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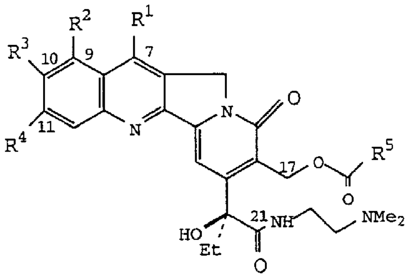
(54) DERIVES CAMPTOTHECINE, PREPARATIONS DE CEUX-CI ET AGENTS ANTITUMORAUX
(54) CAMPTOTHECIN DERIVATIVES, PREPARATIONS THEREOF AND ANTITUMOR AGENTS

(57)
New camptothecin derivatives of the general formula (1), preparations thereof and antitumor agents comprising the same, (see formula 1) wherein R1 represents a hydrogen atom or a C1-C6 alkyl group, R2 represents a hydrogen or a C1-C6 alkoxy group, R3 represents a hydrogen or halogen atom or a C1-C6 alkyl, C1-C6 alkoxy, hydroxyl, C2-C6 acyloxy or methoxyethoxymethoxy group, R4 represents a hydrogen or halogen atom, and R5 represents a C1-C6 alkyl, C3-C6 unsaturated alkyl, alkylthioalkyl, alkoxyalkyl, pyridyl or substituted phenyl group, with the proviso that all of the R2, R3 and R4 substituents should not be a hydrogen atom.



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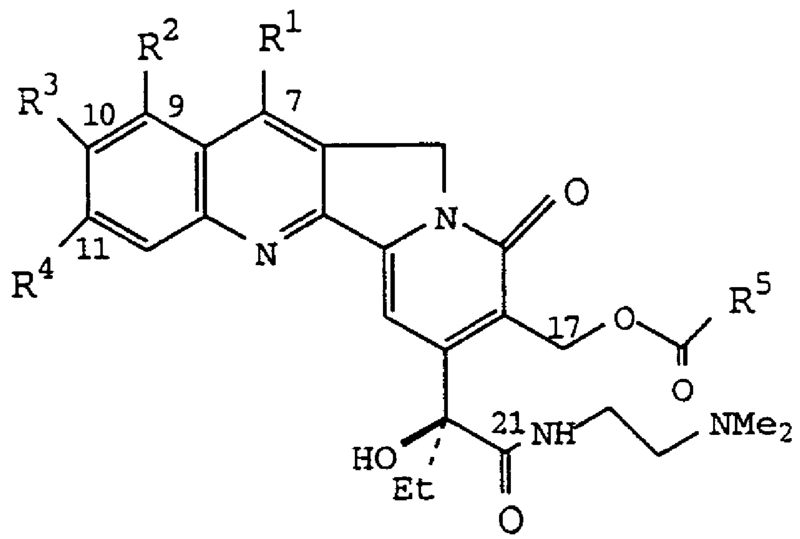

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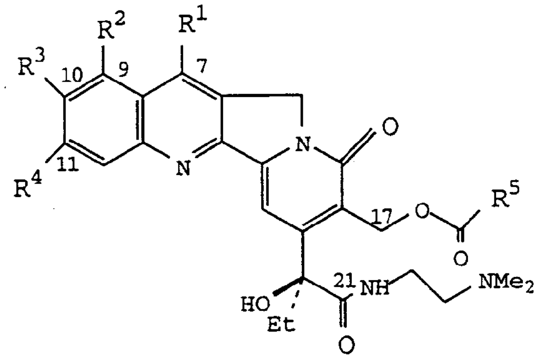
(57) Abrégé/Abstract:
New camptothecin derivatives of the general formula (1), preparations thereof and antitumor agents comprising the same, (see formula 1) wherein R^1 represents a hydrogen atom or a C_1-C_6 alkyl group, R^2 represents a hydrogen or a C_1-C_6 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_2-C_6 acyloxy or methoxyethoxymethoxy group, R^4 represents a hydrogen or halogen atom, and R^5 represents a C_1-C_6 alkyl, C_3-C_6 unsaturated alkyl, alkylthioalkyl, alkoxyalkyl, pyridyl or substituted phenyl group, with the proviso that all of the R^2, R^3 and R^4 substituents should not be a hydrogen atom.

Abstract

New camptothecin derivatives of the general formula (1), preparations thereof and antitumor agents comprising the same,



(1)

wherein R^1 represents a hydrogen atom or a C_1-C_6 alkyl group, R^2 represents a hydrogen or a C_1-C_6 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_2-C_6 acyloxy or methoxyethoxymethoxy group, R^4 represents a hydrogen or halogen atom, and R^5 represents a C_1-C_6 alkyl, C_3-C_6 unsaturated alkyl, alkylthioalkyl, alkoxyalkyl, pyridyl or substituted phenyl group, with the proviso that all of the R^2, R^3 and R^4 substituents should not be a hydrogen atom.

CAMPTOTHECIN DERIVATIVES, PREPARATIONS THEREOF AND ANTITUMOR AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to new water-soluble camptothecin derivatives, a process of the preparation thereof and antitumor agents containing the same as an active ingredient.

There has been a need for new camptothecin (hereinafter referred to CPT) derivatives with excellent antitumor activities. The present inventors have found that totally synthetic CPT derivatives carrying a lower alkyl group in 7-position on the B-ring and also hetero substituent and/or alkyl group in 9-, 10- and 11-position on the A-ring among others showed strong antitumor activity (see JP, A, H1-186892).

There has also been a need of the above CPT derivatives in water-soluble form for ease of administration. Especially, CPT derivatives synthesized by subjecting 7-ethylCPT to open the E-lactone ring by the diamines followed by acylation of the hydroxymethyl group showed excellent water solubility without decrease of antitumor activity contrasting to the known E-ring opened water soluble CPT derivatives (see JP, A, H1-131179).

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There is furthermore a need for such CPT derivatives which have low toxicity and are easy to use.

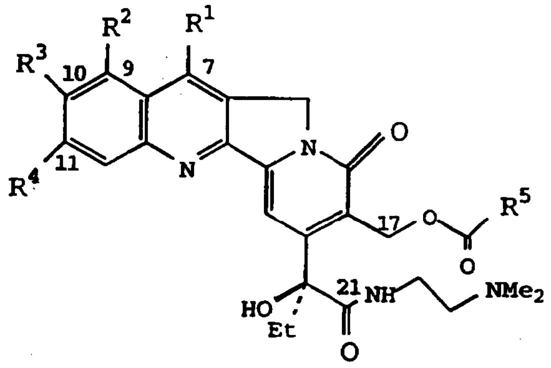
BRIEF SUMMARY OF THE INVENTION

Accordingly, an object of this invention is to provide new CPT derivatives possessing excellent characteristics in antitumor activity. It is another object to provide new CPT derivatives which solve the water solubility problem. In order to achieve those objects, a novel process was developed for the preparation of new water-soluble CPT derivatives prepared from CPT derivatives carrying a lower alkyl group in 7-position on the B-ring and also hetero substituent and/or alkyl group in 9-, 10- and 11-position on the A-ring by subjecting them to open the E-lactone ring by the diamines followed by acylation of the hydroxymethyl group.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided new CPT derivatives represented by the general formula:

A



(1)

wherein R^1 represents a hydrogen atom or a C_1-C_6 alkyl group, R^2 represents a hydrogen or a C_1-C_6 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_2-C_6 acyloxy or methoxyethoxymethoxy group, R^4 represents a hydrogen or halogen atom, and R^5 represents a C_1-C_6 alkyl, C_3-C_6 unsaturated alkyl, alkylthioalkyl, alkoxyalkyl, pyridyl or phenyl group substituted with halogen, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl or phenyl group, with the proviso that all of the R^2, R^3 and R^4 substituents should not be a hydrogen atom, and a process for preparing new camptothecin derivatives. In further accordance with the present invention, there are provided antitumor agents containing new CPT derivatives of general formula (1) as an active ingredient, together with a pharmaceutically acceptable diluent or carrier.

The new CPT derivatives of the invention are prepared from CPT derivatives carrying a hydrogen atom or a lower alkyl group in 7-position and also hetero and/or alkyl group in 9-, 10- and 11-position by N,N-dimethylethylenediamine without solvent followed by acylation of 17-hydroxymethyl group with appropriate acylating agents. The starting CPT derivatives carrying a hydrogen atom or a lower alkyl group in 7-position and also hetero substituent and/or alkyl group in 9-, 10-and 11-position are the known CPT derivatives (9-methoxyCPT, 10-hydroxyCPT, 10-methoxyCPT, 11-hydroxyCPT, 11-methoxyCPT etc.) prepared from natural substances or are obtained semisynthetically or synthetically by the known procedures (see JP, A, S58-39684; JP, A, S58-134095; JP, A, S59-51287; JP, A, S59-51289; JP, A, H1-279891; JP, A, H1-186892; JP, A, H4-503505; JP, A, H5-502017; WO-91/04260; WO-92/11263; USP, 5122606 and others).

Although a reaction condition disclosed by in JP, A, H1-13117 by us for the E-ring opening by N,N-dimethylethylenediamine followed by acylation of 17-hydroxyl group with appropriate acylating agents can be applied, it has been found that aimed compounds were not necessarily prepared in satisfactory yields according to this procedure. We have examined reaction conditions of this procedure and found that in the first step of the E-lactone ring opening reaction by N,N-dimethylethylenediamine, using an excess amount of N,N-dimethylethylenediamine alone without solvent gave the E-ring opened intermediate followed by acylation of 17-hydroxyl group with appropriate acylating agents to afford the aimed compounds in very good yields.

As the acylating agent used for the acylation there is no specific agent, but corresponding acid anhydrides, acid halogenides, for example, acid chlorides, acid bromides and other equivalent acylating agents can be used. A reaction mixture of a corresponding carboxylic acid treated with a condensation agent, for example, dicyclohexylcarbodiimide can be also used for the said acylation.

Illustrative of the corresponding carboxylic acids used as the said acylating agents are, for example, saturated aliphatic acids with 2-20 carbon atoms, unsaturated aliphatic acids with 3-20 carbon atoms, aliphatic acids with a cycloalkyl group, or aliphatic acids with, for example, a halogen atom or alkylthio, amino, acylamino, hydroxyl, alkoxy, or alkoxycarbonyl group, aromatic acids with 6-20 carbon atoms or aromatic acids with, for example, a halogen atom or hydroxyl, alkoxy or lower alkyl group, heteroaromatic acids or amino acids. Examples of the acylating agents include acetyl chloride, benzoyl chloride, propionyl chloride, butyryl chloride, methoxybenzoyl chloride, fluorobenzoyl chloride, bromobenzoyl chloride, chlorobenzoyl chloride, nitrobenzoyl chloride, trifluoromethylbenzoyl chloride, naphthoyl chloride, cyclopropanecarbonyl chloride, thenoyl chloride, crotonyl chloride, cinnamoyl chloride, phenylacetyl chloride, phenylbenzoyl chloride, cyclohexanecarbonyl chloride, stearoyl chloride, oleoyl chloride, methoxycarbonylbezoyl chloride, ethyl succinyl chloride, linoleyl chloride, chlorobutyryl chloride, ethylbenzoyl chloride, methylthiopropionyl chloride, pivaloyl chloride, nicotinoyl chloride, isonicotinoyl chloride and picolinoyl chloride.

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In the said acylation N,N-dimethylaminopyridine or the like can be present in the reaction as a catalyst.

In adding, to keep carefully an anhydrous condition not only in the ring-opening process but in the acylation process and further, for example, in the pulverization, the purification and the crystalization process can increase a yield of an aimed compound.

The new CPT derivatives of this invention show excellent water solubility by being converted to acid addition salts thereof with proper acids such as hydrochloric acid. The compounds of this invention show excellent results in safety and in antitumor activity and therefore can be provided as new antitumor agents.

The present invention will now be illustrated in more detail by way of examples.

Synthetic examples

General synthetic methods

Example 1 Preparation of ring-opened compounds (B_1-B_{13})

As a starting material CPT derivatives (A_1-A_{12}, for each substituent refer Table 1) with each substituent in 7-position and in 9-, 10- and 11-position on the A-ring were prepared according to the above mentioned literature. 9-Methoxy CPT(A_{13}) isolated from natural substances was employed in this example. And for the compounds carrying hydroxyl group on the A-ring, the compound ($A_{10'}$) which was obtained by a usual O-methoxyethoxymethylation was used.

To 3.0 g, for example, of the starting CPT derivative (A_1-A_{13}) was added excess anhydrous N, N-dimethylethylenediamine (5-100 eq. for example 15 ml). The reaction mixture was stirred under nitrogen at 50°C for 1.5 hr. After reacted the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in dry methylene chloride (for example 15 ml), and the solution was poured into large amount of dry n-hexane (for example 500 ml). The precipitated crystals were filtered, washed with dry n-hexane and dried to give the hydroxyamide (B_1-B_{13}, E-lactone-ring opened compounds) in an almost quantitative yield.

The yields and each spectral data are shown in the following Table 2.

Example 2 Acylation of the 17-hydroxyl group

To a solution of the above obtained hydroxyamide (for example 1.0 g) in dry methylene chloride (for example 20 ml) was added dropwise an acylating agent (1.2 eq.)in presence of dimethylaminopyridine (DMPA, for example 100 mg) under ice cooling. The reaction mixture was stirred at room temperature overnight and washed with 7% aqueous sodium hydrogen bicarbonate and saturated aqueous sodium chloride solution. The methylene chloride layer was dried over anhydrous sodium sulfate, followed by removal of insoluble materials, and evaporated to dryness under reduced pressure. The residue was subjected to silica gel column chromatography (10% MeOH-$CHCl_3$) and crystallized from chloroform-n-hexane to give the 17-O-acyl-21-N, N-dimethylaminoethylamide derivative (C_1-C_{48}) related to the invention.

As for an O-methoxyethoxymethyl derivative a solution of the compound in 10% trifluoroacetic acid-methylene chloride was stirred overnight. After stirring triethylamine (eq. mol) was added dropwise under ice cooling to the reaction mixture.

The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride, washed with 7% aqueous sodium hydrogen bicarbonate and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, followed by removal of insoluble materials, and evaporated to dryness under reduced pressure. The residue was subjected to silica gel column chromatography (10% MeOH-$CHCl_3$) and crystallized from acetone-$CHCl_3$ to give the 17-O-acyl-21-N,N-dimethylaminoethylamide derivative (C_{28}, C_{30}, C_{32}, C_{34}, C_{36}, C_{38}) related to the invention.

The yields of the synthesized derivatives and their spectral data are shown in Table 1 and Table 3.

The water solubility data of the obtained new camptothecin derivatives related to the invention are shown in Table 4.

Antitumor Effect

For the obtained new camptothecin derivatives of the invention, their results of antitumor activity, toxicology test, usage-dose, and galenical preparation are described below.

Antitumor Activity

It is well accepted that antitumor effect for a rodent leads to a reliable result for antitumor effect in a warm-blooded animal. The present inventors investigated antitumor effect for mice as a model.

[Antitumor activity for L1210]

$5x10^5$ cells of mouse leukemia L1210 were transplanted intraperitoneally to a group of six female CDF1 mice (7 weeks old, body weight 17-19 g). The test compound was administered intraperitoneally on day 1, 5 and 9 and its life prolonging effect was observed.

In a case of the administration of a test compound as an acid addition salt the test compound was dissolved in water. The total administration amount was 1.56 mg/kg-400 mg/kg. The antitumor activity was expressed by the value (T/C%) wherein T denotes the mean survival days in the drug administered group and C denotes those in the non administered group. In case of equal to or more than 125% the drug is considered to be effective. A therapeutic index was calculated by examining the least effective dose and the maximum tolerance dose.

Experimental Result

The antitumor experimental results of the compounds described in the previous example are shown in Table 5. As shown in Table 5, the new camptothecin derivatives in the present invention showed about 6 fold more favorable therapeutic index than camptothecin itself. At an optimum dose there was the case that 5 mice amoung 6 mice in the group survived. The results also show their effectiveness at lower doses, remarkable increase of antitumor activity and enlargement of a therapeutic margin.

Toxicity Experiment

Acute toxicity test was conducted by intraperitoneal administration using a group of twenty ICR male mice (4 weeks old, body weight around 20 g). The results are shown in Table 6.

LD_{50} value was calculated by the Richfield-Willcokson method from a lethal ratio observing the fate of mice during 1 week after administration of a test compound.

From the above experimental results, it is understood that the new camptothecin derivatives have better antitumor activity and can be used as less toxic drugs than their mother compound, camptothecin, for a treatment of cancer.

The antitumor agents of the present invention can be administered by a injection such as intravenous, intradermal and intramuscular injection, and by oral administration. Especially preferable examples are to administer the compounds as their acid-addition salts appropriate as medicaments by intravenous or oral administration.

In an intravenous administration, the dose of each compound above mentioned depends upon the aim of a therapeutic treatment, and is in range 5-400 mg/body per day, preferably 20-200 mg/body for adults. In an oral administration a range 50-2000 mg/body per day, preferably 100-1000 mg/body for adults.

As a preparation method of the antitumor agents of the present invention, a usual method for each preparation can be selected according to a formulation. As a formulation suitable for absorption through stomach intestine, the antitumor agents of the invention may be prepared in, for example, tablet, powder, granule, capsule or soft capsule, and examples of the oral liquid preparation include water or oil suspension, solution, syrup and elixir etc. A preparation for injection may be stored in an ample or a large container. In these formulation an excipient such an antiseptic or dissolvent can be used.

A formulation of a liquid preparation may be suspension, solution and emulsion with oily or aqueous vehicle, and may include an excipient such as emulsifier. Corresponding to a preparation of the antitumor agents of the invention, a content of the active drug is 0.1% or more, preferably 1-50%.

The preparation examples of the antitumor agents of the invention are further illustrated in, though not limited by, the following examples.

Preparation 1 Injection

After dissolving the compound C_7 ($R^1=C_2H_5$, $R^2=H$, $R^3=CH_3$, $R^4=H$, $R^5=C_2H_4SCH_3$) in 0.1N HCl containing equivalent molar HCl, the solution was filtered, and lyophilized to give 50 mg of the HCl salt of the compound C_7. The salt was sealed into an ample in a germfree condition and stored under cooling in the dark.

Preparation 2 Tablet

Compound C_7	50 mg
Lactose	89 mg
Hydroxypropylcellulose	2.7 mg
Crystalline cellulose	15 mg
Talc	1.6 mg
Magnesium stearate	1.7mg

The above ingredients were mixed and formed directly into tablets (160 mg/tablet) using a tablet machine.

Table 1 (Yields of each compound)

A_{1-13} → B_{1-13} → C_{1-48}

Starting Compd. Hydroxy Amide Compd. 17-O-Acyl Compd.

→ $C_{28,30,32,34,36,38}$

Deprotection

Compd. No.	A	R^1	R^2	R^3	R^4	R^5	Yield(%) A→B	B→C
C_1	A_{11}	Me	H	OEt	H	$-CH_2CH_2SMe$	98	38
C_2	A_{12}	〃	〃	H	Br	〃	99	26
C_3	A_1	Et	〃	Cl	H	Et	94	51
C_4	A_1	〃	〃	〃	〃	Pr	〃	50
C_5	A_1	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	47
C_6	A_2	〃	〃	Br	〃	〃	98	47
C_7	A_3	〃	〃	Me	〃	〃	98	43
C_8	A_4	〃	〃	H	F	Et	95	71
C_9	A_4	〃	〃	〃	F	Pr	〃	75
C_{10}	A_4	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	72
C_{11}	A_4	〃	〃	〃	〃	$-C_6H_4-OMe$	〃	59
C_{12}	A_5	〃	〃	〃	Cl	$-CH_2CH_2SMe$	92	30
C_{13}	A_6	〃	〃	F	F	Et	98	56
C_{14}	A_6	〃	〃	〃	〃	Pr	〃	58
C_{15}	A_6	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	42

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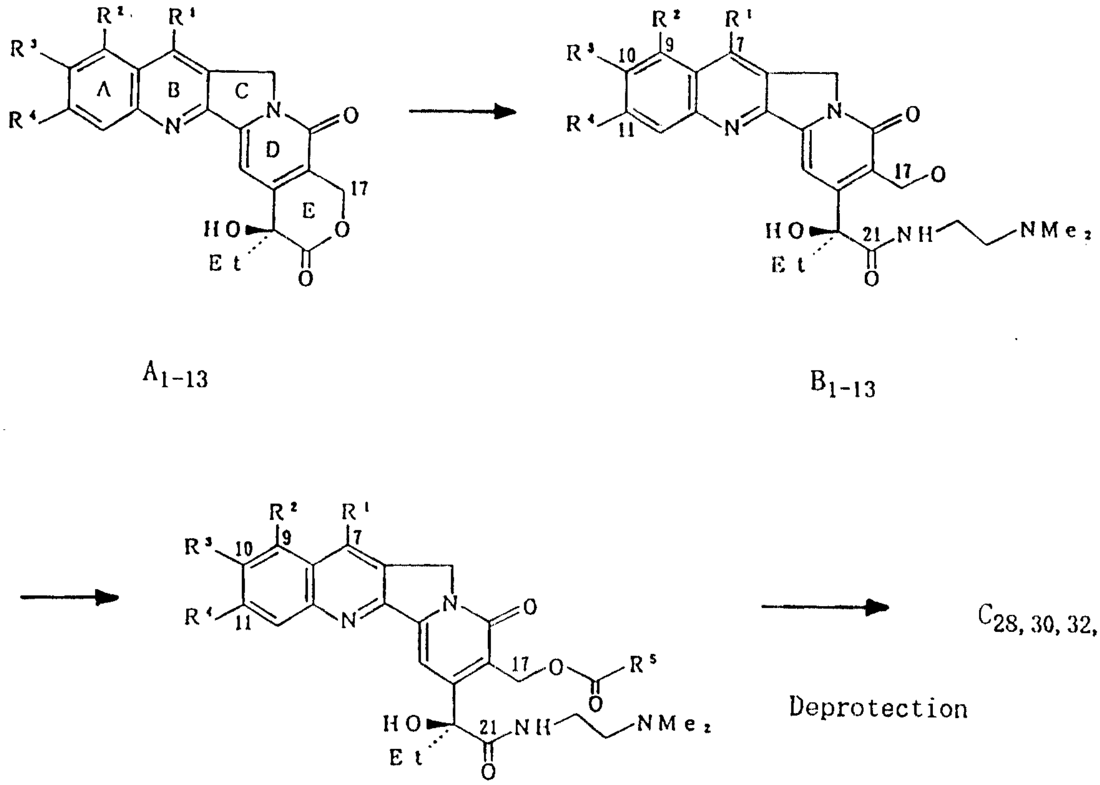
Table 1 (continued)

C_{16}	A_6	Et	H	F	F	$-C_6H_4-OMe$	98	37
C_{17}	A_7	〃	〃	Cl	Cl	Et	92	59
C_{18}	A_7	〃	〃	〃	〃	Pr	〃	60
C_{19}	A_7	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	56
C_{20}	A_8	〃	〃	OMe	F	Et	97	70
C_{21}	A_8	〃	〃	〃	〃	Pr	〃	67
C_{22}	A_8	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	65
C_{23}	A_9	〃	〃	Me	〃	Et	94	84
C_{24}	A_9	〃	〃	〃	〃	Pr	〃	82
C_{25}	A_9	〃	〃	〃	〃	$-CH_2CH_2SMe$	〃	80
C_{26}	A_9	Et	H	Me	F	$-C_6H_4-OMe$	94	78
C_{27}	A_{10}·	〃	〃	OMEM	H	Et	96	65
C_{28}		〃	〃	OH	〃	〃		x61
C_{29}	A_{10}·	〃	〃	OMEM	〃	Pr	〃	64
C_{30}		〃	〃	OH	〃	〃		x65
C_{31}	A_{10}·	〃	〃	OMEM	〃	$-CH_2CH_2SMe$	〃	68
C_{32}		〃	〃	OH	〃	〃		x60
C_{33}	A_{10}·	〃	〃	OMEM	〃	$-CH=CHCH_3$	〃	34
C_{34}		〃	〃	OH	〃	〃		x61
C_{35}	A_{10}·	〃	〃	OMEM	〃	$-C_6H_4-F_{(p)}$	〃	68
C_{36}		〃	〃	OH	〃	〃		x57

Table 1 (continued)

C_{37}	A_{10}·	Et	H	OMEM	H	-C_6H_4-F (m)	96	65
C_{38}		〃	〃	OH	〃	〃		x58
C_{39}	A_3	〃	〃	Me	〃	-4-pyridyl	98	89
C_{40}	A_1	〃	〃	Cl	〃	〃	94	75
C_{41}	A_4	〃	〃	H	F	〃	95	93
C_{42}	A_9	〃	〃	Me	〃	〃	94	85
C_{43}	A_8	〃	〃	OMe	〃	〃	97	95
C_{44}	A_{13}	H	OMe	H	H	-2-pyridyl	96	80.8
C_{45}	A_{10}·	Et	H	OH	H	Me	—	—
C_{46}	A_{10}·	〃	〃	〃	〃	iso-Pr	—	—
C_{47}	A_{10}·	〃	〃	〃	〃	-C_2H_4OEt	—	—
C_{48}	A_{10}	〃	〃	OAc	〃	-C_6H_4-F (p)	83	—

Table 1 (Appendix)



A_{1-13} B_{1-13}

C_{1-48} $C_{28, 30, 32, 34, 36, 38}$

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Table 2 (Spector Data of Hydroxy Amide Compounds)

B_1 (7-Et-10-Cl-)

Yellow powder(from n-Hexane-chloroform)

$C_{26}H_{31}N_4O_4Cl$, MS $[M+H]^+ = 499$,

IR $\nu^{MAX}/_{KBr}$ (cm^{-1}) : 1650, 1590, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.20-2.32(1H, m), 2.27(6H, s), 2.39-2.61(3H, m), 2.90-3.05(2H, m), 3.20-3.33(1H, m), 3.60-3.75(1H, m), 4.78(1H, d, J=13Hz), 5.00(1H, d, J=19Hz), 5.06(1H, d, J= 19Hz), 5.10(1H, d, J=13Hz), 7.44(1H, br-t, J=5Hz), 7.50(1H, s), 7.62(1H, dd, J=2, 9Hz), 7.82(1H, d, J=2Hz), 7.95(1H, d, J=9Hz).

B_2 (7-Et-10-Br-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{26}H_{31}N_4O_4Br$, MS $[M+H]^+ = 543$,

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1645, 1585, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.35(3H, t, J=8Hz), 2.20-2.33(1H, m), 2.29(6H, s), 2.35-2.63(3H, m), 2.99(2H, q, J=8Hz), 3.20-3.35(1H, m), 3.60-3.75(1H, m), 4.78(1H, d, J=13Hz), 5.02(1H, d, J=19Hz), 5.07(1H, d, J= 19Hz), 5.10(1H, d, J=13Hz), 7.43(1H, br-t, J=6Hz), 7.50(1H, s), 7.75(1H, dd, J=2, 9Hz), 7.88(1H, d, J=9Hz), 8.02(1H, d, J=2Hz).

B_3 (7-Et-10-Me-)

Colorless powder(from n-Hexane-chloroform)

$C_{27}H_{34}N_4O_4$, MS $[M+H]^+ = 479$,

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1645, 1580, 1560, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.32(3H, t, J=8Hz), 2.20-2.33(1H, m), 2.27(6H, s), 2.38-2.60(3H, m), 2.57(3H, s), 2.92-3.05(2H, m), 3.20- 3.33(1H, m), 3.61-3.75(1H, m), 4.80(1H, d, J=14Hz), 5.02(1H, d, J=19Hz), 5.08

A

Table 2 (continued)

(1H, d, J=19Hz), 5.12(1H, d, J=14Hz), 7.34(1H, br-t, J=6Hz), 7.51(1H, s), 7.54 (1H, dd, J=2, 9Hz), 7.64(1H, br-s), 7.99(1H, d, J=9Hz).

B_4 (7-Et-11-F-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{26}H_{31}N_4O_4F$, MS $[M+H]^+$ =483,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1645, 1590, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.35(3H, t, J=8Hz), 2.20-2.33(1H, m), 2.28(6H, s), 2.38-2.62(3H, m), 2.97-3.14(2H, m), 3.20-3.33(1H, m), 3.63-3.76(1H, m), 4.78(1H, d, J=13Hz), 5.03(1H, d, J=19Hz), 5.08(1H, d, J=19Hz), 5.12(1H, d, J=13Hz), 7.32(1H, ddd, J=3, 8, 10Hz), 7.39(1H, br-t, J=6Hz), 7.51(1H, s), 7.67(1H, dd, J=3, 10Hz), 7.93(1H, dd, J=6, 9Hz).

B_5 (7-Et-11-Cl-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{26}H_{31}N_4O_4Cl$, MS $[M+H]^+$ =499,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1645, 1600, 1590.

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.20-2.33(1H, m), 2.28(6H, s), 2.39-2.62(3H, m), 2.97-3.12(2H, m), 3.21-3.33(1H, m), 3.62-3.78(1H, m), 4.76(1H, d, J=14Hz), 5.00(1H, d, J=19Hz), 5.05(1H, d, J=19Hz), 5.10(1H, d, J=14Hz), 7.39-7.52(3H, m), 7.84(1H, d, J=9Hz), 7.97(1H, d, J=2Hz).

B_6 (7-Et-10, 11-F_2-)

Yellow powder(from n-Hexane-chloroform)

$C_{26}H_{30}N_4O_4F_2$, MS $[M+H]^+$ =501,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1645, 1590, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.18-2.64(4H, m), 2.29(6H, s), 3.06(2H, q, J=8Hz), 3.22-3.37(1H, m), 3.60-3.78(1H, m),

Table 2 (continued)

4.76(1H, d, J=14Hz), 5.06(1H, d, J=19Hz), 5.11(1H, d, J=19Hz), 5.13(1H, d, J=14Hz), 7.36-7.44(1H, br), 7.51(1H, s), 7.69(1H, dd, J=8, 11Hz), 7.81(1H, dd, J=8, 11Hz).

B_7 (7-Et-10, 11-Cl_2-)

Yellow powder(from n-Hexane-chloroform)

$C_{26}H_{30}N_4O_4Cl_2$, MS $[M+H]^+$ =533,

IRν $^{MAX}/_{KBr}$(cm^{-1}) : 1650, 1595, 1520.

^{1}H-NMR(δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.38(3H, t, J=8Hz), 2.18-2.34(1H, m), 2.29(6H, s), 2.38-2.64(3H, m), 2.94-3.11(2H, m), 3.23-3.38(1H, m), 3.60-3.75(1H, m), 4.71(1H, d, J=14Hz), 4.97(1H, d, J=19Hz), 5.03(1H, d, J=19Hz), 5.06(1H, d, J=14Hz), 7.43(1H, s), 7.51(1H, br-t, J=5Hz), 7.94(1H, s), 8.02(1H, s).

B_8 (7-Et-10-OMe-11-F-)

Yellow powder(from n-Hexane-chloroform)

$C_{27}H_{33}N_4O_5F$, MS $[M+H]^+$ =513,

IRν $^{MAX}/_{KBr}$(cm^{-1}) : 1650, 1590, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 2.20-2.37(1H, m), 2.27(6H, s), 2.41-2.60(3H, m), 2.85-3.04(2H, m), 3.21-3.33(1H, m), 3.60-3.73(1H, m), 4.00(3H, s), 4.73(1H, d, J=13Hz), 4.86(1H, d, J=19Hz), 4.94(1H, d, J=19Hz), 5.05(1H, d, J=13Hz), 6.93(1H, d, J=9Hz), 7.38(1H, s), 7.51(1H, br-t, J=6Hz), 7.55(1H, d, J=12Hz).

B_9 (7-Et-10-Me-11-F-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{27}H_{33}N_4O_4F$, MS $[M+H]^+$ =497,

IRν $^{MAX}/_{KBr}$(cm^{-1}) : 1645, 1585, 1505.

Table 2 (continued)

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^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.35(3H, t, J=8Hz), 2.21-2.35(1H, m), 2.28(6H, s), 2.40-2.62(3H, m), 2.48(3H, s), 2.94-3.12(2H, m), 3.23-3.37(1H, m), 3.59-3.74(1H, m), 4.76(1H, d, J=13Hz), 4.95(1H, d, J=19Hz), 5.01(1H, d, J=19Hz), 5.09(1H, d, J=13Hz), 7.46(1H, s), 7.47(1H, br-t, J=6Hz), 7.52(1H, d, J=11Hz), 7.65(1H, d, J=8Hz).

B_{10}. (7-Et-10-OMEM-)

Yellow powder(from n-Hexane-chloroform)

$C_{30}H_{40}N_4O_7$, MS $[M+H]^+$ =569,

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1650, 1625, 1585, 1510

^{1}H-NMR(δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.20-2.33(1H, m), 2.26(6H, s), 2.39-2.61(3H, m), 2.87-3.03(2H, m), 3.24-3.33(1H, m), 3.39(3H, s), 3.52-3.73(3H, m), 3.83-3.94(2H, m), 4.80(1H, d, J=13Hz), 4.98(1H, d, J=19Hz), 5.04(1H, d, J=19Hz), 5.09(1H, d, J=13Hz), 5.40(1H, d, J=7Hz), 5.43(1H, d, J=7Hz), 7.38-7.44(2H, m), 7.46(1H, s), 7.48(1H, br-t, J=6Hz), 7.97(1H, d, J=9Hz).

B_{11} (7-Me-10-OEt-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{27}H_{34}N_4O_5$, MS $[M+H]^+$ =495,

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1645, 1620, 1590, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 1.54(3H, t, J=7Hz), 2.23-2.33(1H, m), 2.28(6H, s), 2.39(3H, s), 2.43-2.59(3H, m), 3.21-3.37(1H, m), 3.55-3.72(1H, m), 3.97-4.17(2H, m), 4.80(1H, d, J=13Hz), 4.81(1H, d, J=18Hz), 4.89(1H, d, J=18Hz), 5.01(1H, d, J=13Hz), 6.72(1H, d, J=3Hz), 7.30(1H, dd, J=3, 9Hz), 7.40(1H, s), 7.49(1H, br-t, J=6Hz), 7.90(1H, d, J=9Hz).

Table 2 (continued)

B_{12} (7-Me-10-Br-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{25}H_{29}N_4O_4Br$, MS $[M+H]^+$ =529,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1645, 1595, 1515.

^{1}H-NMR(δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 2.18-2.33(1H, m), 2.29(6H, s), 2.40-2.65(3H, m), 2.60(3H, s), 3.20-3.35(1H, m), 3.60-3.75(1H, m), 4.77(1H, d, J=13Hz), 4.87(1H, d, J=19Hz), 4.93(1H, d, J=19Hz), 5.06(1H, d, J=13Hz), 7.40-7.48(2H, m), 7.51(1H, dd, J=2, 9Hz), 7.61(1H, d, J=9Hz), 8.14(1H, d, J=2Hz).

B_{13} (9-OMe-)

Pale yellow powder(from n-Hexane-chloroform)

$C_{25}H_{30}N_4O_5$, MS $[M+H]^+$ =467,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 3360, 1650, 1615, 1585, 1515.

^{1}H-NMR(δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 2.18-2.34(1H, m), 2.23(6H, s), 2.38-2.57(3H, m), 3.16-3.29(1H, m), 3.58-3.72(1H, m), 3.96(3H, s), 4.79(1H, d, J=13Hz), 5.02(1H, d, J=19Hz), 5.08(1H, d, J=13Hz), 5.09(1H, d, J=19Hz), 6.77(1H, d, J=8Hz), 7.38(1H, br-t, J=5Hz), 7.50(1H, s), 7.57(1H, dd, J=8, 8Hz), 7.63(1H, d, J=8Hz), 8.50(1H, s).

Table 3 (Spectral Data of 17-O-Acyl-21-amide Compounds)

C_1

mp 101-106°C, Pale yellow needles(from n-Hexane-chloroform)

$C_{31}H_{40}N_4O_6S \cdot H_2O$, MS $[M+H]^+$ =597,

Anal. (C, H, N): Found(calcd.) 60.67, 6.58, 8.96 (60.57, 6.89, 9.11),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1620, 1590, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.54(3H, t, J=7Hz), 2.09(3H, s), 2.22-2.38(1H, m), 2.28(6H, s), 2.41-2.68(5H, m), 2.57(3H, s), 2.72-2.80(2H, m), 3.24-3.34(1H, m), 3.42-3.53(1H, m), 4.13(2H, q, J=7Hz), 4.82-5.37(1H, br), 4.96(1H, d, J=19Hz), 5.07(1H, d, J=19Hz), 5.49(1H, d, J=12Hz), 5.53(1H, d, J=12Hz), 6.88(1H, br-s), 7.35(1H, dd, J=3, 9Hz), 7.38(1H, br-t, J=6Hz), 7.49(1H, s), 7.98(1H, d, J=9Hz).

C_2

mp 108-118°C, Yellow powder(from n-Hexane-chloroform)

$C_{29}H_{35}N_4O_5BrS \cdot 1/2H_2O$, MS $[M+H]^+$ =631,

Anal. (C, H, N): Found(calcd.) 54.08, 5.76, 8.48 (54.37, 5.66, 8.75)

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.17(3H, t, J=7Hz), 2.09(3H, s), 2.22-2.38(1H, m), 2.29(6H, s), 2.43-2.82(7H, m), 2.65(3H, s), 3.24-3.35(1H, m), 3.44-3.57(1H, m), 4.91(1H, d, J= 19Hz), 5.01(1H, d, J=19Hz), 5.49(2H, s), 7.48(1H, dd, J=2, 9Hz; 1H, s), 7.53(1H, br-t, J=6Hz), 7.59(1H, d, J=9Hz), 8.14(1H, d, J=2Hz).

C_3

mp 130-133°C, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+27.5(CH_3OH, c=0.2), $C_{29}H_{35}N_4O_5Cl \cdot 1/2H_2O$, MS $[M+H]^+$ =555,

Anal. (C, H, N): Found(calcd.) 61.74, 6.43, 9.66 (61.75, 6.43, 9.93),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1730, 1650, 1600, 1515.

Table 3 (continued)

^{1}H-NMR (δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 1.12(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.20-2.59(6H, m), 2.26(6H, s), 2.92-3.10(2H, m), 3.21-3.35(1H, m), 3.38 -3.51(1H, m), 4.99(1H, d, J=19Hz), 5.10(1H, d, J=19Hz), 5.26-5.60(1H, br), 5.47(1H, d,J=12Hz), 5.50(1H, d, J=12Hz), 7.43(1H, br-t, J=5Hz), 7.49(1H, s), 7.62(1H, dd, J=2, 9Hz), 7.73(1H, d, J=2Hz), 7.92(1H, d, J=9Hz).

C_4

mp 136-138°C, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+26.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5Cl \cdot 1/2H_2O$, MS $[M+H]^+$ =569,

Anal. (C, H, N): Found(calcd.) 62.69, 6.58, 9.73 (62.33, 6.63, 9.69),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1595, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 0.92(3H, t, J=7Hz), 1.12(3H, t, J=7Hz), 1.33(3H, t, J=8Hz), 1.64(2H, sextet, J=7Hz), 2.16-2.35(3H, m), 2.25(6H, s), 2.38-2.59(3H, m), 2.90-3.07(2H, m), 3.21-3.32(1H, m), 3.39-3.50(1H, m), 4.96(1H, d, J=19Hz), 5.07(1H, d, J=19Hz), 5.31-5.60(1H, br), 5.45(1H, d, J=12Hz), 5.50(1H, d, J=12Hz), 7.46(1H, br-t, J=5Hz), 7.47(1H, s), 7.60(1H, dd, J=2, 9Hz), 7.68(1H, d, J=2Hz), 7.89(1H, d, J=9Hz).

C_5

mp 139-144°C, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+20.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5ClS \cdot 1/2H_2O$, MS $[M+H]^+$ =601,

Anal. (C, H, N): Found(calcd.) 59.28, 6.31, 9.01 (59.05, 6.28, 9.18),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.09(3H, s), 2.23-2.35(1H, m), 2.31(6H, s), 2.44-2.68(5H, m), 2.70-2.80(2H, m), 2.93-3.09(2H, m), 3.24-3.35(1H, m), 3.43-3.57(1H, m), 5.00(1H, d, J=19Hz), 5.09(1H, d, J=19Hz), 5.51(2H, s), 7.51(1H, s), 7.52(1H, br-t, J=5Hz), 7.62(1H, dd, J=2,

Table 3 (continued)

9Hz), 7.74(1H, d, J=2Hz), 7.93(1H, d, J=9Hz).

C6

mp 149-151°C, Pale yellow needles(from n-Hexane-chloroform),

$[\alpha]^{25}/_{D}$=+18.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5BrS$, MS $[M+H]^+$ =645,

Anal. (C, H, N): Found(calcd.) 55.95, 5.70, 8.50 (55.81, 5.78, 8.68),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1610, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.10(3H, s), 2.22-2.35(1H, m), 2.25(6H, s), 2.38-2.55(3H, m), 2.57-2.68(2H, m), 2.71-2.81(2H, m), 2.97-3.10(2H, m), 3.24-3.34(1H, m), 3.38-3.50(1H, m), 4.98-5.34(1H, br), 5.05(1H, d, J=19Hz), 5.13(1H, d, J=19Hz), 5.49(1H, d, J=12Hz), 5.57(1H, d, J=12Hz), 7.40(1H, br-t, J=6Hz), 7.53(1H, s), 7.77(1H, dd, J=2, 9Hz), 7.90(1H, d, J=9Hz), 8.00(1H, d, J=2Hz).

C7

mp 130-134°C, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_{D}$=+21.5(CH_3OH, c=0.2), $C_{31}H_{40}N_4O_5S$, MS $[M+H]^+$ =581,

Anal. (C, H, N): Found(calcd.) 63.88, 7.02, 9.43 (64.11, 6.94, 9.65),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.32(3H, t, J=8Hz), 2.09(3H, s), 2.20-2.36(1H, m), 2.26(6H, s), 2.41-2.55(3H, m), 2.54(3H, s), 2.57-2.67(2H, m), 2.71-2.81(2H, m), 2.93-3.09(2H, m), 3.25-3.35(1H, m), 3.41-3.52(1H, m), 4.99(1H, d, J=19Hz), 5.07(1H, d, J=19Hz), 5.50(1H, d, J=12Hz), 5.54(1H, d, J=12Hz), 7.44(1H, br-t, J=6Hz), 7.51(1H, dd, J=2, 8Hz), 7.52(1H, s), 7.55(1H, br-s), 7.94(1H, d, J=8Hz).

C8

mp 164-166°C, Pale yellow powder(from n-Hexane-chloroform),

Table 3 (continued)

$[\alpha]^{25}/_D$=+24.0(CH_3OH, c=0.2), $C_{29}H_{35}N_4O_5F\cdot2H_2O$, MS $[M+H]^+$ =539,

Anal. (C, H, N): Found(calcd.) 60.24, 6.80, 9.84 (60.61, 6.84, 9.75),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 1.13(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.24-2.63(6H, m), 2.30(6H, s), 3.02-3.20(2H, m), 3.25-3.55(2H, m), 5.07(1H, d, J=19Hz), 5.14(1H, d, J=19Hz), 5.21-5.41(1H, br), 5.51(2H, br-s), 7.31(1H, ddd, J=2, 9, 10Hz), 7.41(1H, br-t, J=5Hz), 7.55(1H, s), 7.69(1H, dd, J=2, 10Hz), 7.93(1H, dd, J=6, 9Hz).

C_9

mp 134-137°C, Pale yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+22.0(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5F\cdot3/2H_2O$, MS $[M+H]^+$ =553,

Anal. (C, H, N): Found(calcd.) 62.06, 6.85, 9.70 (62.16, 6.96, 9.67),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 0.93(3H, t, J=7Hz), 1.09(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 1.65(2H, sextet, J=7Hz), 2.20-2.36(3H, m), 2.25(6H, s), 2.39-2.53(3H, m), 3.02-3.17(2H, m), 3.25-3.35(1H, m), 3.38-3.49(1H, m), 5.05(1H, d, J=19Hz), 5.12(1H, d, J=19Hz), 5.22-5.40(1H, br), 5.47(1H, d, J=12Hz), 5.53((1H, d, J=12Hz), 7.30(1H, ddd, J=3, 9, 10Hz), 7.38(1H, br-t, J=5Hz), 7.53(1H, s), 7.67(1H, dd, J=3, 10Hz), 7.91(1H, dd, J=6, 9Hz).

C_{10}

mp 135-138°C, Pale yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+16.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5FS\cdot3/2H_2O$, MS $[M+H]^+$ =585

Anal. (C, H, N): Found(calcd.) 58.74, 6.48, 9.21 (58.90, 6.59, 9.16),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1730, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.10(3H,

Table 3 (continued)

s), 2.20-2.36(1H, m), 2.25(6H, s), 2.40-2.54(3H, m), 2.58-2.68(2H, m), 2.72-2.82(2H, m), 3.04-3.18(2H, m), 3.25-3.36(1H, m), 3.39-3.50(1H, m), 4.99-5.31(1H, br), 5.06(1H, d, J=19Hz), 5.14(1H, d, J=19Hz), 5.49(1H, d, J=12Hz), 5.58(1H, d, J=12Hz), 7.31(1H, ddd, J=3, 9, 10Hz), 7.39(1H, br-t, J=5Hz), 7.55(1H, s), 7.68(1H, dd, J=3, 10Hz), 7.93(1H, dd, J=6, 9Hz).

$\underline{C_{11}}$

mp 180-182℃, Pale yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=-59.5(CH_3OH, c=0.2), $C_{34}H_{37}N_4O_6F \cdot H_2O$, MS $[M+H]^+$ =617

Anal. (C, H, N): Found(calcd.) 64.34, 6.40, 8.98 (64.34, 6.19, 8.83),

IR$\nu^{MAX}/_{KBr}$(cm^{-1}) : 1700, 1650, 1600, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.12(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.18(6H, s), 2.29-2.44(3H, m), 2.47-2.59(1H, m), 2.99-3.22(3H, m), 3.30-3.42(1H, m), 5.03(1H, d, J=19Hz), 5.12(1H, d, J=19Hz), 5.58-5.93(1H, br), 5.73(1H, d, J=12Hz), 5.81(1H, d, J=12Hz), 6.82(2H, d, J=9Hz), 7.22-7.28(1H, m), 7.51(1H, br-t, J=5Hz), 7.57(1H, s), 7.63(1H, dd, J=3, 10Hz), 7.85(1H, dd, J=6, 9Hz), 7.96(2H, d, J=9Hz).

$\underline{C_{12}}$

mp 131-133℃, Pale yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+25.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5ClS \cdot H_2O$, MS $[M+H]^+$ =601,

Anal. (C, H, N): Found(calcd.) 57.80, 6.05, 8.91 (58.20, 6.35, 9.05)

IR$\nu^{MAX}/_{KBr}$(cm^{-1}) : 1730, 1650, 1605, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.37(3H, t, J=8Hz), 2.10(3H, s), 2.22-2.36(1H, m), 2.26(6H, s), 2.40-2.54(3H, m), 2.56-2.68(2H, m), 2.70-2.81(2H, m), 3.02-3.18(2H, m), 3.25-3.35(1H, m), 3.40-3.52(1H, m), 4.97-5.35(1H, br), 5.05(1H, d, J=19Hz), 5.13(1H, d, J=19Hz), 5.49(1H, d, J=11Hz), 5.57(1H, d, J=11Hz), 7.42(1H, br-t, J=6Hz), 7.46(1H, dd, J=2, 9Hz), 7.54(1H, s),

Table 3 (continued)

7.85(1H, d, J=9Hz), 8.02(1H, d, J=2Hz).

C_{13}

mp 168-170℃, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+24.0(CH_3OH, c=0.2), $C_{29}H_{34}N_4O_5F_2 \cdot H_2O$, MS $[M+H]^+$ =557,

Anal. (C, H, N): Found(calcd.) 60.91, 6.22, 9.75 (60.62, 6.31, 9.75),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1655, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.07(3H, t, J=7Hz), 1.13(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.18-2.52(6H, m), 2.24(6H, s), 3.07(2H, q, J=8Hz), 3.25-3.36(1H, m), 3.38-3.49(1H, m), 5.06-5.38(1H, br), 5.10(1H, d, J=19Hz), 5.16(1H, d, J=19Hz), 5.48(1H, d, J=12Hz), 5.56(1H, d, J=12Hz), 7.36(1H, br-t, J=5Hz), 7.55(1H, s), 7.69(1H, d, J=8, 11Hz), 7.86(1H, d, J=8, 11Hz).

C_{14}

mp 160-162℃, Yellow powder(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+21.5(CH_3OH, c=0.2), $C_{30}H_{36}N_4O_5F_2 \cdot 1/2H_2O$, MS $[M+H]^+$ =571,

Anal. (C, H, N): Found(calcd.) 61.73, 6.53, 9.75 (62.16, 6.43, 9.67),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1655, 1600, 1520.

^{1}H-NMR (δppm) in $CDCl_3$: 0.93(3H, t, J=7Hz), 1.07(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 1.65(2H, sextet, J=7Hz), 2.16-2.36(3H, m), 2.24(6H, s), 2.38-2.52(3H, m), 3.07(2H, q, J=8Hz), 3.25-3.36(1H, m), 3.37-3.48(1H, m), 5.05-5.34(1H, br), 5.10(1H, d, J=19Hz), 5.16(1H, d, J=19Hz), 5.47(1H, d, J=12Hz), 5.57((1H, d, J=12Hz), 7.35(1H, br-t, J=5Hz), 7.55(1H, s), 7.70(1H, dd, J=8, 11Hz), 7.86(1H,dd, J=8, 11Hz).

C_{15}

mp 119-125℃, Yellow needles(from n-Hexane-chloroform),

$[\alpha]^{25}/_D$=+22.0(CH_3OH, c=0.2), $C_{30}H_{36}N_4O_5F_2S \cdot H_2O$, MS $[M+H]^+$ =603,

Anal. (C, H, N): Found(calcd.) 57.83, 6.03, 9.08 (58.05, 6.17, 9.03),

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Table 3 (continued)

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.10(3H, s), 2.20-2.34(1H, m), 2.25(6H, s), 2.40-2.54(3H, m), 2.58-2.70(2H, m), 2.71-2.83(2H, m), 3.07(2H, q, J=8Hz), 3.26-3.37(1H, m), 3.40-3.52(1H, m), 5.08(1H, d, J=19Hz), 5.15(1H, d, J=19Hz), 5.49(1H, d, J=12Hz), 5.60((1H, d, J=12Hz), 7.43(1H, br-t, J=5Hz), 7.55(1H, s), 7.67(1H, dd, J=8, 11Hz), 7.83(1H, dd, J=8, 11Hz).

C_{16}

mp 175-178°C, Colorless needles(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=-57.0(CH_3OH, c=0.2), $C_{34}H_{37}N_4O_6F_2 \cdot 1/2H_2O$, MS $[M+H]^+$ =635,

Anal. (C, H, N): Found(calcd.) 63.74, 5.79, 8.93 (63.44, 5.79, 8.70),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1695, 1650, 1600, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.35(3H, t, J=8Hz), 2.19(6H, s), 2.26-2.55(4H, m), 3.05(2H, q, J=8Hz), 3.14-3.25(1H, m), 3.30-3.42(1H, m), 5.08(1H, d, J=19Hz), 5.15(1H, d, J=19Hz), 5.55-5.90(1H, br), 5.70(1H, d, J=12Hz), 5.84(1H, d, J=12Hz), 6.84(2H, d, J=9Hz), 7.48(1H, br-t, J=5Hz), 7.57(1H, s), 7.65(1H, dd, J=8, 11Hz), 7.82(1H, dd, J=8, 11Hz), 7.97(2H, d, J=9Hz).

C_{17}

mp 153-156°C, Yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+34.5(CH_3OH, c=0.2), $C_{29}H_{34}N_4O_5Cl_2 \cdot 1/2H_2O$, MS $[M+H]^+$ =589,

Anal. (C, H, N): Found(calcd.) 58.12, 5.74, 9.35 (58.20, 5.89, 9.36),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 1.12(3H, t, J=7Hz), 1.38(3H, t, J=8Hz), 2.19-2.38(3H, m), 2.27(6H, s), 2.40-2.58(3H, m), 2.96-3.14(2H, m), 3.21-3.32(1H, m), 3.40-3.51(1H, m), 4.99(1H, d, J=19Hz), 5.08(1H, d, J=19Hz), 5.45(1H, d, J=12Hz), 5.49(1H, d, J=12Hz), 7.46(1H, s), 7.49(1H, br-t, J=5Hz),

Table 3 (continued)

7.89(1H, s), 8.05(1H, s).

C_{18}

mp 142-147°C, Yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+31.5(CH_3OH, c=0.2),

$C_{30}H_{36}N_4O_5Cl_2\cdot1/2H_2O$, MS $[M+H]^+$ =603,

Anal. (C, H, N): Found(calcd.) 58.97, 5.95, 9.06 (58.82, 6.09, 9.15),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1600, 1515

^{1}H-NMR (δppm) in $CDCl_3$: 0.92(3H, t, J=7Hz), 1.11(3H, t, J=7Hz), 1.38(3H, t, J=8Hz), 1.64(2H, sextet, J=7Hz), 2.18-2.35(3H, m), 2.26(6H, s), 2.39-2.56(3H, m), 2.98-3.14(2H, m), 3.21-3.32(1H, m), 3.38-3.52(1H, m), 5.00(1H, d, J=19Hz), 5.09(1H, d, J=19Hz), 5.48(2H, s), 7.45(1H, br-t, J=5Hz), 7.47(1H, s), 7.92(1 H, s), 8.07(1H, s).

C_{19}

mp 139-142°C, Yellow needles(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+27.5(CH_3OH, c=0.2), $C_{30}H_{36}N_4O_5Cl_2S\cdot1/2H_2O$, MS $[M+H]^+$ =635,

Anal. (C, H, N): Found(calcd.) 55.94, 5.69, 8.79 (55.90, 5.79, 8.69),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1600, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.38(3H, t, J=8Hz), 2.09(3H, s), 2.21-2.37(1H, m), 2.29(6H, s), 2.43-2.67(5H, m), 2.70-2.81(2H, m), 2.99-3.16(2H, m), 3.24-3.35(1H, m), 3.42-3.55(1H, m), 5.03(1H, d, J=19Hz), 5.11(1H, d, J=19Hz), 5.49(1H, d, J=12Hz), 5.54(1H, d, J=12Hz), 7.49(1H, br-t, J=6Hz), 7.50(1H, s), 7.96(1H, s), 8.11(1H, s).

C_{20}

mp 112-117°C, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+28.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_6F\cdot3/2H_2O$, MS $[M+H]^+$ =569,

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Table 3 (continued)

Anal. (C, H, N): Found(calcd.) 60.15, 6.78, 9.40 (60.49, 6.77, 9.41),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1595, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.12(3H, t, J=7Hz), 1.13(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 2.21-2.63(6H, m), 2.28(6H, s), 2.88-3.08(2H, m), 3.18-3.30(1H, m), 3.40-3.52(1H, m), 4.00(3H, s), 4.89(1H, d, J=19Hz), 5.02(1H, d, J=19Hz), 5.41(1H, d, J=12Hz), 5.50(1H, d, J=12Hz), 6.89(1H, d, J=9Hz), 7.40(1H, s), 7.46(1H, br-t, J=6Hz), 7.57(1H, d, J=12Hz).

$\underline{C_{21}}$

mp 109-113°C, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+29.5(CH_3OH, c=0.2), $C_{31}H_{39}N_4O_6F \cdot 2H_2O$, MS $[M+H]^+$ =583,

Anal. (C, H, N): Found(calcd.) 60.09, 6.99, 9.29 (60.18, 7.01, 9.06),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 0.92(3H, t, J=7Hz), 1.13(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 1.63(2H, sextet, J=7Hz), 2.18-2.37(3H, m), 2.28(6H, s), 2.39-2.63(3H, m), 2.87-3.07(2H, m), 3.17-3.30(1H, m), 3.41-3.53(1H, m), 4.00(3H, s), 4.89(1H, d, J=19Hz), 5.02(1H, d, J=19Hz), 5.34-5.57(1H, br), 5.40(1H, d, J=12Hz), 5.49(1H, d, J=12Hz), 6.89(1H, d, J=9Hz), 7.40(1H, s), 7.46(1H, br-t, J=6Hz), 7.57(1H, d, J=12Hz).

$\underline{C_{22}}$

mp 125-129°C, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+22.0(CH_3OH, c=0.2), $C_{31}H_{39}N_4O_6FS \cdot 3/2H_2O$, MS $[M+H]^+$ =615,

Anal. (C, H, N): Found(calcd.) 59.82, 6.40, 9.02 (59.89, 6.60, 8.73),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1650, 1600, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.11(3H, t, J=7Hz), 1.33(3H, t, J=8Hz), 2.09(3H, s), 2.22-2.36(1H, m), 2.26(6H, s), 2.39-2.69(5H, m), 2.71-2.80(2H, m), 2.94-

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Table 3 (continued)

3.10(2H, m), 3.21-3.34(1H, m), 3.39-3.51(1H, m), 4.03(3H, s), 4.93-5.38(1H, br), 4.97(1H, d, J=19Hz), 5.07(1H, d, J=19Hz), 5.50(2H, s), 7.01(1H, d, J=9Hz), 7.38(1H, br-t, J=6Hz), 7.44(1H,s), 7.64(1H, d, J=12Hz).

C_{23}

mp 164-165℃, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+24.5(CH_3OH, c=0.2), $C_{30}H_{37}N_4O_5F \cdot 3/2H_2O$, MS $[M+H]^+$ =553,

Anal. (C, H, N): Found(calcd.) 61.88, 6.85, 9.71 (62.16, 6.96, 9.67),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.09(3H, t, J=7Hz), 1.13(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.19-2.57(6H, m), 2.25(6H, s), 2.48(3H, s), 2.99-3.16(2H, m), 3.23-3.34 (1H, m), 3.38-3.49(1H, m), 5.02(1H, d, J=19Hz), 5.10(1H, d, J=19Hz), 5.49(2H, s), 7.38(1H, br-t, J=5Hz), 7.49(1H, s), 7.58(1H, d, J=11Hz), 7.67(1H, d, J=8Hz).

C_{24}

mp 148-154℃, Pale yellow needles(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+24.0(CH_3OH, c=0.2), $C_{31}H_{39}N_4O_5F \cdot 1/2H_2O$, MS $[M+H]^+$ =567,

Anal. (C, H, N): Found(calcd.) 64.28, 7.07, 9.65 (64.68, 7.00, 9.73),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1600, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 0.93(3H, t, J=7Hz), 1.09(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 1.64(2H, sextet, J=7Hz), 2.19-2.35(3H, m), 2.24(6H, s), 2.38-2.54(3H, m), 2.48(3H, s), 2.99-3.16(2H, m), 3.23-3.34(1H, m), 3.38-3.50(1H, m), 5.02(1H, d, J=19Hz), 5.10(1H, d, J=19Hz), 5.21-5.42(1H, br), 5.47(1H, d, J=12Hz), 5.51(1H, d, J=12Hz), 7.38(1H, br-t, J=5Hz), 7.49(1H, s), 7.58(1H, d, J=11Hz), 7.68(1H, d, J=8Hz).

C_{25}

mp 107-121℃, Yellow needles(from n-hexane-chloroform)

Table 3 (continued)

$[\alpha]^{25}/_D$=+54.0(CH_3OH, c=0.2), $C_{31}H_{39}N_4O_5FS \cdot 2H_2O$, MS $[M+H]^+$ =599,

Anal. (C, H, N): Found(calcd.) 60.75, 6.67, 9.15 (60.55, 6.83, 8.83),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.10(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.09(3H, s), 2.22-2.35(1H, m), 2.28(6H, s), 2.40-2.66(5H, m), 2.46(3H, s), 2.72-2.81(2H, m), 2.97-3.14(2H, m), 3.24-3.34(1H, m), 3.43-3.54(1H, m), 4.98(1H, d, J=19Hz), 5.07(1H, d, J=19Hz), 5.51(2H, s), 7.47(1H, s), 7.48(1H, br-t, J=5Hz), 7.54(1H, d, J=11Hz), 7.63(1H, d, J= 8Hz).

$\underline{C_{26}}$

mp 189-192℃, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=-59.0(CH_3OH, c=0.2), $C_{35}H_{39}N_4O_6F \cdot H_2O$, MS $[M+H]^+$ =631,

Anal. (C, H, N): Found(calcd.) 64.43, 6.57, 8.73 (64.80, 6.37, 8.64)

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1700, 1650, 1605, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.12(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.17(6H, s), 2.28-2.42(3H, m), 2.45(3H, s), 2.48-2.60(1H, m), 2.96-3.18(3H, m), 3.28-3.39(1H, m), 4.98(1H, d, J=19Hz), 5.09(1H, d, J=19Hz), 5.52-5.98(1H, br), 5.74(1H, d, J=12Hz), 5.78(1H, d, J=12Hz), 6.82(2H, d, J=9Hz), 7.48-7.55(3H, m), 7.60(1H, d, J=8Hz), 7.95(1H, d, J=9Hz).

$\underline{C_{27}}$

mp 82-87℃, Yellow prisms(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+24.0(CH_3OH, c=0.2), $C_{33}H_{44}N_4O_8 \cdot H_2O$, MS $[M+H]^+$ =625,

Anal. (C, H, N): Found(calcd.) 61.85, 7.12, 8.81 (61.67, 7.21, 8.72),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1730, 1650, 1620, 1585, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 1.12(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.25-2.41(3H, m), 2.35(6H, s), 2.43-2.66(3H, m), 2.91-3.07(2H, m),

Table 3 (continued)

3.27-3.37(1H, m), 3.39(3H, s), 3.46-3.63(3H, m), 3.83-3.93(2H, m), 4.99(1H, d, J=19Hz), 5.08(1H, d, J=19Hz), 5.27-5.62(1H, br), 5.38(1H, d, J=7Hz), 5.41(1H, d, J=7Hz), 5.46(1H, d, J=12Hz), 5.50(1H, d, J=12Hz), 7.34(1H, d, J=3Hz), 7.39(1H, dd, J=3, 9Hz), 7.44-7.55(2H, s, br-t), 7.95(1H, d, J=9Hz)

C_{28}

mp 214-215℃, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+34.0(CH_3OH, c=0.2), $C_{29}H_{36}N_4O_6$, MS $[M+H]^+$ =537,

Anal. (C, H, N): Found(calcd.) 64.67, 6.69, 10.22 (64.91, 6.76, 10.44),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1720, 1645, 1620, 1585.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.87(3H, t, J=7Hz), 1.05(3H, t, J=8Hz), 1.31(3H, t, J=8Hz), 2.08-2.24(2H, m), 2.27(2H, q, J=8Hz), 2.74(6H, s), 2.99-3.15(4H, m), 3.22-3.54(2H, m), 5.25(2H, s), 5.31(1H, d, J=11Hz), 5.37(1H, d, J=11Hz), 6.28(1H, s), 7.38-7.47(3H, m), 8.02(1H, d, J=10Hz), 8.30(1H, br-t, J=6Hz), 9.43-9.88(1H, br), 10.36(1H, s).

C_{29}

mp 78- 82℃, Yellow needles(from n-hexane-chloroform)

$[\alpha]^{25}/_D$=+22.5(CH_3OH, c=0.2), $C_{34}H_{46}N_4O_8 \cdot 3/2H_2O$, MS $[M+H]^+$ =639,

Anal. (C, H, N): Found(calcd.) 61.61, 7.03, 8.38 (61.34, 7.42, 8.42),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1620, 1585, 1510.

^{1}H-NMR(δppm) in $CDCl_3$: 0.93(3H, t, J=7Hz), 1.08(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 1.64(2H, sext, J=7Hz), 2.23-2.38(3H, m), 2.34(6H, s), 2.43-2.64(3H, m), 2.89-3.08(2H, m), 3.25-3.36(1H, m), 3.39(3H, s), 3.45-3.63(3H, m), 3.83-3.93(2H, m), 4.98(1H, d, J=19Hz), 5.08(1H, d, J=19Hz), 5.30-5.58(1H, br), 5.37(1H, d, J=7Hz), 5.41(1H, d, J=7Hz), 5.46(1H, d, J=12Hz), 5.49(1H, d, J=12Hz), 7.34(1H, d, J=3Hz), 7.39(1H, dd, J=3, 9Hz), 7.44-7.52(2H, s, br-t), 7.95(1H, d, J=9Hz).

Table 3 (continued)

C_{30}

mp 218-219°C, Colorless powder(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+32.5(CH_3OH, c=0.2), $C_{30}H_{38}N_4O_6$, MS $[M+H]^+$ =551,

Anal. (C, H, N): Found(calcd.) 65.34, 6.99, 10.04 (65.44, 6.96, 10.17),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1715, 1645, 1620, 1585.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.87(3H, t, J=7Hz), 0.90(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 1.55(2H, sextet, J=7Hz), 2.12(6H, s), 2.25-2.32(6H, m), 3.02-3.25(4H, m), 5.26(2H, s), 5.29(1H, d, J=11Hz), 5.37(1H, d, J=11Hz), 6.28(1H, s), 7.37(1H, s), 7.38-7.45(2H, m), 7.78(1H, br-t, J=6Hz), 8.04(1H, d, J=10Hz), 10.29(1H, br-s).

C_{31}

mp 84- 90°C, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+18.0(CH_3OH, c=0.2), $C_{34}H_{46}N_4O_8S \cdot H_2O$, MS $[M+H]^+$ =671,

Anal. (C, H, N): Found(calcd.) 59.33, 6.77, 7.96 (59.28, 7.02, 8.13),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1725, 1650, 1620, 1585, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.07(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 2.09(3H, s), 2.24-2.41(1H, m), 2.36(6H, s), 2.42-2.68(5H, m), 2.71-2.80(2H, m), 2.93-3.07(2H, m), 3.27-3.41(1H, m), 3.39(3H, s), 3.49-3.61(3H, m), 3.83-3.92(2H, m), 5.00(1H, d, J=19Hz), 5.10(1H, d, J=19Hz), 5.22-5.60(1H, br), 5.38(1H, d, J=7Hz), 5.42(1H, d, J=7Hz), 5.52(2H, s), 7.37(1H, d, J=3Hz), 7.41(1H, dd, J=3, 9Hz), 7.44-7.54(2H, br-m), 7.97(1H, d, J=9Hz).

C_{32}

mp 172-175°C, Pale yellow powder(from n-hexane-chloroform)

$[\alpha]^{25}/_{D}$=+25.0(CH_3OH, c=0.2), $C_{30}H_{38}N_4O_6S$, MS $[M+H]^+$ =583,

Anal. (C, H, N): Found(calcd.) 61.62, 6.52, 9.44 (61.84, 6.57, 9.61),

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Table 3 (continued)

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1725, 1645, 1620, 1585.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.87(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.02-2.32 (4H, m), 2.07(3H, s), 2.13(6H, s), 2.52-2.59(2H, m), 2.64-2.72(2H, m), 3.00-3.26(4H, m), 5.26(2H, s), 5.34(1H, d, J=11Hz), 5.42(1H, d, J=11Hz), 6.22(1H, s), 7.34-7.48(3H, m), 7.79(1H, br-t, J=6Hz), 8.04(1H, d, J=10Hz), 10.30(1H, br).

$\underline{C_{33}}$

mp 78- 86℃, Yellow needles(from n-Hexane-chloroform)

$C_{34}H_{44}N_4O_8 \cdot 1/2H_2O$, MS $[M+H]^+$ =637,

Anal. (C, H, N): Found(calcd.) 63.02, 7.02, 8.67 (63.24, 7.02, 8.68),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1710, 1650, 1620, 1585, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 1.83(3H, dd, J=2, 7Hz), 2.25(6H, s), 2.26-2.37(1H, m), 2.39-2.53(3H, m), 2.94-3.08(2H, m), 3.21-3.47(1H, m), 3.39(3H, s), 3.54-3.61(2H, m), 3.84-3.91(2H, m), 5.04(1H, d, J=19Hz), 5.12(1H, d, J=19Hz), 5.39(1H, d, J=7Hz), 5.42(1H, d, J=7Hz), 5.53(1H, d, J=12Hz), 5.61(1H, d, J=12Hz), 5.80-5.88(1H, m), 6.98(1H, dq, J=7, 14Hz), 7.32-7.55(4H, m), 8.00(1H, d, J=9Hz).

$\underline{C_{34}}$

Yellow powder(from n-Hexane-chloroform)

$C_{30}H_{36}N_4O_6$, MS $[M+H]^+$ =549,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1705, 1675, 1645, 1590, 1510.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.88(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 1.84(3H, dd, J=2, 7Hz), 2.08-2.26(2H, m), 2.74(6H, s), 2.98-3.04(4H, m), 3.29-3.52(2H, m), 5.26(2H, s), 5.35(1H, d, J=11Hz), 5.42(1H, d, J=11Hz), 5.80-5.90(1H, m), 6.30(1H, s), 6.87(1H, dq, J=7, 16Hz), 7.38-7.48(3H, m), 8.20(1H, d, J=3Hz), 9.46-9.63(1H, br), 10.35(1H, s).

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Table 3 (continued)

C_{35}

mp 102-105°C, Yellow prisms(from n-Hexane-chloroform)

$C_{37}H_{43}N_4O_8F$, MS $[M+H]^+$ =691,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1710, 1650, 1620, 1600, 1505.

^{1}H-NMR (δppm) in $CDCl_3$: 1.14(3H, t, J=7Hz), 1.27(3H, t, J=8Hz), 2.16(6H, s), 2.22-2.42(3H, m), 2.49-2.62(1H, m), 2.82-3.18(3H, m), 3.18-3.42(1H, m), 3.39(3H, s), 3.50-3.64(2H, m), 3.80-3.93(2H, m), 4.94(1H, d, J=19Hz), 5.08(1H, d, J=19Hz), 5.35(1H, d, J=7Hz), 5.40(1H, d, J=7Hz), 5.55-5.77(1H, br), 5.78(2H, s), 7.01(2H, dd, J=9, 9Hz), 7.22(1H, d, J=3Hz), 7.27(1H, s), 7.35(1H, dd, J=3, 9Hz), 7.48(1H, br-t, J=6Hz), 7.50(1H, s), 7.90(1H, d, J=9Hz), 8.02(2H, dd, J=6, 9Hz).

C_{36}

mp 231-232°C, Colorless powder(from n-Hexane-chloroform)

$[\alpha]^{25}/_D$=-6.5(CH_3OH, c=0.2), $C_{33}H_{35}N_4O_6F$, MS $[M+H]^+$ =603,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1710, 1645, 1620, 1595, 1520.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.91(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.11-2.30(2H, m), 2.53(6H, s), 2.62-2.90(2H, m), 2.99-3.40(4H, m), 5.29(2H, s), 5.57(1H, d, J=11Hz), 5.62(1H, d, J=11Hz), 6.36(1H, s), 7.33(1H, dd, J=9, 9Hz), 7.38-7.48(3H, m), 7.97(2H, dd, J=6, 9Hz), 8.04(1H, d, J=9Hz), 8.94-10.27(1H, br), 10.34(1H, s).

C_{37}

mp 105-109°C, Yellow prisms(from n-Hexane-chloroform)

$[\alpha]^{25}/_D$=+62.0($CHCl_3$, c=0.2), $C_{37}H_{43}N_4O_8F$, MS $[M+H]^+$ =691,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1650, 1620, 1590, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.14(3H, t, J=7Hz), 1.27(3H, t, J=8Hz), 2.16(6H,

Table 3 (continued)

s), 2.23-2.43(3H, m), 2.50-2.66(1H, m), 2.83-3.05(1H, m), 3.06-3.19(1H, m), 3.27-3.44(1H, m), 3.39(3H, s), 3.50-3.63(2H, m), 3.80-3.92(2H, m), 4.95(1H, d, 19Hz), 5.08(1H, d, J=19Hz), 5.35(1H, d, J=7Hz), 5.40(1H, d, J=7Hz), 5.50-5.82(1H, br), 5.77(1H, d, J=12Hz), 5.81(1H, d, J=12Hz), 7.13-7.25(2H, m), 7.27-7.39(2H, m), 7.48(1H, br-t, J=6Hz), 7.50(1H, s), 7.66-7.73(1H, m), 7.80(1H, d, J=8Hz), 7.90(1H, d, J=9Hz).

C_{38}

mp 223-224°C, Colorless powder(from n-Hexane-chloroform)

$C_{33}H_{35}N_4O_6F$, MS $[M+H]^+$ =603,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1710, 1645, 1620, 1590, 1520.

^{1}H-NMR (δppm) in DMSO-d_6 : 0.91(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.08-2.34(2H, m), 2.54(6H, s), 2.54-2.75(2H, m), 2.95-3.43(4H, m), 5.29(2H, s), 5.58(1H, d, J=11Hz), 5.65(1H, d, J=11Hz), 6.35(1H, s), 7.34-7.68(6H, m), 7.76(1H, d, J=7Hz), 8.05(1H, d, J=9Hz), 8.08-8.22(1H, br), 9.22-9.66(1H, br), 10.32(1H , s)

C_{39}

mp 162-164°C, Yellow powder(from n-Hexane-chloroform)

$C_{33}H_{37}N_5O_5 \cdot H_2O$, MS $[M+H]^+$ =584,

Anal. (C, H, N): Found(calcd.) 65.44, 6.53, 11.54 (65.87, 6.53, 11.64),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1645, 1595, 1515

^{1}H-NMR (δppm) in $CDCl_3$: 1.13(3H, t, J=7Hz), 1.31(3H, t, J=8Hz), 2.16(6H, s), 2.27-2.42(3H, m), 2.51(3H, s), 2.52-2.63(1H, m), 2.90-3.14(3H, m), 3.30-3.41(1H, m), 4.89(1H, d, 19Hz), 5.10(1H, d, J=19Hz), 5.62-5.84(1H, br), 5.81(1H, d, J=12Hz), 5.86(1H, d, J=12Hz), 7.44-7.53(3H, m), 7.55(1H, s), 7.81(2H, dd, J=1, 5Hz), 7.89(1H, d, J=9Hz), 8.67(2H, dd, J=1, 5Hz).

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Table 3 (continued)

C_{40}

mp 165-167°C, Yellow powder(from n-Hexane-chloroform)

$C_{32}H_{34}N_5O_5Cl\cdot 1/2H_2O$, MS $[M+H]^+$ =604,

Anal. (C, H, N): Found(calcd.) 62.54, 5.78, 11.35 (62.69, 5.75, 11.42),

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1650, 1595, 1515.

^{1}H-NMR (δppm) in $CDCl_3$: 1.14(3H, t, J=7Hz), 1.34(3H, t, J=8Hz), 2.16(6H, s), 2.27-2.41(3H, m), 2.52-2.64(1H, m), 2.93-3.13(3H, m), 3.30-3.40(1H, m), 5.01(1H, d, J=19Hz), 5.12(1H, d, J=19Hz), 5.51-5.57(1H, br), 5.80(1H, d, J=12Hz), 5.86(1H, d, J=12Hz), 7.49(1H, t, J=5Hz), 7.53(1H, s), 7.62(1H, dd, J=2, 9Hz), 7.70(1H, d, J=2Hz), 7.81(2H, dd, J=1, 5Hz), 7.90(1H, d, J=9Hz), 8.68(2H, dd, J=1, 5Hz).

C_{41}

mp ~171°C, Pale yellow powder(from n-Hexane-chloroform)

$C_{30}H_{34}N_4O_4F$, MS $[M+H]^+$ =588,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1650, 1595, 1510.

^{1}H-NMR (δppm) in $CDCl_3$: 1.15(3H, t, J=7Hz), 1.35(3H, t, J=8Hz), 2.16(6H, s), 2.27-2.42(3H, m), 2.52-2.66(1H, m), 2.98-3.18(3H, m), 3.29-3.40(1H, m), 5.02(1H, d, 19Hz), 5.12(1H, d, J=19Hz), 5.72-5.91(1H, br, D_2Oex.), 5.81(1H, d, J=12Hz), 5.87(1H, d, J=12Hz), 7.23(1H, ddd, J=3, 8, 10Hz), 7.52(1H, t, J=5Hz, D_2Oex.), 7.55(1H, s), 7.57(1H, dd, J=3, 10Hz), 7.80(2H, dd, J=2, 4Hz), 7.82(1H, dd, J=6, 9Hz), 8.67(2H, dd, J=2, 4Hz)

C_{42}

mp ~169°C, Pale yellow powder(from n-Hexane-chloroform)

$C_{31}H_{36}N_4O_4F$, MS $[M+H]^+$ =602,

IR $\nu^{MAX}/_{KBr}(cm^{-1})$: 1720, 1650, 1600, 1505.

Table 3 (continued)

^1H-NMR (δppm) in $CDCl_3$: 1.13(3H, t, J=7Hz), 1.36(3H, t, J=8Hz), 2.17(6H, s), 2.28-2.60(4H, m), 2.47(3H, m), 2.98-3.17(3H, m), 3.29-3.40(1H, m), 5.02(1H, d, J=19Hz), 5.13(1H, d, J=19Hz), 5.30-5.50(1H, br), 5.81(1H, d, J=12Hz), 5.84(1H, d, J=12Hz), 7.39(1H, br-t, J=5Hz, D_2Oex.), 7.52(1H, s), 7.54(1H, d, J=12Hz), 7.64(1H, d, J=8Hz), 7.81(2H, dd, J=2, 5Hz), 8.68(2H, dd, J=2, 5Hz).

C_{43}

mp 159-164°C, Yellow needles(from n-Hexane-chloroform)

$C_{31}H_{36}N_4O_5F$, MS $[M+H]^+$ =618,

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 1720, 1650, 1595, 1510.

^1H-NMR (δppm) in $CDCl_3$: 1.17(3H, t, J=7Hz), 1.30(3H, t, J=8Hz), 2.17(6H, s), 2.26-2.42(3H, m), 2.54-2.68(1H, m), 2.87-3.08(3H, m), 3.28-3.41(1H, m), 4.00(3H, s), 4.90(1H, d, J=19Hz), 5.04(1H, d, J=19Hz), 5.48-5.82(1H, br, D_2Oex.), 5.76(1H, d, J=12Hz), 5.86(1H, d, J=12Hz), 6.85(1H, d, J=9Hz), 7.45(1H, s), 7.52(1H, t, J=6Hz, D_2Oex.), 7.55(1H, d, J=12Hz), 7.81(2H, dd, J=2, 5Hz), 8.67(2H, dd, J=2, 5Hz).

C_{44}

mp 147-150°C, Yellow powder(from n-Hexane-chloroform)

$C_{31}H_{33}N_5O_6 \cdot H_2O$, MS $[M+H]^+$ =572,

Anal. (C, H, N): Found(calcd.) 62.85, 6.03, 11.78 (63.15, 5.98, 11.88),

IR $\nu^{MAX}/_{KBr}$(cm^{-1}) : 3390, 1710, 1650, 1615, 1590, 1520.

^1H-NMR (δppm) in $CDCl_3$: 1.08(3H, t, J=7Hz), 2.15(6H, s), 2.29-2.55(4H, m), 3.22-3.41(2H, m), 4.02(3H, s), 5.14(1H, d, J=19Hz), 5.20(1H, d, J=19Hz), 5.34(1H, br-s), 5.77(1H, d, J=12Hz), 5.94(1H, d, J=12Hz), 6.87(1H, d, J=8Hz), 7.39-7.47(2H, m), 7.60-7.68(2H, m), 7.73(1H, d, J=9Hz), 7.80(1H, ddd, J=2, 8, 8Hz), 8.13(1H, d, J=8Hz), 8.65-8.70(2H, m).

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Table 3 (continued)

$\underline{C_{45}}$

Colorless powder(from n-Hexane-chloroform)

$C_{28}H_{34}N_4O_6$, MS $[M+H]^+$ =523,

$\underline{C_{46}}$

Yellow powder(from n-Hexane-chloroform)

$C_{30}H_{38}N_4O_6$, MS $[M+H]^+$ =551,

$\underline{C_{47}}$

Yellow powder(from n-Hexane-chloroform)

$C_{31}H_{40}N_4O_7$, MS $[M+H]^+$ =581,

$\underline{C_{48}}$

mp 179-182°C, Colorless powder(from n-Hexane-chloroform)

$C_{35}H_{37}N_4O_7F$, MS $[M+H]^+$ =645,

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Table 4 (Water solubility)

Compd. No.	solubility(mg/ml)	Compd. No.	solubility(mg/ml)
C_1	>64	C_{21}	>63
C_2	>67	C_{22}	>65
C_3	29	C_{23}	20
C_4	41	C_{24}	42
C_5	21	C_{25}	>63
C_6	25	C_{26}	9
C_7	21	C_{28}	>56
C_8	20	C_{30}	>58
C_9	>59	C_{32}	>62
C_{10}	>62	C_{34}	>59
C_{11}	8	C_{36}	17
C_{12}	>64	C_{38}	6
C_{13}	>59		
C_{14}	>60		
C_{15}	>64		
C_{16}	6		
C_{17}	>64		
C_{18}	35		
C_{19}	24		
C_{20}	>60		

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Table 5 (Antitumor activity of camptothecin derivatives)

Compound No.	Optimum dose and antitumor activity: Total dose(mg/kg)	T/C%	40-day survivors	Therapeutic Index (Maximum torelable dose/ Minimum effective dose)
C_1	6.25	252	0/6	4(6.25/1.56)
C_2	25	214	0/6	8(25/3.13)
C_3	6.25	275	1/6	>4(6.25/<1.56)
C_4	6.25	280	1/6	>4(6.25/<1.56)
C_5	6.25	295	3/6	>4(6.25/<1.56)
C_6	6.25	183	1/6	>4(6.25/<1.56)
C_7	100	368	5/6	32(100/3.13)
C_8	12.5	364	4/6	8(12.5/1.56)
C_9	12.5	293	2/6	8(12.5/1.56)
C_{10}	12.5	240	1/6	8(12.5/1.56)
C_{11}	50	243	0/6	8(50/6.25)
C_{12}	25	281	1/6	16(25/6.25)
C_{13}	1.56	214	0/6	—
C_{14}	1.56	257	1/6	—
C_{15}	1.56	260	0/6	—
C_{16}	12.5	259	0/6	2(12.5/6.25)
C_{17}	6.25	286	2/6	4(6.25/1.56)
C_{18}	3.13	225	0/6	>2(3.13/<1.56)
C_{19}	3.13	198	0/6	>2(3.13/<1.56)
C_{20}	3.13	312	0/6	>2(3.13/<1.56)
C_{21}	3.13	265	0/6	>2(3.13/<1.56)
C_{22}	1.56	228	0/6	—

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Table 5 (continued)

Compound No.	Optimum dose and antitumor activity: Total dose(mg/kg)	T/C%	40-day survivors	Therapeutic Index (Maximum torelable dose/ Minimum effective dose)
C_{23}	12.5	317	0/6	>8(12.5/<1.56)
C_{24}	25	326	1/6	>16(25/<1.56)
C_{25}	12.5	300	1/6	>8(12.5/<1.56)
C_{26}	50	264	0/6	>4(50/12.5)
C_{28}	200	180	0/6	16(200/12.5)
C_{30}	200	235	0/6	32(200/6.25)
C_{32}	200	198	0/6	32(200/6.25)
C_{36}	200	214	0/6	16(200/12.5)
C_{38}	200	226	0/6	16(200/12.5)
C_{39}	50	376	3/6	16(50/3.13)
C_{40}	12.5	266	1/6	4(6.25/1.56)
C_{41}	25	300	2/6	>16(25/<1.56)
C_{42}	12.5	257	2/6	>8(12.5/1.56)
C_{43}	6.25	275	2/6	>4(6.25/1.56)
C_{45}	400	147	0/6	4(400/100)
C_{46}	400	189	0/6	16(400/25)
C_{47}	400	156	0/6	4(200/50)
C_{48}	200	188	0/6	8(200/25)
control				
CPT-Na salt	60	203	0/6	6(60/10)

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Table 6 (Acute Toxicity of camptothecin derivatives)

Compd. No.	LD_{50} value(mg/kg)	Compd. No.	LD_{50} value(mg/kg)
C_1	164.5	C_{22}	68.6
C_2	241.1	C_{23}	184.2
C_3	185.6	C_{24}	203.2
C_4	142.4	C_{25}	154.3
C_5	167.5	C_{26}	113.0
C_6	116.3	C_{28}	340.6
C_7	234.5	C_{30}	361.5
C_8	124.5	C_{32}	307.0
C_9	152.1	C_{36}	477.2
C_{10}	145.8	C_{38}	420.6
C_{11}	146.1	C_{39}	320.1
C_{12}	284.5	C_{40}	213.4
C_{13}	67.6	C_{41}	220.1
C_{14}	98.3	C_{42}	310.5
C_{15}	85.2	C_{43}	164.9
C_{16}	65.6	C_{45}	376.2
C_{17}	112.0	C_{46}	478.3
C_{18}	92.3	C_{47}	471.2
C_{19}	94.8	C_{48}	418.3
C_{20}	84.5	Control	
C_{21}	124.3	CPT-Na salt	227.0

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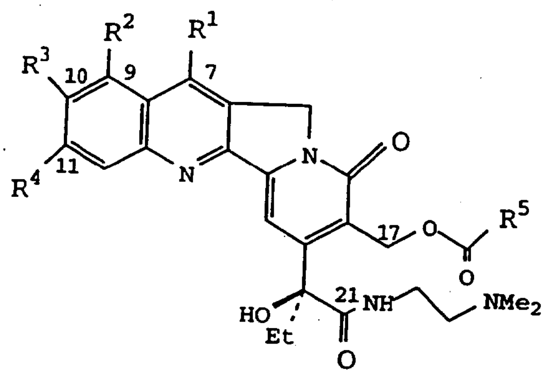
CLAIMS:

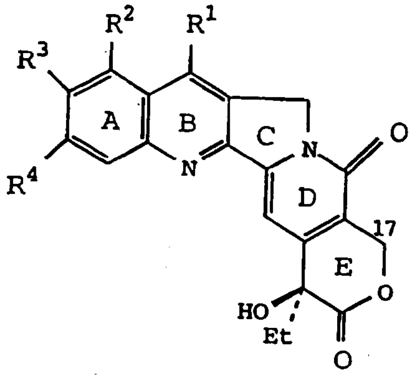
1. New camptothecin derivatives of the general formula (1)



(1)

wherein R^1 represents a hydrogen atom or a C_1-C_6 alkyl group, R^2 represents a hydrogen or a C_1-C_6 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_2-C_6 acyloxy or methoxyethoxymethoxy group, R^4 represents a hydrogen or halogen atom, and R^5 represents a C_1-C_6 alkyl, C_3-C_6 unsaturated alkyl, alkylthioalkyl, alkoxyalkyl, pyridyl or phenyl group substituted with halogen, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl or phenyl group, with the proviso that all of the R^2, R^3 and R^4 substituents should not simultaneously be a hydrogen atom.

2. A process for the preparation of new camptothecin derivatives of the general formula (1) according to claim 1, wherein camptothecin derivatives of the general formula (2)



(2)

wherein R^1, R^2, R^3 and R^4 are as defined in claim 1, and, are subjected to reaction with an excess amount of N-dimethylethylenediamine without solvent to open the E-lactone ring followed by the acylation of 17-hydroxyl group with corresponding acylating agents.

3. An antitumor agent containing as the active ingredient a camptothecin derivative of the general formula (1) according to claim 1, together with a pharmaceutically acceptable diluent or carrier.

4. Use of a camptothecin derivative of the general formula (1) according to claim 1 as an antitumor agent.