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Discovery of hydroxamic acid analogs as dual inhibitors of phosphodiesterase-1 and -5

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Abstract—HTS and the following synthesis of a series of the compounds led us to the discovery of hydroxamic acid analogs as potent dual inhibitors of phosphodiesterase (PDE)-1 and 5. These compounds have highly related structure and deviation of the structure usually resulted in reduced potency. This result can be used to design other molecules that may be utilized for the therapy of cardiovascular symptoms that relates to cGMP level.

cGMP is one of the representative second messengers of intracellular signal transduction and mediates various cell functions. The signal transduction is based on the phosphorylation of some target proteins that are catalyzed by cGMP-dependent protein kinase. Phosphodiesterase type 1 (PDE-1) and 5 (PDE-5) are the major cGMP hydrolyzing enzymes in blood vessel,[1] and regulate levels of the mediators with guanylyl cyclase which catalyzes the synthesis of cGMP from GTP. PDE-1 and -5 have also been identified in platelets.[2] The inhibitors of PDE-1 and -5 are expected as drug candidates for cardiovascular diseases, such as hypertension, angina, cardiac failure, and obstructive arteriosclerosis. SCH51866 is known as a dual inhibitor of PDE-1 and -5 (Fig. 1).[3]

We found hydroxamic acid derivative **1** (Fig. 1), which showed dual inhibition of PDE-1 and -5, by high throughput screening of ca. 100,000 compounds which were selected at random from our in-house library. Compound **1** shows potent inhibition toward PDE-5 (IC_{50} = 0.013 μM), while it shows moderate inhibition for PDE-1 (IC_{50} = 2.41 μM, about 200-fold less potent than PDE-5).[4] We started exploratory studies for potent dual inhibitors with strong inhibition of both PDE-1 and -5.

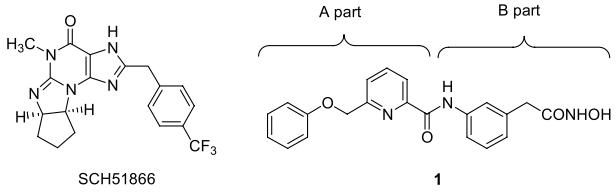

Figure 1. The known dual inhibitor and structure **1** as initial lead.

1. Chemistry

We synthesized the 102 compounds that are listed in Tables 1–3 by the synthetic routes shown in Schemes 1–3. Twenty-eight compounds are listed in a category as Molecule **I**, and their chemical structures are represented in Table 1. Similarly, 27 compounds are listed as Molecule **II** as shown in Table 2. And 47 compounds in Table 3 are shown as Molecule **III**.

1.1. Synthesis of molecule I (Scheme 1)

Reduction of 2,6-pyridinecarboxylic acid diethyl ester (**I-1**) by $NaBH_4$, chlorination by $SOCl_2$, coupling with phenol and saponification under basic condition gave a carboxylic derivative **I-4**. A series of desirable carboxylic acid and hydroxamic acid derivatives were synthesized by amide formation reaction with **I-4** and various kinds of aminobenzoate, amino phenyl acetate, amino thiazole, amino thiadiazole, and amino pyridine acetate derivatives and so on.

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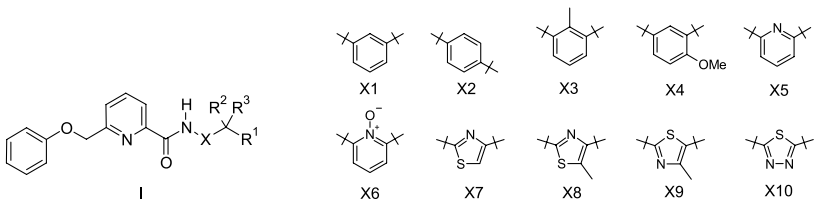
Table 1. Preliminary modification of B-part



Entry	X	*n*	R^2	R^3	R^1	PDE1 IC_{50} (μM)	PDE5 IC_{50} (μM)
1	1	1	H	H	–CONHOH	2.41	0.013
2	3	0	—	—	–CONHOH	>10	2.66
3	4	0	—	—	–CONHOH	>10	3.50
4	5	0	—	—	–CONHOH	>10	1.47
5	9	0	—	—	–CONHOH	>10	0.77
6	9	0	—	—	–COOH	4.48	4.99
7	1	1	H	H	–COOH	>10	10.0
8	5	1	H	H	–CONHOH	>10	0.040
9	5	1	H	H	–COOH	>10	9.43
10	7	1	H	H	–CONHOH	0.92	0.19
11	8	1	H	H	–CONHOH	4.52	0.040
12	7	1	*i*-Pr	H	–CONHOH	3.90	2.42
13	7	1	*n*-Bu	H	–CONHOH	0.20	0.27
14	7	1	*n*-Bu	H	–COOH	>10	6.49
15	7	1	*i*-Bu	H	–CONHOH	3.94	0.62
16	7	1	*i*-Bu	H	–COOH	>10	6.25
17	7	1	$–(CH_2)_5CH_3$	H	–CONHOH	5.70	0.23
18	7	1	$–(CH_2)_5CH_3$	H	–COOH	>10	4.58
19	7	1	Bn	H	–COOH	>10	10.0
20	7	1	Bn	H	–CONHOH	1.36	0.83
21	7	1	$–(CH_2)_2COOH$	H	–COOH	>10	10.0
22	7	1	Me	Me	–CONHOH	0.67	0.52
23	7	1	$–(CH_2)_2COOH$	$–(CH_2)_2COOH$	–COOH	>10	9.28
24	7	1	$–(CH_2)_2–$		–CONHOH	0.63	0.89
25	7	1	$–(CH_2)_2–$		–COOH	>10	8.58
26	7	1	$–(CH_2)_2O(CH_2)_2–$		–CONHOH	2.93	2.49
27	7	1	$–(CH_2)_2O(CH_2)_2–$		–COOH	>10	10.0
28	7	1	=O		–CONHOH	>10	2.20

1.2. Synthesis of molecule II (Scheme 2)

Protection of commercially available ethyl 2-amino-1,3-thiazole-4-carboxylate (**II-1**) with allyloxycarbonyl group and saponification with NaOH yield **II-2**.[5] In the meantime, the resin linked hydroxylamine **II-3** was prepared from Sasrin resin by three steps.[6] Coupling reaction with **II-2** and the resin linked hydroxylamine **II-3**, and removal of the allyloxycarbonyl group gave an O-immobilized amino thiazole derivative **II-4**.[7] Solid-phase combinatorial synthesis was performed by coupling with **II-4** and various aryl acid derivatives and the following deprotection reaction gave a hydroxamic acid library.[8]

1.3. Synthesis of molecule III (Scheme 3)

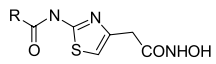
Freidel–Crafts acylation of 4-ethylresorcinol (**III-1**) with $ZnCl_2$, condensation with **III-3** and saponification gave a carboxylic acid derivative **III-4**. A series of desirable carboxylic acid, ester, and hydroxamic acid derivatives were synthesized by amide formation reaction with the **III-4** and various kinds of amino acid, amino pyridine acetate, amino thiazole, and amino thiadiazole derivatives and so on.

2. Preliminary modification of B-part

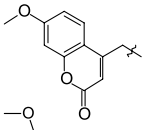
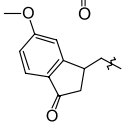
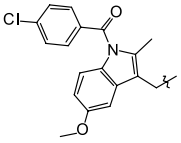
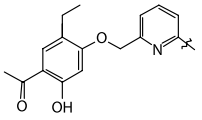
Compound **1** can be retro-synthesized by condensation of A-part and B-part (Fig. 1). First, we carried out preliminary study on the effect of B-part using a corresponding free acid of A-part (Table 1). Compounds **1**–**28** were obtained by amide formation with various building blocks having amino group. Seven aromatic moieties were selected for X as shown in Table 1 (X1, X3–X5, and X7–X9). The number of Carbon linkers between X and carboxylic acid derivatives represented as *n* was selected to be 0 or 1, and free carboxylic acid and hydroxamic acid were synthesized.

Compounds **2**–**6** (*n* = 0) showed reduced (10- to 100-fold less) inhibition of PDE-5 compared to compound **1**. Compound **6** with thiazole (**X9**) and carboxylic acid showed weak but similar level of inhibition of PDE-1 and 5. Compounds **7**–**11**, with unsubstituted methylene linkers (***n*** = 1), showed more potent inhibition than compounds **2**–**6** (***n*** = 0). Especially, compounds **8** and **11** showed comparable PDE-5 inhibition with compound **1**, but in the case of compound **1**, only weaker PDE-1 inhibition compared to PDE-5 (100-fold weaker) was observed. On the other hand, compound **10**, with

Table 2. Modification of A-part



II

Entry	R	PDE1 IC_{50} (μM)	PDE5 IC_{50} (μM)
29	3-(CF_3)Bn	>10	2.07
30	1-Phenylpropyl	>10	6.19
31	1-Naphthylamino	>10	3.81
32		>10	5.99
33		>10	3.16
34		2.80	1.28
35	Phenoxymethyl	>10	5.62
36	4-Chlorophenoxymethyl	1.81	1.69
37	–($CH2)_2$COPh	>10	4.52
38	–($CH_2)_5$Ph	4.50	1.90
39	–($CH_2)_{10}CH_3$	>10	1.80
40	Ph	>10	3.25
41	2-(F)Ph	>10	7.56
42	3-(Me_2N)Ph	>10	5.47
43	3-(CF_3S)Ph	1.72	0.43
44	3-(Bz)Ph	1.72	3.41
45	3,5-(Me)Ph	>10	1.83
46	2,4-(Cl)Ph	>10	4.25
47	2-(Br)-3-(Me)Ph	3.87	8.43
48	2,3,5-(MeO)Ph	>10	2.58
49	2-Pyridyl	7.10	3.20
50	4-Chlorophenoxy-3-pyridyl	2.67	0.32
51		0.087	0.026
52	1-Naphthyl	1.00	1.10
53	2-Quinolyl	8.00	0.14
54	2-Quinoxalyl	>10	1.84
55	1-(Ph)-4-Quinolyl	0.38	0.79

unsubstituted thiazole (**X7**), showed considerably potent inhibition (less than 1 μM) of both PDE-1 and 5.

Further modifications based on the structure of compound **10** was carried out. Monoalkyl and dialkyl substitution was introduced to the methylene carbon of compound **10** (compounds **12**–**22** and **23**–**28**, respectively). Both free carboxylic acid and hydroxyamic acid were synthesized. In mono-substituted compounds **12**–**21**, PDE-5 inhibitory activity remained. PDE-1 inhibition was generally weak but compound **13** with *n*-butyl group showed considerably potent PDE-1 and -5 inhibition. Among di-substituted compounds **22**–**28**, dimethyl derivative (**22**) and cyclopentyl derivative (**24**) showed potent inhibition profile similar to compounds **10** and **13**. Generally, conversion of carboxylic acid to hydroxamic acid increased inhibitory activities.

3. Modification of A-part

Having compound **10**, weak dual inhibitor of PDE-1 and -5, we carried out modification of A-part (Table 2). Appropriate carboxylic acid derivatives were selected as starting material from commercially available reagents or in-house carboxylic acid library.

Compounds **29**–**39** have alkyl group or substituted alkyl group as R group, but no potent PDE-5 inhibition was found in these compounds, and several compounds did not show PDE-1 inhibition. Substituted benzoic acid derivatives are used as starting materials to synthesize compounds **40**–**48**. Only compound **43** among them showed similar to slightly weaker inhibition than compound **10**, but the other compounds did not show satisfactory inhibition.

Compounds **49**–**51**, to which pyridine moieties were introduced, showed very strong PDE-1 and -5 inhibition, especially compound **51** showed 10-fold stronger inhibition than compound **10**. Two-membered rings were introduced to compounds **52**–**55** and these compounds showed moderately strong PDE-5 inhibition. Compound **55** showed comparable inhibition of PDE-1 and -5 with compound **10**.

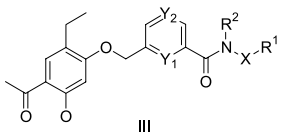
4. Modification of B-part

After discovering compound **51**, we once again fixed the A-part to a substructure of compound **51**, and screened the optimized structure for B-part. The effect of nitrogen atom of the pyridine ring in A-part was also examined. X represents either one of three aromatic rings shown in Table 1 (**X1**, **X2**, and **X7**) or nothing (R^1 directly linked to nitrogen). PDE-5 inhibition was evaluated first and PDE-1 inhibition was evaluated only when considerable PDE-5 inhibition was observed (Table 3).

Compounds **56**–**85** do not have a ring structure (X = none). Compounds **56**–**61** have benzene ring (Y1 = C, Y2 = C) and acetic acid moieties as R^1. The effect of the nitrogen atom in the aromatic ring (Y1, Y2) was generally small (Table 3). Compounds **63** and **66** with hydroxamic acid showed more potent inhibition to PDE-5 compared to corresponding carboxylic acid or esters. In compounds **64**–**74**, various substituted alkyl group were introduced to α-position of terminal acid carbonyl group. Compounds **75**–**81** showed that introduction of further carbon atom between terminal acid moieties and nitrogen atom in R^1 reduced PDE-5 inhibition. In compounds **82**–**85**, various functional groups were introduced to replace free acid and hydroxamic acid, but no stronger inhibition was observed.

Compounds **86**–**89** have 1,3-substituted benzene as a part shown as X. These compounds showed strong

Table 3. Modification of B-part



III

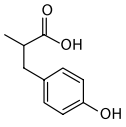
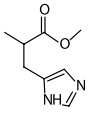
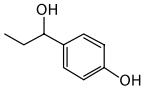
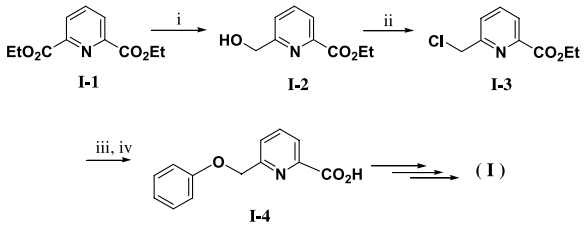
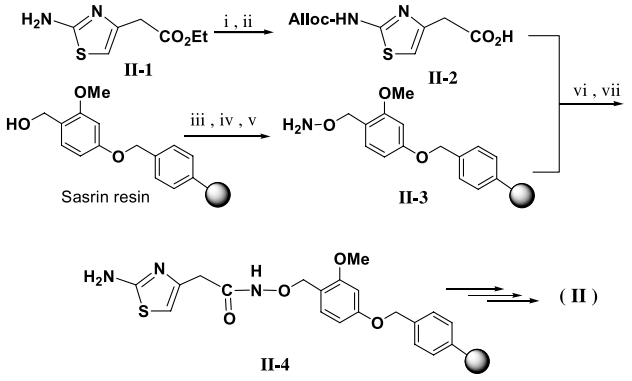
Entry	Y1	Y2	X	R^1	R^2	PDE1 IC_{50} (μM)	PDE5 IC_{50} (μM)
56	C	C	—	–CH_2COOH	H	—	0.92
57	C	C	—	–CH(Me)COOH	H	—	0.13
58	C	C	—	–CH(Me)COOMe	H	—	2.13
59	C	C	—	–$CH(CH_2OH)COOH$	H	—	0.68
60	C	C	—	–$CH(CH_2COOH)COOH$	H	—	8.76
61	C	C	—	–$CH(CH_2COOEt)COOEt$	H	—	0.65
62	N	C	—	–CH_2COOH	H	—	1.70
63	N	C	—	–$CH_2CONHOH$	H	—	0.50
64	N	C	—	(*R*)–CH(Me)COOH	H	—	1.03
65	N	C	—	(*S*)–CH(Me)COOH	H	—	0.46
66	N	C	—	–CH(Me)CONHOH	H	—	0.35
67	N	C	—	–CH(iPr)COOH	H	—	1.24
68	N	C	—	–$CH(CH_2OH)COOBn$	H	—	8.62
69	N	C	—	–$CH(CH_2COOH)COOH$	H	—	2.93
70	N	C	—	–$CH(CH_2OCOEt)COOH$	H	—	6.68
71	N	C	—	–$CH(CH_2OCO(CH_2)_6CH_3)COOH$	H	—	3.28
72	N	C	—		H	—	3.68
73	N	C	—		H	—	3.35
74	N	C	—		H	—	9.07
75	N	C	—	–$CH(OH)CH_2COOMe$	H	—	6.07
76	N	C	—	–$CH(CH_2OH)CH_2COOH$	H	—	9.46
77	N	C	—	–$CH(CH_2OH)CH_2COOMe$	H	—	3.10
78	N	C	—	–$CH(Ph)CH_2COOH$	H	—	1.45
79	N	C	—	–$(CH_2)_2COOH$	–$CH_2CH{=}CH_2$	—	9.87
80	N	C	—	–$(CH_2)_5COOH$	H	—	7.65
81	N	C	—	–$CH(CH_2OH)CH_2CH_2COOMe$	H	—	2.64
82	N	C	—	–$C(CH_2OH)_3$	H	—	8.91
83	N	C	—		H	—	3.19
84	N	C	—		H	—	7.82
85	N	C	—		H	—	5.15
86	N	C	1	–COOH	H	—	0.16
87	N	C	1	–CONHOH	H	0.39	0.028
88	N	C	1	–CH_2COOH	H	—	0.27
89	N	C	1	–OCH_2COOH	H	—	0.27
90	N	C	2	–OCH_2COOH	H	—	3.19
91	N	C	2	–OCH_2COOEt	H	—	6.09
92	C	C	7	–CH_2COOH	H	—	0.63
93	C	C	7	–CH_2COOEt	H	—	8.90
94	N	N	7	–CH_2COOH	H	—	1.51
95	N	C	7	–CONHOH	H	0.043	0.074
96	N	C	7	–CH_2COOH	H	2.00	0.096

Table 3 (*continued*)

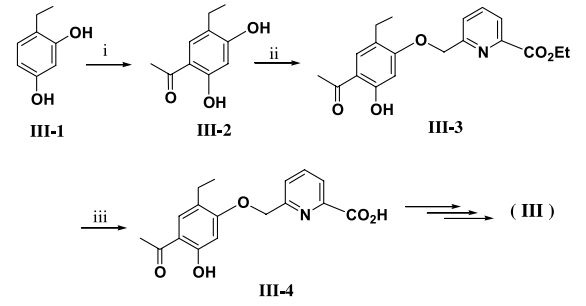
Entry	Y1	Y2	X	R^1	R^2	PDE1 IC_{50} (μM)	PDE5 IC_{50} (μM)
97	N	C	7	$-CH_2CH_2COOH$	H	2.70	0.074
98	N	C	7	$-CH_2CH_2CONHOH$	H	1.10	0.017
99	N	C	7	$-CH_2COOEt$	Me	—	2.72
100	N	C	7	$-CH_2CONH_2$	Me	—	6.35
101	N	C	7	$-CH_2CONH_2$	Et	—	1.21
102	N	C	7	$-CH_2CONH_2$	1-Methylpropyl	—	3.30



Scheme 1. Reagent and conditions: (i) $NaBH_4$,EtOH, 50 °C, 4 h; (ii) $SOCl_2$, $CHCl_3$, rt, 1 h; (iii) phenol, K_2CO_3, DMF, rt, 16 h; (iv) LiOH, THF, rt, 1 h, then Dowex50W-X8(H+).



Scheme 2. Reagent and conditions: (i) Alloc-Cl, pyridine, rt, 15 h; (ii) NaOH, MeOH-THF, rt, 15 h, then Dowex50W-X8(H+); (iii) $MeSO_2Cl$, DIEA, CH_2Cl_2, rt, 1 h; (iv) *N*-hydroxyphtalimide, Cs_2CO_3, NMP, 80 C, 16 h; (v) anhydrous hydrazine, EtOH, rt, 20 h; (vi) DIC, HOBt, DMF, rt, 16 h; (vii) $Pd(PPh_3)_4$, morphorine, THF, rt, 18 h.



Scheme 3. Reagent and conditions: (i) $ZnCl_2$, AcOH, reflux; (ii) phenol, K_2CO_3, DMF, rt, 16 h; (iii) LiOH, THF, rt, 1 h, then Dowex50W-X8(H+).

inhibition to PDE-5. Hydroxamic acid **87** showed comparable inhibition of PDE-5 to compound **51**. But these compounds showed weak inhibition of PDE-1. Compounds **90** and **91**, which have 1,4-substituted benzene as X, showed reduced inhibition of PDE-5 compared to the case of 1,3-substituted benzene.

Compounds **92**–**102** have thiazole moiety as X similar to compound **51**. Compounds **92**, **94**, and **96** showed the effect of different aromatic ring in A-part. The order of PDE-5 inhibition was Pyridine (Y1 = N, Y2 = C) > benzene (Y1 = Y2 = C) > pyradine (Y1 = Y2 = N). Hydroxamic acid derivatives were more potent than their carboxylic acid equivalent (compound **92** and **93**, **96** and **99**). Compounds **95**–**98** showed comparable potent inhibition of PDE-5, and compound **95** showed more potent PDE-1 inhibition than compound **51**.

5. Vasodilatory effects

Both compounds **51** and **10** showed relatively good metabolic stability. Therefore, we studied the vasodilatory effects in isolated vessel of rat[9] (Table 4). Compound **51**, which was one of the potent dual inhibitors, showed the expected potent vasodilatory effects (EC_{50} = 0.9 μM). On the other hand, compound **10** is about 10-fold less potent dual inhibitor than compound **51**. In a reflection of the effects for PDE-1 and -5, the vasodilatory effects of compound **10** was weaker than compound **51** (EC_{50} = 3.9 μM).

The level of cGMP in the conditions of compound **51** rose 3.4 times (10 μM), but the level of cAMP had almost no variation (1.5 times at 10 μM). It was suggested that the vasodilatory effects of compound **51** was not dependent on the level of cAMP regulated mainly by PDE-3, but cGMP was regulated by mainly PDE-1 and -5. In addition, selectivities for other PDEs, which are considered to have no effects on vasodilation[1], are not investigated.

In conclusion, we discovered several potent dual inhibitors for PDE-1 and -5. It was noted that this potent inhibition was found only in limited diversity of structure; then we thought that it resulted from a highly specific interaction between PDE and these inhibitors. Unfortunately, bioavailability of these inhibitors are very low

Table 4. The vasodilatory effects in isolated vessel of rat of compound **51** and **10**

Entry	IC_{50}, μM			Vasodilatory effects EC_{50}, μM
	PDE-1	PDE-5	PDE-3	
10	0.920	0.190	>10	3.9
51	0.087	0.026	1.3	0.9

due to their aqueous solubility. Therefore, they are not suitable for oral drug candidates. However, it is thought that new dual inhibitors for PDE-1 and -5 will be found efficiently by ligand-based virtual screening using the data of the structure–activity relationships of hydroxamic acid analogs. We will report the results about this study in another article at an early date.

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5. Synthesis of II-2 for compound **51**. To a stirred suspension of II-1 (20 g, 107 mmol) in pyridine (300 ml) was added chloroformic acid allyl ester (12.54 ml, 118 mmol) dropwise at 0 °C, and stirring was continued for 30 min at 0 °C and for 15 h at room temperature. After adding MeOH, the reaction mixture was evaporated and purified by silica gel chromatography (SiO_2 350 g; $CHCl_3 \rightarrow CHCl_3$–MeOH 100:1) to give *N*-alloc protected thiazole derivative (19.67 g, 67.8%). Then, to a stirred suspension of this product (19.5 g, 72.1 mmol) in MeOH-THF (9:2; 220 ml) was added 1 N NaOH aq (60 ml) at room temperature. After the reaction mixture was stirred at room temperature for 15 h, it was neutrized by Dowex 50W-X8 (H^+) and filtrated. The filtrate was concentrated to give II-2 (15.98 g, 91.4%) as a pale yellow solid.
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7. Synthesis of II-4 for compound **51**. To II-2 (7.268 g, 30.0 mmol) in DMF (150 ml) was added di-isopropylcarbodiimide (DIC; 2.35 ml, 15.0 mmol) at room temperature and stirring was continued for 30 min. To the reaction mixture, H_2NO-resin II-3 (1.00 mmol/g; 6 g, 6 mmol) was added at room temperature. After the reaction suspension was stirred at room temperature for 16 h, the resulting resin was drained and washed with MeOH, DMF, MeOH, and CH_2Cl_2 (each 70 ml × 3) to give 2-allyloxycarbonylamino-4-thiazolyl derivative bound to hydroxyamine resin (6.99 g, 0.817 mmol/g). To the suspension of this resulting resin in THF (90 ml) and morpholine (9 ml) was added $Pd(PPh3)_4$ (130 mg, 11 mmol) under nitrogen. The mixture was stirred for 18 h at room temperature. After the reaction, the resin was drained and washed with DMF, 0.5%Et2NCS2Na–0.5% iPr_2NEt in DMF, DMF, MeOH, CH_2Cl_2 (each 50 ml × 3) and dried to give desirable 2-amino-4-thiazolyl derivative bound to hydroxyamine resin II-4 (6.31 g, 0.876 mmol/g).
8. Synthesis of compound **51**. To a suspension of B-4 (200 mg, 0.175 mmol) in DMF (4 ml) were added C-4 (276 mg, 0.875 mmol), DIC (0.137 ml, 0.875 mmol) and HOBt (118 mg, 0.875 mmol) at room temperature. After the reaction suspension was agitated by 360° rotator for 18 h at room temperature, the resin was filtered, washed (MeOH, DMF-H_2O (1:1), DMF, MeOH, and CH_2Cl_2: 3 × 5 ml each) and dried in vacuo. The resulting resin was suspended in 50% TFA/CH_2Cl_2 (3 ml) and agitated by 360° rotator for 3 h at room temperature, then filtered off. The filtrate was concentrated by SpeedVac concentrator and purified by Gilson HPLC system to afford compound 51 (20.5 mg) as a colorless solid. Mass spectrum *m/z* 471 $(M+H)^+$.
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