C. J.; Lee, H.-S.; Park, M. J.; Kim, Y. C. *Planta Med.* **2004**, *70*, 391.
7. Anticancer: (a) Kim, S.-K.; Ryu, S. Y.; No, J.; Choi, S. U.; Kim, Y. S. *Arch. Pharm. Res.* **2001**, *24*, 518; (b) Park, J. D.; Baek, N. I.; Lee, Y. H.; Kim, S. I. *Arch. Pharm. Res.* **1996**, *19*, 559; (c) Wu, T.-S.; Ou, L.-F.; Teng, C.-M. *Phytochemistry* **1994**, *36*, 1063; (d) Omar, S.; Chee, C. L.; Ahmad, F.; Ni, J. X.; Jaber, H.; Huang, J.; Nakatsu, T. *Phytochemistry* **1992**, *31*, 4395; (e) Tsai, I.-L.; Lee, F.-P.; Wu, C.-C.; Duh, C.-Y.; Ishikawa, T.; Chen, J.-J.; Chen, Y.-C.; Seki, H.; Chen, I.-S. *Planta Med.* **2005**, *71*, 535.
8. (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432; (b) Benesch, L.; Bury, P.; Guillaneux, D.; Houldsworth, S.; Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 961.
9. (a) Estevez, J. C.; Villaverde, M. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **1992**, *33*, 5145; (b) Castedo, L.; Guitian, E.; Saa, J. M.; Suau, R. *Heterocycles* **1982**, *19*, 279; (c) Castedo, L.; Guitian, E.; Saa, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457; (d) Atanes, N.; Castedo, L.; Guitian, E.; Saa, C.; Saa, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984; (e) Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801; (f) Estevez, J. C.; Estevez, R. J.; Guitian, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785.
10. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Synlett* **1997**, 1475; (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128; (c) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064; (d) Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2003**, 1231.
11. Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557.
12. (a) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, *10*, 3543; (b) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2008**, *73*, 495.
13. *Typical procedure for synthesis of isoindolin-1-ones*. To a solution of 2-(bromomethyl)benzoate **1** (1.0 mmol) in 5 mL of THF was added amine (5.0 mmol). The mixture was stirred at room temperature for 2 h–2 d while monitoring the reaction progress. After removing THF under reduced pressure, the residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization (EtOAc/hexanes) to provide isoindolin-1-one **2**. ^{1}H NMR (300 MHz, $CDCl_3$) data for **2e** (80%): δ 7.33 (s, 1H), 4.23 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.67 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz). Compound **2f** (88%): δ 7.25 (s, 1H), 4.56 (heptet, 1H, *J* = 6.9 Hz), 4.11 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.23 (d, 6H, *J* = 6.9 Hz). Compound **2g** (98%): δ 7.34 (s, 1H), 4.44 (d, 2H, *J* = 2.5 Hz), 4.36 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.31 (t, 1H, *J* = 2.5 Hz). Compound **2h** (88%): δ 7.34 (s, 1H), 4.37 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.80 (t, 2H, *J* = 4.9 Hz), 3.63 (t, 2H, *J* = 4.9 Hz), 3.37 (s, 3H). Compound **2i** (98%): δ 7.34 (s, 1H), 4.35 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.48 (d, 2H, *J* = 7.1 Hz), 1.11–1.00 (m, 1H), 0.63–0.56 (m, 2H), 0.37–0.32 (m, 2H). Compound **2j** (66%): δ 7.30–7.17 (m, 6H), 4.07 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (t, 2H, *J* = 7.2 Hz), 2.97 (t, 2H, *J* = 7.2 Hz). Compound **2k** (98%): δ 7.37 (s, 1H), 7.25 (d, 1H, *J* = 4.9 Hz), 7.05 (d, 1H, *J* = 3.3 Hz), 6.99–6.96 (dd, 1H, *J* = 4.9, 3.6 Hz), 4.96 (s, 2H), 4.20 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H). Compound **2l** (89%): δ 7.74 (d, 2H, *J* = 8.7 Hz), 7.46 (d, 2H, J = 8.6 Hz), 7.40 (s, 1H), 4.68 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 1.34 (s, 9H). Compound **2m** (90%): δ 7.73 (d, 2H, *J* = 9.0 Hz), 7.41 (s, 1H), 6.99 (d, 2H, *J* = 9.0 Hz), 4.67 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.85 (s, 3H). Compound **2n** (82%): δ 8.59 (d, 2H, *J* = 6.6 Hz), 7.39 (s, 1H), 7.20 (d, 2H, *J* = 7.8 Hz), 4.80 (s, 2H), 4.16 (s, 2H), 3.954 (s, 3H), 3.951 (s, 3H). Compound **2o** (98%): δ 7.33 (s, 1H), 4.32 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.72 (t, 2H, *J* = 6.5 Hz), 2.58 (t, 2H, *J* = 6.4 Hz), 2.28 (s, 6H). Compound **2p** (89%): δ 7.33 (s, 1H), 4.35 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.70 (t, 2H, *J* = 6.6 Hz), 2.73 (t, 2H, *J* = 6.6 Hz), 2.60 (q, 4H, *J* = 7.1 Hz), 1.03 (t, 6H, *J* = 7.1 Hz). Compound **2q** (98%): δ 7.33 (s, 1H), 4.33 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.74 (t, 2H, *J* = 6.3 Hz), 3.69 (t, 4H, *J* = 3.6 Hz), 2.64 (t, 2H, *J* = 6.3 Hz), 2.52 (bs, 4H). Compound **2r** (99%): δ 7.33 (s, 1H), 4.35 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.72 (t, 2H, *J* = 6.6 Hz), 2.58 (t, 2H, *J* = 6.6 Hz), 2.44 (s, 4H), 1.61–1.47 (m, 4H), 1.45–1.41 (m, 2H).
14. *Typical procedure for synthesis of phenanthrene lactams*. To a thick-well borosilicate glass vial (3 mL) was added isoindolin-1-one **2** (0.5 mmol), boronic acid (0.6 mmol), $Pd(PPh_3)_4$ (4 mol %), and Cs_2CO_3 (1.5 mmol)

sequentially. The mixture was suspended in toluene/EtOH (2 mL/1 mL). Then, the reaction vial was sealed and irradiated at 150 °C for 10 min using a microwave reactor. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (EtOAc/hexanes) to afford a phenanthrene lactam product. ^{1}H NMR (300 MHz, $CDCl_3$) data for compound **17**: δ 9.23–9.20 (m, 1H), 7.84–7.81 (m, 1H), 7.79 (s, 1H), 7.59–7.54 (m, 2H), 7.01 (s, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.02 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). Compound **18**: δ 9.24–9.20 (m, 1H), 7.83–7.80 (m, 1H), 7.78 (s, 1H), 7.59–7.54 (m, 2H), 7.15 (s, 1H), 4.93 (heptet, 1H, J = 6.9 Hz), 4.09 (s, 3H), 4.06 (s, 3H), 1.63 (d, 2H, J = 6.9 Hz). Compound **19**: δ 9.28–9.26 (m, 1H), 8.28–8.26 (m, 1H), 7.57–7.48 (m, 3H), 7.07 (s, 1H), 4.11 (s, 3H), 4.05 (s, 3H), 3.92 (d, 2H, J = 2.5 Hz), 1.25 (t, 1H, J = 2.5 Hz). Compound **20**: δ 9.23–9.20 (m, 1H), 7.85–7.83 (m, 1H), 7.82 (s, 1H), 7.80–7.54 (m, 2H), 7.11 (s, 1H), 4.15 (t, 2H, J = 5.6 Hz), 4.11 (s, 3H), 4.06 (s, 3H), 3.75 (t, 2H, J = 5.6 Hz), 3.36 (s, 3H). Compound **21**: δ 9.24–9.21 (m, 1H), 7.84–7.81 (m, 1H), 7.79 (s, 1H), 7.60–7.53 (m, 2H), 7.05 (s, 1H), 4.11 (s, 3H), 4.06 (s, 3H), 3.85 (d, 2H, J = 6.8 Hz), 1.28–1.26 (m, 1H), 0.57–0.45 (m, 4H). Compound **22**: δ 9.18–9.14 (m, 1H), 7.71–7.67 (m, 2H), 7.53–7.48 (m, 2H), 7.26–7.15 (m, 5H), 6.73 (s, 1H), 4.12 (t, 2H, J = 7.2 Hz), 4.07 (s, 3H), 4.00 (s, 3H), 3.07 (t, 2H, J = 7.3 Hz). Compound **23**: δ 9.23–9.20 (m, 1H), 7.83–7.79 (m, 2H), 7.60–7.54 (m, 2H), 7.18 (dt, 1H, J = 5.1, 0.5 Hz), 7.12 (d, 1H, J = 3.5 Hz), 7.01 (s, 1H), 6.92 (dd, 1H, J = 5.1, 3.5 Hz), 5.29 (s, 2H), 4.09 (s, 3H), 4.04 (s, 3H). Compound **24**: δ 9.28–9.25 (m, 1H), 7.88 (s, 1H), 7.77–7.76 (m, 1H), 7.74–7.51 (m, 5H), 7.36–7.34 (m, 1H), 7.09 (s, 1H), 4.13 (s, 3H), 4.08 (s, 3H), 1.40 (s, 9H). Compound **25**: δ 9.26–9.24 (m, 1H), 7.88 (s, 1H), 7.77–7.74 (m, 1H), 7.65–7.48 (m, 4H), 7.11–7.09 (m, 2H), 7.01 (s, 1H), 4.18 (s, 3H), 4.14 (s, 3H), 3.90 (s, 1H). Compound **26**: δ 9.26–9.22 (m, 1H), 8.55 (d, 2H, J = 6.0 Hz), 7.87 (s, 1H), 7.75–7.72 (m, 1H), 7.59–7.52 (m, 2H), 7.24 (s, 2H), 6.83 (s, 1H), 5.24 (s, 2H), 4.18 (s, 3H), 4.13 (s, 3H). Compound **27**: δ 9.23 (t, 1H, J = 5.2 Hz), 7.84–7.80 (m, 2H), 7.60–7.54 (m, 2H), 7.04 (s, 1H), 4.12–4.07 (m, 8H), 3.69 (t, 4H, J = 4.5 Hz), 2.76 (t, 2H, J = 6.9 Hz), 2.58 (t, 4H, J = 4.5 Hz). Compound **28**: δ 9.22 (t, 1H, J = 6.3 Hz), 7.84–7.79 (m, 2H), 7.60–7.53 (m, 2H), 7.08 (s, 1H), 4.12–4.07 (m, 8H), 2.71 (t, 2H, J = 7.5 Hz), 2.54 (t, 4H, J = 4.5 Hz), 1.64–1.57 (m, 4H), 1.48–1.42 (m, 2H). Compound **29**: δ 8.77 (s, 1H), 7.76 (s, 1H), 7.23 (s, 1H), 7.00 (s, 1H), 4.11 (s, 3H), 4.08 (s, 3H), 4.06 (s, 3H), 4.05 (s, 3H), 2.72 (t, 2H, J = 7.4 Hz), 2.55 (s, 4H), 1.65–1.57 (m, 4H), 1.49–1.45 (m, 2H). Compound **30**: δ 8.79 (d, 1H, J = 2.6 Hz), 7.80 (s, 1H), 7.74 (d, 1H, J = 8.7 Hz), 7.22 (dd, 1H, J = 8.7, 2.7 Hz), 7.06 (s, 1H), 4.14–4.09 (m, 5H), 4.06 (s, 3H), 3.99 (s, 3H), 2.75 (t, 2H, J = 7.3 Hz), 2.60–2.56 (m, 4H), 1.65–1.59 (m, 4H), 1.48–1.46 (m, 2H). Compound **31**: δ 8.81 (d, 1H, J = 8.7 Hz), 7.70 (s, 1H), 7.12 (d, 1H, J = 8.7 Hz), 7.10 (s, 1H), 6.17 (s, 2H), 4.11–4.05 (m, 8H), 2.73–2.70 (m, 2H), 2.55–2.52 (m, 4H), 1.63–1.56 (m, 4H), 1.46–1.43 (m, 2H). Compound **32**: δ 9.11 (d, 1H, J = 8.9 Hz), 7.76 (s, 2H), 7.45 (dd, 1H, J = 8.8, 2.2 Hz), 6.94 (s, 1H), 4.09–4.04 (m, 8H), 2.70 (t, 2H, J = 7.2 Hz), 2.54–2.51 (m, 4H), 1.63–1.56 (m, 4H), 1.48–1.43 (m, 2H). Compound **33**: δ 8.79 (s, 1H), 7.77 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 4.12–4.04 (m, 14H), 2.70 (t, 2H, J = 7.2 Hz), 2.37 (s, 6H). Compound **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H, J = 8.7 Hz), 7.70 (s, 1H), 7.11 (d, 1H, J = 8.7 Hz), 7.04 (s, 1H), 6.17 (s, 2H), 4.08–4.04 (m, 8H), 2.70 (t, 2H, J = 7.1 Hz), 2.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 154.6, 150.4, 145.3, 143.3, 136.7, 122.6, 121.9, 121.6, 121.4, 121.2, 119.4, 108.5, 107.2, 101.4, 96.2, 60.1, 57.4, 56.8, 45.7, 38.5; MS (EI) m/z 394 (M^+, 4), 336 (9), 323 (100). Compound **35**: δ 8.56–8.53 (m, 2H), 8.08–8.05 (m, 2H), 7.76 (t, 1H, J = 7.8 Hz), 7.65–7.59 (m, 2H), 3.75 (s, 3H), 2.84 (s, 3H). Compound **36**: δ 9.34 (dd, 1H, J = 8.0, 1.5 Hz), 8.06 (dd, 1H, J = 7.9, 1.6 Hz), 7.78 (s, 1H), 7.67–7.56 (m, 2H), 4.09 (s, 3H), 4.06 (s, 3H), 3.76 (s, 3H), 2.83 (s, 3H). Compound **37**: δ 9.33 (dd, 1H, J = 6.5, 1.6 Hz), 8.09 (dd, 1H, J = 7.7, 1.6 Hz), 8.07 (s, 1H), 7.77–7.59 (m, 2H), 4.36 (t, 2H, J = 7.2 Hz), 4.06 (s, 3H), 4.04 (s, 3H), 2.82 (s, 3H), 2.69 (t, 2H, J = 7.2 Hz), 2.55–2.53 (m, 4H), 1.62–1.57 (m, 4H), 1.43–1.40 (m, 2H).

15. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.
16. Stähelin, H. F.; von Wartburg, A. *Cancer Res.* **1991**, *51*, 5. and references cited therein.