Novel Cyclopropapyrroloindole Derivative (AT-3510) Bearing Methoxycarbonyl and Trifluoromethyl Groups

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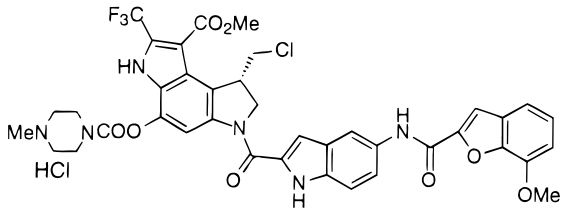
The seco-Cl 3-methoxycarbonyl-2-trifluoromethylcyclopropapyrroloindole (MCTFCPI) derivatives *dl*- and/or (*S*)-**10** carrying various acyl moieties at the N6-position were synthesized along with their prodrugs (*S*)-**12**, and their antitumor activity was evaluated. Among these derivatives, AT-3510 [(*S*)-**12m**], the novel prodrug MCTFCPI derivative carrying a 5-(7-methoxybenzofuran-2-ylcarbonyl)aminoindole-2-carbonyl group at the N6-position, was found to exhibit more excellent antitumor activity against human tumor xenografts than the clinical trial candidates carzelesin (**6**) and KW-2189 (**7**) and cisplatin.

Introduction

CC-1065 (**1**),[1] duocarmycin A (**2**),[2] and duocarmycin SA (**3**)[3] (Chart 1), carrying a cyclopropapyrroloindole (CPI) moiety as the common pharmacophore, are potent antitumor antibiotics isolated from *Streptomyces sp*. The CPI system has been recognized to be responsible for their prominent cytotoxicity through sequence-selective alkylation of double-strand DNA.[4] Since unusual delayed lethality was observed for **1**,[5] various types of congeners have been synthesized and evaluated to explore less toxic analogues of **1**, resulting in the development of U-68415 (*dl*-**4**),[4c] U-73,975 (adozelesin) (**5**),[6] and U-80,244 (carzelesin) (**6**)[7] as novel antitumor agents showing no delayed toxicity. As for **2**, synthetic efforts have been devoted to the preparation of its congeners, culminating in the exploration of KW-2189 (**7**)[8] as a semisynthetic antitumor agent. These novel antitumor agents **6** and **7** are presently under clinical trials (Chart 1).

Recently, we have succeeded in the design and synthesis of the racemic bis(methoxycarbonyl)CPI (MC_2-CPI) derivatives *dl*-**9a**,**b**,**f**,**i** bearing two methoxycarbonyl groups at the vicinal positions of the pyrrole ring.[9a] Among *dl*-**9a**,**b**,**f**,**i**, *dl*-**9f**,**i** were found to exhibit promising cytotoxicity (in vitro) and antitumor activity (in vivo) against P388 murine leukemia. These results let us develop a novel CPI system which can exhibit even more prominent antitumor activity than *dl*-**9f**,**i** and also **6** and **7**. Taking into account structural characteristics of the CPI systems so far reported, we designed a novel CPI system, the 3-methoxycarbonyl-2-trifluoromethylCPI (MCTFCPI) system, which carries methoxycarbonyl and trifluoromethyl groups at the vicinal positions of the pyrrole ring.[9b] It is well-known that various fluorinated drugs often show unique pharmacological properties. Therefore, the antitumor activity of the novel MCTFCPI derivatives *dl*- and/or (*S*)-**11**, their seco-type compounds *dl*- and/or (*S*)-**10**, and the prodrugs (*S*)-**12** and (*S*)-**13** was expected to be quite promising (Chart 2). To explore superiority of this novel MCTFCPI system to the known CPI systems, we first examined the synthesis and evaluation of the MCTFCPI derivatives *dl*- and/or (*S*)-**11a**,**b**,**f**,**i**, and the prodrug (*S*)-**13b** bearing known acyl moieties at the N6-position.[9b] On the basis of the results obtained by these studies, our next efforts were the synthesis and evaluation of the racemic or optically active seco-Cl-MCTFCPI derivatives *dl*- and/or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w** bearing novel acyl moieties at the N6-position. Among *dl*- and/or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w**, *dl*- or (*S*)-**10k**−**n**,**q**,**v** were found to show more promising antitumor activity. Subsequently, (*S*)-**10k**−**n**,**q**,**v** were masked with an *N*-methylpiperazinylcarbamoyl group which had been introduced as the prodrug moiety of **7**, affording the optically active prodrugs (*S*)-**12k**−**n**,**q**,**v**. This sort of research strategy was taken by considering the successful results for **1** and **2** in which **6** and **7** had been developed based on the studies on their acyl and prodrug moieties. As the results of our studies, AT-3510 [(*S*)-**12m**], the novel prodrug MCTFCPI derivative carrying a 5-(7-methoxybenzofuran-2-ylcarbonyl)aminoindole-2-carbonyl group at the N6-position, was found to exhibit more excellent antitumor activity than all of the CPI derivatives so far reported.[6−9] Herein, we wish to report on the synthesis and antitumor activity of *dl*- and/or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w** and (*S*)-**12k**−**n**,**q**,**v** including (*S*)-**12m** which carries novel acyl moieties at the N6-position.



(*S*)-**12m**

Results and Discussion

Chemistry. According to a preceding paper,[9b] we completed the synthesis of the novel seco-Cl-MCTFCPI derivatives *dl*- and/or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w** by coupling the racemic or optically active phenol *dl*- or (*S*)-**15** with

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Chart 1

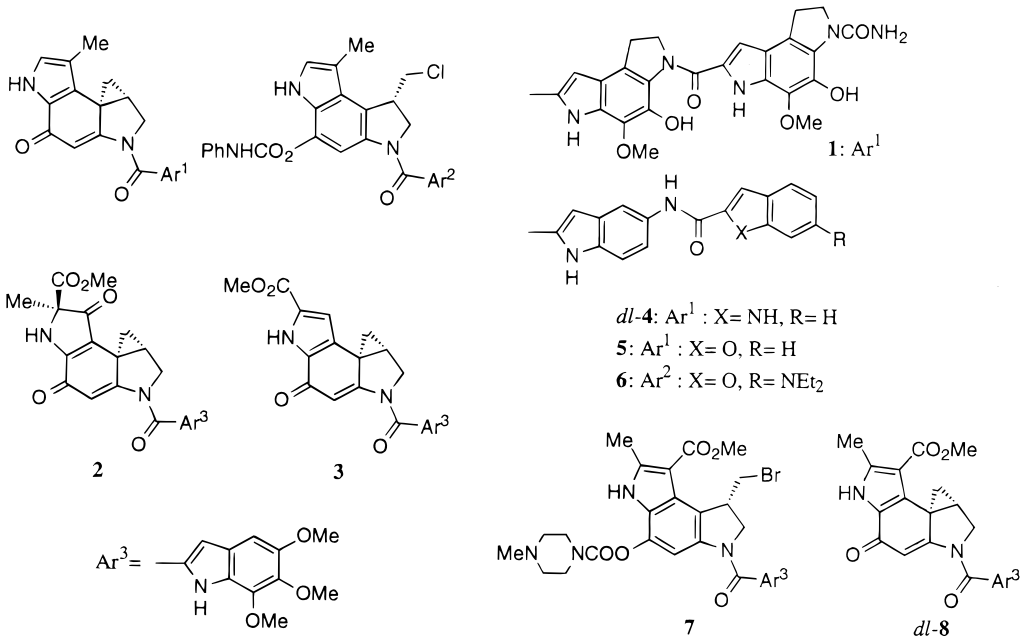
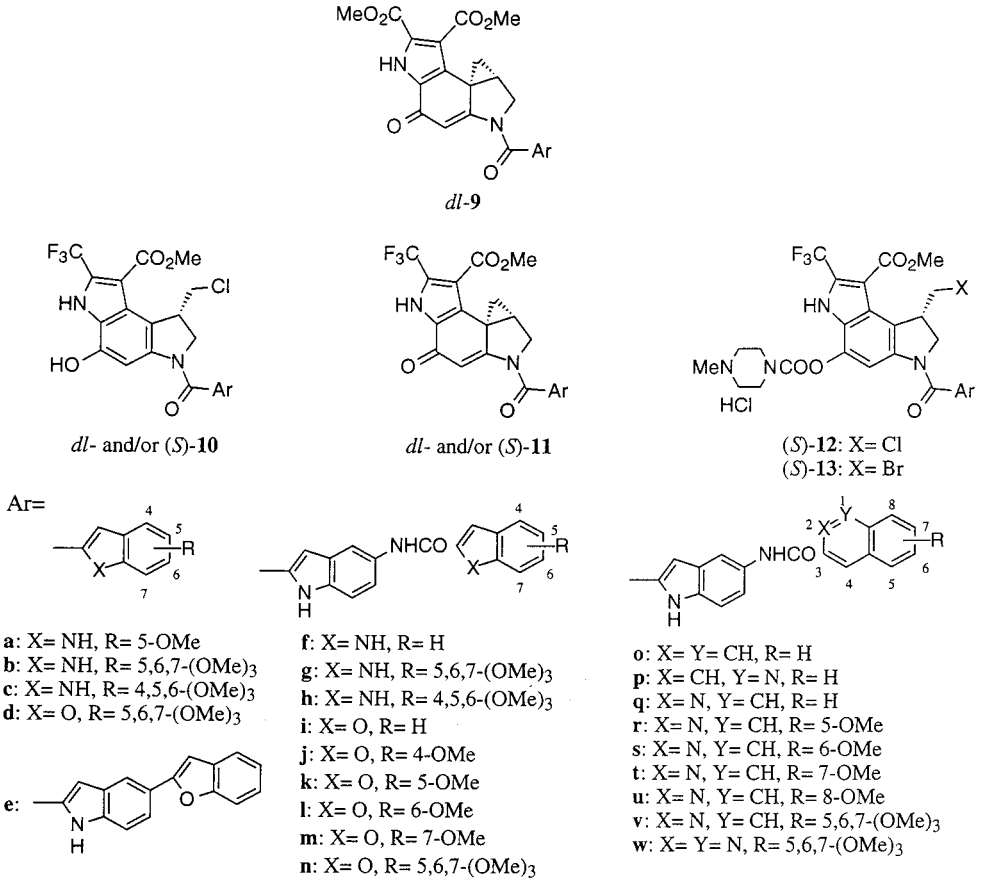


Chart 2

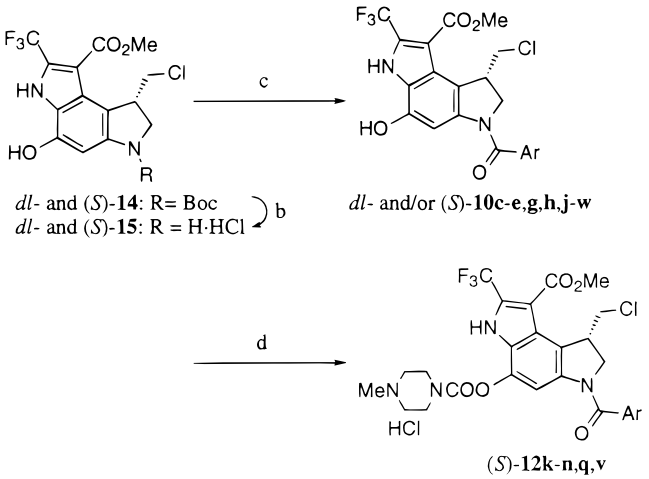


various carboxylic acids **16c**−**e**,**g**,**h**,**j**−**w**. Among *dl*- or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w**, *dl*- or (*S*)-**10k**−**n**,**q**,**v** were found to show more promising antitumor activity. Subsequently, (*S*)-**10k**−**n**,**q**,**v** were masked with an *N*-methylpiperazinylcarbamoyl group which had been introduced as the prodrug moiety of **7**, affording the prodrugs (*S*)-**12k**−**n**,**q**,**v** (Scheme 1).

According to the reported method,[4c] 5-acylaminoindole-2-carboxylic acids **16f**−**w** were prepared by acylation of ethyl 5-aminoindole-2-carboxylate[4c] with appropriate carboxylic acids followed by alkaline hydrolysis. Syntheses of the hitherto unknown carboxylic acids **16d**,**e**, **27b**, **31**, **35a**,**b**, and **41** were carried out as shown in Schemes 2 and 3. The other carboxylic acids employed in this work are commercially available or readily obtainable according to the reported procedures.[4c,9,10]

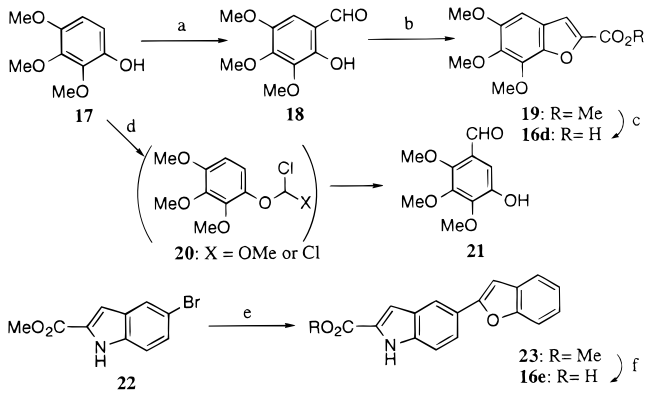
Thus, 5,6,7-trimethoxybenzofuran-2-carboxylic acid (**16d**) was prepared from the phenol **17** by way of 3,4,5-

Scheme 1[a]



[a] (a) For **c**−**e,g,h,j**−**w**, see Chart 2; (b) 3 M Hcl−AcOEt; (c) EDCI, $ArCO_2H$ (**16c**−**e,g,h,j**−**w**), 42−89% (2 steps); (d) (i) $ClCO_2PhNO_2$, Et_3N, (ii) *N*-methylpiperazine, (iii) saturated HCl−MeOH, 14−64% (3 steps).

Scheme 2[a]



[a] (a) Hexamethylenetetramine, TFA, 90 °C, 69%; (b) ethyl bromoacetate, K_2CO_3, DMF, 80 °C, 62%; (c) 20% KOH, EtOH, 0 °C, 79%; (d) benzofuran-2-boric acid, $Pd(PPh_3)_4$, Et_3N, DMF, 100 °C, 44%; (e) 20% KOH, MeOH, DMSO, 60 °C, 98%.

trimethoxysalicylaldehyde (**18**) according to the reported method.[12] In the synthesis of **18**,[11] direct formylation of **17** by the Duff reaction was found to provide **18** exclusively. On the other hand, direct formylation of **17** with 1,1-dichlorodimethyl ether−$TiCl_4$ was found to exclusively give the benzaldehyde **21** regioisomeric to **18**. This unusual reaction might take place by way of formylation of the intermediate **20**. The Suzuki coupling of the 5-bromoindole **22** with benzofuran-2-boric acid and subsequent alkaline hydrolysis furnished **16e** (Scheme 2).

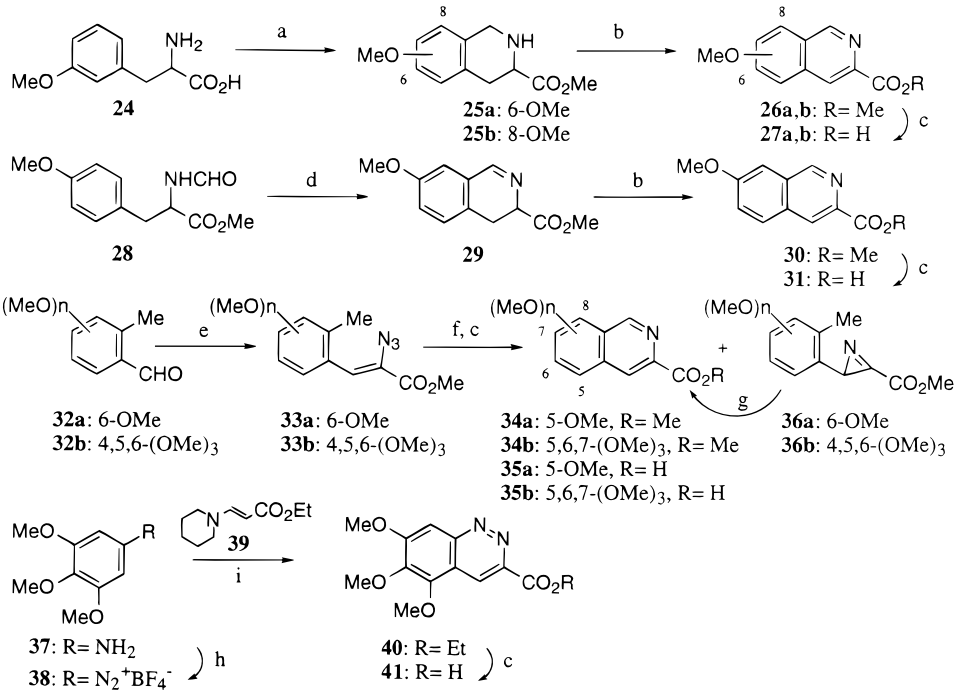
To the best of our knowledge, 5-, 7-, and 8-methoxy- and 5,6,7-trimethoxyisoquinoline-3-carboxylic acids (**35a**, **31**, **27b**, and **35b**) and 5,6,7-trimethoxycinnoline-3-carboxylic acid (**41**) had not been reported to date. Therefore, we examined their syntheses as shown in Scheme 3. According to the reported method,[12] the synthesis of methyl 6-methoxyisoquinoline-3-carboxylate (**26a**) was first attempted. The Bischler−Napieralski reaction of 3-methoxyphenylalanine (**24**) and subsequent dehydrogenation afforded **26a** along with a small amount of unreported methyl 8-methoxyisoquinoline-3-carboxylate (**26b**). Methyl 7-methoxyisoquinoline-3-carboxylate (**30**) was next prepared from the tyrosine derivative **28** by employing the modified Bischler−Napieralski procedure[13] followed by dehydrogenation. Syntheses of methyl 5-methoxy- and 5,6,7-trimethoxyisoquinoline-3-carboxylates (**34a**,**b**) were achieved by C−H bond insertion reaction of the nitrenes generated from the vinyl azides **33a**,**b**.[14] Thus, condensation of the benzaldehyde **32a** with methyl 2-azidoacetate produced **33a**. Upon heating in refluxing xylene, **33a** gave rise to **34a** and the azirine **36a**. The latter compound **36a** was further cyclized to **34a** in refluxing 1,2-dichlorobenzene. By employing the same procedure, **33b** derived from the benzaldehyde **32b** was also successfully transformed to **34b**. The resulting esters **26a**,**b**, **30**, and **34a**,**b** gave the corresponding carboxylic acids **27a**,**b**, **31**, and **35a**,**b** by alkaline hydrolyses. The synthesis of 5,6,7-trimethoxycinnoline-3-carboxylic acid (**41**) was also achieved according to the reported method.[15] Thus, the reaction of diazonium salt **38** derived from the aniline **37** with enamino ester **39** cleanly provided **40**, which upon hydrolysis gave rise to **41**.

Cytotoxicity and Antitumor Activity. The results of cytotoxicity assay (in vitro) against P388 murine leukemia and antitumor activity assay (in vivo) against P388 murine leukemia and S180 murine sarcoma of the MCTFCPI derivatives *dl*-**11a**,**b**,**f**,**i** are summarized in Table 1, along with those for *dl*-**4**,[16] *dl*-**9f**,**i**, and *dl*-**8** (DU-86)[16] which is the parent compound of **7**. It appeared evident that the MCTFCPI derivatives *dl*-**11b**,**f**,**i** exhibit promising antitumor activity against murine leukemia and solid tumor.[9b]

Aiming to definitely explore the fact that the MCTFCPI system is superior to the known CPI systems in light of antitumor activity, we next evaluated optically active (*S*)-**11i** and (*S*)-**13b** which bear the same acyl moieties as **5** and the clinical trial candidate **7**, respectively, by comparing their antitumor activity with that of **5** and **7**.[16] From the results shown in Table 2, it appeared that the cytotoxicity against HeLaS3 human uterine cervix carcinoma of (*S*)-**11i** is 10 times weaker than that of **5** and that the prodrugs (*S*)-**13b** and **7** exhibit comparable weak cytotoxicity. On the other hand, antitumor activity of (*S*)-**11i** and (*S*)-**13b** against Colon 26 murine adenocarcinoma was found to be comparable to that of **5** and **7**, respectively.[9b]

With the results delineated above, the racemic or optically active seco-Cl-MCTFCPI derivatives *dl*- or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w** bearing novel acyl moieties at the N6-position were next evaluated. They were subjected to cytotoxicity assay (in vitro) against HeLaS3 human uterine cervix carcinoma and antitumor activity assay (in vivo) against Colon 26 murine adenocarcinoma. As shown in Table 3, *dl*-**10c**,**h** having a methoxy group at the C4-position on the indole ring exhibited significantly less cytotoxicity than *dl*-**10b**,**g** which lack a methoxy group at the same position. It appeared that a methoxy group at the C4-position on the indole ring might debilitate cytotoxicity due to the steric interaction in a minor groove of duplex DNA. Cytotoxicity of the benzofuran derivative (*S*)-**10d** was comparable to that of *dl*-**10b**. It was also found that *dl*-**10e** lacking an amide group between the indole and the benzofuran rings shows less cytotoxicity than *dl*-**10i**, suggesting that the amide group is essential for strong cytotoxicity. Cyto-

Scheme 3[a]



[a] (a) (i) HCHO, (ii) HCl, MeOH; (b) 10% Pd−C, xylene, reflux, 9.6% (**26a** from **24**), 0.6% (**26b** from **24**), 8% (**30** from **28**); (c) 20% KOH, MeOH, 79% (for **27a**), 76% (for **27b**), 77% (for **31**), 73% (for **35a**), 83% (for **35b**), 77% (for **41**); (d) (i) $(COCl)_2$, CH_2Cl_2, (ii) $FeCl_3$, (iii) MeOH, H_2SO_4; (e) methyl azidoacetate, NaOMe, MeOH, 63% (for **33a**), 41% (for **33b**); (f) xylene, reflux; (g) 1,2-dichlorobenzene, reflux, 49% (for **34a**), 41% (for **34b**); (h) $NaNO_2$, concd HCl, $NaBF_4$, 81%; (i) MeCN, 80 °C, 93%.

Table 1. Cytotoxicity of U-68415 (*dl*-**4**), the MC_2CPI Derivatives *dl*-**9f,i**, the MCTFCPI Derivatives *dl*-**10a,b,f,i**, and DU-86 (*dl*-**8**) against P388 Murine Leukemia Cells and Their in Vivo Antitumor Activity against P388 Murine Leukemia Cells and S180 Murine Sarcoma Cells

compd	IC_{50} (ng/mL)[a]	P388 ILS (%)[b] (mg/kg)	S180 TGI (%)[c] (mg/kg)
dl-**11a**	0.23	69 (0.125)	54 (0.25)
dl-**11b**	0.24	94 (0.125)	92 (0.5)
dl-**11f**	0.86	2/2[d] (0.25)	84 (0.25)
dl-**11i**	0.53	2/2[d] (0.25)	83 (0.25)
dl-**9f**	0.31	102 (0.125)	44 (0.5)
dl-**9i**	0.66	79 (0.125)	26 (0.5)
dl-**8**	0.34	80 (0.125)	81 (0.5)
dl-**4**	0.028	210 (0.125)	86 (0.125)

[a] Drug concentration required to inhibit the growth of P388 murine leukemia cells by 50%. [b] Percentage increase in life span as compared with the untreated group. [c] Percentage tumor growth inhibition as compared with the untreated group. [d] Cured mice (>60-day survivors).

Table 2. Cytotoxicity of Adozelesin (**5**), KW-2189 (**7**), the MCTFCPI Derivative (*S*)-**11i**, and the Prodrug of the MCTFCPI Derivative (*S*)-**13b** against HeLaS3 Human Uterine Cervix Carcinoma Cells and Their in Vivo Antitumor Activity against Colon 26 Murine Adenocarcinoma Cells

compd	IC_{50} (ng/mL)[a]	TGI (%) (mg/kg)[b]	TGI_{50} (mg/kg)[c]	MTD^d/TGI_{50}
(*S*)-**11i**	0.365	85 (0.177)	0.0410	4.3
5	0.0364	79 (0.0884)	0.0444	2.0
(*S*)-**13b**	18.8	93 (0.500)	0.0429	11.7
7	18.1	90 (0.707)	0.209	3.4

[a] Drug concentration required to inhibit the growth of HeLaS3 cells by 50%. [b] Percentage tumor growth inhibition as compared with the untreated group. [c] Drug concentration required to inhibit the tumor growth by 50%. [d] Maximum dose within 10% body weight loss.

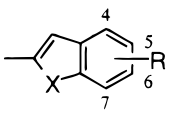
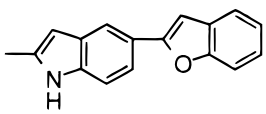
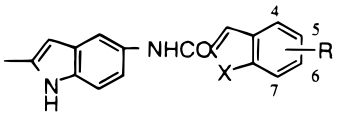
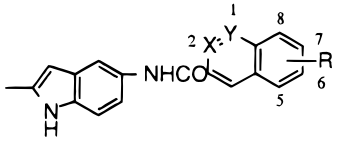
toxicity and antitumor activity of (*S*)-**10j**−**n**,**r**−**v** carrying a methoxy or trimethoxy group(s) on the benzofuran and isoquinoline rings, respectively, were comparable to those of *dl*-**10i**,**q** which have no methoxy group on the benzofuran and isoquinoline rings, respectively. Comparing with *dl*-**10o** and (*S*)-**10v**, *dl*-**10p** and *dl*-**10w**, to which a nitrogen atom is introduced to the C1-position, exhibited less cytotoxicity. Summing up the above results, it appeared evident that almost all the seco-Cl derivatives *dl*- or (*S*)-**10d**,**e**,**g**−**v** tested exhibited promising antitumor activity.

Since the seco-Cl derivatives *dl*- or (*S*)-**10k**−**n**,**q**,**v** showed more promising antitumor activity, the optically active prodrugs (*S*)-**12k**−**n**,**q**,**v** were prepared from (*S*)-**10k**−**n**,**q**,**v** by masking with an *N*-methylpiperazinylcarbamoyl group as shown in Scheme 1. These novel prodrugs (*S*)-**12k**−**n**,**q**,**v** were subjected to antitumor activity assay (in vivo) against Colon 26 murine adenocarcinoma. From the results shown in Table 4, all these prodrugs showed excellent antitumor activity against Colon 26 murine adenocarcinoma. Among these prodrugs, (*S*)-**12m**,**q** were found to exhibit more excellent antitumor activity than the others. Accordingly, both (*S*)-**12m**,**q** were subjected to antitumor activity assay against human tumor xenografts for further evaluation. As shown in Table 5, (*S*)-**12m** showed better antitumor activity against human tumor xenografts than (*S*)-**12q**, the clinical trial candidates **6**[16] and **7**, and the clinically widely used anticancer agent cisplatin.

Conclusion

As described above, we have succeeded in the synthesis of the MCTFCPI derivatives *dl*- and/or (*S*)-**11a**,**b**,**f**,**i**, the seco-Cl-MCTFCPI derivatives *dl*- or (*S*)-**10c**−**e**,**g**,**h**,**j**−**w** carrying novel acyl moieties at the N6-position, and their prodrugs (*S*)-**12k**−**n**,**q**,**v**. On the basis of these studies, the novel prodrug (*S*)-**12m** was

Table 3. Cytotoxicity of the Seco-Cl-MCTFCPI Derivatives *dl*- or (*S*)-**10b**−**e,g**−**w** against HeLaS3 Human Uterine Cervix Carcinoma Cells and Their in Vivo Antitumor Activity against Colon 26 Murine Adenocarcinoma Cells

dl- or (*S*)-**10**[a]	Ar	X	Y	R	IC_{50} (ng/mL)[b]	TGI (%) (mg/kg)[c]
b*		NH		5,6,7-$(OMe)_3$	0.25	NT[d]
c*		NH		4,5,6-$(OMe)_3$	32	NT
d		O		5,6,7-$(OMe)_3$	0.12	75 (0.5)
e*					3.6	84 (1.0)
g*		NH		5,6,7-$(OMe)_3$	0.20	83 (0.25)
h*		NH		4,5,6-$(OMe)_3$	0.94	95 (0.5)
i*		O		H	0.53	85 (0.5)
j		O		4-OMe	0.87	83 (0.5)
k		O		5-OMe	0.064	94 (0.5)
l		O		6-OMe	0.12	94 (0.5)
m		O		7-OMe	0.51	96 (0.5)
n		O		5,6,7-$(OMe)_3$	0.17	74 (0.125)
o*		CH	CH	H	0.22	84 (0.5)
p*		CH	N	H	1.5	84 (0.5)
q*		N	CH	H	0.24	82 (0.25)
r		N	CH	5-OMe	0.20	67 (0.125)
s		N	CH	6-OMe	0.18	90 (0.25)
t		N	CH	7-OMe	0.11	82 (0.25)
u		N	CH	8-OMe	0.51	90 (0.25)
v		N	CH	5,6,7-$(OMe)_3$	0.20	93 (0.25)
w*		N	N	5,6,7-$(OMe)_3$	6.5	NT

[a] An asterisk (*) indicates the racemic form. [b] Drug concentration required to inhibit the growth of HeLaS3 cells by 50%. [c] Colon 26 (10^6/mouse) cells were inoculated sc into male CDF1 mice on day 0. Drugs were administered iv on day 7. Percentage tumor growth inhibition as compared with the untreated group. [d] NT, not tested.

Table 4. In Vivo Antitumor Activity of the Prodrugs of the Seco-Cl-MCTFCPI Derivatives (*S*)-**12k**−**n,q,v** against Colon 26 Murine Adenocarcinoma

(*S*)-**12**	TGI (%) (mg/kg)[a]	TGI_{50} (mg/kg)[b]	MTD^c/TGI_{50}
k	86 (1.0)	0.148	6.8
l	89 (0.5)	0.108	4.6
m	95 (2.0)	0.265	7.6
n	90 (0.25)	0.0533	4.5
q	93 (0.5)	0.082	6.1
v	89 (0.5)	0.130	3.9

[a] Percentage tumor growth inhibition as compared with the untreated group. [b] Drug concentration required to inhibit the tumor growth by 50%. [c] Maximum dose within 10% body weight loss.

Table 5. In Vivo Antitumor Activity of Carzelesin (**6**), KW-2189 (**7**), Cisplatin, and the Prodrugs of the Seco-Cl-MCTFCPI Derivatives (*S*)-**12m,q** against Human Tumor Xenografts[a]

		max TGI (%)[b]			
compd	dose (mg/kg)	NUGC-3 (stomach)	HCT-116 (colon)	DLD-1 (colon)	WiDr (colon)
(*S*)-**12m**	3.13	100	90	83	86
(*S*)-**12q**	0.845	97	77[d]	76	NT[e]
6	0.584	98	82	79	56
7	1.00	91[c]	73	65	59
cisplatin	9.81	87	34	25	44

[a] Tumor fragments (2−3 mm^3) were implanted sc into female BALB/cA Jcl-nu mice on day 0. Drugs were administered single iv when tumor volume reached about 100 mm^3. [b] Percentage of maximum tumor growth inhibition as compared with the untreated group. [c] Dose was 0.716 mg/kg. [d] Dose was 0.800 mg/kg. [e] NT, not tested.

found to exhibit prominent antitumor activity against murine solid tumor. Moreover, it should be noted that (*S*)-**12m** shows better antitumor activity against human tumor xenografts than the clinical trial candidates **6** and **7** and the clinically widely used anticancer agent cisplatin. Further evaluation is being undertaken to confirm whether (*S*)-**12m** can be selected as a potential candidate for clinical trial.

Experimental Section

All melting points were determined with a Yamato MP-500 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a JASCODIP-360 automatic digital polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-EX-400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ-value) downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual solvents such as chloroform ($\delta = 7.26$) and benzene ($\delta = 7.20$) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra were performed with a Hitachi M-2000 mass spectrometer. Data for elemental analysis are within ±0.3% of theoretical values and were determined by a Yanaco CHN corder MT-5. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Especially, tetrahydrofuran and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Throughout this work, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm; Art. 5715) were used for thin layer chromatographic (TLC) analyses. Wako Gel C-200 and C-300 were used as an adsorbent for flash column chromatography. To minimize the health risks posed by these potent cytotoxic compounds to analytical service personnel of our laboratory and to allow preparation of only the very limited quantities needed for testing, infrared spectra and combustion elemental analyses were not obtained on the final analogues except for (*S*)-**12m**.[4c]

***dl*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-(4,5,6-trimethoxy-1*H*-indol-2-ylcarbonyl)-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10c).** A solution of *dl*-**14** (10.3 mg, 23 μmol) in 3 M HCl−AcOEt (0.4 mL) was

stirred at room temperature for 2 h. Concentration of the mixture in vacuo gave the crude hydrochloride *dl*-**15** as a pale yellow powder, which was directly added to a solution of **16c** (5.8 mg, 23 μmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (13.2 mg, 69 μmol) in DMF (0.25 mL). The mixture was stirred at room temperature for overnight. After dilution with AcOEt and water, the mixture was washed with 5% $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography ($CHCl_3$:MeOH = 15:1) of the residue gave *dl*-**10c** as pale yellow crystals (10.3 mg, 77%). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.35 (t, *J* = 10.7 Hz, 1H), 3.86−3.89 (m, 1H), 3.88, 3.89, 3.98, 4.15 (sx4, each 3H), 4.44 (m, 1H), 4.56 (t, *J* = 9.8 Hz, 1H), 4.74 (d, *J* = 10.3 Hz, 1H), 6.68 (s, 1H), 8.04 (brs, 1H), 9.08 (s, 1H), 9.85 (s, 1H), 11.40 (brs, 1H). MS (FAB) *m*/*z*: 582 (MH^+). HRMS (FAB) for $C_{26}H_{24}ClF_3N_3O_7$ (MH^+): calcd, 582.1255; found, 582.1279. Other racemic and/or optically active seco-Cl-MCTFCPI derivatives *dl*- and/or (*S*)-**10b**−**w** were prepared in the same manner as described above by employing *dl*- and/or (*S*)-**15** prepared from *dl*- and/or (*S*)-**14** and **16b**−**w**.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [(*S*)-10d].** This compound (*S*)-**10d** (10.5 mg, 72%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16d** (6.3 mg, 25 μmol). $[\alpha]_D^{23} = +18°$ (*c* = 0.20, THF). ^{1}H NMR ($CDCl_3$): δ 3.36 (t, *J* = 10.8 Hz, 1H), 3.85−3.95 (m, 1H), 3.91, 3.95, 3.97, 4.28 (sx4, each 3H), 4.46−4.51 (m, 1H), 4.65 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 6.83 (s, 1H), 7.68 (s, 1H), 8.54 (s, 1H), 9.72 (brs, 1H), 11.17 (brs, 1H). MS (FAB) *m*/*z*: 583 (MH^+). HRMS (FAB) for $C_{26}H_{23}ClF_3N_2O_8$ (MH^+): calcd, 583.1095; found, 583.1074.

***dl*-Methyl 6-(Benzofuran-2-yl-1*H*-indol-2-ylcarbonyl)-4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10e).** This compound *dl*-**10e** (10.6 mg, 76%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16e** (6.4 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.37 (t, *J* = 10.3 Hz, 1H), 3.90 (dd, *J* = 10.3 Hz, 2.9 Hz, 1H), 3.98 (s, 3H), 4.47 (m, 1H), 4.59 (t, *J* = 10.3 Hz, 1H), 4.78 (d, *J* = 10.7 Hz, 1H), 7.00 (s, 1H), 7.14 (s, 1H), 7.21−7.29 (m, 2H), 7.52−7.59 (m, 3H), 7.81 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 8.02 (br, 1H), 8.27 (s, 1H), 9.17 (s, 1H), 10.31 (s, 1H), 11.52 (br, 1H). MS (FAB) *m*/*z*: 608 (MH^+). HRMS (FAB) for $C_{31}H_{22}ClF_3N_3O_5$ (MH^+): calcd, 608.1200; found, 608.1205.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10g).** This compound *dl*-**10g** (13.2 mg, 78%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16g** (9.4 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.36 (t, *J* = 9.8 Hz, 1H), 3.89 (m, 1H), 3.92, 3.95, 3.98, 4.10 (sx4, each 3H), 4.45 (m, 1H), 4.57 (t, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 9.8 Hz, 1H), 6.86 (s, 1H), 7.06 (s, 1H), 7.17 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.53 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 8.02 (s, 1H), 8.20 (s, 1H), 9.07 (s, 1H), 9.11 (s, 1H), 9.87 (s, 1H), 9.91 (s, 1H), 11.39 (s, 1H). MS (FAB) *m*/*z*: 740 (MH^+). HRMS (FAB) for $C_{35}H_{30}ClF_3N_5O_8$ (MH^+): calcd, 740.1735; found, 740.1745.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-[5-[(4,5,6-trimethoxy-1*H*-indol-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10h).** This compound *dl*-**10h** (8.5 mg, 50%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16h** (9.4 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.36 (t, *J* = 9.8 Hz, 1H), 3.81−3.93 (m, 1H), 3.877, 3.879, 3.98, 4.15 (sx4, each 3H), 4.45 (m, 1H), 4.57 (t, *J* = 10.3 Hz, 1H), 4.77 (d, *J* = 10.3 Hz, 1H), 6.68 (s, 1H), 7.06 (s, 1H), 7.35 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 8.21 (s, 1H), 8.99 (s, 1H), 9.15 (s, 1H), 10.02 (s, 1H), 10.09 (s, 1H), 11.44 (s, 1H). MS (FAB) *m*/*z*: 740 (MH^+). HRMS (FAB) for $C_{35}H_{30}ClF_3N_5O_8$ (MH^+): calcd, 740.1735; found, 740.1774.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(4-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]-indole-3-carboxylate [(*S*)-10j].** This compound (*S*)-**10j** (12.5 mg, 73%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16j** (8.8 mg, 25 μmol). $[\alpha]_D^{25} = +57°$ (*c* = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 3.82−3.92 (m, 1H), 3.88, 3.97 (sx2, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.72 (t, *J* = 10.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.58−7.64 (m, 1H), 7.79 (s, 1H), 7.95 (brs, 1H), 8.21 (s, 1H), 10.39 (s, 1H), 10.59 (brs, 1H), 11.74 (s, 1H), 13.10 (brs, 1H). MS (FAB) *m*/*z*: 681 (MH^+). HRMS (FAB) for $C_{33}H_{25}ClF_3N_4O_7$ (MH^+): calcd, 681.1364; found, 681.1388.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(5-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]-indole-3-carboxylate [(*S*)-10k].** This compound (*S*)-**10k** (10.7 mg, 63%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16k** (8.8 mg, 25 μmol). $[\alpha]_D^{25} = +44°$ (*c* = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.46 (dd, *J* = 10.8 Hz, 7.8 Hz, 1H), 3.78−3.84 (m, 1H), 3.77, 3.81 (sx2, each 3H), 4.18−4.26 (m, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.65 (t, *J* = 10.8 Hz, 1H), 7.02 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.11 (s, 1H), 7.25 (d, *J* = 2.9 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.53−7.57 (m, 2H), 7.62 (s, 1H), 7.89 (brs, 1H), 8.14 (s, 1H), 10.38 (s, 1H), 10.53 (brs, 1H), 11.67 (s, 1H), 13.04 (brs, 1H). MS (FAB) *m*/*z*: 681 (MH^+). HRMS (FAB) for $C_{33}H_{25}ClF_3N_4O_7$ (MH^+): calcd, 681.1364; found, 681.1382.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(6-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]-indole-3-carboxylate [(*S*)-10l].** This compound (*S*)-**10l** (13.7 mg, 81%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16l** (8.8 mg, 25 μmol). $[\alpha]_D^{26} = +42°$ (*c* = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 3.82−3.92 (m, 1H), 3.87, 3.89 (sx2, each 3H), 4.25−4.28 (m, 1H), 4.54 (d, *J* = 9.8 Hz, 1H), 4.70−4.75 (m, 1H), 7.00 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.18 (s, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.60 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.66−7.74 (m, 2H), 7.95 (brs, 1H), 8.20 (s, 1H), 10.34 (s, 1H), 10.59 (s, 1H), 11.73 (s, 1H), 13.11 (s, 1H). MS (FAB) *m*/*z*: 681 (MH^+). HRMS (FAB) for $C_{33}H_{25}ClF_3N_4O_7$ (MH^+): calcd, 681.1364; found, 681.1388.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]-indole-3-carboxylate [(*S*)-10m].** This compound (*S*)-**10m** (11.8 mg, 76%) was prepared from (*S*)-**14** (10.3 mg, 23 μmol) and **16m** (8.1 mg, 23 μmol). $[\alpha]_D^{24} = +53°$ (*c* = 0.36, THF). ^{1}H NMR (DMSO-d_6): δ = 3.53 (dd, *J* = 10.5 Hz, 8.3 Hz, 1H), 3.80−3.90 (m, 1H), 3.88, 4.00 (sx2, each 3H), 4.26−4.30 (m, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.72 (t, *J* = 9.3 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.19 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 8.8 Hz, 1.7 Hz, 1H), 7.76 (s, 1H), 7.95 (s, 1H), 8.19 (s, 1H), 10.43 (s, 1H), 10.60 (s, 1H), 11.75 (s, 1H), 13.12 (s, 1H). MS (FAB) *m*/*z*: 681 (MH^+). HRMS (FAB) for $C_{33}H_{25}ClF_3N_4O_7$ (MH^+): calcd, 681.1364; found, 681.1327.

***(S)*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]-indole-3-carboxylate [(*S*)-10n].** This compound (*S*)-**10n** (8.7 mg, 59%) was prepared from (*S*)-**14** (9.0 mg, 20 μmol) and **16n** (8.2 mg, 20 μmol). $[\alpha]_D^{25} = +55°$ (*c* = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 3.82−3.92 (m, 1H), 3.81, 3.86, 3.88, 4.17 (sx4, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.72 (t, *J* = 10.8 Hz, 1H), 7.08 (s, 1H), 7.18 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.69 (s, 1H), 7.95 (brs, 1H), 8.17 (s, 1H), 10.32 (s, 1H), 10.60 (brs, 1H), 11.75 (s, 1H), 13.10 (brs, 1H). MS (FAB) *m*/*z*: 741 (MH^+). HRMS (FAB) for $C_{35}H_{29}ClF_3N_4O_9$ (MH^+): calcd, 741.1575; found, 741.1568.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(naphthalen-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10o).** This compound *dl*-**10o** (10.1 mg, 80%) was prepared from *dl*-**14** (8.5 mg, 19 μmol) and **16o** (6.3 mg, 19 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.37 (t, *J* = 10.3 Hz,

1H), 3.89 (dd, J = 10.7 Hz, 2.9 Hz, 1H), 3.98 (s, 3H), 4.44 (m, 1H), 4.57 (t, J = 9.8 Hz, 1H), 4.76 (d, J = 10.7 Hz, 1H), 7.07 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.55−7.61 (m, 3H), 7.90−8.00 (m, 4H), 8.07 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H), 8.54 (s, 1H), 9.24 (s, 1H), 9.36 (s, 1H), 10.22 (s, 1H), 11.60 (br, 1H). MS (FAB) *m/z*: 661 (MH^+). HRMS (FAB) for $C_{34}H_{25}ClF_3N_4O_5$ (MH^+): calcd, 661.1466; found, 661.1442.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(quinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10p).** This compound *dl*-**10p** (6.4 mg, 42%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16p** (7.6 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 3.37 (t, J = 10.3 Hz, 1H), 3.89 (dd, J = 10.8 Hz, 2.9 Hz, 1H), 3.98 (s, 3H), 4.44 (m, 1H), 4.58 (t, J = 9.8 Hz, 1H), 4.77 (d, J = 10.7 Hz, 1H), 7.07 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 9.8 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.83 (t, J = 7.3 Hz, 1H), 7.97−8.01 (m, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.25 (s, 1H), 8.87 (s, 1H), 9.23 (s, 1H), 9.53 (s, 1H), 9.77 (br, 1H), 10.12 (br, 1H), 10.79 (br, 1H), 11.51 (br, 1H). MS (FAB) *m/z*: 662 (MH^+). HRMS (FAB) for $C_{33}H_{24}ClF_3N_5O_5$ (MH^+): calcd, 662.1418; found, 662.1450.

***dl*- and (*S*)-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(isoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [*dl*- and (*S*)-10q].** These compounds *dl*-**10q** (8.3 mg, 54%) and (*S*)-**10q** (10.3 mg, 68%) were prepared from *dl*- and (*S*)-**14** (each 10.3 mg, 23 μmol) and **16q** (each 7.6 mg, 23 μmol), respectively. *dl*-**10q**: ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.37 (t, J = 8.3 Hz, 1H), 3.87−3.98 (m, 1H), 3.98 (s, 3H), 4.44 (m, 1H), 4.58 (t, J = 8.3 Hz, 1H), 4.77 (d, J = 10.7 Hz, 1H), 7.09 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 8.01−8.06 (m, 2H), 8.10 (d, J = 8.3 Hz, 1H), 8.39 (s, 1H), 8.74 (s, 1H), 9.22 (brs, 1H), 9.26 (s, 1H), 10.19 (brs, 1H), 10.31 (s, 1H), 11.56 (brs, 1H). MS (FAB) *m/z*: 662 (MH^+). HRMS (FAB) for $C_{33}H_{24}ClF_3N_5O_5$ (MH^+): calcd, 662.1418; found, 662.1426. (*S*)-**10q**: $[\alpha]_D^{24}$ = +63° (c = 0.24, THF). The ^{1}H NMR spectrum of (*S*)-**10q** was identical to that described above.

(*S*)-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(5-methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [(*S*)-10r]. This compound (*S*)-**10r** (11.1 mg, 64%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16r** (9.0 mg, 25 μmol). $[\alpha]_D^{25}$ = +66° (c = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (t, J = 10.8 Hz, 1H), 3.84−3.95 (m, 1H), 3.88, 4.08 (sx2, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.73 (t, J = 10.8 Hz, 1H), 7.19 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.95 (brs, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.83 (s, 1H), 9.44 (s, 1H), 10.60 (brs, 1H), 10.68 (s, 1H), 11.72 (s, 1H), 13.10 (brs, 1H). MS (FAB) *m/z*: 692 (MH^+). HRMS (FAB) for $C_{34}H_{26}ClF_3N_5O_6$ (MH^+): calcd, 692.1524; found, 692.1541.

(*S*)-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(6-methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [(*S*)-10s]. This compound (*S*)-**10s** (13.6 mg, 78%) was prepared from (*S*)-**14** (11.2 mg, 25 μmol) and **16s** (9.0 mg, 25 μmol). $[\alpha]_D^{25}$ = +60° (c = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, J = 10.8 Hz, 8.8 Hz, 1H), 3.84−3.94 (m, 1H), 3.89, 3.97 (sx2, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.73 (t, J = 10.8 Hz, 1H), 7.18 (s, 1H), 7.45 (dd, J = 8.8 Hz, 2.9 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.95 (brs, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.38 (s, 1H), 8.61 (s, 1H), 9.32 (s, 1H), 10.59 (s, 1H), 10.66 (s, 1H), 11.72 (s, 1H), 13.11 (s, 1H). MS (FAB) *m/z*: 692 (MH^+). HRMS (FAB) for $C_{34}H_{26}ClF_3N_5O_6$ (MH^+): calcd, 692.1524; found, 692.1510.

(*S*)-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(7-methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [(*S*)-10t]. This compound (*S*)-**10t** (9.4 mg, 68%) was prepared from (*S*)-**14** (9.0 mg, 20 μmol) and **16t** (7.3 mg, 20 μmol). $[\alpha]_D^{25}$ = +71° (c=0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, J = 9.8 Hz, 7.8 Hz, 1H), 3.83−3.93 (m, 1H), 3.88, 3.98 (sx2, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, J = 9.8 Hz, 1H), 4.73 (t, J = 9.8 Hz, 1H), 7.18 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.55 (dd, J = 8.8 Hz, 2.9 Hz, 1H), 7.68−7.76 (m, 2H), 7.95 (brs, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.65 (s, 1H), 9.37 (s, 1H), 10.59 (brs, 1H), 10.62 (s, 1H), 11.71 (s, 1H), 13.10 (brs, 1H). MS (FAB) *m/z*: 692 (MH^+). HRMS (FAB) for $C_{34}H_{26}ClF_3N_5O_6$ (MH^+): calcd, 692.1524; found, 692.1557.

(*S*)-Methyl 4-Chloromethyl-8-hydroxy-6-[5-[(8-methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate [(*S*)-10u]. This compound (*S*)-**10u** (4.0 mg, 52%) was prepared from (*S*)-**14** (4.9 mg, 11 μmol) and **16u** (4.0 mg, 11 μmol). $[\alpha]_D^{25}$ = +53° (c = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.52 (t, J = 9.8 Hz, 1H), 3.82−3.95 (m, 1H), 3.88, 4.08 (sx2, each 3H), 4.25−4.35 (m, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.71 (t, J = 9.8 Hz, 1H), 7.18 (brs, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.95 (brs, 1H), 8.38 (brs, 1H), 8.66 (s, 1H), 9.60 (s, 1H), 10.60 (brs, 1H), 10.70 (s, 1H), 11.72 (s, 1H), 13.10 (brs, 1H). MS (FAB) *m/z*: 692 (MH^+). HRMS (FAB) for $C_{34}H_{26}ClF_3N_5O_6$ (MH^+): calcd, 692.1524; found, 692.1570.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10v).** This compound *dl*-**10v** (15.4 mg, 89%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16v** (9.7 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.37 (t, J = 9.8 Hz, 1H), 3.89 (m, 1H), 3.98, 4.05, 4.07, 4.12 (sx4, each 3H), 4.44 (m, 1H), 4.58 (m, 1H), 4.77 (d, J = 7.3 Hz, 1H), 7.08 (s, 1H), 7.17 (s, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.60 (m, 1H), 8.00 (brs, 1H), 8.37 (s, 1H), 8.87 (s, 1H), 9.06 (s, 1H), 9.23 (s, 1H), 10.25 (br, 1H), 10.92 (br, 1H), 11.58 (br, 1H). MS (FAB) *m/z*: 752 (MH^+). HRMS (FAB) for $C_{36}H_{30}ClF_3N_5O_8$ (MH^+): calcd, 752.1735; found, 752.1759.

***dl*-Methyl 4-Chloromethyl-8-hydroxy-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxycinnolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate (*dl*-10w).** This compound *dl*-**10w** (13.4 mg, 77%) was prepared from *dl*-**14** (10.3 mg, 23 μmol) and **16w** (9.7 mg, 23 μmol). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 3.41 (t, J = 10.3 Hz, 1H), 3.91 (d, J = 10.3 Hz, 1H), 3.99, 4.090, 4.094, 4.15 (sx4, each 3H), 4.45 (m, 1H), 4.60 (t, J = 10.3 Hz, 1H), 4.78 (d, J = 10.7 Hz, 1H), 7.08 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 8.06 (brs, 1H), 8.36 (s, 1H), 8.97 (s, 1H), 9.39 (br, 1H), 10.44 (br, 1H), 10.47 (s, 1H), 11.67 (br, 1H). MS (FAB) *m/z*: 753 (MH^+). HRMS (FAB) for $C_{35}H_{29}ClF_3N_6O_8$ (MH^+): calcd, 753.1687; found, 753.1679.

(*S*)-Methyl 4-Chloromethyl-6-[5-[(5-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12k]. To a solution of (*S*)-**10k** (5.6 mg, 8 μmol) and *p*-nitrophenyl chloroformate (2.0 mg, 10 μmol) in CH_2Cl_2 was added Et_3N (1.4 μL, 10 μmol) at 0 °C, and the mixture was stirred for 50 min. After addition of 4-methylpiperazine (1.4 μL, 12 μmol), the mixture was further stirred overnight. After dilution with $CHCl_3$, the resulting mixture was washed with 10% $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography ($CHCl_3$:MeOH:acetone = 40:3:1) of the residue gave the free base of (*S*)-**12k**. Treatments of this free base with saturated HCl−MeOH (0.1 mL) gave (*S*)-**12k** [1.9 mg, 27% from (*S*)-**10k**]. $[\alpha]_D^{24}$ = +12° (c = 0.19, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.85 (brs, 3H), 3.11−3.70 (m, 7H), 3.80−3.90 (m, 1H), 3.83, 3.92 (sx2, each 3H), 4.10−4.23 (m, 1H), 4.42 (brs, 2H), 4.59 (d, J = 10.8 Hz, 1H), 4.81 (t, J = 10.8 Hz, 1H), 7.09 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.22 (s, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.55−7.65 (m, 2H), 7.70 (s, 1H), 8.20 (s, 1H), 8.22 (s, 1H), 10.46 (s, 1H), 10.85 (brs, 1H), 11.66 (s, 1H), 13.17 (brs,

1H). MS (FAB) *m/z*: 807 (free base) (MH^+). HRMS (FAB) for $C_{39}H_{35}ClF_3N_6O_8$ (free base) (MH^+): calcd, 807.2157; found, 807.2125.

Other prodrugs of the seco-Cl-MCTFCPI derivatives (*S*)-**12l**−**n**,**q**,**v** were prepared in the same manner as described above.

(*S*)-Methyl 4-Chloromethyl-6-[5-[(6-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12l]. This compound (*S*)-**12l** (3.7 mg, 46%) was prepared from (*S*)-**10l** (6.5 mg, 10 μmol). $[\alpha]_D^{24} = +5.8°$ (*c* = 0.13, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.86 (brs, 3H), 3.10−3.70 (m, 7H), 3.88−3.97 (m, 1H), 3.87, 3.92 (sx2, each 3H), 4.16 (m, 1H), 4.42 (m, 2H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H), 7.00 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.22 (s, 1H), 7.27 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.66−7.76 (m, 2H), 8.20 (s, 1H), 8.21 (s, 1H), 10.35 (s, 1H), 10.55 (brs, 1H), 11.64 (s, 1H), 13.15 (brs, 1H). MS (FAB) *m/z*: 807 (free base) (MH^+). HRMS (FAB) for $C_{39}H_{35}ClF_3N_6O_8$ (free base) (MH^+): calcd, 807.2157; found, 807.2155.

(*S*)-Methyl 4-Chloromethyl-6-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12m]. This compound (*S*)-**12m** (17.5 mg, 61%) was prepared from (*S*)-**10m** (23.0 mg, 34 μmol). Mp: 225−240 °C dec. $[\alpha]_D^{24} = +26°$ (*c* = 0.4, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.86 (s, 3H), 3.20−3.69 (m, 6H), 3.62 (t, *J* = 10.3 Hz, 1H), 3.94 (m, 1H), 3.92, 4.01 (sx2, each 3H), 4.19 (m, 1H), 4.43 (m, 2H), 4.63 (d, *J* = 10.3 Hz, 1H), 4.78 (t, *J* = 9.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.62 (dd, *J* = 8.8 Hz, 1.5 Hz, 1H), 7.75 (s, 1H), 8.20 (s, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 10.40 (s, 1H), 11.21 (brs, 1H), 11.63 (s, 1H), 13.11 (s, 1H). IR (KBr): 3411, 1720 cm^{-1}. MS (FAB) *m/z*: 807 (MH^+). HRMS (FAB) for $C_{39}H_{35}ClF_3N_6O_8$ (free base) (MH^+): calcd, 807.2157; found, 807.2191. Anal. ($C_{39}H_{34}ClF_3N_6O_8$·HCl·9/2H_2O) C, H, N.

(*S*)-Methyl 4-Chloromethyl-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12n]. This compound (*S*)-**12n** (1.0 mg, 14%) was prepared from (*S*)-**10n** (5.7 mg, 8 μmol). $[\alpha]_D^{25} = +22°$ (*c* = 0.13, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.86 (brs, 3H), 3.10−3.70 (m, 7H), 3.89−3.98 (m, 1H), 3.81, 3.86, 3.91, 4.17 (sx4, each 3H), 4.01−4.24 (m, 1H), 4.42 (m, 2H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.81 (t, *J* = 10.8 Hz, 1H), 7.08 (s, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.69 (s, 1H), 8.18 (brs, 1H), 8.20 (s, 1H), 10.33 (s, 1H), 10.70 (brs, 1H), 11.67 (s, 1H), 13.16 (brs, 1H). MS (FAB) *m/z*: 867 (free base) (MH^+). HRMS (FAB) for $C_{41}H_{39}ClF_3N_6O_{10}$ (free base) (MH^+): calcd, 867.2368; found, 867.2365.

(*S*)-Methyl 4-Chloromethyl-6-[5-[(isoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12q]. This compound (*S*)-**12q** (37.8 mg, 66%) was prepared from (*S*)-**10q** (40.2 mg, 70 μmol). $[\alpha]_D^{25} = +40°$ (*c* = 0.20, DMF). ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 3H), 3.20−3.65 (m, 7H), 3.85−4.00 (m, 1H), 3.92 (s, 3H), 4.15−4.25 (m, 1H), 4.43 (m, 2H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.82 (t, *J* = 10.3 Hz, 1H), 7.23 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 6.8 Hz, 1.0 Hz, 1H), 7.92 (dd, *J* = 6.8 Hz, 1.0 Hz, 1H), 8.21 (s, 2H), 8.27 (d, *J* = 8.3 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.41 (s, 1H), 8.73 (s, 1H), 9.49 (s, 1H), 10.45 (br, 1H), 10.71 (s, 1H), 11.65 (brs, 1H), 13.14 (s, 1H). MS (FAB) *m/z*: 788 (free base) (MH^+). HRMS (FAB) for $C_{39}H_{34}ClF_3N_7O_6$ (free base) (MH^+): calcd, 788.2211; found, 788.2185.

(*S*)-Methyl 4-Chloromethyl-8-[(4-methylpiperazin-1-ylcarbonyl)oxy]-2-trifluoromethyl-6-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indol-2-ylcarbonyl]-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate Hydrochloride [(*S*)-12v]. This compound (*S*)-**12v** (12.4 mg, 50%) was prepared from (*S*)-**10v** (20.4 mg, 27 μmol). $[\alpha]_D^{26} = +38°$ (*c* = 0.40, MeOH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.30 (s, 3H), 2.47 (s, 4H), 3.39 (t, *J* = 9.3 Hz, 1H), 3.63 (s, 2H), 3.78 (s, 2H), 3.84 (dd, *J* = 11.2 Hz, 3.4 Hz, 1H), 3.96, 4.04, 4.05, 4.12 (sx4, each 3H), 4.52−4.59 (m, 2H), 4.74 (d, *J* = 9.8 Hz, 1H), 7.01 (s, 1H), 7.12 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 8.90 (s, 1H), 9.02 (s, 1H), 9.57 (br, 1H), 10.20 (s, 1H). MS (FAB) *m/z*: 878 (free base) (MH^+). HRMS (FAB) for $C_{42}H_{40}ClF_3N_7O_9$ (free base) (MH^+): calcd, 878.2528; found, 878.2532.

5,6,7-Trimethoxybenzofuran-2-carboxylic Acid (16d). A solution of **17** (100 mg, 0.54 mmol) and hexamethylenetetramine (75.7 mg, 0.54 mmol) in TFA (0.5 mL) was heated at reflux for 4 h. After the reaction was quenched with addition of ice, the resulting mixture was further stirred for 15 min and extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (benzene:acetone = 10:1) of the residue gave **18** as a powder (79.4 mg, 69%). Mp: 41−43 °C (recrystallized from hexane) (lit.[13] mp 39−40 °C). ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 6.72 (s, 1H), 9.76 (s, 1H), 10.97 (brs, 1H).

A suspension of **18** (531 mg, 2.5 mmol), ethyl bromoacetate (0.30 mL, 2.8 mmol), and K_2CO_3 (691 mg, 5.0 mmol) in DMF (5 mL) was heated at 80 °C for 20 h. After cooling, filtration and concentration in vacuo gave a residue, which was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (benzene:AcOEt = 20:1) of the residue gave **19** as colorless needles (435 mg, 62%). Mp: 55−57 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 4.24 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 6.78 (s, 1H), 7.43 (s, 1H). IR (KBr): 1720 cm^{-1}. MS (EI) *m/z*: 280 (M^+). Anal. ($C_{14}H_{16}O_6$) C, H, N.

A mixture of **19** (100 mg, 0.36 mmol) and 20% KOH (0.3 mL) in EtOH (1.5 mL) was stirred at 0 °C for 2.5 h. After the reaction was quenched with addition of 10% citric acid solution, the resulting precipitates were collected by filtration, washed with hexane, and then dried in vacuo to give **16d** as a colorless powder (71.6 mg, 79%). Mp: 185−187 °C. ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H), 3.83 (s, 3H), 4.07 (s, 3H), 7.03 (s, 1H), 7.56 (s, 1H), 13.50 (brs, 1H). IR (KBr): 1686 cm^{-1}. MS (EI) *m/z*: 252 (M^+). Anal. ($C_{12}H_{12}O_6$) C, H, N.

5-(Benzofuran-2-yl)-1*H*-indole-2-carboxylic Acid (16e). A solution of **22** (254 mg, 1.0 mmol), benzofuran-2-boric acid (194 mg, 1.2 mmol, commercially available), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), and Et_3N (1.4 mL, 10 mmol) was heated at 100 °C for 2.5 h. After dilution with water, the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2) of the residue gave **23** as pale yellow crystals (128 mg, 44%). Mp: 220.5−221.5 °C. ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H), 7.00 (s, 1H), 7.20−7.27 (m, 3H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.77 (dd, *J* = 8.8 Hz, 1.5 Hz, 1H), 8.20 (s, 1H).

A mixture of **23** (84.2 mg, 0.29 mmol) and 20% KOH (0.7 mL) in MeOH (0.7 mL) and DMSO (0.7 mL) was stirred at 50 °C for 1 h. After the reaction was quenched by the addition of 10% citric acid solution, the resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **16e** as a pale yellow powder (78.2 mg, 98%). Mp: 280 °C dec. ^{1}H NMR (DMSO-d_6): δ 7.20−7.31 (m, 4H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.60−7.64 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 8.21 (s, 1H), 11.98 (s, 1H), 13.11 (br, 1H). IR (KBr): 3439, 1672 cm^{-1}. MS (EI) *m/z*: 277 (M^+). Anal. ($C_{17}H_{11}NO_3$ 1/10H_2O) C, H, N.

5-[(5,6,7-Trimethoxy-1*H*-indol-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16g). To a solution of ethyl 5-aminoindole-2-carboxylate[4c] (102 mg, 0.50 mmol) and **16b**[9] (126 mg, 0.50 mmol) was added EDCI (288 mg, 1.5 mmol) at room temperature, and the mixture was stirred for overnight. After dilution with water, the resulting precipitates were

collected by filtration, washed with water and MeOH, and then dried in vacuo to give the ethyl ester of **16g** as pale yellow crystals (162 mg, 74%). Mp: 272−273 °C. ^{1}H NMR (DMSO-d_6): δ 1.36 (t, J = 6.8 Hz, 3H), 3.80, 3.82, 3.97 (sx3, each 3H), 4.35 (q, J = 6.8 Hz, 2H), 6.94 (s, 1H), 7.15 (s, 1H), 7.23 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.57 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 8.15 (s, 1H), 10.03 (s, 1H), 11.42 (s, 1H), 11.86 (s, 1H). Anal. ($C_{23}H_{23}N_3O_6$) C, H, N.

A mixture of the ethyl ester of **16g** (131.2 mg, 0.30 mmol) and 20% KOH (1 mL) in EtOH (1 mL) was stirred at 60 °C for 1 h. After the reaction was quenched by the addition of concentrated HCl, the resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **16g** as a pale yellow powder (109 mg, 89%). Mp: 237−238 °C. ^{1}H NMR (DMSO-d_6): δ 3.79, 3.82, 3.96 (sx3, each 3H), 6.95 (s, 1H), 7.08 (d, J = 1.5 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 9.3 Hz, 1H), 7.54 (dd, J = 9.3 Hz, 2.0 Hz, 1H), 8.12 (s, 1H), 10.02 (s, 1H), 11.44 (s, 1H), 11.74 (s, 1H), 12.96 (br, 1H). IR (KBr): 3416, 1699, 1647 cm^{-1}. MS (FAB) *m/z*: 410 (MH^+). Anal. ($C_{21}H_{19}N_3O_6$) C, H, N.

Other carboxylic acids **16h**,**j**−**w** were prepared in the same manner as described above.

5-[(4,5,6-Trimethoxy-1*H*-indol-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16h). The ethyl ester of **16h** (151 mg, 69%) was prepared from ethyl 5-aminoindole-2-carboxylate (102 mg, 0.50 mmol) and **16c** (126 mg, 0.50 mmol). Hydrolysis of the ethyl ester of **16h** (87.5 mg, 0.20 mmol) gave **16h** (75.4 mg, 63%). Mp: 284−285 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.71, 3.81, 4.05 (sx3, each 3H), 6.71 (s, 1H), 7.08 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.57 (dd, J = 9.3 Hz, 2.0 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 9.99 (s, 1H), 11.51 (d, J = 2.0 Hz, 1H), 11.73 (s, 1H), 12.91 (brs, 1H). IR (KBr): 3298, 1685, 1630 cm^{-1}. MS (EI) *m/z*: 409 (M^+). Anal. ($C_{21}H_{19}N_3O_6 \cdot 9/5H_2O$) C, H, N.

5-[(4-Methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16j). The ethyl ester of **16j** (48.5 mg, 53%) was prepared from ethyl 5-aminoindole-2-carboxylate (49.0 mg, 0.24 mmol) and 4-methoxybenzofuran-2-carboxylic acid (46.1 mg, 0.24 mmol). Hydrolysis of the ethyl ester of **16j** (45.4 mg, 0.12 mmol) gave **16j** (20.4 mg, 49%). Mp: 255−257 °C. ^{1}H NMR (DMSO-d_6): δ 3.96 (s, 3H), 6.89 (d, J = 7.8 Hz, 1H), 7.07 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.56 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.78 (s, 1H), 8.14 (s, 1H), 10.35 (s, 1H), 11.72 (brs, 1H), 13.00 (brs, 1H). IR (KBr): 3293, 1688 cm^{-1}. MS (EI) *m/z*: 350 (M^+). HRMS (EI) for $C_{19}H_{14}N_2O_5$ (M^+): calcd, 350.0903; found, 350.0945.

5-[(5-Methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16k). The ethyl ester of **16k** (108 mg, 58%) was prepared from ethyl 5-aminoindole-2-carboxylate (100 mg, 0.49 mmol) and 5-methoxybenzofuran-2-carboxylic acid (94.2 mg, 0.49 mmol). Hydrolysis of the ethyl ester of **16k** (100 mg, 0.26 mmol) gave **16k** (61.1 mg, 67%). Mp: 232−235 °C. ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 3H), 7.08 (dd, J = 8.8 Hz, 2.9 Hz, 1H), 7.09 (s, 1H), 7.31 (d, J = 2.9 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.58 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 8.13 (s, 1H), 10.41 (brs, 1H), 11.27 (brs, 1H), 11.77 (brs, 1H). IR (KBr): 3238, 1672 cm^{-1}. MS (EI) *m/z*: 350 (M^+). Anal. ($C_{19}H_{14}N_2O_5 \cdot H_2O$) C, H, N.

5-[(6-Methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16l). The ethyl ester of **16l** (44.0 mg, 24%) was prepared from ethyl 5-aminoindole-2-carboxylate (100 mg, 0.49 mmol) and 6-methoxybenzofuran-2-carboxylic acid (94.2 mg, 0.49 mmol). Hydrolysis of the ethyl ester of **16l** (45.4 mg, 0.12 mmol) gave **16l** (30.0 mg, 78%). Mp: 278−281 °C. ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H), 7.00 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.01 (s, 1H), 7.28 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.66−7.74 (m, 2H), 8.13 (s, 1H), 10.30 (s, 1H), 11.74 (s, 1H), 12.60−13.40 (br, 1H). IR (KBr): 3281, 1671 cm^{-1}. MS (EI) *m/z*: 350 (M^+). Anal. ($C_{19}H_{14}N_2O_5 \cdot 1/2H_2O$) C, H, N.

5-[(7-Methoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16m). This compound **16m** (5.84 g, 83%) was prepared from ethyl 5-aminoindole-2-carboxylate (4.08 g, 20 mmol) and 7-methoxybenzofuran-2-carboxylic acid (3.84 g, 20 mmol). Ethyl ester of **16m**: mp 196.5−197.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.35 (t, J = 6.8 Hz, 1H), 4.00 (s, 3H), 4.35 (q, J = 14.2 Hz, 6.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 1H), 7.17 (s, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 9.3 Hz, 1H), 7.61 (m, 1H), 7.74 (d, J = 1.0 Hz, 1H), 8.15 (dd, J = 4.4 Hz, 2.0 Hz, 1H), 10.40 (s, 1H), 11.89 (s, 1H). IR (KBr): 3321, 1697 cm^{-1}. MS (EI) *m/z*: 378 (M^+). Anal. ($C_{21}H_{18}N_2O_5 \cdot 1/2H_2O$) C, H, N.

16m: mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 3.99 (s, 3H), 7.09−7.11 (m, 2H), 7.28 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.58 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.74 (s, 1H), 8.14 (s, 1H), 10.38 (s, 1H), 11.76 (s, 1H), 12.97 (br, 1H). IR (KBr): 3260, 1670 cm^{-1}. MS (EI) *m/z*: 350 (M^+). Anal. ($C_{19}H_{14}N_2O_5 \cdot 1/4H_2O$) C, H, N.

5-[(5,6,7-Trimethoxybenzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16n). The ethyl ester of **16n** (26.8 mg, 61%) was prepared from ethyl 5-aminoindole-2-carboxylate (20.4 mg, 0.10 mmol) and **16d** (25.2 mg, 0.10 mmol). Hydrolysis of the ethyl ester of **16n** (25.0 mg, 57 mmol) gave **16n** (17.5 mg, 75%). Mp: 259−261 °C. ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H), 3.85 (s, 3H), 4.16 (s, 3H), 7.08 (s, 1H), 7.09 (s, 1H), 7.42 (d, J = 9.8 Hz, 1H), 7.52−7.59 (m, 1H), 7.69 (s, 1H), 8.09 (s, 1H), 10.28 (s, 1H), 11.76 (brs, 1H), 13.00 (brs, 1H). IR (KBr): 3275, 1676 cm^{-1}. MS (EI) *m/z*: 410 (M^+). Anal. ($C_{21}H_{18}N_2O_7 \cdot 5/4H_2O$) C, H, N.

5-[(Naphthalen-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16o). To a solution of ethyl 5-aminoindole-2-carboxylate (30.6 mg, 0.15 mmol) and Et_3N (21 μL, 0.15 mmol) in THF (1 mL) was added a solution of 2-naphthoyl chloride (28.6 mg, 0.15 mmol) in THF (1 mL) at 0 °C, and the mixture was stirred for 1 h. After concentration of the reaction mixture in vacuo, the crude ethyl ester was hydrolyzed in the same manner as described for the preparation of **16g**, giving **16o** (48.0 mg, 97%). Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.72 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.46 (m, 1H), 7.60−7.66 (m, 2H), 8.00−8.10 (m, 5H), 8.60 (s, 1H), 10.27 (s, 1H), 11.15 (br, 1H). IR (KBr): 3256, 1639 cm^{-1}. MS (FAB) *m/z*: 331 (MH^+). HRMS (FAB) for $C_{20}H_{15}N_2O_3$ (MH^+): calcd, 331.1083; found, 331.1064.

5-[(Quinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16p). The ethyl ester of **16p** (153 mg, 85%) was prepared from ethyl 5-aminoindole-2-carboxylate (102 mg, 0.50 mmol) and quinoline-3-carboxylic acid (86.6 mg, 0.50 mmol, commercially available). Hydrolysis of the ethyl ester of **16p** (108 mg, 0.30 mmol) gave **16p** (71.7 mg, 72%). Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 7.12 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.60 (dd, J = 9.3 Hz, 2.0 Hz, 1H), 7.73 (t, J = 6.8 Hz, 1H), 7.90 (t, J = 6.8 Hz, 1H), 8.12−8.20 (m, 3H), 8.98 (d, J = 2.0 Hz, 1H), 9.32 (d, J = 2.0 Hz, 1H), 9.39 (d, J = 2.4 Hz, 1H), 10.55 (s, 1H), 11.79 (s, 1H), 12.76 (br, 1H). IR (KBr): 3287, 1647 cm^{-1}. MS (FAB) *m/z*: 332 (MH^+). Anal. ($C_{19}H_{13}N_3O_3 \cdot 1/2H_2O$) C, H, N.

5-[(Isoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16q). This compound **16q** (62.7 mg, 38%), mp >300 °C, was prepared from ethyl 5-aminoindole-2-carboxylate (102 mg, 0.50 mmol) and isoquinoline-3-carboxylic acid (86.6 mg, 0.50 mmol, commercially available). ^{1}H NMR (DMSO-d_6): δ 7.09 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.71 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.85 (t, J = 6.8 Hz, 1H), 7.92 (t, J = 6.8 Hz, 1H), 8.26−8.33 (m, 3H), 8.71 (s, 1H), 9.48 (s, 1H), 10.67 (s, 1H), 11.75 (s, 1H). IR (KBr): 3298, 1667, 1535 cm^{-1}. MS (FAB) *m/z*: 332 (MH^+). Anal. ($C_{19}H_{13}N_3O_3 \cdot 1/2H_2O$) C, H, N.

5-[(5-Methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16r). The ethyl ester of **16r** (25.1 mg, 54%) was prepared from ethyl 5-aminoindole-2-carboxylate (24.5 mg, 0.12 mmol) and **35a** (25.0 mg, 0.12 mmol). Hydrolysis of the ethyl ester of **16r** (23.0 mg, 60 μmol) gave **16r** (18.6 mg, 86%). Mp: 265−267 °C. ^{1}H NMR (DMSO-d_6): δ 4.08 (s, 3H), 6.93 (brs, 1H), 7.34−7.42 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.58−7.66 (m, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.25 (brs, 1H), 8.80 (s, 1H), 9.43 (s, 1H), 10.60 (brs, 1H), 11.49 (brs, 1H). IR (KBr): 3312, 1684, 1652 cm^{-1}. MS (FAB) *m/z*: 362 (MH^+). Anal. ($C_{20}H_{15}N_3O_4 \cdot 6/5H_2O$) C, H, N.

5-[(6-Methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16s). The ethyl ester of **16s** (82.9 mg, 61%) was prepared from ethyl 5-aminoindole-2-carboxylate (71.5 mg, 0.35 mmol) and **27a** (71.1 mg, 0.35 mmol). Hydrolysis of the ethyl ester of **16s** (80.0 mg, 0.21 mmol) gave **16s** (61.5 mg, 81%). Mp: 267−269 °C. ^{1}H NMR (DMSO-d_6): δ 3.97 (s, 3H), 7.09 (s, 3H), 7.43 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 8.8 Hz, 2.9 Hz, 1H), 7.67 (d, J = 2.9 Hz, 1H), 7.69 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H), 8.59 (s, 1H), 9.31 (s, 1H), 10.63 (s, 1H), 11.74 (s, 1H). IR (KBr): 3292, 1698, 1624 cm^{-1}. MS (FAB) *m/z*: 362 (MH^+). Anal. ($C_{20}H_{15}N_3O_4 \cdot 1/4H_2O$) C, H, N.

5-[(7-Methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16t). The ethyl ester of **16t** (29.5 mg, 58%) was prepared from ethyl 5-aminoindole-2-carboxylate (25.5 mg, 0.13 mmol) and **31** (25.5 mg, 0.13 mmol). Hydrolysis of the ethyl ester of **16t** (28.5 mg, 70 μmol) gave **16t** (19.4 mg, 73%). Mp: 290−293 °C. ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 3H), 6.95 (brs, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.54 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.64 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.27 (brs, 1H), 8.63 (s, 1H), 9.35 (s, 1H), 10.55 (s, 1H), 11.52 (s, 1H). IR (KBr): 3335, 1679, 1620 cm^{-1}. MS (FAB) *m/z*: 362 (MH^+). Anal. ($C_{20}H_{15}N_3O_4 \cdot 1/4H_2O$) C, H, N.

5-[(8-Methoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16u). This compound **16u** (4.4 mg, 52%) was prepared from ethyl 5-aminoindole-2-carboxylate (4.7 mg, 23 μmol) and **27b** (4.7 mg, 23 μmol). ^{1}H NMR (DMSO-d_6): δ = 4.08 (s, 3H), 6.59 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.65 (brs, 1H), 7.77−7.86 (m, 2H), 8.26 (s, 1H), 8.63 (s, 1H), 9.58 (s, 1H), 10.64 (brs, 1H), 11.64 (brs, 1H). Without collecting further analytical data, **16u** was directly subjected to the next reaction.

5-[(5,6,7-Trimethoxyisoquinolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16v). This compound **16v** (16.8 mg, 50%) was prepared from ethyl 5-aminoindole-2-carboxylate (16.3 mg, 80 μmol) and **35b** (21 mg, 80 μmol). MS (FAB) *m/z*: 422 (MH^+). HRMS (FAB) for $C_{22}H_{20}N_3O_6$ (MH^+): calcd, 422.1352; found, 422.1380. Without collecting further analytical data, **16v** was directly subjected to the next reaction.

5-[(5,6,7-Trimethoxycinnolin-3-ylcarbonyl)amino]-1*H*-indole-2-carboxylic Acid (16w). This compound **16w** (29.5 mg, 47%), mp 260 °C dec, was prepared from ethyl 5-aminoindole-2-carboxylate (30.6 mg, 0.15 mmol) and **41** (39.6 mg, 0.15 mmol). ^{1}H NMR (DMSO-d_6): δ 4.01, 4.10, 4.12 (sx3, each 3H), 7.11 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 8.33 (s, 1H), 8.69 (s, 1H), 11.07 (s, 1H), 11.77 (s, 1H), 12.97 (br, 1H). IR (KBr): 3290, 1684 cm^{-1}. MS (FAB) *m/z*: 423 (MH^+). HRMS (FAB) for $C_{21}H_{19}N_4O_6$ (MH^+): calcd, 423.1305; found, 423.1298.

6-Methoxyisoquinoline-3-carboxylic Acid (27a) and 8-Methoxyisoquinoline-3-carboxylic Acid (27b). To a solution of **24** (1.00 g, 5.1 mmol) in 0.5 N NaOH solution (7 mL) was added 37% formaldehyde solution (0.8 mL), and the mixture was stirred at 37 °C for 27 h. After the reaction mixture was concentrated in vacuo to one-half volume, concentrated HCl (1 mL) was added. The acidic mixture was concentrated in vacuo, and the residue was dissolved in MeOH (12 mL). The cooled methanolic solution was saturated with dry hydrogen chloride and heated at reflux for 2 h. After concentration in vacuo, the residue was added to cold water. The aqueous solution was saturated with Na_2CO_3 and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo, giving a mixture of **25a**,**b** as a yellow oil (344 mg, 30%). This mixture was directly used for the next step without separation and collecting analytical data. A suspension of the mixture of **25a**,**b** and 10% Pd−C (275 mg) in xylene (30 mL) was heated at reflux for 3.5 h. After filtration, the reaction mixture was concentrated in vacuo, and the residue was separated by flash chromatography (CH_2Cl_2:AcOEt = 7:3) to give **26a** as a colorless powder (106 mg, 9.6% from **24**) and **26b** as a colorless powder (6.6 mg, 0.6% from **24**). **26a**: ^{1}H NMR ($CDCl_3$): δ 3.98, 4.06 (sx2, each 3H), 7.21 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.51 (s, 1H), 9.19 (s, 1H). **26b**: ^{1}H NMR ($CDCl_3$): δ 4.06 (s, 3Hx2), 7.03 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 8.53 (s, 1H), 9.69 (s, 1H).

Hydrolysis of **26a**,**b** in a manner similar to that described for the preparation of **16d** from **19** gave **27a** (79.0 mg, 79%) and **27b** (4.7 mg, 76%), respectively. **27a**: mp 178−180 °C. ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H), 7.25−7.26 (m, 1H), 7.41 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.56 (s, 1H), 9.07 (s, 1H). IR (KBr): 3411, 1649 cm^{-1}. MS (EI) *m/z*: 203 (M^+). Anal. ($C_{11}H_9NO_3 \cdot 5/4H_2O$) C, H, N. As for **27b**, it was directly subjected to the next reaction without collecting analytical data.

7-Methoxyisoquinoline-3-carboxylic Acid (31). To a solution of **28** (500 mg, 2.1 mmol) was added oxalyl chloride (0.20 mL, 2.3 mmol) at room temperature, and the mixture was stirred for 30 min. To the mixture was added $FeCl_3$ (409 mg, 2.5 mmol) at −10 °C, and the resulting mixture was stirred at room temperature for 5 h. After the reaction was quenched by the addition of 1 N HCl, the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was dissolved in MeOH−H_2SO_4 (19:1) (12 mL), and the solution was heated at reflux for 4 h. After the reaction was quenched by the addition of 10% $NaHCO_3$ solution, the mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2) of the residue gave **29** (64.9 mg). This material was directly subjected to the next reaction without collecting analytical data. A suspension of **29** (64.9 mg) and 10% Pd−C (52 mg) in xylene (5 mL) was heated at 100 °C for 3.5 h. The reaction mixture was concentrated in vacuo after filtration, and the residue was purified by preparative TLC (CH_2Cl_2:AcOEt = 7:3) to give **30** as a pale yellow powder (37.1 mg, 8.1% from **28**). ^{1}H NMR ($CDCl_3$): δ 3.99, 4.05 (sx2, each 3H), 7.31 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 8.52 (s, 1H), 9.23 (s, 1H). **30**: ^{1}H NMR ($CDCl_3$): δ 4.01 (s, 3H), 7.34 (d, J = 2.0 Hz, 1H), 7.48 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 8.60 (s, 1H), 9.10 (s, 1H).

Hydrolysis of the ethyl ester **30** in MeOH in a manner similar to that described for the preparation of **16d** from **19** gave **31** (26.5 mg, 77%). Without collecting further analytical data, **31** was directly subjected to the next reaction.

5-Methoxyisoquinoline-3-carboxylic Acid (35a). To a solution of **32a** (500 mg, 3.3 mmol) and methyl azidoacetate (3.80 g, 33 mmol) in MeOH (16 mL) was added NaOMe solution [prepared from Na (607 mg) in MeOH (6 mL)] at −10 °C, and the mixture was stirred at 0 °C for 17.5 h. After the reaction was quenched by the addition of ice, the resulting precipitates were collected by filtration, washed with water, and dried in vacuo to give **33a** as a pale yellow powder (512 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 2.26, 3.83, 3.91 (sx3, each 3H), 6.76 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 7.23 (t, J = 7.8 Hz, 1H).

This material **33a** was directly subjected to the next reaction. A solution of **33a** (500 mg, 2.0 mmol) in xylene (30 mL) was heated at reflux for 9.5 h. After concentration in vacuo, flash chromatography (CH_2Cl_2) of the residue gave **34a** (43.3 mg, 10%) and **36a** (332 mg). ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.74 (s, 1H).

Without collecting further analytical data, **36a** was directly subjected to the next reaction. A solution of **36a** in 1,2-dichlorobenzene (20 mL) was heated at reflux for 6 h. After concentration in vacuo, flash chromatography (CH_2Cl_2) of the residue gave **34a** (total 212 mg, 49%) as a colorless powder. ^{1}H NMR ($CDCl_3$): δ 4.056, 4.064 (sx2, each 3H), 7.09 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 8.96 (s, 1H), 9.28 (s, 1H).

Hydrolysis of the ethyl ester **34a** (42.0 mg, 0.19 mmol) in MeOH in a manner similar to that described for the preparation of **16d** from **19** gave **35a** (28.3 mg, 73%). Mp: 104−106

°C. ^{1}H NMR ($CDCl_3$): δ 4.056, 4.064 (sx2, each 3H), 7.09 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 8.96 (s, 1H), 9.28 (s, 1H). IR (KBr): 1727 cm^{-1}. MS (EI) m/z: 217 (M^+). Anal. ($C_{12}H_{11}NO_3$) C, H, N.

5,6,7-Trimethoxyisoquinoline-3-carboxylic Acid (33b). The same treatments of **32b** (930 mg, 4.4 mmol) as described for the preparation of **33a** gave **33b** (552 mg, 41%). IR (KBr): 2126, 1717 cm^{-1}.

Treatments of **33b** (307 mg, 1.0 mmol) in a manner similar to that described for the preparation of **34a** from **33a** gave **34b** (113 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 4.03, 4.045, 4.054, 4.10 (sx4, each 3H), 7.12 (s, 1H), 8.76 (s, 1H), 9.14 (s, 1H). IR (KBr): 1711 cm^{-1}. MS (EI) m/z: 277 (M^+). HRMS (EI) for $C_{14}H_{15}NO_5$ (M^+): calcd, 277.0950; found, 277.0961.

Hydrolysis of **34b** (65.3 mg, 0.24 mmol) in the same manner as described for the preparation of **35a** from **33a** gave **35b** (51.6 mg, 83%). MS (EI) m/z: 263 (M^+). HRMS (EI) for $C_{13}H_{13}NO_5$ (M^+): calcd, 263.0794; found, 263.0793. Without collecting further analytical data, **38b** was directly subjected to the next reaction.

5,6,7-Trimethoxycinnoline-3-carboxylic acid (41). To a solution of **37** (3.66 g, 20 mmol) in water (50 mL) and concentrated HCl (4.2 mL) was added a solution of $NaNO_2$ (1.73 g, 25 mmol) in water (5 mL) at 2−3 °C, and the mixture was stirred at the same temperature for 5 min. To a solution of the diazonium salt were added concentrated HCl (6.7 mL) and $NaBF_4$ (8.78 g, 80 mmol) at 0 °C, and the mixture was further stirred for 30 min. The resulting precipitates were collected by filtration, washed with water, MeOH, and ether, and then dried in vacuo to give **38** as colorless crystals (4.58 g, 81%). The diazonium salt **38** was used for the next step without further purification. To a solution of **39** (0.92 g, 5.0 mmol) in MeCN (75 mL) was added **38** (1.41 g, 5.0 mmol) at room temperature, and the mixture was stirred for 2.5 h. The reaction mixture was heated at 80 °C for 2 h. After cooling, the mixture was concentration in vacuo. The residue was purified by flash chromatography (CH_2Cl_2:AcOEt = 4:1) followed by washing with ether giving **40** as pale yellow needles (1.35 g, 93%). Mp: 147−148 °C. ^{1}H NMR ($CDCl_3$): δ 1.52 (t, J = 7.3 Hz, 3H), 4.06, 4.118, 4.124 (sx3, each 3H), 4.61 (q, J = 14.2 Hz, 7.3 Hz, 2H), 7.72 (s, 1H), 8.78 (s, 1H). IR (KBr): 1712 cm^{-1}. MS (EI) m/z: 292 (M^+). Anal. ($C_{14}H_{16}N_2O_5$) C, H, N.

Hydrolysis of the ester **40** (292 mg, 1.0 mmol) in a manner similar to that described for the preparation of **16d** from **19** gave **41** as pale yellow crystals (202 mg, 77%). Mp: 195 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.98, 4.07, 4.10 (sx3, each 3H), 7.80 (s, 1H), 8.58 (s, 1H), 13.64 (br, 1H). IR (KBr): 3535, 1608 cm^{-1}. MS (EI) m/z: 264 (M^+). Anal. ($C_{12}H_{12}N_2O_5 \cdot 3/2H_2O$) C, H, N.

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Supporting Information Available: Synthetic procedures and characterization data for the compounds *dl*- and (*S*)-**14**, *dl*- and/or (*S*)-**10a**,**b**,**f**,**i**, *dl*- and/or (*S*)-**11a**,**b**,**f**,**i**, and (*S*)-**13b**. This information is available free of charge via the Internet at http://pubs.acs.org.

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