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Discovery of Pyrrole−Indoline-2-ones as Aurora Kinase Inhibitors with a Different Inhibition Profile

Chao-Cheng Chiang,[†] Yu-Hsiang Lin,[†] Shu Fu Lin,[†] Chun-Liang Lai,[†] Chiawei Liu,[†] Win-Yin Wei, Sheng-chuan Yang, Ru-Wen Wang, Li-Wei Teng, Shih-Hsien Chuang, Jia-Ming Chang, Ta-Tung Yuan, Ying-Shuen Lee, Paonien Chen, Wei-Kuang Chi, Ju-Ying Yang, Hung-Jyun Huang, Chu-Bin Liao, and Jiann-Jyh Huang*

Development Center for Biotechnology, No. 101, Lane 169, Kangning Street, Xizhi City, Taipei County, Taiwan 221, R.O.C. [†]*These authors contributed equally to this work.*

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A series of pyrrole−indolin-2-ones were synthesized, and their inhibition profile for Aurora kinases was studied. The potent compound **33** with phenylsulfonamido at the C-5 position and a carboxyethyl group at the C-3′ position selectively inhibited Aurora A over Aurora B with IC_{50} values of 12 and 156 nM, respectively. Replacement of the carboxyl group with an amino group led to compound **47**, which retained the activity for Aurora B and lost activity for Aurora A (IC_{50} = 2.19 μM). Computation modeling was used to address the different inhibition profiles of **33** and **47**. Compounds **47** and **36** (the ethyl ester analogue of **33**) inhibited the proliferation of HCT-116 and HT-29 cells and suppressed levels of the phosphorylated substrates of Aurora A and Aurora B in the Western blots.

Introduction

Aurora kinases belong to the serine/threonine subclass of kinases and play a critical role in the regulation of many process that are pivotal in mitosis.[1] Three isoforms of the enzymes have been identified, namely, Aurora A, B, and C, which possess a very conserved catalytic domain and an N-terminal domain that varies in sequence and in length.[2] Aurora A and Aurora B are both overexpressed in solid tumors and leukemias[3−6] and are considered interesting targets for new anticancer drugs.[7] However, it is not clear whether Aurora A or Aurora B is the better target for cancer therapy.[8] Compounds with different inhibition profiles, including pan-Aurora VX-680[9,10] and PHA-739358,[11,12] Aurora-A-selective MLN8054,[13] and Aurora-B-selective AZD1152[14,15], have shown promising in vivo antitumor activity and entered clinical trials for the treatment of various cancers.

Pyrrole−indoline-2-ones were among the first structures identified as kinase inhibitors and have been intensively studied for the inhibition of VEGFR,[a] c-Kit, FLT3, PDGFR-α/β, and CSF-1-R.[16] The first compound of this type reaching the clinic was sunitinib (Figure 1), which is approved for the treatment of advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST). Compound **1** (SU6668)[16] is the precedent to sunitinib, originally developed as a multiple-kinase inhibitor for VEGFR-2, PDGFR, and FGFR. In a follow-up proteomic study, it is also found to inhibit Aurora kinases.[17] Sharing a similar indolin-2-one scaffold with the reported Aurora B inhibitor Hesperadin,[18] compound **1** inhibited Aurora A with an IC_{50} value of 438.5 nM [determined in house (see Figure 1)]. This finding led us to hypothesize that Aurora kinase inhibitors could be designed on the basis of this scaffold that would have a different inhibition profile.

In this paper, we report the synthesis of a series of new pyrrole−indoline-2-ones of scaffold **A** (Figure 1), the structure−activity relationship of these compounds for the inhibition of Aurora kinases, and the finding that selective inhibitors of Aurora A and Aurora B can be designed. Sulfonamido substituents at the C-5 position of scaffold **A** greatly improved the activity for both Aurora A and Aurora B inhibition. The carboxyethyl group at the C-3′ position of the pyrrole (X = COOH) provided selective inhibitors of Aurora A. Compounds **33** and **47**, differing only by a single functionality, are selective Aurora A and Aurora B inhibitors, respectively. Docking experiments attributed the selectivity to the affinity of the carboxyl group for residues Arg220 and Thr217 in Aurora A and Lys164 and Glu161 in Aurora B. Compounds **33** and **47** will serve as tools for the study of biological functions for Aurora kinases.

Results and Discussion

For the initial exploration of the structure−activity relationship of pyrrole−indolin-2-ones of scaffold **A** as Aurora kinase inhibitors, we first varied the substituents on the pyrrole moiety by the synthetic methods illustrated in Schemes 1 and 2. 2-Formylpyrroles **5a**−**c** fused with cycloalkanones as

*To whom correspondence should be addressed. Telephone: +886 2 2695 6933, ext. 2501. Fax: +886 2 2695 7474. E-mail: lukehuang0226@gmail.com.

[a] Abbreviations: ABL1 (ABL), c-abl oncogene 1 receptor tyrosine kinase; AKT1 (PRKBA), *v*-akt murine thymoma viral oncogene homologue 1; ALK, anaplastic lympoma kinase; B-Raf, *v*-raf murine sarcoma viral oncogene homologue B1; CDC2, cell division control protein 2 homologue; CDI, 1,1-carbonyldiimidazole; cdk2, cyclin-dependent kinase 2; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; C-Raf, *v*-raf leukemia viral oncogene 1; CSF-1-R (FMS), colony-stimulating factor 1 receptor; EGFR, epidermal growth factor receptor; EPHA1, EPH receptor A1; ERBB2 (HER2), V-erb-b2 erythroblastic leukemia viral oncogene homologue 2; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumors; GSK3B (GSK3 β), glycogen synthase kinase 3; IC_{50}, half-maximal inhibition; IGF-1R, insulin-like growth factor 1 receptor; JAK2, Janus-activated kinase 2; c-Kit, stem cell factor receptor; MAPK14 (p38α), mitogen-activated protein kinase 14; c-Met, hepatocyte growth factor receptor; PDGFR-α/β, platelet-derived growth factor receptor α/β; PDK1, 3-phosphoinositide-dependent protein kinase; PI3K, phosphoinositide 3-kinase; PLK1, polo-like kinase; pS10-H3, histone H3 serine-10 phosphorylation; RCC, renal cell carcinoma; TFA, trifluoroacetic acid; mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor receptor.

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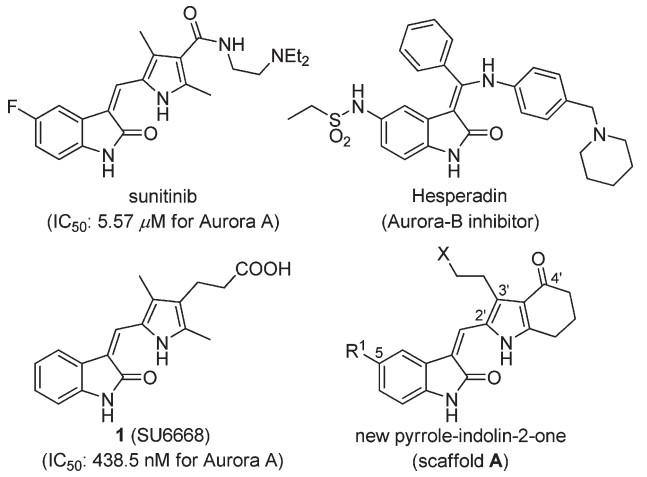
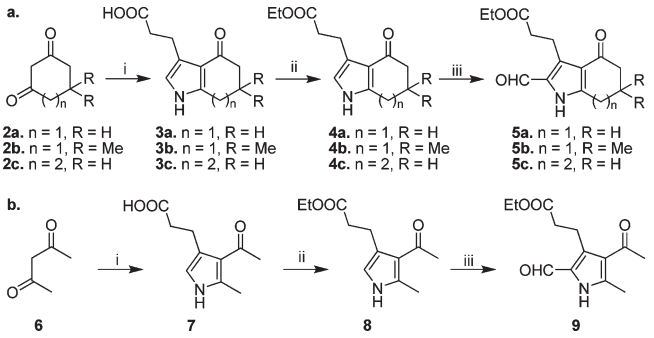


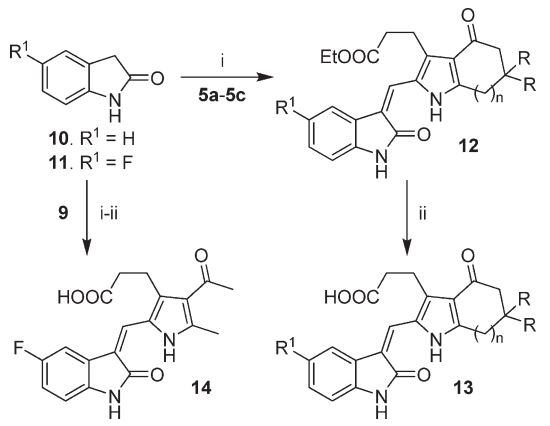
Figure 1. Structure of sunitinib, Hesperadin, **1**, and new pyrrole−indolin-2-one (scaffold **A**). The enzymatic IC_{50} values of sunitinib and **1** were determined in house by radiometric assay as described in the Experimental Section.

Scheme 1. Synthesis of 2-Formylpyrroles **5a**−**c** and **9** as the Precursors[a]



[a] Reagents and conditions: (i) 5-aminolevulinic acid hydrochloride, NaOAc, H_2O, 100 °C, 16 h, 75−87%; (ii) H_2SO_4 (catalytic), EtOH, reflux, 12 h, >99%; (iii) $CH(OMe)_3$, TFA, 19−21%.

Scheme 2. Synthesis of Pyrrole−Indolin-2-ones **12**−**14** from **5a**−**c** and **9**[a]



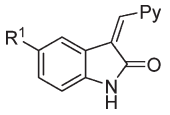
[a] Reagents and conditions: (i) piperidine, EtOH, reflux, 12 h; (ii) (a) NaOH, EtOH, (b) 3.0 N HCl.

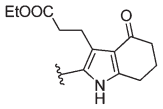
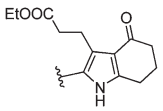
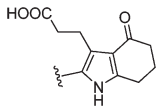
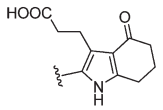
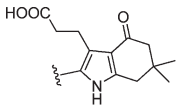
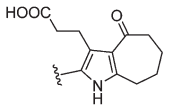
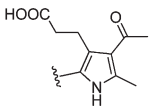
the precursors were synthesized by the reaction of diketones **2a**−**c** with 5-aminolevulinic acid hydrochloride in the presence of NaOAc in H_2O to provide the corresponding pyrroles **3a**−**c**, respectively, in 75−87% yield by Knorr pyrrole synthesis (Scheme 1a).[19] Esterification of **3a**−**c** with EtOH produced **4a**−**c**, respectively, which were formylated with trimethylorthoformate [$CH(OMe)_3$] in TFA[20] to give **5a**−**c**, respectively, in 19−21% yield. Application of the same methods with 2,4-pentanedione (**6**) as the starting material gave 2-formylpyrrole **9** through intermediates **7** and **8** (Scheme 1b). Compounds **5a**−**c** were reacted with indolin-2-one **10** or **11** via aldol condensation under basic conditions to give the corresponding pyrrole−indolin-2-one **12** (Scheme 2). Subsequent saponification converted **12** to **13**. For the preparation of pyrrole−indolin-2-one **14**, pyrrole **9** was reacted with **11** by the aforementioned methods.

In the formylation step for the synthesis, application of the traditional Vilsmeier−Haack reaction did not provide 2-formylpyrrole **5a**−**c** and **9**, possibly due to the formation of the vinyl chloride functionality from the carbonyl group.[21] The reaction was accomplished with $CH(OMe)_3$ in TFA, and the resulting 2-formylpyrroles **5a**−**c** and **9** were used directly for the next step without optimization of the reaction conditions.

The IC_{50} values of pyrrole−indolin-2-ones **12**−**14** for the inhibition of Aurora kinases are presented in Table 1. Compounds **13a** and **13b** that contain the carboxyethyl group on the pyrrole moiety were more potent than their ethyl ester analogues **12a** and **12b**, respectively, for Aurora A inhibition. The unsubstituted 4′-oxo-4′,5′,6′,7′-tetrahydroindole moiety

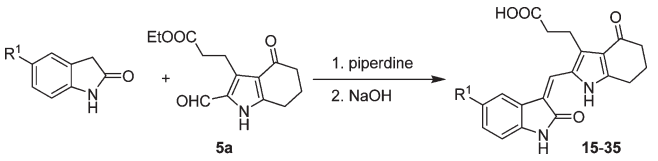
Table 1. Inhibition of the Kinase Activities of Aurora A and Aurora B by Pyrrole−Indolin-2-ones **12a**, **12b**, **13a**−**d**, and **14**

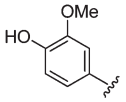
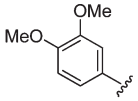
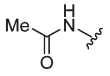
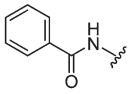
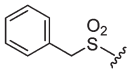
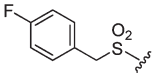


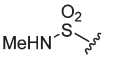
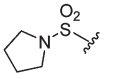
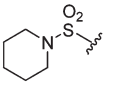
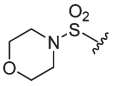
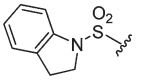
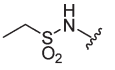
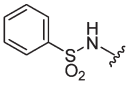
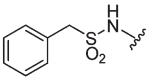
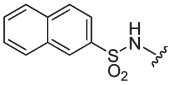
compd	R^1	Py	enzyme IC_{50} (μM)[a]	
			Aurora A	Aurora B
12a	H		1.78	(2.3%)[b]
12b	F		1.98	(3.0%)
13a	H		0.208	(13.0%)
13b	F		0.178	(11.6%)
13c	F		0.456	(17.3%)
13d	F		(45.5%)	(2.0%)
14	F		0.362	(17.5%)

[a] The IC_{50} values were averaged from two independent dose−response curves; the variation was generally <15%. [b] The numbers in parentheses are the percent inhibition values of compounds at 1.0 μM.

Table 2. Synthesis of 5-Substituted Pyrrole−Indolin-2-ones **15**−**35** and Their Inhibition of the Kinase Activities for Aurora A and Aurora B



compd	R^1	enzyme IC_{50} (μM)[a]	
		Aurora A	Aurora B
15	Br	0.210	(6.8%)[b]
16	NO_2	0.724	(3.4%)
17		0.357	(12.4%)
18		0.560	(5.1%)
19		0.252	(12.8%)
20		0.720	(14.2%)
21		0.057	(7.0%)
22		0.039	(32.5%)
23		0.271	(11.2%)
24		0.443	(15.5%)
25		0.061	(34.1%)

compd	R^1	enzyme IC_{50} (μM)[a]	
		Aurora A	Aurora B
26		0.031	(2.6%)
27		0.021	1.72
28		0.007	0.441
29		0.014	0.495
30		0.029	1.87
31		0.008	0.292
32		0.034	(7.3%)
33		0.012	0.156
34		0.063	0.402
35		(40.6%)	(21.0%)

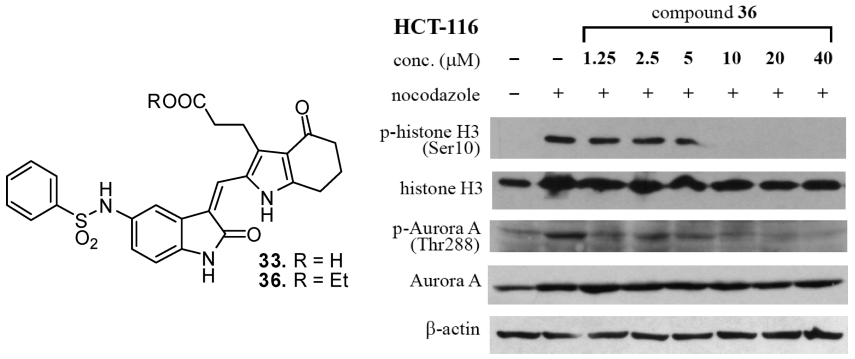
[a] The IC_{50} values were averaged from two independent dose−response curves; the variation was generally <15%. [b] The numbers in parentheses are the percent inhibition values of compounds at 1.0 μM.

in compound **13b** was more potent than its analogous 6′-dimethyl-substituted **13c**, seven-membered **13d**, and acyclic **14**. Therefore, the pyrrole moiety of **13b** that originated from **5a** served as the template for optimization. Selective inhibition of Aurora A over Aurora B was observed on these compounds (Table 1).

For further investigation of the structure−activity relationship, a series of pyrrole−indolin-2-ones **15**−**35** possessing various substituents at the C-5 position[22] were synthesized and evaluated (Table 2). In comparison with compound **13b** (R = F), the potencies of compounds **15**−**20** possessing a bromo, nitro, aryl, or amido group were not improved for Aurora A inhibition. Ethyl- and allylsulfonyl substitution gave compounds **21** and **22** with improved activity (IC_{50} = 0.057 and 0.039 μM, respectively) versus benzyl- and 4-fluorobenzylsulfonyl derivatives **23** and **24**. Sulfamoyl substitutions greatly improved the activity of compounds **25**−**31**, with IC_{50} values of <0.1 μM for Aurora A. Pyrrolidin-1-ylsulfonyl derivative **28** was the most potent in this series with an IC_{50} of 7 nM for Aurora A and also showed moderate inhibition of Aurora B (IC_{50} = 0.441 μM). For 5-indolin-1-ylsulfonyl derivative **31**, the potency was similar to that of **28** for Aurora A with a 1.7-fold improvement for Aurora B (IC_{50} = 0.292 μM). For pyrrole−indolin-2-ones **32**−**34** bearing C-5 alkyl- or aryl-sulfonamido substituents, the activity was also potent against Aurora A. Compound **33** was most active against Aurora B in this series with an IC_{50} value of 0.156 μM and also showed activity (IC_{50} = 12 nM) comparable to that of compound **28** against Aurora A. Replacement of the phenylsulfonamido group with a benzylsulfonamido or 2-naphthylsulfonamido group reduced the potency for both Aurora A and Aurora B inhibition (see compounds **34** and **35** in Table 2).

Potent compounds **28**, **31**, and **33** (Table 2) lacked antiproliferative activity in HCT-116 cells ($IC_{50} > 10$ μM). The lack of activity in the cell-based assay was hypothesized to be from poor cell membrane permeability caused by the carboxylic acid group. We thus analyzed compound **36**, the ethyl ester analogue to **33**, in the cell-based assay, and the compound was active (see Table 3). In addition, **36** induced a

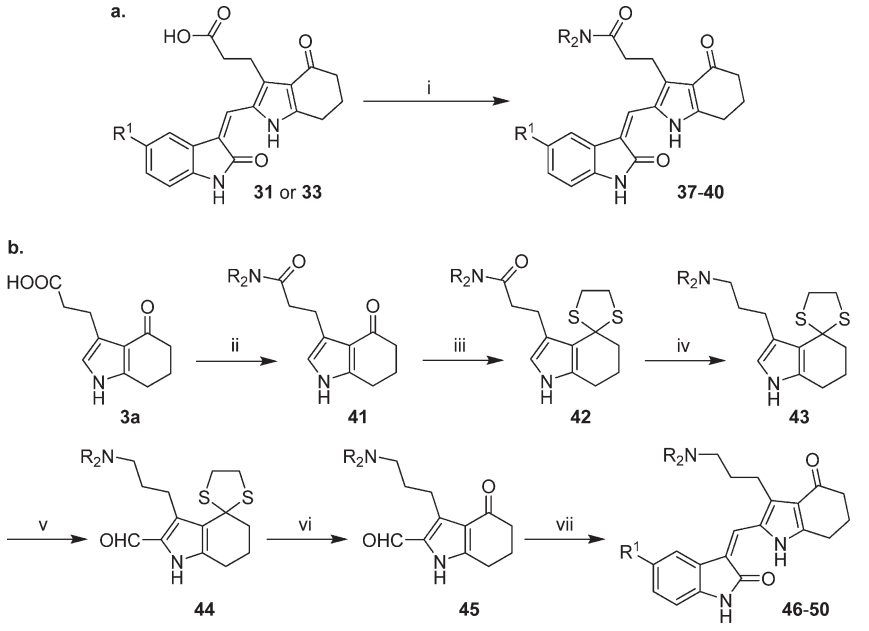
Table 3. Enzymatic and Cellular Activities of Compounds **33** and **36**



	IC_{50} (μM)[a]				
compd	Aurora A	Aurora B	HCT-116	HCT-116[b]	HT-29
33	0.012 ± 0.001	0.156 ± 0.012	>10	>10	>10
36	0.084 ± 0.005	0.214 ± 0.020	3.74 ± 0.54	1.02 ± 0.12	3.23 ± 0.32

[a] The IC_{50} values were averaged from two independent dose−response curves. [b] The concentration that reduced the level of [^{3}H]thymidine incorporation by 50%.

Scheme 3. Preparation of Compounds **37**−**40** and **46**−**50**[a]

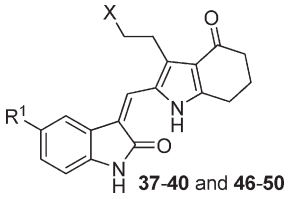


[a] Reagents and conditions: (i) R_2NH, CDI, CH_2Cl_2, 66−98%; (ii) CDI, CH_2Cl_2, HNR_2, 73−96%; (iii) ethane-1,2-dithiol, $BF_3 \cdot OEt_2$, THF, 85−93%; (iv) $LiAlH_4$, THF, reflux, 60−96%; (v) DMF, $POCl_3$, CH_2Cl_2, 71−97%; (vi) $HgCl_2$, MeOH, $CaCO_3$, 66−93%; (vii) indolin-2-ones, piperidine, EtOH, reflux, 12 h, 45−97%.

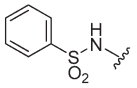
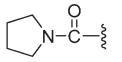
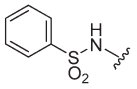
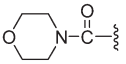
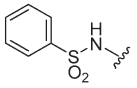
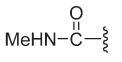
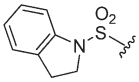
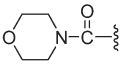
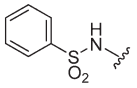
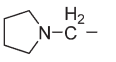
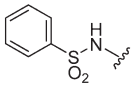
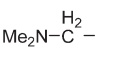
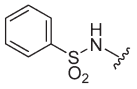
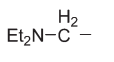
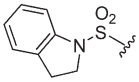
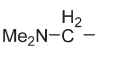
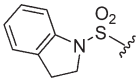
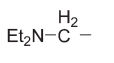
complete suppression in phosphorylation of the substrate of Aurora kinases, histone H3 at serine 10, which is regarded as a biomarker of Aurora B inhibition in HCT-116 cells (Table 3).[23] Decreased levels of phospho-Aurora A (pThr288)[12] were also observed. As an ester analogue to **33**, compound **36** might possess better cell permeabilizing ability, thus demonstrating cellular activity in its original form or acid form (i.e., **33**) after entering the cell.

To improve the activity within the cell and to replace the potentially labile ester group in compound **36**, we synthesized a series of amides and amine analogues of compounds **31** and **33** as illustrated in Scheme 3. The preparation of amide analogues **37**−**40** was straightforward from the reaction of **31** or **33** with different amines using CDI as the coupling agent (Scheme 3a). The preparation of amine analogues **46**−**50**, however, required the protection−deprotection methodology (Scheme 3b). Compound **3a** was coupled with different amines using CDI, and the obtained amide **41** was protected by ethane-1,2-dithiol to produce compound **42**. Hydride reduction of **42** provided amine **43**, which was then formylated by the Vilsmeier−Haack method to give compound **44**. Removal of the dithilane protection in **44** by mercuric chloride ($HgCl_2$) under basic conditions gave 2-formylpyrrole **45**. After condensation with indolin-2-ones, compound **45** was converted to pyrrole−indolin-2-ones **46**−**50** possessing the amino group in the side chain. In the search for protection methods for compound **41**, we found the use of ethylene glycol with an acid catalyst was not feasible because the conjugation between the pyrrole nitrogen and carbonyl group deactivates both functions.[24] Use of ethane-1,2-dithiol as an alternative,

Table 4. Enzymatic and Cellular Activities of Compounds **37**−**40** and **46**−**50**



37-40 and **46-50**

compd	R^1	X	enzyme IC_{50} (μM)[a]		antiproliferation IC_{50} (μM)[a]		
			Aurora A	Aurora B	HCT-116	Hela	HT-29
37			0.218	0.719	>10	>10	>10
38			0.281	0.906	>10	>10	>10
39			0.117	0.320	>10	>10	>10
40			0.563	3.154	>10	>10	>10
46			2.17	0.310	>10	>10	3.318
47			2.19	0.235	3.69	7.80	2.97
48			2.45	0.356	>10	8.61	>10
49			2.27	0.312	0.90	1.62	0.75
50			2.34	0.616	2.66	3.27	2.13

[a] The IC_{50} values were averaged from two independent dose−response curves; the variation was generally <15%.

which is not reported for the protection of 4-oxo-4,5,6,7-tetrahydroindoles, gave the corresponding product **42** in high yields. The protection of the 4-oxo group also improved the yield of the formylation step from **43** to **44** in comparison with the step from **4a** to **5a** shown in Scheme 1.

Table 4 summarizes the activities of compounds **37**−**40** and **46**−**50** in biochemical assays and revealed their antiproliferative activities on HCT-116, HeLa, and HT-20 cells. In comparison with those of carboxylic acid analogues **31** and **33**, the potency of compounds **37**−**40** with an amido side chain decreased significantly against Aurora A (~10−70-fold) and moderately against Aurora B. Surprisingly, the substantial loss of activity for Aurora A (IC_{50} > 2.0 μM, ~200-fold less potent) and retention of Aurora B inhibition were observed for compounds **46**−**50** with an amino side chain. The results indicate that the carboxyl group is important for Aurora A inhibition but not for Aurora B and could be considered as the change in the inhibition profile form Aurora A to Aurora B by a single functionality variation. Because the indolin-2-one would bind to the hinge region,[25] the finding that different equivalent residues interacted with the carboxyl group of **31** and **33** in Aurora A and Aurora B will be helpful for the development of selective inhibitors. Targeting the pocket near the C-5 position, however, would promote the activities for both kinases (Table 2). Compounds **46**−**50** showed better antiproliferative activity than **31** and **33** on cancer cells, and we attributed the cellular activity to membrane-penetrating ability as the predescribed ester **36**.

In the Western blot analysis shown in Figure 2A, compound **47** exhibited an apparent suppression of phosphorylated histone H3 at serine 10 in HCT-116 cells equivalent to that for compound **36** (cf. Table 3). A reduction of pSer10 was observed when cells were treated with both compounds at a concentration of 10 μM. However, the suppression of phospho-Aurora A (pThr288) by compound **47** was not as significant as for compound **36**. Compound **47** also demonstrated the same cell cycle profile with Aurora kinase inhibitors from literature,[11,26] for the incubation of HCT-116 cells

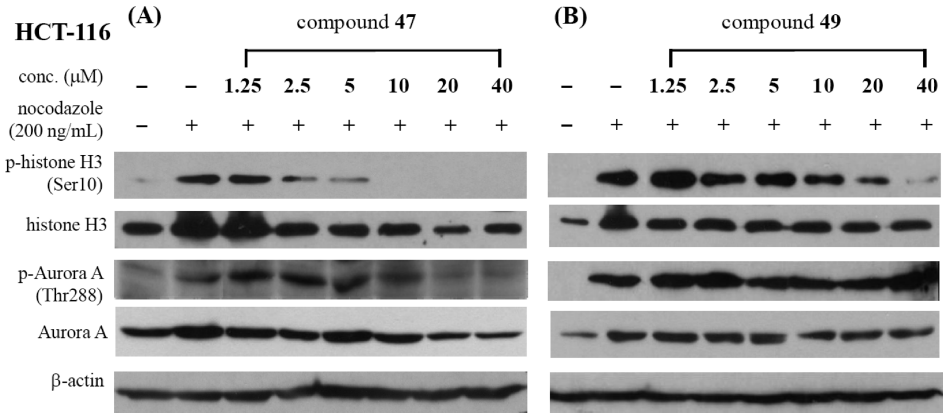


Figure 2. Western blot analysis of phospho-histone H3 and phospho-Aurora A (T288) in HCT-116 cells by compounds **47** and **49**. An antibody recognizing β-actin was used as a loading control.

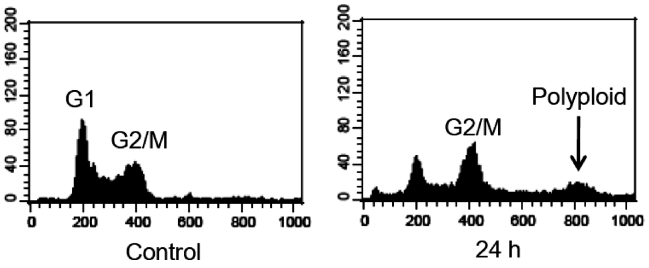


Figure 3. Cell cycle profile of HCT-116 cells treated with 4 μM compound **47** for 24 h.

with **47** for 24 h resulted in an increase of tetraploid 4 N DNA and multinucleated octoploid (≥8 N DNA) populations (Figure 3). Because compounds **36** and **47** presented similar enzymatic and cellular activities for Aurora B with comparable antiproliferative IC_{50} values, it is likely to refer the antiproliferative effects of both compounds to Aurora B inhibition. However, the inhibition of other kinases could not be excluded because **36** and **47** shared a similar scaffold with the multiple-kinase inhibitor sunitinib.[16] To explore the inhibition profiles of **36** and **47** against various kinases, we first used a radiometric method to examine both compounds against a panel of 30 kinases. The results revealed that **47** hit the reported targets of sunitinib, including VEGFR-2, c-Kit, FLT3, PDGFR-β, and CSF-1-R with IC_{50} values of $<1.0\,\mu$M while compound **36** was less active against c-Kit, PDGFR-β, and CSF-1-R in comparison with **47** ($IC_{50} > 1.0\,\mu$M) (see Table 5). An extensive test was conducted using **36** and **47** at 1.0 μM against a panel of 442 kinases on Ambit Biosciences Kinome*scan scan*Max plateform.[27] Kinases, including AXL, DDR1, FLT3, GRK7, LCK, LOK, MAP4K3, MAP4K5, MERTK, MUSK, PHKG1, PIP5K2C, RET, and TRK, were found to be inhibited significantly by both compounds with a percentage of control of < 10% (see the table in the Supporting Information). As for compound **49** with the best antiproliferative activity in this series, the inhibition of pSer10 and pT228 was inferior to that of **36** and **47** (Figure 2B). The contribution of other targets to the antiproliferative activity of **49** could not be ruled out.

To determine the structural basis of compounds **33** and **47** for the different selective inhibition profiles, we used docking simulations to model the binding modes. After energy minimization, both compounds fit the ATP pocket of Aurora A and Aurora B as shown in Figure 4. For Aurora B, compounds **33** and **47** formed two H-bonds from N^1−H and

Table 5. Kinase Profiling of **36** and **47** by the Radiometric Method

	% inhibition at 1.0 μM	
kinase tested	compound **36**	compound **47**
ABL1 (ABL)[a]	31	−17
AKT1 (PRKBA)[a]	11	9
ALK[a]	80	85
CDC2[b]	33	12
cdk2/cyclin A[b]	71	46
CHK1[b]	10	58
CHK2[b]	17	56
CSF-1-R (FMS)[a]	34	56
EGFR[b]	5	4
EGFR (T790M)[b]	14	8
EPHA1 (EphA1)[a]	29	24
ERBB2 (HER2)[a]	−28	−19
FGFR-1[b]	77	41
FLT3[b]	97	95
GSK3B (GSK3 β)[a]	47	24
IGF-1R[b]	24	6
JAK2[a]	30	−3
c-Kit[b]	41	65
MAPK14 (p38α)[a]	4	11
c-Met[b]	32	32
PDGFR-β[b]	47	70
PDK1[a]	24	11
PI3K (p110α/p85α)[b]	11	5
PI3K (p110β/p85α)[b]	1	−2
PLK1[a]	−20	−24
mTOR[b]	9	25
B-Raf[b]	−1	2
B-Raf (V600E)[b]	3	−4
C-Raf[b]	−8	−7
VEGFR-2[b]	74	51

[a] Conducted by Ricerca Taiwan Ltd. [b] Conducted in house.

C^2=O groups with Glu171 and Ala173 in the hinge region and two H-bonds from the oxygen atom in sulfonamide with Lys103 and Lys122 (Figure 4A,B). The binding was similar to that of Hesperadin[25] because they shared the same indolin-2-one scaffold. An additional hydrogen bonding interaction was found for the carboxyl group in **33** with Lys122, and the interaction was absent in **47** possessing the dimethylamino group at the same position. We rationalized that the contribution of the additional H-bond would not be important for the activity because similar activity was observed for compounds **33** and **47** in the inhibition of Aurora B.

The interaction of **33** and **47** with Aurora A was different from that with Aurora B, because the N^1-H group and the

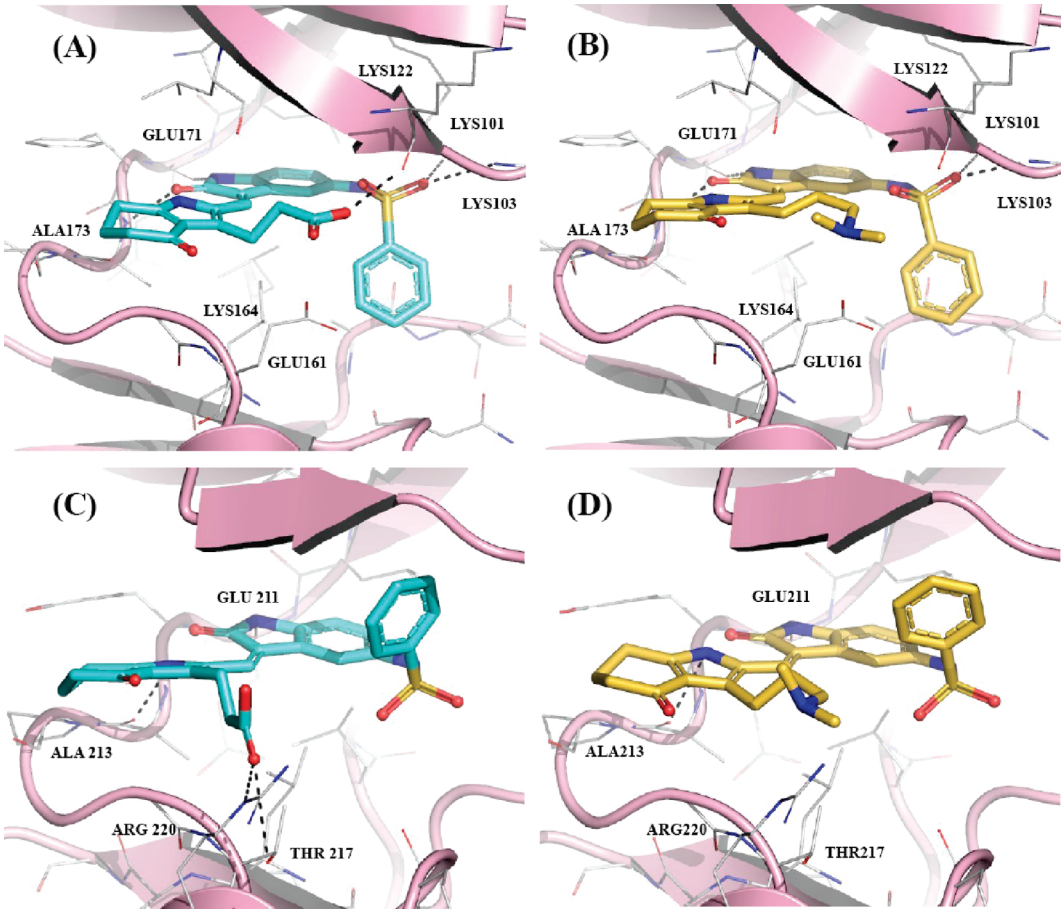


Figure 4. Docked binding modes of compounds **33** and **47** in the ATP binding site of Aurora A and Aurora B: (A) **33** in Aurora B, (B) **47** in Aurora B, (C) **33** in Aurora A, and (D) **47** in Aurora A. Compounds are shown as light blue or yellow sticks; hydrogen bonds are shown as dashed gray line, and the oxygen, nitrogen, and sulfur atoms are colored red, blue, and orange, respectively.

pyrrole N-H group were responsible for hinge binding [Glu211 and Ala213 (see Figure 4C,D)]. The carboxyl group in **33** formed two H-bonds with Arg220 and Thr217,[28] but such interaction was not found for the dimethylamino group at the same position in **47**. The substantial shift in IC_{50} from **33** to **47** (12 nM to 2.19 μM) for Aurora A inhibition would imply the importance of H-bonds from the carboxyl group. The poor interaction of the amino groups with Aurora A deduced from the docking experiments also explained the similar IC_{50} values of compounds **46**−**50**. As the residues equivalent to Arg220 and Thr217, respectively, in Aurora A, Lys164 and Glu161 in Aurora B could not form strong H-bonds with the carboxyl group in **33**. As a result, conversion of the carboxyl to an amino group at the side chain of the pyrrole caused a great loss of activity for Aurora A and retained that for Aurora B, as demonstrated in compounds **33** and **47**. These results revealed the possibility of designing a single appropriate functionality for selective Aurora A or Aurora B inhibitors by targeting these residues.

Conclusion

In conclusion, we synthesized a series of pyrrole−indolin-2-ones and explored their inhibition profile against Aurora kinases. Varying the substituents at the C-5 position on scaffold **A** showed the same tendency for activity against Aurora A and Aurora B. The carboxyethyl group on the pyrrole ring was important for Aurora A inhibition but not for Aurora B. Results of computational modeling indicated that the equivalent residues Arg220 and Thr217 in Aurora A and Lys164 and Glu161 in Aurora B were responsible for the different inhibition profile. Targeting the residues would thus be helpful in the development of selective inhibitors for Aurora kinases. Consistent results in the enzymatic activity were found for compounds **47** and **36** (the ethyl ester analogue to **33**), which showed antiproliferative effects in cancer cells and suppression of phosphorylation of substrates for Aurora A and Aurora B at the cellular level.

Experimental Section

General Procedure. Reagents were used as purchased without further purification. 5-Substituted indolin-2-ones were purchased from commercial sources or prepared according to literature procedures.[22] Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was conducted using Merck Reagents Silica Gel 60 (particle size of 0.063−0.200 mm, 70−230 mesh ASTM). Proton NMR spectra were recorded on a Bruker (300 MHz) spectrometer with $CDCl_3$ and DMSO-d_6 as solvents. Multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). ESI-MS spectra were recorded with an Applied Biosystems API 300 mass spectrometer. The purities of the compounds were greater than 95% as determined by reversed-phase HPLC.

General Procedure for the Synthesis of Pyrroles 3a−c and 7. A mixture of 5-aminolevulinic acid hydrochloride (~0.30 mol, 1.0 equiv), diketone **2a**, **2b**, **2c**, or **6** (1.2 equiv), and sodium acetate (2.0 equiv) in water (125 mL) was heated at 100 °C for 16 h.

The solution was cooled to room temperature, and the resultant precipitate was filtered, washed with water (2 × 200 mL), and dried under vacuum to give the desired pyrrole **3a**, **3b**, **3c**, or **7**, respectively, as a yellow solid in 75−87% yield.

3-(4-Oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic acid (3a). Yield: 87%. ^{1}H NMR (DMSO-d_6): δ 11.02 (s, 1 H), 6.46 (s, 1 H), 2.77 (t, J = 7.7 Hz, 2 H), 2.70 (t, J = 6.0 Hz, 2 H), 2.42−2.48 (m, 2 H), 2.27 (t, J = 6.2 Hz, 2 H), 1.94−2.00 (m, 2 H). ESI-MS: m/z 208.0 $(M + H)^+$.

3-(6,6-Dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic acid (3b). Yield: 76%. ^{1}H NMR (DMSO-d_6): δ 10.99 (s, 1 H), 6.47 (s, 1 H), 2.74−2.81 (m, 2 H), 2.59 (s, 2 H), 2.43−2.48 (m, 2 H), 2.18 (s, 2 H), 1.02 (s, 6 H). ESI-MS: m/z 236.0 $(M + H)^+$.

3-(4-Oxo-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrol-3-yl)propanoic acid (3c). Yield: 75%. ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1 H), 6.42 (s, 1 H), 3.04 (t, J = 7.2 Hz, 2 H), 2.80−2.88 (m, 2 H), 2.57−2.65 (m, 4 H), 1.80−1.90 (m, 4 H). ESI-MS: m/z 222.0 $(M + H)^+$.

3-(4-Acetyl-5-methyl-1*H*-pyrrol-3-yl)propanoic acid (7). Yield: 85%. ^{1}H NMR (DMSO-d_6): δ 11.96 (brs, 1 H), 10.95 (s, 1 H), 6.39 (s, 1 H), 2.80 (t, J = 7.7 Hz, 2 H), 2.37−2.45 (m, 5 H), 2.30 (s, 3 H). ESI-MS: m/z 196.0 $(M + H)^+$.

General Procedure for the Synthesis of Esters 4a−c and 8. Pyrrole **3a**, **3b**, **3c**, or **7** (∼0.25 mol, 1.0 equiv) in ethanol was added with sulfuric acid (1.0 mL). The reaction mixture was heated at reflux for 12 h. The solution was concentrated under reduced pressure, and the resultant solids were washed with water (2 × 200 mL). The solids were dried under vacuum to give the desired ester **4a**, **4b**, **4c**, or **8**, respectively, as a yellow solid in >99% yield.

Ethyl 3-(4-Oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoate (4a). ^{1}H NMR (DMSO-d_6): δ 11.03 (s, 1 H), 6.47 (s, 1 H), 4.03 (q, J = 7.1 Hz, 2 H), 2.77−2.83 (m, 2 H), 2.70 (t, J = 6.2 Hz, 2 H), 2.50−2.53 (m, 2 H), 2.24−2.31 (m, 2 H), 1.93−2.01 (m, 2 H), 1.16 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 236.0 $(M + H)^+$.

Ethyl 3-(6,6-Dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoate (4b). ^{1}H NMR (DMSO-d_6): δ 11.00 (s, 1 H), 6.47 (s, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 2.79 (t, J = 7.7 Hz, 2 H), 2.58 (s, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.17 (s, 2 H), 1.15 (t, J = 7.1 Hz, 3 H), 1.00 (s, 6 H). ESI-MS: m/z 264.0 $(M + H)^+$.

Ethyl 3-(4-Oxo-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrol-3-yl)propanoate (4c). ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1 H), 6.41 (s, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 3.01 (t, J = 7.4 Hz, 2 H), 2.86−2.92 (m, 2 H), 2.59−2.69 (m, 4 H), 1.82−1.91 (m, 4 H), 1.22 (t, J = 7.2 Hz, 3 H). ESI-MS: m/z 250.0 $(M + H)^+$.

Ethyl 3-(4-Acetyl-5-methyl-1*H*-pyrrol-3-yl)propanoate (8). ^{1}H NMR (DMSO-d_6): δ 8.30 (s, 1 H), 6.39 (s, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 3.02 (t, J = 7.5 Hz, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.50 (s, 3 H), 2.43 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 224.0 $(M + H)^+$.

General Procedure for the Synthesis of 2-Formylpyrroles 5a−c and 9. To a trifluoroacetic acid solution (50 mL) containing compound **4a**, **4b**, **4c**, or **8** (∼10 g, 1.0 equiv) was added trimethyl orthoformate (3.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature, and stirred at room temperature for 2.0 h. To the solution were added ethyl acetate (250 mL), water (200 mL), and NaOH (18 g). The organic layer was collected and washed with saturated aqueous $NaHCO_3$ (200 mL), dried over $MgSO_4$(s), and concentrated under reduced pressure. The oily residue was purified by gravity column chromatography (50% EtOAc in hexanes) to give 2-formylpyrrole **5a**, **5b**, **5c**, and **9**, respectively, as a yellow solid in 19−21% yield.

Ethyl 3-(2-Formyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)-propanoate (5a). Yield: 21%. ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.28 (t, J = 7.1 Hz, 2 H), 2.87 (t, J = 6.2 Hz, 2 H), 2.74 (t, J = 7.1 Hz, 2 H), 2.50 (t, J = 6.2 Hz, 2 H), 2.11−2.20 (m, 2 H), 1.20 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 264.0 $(M + H)^+$.

Ethyl 3-(2-Formyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoate (5b). Yield: 20%. ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1 H), 9.73 (s, 1 H), 4.07 (q, J = 7.2 Hz, 2 H), 3.29 (t, J = 7.1 Hz, 2 H), 2.71−2.77 (m, 4 H), 2.38 (s, 2 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.12 (s, 6 H). ESI-MS: m/z 292.0 $(M + H)^+$.

Ethyl 3-(2-Formyl-4-oxo-1,4,5,6,7,8-hexahydrocyclohepta-[*b*]pyrrol-3-yl)propanoate (5c). Yield: 19%. ^{1}H NMR ($CDCl_3$): δ 10.21 (brs, 1 H), 9.71 (s, 1 H), 4.08 (q, J = 7.2 Hz, 2 H), 3.29 (t, J = 7.4 Hz, 2 H), 3.04 (t, J = 7.4 Hz, 2 H), 2.63−2.70 (m, 4 H), 1.88−1.95 (m, 4 H), 1.20 (t, J = 7.2 Hz, 3 H). ESI-MS: m/z 278.0 $(M + H)^+$.

Ethyl 3-(4-Acetyl-2-formyl-5-methyl-1*H*-pyrrol-3-yl)propanoate (9). Yield: 21%. ^{1}H NMR ($CDCl_3$): δ 10.25 (s, 1 H), 9.71 (s, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.31 (t, J = 7.2 Hz, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 2.62 (s, 3 H), 2.47 (s, 3 H), 1.21 (q, J = 7.1 Hz, 3 H). ESI-MS: m/z 252.0 $(M + H)^+$.

General Procedure for the Synthesis of Pyrroles 41a−c. Compound **3a** (∼5.0 g, 1.0 equiv) was suspended in CH_2Cl_2 (100 mL) and supplemented with CDI (1.2 equiv). The reaction mixture was stirred at room temperature for 3.0 h. To the solution was added dimethylamine, diethylamine, or pyrrolidine (2.0 equiv), and the solution was stirred at room temperature for 12 h. The solution was diluted with CH_2Cl_2 (200 mL) and washed with 0.1 N HCl (50 mL), saturated Na_2CO_3 (50 mL), and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$(s) and concentrated under reduced pressure to provide the desired **41a−c** as white solids in 73−96% yield.

***N*,*N*-Dimethyl-3-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)-propanamide (41a).** Yield: 73%. ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1 H), 6.45 (d, J = 1.8 Hz, 1 H), 3.11 (s, 3 H), 2.91−2.98 (m, 5 H), 2.77 (t, J = 6.2 Hz, 2 H), 2.68−2.72 (m, 2 H), 2.41−2.46 (m, 2 H), 2.06−2.13 (m, 2 H). ESI-MS: m/z 235.0 $(M + H)^+$.

***N*,*N*-Diethyl-3-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanamide (41b).** Yield: 96%. ^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1 H), 6.52 (s, 1 H), 3.35−3.49 (m, 4 H), 2.97−3.02 (m, 2 H), 2.78 (t, J = 6.2 Hz, 2 H), 2.69−2.75 (m, 2 H), 2.43−2.48 (m, 2 H), 2.09−2.16 (m, 2 H), 1.08−1.20 (m, 6 H). ESI-MS: m/z 263.0 $(M + H)^+$.

3-[3-Oxo-3-(pyrrolidin-1-yl)propyl]-6,7-dihydro-1*H*-indol-4(5*H*)-one (41c). Yield: 92%. ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1 H), 6.49 (s, 1 H), 3.50 (t, J = 6.9 Hz, 2 H), 3.44 (t, J = 6.9 Hz, 2 H), 2.95−3.02 (m, 2 H), 2.77 (t, J = 6.2 Hz, 2 H), 2.60−2.65 (m, 2 H), 2.42−2.47 (m, 2 H), 2.07−2.15 (m, 2 H), 1.88−1.95 (m, 2 H), 1.79−1.86 (m, 2 H). ESI-MS: m/z 261.0 $(M + H)^+$.

General Procedure for the Synthesis of Protected Pyrroles 42a−c. To a MeOH solution (50 mL) containing compounds **41a−c** (∼3.0 g, 1.0 equiv) and ethane-1,2-dithiol (2.0 equiv) was added $BF_3 \cdot OEt_2$ (0.50 equiv). The reaction mixture was stirred at room temperature for 12 h. The solution was mixed with water (100 mL), and the resultant precipitate was filtered and dried under vacuum to provide the desired **42a−c** as yellow solids in 85−93% yield.

***N*,*N*-Dimethyl-3-(1′,5′,6′,7′-tetrahydrospiro[[1,3]dithiolane-2,4′-indole]-3′-yl)propanamide (42a).** Yield: 93%. ^{1}H NMR ($CDCl_3$): δ 7.63 (s, 1 H), 6.46 (s, 1 H), 3.45−3.53 (m, 2 H), 3.33−3.40 (m, 2 H), 3.07−3.13 (m, 2 H), 3.00 (s, 3 H), 2.96 (s, 3 H), 2.69−2.75 (m, 2 H), 2.54 (t, J = 6.2 Hz, 2 H), 2.30−2.34 (m, 2 H), 1.99−1.92 (m, 2 H). ESI-MS: m/z 311.0 $(M + H)^+$.

***N*,*N*-Diethyl-3-(1′,5′,6′,7′-tetrahydrospiro[[1,3]dithiolane-2,4′-indole]-3′-yl)propanamide (42b).** Yield: 92%. ^{1}H NMR ($CDCl_3$): δ 7.60 (s, 1 H), 6.45 (s, 1 H), 3.46−3.53 (m, 2 H), 3.28−3.42 (m, 6 H), 3.09−3.14 (m, 2 H), 2.68−2.74 (m, 2 H), 2.54 (t, J = 6.2 Hz, 2 H), 2.30−2.35 (m, 2 H), 1.93−1.99 (m, 2 H), 1.10−1.15 (m, 6 H). ESI-MS: m/z 339.0 $(M + H)^+$.

1-(Pyrrolidin-1-yl)-3-(1′,5′,6′,7′-tetrahydrospiro[[1,3]dithiolane-2,4′-indole]-3′-yl)propan-1-one (42c). Yield: 85%. ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1 H), 6.46 (s, 1 H), 3.45−3.55 (m, 4 H), 3.31−3.43 (m, 4 H), 3.07−3.16 (m, 2 H), 2.65−2.70 (m, 2 H), 2.50−2.56 (m, 2 H), 2.31−2.34 (m, 2 H), 1.78−2.01 (m, 6 H). ESI-MS: m/z 337.0 $(M + H)^+$.

General Procedure for the Synthesis of Amines 43a−c. To a THF solution (200 mL) containing protected pyrroles **42a−c** (∼5.0 g, 1.0 equiv) was added $LiAlH_4$ (4.0 equiv) at 0 °C.

The reaction mixture was warmed to room temperature and stirred for 12 h. The solution was mixed with 15% NaOH, and the insoluble white solids were filtered off. The filtrate was concentrated under reduced pressure to give the desired **43a**−**c** as a yellow liquid in 60−96% yield.

***N*,*N*-Dimethyl-3-(1′,5′,6′,7′-tetrahydrospiro[[1,3]dithiolane-2,4′-indole]-3′-yl)propan-1-amine (43a).** Yield: 95%. ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1 H), 6.44 (s, 1 H), 3.42−3.51 (m, 2 H), 3.33−3.40 (m, 2 H), 2.73−2.79 (m, 2 H), 2.54 (t, J = 6.1 Hz, 2 H), 2.30−2.45 (m, 4 H), 2.25 (s, 6 H), 1.92−1.99 (m, 2 H), 1.82−1.90 (m, 2 H). ESI-MS: m/z 297.0 $(M + H)^+$.

***N*,*N*-Diethyl-3-(1′,5′,6′,7′-tetrahydrospiro[[1,3]dithiolane-2,4′-indole]-3′-yl)propan-1-amine (43b).** Yield: 96%. ^{1}H NMR ($CDCl_3$): δ 7.59 (s, 1 H), 6.44 (s, 1 H), 3.45−3.48 (m, 2 H), 3.36−3.40 (m, 2 H), 2.72−2.77 (m, 2 H), 2.50−2.58 (m, 8 H), 2.31−2.35 (m, 2 H), 1.94−1.98 (m, 2 H), 1.82−1.86 (m, 2 H), 1.04 (t, J = 7.2 Hz, 6 H). ESI-MS: m/z 325.0 $(M + H)^+$.

3′-[3-(Pyrrolidin-1-yl)propyl]-1′,5′,6′,7′-tetrahydrospiro[[1,3]-dithiolane-2,4′-indole] (43c). Yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1 H), 6.45 (s, 1 H), 3.42−3.51 (m, 2 H), 3.31−3.41 (m, 2 H), 2.75−2.82 (m, 2 H), 2.50−2.57 (m, 8 H), 2.27−2.36 (m, 2 H), 1.87−2.00 (m, 4 H), 1.75−1.82 (m, 4 H). ESI-MS: m/z 323.0 $(M + H)^+$.

General Procedure for the Synthesis of the Protected 2-Formylpyrroles 44a−**c.** $POCl_3$ (2.0 equiv) was slowly added to DMF (50 mL) at 0 °C, and the resultant solution was stirred for 30 min. Amines **43a**−**c** (∼15 g, 1.0 equiv) was dissolved in 30 mL of DMF and added to the solution. The reaction mixture was heated at 120 °C for 60 min. The solution was cooled to room temperature, and 10 N NaOH was added until the pH reached 10. The solution was mixed with water, and the resultant solids were boiled in hot water, filtered, and dried under vacuum to provide the desired **44a**−**c** as yellow solids in 66−96% yield.

3′-[3-(Dimethylamino)propyl]-1′,5′,6′,7′-tetrahydrospiro[[1,3]-dithiolane-2,4′-indole]-2′-carbaldehyde (44a). Yield: 97%. ^{1}H NMR ($CDCl_3$): δ 9.55 (s, 1 H), 3.45−3.53 (m, 2 H), 3.35−3.43 (m, 2 H), 3.00−3.05 (m, 2 H), 2.61 (t, J = 6.2 Hz, 2 H), 2.37 (t, J = 7.3 Hz, 2 H), 2.27−2.32 (m, 2 H), 2.24 (s, 6 H), 1.91−2.00 (m, 4 H). ESI-MS: m/z 325.0 $(M + H)^+$.

3′-[3-(Diethylamino)propyl]-1′,5′,6′,7′-tetrahydrospiro[[1,3]-dithiolane-2,4′-indole]-2′-carbaldehyde (44b). Yield: 92%. ^{1}H NMR ($CDCl_3$): δ 9.57 (s, 1 H), 9.07 (s, 1 H), 3.46−3.54 (m, 2 H), 3.37−3.45 (m, 2 H), 2.98−3.05 (m, 2 H), 2.56−2.70 (m, 8 H), 2.27−2.34 (m, 2 H), 1.93−2.03 (m, 4 H), 1.09 (t, J = 7.1 Hz, 6 H). ESI-MS: m/z 353.0 $(M + H)^+$.

3′-[3-(Pyrrolidin-1-yl)propyl]-1′,5′,6′,7′-tetrahydrospiro[[1,3]-dithiolane-2,4′-indole]-2′-carbaldehyde (44c). Yield: 71%. ^{1}H NMR ($CDCl_3$): δ 9.54 (s, 1 H), 3.44−3.51 (m, 2 H), 3.34−3.42 (m, 2 H), 3.01−3.07 (m, 2 H), 2.61 (t, J = 6.3 Hz, 2 H), 2.48−2.55 (m, 6 H), 2.27−2.31 (m, 2 H), 1.91−2.03 (m, 4 H), 1.72−1.80 (m, 4 H). ESI-MS: m/z 351.0 $(M + H)^+$.

General Procedure for the Synthesis of the 2-Formylpyrroles 45a−**c.** Compounds **44a**−**c** (1.0 equiv) in a solution of 80% CH_3CN and 20% H_2O were mixed with $HgCl_2$ (2.2 equiv) and $CaCO_3$ (2.2 equiv). The reaction mixture was heated at reflux for 12 h. The solution was filtered through Celite, and the cake was washed with CH_2Cl_2. The filtrate was washed with aqueous NH_4Cl solution (5.0 M), water, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the desired **45a**−**c** as solids in 66−93% yield.

3-[3-(Dimethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde (45a). Yield: 66%. ^{1}H NMR ($CDCl_3$): δ 9.84 (s, 1 H), 3.08−3.14 (m, 2 H), 2.80−2.86 (m, 2 H), 2.48−2.52 (m, 2 H), 2.24−2.34 (m, 4 H), 2.20 (s, 6 H), 1.78−1.85 (m, 2 H). ESI-MS: m/z 249.0 $(M + H)^+$.

3-[3-(Diethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde (45b). Yield: 93%. ^{1}H NMR ($CDCl_3$): δ 9.82 (s, 1 H), 3.06−3.12 (m, 2 H), 2.84−2.88 (m, 2 H), 2.68−2.74 (m, 2 H), 2.40−2.66 (m, 6 H), 2.16−2.22 (m, 2 H), 1.77−1.83 (m, 2 H), 1.02 (t, J = 7.1 Hz, 6 H). ESI-MS: m/z 277.0 $(M + H)^+$.

4-Oxo-3-[3-(pyrrolidin-1-yl)propyl]-4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde (45c). Yield: 70%. ^{1}H NMR ($CDCl_3$): δ 9.69 (s, 1 H), 3.06−3.10 (m, 2 H), 2.84−2.90 (m, 2 H), 2.40−2.52 (m, 8 H), 2.12−2.20 (m, 2 H), 1.84−1.92 (m, 2 H), 1.72−1.80 (m, 4 H). ESI-MS: m/z 275.0 $(M + H)^+$.

General Procedure for the Synthesis of Pyrrole−**Indoline-2-ones 12**−**14, 15**−**36, and 46**−**50.** A mixture of 2-formylpyrrole **5a**, **5b**, **5c**, **9**, **45a**, **45b**, or **45c** (∼0.50 mmol, 1.0 equiv) and the corresponding indolin-2-one (1.0 equiv) was mixed with EtOH (5.0 mL) and piperidine (0.1 mL). The reaction mixture was heated at reflux for 12 h. The resultant precipitate was filtered and washed with EtOH to provide the corresponding pyrrole−indoline-2-one in ethyl ester form. The compound was suspended in MeOH and mixed with aqueous NaOH (3.0 equiv). The solution was heated at reflux until all the solids were dissolved. The solution was mixed with 3 N HCl, and the resultant precipitant was filtered, washed with MeOH, and dried in a vacuum oven at 50 °C to provide the desired pyrrole−indoline-2-one in acid form.

(*Z*)-Ethyl 3-{4-Oxo-2-[(2-oxoindolin-3-ylidene)methyl]-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoate (12a). Yield: 84%. ^{1}H NMR ($CDCl_3$): δ 13.49 (s, 1 H), 7.93 (s, 1 H), 7.61 (s, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 7.19 (dd, J = 7.6, 7.6 Hz, 1 H), 7.09 (dd, J = 7.6, 7.6 Hz, 1 H), 6.89 (d, J = 7.6 Hz, 1 H), 4.06 (q, J = 7.1 Hz, 2 H), 3.27 (t, J = 7.1 Hz, 2 H), 2.91 (t, J = 6.1 Hz, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 2.52 (t, J = 6.1 Hz, 2 H), 2.13−2.20 (m, 2 H), 1.18 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 379.0 $(M + H)^+$.

(*Z*)-Ethyl 3-{2-[(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoate (12b). Yield: 89%. ^{1}H NMR ($CDCl_3$): δ 13.49 (s, 1 H, NH), 7.73 (s, 1 H, NH), 7.59 (s, 1 H), 7.30 (dd, J = 8.5, 2.2 Hz, 1 H), 6.89 (dt, J = 2.3, 9.0 Hz, 1 H), 6.81 (dd, J = 8.4, 4.2 Hz, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 3.27 (t, J = 7.0 Hz, 2 H), 2.92 (t, J = 6.2 Hz, 2 H), 2.74 (t, J = 7.1 Hz, 2 H), 2.52 (t, J = 6.2 Hz, 2 H), 2.14−2.21 (m, 2 H), 1.19 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 397.0 $(M + H)^+$.

(*Z*)-3-{4-Oxo-2-[(2-oxoindolin-3-ylidene)methyl]-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (13a). Yield: 72%. ^{1}H NMR (DMSO-d_6): δ 13.76 (s, 1 H), 11.01 (s, 1 H), 7.76−7.78 (m, 2 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.90 (d, J = 7.7 Hz, 1 H), 3.15 (t, J = 7.4 Hz, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.38−2.43 (m, 2 H), 2.20−2.09 (m, 2 H).[29] ESI-MS: m/z 351.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (13b). Yield: 79%. ^{1}H NMR (DMSO-d_6): δ 13.79 (s, 1 H), 11.01 (s, 1 H), 7.83 (s, 1 H), 7.75 (dd, J = 9.2, 2.4 Hz, 1 H), 6.97 (dt, J = 9.4, 2.5 Hz, 1 H), 6.86 (dd, J = 8.4, 4.4 Hz, 1 H), 3.17 (t, J = 7.5 Hz, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.38−2.44 (m, 2 H), 2.02−2.09 (m, 2 H). ESI-MS: m/z 369.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (13c). Yield: 84%. ^{1}H NMR ($CDCl_3$): δ 13.78 (s, 1 H), 11.01 (s, 1 H), 7.81 (s, 1 H), 7.74 (dd, J = 9.2, 2.4 Hz, 1 H), 6.97 (dt, J = 9.4, 2.5 Hz, 1 H), 6.86 (dd, J = 8.4, 4.5 Hz, 1 H), 3.17 (t, J = 7.5 Hz, 2 H), 2.81 (s, 2 H), 2.31 (s, 2 H), 1.04 (s, 6 H). ESI-MS: m/z 397.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-4-oxo-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrol-3-yl}propanoic Acid (13d). Yield: 76%. ^{1}H NMR (DMSO-d_6): δ 13.86 (s, 1 H), 10.99 (s, 1 H), 7.81 (s, 1 H), 7.73 (dd, J = 9.2, 2.4 Hz, 1 H), 6.97 (dt, J = 9.4, 2.4 Hz, 1 H), 6.86 (dd, J = 8.4, 4.5 Hz, 1 H), 3.17 (t, J = 7.6 Hz, 2 H), 2.99−3.05 (m, 2 H), 2.59−2.65 (m, 2 H), 2.44 (t, J = 7.6 Hz, 2 H), 1.74−1.90 (m, 4 H). ESI-MS: m/z 383.0 $(M + H)^+$.

(*Z*)-3-{4-Acetyl-2-[(5-fluoro-2-oxoindolin-3-ylidene)methyl]-5-methyl-1*H*-pyrrol-3-yl}propanoic Acid (14). Yield: 58%. ^{1}H NMR (DMSO-d_6): δ 13.92 (s, 1 H), 10.99 (s, 1 H), 7.80 (s, 1 H), 7.74 (d, J = 9.2, 2.3 Hz, 1 H), 6.97 (dt, J = 9.3, 2.5 Hz, 1 H), 6.87 (dd, J = 8.4, 4.5 Hz, 1 H), 3.20 (t, J = 7.5 Hz, 2 H), 2.61 (s, 3 H), 2.41−2.47 (m, 5 H). ESI-MS: m/z 357.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Bromo-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (15). Yield: 71%. ^{1}H NMR (DMSO-d_6): δ 13.74 (s, 1 H), 11.12 (s, 1 H),

8.08 (d, J = 1.7 Hz, 1 H), 7.88 (s, 1 H), 7.31 (dd, J = 8.2, 1.7 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 3.19 (t, J = 7.5 Hz, 2 H), 2.92 (t, J = 6.0 Hz, 2 H), 2.38−2.44 (m, 2 H), 1.99−2.11 (m, 2 H). ESI-MS: m/z 429.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Nitro-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (16). Yield: 73%. ^{1}H NMR (DMSO-d_6): δ 13.52 (s, 1 H), 12.07 (brs, 1 H), 11.57 (s, 1 H), 8.73 (d, J = 2.3 Hz, 1 H), 8.04 (dd, J = 8.6, 2.3 Hz, 1 H), 8.02 (s, 1 H), 7.00 (d, J = 8.6 Hz, 1 H), 3.18 (t, J = 7.6 Hz, 2 H), 2.89 (t, J = 6.1 Hz, 2 H), 2.36−2.41 (m, 2 H), 1.98−2.09 (m, 2 H). ESI-MS: m/z 396.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(4-Hydroxy-3-methoxyphenyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (17). Yield: 72%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 11.01 (s, 1 H), 8.08 (s, 1 H), 8.02 (s, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.23 (s, 1 H), 7.21 (s, 1 H), 7.09 (dd, J = 9.0, 1.5 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 1 H), 6.84 (d, J = 8.2 Hz, 1 H), 3.86 (s, 3 H), 3.13 (t, J = 7.2 Hz, 2 H), 2.89 (t, J = 6.0 Hz, 2 H), 2.35−2.42 (m, 2 H), 2.13−2.23 (m, 2 H), 2.00−2.08 (m, 2 H). ESI-MS: m/z 473.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(3,4-Dimethoxyphenyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (18). Yield: 77%. ^{1}H NMR (DMSO-d_6): δ 13.70 (s, 1 H), 11.03 (s, 1 H), 7.93−8.10 (m, 2 H), 7.40 (d, J = 7.4 Hz, 1 H), 7.25 (s, 1 H), 7.21 (d, J = 7.0 Hz, 1 H), 7.00 (d, J = 7.4 Hz, 1 H), 6.92 (d, J = 7.3 Hz, 1 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.10−3.19 (m, 2 H), 2.84−2.95 (m, 2 H), 2.32−2.43 (m, 2 H), 2.20−2.32 (m, 2 H), 1.91−2.11 (m, 2 H). ESI-MS: m/z 487.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Acetamido-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (19). Yield: 56%. ^{1}H NMR (DMSO-d_6): δ 13.79 (s, 1 H), 12.08 (s, 1 H), 10.94 (s, 1 H), 9.84 (s, 1 H), 7.77 (d, J = 1.7 Hz, 1 H), 7.60 (s, 1 H), 7.39 (dd, J = 8.3, 1.7 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 3.10 (t, J = 7.3 Hz, 2 H), 2.91 (t, J = 6.1 Hz, 2 H), 2.52−2.56 (m, 2 H), 2.37−2.44 (m, 2 H), 2.04−2.09 (m, 2 H), 2.02 (s, 3 H). ESI-MS: m/z 408.0 $(M + H)^+$.

(*Z*)-3-{2-[(5-Benzamido-2-oxoindolin-3-ylidene)methyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (20). Yield: 70%. ^{1}H NMR (DMSO-d_6): δ 13.81 (s, 1 H), 12.09 (s, 1 H), 11.01 (s, 1 H), 10.20 (s, 1 H), 7.94−8.05 (m, 3 H), 7.67 (s, 1 H), 7.48−7.61 (m, 4 H), 6.89 (d, J = 8.3 Hz, 1 H), 3.12 (t, J = 7.4 Hz, 2 H), 2.92 (t, J = 6.0 Hz, 2 H), 2.38−2.45 (m, 2 H), 2.01−2.10 (m, 2 H). ESI-MS: m/z 470.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Ethylsulfonyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (21). Yield: 50%. ^{1}H NMR (DMSO-d_6): δ 13.69 (s, 1 H), 11.49 (s, 1 H), 8.35 (s, 1 H), 8.01 (s, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 3.19−3.30 (m, 4 H), 2.93 (t, J = 6.0 Hz, 2 H), 2.38−2.45 (m, 2 H), 2.01−2.10 (m, 2 H), 1.13 (t, J = 7.3 Hz, 3 H). ESI-MS: m/z 443.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Allylsulfonyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (22). Yield: 71%. ^{1}H NMR (DMSO-d_6): δ 13.67 (s, 1 H), 11.48 (s, 1 H), 8.32 (s, 1 H), 7.99 (s, 1 H), 7.63 (dd, J = 8.2, 1.6 Hz, 1 H), 7.08 (d, J = 8.2 Hz, 1 H), 5.67−5.77 (m, 1 H), 5.32 (d, J = 10.0 Hz, 1 H), 5.24 (d, J = 17.0 Hz, 1 H), 4.08 (d, J = 7.2 Hz, 2 H), 3.21 (t, J = 7.5 Hz, 2 H), 2.93 (t, J = 6.0 Hz, 2 H), 2.52−2.55 (m, 2 H), 2.38−2.45 (m, 2 H), 2.02−2.10 (m, 2 H). ESI-MS: m/z 455.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Benzylsulfonyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (23). Yield: 44%. ^{1}H NMR (DMSO-d_6): δ 13.66 (s, 1 H), 11.49 (brs, 1 H), 8.18 (s, 1 H), 7.91 (s, 1 H), 7.43 (dd, J = 8.1, 1.8 Hz, 1 H), 7.27−7.30 (m, 3 H), 7.17−7.22 (m, 2 H), 7.00 (d, J = 8.1 Hz, 1 H), 4.61 (s, 2 H), 3.20 (t, J = 7.6 Hz, 2 H), 2.94 (t, J = 6.1 Hz, 2 H), 2.51−2.57 (m, 2 H), 2.39−2.45 (m, 2 H), 2.03−2.10 (m, 2 H). ESI-MS: m/z 505.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(4-Fluorobenzylsulfonyl)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (24). Yield: 77%. ^{1}H NMR (DMSO-d_6): δ 13.67 (s, 1 H), 12.11 (s, 1 H), 11.49 (s, 1 H), 8.22 (d, J = 1.4 Hz, 1 H), 7.94 (s, 1 H), 7.40 (dd, J = 8.2, 1.7 Hz, 1 H), 7.19−7.26 (m, 2 H), 7.14 (t, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.2 Hz, 1 H), 4.63 (s, 2 H), 3.21 (t, J = 6.0 Hz, 2 H), 2.94 (t, J = 6.0 Hz, 2 H), 2.51−2.56 (m, 2 H), 2.39−2.46 (m, 2 H), 2.02−2.12 (m, 2 H). ESI-MS: m/z 523.0 $(M + H)^+$.

(*Z*)-3-{4-Oxo-2-[(2-oxo-5-sulfamoylindolin-3-ylidene)methyl]-4,5,6,7-tetrahydro-1*H*-indol-3-yl}propanoic Acid (25). Yield: 75%. ^{1}H NMR (DMSO-d_6): δ 13.67 (s, 1 H), 11.36 (brs, 1 H), 8.21 (d, J = 1.4 Hz, 1 H), 7.86 (s, 1 H), 7.65 (dd, J = 8.1, 1.5 Hz, 1 H), 7.21 (s, 2 H), 7.02 (d, J = 8.2 Hz, 1 H), 3.16 (t, J = 7.4 Hz, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.52−2.55 (m, 2 H), 2.37−2.43 (m, 2 H), 2.00−2.09 (m, 2 H). ESI-MS: m/z 430.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(*N*-Methylsulfamoyl)-2-oxoindolin-3-ylidene]-methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (26). Yield: 86%. ^{1}H NMR (DMSO-d_6): δ 13.71 (s, 1 H), 12.08 (brs, 1 H), 11.42 (s, 1 H), 8.20 (d, J = 1.4 Hz, 1 H), 7.94 (s, 1 H), 7.60 (dd, J = 8.2, 1.7 Hz, 1 H), 7.25 (q, J = 5.0 Hz, 1 H), 7.07 (d, J = 8.2 Hz, 1 H), 3.19 (t, J = 7.5 Hz, 2 H), 2.93 (t, J = 6.1 Hz, 2 H), 2.51−2.56 (m, 2 H), 2.40−2.44 (d, J = 5.0 Hz, 5 H), 2.02−2.10 (m, 2 H). ESI-MS: m/z 444.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(*N*,*N*-Dimethylsulfamoyl)-2-oxoindolin-3-ylidene]-methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (27). Yield: 87%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 12.04 (s, 1 H), 11.45 (s, 1 H), 8.21 (s, 1 H), 8.02 (s, 1 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 3.22 (t, J = 7.3 Hz, 2 H), 2.93 (t, J = 6.0 Hz, 2 H), 2.62 (s, 6 H), 2.52−2.56 (m, 2 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.02−2.11 (m, 2 H). ESI-MS: m/z 458.0 $(M + H)^+$.

(*Z*)-3-(4-Oxo-2-{[2-oxo-5-(pyrrolidin-1-ylsulfonyl)indolin-3-ylidene]methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (28). Yield: 61%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 11.44 (s, 1 H), 8.26 (d, J = 1.5 Hz, 1 H), 8.03 (s, 1 H), 7.61 (d, J = 9.8 Hz, 1 H), 7.08 (d, J = 8.2 Hz, 1 H), 3.22 (t, J = 7.4 Hz, 2 H), 3.13−3.18 (m, 4 H), 2.93 (t, J = 6.1 Hz, 2 H), 2.51−2.55 (m, 2 H), 2.38−2.45 (m, 2 H), 1.99−2.10 (m, 2 H), 1.62−1.68 (m, 4 H). ESI-MS: m/z 484.0 $(M + H)^+$.

(*Z*)-3-(4-Oxo-2-{[2-oxo-5-(piperidin-1-ylsulfonyl)indolin-3-ylidene]methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (29). Yield: 89%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 11.45 (s, 1 H), 8.18 (s, 1 H), 8.01 (s, 1 H), 7.53 (d, J = 8.2 Hz, 1 H), 7.09 (d, J = 8.2 Hz, 1 H), 3.22 (t, J = 7.4 Hz, 2 H), 2.85−2.95 (m, 6 H), 2.39−2.44 (m, 2 H), 2.02−2.10 (m, 2 H), 1.50−1.59 (m, 4 H), 1.31−1.39 (m, 2 H). ESI-MS: m/z 498.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Morpholinosulfonyl)-2-oxoindolin-3-ylidene]-methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (30). Yield: 72%. ^{1}H NMR (DMSO-d_6): δ 13.71 (s, 1 H), 11.49 (s, 1 H), 8.19 (d, J = 1.3 Hz, 1 H), 8.01 (s, 1 H), 7.54 (dd, J = 8.2, 1.5 Hz, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 3.59−3.69 (m, 4 H), 3.15−3.26 (m, 2 H), 2.93 (t, J = 6.0 Hz, 2 H), 2.86−2.90 (m, 4 H), 2.52−2.55 (m, 2 H), 2.38−2.44 (m, 2 H), 2.02−2.09 (m, 2 H). ESI-MS: m/z 500.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Indolin-1-ylsulfonyl)-2-oxoindolin-3-ylidene]-methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (31). Yield: 85%. ^{1}H NMR (DMSO-d_6): δ 13.60 (s, 1 H), 12.13 (brs, 1 H), 11.42 (s, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 7.93 (s, 1 H), 7.53−7.60 (m, 2 H), 7.20 (t, J = 7.7 Hz, 1 H), 7.13 (d, J = 7.3 Hz, 1 H), 6.91−7.02 (m, 2 H), 3.92 (t, J = 8.3 Hz, 2 H), 3.24 (t, J = 7.5 Hz, 2 H), 2.85−2.95 (m, 4 H), 2.51−2.54 (m, 2 H), 2.38−2.45 (m, 2 H), 2.00−2.10 (m, 2 H). ESI-MS: m/z 532.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Ethylsulfonamido)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (32). Yield: 62%. ^{1}H NMR (DMSO-d_6): δ 13.79 (s, 1 H), 11.03 (s, 1 H), 9.44 (s, 1 H), 7.68 (s, 1 H), 7.55 (s, 1 H), 7.06 (d, J = 8.5 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 3.00−3.16 (m, 4 H), 2.90−2.94 (m, 2 H), 2.38−2.46 (m, 2 H), 2.02−2.10 (m, 2 H), 1.46 (t, J = 7.2 Hz, 3 H). ESI-MS: m/z 458.0 $(M + H)^+$.

(*Z*)-3-(4-Oxo-2-{[2-oxo-5-(phenylsulfonamido)indolin-3-ylidene]-methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (33). Yield: 47%. ^{1}H NMR (DMSO-d_6): δ 13.72 (s, 1 H), 10.93

(s, 1 H), 7.73 (d, J = 7.3 Hz, 2 H), 7.46−7.63 (m, 4 H), 7.38 (s, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 6.70 (d, J = 8.2 Hz, 1 H), 3.08−3.15 (m, 2 H), 2.85−2.94 (m, 2 H), 2.52−2.55 (m, 2 H), 2.35−2.42 (m, 2 H), 1.99−2.06 (m, 2 H). ESI-MS: m/z 506.0 $(M + H)^+$.

(*Z*)-3-(4-Oxo-2-{[2-oxo-5-(phenylmethylsulfonamido)indolin-3-ylidene]methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (34). Yield: 56%. ^{1}H NMR (DMSO-d_6): δ 13.81 (s, 1 H), 12.11 (s, 1 H), 11.05 (s, 1 H), 9.55 (s, 1 H), 7.66 (s, 1 H), 7.50 (d, J = 1.2 Hz, 1 H), 7.28−7.41 (m, 6 H), 7.04 (dd, J = 8.3, 1.6 Hz, 1 H), 6.88 (d, J = 8.3 Hz, 1 H), 4.41 (s, 2 H), 3.15 (t, J = 7.4 Hz, 2 H), 2.94 (t, J = 5.9 Hz, 2 H), 2.39−2.45 (m, 2 H), 2.05−2.11 (m, 2 H). ESI-MS: m/z 520.0 $(M + H)^+$.

(*Z*)-3-(2-{[5-(Naphthalene-2-sulfonamido)-2-oxoindolin-3-ylidene]methyl}-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoic Acid (35). Yield: 77%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 12.09 (brs, 1 H), 10.94 (s, 1 H), 10.04 (s, 1 H), 8.37 (s, 1 H), 8.10 (d, J = 8.7 Hz, 2 H), 8.00 (d, J = 8.1 Hz, 1 H), 7.79 (dd, J = 8.6, 1.4 Hz, 1 H), 7.54−7.71 (m, 3 H), 7.50 (d, J = 1.1 Hz, 1 H), 6.76 (dd, J = 8.3, 1.5 Hz, 1 H), 6.68 (d, J = 8.3 Hz, 1 H), 3.10 (t, J = 7.3 Hz, 2 H), 2.89 (t, J = 5.8 Hz, 2 H), 2.32−2.44 (m, 2 H), 1.95−2.08 (m, 2 H). ESI-MS: m/z 556.0 $(M + H)^+$.

(Z)-Ethyl 3-(4-Oxo-2-{[2-oxo-5-(phenylsulfonamido)indolin-3-ylidene]methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)propanoate (36). Yield: 80%. ^{1}H NMR (DMSO-d_6): δ 13.74 (s, 1 H), 10.98 (s, 1 H), 7.72 (d, J = 7.5 Hz, 2 H), 7.50−7.62 (m, 4 H), 7.45 (s, 1 H), 6.71−6.77 (m, 2 H), 3.99 (q, J = 7.1 Hz, 2 H), 3.15 (t, J = 7.1 Hz, 2 H), 2.90 (t, J = 6.0 Hz, 2 H), 2.62 (t, J = 7.2 Hz, 2 H), 2.38−2.43 (m, 2 H), 2.02−2.07 (m, 2 H), 1.09 (t, J = 7.1 Hz, 3 H). ESI-MS: m/z 534.0 $(M + H)^+$.

(*Z*)-*N*-[2-Oxo-3-({4-oxo-3-[3-(pyrrolidin-1-yl)propyl]-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)indolin-5-yl]benzenesulfonamide (46). Yield: 45%. ^{1}H NMR (DMSO-d_6): δ 13.71 (s, 1 H), 10.96 (s, 1 H), 7.70 (d, J = 7.5 Hz, 2 H), 7.49−7.60 (m, 4 H), 7.37 (s, 1 H), 6.69−6.75 (m, 2 H), 2.97 (t, J = 6.8 Hz, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.33−2.43 (m, 6 H), 2.30 (t, J = 6.6 Hz, 2 H), 2.01−2.08 (m, 2 H), 1.63−1.74 (m, 6 H). ESI-MS: m/z 545.0 $(M + H)^+$.

(*Z*)-*N*-[3-({3-[3-(Dimethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)-2-oxoindolin-5-yl]benzenesulfonamide (47). Yield: 96%. ^{1}H NMR (DMSO-d_6): δ 13.68 (s, 1 H), 10.95 (s, 1 H), 7.63−7.76 (m, 3 H), 7.48−7.60 (m, 4 H), 7.31 (s, 1 H), 6.80 (d, J = 8.3 Hz, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 2.87−2.97 (m, 4 H), 2.35−2.42 (m, 2 H), 1.99−2.13 (m, 10 H), 1.63−1.71 (m, 2 H). ESI-MS: m/z 519.0 $(M + H)^+$.

(*Z*)-*N*-[3-({3-[3-(Diethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)-2-oxoindolin-5-yl]benzenesulfonamide (48). Yield: 78%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 10.96 (s, 1 H), 7.69 (d, J = 7.5 Hz, 2 H), 7.48−7.62 (m, 5 H), 7.38 (s, 1 H), 6.70−6.76 (m, 2 H), 2.89−2.94 (m, 4 H), 2.33−2.46 (m, 8 H), 1.99−2.09 (m, 2 H), 1.63−1.71 (m, 2 H), 0.92 (t, J = 7.1 Hz, 6 H). ESI-MS: m/z 547.0 $(M + H)^+$.

(*Z*)-3-({3-[3-(Dimethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)-5-(indolin-1-ylsulfonyl)indolin-2-one (49). Yield: 97%. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1 H), 8.13 (s, 1 H), 7.92 (s, 1 H), 7.53−7.62 (m, 2 H), 7.19 (t, J = 7.7 Hz, 1 H), 7.14 (d, J = 7.2 Hz, 1 H), 6.92−7.04 (m, 2 H), 3.91 (t, J = 8.3 Hz, 2 H), 3.02−3.06 (m, 2 H), 2.86−2.96 (m, 4 H), 2.38−2.43 (m, 2 H), 2.00−2.20 (m, 10 H), 1.65−1.70 (m, 2 H). ESI-MS: m/z 545.0 $(M + H)^+$.

(*Z*)-3-({3-[3-(Diethylamino)propyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)-5-(indolin-1-ylsulfonyl)indolin-2-one (50). Yield: 91%. ^{1}H NMR (DMSO-d_6): δ 13.63 (s, 1 H), 8.21 (s, 1 H), 7.87 (s, 1 H), 7.52−7.61 (m, 2 H), 7.10−7.23 (m, 2 H), 6.89−7.03 (m, 2 H), 3.85−3.97 (m, 2 H), 2.99−3.07 (m, 2 H), 2.83−2.96 (m, 4 H), 2.33−2.43 (m, 8 H), 2.01−2.10 (m, 2 H), 1.66−1.71 (m, 2 H), 0.94 (t, J = 7.1 Hz, 6 H). ESI-MS: m/z 573.0 $(M + H)^+$.

General Procedure for the Synthesis of Pyrrole−Indolin-2-ones 37−40. Compound **31** or **33** (∼1.0 g, 1.0 equiv) was suspended in CH_2Cl_2 (20 mL) and mixed with CDI (1.2 equiv). The reaction mixture was stirred at room temperature for 3.0 h. To the solution was added pyrrolidine, morpholine, or methylamine (2.0 equiv), and the mixture was stirred at room temperature for 12 h. The solution was diluted with CH_2Cl_2 (200 mL) and washed with 0.1 N HCl (50 mL), saturated Na_2CO_3 (50 mL), and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$(s) and concentrated under reduced pressure to provide the desired **37−40** as yellow solids in 66−98% yield.

(*Z*)-*N*-[2-Oxo-3-({4-oxo-3-[3-oxo-3-(pyrrolidin-1-yl)propyl]-4,5,6,7-tetrahydro-1*H*-indol-2-yl}methylene)indolin-5-yl]benzenesulfonamide (37). Yield: 66%. ^{1}H NMR (DMSO-d_6): δ 13.73 (s, 1 H), 10.96 (s, 1 H), 9.93 (s, 1 H), 7.73 (d, J = 7.3 Hz, 2 H), 7.50−7.62 (m, 4 H), 7.42 (d, J = 1.5 Hz, 1 H), 6.70−6.77 (m, 2 H), 3.22−3.31 (m, 4 H), 3.13 (t, J = 7.4 Hz, 2 H), 2.90 (t, J = 6.0 Hz, 2 H), 2.39−2.43 (m, 2 H), 2.01−2.09 (m, 2 H), 1.78−1.85 (m, 2 H), 1.68−1.74 (m, 2 H). ESI-MS: m/z 559.0 $(M + H)^+$.

(*Z*)-*N*-(3-{[3-(3-Morpholino-3-oxopropyl)-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl]methylene}-2-oxoindolin-5-yl)benzenesulfonamide (38). Yield: 66%. ^{1}H NMR (DMSO-d_6): δ 13.75 (s, 1 H), 10.97 (s, 1 H), 9.93 (s, 1 H), 7.73 (d, J = 7.4 Hz, 2 H), 7.57−7.61 (m, 1 H), 7.51−7.56 (m, 3 H), 7.42 (s, 1 H), 6.71−6.79 (m, 2 H), 3.39−3.50 (m, 8 H), 3.14 (t, J = 7.4 Hz, 2 H), 2.91 (t, J = 5.8 Hz, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 2.38−2.44 (m, 2 H), 2.01−2.09 (m, 2 H). ESI-MS: m/z 575.0 $(M + H)^+$.

(*Z*)-*N*-Methyl-3-(4-oxo-2-{[2-oxo-5-(phenylsulfonamido)-indolin-3-ylidene]methyl}-4,5,6,7-tetrahydro-1*H*-indol-3-yl)-propanamide (39). Yield: 69%. ^{1}H NMR (DMSO-d_6): δ 13.71 (s, 1 H), 10.96 (s, 1 H), 9.95 (s, 1 H), 7.69−7.73 (m, 3 H), 7.49−7.63 (m, 4 H), 7.45 (d, J = 1.4 Hz, 1 H), 6.70−6.77 (m, 2 H), 3.14 (t, J = 7.1 Hz, 2 H), 2.90 (t, J = 6.0 Hz, 2 H), 2.31−2.41 (m, 5 H), 2.02−2.08 (m, 2 H). ESI-MS: m/z 519.0 $(M + H)^+$.

(*Z*)-5-(Indolin-1-ylsulfonyl)-3-{[3-(3-morpholino-3-oxopropyl)-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-2-yl]methylene}indolin-2-one (40). Yield: 98%. ^{1}H NMR (DMSO-d_6): δ 13.63 (s, 1 H), 11.39 (s, 1 H), 8.27 (s, 1 H), 7.92 (s, 1 H), 7.59 (dd, J = 8.2, 1.4 Hz, 1 H), 7.53 (d, J = 8.1 Hz, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 7.13 (d, J = 7.3 Hz, 1 H), 6.99 (d, J = 8.1 Hz, 1 H), 6.94 (t, J = 7.5 Hz, 1 H), 3.94 (t, J = 8.4 Hz, 2 H), 3.38−3.50 (m, 8 H), 3.20−3.28 (m, 2 H), 2.85−2.96 (m, 4 H), 2.55−2.60 (m, 2 H), 2.40−2.44 (m, 2 H), 2.02−2.08 (m, 2 H). ESI-MS: m/z 601.0 $(M + H)^+$.

Aurora Assays. Inhibition of kinase activity by the test compound was measured by quantifying the amount of ^{33}P incorporated into the substrate in the presence of a test compound. Standard assay conditions utilized 1 ng of recombinant Aurora A or Aurora B kinase (Upstate Biotechnology), 2 μg of peptide substrate (tetra-LRRLSLG, synthesized by Genesis Biotech Inc.), 10 μM ATP (for Aurora A) or 40 μM ATP (for Aurora B), 0.2 μCi of [^{33}P]ATP (specific activity of 3000 Ci/mmol, PerkinElmer), 8 mM MOPS-NaOH (pH 7.0), and 1 mM EDTA in a total volume of 25 μL. Reaction mixtures were incubated at 30 °C for 30 min and reactions stopped by addition of 3% phosphoric acid; mixtures were harvested onto a 96-well GF/B UniFilter (PerkinElmer) using a unifilter harvester (PerkinElmer) and counted with a TopCount microplate scintillation counter (PerkinElmer). The IC_{50} values of inhibitors were determined after assays were conducted at 3-fold serially diluted concentrations of each compound in duplicate. The results were analyzed using linear regression software (GraphPad Prism version 4, GraphPad Software Inc., San Diego, CA).

Cell Proliferation Assay. The antiproliferative activity of the compounds with respect to three human cancer cell lines (HCT-116, HeLa, and HT-29) was measured using the CellTiter96 assay kit (Promega) following the manufacturer's instructions. In brief, the cells were maintained in DMEM containing 10% FCS and incubated at 37 °C in a 5% CO_2 atmosphere. Cells were plated at a density of 2000 cells/well on a 96-well plate for 24 h, then treated with different concentrations of the compounds, and incubated for an additional 72 h. At the end of the incubation, CellTiter 96

Aqueous One Solution Reagent (Promega) was added and incubated for an additional 4.0 h. Cell viability was determined by measuring the absorbance at 490 nm using an EMax microplate reader (Molecular Devices). Data were processed and analyzed using GraphPad Prism version 4.

Cell Cycle Analysis by Flow Cytometry (FACS). Drug-treated HCT-116 cells were harvested by trypsinization, washed in PBS, resuspended in ice-cold 70% ethanol, and stored at −20 °C overnight. Cells were then washed twice with PBS, resuspended in PBS containing 2 μg/mL RNase A and 5 μg/mL propidium iodide, and stained for 30 min. DNA content was analyzed by FACSan (Becton Dickinson) using CellQuest.

Western Blot Analysis. The effect of Aurora inhibitors on cellular protein phosphorylation was evaluated by Western blot analysis on G2/M synchronized cells. Cells were treated with 200 ng/mL nocodazole for 17 h and further treated with various concentrations of the Aurora inhibitors for an additional 3.0 h. Drug-treated cells were then harvested and washed twice with PBS, and the cell pellets were boiled in 2× SDS sample buffer and subjected to SDS−PAGE and immunoblotting analysis. The rabbit antibodies against pT288 Aurora A (Cell Signaling), Aurora A (Cell Signaling), pS10-H3 (Upstate), and histone H3 (Millipore), mouse antibody against β-actin (Chemicon), and horseradish peroxidase-conjugated secondary antibodies (Cell Signaling) were used.

Computational Method. The three-dimensional structures of Aurora A and Aurora B complexes with an inhibitor 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole bicycle and Hesperadin were obtained from the Protein Data Bank (entries 2BMC and 2BFY, respectively).[25,26] Hydrogen atoms were added, and water molecules cocrystallized with the protein were removed from the original structure using Accelrys Discovery Studio 2.5 (Accelrys, Inc.). The modified crystal structures of Aurora A and Aurora B were docked by a genetic algorithm-based program (GOLD) using ASP scoring (CCDC Software Limited, Cambridge, U.K.). The genetic algorithm was executed at the default settings, and the active site radius is 10 Å from inhibitor complexes for the docking study. Two hundred genetic algorithm (GA) runs were performed for docking of compounds **33** and **47**. GOLD was run to save up to best docking solutions for each ligands. The results were visually analyzed using PyMOL (http://www.pymol.org/).

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Supporting Information Available: Kinase profiling data of **36** and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Fu, J.; Bian, M.; Jiang, Q.; Zhang, C. Roles of Aurora kinases in mitosis and tumorigenesis. *Mol. Cancer Res.* **2007**, *5*, 1–10.
(2) Carmena, M.; Earnshaw, W. C. The cellular geography of aurora kinases. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 842–854.
(3) Sen, S.; Zhou, H.; White, R. A. A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is amplified and overexpressed in human breast cancer cell lines. *Oncogene* **1997**, *14*, 2195–2200.
(4) Bischoff, J. R.; Anderson, L.; Zhu, Y.; Mossie, K.; Ng, L.; Souza, B.; Schryver, B.; Flanagan, P.; Clairvoyant, F.; Ginther, C.; Chan, C. S.; Novotny, M.; Slamon, D. J.; Plowman, G. D. A homologue of *Drosophila* Aurora kinase is oncogenic and amplified in human colorectal cancers. *EMBO J.* **1998**, *17*, 3052–3065.
(5) Katayama, H.; Ota, T.; Jisaki, F.; Ueda, Y.; Tanaka, T.; Odashima, S.; Suzuki, F.; Terada, Y.; Tatsuka, M. Mitotic kinase expression and colorectal cancer progression. *J. Natl. Cancer Inst.* **1999**, *91*, 1160–1162.
(6) Kamada, K.; Yamada, Y.; Hirao, T.; Fujimoto, H.; Takahama, Y.; Ueno, M.; Takayama, T.; Naito, A.; Hirao, S.; Nakajima, Y. Amplification/overexpression of Aurora-A in human gastric carcinoma: Potential role in differentiated type gastric carcinogenesis. *Oncol. Rep.* **2004**, *12*, 593–599.
(7) For the reviews of Aurora kinases as the target for anticancer drugs, see: (a) Keen, N.; Taylor, S. Aurora-kinase inhibitors as anticancer agents. *Nat. Rev. Cancer* **2004**, *4*, 927–936. (b) Andrews, P. D. Aurora kinases: Shining lights on the therapeutic horizon. *Oncogene* **2005**, *24*, 5005–5015. (c) Jackson, J. R.; Patrick, D. R.; Dar, M. M.; Huang, P. S. Targeted anti-mitotic therapies: Can we improve on tubulin agents? *Nat. Rev. Cancer* **2007**, *7*, 107–117. (d) Giet, R.; Petretti, C.; Prigent, C. Aurora kinases, aneuploidy and cancer, a coincidence or a real link. *Trends Cell Biol.* **2005**, *15*, 241–250.
(8) Gautschi, O.; Heighway, J.; Mack, P. C.; Purnell, P. R.; Lara, P. N., Jr.; Gandara, D. R. Aurora kinases as anticancer drug targets. *Clin. Cancer Res.* **2008**, *14*, 1639–1648.
(9) Cheetham, G. M. T.; Charlton, P. A.; Golec, J. M. C.; Pollard, J. R. Structural basis for potent inhibition of the Aurora kinases and a T315I multi-drug resistant mutant form of Abl kinase by VX-680. *Cancer Lett.* **2007**, *251*, 323–329.
(10) Harrington, E. A.; Bebbington, D.; Moore, J.; Rasmussen, R. K.; Ajose-Adeogun, A. O.; Nakayama, T.; Graham, J. A.; Demur, C.; Hercend, T.; Diu-Hercend, A.; Su, M.; Golec, J. M. C.; Miller, K. M. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth *in vivo*. *Nat. Med.* **2004**, *10*, 262–267.
(11) Fancelli, D.; Moll, J.; Varasi, M.; Bravo, R.; Artico, R.; Berta, D.; Bindi, S.; Cameron, A.; Candiani, I.; Cappella, P.; Carpinelli, P.; Croci, W.; Forte, B.; Giorgini, M. L.; Klapwijk, J.; Marsiglio, A.; Pesenti, E.; Rocchetti, M.; Roletto, F.; Severino, D.; Soncini, C.; Storici, P.; Tonani, R.; Zugnoni, P.; Vianello, P. 1,4,5,6-Tetrahydropyrrolo[3,4-*c*]pyrazoles: Identification of a potent Aurora kinase inhibitor with a favorable antitumor kinase inhibition profile. *J. Med. Chem.* **2006**, *49*, 7247–7251.
(12) Carpinelli, P.; Ceruti, R.; Giorgini, M. L.; Cappella, P.; Gianellini, L.; Croci, V.; Degrassi, A.; Texido, G.; Rocchetti, M.; Vianello, P.; Rusconi, L.; Storici, P.; Zugnoni, P.; Arrigoni, C.; Soncini, C.; Alli, C.; Patton, V.; Marsiglio, A.; Ballinari, D.; Pesenti, E.; Fancelli, D.; Moll, J. PHA-739358, a potent inhibitor of Aurora kinases with a selective target inhibition profile relevant to cancer. *Mol. Cancer Ther.* **2007**, *6*, 3158–3168.
(13) Manfredi, M. G.; Ecsedy, J. A.; Meetze, K. A.; Balani, S. K.; Burenkova, O.; Chen, W.; Galvin, K. M.; Hoar, K. M.; Huck, J. J.; LeRoy, P. J.; Ray, E. T.; Sells, T. B.; Stringer, B.; Stroud, S. G.; Vos, T. J.; Weatherhead, G. S.; Wysong, D. R.; Zhang, M.; Bolen, J. B.; Claiborne, C. F. Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 4106–4111.
(14) Mortlock, A. A.; Foote, K. M.; Heron, N. M.; Jung, F. H.; Pasquet, G.; Lohmann, J.-J. M.; Warin, N.; Renaud, F.; De Savi, C.; Roberts, N. J.; Johnson, T.; Dousson, C. B.; Hill, G. B.; Perkins, D.; Hatter, G.; Wilkinson, R. W.; Wedge, S. R.; Heaton, S. P.; Odedra, R.; Keen, N. J.; Crafter, C.; Brown, E.; Thompson, K.; Brightwell, S.; Khatri, L.; Brady, M. C.; Kearney, S.; McKillop, D.; Rhead, S.; Parry, T.; Green, S. Discovery, synthesis, and *in vivo* activity of a new class of pyrazoloquinazolines as selective inhibitors of Aurora B kinase. *J. Med. Chem.* **2007**, *50*, 2213–2224.
(15) Wilkinson, R. W.; Odedra, R.; Heaton, S. P.; Wedge, S. R.; Keen, N. J.; Crafter, C.; Foster, J. R.; Brady, M. C.; Bigley, A.; Brown, E.; Byth, K. F.; Barrass, N. C.; Mundt, K. E.; Foote, K. M.; Heron, N. M.; Jung, F. H.; Mortlock, A. A.; Boyle, F. T.; Green, S. AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. *Clin. Cancer Res.* **2007**, *13*, 3682–3688.
(16) Krug, M.; Hilgeroth, A. Recent advances in the development of multi-kinase inhibitors. *Mini Rev. Med. Chem.* **2008**, *8*, 1312–1327.
(17) Godl, K.; Gruss, O. J.; Eickhoff, J.; Wissing, J.; Blencke, S.; Weber, M.; Degen, H.; Brehmer, D.; Orfi, L.; Horváth, Z.; Kéri, G.; Müller, S.; Cotten, M.; Ullrich, A.; Daub, H. Proteomic characterization of the angiogenesis inhibitor SU6668 reveals multiple impacts on cellular kinase signaling. *Cancer Res.* **2005**, *65*, 6919–6926.
(18) Hauf, S.; Cole, R. W.; LaTerra, S.; Zimmer, C.; Schnapp, G.; Walter, R.; Heckel, A.; van Meel, J.; Rieder, C. L.; Peters, J.-M. The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. *J. Cell Biol.* **2003**, *161*, 281–294.
(19) Gribble, G. W. Knorr and Paal-Knorr pyrrole syntheses. In *Name Reaction in Heterocyclic Chemistry*; Li, J.-J., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005; Chapter 2.2.
(20) (a) Smith, K. M.; Pandey, R. K. Cyclization of terminally substituted *a,c*-biladiene salts to give *meso*-substituted porphyrins. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1229–1236. (b) Taber, D. F.; Nakajima, K. Unsymmetrical ozonolysis of a Diels−Alder adduct: Practical preparation of a key intermediate for heme total synthesis. *J. Org. Chem.* **2001**, *66*, 2515–2517.

(21) Remers, W. A.; Weiss, M. J. Synthesis of indoles from 4-oxo-4,5,6,7-tetrahydroindoles. III. Introduction of substitutents by electrophilic substitution. *J. Org. Chem.* **1971**, *36*, 1241–1247.
(22) For the preparation of 5-subsituted indolin-2-ones as the starting materials to pyrrole−indolin-2-one 15−35, see: (a) Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. Synthesis and biological evaluations of 3-substituted indolin-2-ones: A novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases. *J. Med. Chem.* **1998**, *41*, 2588–2603. (b) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. Design, synthesis, and evaluations of substituted 3-[(3- or 4-carboxyethylpyrrol-2-yl)methylidenyl]indolin-2-ones as inhibitors of VEGF, FGF, and PDGF receptor tyrosine kinases. *J. Med. Chem.* **1999**, *42*, 5120–5130. (c) Guan, H.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C. Design and synthesis of aminopropyl tetrahydroindole-based indolin-2-ones as selective and potent inhibitors of Src and Yes tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 187–190.
(23) Crosio, C.; Fimia, G. M.; Loury, R.; Kimura, M.; Okano, Y.; Zhou, H.; Sen, S.; Allis, C. D.; Sassone-Corsi, P. Mitotic phosphorylation of histone H3: Spatio-temporal regulation by mammalian Aurora kinases. *Mol. Cell. Biol.* **2002**, *22*, 874–885.
(24) Masaguer, C. F.; Casariego, I.; Raviña, E. Conformationally restricted butyrophenones with mixed dopaminergic (D_2) and serotoninergic (5-HT_{2A}) affinities. Synthesis of 5-aminoethyl- and 6-aminomethyl-4-oxotetrahydroindoles as potent atypical antipsychotics. *Chem. Pharm. Bull.* **1999**, *47*, 621–632.
(25) Sessa, F.; Mapelli, M.; Ciferri, C.; Tarricone, C.; Areces, L. B.; Schneider, T. R.; Stukenberg, P. T.; Musacchio, A. Mechanism of Aurora B activation by INCENP and inhibition by Hesperadin. *Mol. Cell* **2005**, *18*, 379–391.
(26) Fancelli, D.; Berta, D.; Bindi, S.; Cameron, A.; Cappella, P.; Carpinelli, P.; Catana, C.; Forte, B.; Giordano, P.; Giorgini, M. L.; Mantegani, S.; Marsiglio, A.; Meroni, M.; Moll, J.; Pittalà, V.; Roletto, F.; Severino, D.; Soncini, C.; Storici, P.; Tonani, R.; Varasi, M.; Vulpetti, A.; Vianello, P. Potent and selective Aurora inhibitors identified by the expansion of a novel scaffold for protein kinase inhibition. *J. Med. Chem.* **2005**, *48*, 3080–3084.
(27) Fabian, M. A.; Biggs, W. H., III; Treiber, D. K.; Atteridge, C. E.; Azimioara, M. D.; Benedetti, M. G.; Carter, T. A.; Ciceri, P.; Edeen, P. T.; Floyd, M.; Ford, J. M.; Galvin, M.; Gerlack, J. L.; Grotzfeld, R. M.; Herrgard, S.; Insko, D. E.; Insko, M. A.; Lai, A. G.; Lelias, J.-M.; Mehta, S. A.; Milanov, Z. V.; Velasco, A. M.; Wodicka, L. M.; Patel, H. K.; Zarrinkar, P. P.; Lockhart, D. J. A small molecule−kinase interaction map for clinical kinase inhibitors. *Nat. Biotechnol.* **2005**, *23*, 329–336.
(28) Several publications also mention the interaction of Thr217 in Aurora A with inhibitors. See: (a) Myrianthopoulos, V.; Magiatis, P.; Ferandin, Y.; Skaltsounis, A.-L.; Meijer, L.; Mikros, E. An integrated computational approach to the phenomenon of potent and selective inhibition of Aurora kinases B and C by a series of 7-substituted indirubins. *J. Med. Chem.* **2007**, *50*, 4027–4037. (b) Coumar, M. S.; Leou, J.-S.; Shukla, P.; Wu, J.-S.; Dixit, A. K.; Lin, W.-H.; Chang, C.-Y.; Lien, T.-W.; Tan, U.-K.; Chen, C.-H.; Hsu, J. T.-A.; Chao, Y.-S.; Wu, S.-Y.; Hsieh, H.-P. Structure-based drug design of novel Aurora kinase A inhibitors: Structural basis for potency and specificity. *J. Med. Chem.* **2009**, *52*, 1050–1062. (c) Aliagas-Martin, I.; Burdick, D.; Corson, L.; Dotson, J.; Drummond, J.; Fields, C.; Huang, O. W.; Hunsaker, T.; Kleinheinz, T.; Krueger, E.; Liang, J.; Moffat, J.; Phillips, G.; Pulk, R.; Rawson, T. E.; Ultsch, M.; Walker, L.; Wiesmann, C.; Zhang, B.; Zhu, B.-Y.; Cochran, A. G. A class of 2,4-bisanilinopyrimidine Aurora A inhibitors with unusually high selectivity against Aurora B. *J. Med. Chem.* **2009**, *52*, 3300–3307.
(29) In some of the compounds, one CH_2 peak was not reported for its overlapping with the DMSO peak at ∼2.50 ppm.