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Sparsomycin Analogs. III.[1] Synthesis and Biological Activities of (*E*)-β-(6-Methyluracil-5-yl)acrylic Acid Derivatives

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In order to study the structure–activity relationship of sparsomycin, an antitumor antibiotic, 26 sparsomycin analogs (**3**—**5**) were synthesized and their antibacterial activities and lytic actions on Ehrlich ascites carcinoma cells were tested. It was found that *N*-[(*E*)-β-(6-methyluracil-5-yl)acryloyl]-*S*-methyl-D-cysteinol (**5g**) and *N*-[(*E*)-β-(6-methyluracil-5-yl)acryloyl]-D-methioninol (**5i**) showed significant antibacterial activity (minimum inhibitory concentration 25 μg/ml) against *Streptococcus pyogenes*.

Keywords——sparsomycin; sparsomycin analog; (*E*)-β-(6-methyluracil-5-yl)acrylic acid derivative; antibacterial activity; sheet method

Sparsomycin is an antitumor antibiotic having a wide range of biological activity.[2] Biological and structural studies[3a] of this antibiotic have been made since it was isolated in 1962.[2a] Recently, the configuration of the chiral sulfur atom was shown to be (*R*)[3b] and the absolute configuration of sparsomycin was determined entirely.[3] Syntheses of sparsomycin and its stereoisomers have also been reported.[4]

The unique structural and biological properties of sparsomycin prompted us to investigate the structure–activity relationship of sparsomycin analogs. Structure–activity relationship studies have already been reported on compounds related to sparsomycin, but none with biological activity superior to that of sparsomycin has ever been found.[5] In the preceding paper,[1] we reported the synthesis of 26 kinds of 5-carboxy-6-methyluracil derivatives lacking the ethylene moiety of the acryloyl portion of sparsomycin (Fig. 1) and described their biological activities.

As a continuation of our study on this series of analogs, we report here the synthesis and biological activities of (*E*)-β-(6-methyluracil-5-yl)acrylic acid derivatives. Three types of derivatives were synthesized. The first type consisted of the compounds **3a**—**i** which were condensed compounds of carboxylic acid (**1**) with one of nine amino acid esters, *i.e.*, glycine methyl ester, L- and D-alanine methyl esters, L- and D-serine methyl esters, *S*-methyl-L- and D-cysteine methyl esters, and L- and D-methionine methyl esters. The second type consisted of **4a**—**i**, which are products of hydrolysis of the ester portions of **3a**—**i**. The last type consisted

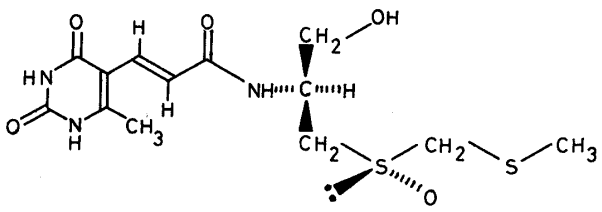
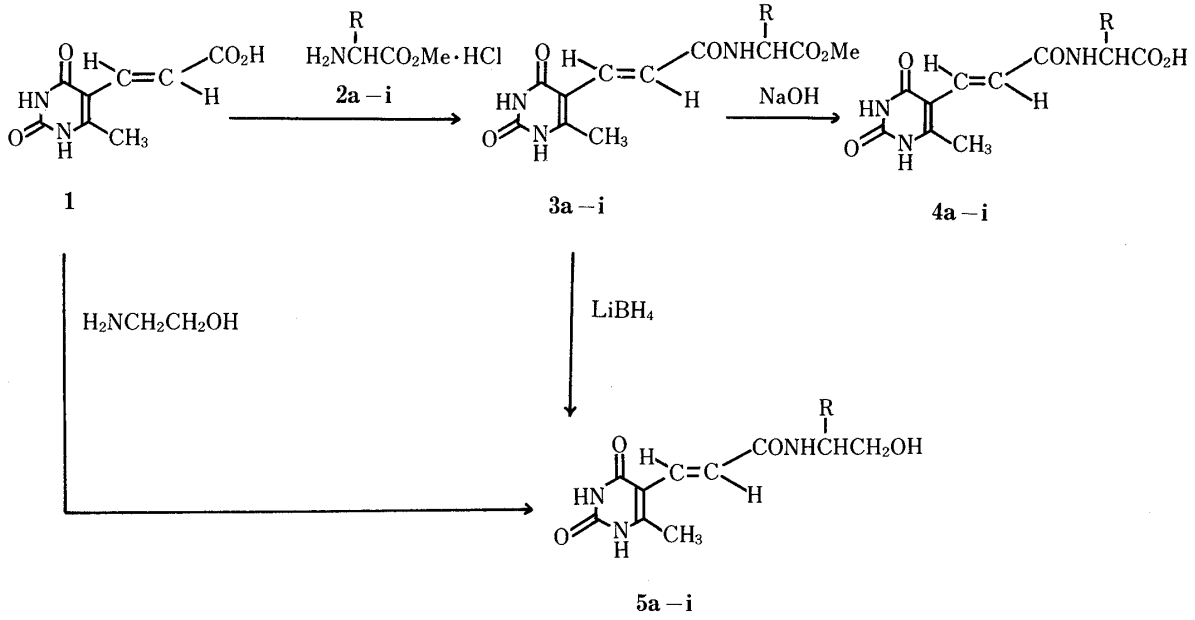


Fig. 1. Sparsomycin (S_c, R_s)



a: R=H
b: R=CH_3 (L)
c: R=CH_3 (D)
d: R=CH_2OH (L)
e: R=CH_2OH (D)
f: R=CH_2SCH_3 (L)
g: R=CH_2SCH_3 (D)
h: R=$CH_2CH_2SCH_3$ (L)
i: R=$CH_2CH_2SCH_3$ (D)

5d and **5e** are equivalent to each other

Chart 1

of **5a**—**i**, which are reduction products of the ester portions of **3a**—**i**.

The routes of synthesis of these compounds are shown in Chart 1. First, (*E*)-β-(6-methyluracil-5-yl)acrylic acid (**1**), prepared by the reported method,[3a] was condensed with amino acid methyl esters (**2a**—**i**) by the mixed anhydride (MA) method[6] using isobutylchlorocarbonate (BCC) to give the corresponding *N*-[(*E*)-β-(6-methyluracil-5-yl)acryloyl]amino acid methyl esters (**3a**—**i**) in 50—70% yields. Each compound in the **3a**—**i** group was checked by elemental analysis, and mass, ultraviolet (UV), infrared (IR), and proton nuclear magnetic resonance (NMR) spectroscopy. These esters **3a**—**i** were then hydrolyzed with 1 N NaOH to give the carboxylic acids (**4a**—**i**) in 53—79% yields. In the mass spectra (MS) of **4a**—**i**, no M^+ peak was observed but their methylated derivatives after diazomethane treatment provided M^+ peaks as the trimethylates (Table I). On the other hand, the esters **3a**—**i** were reduced with lithium borohydride to give the corresponding alcohols **5a**—**i** in 34—67% yields. Table I shows the yields, optical rotations, MS data and elemental analyses of the products **3a**—**i**, **4a**—**i**, and **5a**—**i**. In the NMR spectra of **5a**—**i**, the signals of ester methyl protons had disappeared, and new signals due to CH_2OH appeared at δ 4.00—4.77 ppm. It should be noted that the reduction products, **5d** and **5e**, from **3d** and **3e** are identical. Compound **5a** was also obtained by condensation of the carboxylic acid (**1**) with ethanolamine hydrochloride. Thus, 26 kinds of sparsomycin analogs, **3a**—**i**, **4a**—**i**, and **5a**—**i** were synthesized.

The antibacterial activities of the newly synthesized sparsomycin analogs were tested by the standard method recommended by the Japan Society of Chemotherapy.[7] In this test, sparsomycin was employed as the control.

It was found that *N*-[(*E*)-β-(6-methyluracil-5-yl)acryloyl]-*S*-methyl-D-cysteinol (**5g**) and *N*-[(*E*)-β-(6-methyluracil-5-yl)acryloyl]-D-methioninol (**5i**) showed significant antibacterial activity [minimum inhibitory concentration (MIC) 25 μg/ml] against *Streptococcus pyogenes* COOK. In contrast to **5g** and **5i**, in which the chiral carbon atom possesses (*S*) configuration,

TABLE I. (*E*)-β-(6-Methyluracil-5-yl)acrylic Acid Derivatives

Compd.	Yield (%)	$[\alpha]_D^{28}$ [a] (°)	MS (*m/z*)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
3a	67		267 (M^+)	$C_{11}H_{13}N_3O_5 \cdot H_2O$	46.32	5.30	14.73
					(45.97	4.99	14.51)
3b	50	−8.6	281 (M^+)	$C_{12}H_{15}N_3O_5 \cdot H_2O$	48.16	5.73	14.04
					(48.49	5.36	14.35)
3c	63	+8.4	281 (M^+)	$C_{12}H_{15}N_3O_5 \cdot H_2O$	48.16	5.73	14.04
					(48.48	5.27	14.39)
3d	65	−4.0	279 (M−18)	$C_{12}H_{15}N_3O_6 \cdot 1/2H_2O$	47.06	5.27	13.72
					(47.18	5.06	13.93)
3e	70	+4.2	279 (M−18)	$C_{12}H_{15}N_3O_6 \cdot 1/2H_2O$	47.06	5.27	13.72
					(47.08	4.97	13.82)
3f	62	−64.2	327 (M^+)	$C_{13}H_{17}N_3O_5S$	47.70	5.23	12.84
					(47.68	5.26	12.86)
3g	66	+64.5	327 (M^+)	$C_{13}H_{17}N_3O_5S$	47.70	5.23	12.84
					(47.70	5.19	12.73)
3h	56	−5.0	341 (M^+)	$C_{14}H_{19}N_3O_5S$	49.26	5.61	12.31
					(48.84	5.54	12.30)
3i	68	+4.8	341 (M^+)	$C_{14}H_{19}N_3O_5S$	49.26	5.61	12.31
					(48.77	5.50	12.28)
4a	79		295[c]	$C_{10}H_{11}N_3O_5$	47.43	4.38	16.59
					(47.81	4.52	16.33)
4b	64	+16.3	309[c]	$C_{11}H_{13}N_3O_5 \cdot H_2O$	46.31	5.30	14.73
					(46.44	4.91	14.77)
4c	56	−16.8	309[c]	$C_{11}H_{13}N_3O_5 \cdot H_2O$	46.31	5.30	14.73
					(46.58	4.92	14.75)
4d	60	+7.1	325[c]	$C_{11}H_{13}N_3O_6$	46.64	4.63	14.84
					(46.36	4.69	14.58)
4e	60	−7.7	325[c]	$C_{11}H_{13}N_3O_6$	46.64	4.63	14.84
					(46.35	4.70	14.76)
4f	53	−45.8	355[c]	$C_{12}H_{15}N_3O_5S$	46.00	4.83	13.41
					(45.73	4.70	13.41)
4g	56	+45.4	355[c]	$C_{12}H_{15}N_3O_5S$	46.00	4.83	13.41
					(45.75	4.71	13.21)
4h	55	−5.2	369[c]	$C_{13}H_{17}N_3O_5S$	47.71	5.23	12.84
					(47.54	5.10	12.81)
4i	53	+5.9	369[c]	$C_{13}H_{17}N_3O_5S$	47.71	5.23	12.84
					(47.65	5.12	12.85)
5a	34		239 (M^+)	$C_{10}H_{13}N_3O_4 \cdot 1/2H_2O$	48.38	5.68	16.93
					(48.17	5.51	16.73)
5b	67	+13.2	253 (M^+)	$C_{11}H_{15}N_3O_4 \cdot H_2O$	48.70	6.32	15.49
					(48.92	6.19	15.51)
5c	48	−13.8	253 (M^+)	$C_{11}H_{15}N_3O_4 \cdot H_2O$	48.70	6.32	15.49
					(48.84	6.13	15.40)
5d	50		269 (M^+)	$C_{11}H_{15}N_3O_5$	49.07	5.62	15.61
					(48.93	5.62	15.40)
5e	50		269 (M^+)	$C_{11}H_{15}N_3O_5$	49.07	5.62	15.61
					(48.79	5.63	15.44)
5f	42	−60.5[b]	281 (M−18)	$C_{12}H_{17}N_3O_4S$	48.16	5.73	14.04
					(47.81	5.84	13.89)
5g	54	+56.9	281 (M−18)	$C_{12}H_{17}N_3O_4S$	48.16	5.73	14.04
					(47.88	5.86	13.91)
5h	44	−11.1	341[d]	$C_{13}H_{19}N_3O_4S \cdot H_2O$	47.12	6.39	12.68
					(47.00	6.09	12.74)
5i	38	+10.4	341[d]	$C_{13}H_{19}N_3O_4S \cdot H_2O$	47.12	6.39	12.68
					(47.10	6.25	12.48)

a) $c = 1.0$, DMSO.
b) Lit.,[5a] $[\alpha]_D^{26} - 77.96$ ($c = 0.94$, DMSO).
c) M^+ peak as trimethylates.
d) M^+ peak as dimethylate (in both **5h** and **5i**, no M^+ peak appeared).

5f and **5h** (possessing (*R*) configuration) and the other synthetic compounds did not show antibacterial activity even at a concentration of 200 μg/ml against any of the 8 kinds of test microorganisms, whereas sparsomycin showed potent activity. Lytic action on Erhlich ascites carcinoma cells was also tested by the sheet method.[8] None of the 26 compounds showed lytic action. Dubois *et al.*[5a] reported that **5f** and its racemate were inactive towards lymphocytic leukemia P-388 and KB cell culture.

The results described above suggest that the sulfur function in the amino alcohol moiety and the (*S*) configuration of the chiral carbon of sparsomycin analogs are essential for biological activity. Further studies on the structure–activity relationship of the side chain of sparsomycin are in progress.

Experimental

General experimental methods employed in this work were essentially the same as described in Part II[1] of this series. Gas liquid chromatographic (GLC) analysis of compounds **3**—**5** was carried out on the trimethylsilyl derivatives prepared by the reported procedure[9] using a GC-4CMPF gas chromatograph equipped with a hydrogen flame ionization detector (Shimadzu, Kyoto) and a glass column (1 m × 3 mm, i.d.) packed with 1% OV-1 on Chromosorb W (AW-DMCS, 60—80 mesh) with nitrogen as a carrier gas at the flow rate of 40 ml/min. The column temperature was 210 °C. *Rf* values on thin layer chromatography (TLC) refer to the following solvent systems: Rf_1, MeCOEt : Me_2CO : H_2O (7 : 2 : 1); Rf_2, EtOH : MeOH : H_2O (50 : 45 : 5); Rf_3, C_6H_6 : MeOH : AcOH (45 : 8 : 4).

General Procedure for the Synthesis of Compounds 3a—i——Compounds **3a**—**i** were synthesized from (*E*)-β-(6-methyluracil-5-yl)acrylic acid (**1**) by the same general procedure as described in Part II.[1] Table I shows the yields, optical rotations, MS data, and elemental analyses of the products. Other physicochemical properties of the products are as follows.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]glycinate (**3a**): Colorless needles, mp 274—276 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (19500). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1720 (COO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.29 (3H, s, 6-CH_3), 3.79 (3H, s, $COOCH_3$), 3.94 (2H, d, CH_2), 7.26 (2H, dd, J = 15.6 Hz, CH=CH), 8.58 (1H, t, CONH), 11.32 and 11.38 (2H, br, N^1H and N^3H). GLC (t_R, min): 5.5. TLC: Rf_1, 0.71; Rf_2, 0.68; Rf_3, 0.61.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-alaninate (**3b**): Colorless needles, mp 247—249 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (21500). IR ν_{max}^{KBr} cm^{-1}: 3450 (NH), 1720 (COO), 1651 (CONH). NMR (DMSO-d_6) δ: 1.30 (3H, d, $CHCH_3$), 2.28 (3H, s, 6-CH_3), 3.33 (3H, s, $COOCH_3$), 4.30 (1H, qui, C<u>H</u>CH_3), 7.70 (2H, dd, J = 15.6 Hz, CH=CH), 8.35 (1H, d, CONH), 11.00 and 11.04 (2H, br, N^1H and N^3H), GLC (t_R, min): 5.4. TLC: Rf_1, 0.62; Rf_2, 0.70; Rf_3, 0.69.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-alaninate (**3c**): Colorless needles, mp 247—249 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (21400). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1720 (COO), 1650 (CONH). NMR (DMSO-d_6) δ: 1.31 (3H, d, $CHCH_3$), 2.29 (3H, s, 6-CH_3), 3.33 (3H, s, $COOCH_3$), 4.31 (1H, qui, C<u>H</u>CH_3), 7.07 (2H, dd, J = 15.6 Hz, CH=CH), 8.36 (1H, d, CONH), 11.01 and 11.05 (2H, br, N^1H and N^3H). GLC (t_R, min): 5.4. TLC: Rf_1, 0.61; Rf_2, 0.71; Rf_3, 0.69.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-serinate (**3d**): Colorless needles, mp 190—193 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302.5 (21200). IR ν_{max}^{KBr} cm^{-1}: 3450, 3370 (OH, NH), 1730 (COO), 1660 (CONH). NMR (DMSO-d_6) δ: 2.31 (3H, s, 6-CH_3), 3.71 (3H, s, $COOCH_3$), 3.76 (2H, d, CH_2), 4.52 (1H, q, C<u>H</u>CH_2), 5.04 (1H, br, OH), 7.31 (2H, dd, J = 15.6 Hz, CH=CH), 8.47 (1H, d, CONH), 11.32 and 11.36 (2H, br, N^1H and N^3H). GLC (t_R, min): 14.5. TLC: Rf_1, 0.56; Rf_2, 0.68; Rf_3, 0.65.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-serinate (**3e**): Colorless needles, mp 190—193 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302.5 (21600). IR ν_{max}^{KBr} cm^{-1}: 3450, 3370 (OH, NH), 1735 (COO), 1650 (CONH). NMR (DMSO-d_6) δ: 2.31 (3H, s, 6-CH_3), 3.72 (3H, s, $COOCH_3$), 3.76 (2H, d, CH_2), 4.54 (1H, q, C<u>H</u>CH_2), 5.05 (1H, br, OH), 7.31 (2H, dd, J = 15.6 Hz, CH=CH), 8.46 (1H, d, CONH), 11.32 and 11.36 (2H, br, N^1H and N^3H). GLC (t_R, min): 14.5. TLC: Rf_1, 0.56; Rf_2, 0.68; Rf_3, 0.65.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-L-cysteinate (**3f**): Colorless needles, mp 230—233 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (22800). IR ν_{max}^{KBr} cm^{-1}: 3415 (NH), 1740 (COO), 1653 (CONH). NMR (DMSO-d_6) δ: 2.11 (3H, s, SCH_3), 2.31 (3H, s, 6-CH_3), 2.88 (2H, m, CH_2), 3.72 (3H, s, $COOCH_3$), 4.64 (1H, dq, NHC<u>H</u>), 7.30 (2H, dd, J = 15.6 Hz, CH=CH), 8.66 (1H, d, CONH), 11.32 and 11.36 (2H, br, N^1H and N^3H). GLC (t_R, min): 16.0. TLC: Rf_1, 0.72; Rf_2, 0.73; Rf_3, 0.79.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-D-cysteinate (**3g**): Colorless needles, mp 230—233 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (23700). IR ν_{max}^{KBr} cm^{-1}: 3415 (NH), 1740 (COO), 1650 (CONH). NMR (DMSO-d_6) δ: 2.10 (3H, s, SCH_3), 2.31 (3H, s, 6-CH_3), 2.87 (2H, m, CH_2), 3.72 (3H, s, $COOCH_3$), 4.65 (1H, dq, NHC<u>H</u>), 7.30 (2H, dd, J = 15.6 Hz, CH=CH), 8.65 (1H, d, CONH), 11.33 and 11.37 (2H, br, N^1H and N^3H). GLC (t_R, min): 16.0. TLC:

Rf_1, 0.72; Rf_2, 0.73; Rf_3, 0.79.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-methioninate (**3h**): Colorless needles, mp 227—229 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (19900). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1735 (COO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.00 (2H, m, CHC$\underline{H}_2$), 2.08 (3H, s, SCH$_3$), 2.32 (3H, s, 6-CH$_3$), 2.56 (2H, t, CH$_2$S), 3.71 (3H, s, COOCH$_3$), 4.56 (1H, q, NHC$\underline{H}$), 7.32 (2H, dd, J=15.6 Hz, CH=CH), 8.60 (1H, d, CONH), 11.33 and 11.37 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 24.0. TLC: Rf_1, 0.58; Rf_2, 0.71; Rf_3, 0.79.

Methyl *N*-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-methioninate (**3i**): Colorless needles, mp 227—229 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (20300). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1735 (COO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.00 (2H, m, CHC$\underline{H}_2$), 2.09 (3H, s, SCH$_3$), 2.33 (3H, s, 6-CH$_3$), 2.56 (2H, t, CH$_2$S), 3.71 (3H, s, COOCH$_3$), 4.57 (1H, q, NHC$\underline{H}$), 7.31 (2H, dd, J=15.6 Hz, CH=CH), 8.60 (1H, d, CONH), 11.33 and 11.37 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 24.0. TLC: Rf_1, 0.58; Rf_2, 0.71; Rf_3, 0.79.

General Procedure for the Synthesis of Compounds 4a—i——Compounds **4a—i** were synthesized from **3a—i** by the same general procedure as described in Part II.[1] Table I shows the yields, optical rotation, MS data, and elemental analyses of the products. Other physicochemical properties of the products are as follows.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]glycine (**4a**): Colorless needles, mp 288—290 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19400). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1725 (CO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.30 (3H, s, 6-CH$_3$), 3.80 (1H, br, COOH), 3.90 (2H, d, NHC$\underline{H}_2$), 7.29 (2H, dd, J=15.6 Hz, CH=CH), 8.49 (1H, t, CONH), 11.32 and 11.36 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 9.4. TLC: Rf_1, 0.18; Rf_2, 0.41; Rf_3, 0.15.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-alanine (**4b**): White crystals, mp 260—262 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (20400). IR ν_{max}^{KBr} cm^{-1}: 3480 (NH), 1710 (CO), 1645 (CONH). NMR (DMSO-d_6) δ: 1.28 (3H, d, CHC$\underline{H}_3$), 2.24 (3H, s, 6-CH$_3$), 3.50 (1H, br, COOH), 4.24 (1H, qui, NHC$\underline{H}$), 7.07 (2H, dd, J=15.6 Hz, CH=CH), 8.24 (1H, d, CONH), 10.99 and 11.02 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 9.5. TLC: Rf_1, 0.21; Rf_2, 0.30; Rf_3, 0.31.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-alanine (**4c**): White crystals, mp 260—262 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (20500). IR ν_{max}^{KBr} cm^{-1}: 3480 (NH), 1710 (CO), 1645 (CONH). NMR (DMSO-d_6) δ: 1.27 (3H, d, CHC$\underline{H}_3$), 2.23 (3H, s, 6-CH$_3$), 3.50 (1H, br, COOH), 4.24 (1H, qui, NHC$\underline{H}$), 7.06 (2H, dd, J=15.6 Hz, CH=CH), 8.24 (1H, d, CONH), 10.99 and 11.02 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 9.5. TLC: Rf_1, 0.21; Rf_2, 0.30; Rf_3, 0.31.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-serine (**4d**): White crystals, mp 284—286 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (20800). IR ν_{max}^{KBr} cm^{-1}: 3380, 3200 (OH, NH), 1715 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 2.31 (3H, s, 6-CH$_3$), 3.77 (2H, d, CH$_2$), 4.00 (2H, br, COOH and OH), 4.46 (1H, q, C$\underline{H}$CH$_2$), 7.31 (2H, dd, J=15.6 Hz, CH=CH), 8.32 (1H, d, COHN), 11.30 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 17.7. TLC: Rf_1, 0.17; Rf_2, 0.12; Rf_3, 0.06.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-serine (**4e**): White crystals, mp 284—286 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 302 (20600). IR ν_{max}^{KBr} cm^{-1}: 3380, 3210 (OH, NH), 1715 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 2.31 (3H, s, 6-CH$_3$), 3.78 (2H, d, CH$_2$), 4.00 (2H, br, COOH and OH), 4.47 (1H, q, C$\underline{H}$CH$_2$), 7.32 (2H, dd, J=15.6 Hz, CH=CH), 8.32 (1H, d, CONH), 11.30 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 17.7. TLC: Rf_1, 0.17; Rf_2, 0.12; Rf_3, 0.06.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-L-cysteine (**4f**): White crystals, mp 287—289 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (19800). IR ν_{max}^{KBr} cm^{-1}: 3420 (NH), 1720 (CO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.09 (3H, d, SCH$_3$), 2.29 (3H, s, 6-CH$_3$), 2.87 (2H, m, CH$_2$), 3.60 (1H, br, COOH), 4.54 (1H, dq, NHC$\underline{H}$), 7.30 (2H, dd, J=15.6 Hz, CH=CH), 8.52 (1H, d, CONH), 11.28 and 11.34 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 23.4. TLC: Rf_1, 0.20; Rf_2, 0.10; Rf_3, 0.37.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-D-cysteine (**4g**): White crystals, mp 287—289 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (20200). IR ν_{max}^{KBr} cm^{-1}: 3420 (NH), 1720 (CO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.08 (3H, s, SCH$_3$), 2.28 (3H, s, 6-CH$_3$), 2.87 (2H, m, CH$_2$), 3.60 (1H, br, COOH), 4.54 (1H, dq, NHC$\underline{H}$), 7.31 (2H, dd, J=15.6 Hz, CH=CH), 8.53 (1H, d, CONH), 11.28 and 11.34 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 23.4. TLC: Rf_1, 0.20; Rf_2, 0.10; Rf_3, 0.37.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-methionine (**4i**): White crystals, mp 233—235 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (20800). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1715 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.96 (2H, m, CHC$\underline{H}_2$), 2.08 (3H, s, SCH$_3$), 2.30 (3H, s, 6-CH$_3$), 2.56 (2H, t, CH$_2$S), 3.80 (1H, br, COOH), 4.50 (1H, q, NHC$\underline{H}$), 7.30 (2H, dd, J=15.6 Hz, CH=CH), 8.48 (1H, d, CONH), 11.32 and 11.36 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 30.9. TLC: Rf_1, 0.20; Rf_2, 0.10; Rf_3, 0.44.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-methionine (**4i**): White crystals, mp 233—235 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 303 (20500). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1715 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.96 (2H, m, CHC$\underline{H}_2$), 2.08 (3H, s, SCH$_3$), 2.31 (3H, s, 6-CH$_3$), 2.56 (2H, t, CH$_2$S), 3.80 (1H, br, COOH), 4.50 (1H, q, NHC$\underline{H}$), 7.30 (2H, dd, J=15.6 Hz, CH=CH), 8.47 (1H, d, CONH), 11.32 and 11.36 (2H, br, N^{1}H and N^{3}H). GLC (t_R, min): 30.9. TLC: Rf_1, 0.20; Rf_2, 0.10; Rf_3, 0.44.

General Procedure for the Synthesis of Compounds 5a—i——Compounds **5a—i** were synthesized from **3a—i** by the same general procedure as described in the previous paper.[1] Table I shows the yields, optical rotations, MS data and elemental analyses of **5a—i**. Other physicochemical properties of the products are as follows.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]glycinol (**5a**): Colorless needles, mp 275—277 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19800). IR ν_{max}^{KBr} cm^{-1}: 3370, 3280 (OH, NH), 1720 (CO), 1653 (CONH). NMR (DMSO-d_6) δ: 2.30 (3H, s, 6-CH$_3$), 3.28 (2H, t, C$\underline{H}_2$OH), 3.46 (2H, m, NHC$\underline{H}_2$), 4.68 (1H, br, OH), 7.22 (2H, dd, J=15.6 Hz, CH=CH), 8.12

(1H, t, CONH), 11.28 and 11.35 (2H, br, N^1H and N^3H). GLC (t_R, min): 6.6. TLC: Rf_1, 0.46; Rf_2, 0.51; Rf_3, 0.23.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-alaninol (**5b**): White crystals, mp 252—254 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19800). IR ν_{max}^{KBr} cm^{-1}: 3420, 3250 (OH, NH), 1720 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.04 (3H, d, $CHC\underline{H}_3$), 2.24 (3H, s, 6-CH_3), 3.28 (2H, t, $C\underline{H}_2OH$), 3.84 (1H, m, $NHC\underline{H}$), 4.00 (1H, br, OH), 7.04 (2H, dd, J= 15.6 Hz, CH=CH), 7.74 (1H, d, CONH), 10.98 and 11.00 (2H, br, N^1H and N^3H). GLC (t_R, min): 6.8. TLC: Rf_1, 0.45; Rf_2, 0.59; Rf_3, 0.28.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-alaninol (**5c**): White crystals, mp 252—254 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19800). IR ν_{max}^{KBr} cm^{-1}: 3420, 3250 (OH, NH), 1720 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.03 (3H, d, $CHC\underline{H}_3$), 2.24 (3H, s, 6-CH_3), 3.28 (2H, t, $C\underline{H}_2OH$), 3.84 (1H, m, $NHC\underline{H}$), 4.00 (1H, br, OH), 7.04 (2H, dd, J= 15.6 Hz, CH=CH), 7.75 (1H, d, CONH), 10.98 and 11.00 (2H, br, N^1H and N^3H). GLC (t_R, min): 6.8. TLC: Rf_1, 0.45; Rf_2, 0.59; Rf_3, 0.28.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]serinol (**5d**, **5e**): i) **5d** (from **3d**). Colorless needles, mp 301—303 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19800). IR ν_{max}^{KBr} cm^{-1}: 3440, 3270 (OH, NH), 1703 (CO), 1679 (CONH). NMR (DMSO-d_6) δ: 2.30 (3H, s, 6-CH_3), 3.50 (4H, d, $C\underline{H}_2OH \times 2$), 3.83 (1H, m, $NHC\underline{H}$), 4.57 (2H, br, OH × 2), 7.23 (2H, dd, J=15.6 Hz, CH=CH), 7.88 (1H, d, CONH), 11.32 (2H, br, N^1H and N^3H). GLC (t_R, min): 13.9. TLC: Rf_1, 0.53; Rf_2, 0.50; Rf_3, 0.25. ii) **5e** (from **3e**). Colorless needles, mp 301—303 °C (dec.). This product was identical (by comparison of UV, IR, mass, and NMR spectra) with **5d** derived from **3d**.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-L-cysteinol (**5f**): White crystals, mp 219—221 °C (dec.) (lit.,[5a] mp 218—223 °C). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19800). IR ν_{max}^{KBr} cm^{-1}: 3390, 3200 (OH, NH), 1705 (CO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.11 (3H, s, SCH_3), 2.32 (3H, s, 6-CH_3), 2.62 (2H, m, CH_2S), 3.52 (2H, m, $C\underline{H}_2OH$), 4.00 (2H, m, OH and $NHC\underline{H}$), 7.24 (2H, dd, J=15.6 Hz, CH=CH), 8.04 (1H, d, CONH), 11.28 and 11.32 (2H br, N^1H and N^3H). GLC (t_R, min): 22.6. TLC: Rf_1, 0.45; Rf_2, 0.65; Rf_3, 0.40.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-*S*-methyl-D-cysteinol (**5g**): White crystals, mp 219—221 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (20500). IR ν_{max}^{KBr} cm^{-1}: 3390, 3200 (OH, NH), 1705 (CO), 1655 (CONH). NMR (DMSO-d_6) δ: 2.11 (3H, s, SCH_3), 2.32 (3H, s, 6-CH_3), 2.61 (2H, m, CH_2S), 3.51 (2H, m, $C\underline{H}_2OH$), 4.00 (2H, m, OH and $NHC\underline{H}$), 7.23 (2H, dd, J=15.6 Hz, CH=CH), 8.03 (1H, d, CONH), 11.28 and 11.32 (2H, br, N^1H and N^3H). GLC (t_R, min): 22.6. TLC: Tf_1, 0.45; Rf_2, 0.65; Rf_3, 0.40.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-L-methioninol (**5h**): White crystals, mp 215—218 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19200). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH, NH), 1710 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.72 (2H, m, $CHC\underline{H}_2$), 2.05 (3H, s, SCH_3), 2.29 (3H, s, 6-CH_3), 2.48 (2H, t, CH_2S), 3.40 (2H, m, $C\underline{H}_2OH$), 3.88 (1H, m, $NHC\underline{H}$), 4.76 (1H, t, OH), 7.24 (2H, dd, J=15.6 Hz, CH=CH), 7.86 (1H, d, CONH), 11.28 (2H, br, N^1H and N^3H). GLC (t_R, min): 35.0. TLC: Rf_1, 0.48; Rf_2, 0.67; Rf_3, 0.45.

N-[(*E*)-β-(6-Methyluracil-5-yl)acryloyl]-D-methioninol (**5i**): White crystals, mp 215—218 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 301 (19500). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH, NH), 1710 (CO), 1660 (CONH). NMR (DMSO-d_6) δ: 1.72 (2H, m, $CHC\underline{H}_2$), 2.06 (3H, s, SCH_3), 2.29 (3H, s, 6-CH_3), 2.49 (2H, t, CH_2S), 3.40 (2H, m, $C\underline{H}_2OH$), 3.88 (1H, m, $NHC\underline{H}$), 4.77 (1H, t, OH), 7.24 (2H, dd, J=15.6 Hz, CH=CH), 7.86 (1H, d, CONH), 11.28 (2H, br, N^1H and N^3H). GLC (t_R, min): 35.0. TLC: Rf_1, 0.48; Rf_2, 0.67; Rf_3, 0.45.

Reaction of the Carboxylic Acid (1) with Ethanolamine Giving 5a——A solution of **1** (1.96 g, 10 mmol) in DMF (25 ml) was cooled to −10 °C, then BCC (1.37 g, 10 mmol) and triethylamine (TEA) (1.06 g, 10.5 mmol) were added. The mixture was stirred for 15 min at −10 °C, then a precooled solution of ethanolamine hydrochloride (1.07 g, 11 mmol) and TEA (1.11 g, 11 mmol) in DMF was added, and the whole was stirred for 1 h at −5 °C, then overnight at room temperature. The liquid phase was then separated, the solvent was removed *in vacuo*, and the residue was triturated with H_2O. The crude product was filtered off with suction and recrystallized from H_2O to give colorless needles [0.97 g, 40.6%, mp 275—277 °C (dec.)], whose spectral data (UV, IR, MS, and NMR) were identical with those of **5a** obtained by $LiBH_4$ reduction of the ester **3a**.

Antibacterial Potency on Microorganisms and Lytic Action on Carcinoma Cells——The MIC values of the synthesized compounds towards eight kinds of microorganisms (*Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis, Escherichia coli, Krebsiella pneumoniae, Salmonella typhi, Pseudomonas aeruginosa, Proteus vulgaris*), and the lytic action on carcinoma cells were determined by the same procedures as described in the previous paper.[1)]

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