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COMPLEMENTACION DE INFORMACION

Ref.: Expediente No. 00.087.752

Solicitud de Patente de Invención para:

"COMPUESTO DE ANILLO FUSIONADO Y USO FARMACEUTICO DEL MISMO".

Solicitante: **JAPAN TOBACCO INC.**

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, me permito complementar la traducción simple en inglés de la copia certificada de Japón del documento de prioridad No. 369008/1999 de Diciembre 27 de 1999. Teniendo en cuenta que la traducción simple en Inglés y en Español de la carátula y reivindicaciones se presentaron con el memorial de fecha de radicación de Marzo 22 de 2001.

Atentamente solicito a Ud. se anexe dicha traducción al expediente de la referencia y se continúe con el trámite correspondiente a esta solicitud de Patente de Invención.

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(Translation)

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J A P A N E S E G O V E R N M E N T

This is to certify that the annexed is a true copy of the
following application as filed with this Office.

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Application Number : 369008/1999

Applicant(s) : Japan Tobacco Inc.

December 15, 2000

Commissioner, Patent Office
Kouzou OIKAWA
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[Reference Number] J99-0317

[To] Commissioner of the Patent Office

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[List of the Annexed Documents]

[Document] Specification One copy

[Document] Abstract One copy

[Number of General Power of Attorney] 9803681

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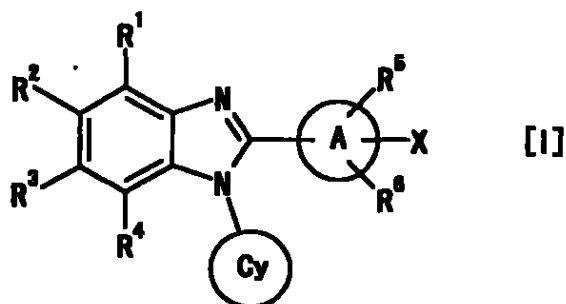
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[Document] SPECIFICATION

**[Title of the Invention] Benzimidazole Compound And
Pharmaceutical Use Thereof**

[What is Claimed is]

- 5 **[Claim 1]** A therapeutic agent for hepatitis C, which
comprises a benzimidazole compound of the following formula [I] or
a pharmaceutically acceptable salt thereof as an active
ingredient:



10 wherein

R^1 , R^2 , R^3 and R^4 are each independently,

- (1) hydrogen atom,
- (2) C_{1-6} alkanoyl,
- (3) carboxyl,
- 15 (4) cyano,
- (5) nitro,
- (6) C_{1-6} alkyl optionally substituted by 1 to 3 substituent(s)
selected from the following group A,
group A; halogen atom, hydroxyl group, carboxyl, amino,
- 20 C_{1-6} alkoxy carbonyl or C_{1-6} alkylamino,
- (7) $-COOR^{a1}$

wherein R^{a1} is optionally substituted C_{1-6} alkyl (as
defined above) or C_{6-14} aryl C_{1-6} alkyl optionally
substituted by 1 to 5 substituent(s) selected from the
following group B,

group B; halogen atom, C_{1-6} alkyl, cyano, nitro,
halogenated C_{1-6} alkyl, C_{1-6} alkanoyl, $-COOR^{b1}$,
 $-CONR^{b1}R^{b2}$, $-NR^{b1}R^{b2}$, $-NR^{b1}-COR^{b2}$, $-NHSO_2R^{b1}$, $-OR^{b1}$,
 $-SR^{b1}$, $-SO_2R^{b1}$ or $-SO_2NR^{b1}R^{b2}$

wherein R^{b1} and R^{b2} are each independently
hydrogen atom or C_{1-6} alkyl,

- (8) $-CONR^{a2}R^{a3}$

wherein R^{a2} and R^{a3} are each independently hydrogen atom, C_{1-6} alkoxy or optionally substituted C_{1-6} alkyl (as defined above),

5 (9) $-C(=NR^{a4})NH_2$
wherein R^{a4} is hydrogen atom or hydroxyl group,

(10) $-NHR^{a5}$
wherein R^{a5} is hydrogen atom, C_{1-6} alkanoyl or C_{1-6} alkylsulfonyl,

10 (11) $-OR^{a6}$
wherein R^{a6} is hydrogen atom or optionally substituted C_{1-6} alkyl (as defined above),

(12) $-SO_2R^{a7}$
wherein R^{a7} is hydroxyl group, amino, C_{1-6} alkyl or C_{1-6} alkylamino

15 or

(13) $-P(=O)(OR^{a31})_2$
wherein R^{a31} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above), and

20 ring Cy is

(1) C_{3-8} cycloalkyl optionally substituted by 1 to 5 substituent(s) selected from the following group C, group C; hydroxyl group, halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy, or

25 (2) C_{3-8} cycloalkenyl optionally substituted by 1 to 5 substituent(s) selected from the above group C,

ring A is

30 (1) C_{6-14} aryl,
(2) C_{3-8} cycloalkyl,
(3) C_{3-8} cycloalkenyl or
(4) heterocyclic group having 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom,

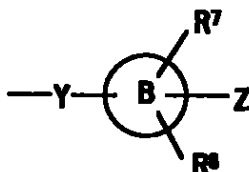
R^5 and R^6 are each independently

35 (1) hydrogen atom,
(2) halogen atom,
(3) optionally substituted C_{1-6} alkyl (as defined above) or
(4) $-OR^{a8}$

wherein R^{a8} is hydrogen atom, C_{1-6} alkyl or C_{6-14} aryl C_{1-6}

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- alkyl, and
- X is
- (1) hydrogen atom,
 - (2) halogen atom,
 - 5 (3) cyano,
 - (4) nitro,
 - (5) C₁₋₆ alkanoylamino,
 - (6) C₁₋₆ alkylsulfonyl,
 - (7) optionally substituted C₁₋₆ alkyl (as defined above),
 - 10 (8) C₂₋₆ alkenyl optionally substituted by 1 to 3
substituent(s) selected from the above group A,
 - (9) -COOR^{a9}
wherein R^{a9} is hydrogen atom or C₁₋₆ alkyl,
 - 15 (10) -CONH-(CH₂)₁-R^{a10}
wherein R^{a10} is optionally substituted C₁₋₆ alkyl (as
defined above), C₁₋₆ alkoxy carbonyl or C₁₋₆ alkanoylamino
and 1 is 0 or an integer of 1 to 6,
 - (11) -OR^{a11}
wherein R^{a11} is hydrogen atom or optionally substituted
20 C₁₋₆ alkyl (as defined above)
- or
- (12)



- wherein
- 25 Y is
- (1') a single bond,
 - (2') C₁₋₆ alkylene,
 - (3') C₁₋₆ alkenylene,
 - (4') -(CH₂)_m-O-(CH₂)_n-,
30 (hereinafter m and n are each independently 0
or an integer of 1 to 6),
 - (5') -CO-,
 - (6') -CO₂-(CH₂)_n-,
 - (7') -CONH-(CH₂)_n-NH-,
 - 35 (8') -NHCO₂-,

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- (9') -NHCONH-,
(10') -O-(CH₂)_n-CO-,
(11') -O-(CH₂)_n-O-,
(12') -SO₂-,
5 (13') -(CH₂)_n-NR^{a12}-(CH₂)_n-
wherein R^{a12} is
(1") hydrogen atom,
(2") optionally substituted C₁₋₆ alkyl (as
defined above),
10 (3") optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above)
(4") C₆₋₁₄ aryl optionally substituted by 1 to 5
substituent(s) selected from the above
group B,
15 (5") -COR^{b5}
wherein R^{b5} is hydrogen atom, optionally
substituted C₁₋₆ alkyl (as defined above),
optionally substituted C₆₋₁₄ aryl (as
defined above) or optionally substituted
20 C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above)
(6") -COOR^{b5} (R^{b5} is as defined above) or
(7") -SO₂R^{b5} (R^{b5} is as defined above),
(14') -NR^{a12}CO- (R^{a12} is as defined above),
(15') -CONR^{a13}-(CH₂)_n-
25 wherein R^{a13} is hydrogen atom, optionally
substituted C₁₋₆ alkyl (as defined above) or
optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as
defined above)
(16') -CONH-CHR^{a14}-
30 wherein R^{a14} is optionally substituted C₆₋₁₄ aryl
(as defined above)
(17') -O-(CH₂)_n-CR^{a15}R^{a16}-(CH₂)_n-
wherein R^{a15} and R^{a16} are each independently
(1") hydrogen atom,
35 (2") carboxyl,
(3") C₁₋₆ alkyl,
(4") optionally substituted C₆₋₁₄ aryl (as
defined above)

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(5'') optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above)

(6'') -OR^{b6}

wherein R^{b6} is C₁₋₆ alkyl or C₆₋₁₄ aryl C₁₋₆ alkyl,
or

(7'') -NHR^{b7}

wherein R^{b7} is hydrogen atom, C₁₋₆ alkyl, C₁₋₆
alkanoyl or C₆₋₁₄ aryl C₁₋₆ alkyloxycarbonyl,

(18') -(CH₂)_n-NR^{a12}-CHR^{a15}- (R^{a12} and R^{a15} are each as
defined above), or

(19') -NR^{a17}SO₂-

wherein R^{a17} is hydrogen atom or C₁₋₆ alkyl,

ring B is

(1') C₆₋₁₄ aryl,

(2') C₃₋₈ cycloalkyl or

(3') heterocyclic group (as defined above),

Z is

(1') hydrogen atom,

(2') halogen atom,

(3') carbamoyl,

(4') cyano,

(5') nitro,

(6') C₁₋₆ alkylamino,

(7') optionally substituted C₁₋₆ alkyl (as defined
above),

(8') -COR^{a18},

wherein R^{a18} is optionally substituted C₁₋₆ alkyl
(as defined above) or optionally substituted
C₆₋₁₄ aryl (as defined above),

(9') -COOR^{a19},

wherein R^{a19} is hydrogen atom, optionally
substituted C₁₋₆ alkyl (as defined above) or
optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as
defined above),

(10') -OR^{a20}

wherein R^{a20} is

(1'') hydrogen atom,

(2'') optionally substituted C₁₋₆ alkyl (as

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- defined above),
- (3") optionally substituted C₂₋₆ alkenyl (as defined above),
- 5 (4") C₂₋₆ alkynyl optionally substituted by 1 to 3 substituent(s) selected from the above group A,
- (5") optionally substituted C₆₋₁₄ aryl (as defined above),
- 10 (6") optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above),
- 15 (7") optionally substituted heterocyclic group wherein this group is optionally substituted by 1 to 5 substituent(s) selected from the above group B, and has 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, or
- 20 (8") optionally substituted heterocycle C₁₋₆ alkyl wherein this group is C₁₋₆ alkyl substituted by optionally substituted heterocyclic group, as defined above
- (11') -O-(CH₂)_p-COR^{a21}
wherein R^{a21} is C₁₋₆ alkylamino or optionally substituted heterocyclic group (as defined above) and p is 0 or an integer of 1 to 6,
- 25 (12') -NR^{a22}R^{a23}
wherein R^{a22} and R^{a23} are each independently
- 30 (1") hydrogen atom,
- (2") optionally substituted C₁₋₆ alkyl (as defined above),
- (3") optionally substituted C₆₋₁₄ aryl (as defined above)
- 35 (4") optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above) or
- (5") optionally substituted heterocycle C₁₋₆ alkyl (as defined above),
- (13') -NHCO-R^{a24}

- wherein R^{a24} is optionally substituted C_{1-6} alkyl (as defined above), optionally substituted C_{6-14} aryl (as defined above) or optionally substituted heterocyclic group (as defined above)
- (14') $-NHSO_2-R^{a25}$
 wherein R^{a25} is optionally substituted C_{6-14} aryl or optionally substituted heterocyclic group (as defined above),
- (15') $-SO_2-R^{a25}$
 wherein R^{a25} is as defined above, and
- (16') $-SO_2-NHR^{a26}$
 wherein R^{a26} is hydrogen atom, optionally substituted C_{6-14} aryl (as defined above), or optionally substituted heterocyclic group (as defined above),
- (17') optionally substituted C_{6-14} aryl (as defined above),
- (18') optionally substituted C_{3-8} cycloalkyl (as defined above),
- (19') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above) or
- (20') optionally substituted heterocyclic group (as defined above)
- R^7 and R^8 are each independently
- (1') hydrogen atom,
- (2') halogen atom,
- (3') nitro,
- (4') cyano,
- (5') optionally substituted C_{1-6} alkyl (as defined above),
- (6') $-OR^{a27}$
 wherein R^{a27} is hydrogen atom or C_{1-6} alkyl,
- (7') $-COOR^{a27}$
 wherein R^{a27} is as defined above,
- (8') $-CONR^{a27}R^{a28}$
 wherein R^{a27} and R^{a28} are each independently hydrogen atom or C_{1-6} alkyl,

(9') $-C(=NR^{a33})NH_2$

wherein R^{a33} is hydrogen atom or C_{1-6} alkyl,

(10') $-SO_2R^{a32}$

wherein R^{a32} is hydrogen atom, C_{1-6} alkyl or C_{1-6} alkylamino,

(11') $-NR^{a29}R^{a30}$

wherein R^{a29} and R^{a30} are each independently hydrogen atom, C_{1-6} alkyl or C_{1-6} alkanoyl, or

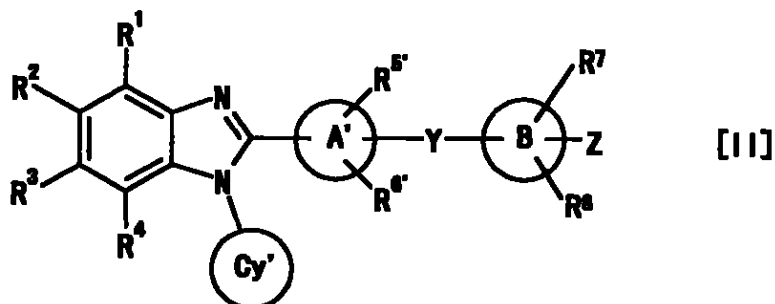
(12') optionally substituted heterocyclic group (as defined above).

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[Claim 2] The therapeutic agent of claim 1, wherein at least one of R^1 , R^2 , R^3 and R^4 is carboxyl, $-COOR^{a1}$ (as defined above) or $-CONR^{a2}R^{a3}$ (as defined above).

15 [Claim 3] The therapeutic agent of claim 1 or 2, wherein the ring Cy is cyclopentyl, cyclohexyl or cycloheptyl.

[Claim 4] The therapeutic agent of claims 1 to 3, wherein the ring A is C_{6-14} aryl.

[Claim 5] A benzimidazole compound of the following formula [II]



20 wherein

R^1 , R^2 , R^3 and R^4 are each independently,

(1) hydrogen atom,

(2) C_{1-6} alkanoyl,

25 (3) carboxyl,

(4) cyano,

(5) nitro,

(6) C_{1-6} alkyl optionally substituted by 1 to 3 substituent(s) selected from the following group A,

30 group A; halogen atom, hydroxyl group, carboxyl, amino, C_{1-6} alkoxy carbonyl or C_{1-6} alkylamino,

(7) $-COOR^{a1}$

wherein R^{a1} is optionally substituted C_{1-6} alkyl (as defined above) or C_{6-14} aryl C_{1-6} alkyl optionally substituted by 1 to 5 substituent(s) selected from the following group B,

5 group B; halogen atom, C_{1-6} alkyl, cyano, nitro, halogenated C_{1-6} alkyl, C_{1-6} alkanoyl, $-COOR^{b1}$, $-CONR^{b1}R^{b2}$, $-NR^{b1}R^{b2}$, $-NR^{b1}-COR^{b2}$, $-NHSO_2R^{b1}$, $-OR^{b1}$, $-SR^{b1}$, $-SO_2R^{b1}$ or $-SO_2NR^{b1}R^{b2}$ wherein R^{b1} and R^{b2} are each independently hydrogen atom or C_{1-6} alkyl,

10 (8) $-CONR^{a2}R^{a3}$ wherein R^{a2} and R^{a3} are each independently hydrogen atom, C_{1-6} alkoxy or optionally substituted C_{1-6} alkyl (as defined above),

15 (9) $-C(=NR^{a4})NH_2$ wherein R^{a4} is hydrogen atom or hydroxyl group,

(10) $-NHR^{a5}$ wherein R^{a5} is hydrogen atom, C_{1-6} alkanoyl or C_{1-6} alkylsulfonyl,

20 (11) $-OR^{a6}$ wherein R^{a6} is hydrogen atom or optionally substituted C_{1-6} alkyl (as defined above),

(12) $-SO_2R^{a7}$ wherein R^{a7} is hydroxyl group, amino, C_{1-6} alkyl or C_{1-6} alkylamino or

25 (13) $-P(=O)(OR^{a31})_2$ wherein R^{a31} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

30 ring Cy' is

(1) C_{3-8} cycloalkyl optionally substituted by 1 to 5 substituent(s) selected from the following group C, group C; hydroxyl group, halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy,

35 ring A' is a group selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, cyclohexyl or cyclohexenyl,

$R^{5'}$ and $R^{6'}$ are each independently

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- (1) hydrogen atom,
- (2) halogen atom,
- (3) optionally substituted C_{1-6} alkyl (as defined above) or
- (4) hydroxyl group,

5 Y is

- (1) a single bond,
- (2) C_{1-6} alkylene,
- (3) C_{1-6} alkenylene,
- (4) $-(CH_2)_m-O-(CH_2)_n-$,

10 (hereinafter m and n are each independently 0 or an integer of 1 to 6),

- (5) $-CO-$,
- (6) $-CO_2-(CH_2)_n-$,
- (7) $-CONH-(CH_2)_n-NH-$,

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- (8) $-NHCO_2-$,
- (9) $-NHCONH-$,
- (10) $-O-(CH_2)_n-CO-$,
- (11) $-O-(CH_2)_n-O-$,

- (12) $-SO_2-$,

20

- (13) $-(CH_2)_m-NR^{a12}-(CH_2)_n-$

 wherein R^{a12} is

- (1') hydrogen atom,
- (2') optionally substituted C_{1-6} alkyl (as defined above),
- (3') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),
- (4') C_{6-14} aryl optionally substituted by 1 to 5 substituent(s) selected from the above group B,
- (5') $-COR^{b5}$

30

 wherein R^{b5} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above), optionally substituted C_{6-14} aryl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

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- (6') $-COOR^{b5}$ (R^{b5} is as defined above) or
- (7') $-SO_2R^{b5}$ (R^{b5} is as defined above),
- (14) $-NR^{a12}CO-$ (R^{a12} is as defined above),
- (15) $-CONR^{a13}-(CH_2)_n-$

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wherein R^{a13} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

5 (16) $-\text{CONH}-\text{CHR}^{a14}-$

wherein optionally substituted R^{a14} is C_{6-14} aryl (as defined above),

(17) $-\text{O}-(\text{CH}_2)_m-\text{CR}^{a15}\text{R}^{a16}-(\text{CH}_2)_n-$

wherein R^{a15} and R^{a16} are each independently

10 (1') hydrogen atom,

(2') carboxyl,

(3') C_{1-6} alkyl,

(4') optionally substituted C_{6-14} aryl (as defined above),

15 (5') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(6') $-\text{OR}^{b6}$

wherein R^{b6} is C_{1-6} alkyl or C_{6-14} aryl C_{1-6} alkyl, or

(7') $-\text{NHR}^{b7}$

20 wherein R^{b7} is hydrogen atom, C_{1-6} alkyl, C_{1-6} alkanoyl or C_{6-14} aryl C_{1-6} alkyloxycarbonyl,

(18) $-(\text{CH}_2)_n-\text{NR}^{a12}-\text{CHR}^{a15}-$ (R^{a12} and R^{a15} are each as defined above), or

(19) $-\text{NR}^{a17}\text{SO}_2-$

25 wherein R^{a17} is hydrogen atom or C_{1-6} alkyl,

ring B is

(1) C_{6-14} aryl,

(2) C_{3-8} cycloalkyl or

(3) heterocyclic group (as defined above),

30 Z is

(1) hydrogen atom,

(2) halogen atom,

(3) carbamoyl,

(4) cyano,

35 (5) nitro,

(6) C_{1-6} alkylamino,

(7) optionally substituted C_{1-6} alkyl (as defined above),

(8) $-\text{COR}^{a18}$,

wherein R^{a18} is optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl (as defined above),

(9) $-COOR^{a19}$

wherein R^{a19} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(10) $-OR^{a20}$

wherein R^{a20} is

(1') hydrogen atom,

(2') optionally substituted C_{1-6} alkyl (as defined above),

(3') optionally substituted C_{2-6} alkenyl (as defined above),

(4') C_{2-6} alkynyl optionally substituted by 1 to 3 substituent(s) selected from the above group A,

(5') optionally substituted C_{6-14} aryl (as defined above),

(6') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(7') optionally substituted heterocyclic group wherein this group is optionally substituted by 1 to 5 substituent(s) selected from the above group B, and has 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, or

(8') optionally substituted heterocycle C_{1-6} alkyl wherein this group is C_{1-6} alkyl substituted by optionally substituted heterocyclic group (as defined above),

(11) $-O-(CH_2)_p-COR^{a21}$

wherein R^{a21} is C_{1-6} alkylamino or optionally substituted heterocyclic group (as defined above) and p is 0 or an integer of 1 to 6,

(12) $-NR^{a22}R^{a23}$

wherein R^{a22} and R^{a23} are each independently (1') hydrogen atom,

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- (2') optionally substituted C₁₋₆ alkyl (as defined above),
(3') optionally substituted C₆₋₁₄ aryl (as defined above)
5 (4') optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above) or
(5') optionally substituted heterocycle C₁₋₆ alkyl (as defined above),
(13) -NHCO-R^{a24}
10 wherein R^{a24} is optionally substituted C₁₋₆ alkyl (as defined above), optionally substituted C₆₋₁₄ aryl (as defined above) or optionally substituted heterocyclic group (as defined above)
(14) -NHSO₂-R^{a25}
15 wherein R^{a25} is optionally substituted C₆₋₁₄ aryl or optionally substituted heterocyclic group (as defined above),
(15) -SO₂-R^{a25}
wherein R^{a25} is as defined above, and
20 (16) -SO₂-NHR^{a26}
wherein R^{a26} is hydrogen atom, optionally substituted C₆₋₁₄ aryl (as defined above) or optionally substituted heterocyclic group (as defined above),
25 (17) optionally substituted C₆₋₁₄ aryl (as defined above),
(18) optionally substituted C₃₋₈ cycloalkyl (as defined above),
(19) optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above) or
(20) optionally substituted heterocyclic group (as defined above),
30 R⁷ and R⁸ are each independently
(1) hydrogen atom,
(2) halogen atom,
(3) nitro,
35 (4) cyano,
(5) optionally substituted C₁₋₆ alkyl (as defined above),
(6) -OR^{a27}
wherein R^{a27} is hydrogen atom or C₁₋₆ alkyl,

(7) $-\text{COOR}^{\text{a27}}$

wherein R^{a27} is as defined above,

(8) $-\text{CONR}^{\text{a27}}\text{R}^{\text{a28}}$

wherein R^{a27} and R^{a28} are each independently
hydrogen atom or C_{1-6} alkyl,

(9) $-\text{C}(=\text{NR}^{\text{a33}})\text{NH}_2$

wherein R^{a33} is hydrogen atom or C_{1-6} alkyl,

(10) $-\text{SO}_2\text{R}^{\text{a32}}$

wherein R^{a32} is hydrogen atom, C_{1-6} alkyl or C_{1-6}
alkylamino,

(11) $-\text{NR}^{\text{a29}}\text{R}^{\text{a30}}$

wherein R^{a29} and R^{a30} are each independently
hydrogen atom, C_{1-6} alkyl or C_{1-6} alkanoyl, or

(12) optionally substituted heterocyclic group (as defined
above)

or a pharmaceutically acceptable salt thereof.

【Claim 6】 The benzimidazole compound of claim 5, wherein at
least one of R^1 , R^2 , R^3 and R^4 is carboxyl or $-\text{COOR}^{\text{a1}}$ (as defined
above), or a pharmaceutically acceptable salt thereof.

【Claim 7】 The benzimidazole compound of claim 5 or 6,
wherein the ring Cy' is cyclopentyl, cyclohexyl or cycloheptyl, or
a pharmaceutically acceptable salt thereof.

【Claim 8】 The benzimidazole compound of claims 5 to 7,
wherein R^2 is carboxyl and R^1 , R^3 and R^4 are hydrogen atoms, or a
pharmaceutically acceptable salt thereof.

【Claim 9】 The benzimidazole compound of claims 5 to 8,
wherein the ring A' is phenyl, or a pharmaceutically acceptable
salt thereof.

【Claim 10】 The benzimidazole compound of claims 5 to 9,
wherein the Y is $-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_n-$, $-\text{NHCO}_2-$, $-\text{CONH}-\text{CHR}^{\text{a14}}-$,
 $-(\text{CH}_2)_m-\text{NR}^{\text{a12}}-(\text{CH}_2)_n-$, $-\text{CONR}^{\text{a13}}-(\text{CH}_2)_n-$, $-\text{O}-(\text{CH}_2)_m-\text{CR}^{\text{a15}}\text{R}^{\text{a16}}-(\text{CH}_2)_n-$ or
 $-(\text{CH}_2)_m-\text{NR}^{\text{a12}}-\text{CHR}^{\text{a15}}-$ (wherein each symbol is as defined above), or
a pharmaceutically acceptable salt thereof.

【Claim 11】 The benzimidazole compound of claims 5 to 10,
wherein the Y is $-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_n-$ or $-\text{O}-(\text{CH}_2)_m-\text{CR}^{\text{a15}}\text{R}^{\text{a16}}-(\text{CH}_2)_n-$
(wherein each symbol is as defined above), or a pharmaceutically
acceptable salt thereof.

5 **【Claim 12】** A pharmaceutical composition comprising a benzimidazole compound of claim 5 to 11, or a pharmaceutically acceptable salt thereof.

【Claim 13】 A hepatitis C virus polymerase inhibitor
5 comprising a benzimidazole compound of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

【Claim 14】 An anti-hepatitis C virus agent comprising a benzimidazole compound of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

10 **【Claim 15】** A therapeutic agent for hepatitis C comprising a benzimidazole compound of claims 5 to 11, or a pharmaceutically acceptable salt thereof.

【Technical Field to which the Invention pertains】

 The present invention relates to a novel benzimidazole
15 compound and a pharmaceutically acceptable salt thereof useful as a therapeutic agent for hepatitis C. The present invention also relates to a novel use of a certain benzimidazole compound or a pharmaceutically acceptable salt thereof as a therapeutic agent for hepatitis C. More particularly, the present invention relates
20 to a therapeutic agent for hepatitis C, which contains a novel benzimidazole compound or a pharmaceutically acceptable salt thereof, which is effective for the prophylaxis or treatment of hepatitis C and which shows anti-hepatitis C virus (HCV) activity, particularly anti-HCV activity based on an RNA-dependent RNA
25 polymerase inhibitory activity.

【Prior Art】

 In 1989, a main causative virus of non-A non-B
posttransfusion hepatitis was found and named hepatitis C virus (HCV). Since then, several types of hepatitis viruses have been
30 found besides type A, type B and type C, wherein hepatitis caused by HCV is called hepatitis C.

 The patients infected with HCV are considered to involve several percent of the world population, and the infection with HCV characteristically becomes chronic.

35 HCV is an envelope RNA virus, wherein the genome is a single strand plus-strand RNA, and belongs to the genus Hepacivirus of Flavivirus (from The International Committee on Taxonomy of Viruses, International Union of Microbiological

Societies). Of the same hepatitis viruses, for example, hepatitis B virus (HBV), which is a DNA virus, is eliminated by the immune system and the infection with this virus ends in an acute infection except for neonates and infants having yet immature immunological competence. In contrast, HCV somehow avoids the immune system of the host due to an unknown mechanism. Once infected with this virus, even an adult having a mature immune system frequently develops persistent infection.

When chronic hepatitis is associated with the persistent infection with HCV, it advances to cirrhosis or hepatic cancer in a high rate. Enucleation of tumor by operation does not help much, because the patient often develops recurrent hepatic cancer due to the sequela inflammation in non-cancerous parts.

Thus, an effective therapeutic method of hepatitis C is desired. Apart from the symptomatic therapy to suppress inflammation with an anti-inflammatory agent, the development of a therapeutic agent that reduces HCV to a low level free from inflammation and that eradicates HCV has been strongly demanded.

At present, a treatment with interferon is the only effective method known for the eradication of HCV. However, interferon can eradicate the virus only in about one-third of the patient population. For the rest of the patients, it has no effect or provides only a temporary effect. Therefore, an anti-HCV drug to be used in the place of or concurrently with interferon is awaited in great expectation.

Also, an attempt has been made to potentiate the immunocompetence of the patient with an interferon agonist, an interleukin-12 agonist and the like, thereby to eradicate the virus, but an effective pharmaceutical agent has not been found yet.

In addition, the inhibition of HCV growth, wherein HCV-specific protein is targeted, has been drawing attention these days.

The gene of HCV encodes a protein such as serine protease, RNA helicase, RNA-dependent RNA polymerase and the like. These proteins function as a specific protein essential for the growth of HCV.

One of the specific proteins, RNA-dependent RNA polymerase (hereinafter to be also briefly referred to as an HCV polymerase), is an enzyme virus essential for the growth of the virus. The gene replication of HCV having a plus-strand RNA gene is
5 considered to involve synthesis of a complementary minus-strand RNA by the use of the plus-strand RNA as a template, and, using the obtained minus-strand RNA as a template, amplifying the plus-strand RNA. The portion called NS5B of a protein precursor, that HCV codes for, has been found to show an RNA-dependent RNA
10 polymerase activity (EMBO J., 15, 12-22, 1996), and is considered to play a central role in the HCV gene replication.

Therefore, an HCV polymerase inhibitor can be a target in the development of an anti-HCV drug, and the development thereof is eagerly awaited. However, an effective pharmaceutical agent
15 has not been developed yet, like in other attempts to develop a drug based on other action mechanisms. As the situation stands, interferon is only an effective anti-HCV drug.

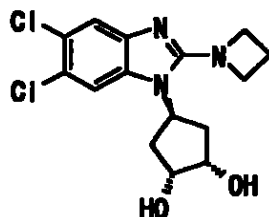
The following discloses known benzimidazole compounds relatively similar to the compound of the present invention.

20 A known anti-hepatitis virus agent having a benzimidazole skeleton is disclosed in WO97/25316 and Japanese Patent Application under PCT laid-open under kohyo No. 10-505092 (WO96/7646).

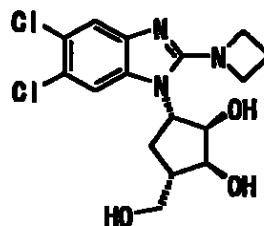
WO97/25316 discloses the following compound A and the like,
25 wherein the use thereof is for a treatment of viral infection. The target virus is a DNA virus such as hepatitis B virus and the like. However, this publication does not include the compound disclosed in the present specification or a description regarding or suggestive of HCV.

30 Japanese Patent Application under PCT laid-open under kohyo No. 10-505092 discloses the following compound B and the like, wherein the use thereof is for a treatment of viral infection. The target virus is a DNA virus such as herpesvirus and hepatitis B virus. However, this publication does not include the compound
35 disclosed in the present specification or a description regarding or suggestive of HCV.

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compound A

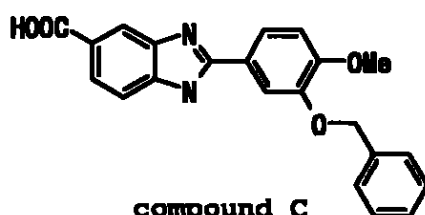


compound B

The benzimidazole derivatives having an antiviral activity have been disclosed in JP-A-3-31264, US3644382 and US3778504. In addition, WO98/37072 discloses, as a production inhibitor of tumor necrosis factor (TNF) and cyclic AMP, a benzimidazole derivative for the use as an anti-human immunodeficiency virus (HIV) agent and an anti-inflammation agent. WO98/05327 discloses, as a reverse transcriptase inhibitor, a benzimidazole derivative for the use as an anti-HIV agent. J. Med. Chem. (13(4), 697-704, 1970) discloses, as a neuraminidase inhibitor, a benzimidazole derivative for the use as an anti-influenza virus agent.

However, none of these publications includes the compound of the present invention or a description regarding or suggestive of an anti-HCV effect.

Known benzimidazole derivatives having a pharmaceutical use other than as an antiviral agent are disclosed in JP-A-8-501318 (US5824651) and JP-A-8-134073 (US5563243). These publications disclose the following compound C and the like as a catechol diether compound, and the use thereof as an anti-inflammation agent. However, neither of the publications includes the compound of the present invention, and as the action mechanism, the former discloses phosphodiesterase IV and the latter discloses TNF. These publications do not include a description regarding or suggestive of an anti-HCV effect.



compound C

WO98/50029, WO98/50030 and WO98/50031 disclose benzimidazole derivatives as an antitumor agent having a protein

isoprenyl transferase action. While this publication discloses a wide scope of the claims, at least it does not include a compound analogous to the compound of the present invention or a description regarding or suggestive of an anti-HCV effect.

5 JP-A-8-109169 (EP694535) discloses the application of a tachykinin receptor antagonist to treat an inflammatory disease, and WO96/35713 discloses the application thereof as a growth hormone release promoter to treat a growth hormone-related disease such as osteoporosis and the like. However, none of these
10 publications includes a description regarding or suggestive of an anti-HCV effect.

JP-A-53-14735 discloses a benzimidazole derivative as a brightener besides its pharmaceutical use, but this publication does not include the compound of the present invention.

15 **[Problems to be Solved by the Invention]**

Based on these findings, it has been elucidated that a pharmaceutical agent having an anti-HCV activity is effective for the prophylaxis and treatment of hepatitis C, and particularly an anti-HCV agent having an inhibitory activity on RNA-dependent RNA
20 polymerase of HCV can be a prophylactic and therapeutic agent effective against hepatitis C and a prophylactic and therapeutic agent for the disease caused by hepatitis C.

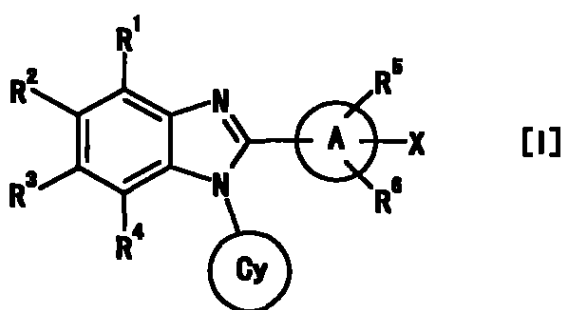
Accordingly, the present invention provides a pharmaceutical agent having an anti-HCV activity, particularly a
25 pharmaceutical agent having an RNA-dependent RNA polymerase inhibitory activity.

[Means of Solving the Problems]

The present inventors have conducted intensive studies in an attempt to find a compound having an anti-HCV activity,
30 particularly RNA-dependent RNA polymerase inhibitory activity, and completed the present invention.

Thus, the present invention provides the following (1) to (15).

(1) A therapeutic agent for hepatitis C, which comprises a
35 benzimidazole compound of the following formula [I] or a pharmaceutically acceptable salt thereof as an active ingredient:



wherein

R¹, R², R³ and R⁴ are each independently,

- 5 (1) hydrogen atom,
- (2) C₁₋₆ alkanoyl,
- (3) carboxyl,
- (4) cyano,
- (5) nitro,
- 10 (6) C₁₋₆ alkyl optionally substituted by 1 to 3 substituent(s) selected from the following group A, group A; halogen atom, hydroxyl group, carboxyl, amino, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkylamino,
- (7) -COOR^{a1} wherein R^{a1} is optionally substituted C₁₋₆ alkyl (as defined above) or C₆₋₁₄ aryl C₁₋₆ alkyl optionally substituted by 1 to 5 substituent(s) selected from the following group B, group B; halogen atom, C₁₋₆ alkyl, cyano, nitro, halogenated C₁₋₆ alkyl, C₁₋₆ alkanoyl, -COOR^{b1}, -CONR^{b1}R^{b2}, -NR^{b1}R^{b2}, -NR^{b1}-COR^{b2}, -NHSO₂R^{b1}, -OR^{b1}, -SR^{b1}, -SO₂R^{b1} or -SO₂NR^{b1}R^{b2} wherein R^{b1} and R^{b2} are each independently hydrogen atom or C₁₋₆ alkyl,
- 20 (8) -CONR^{a2}R^{a3} wherein R^{a2} and R^{a3} are each independently hydrogen atom, C₁₋₆ alkoxy or optionally substituted C₁₋₆ alkyl (as defined above),
- 25 (9) -C(=NR^{a4})NH₂ wherein R^{a4} is hydrogen atom or hydroxyl group,
- 30 (10) -NHR^{a5} wherein R^{a5} is hydrogen atom, C₁₋₆ alkanoyl or C₁₋₆ alkylsulfonyl,

(11) $-OR^{a6}$
wherein R^{a6} is hydrogen atom or optionally substituted C_{1-6} alkyl (as defined above),

5 (12) $-SO_2R^{a7}$
wherein R^{a7} is hydroxyl group, amino, C_{1-6} alkyl or C_{1-6} alkylamino

or

10 (13) $-P(=O)(OR^{a1})_2$
wherein R^{a1} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above), and

ring Cy is

15 (1) C_{3-8} cycloalkyl optionally substituted by 1 to 5 substituent(s) selected from the following group C, group C; hydroxyl group, halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy, or

(2) C_{3-8} cycloalkenyl optionally substituted by 1 to 5 substituent(s) selected from the above group C,

ring A is

20 (1) C_{6-14} aryl,
(2) C_{3-8} cycloalkyl,
(3) C_{3-8} cycloalkenyl or
(4) heterocyclic group having 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom,

25 R^5 and R^6 are each independently

(1) hydrogen atom,
(2) halogen atom,
(3) optionally substituted C_{1-6} alkyl (as defined above) or
(4) $-OR^{a8}$

30 wherein R^{a8} is hydrogen atom, C_{1-6} alkyl or C_{6-14} aryl C_{1-6} alkyl, and

X is

35 (1) hydrogen atom,
(2) halogen atom,
(3) cyano,
(4) nitro,
(5) C_{1-6} alkanoylamino,
(6) C_{1-6} alkylsulfonyl,

(7) optionally substituted C₁₋₆ alkyl (as defined above),

(8) C₂₋₆ alkenyl optionally substituted by 1 to 3
substituent(s) selected from the above group A,

(9) -COOR^{a9}

5 wherein R^{a9} is hydrogen atom or C₁₋₆ alkyl,

(10) -CONH-(CH₂)₁-R^{a10}

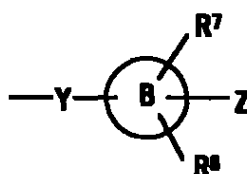
wherein R^{a10} is optionally substituted C₁₋₆ alkyl (as
defined above), C₁₋₆ alkoxycarbonyl or C₁₋₆ alkanoylamino
and 1 is 0 or an integer of 1 to 6,

10 (11) -OR^{a11}

wherein R^{a11} is hydrogen atom or optionally substituted
C₁₋₆ alkyl (as defined above)

or

(12)



15

wherein

Y is

(1') a single bond,

(2') C₁₋₆ alkylene,

20 (3') C₁₋₆ alkenylene,

(4') -(CH₂)_m-O-(CH₂)_n-,

(hereinafter m and n are each independently 0
or an integer of 1 to 6),

(5') -CO-,

25 (6') -CO₂-(CH₂)_n-,

(7') -CONH-(CH₂)_n-NH-,

(8') -NHCO₂-,

(9') -NHCONH-,

(10') -O-(CH₂)_n-CO-,

30 (11') -O-(CH₂)_n-O-,

(12') -SO₂-,

(13') -(CH₂)_m-NR^{a12}-(CH₂)_n-

wherein R^{a12} is

(1'') hydrogen atom,

35 (2'') optionally substituted C₁₋₆ alkyl (as

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- defined above),
- (3") optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above)
- 5 (4") C₆₋₁₄ aryl optionally substituted by 1 to 5
substituent(s) selected from the above
group B,
- (5") -COR^{b5}
wherein R^{b5} is hydrogen atom, optionally
substituted C₁₋₆ alkyl (as defined above),
10 optionally substituted C₆₋₁₄ aryl (as
defined above) or optionally substituted
C₆₋₁₄ aryl C₁₋₆ alkyl (as defined above)
- (6") -COOR^{b5} (R^{b5} is as defined above) or
(7") -SO₂R^{b5} (R^{b5} is as defined above),
15 (14') -NR^{a12}CO- (R^{a12} is as defined above),
(15') -CONR^{a13}-(CH₂)_n-
wherein R^{a13} is hydrogen atom, optionally
substituted C₁₋₆ alkyl (as defined above) or
optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl (as
20 defined above)
- (16') -CONH-CHR^{a14}-
wherein R^{a14} is optionally substituted C₆₋₁₄ aryl
(as defined above)
- (17') -O-(CH₂)_m-CR^{a15}R^{a16}-(CH₂)_n-
25 wherein R^{a15} and R^{a16} are each independently
(1") hydrogen atom,
(2") carboxyl,
(3") C₁₋₆ alkyl,
(4") optionally substituted C₆₋₁₄ aryl (as
30 defined above)
(5") optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above)
- (6") -OR^{b6}
wherein R^{b6} is C₁₋₆ alkyl or C₆₋₁₄ aryl C₁₋₆ alkyl,
35 or
(7") -NHR^{b7}
wherein R^{b7} is hydrogen atom, C₁₋₆ alkyl, C₁₋₆
alkanoyl or C₆₋₁₄ aryl C₁₋₆ alkyloxycarbonyl,

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(18') $-(CH_2)_n-NR^{a12}-CHR^{a15}-$ (R^{a12} and R^{a15} are each as defined above), or

(19') $-NR^{a17}SO_2-$

wherein R^{a17} is hydrogen atom or C_{1-6} alkyl,

5 ring B is

(1') C_{6-14} aryl,

(2') C_{3-8} cycloalkyl or

(3') heterocyclic group (as defined above),

Z is

10 (1') hydrogen atom,

(2') halogen atom,

(3') carbamoyl,

(4') cyano,

(5') nitro,

15 (6') C_{1-6} alkylamino,

(7') optionally substituted C_{1-6} alkyl (as defined above),

(8') $-COR^{a18}$,

20 wherein R^{a18} is optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl (as defined above),

(9') $-COOR^{a19}$

25 wherein R^{a19} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(10') $-OR^{a20}$

wherein R^{a20} is

30 (1") hydrogen atom,

(2") optionally substituted C_{1-6} alkyl (as defined above),

(3") optionally substituted C_{2-6} alkenyl (as defined above),

35 (4") C_{2-6} alkynyl optionally substituted by 1 to 3 substituent(s) selected from the above group A,

(5") optionally substituted C_{6-14} aryl (as defined above),

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- (6'') optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above),
- 5 (7'') optionally substituted heterocyclic group
wherein this group is optionally
substituted by 1 to 5 substituent(s)
selected from the above group B, and has
1 to 4 heteroatom(s) selected from an
oxygen atom, a nitrogen atom and a sulfur
atom, or
- 10 (8'') optionally substituted heterocycle C₁₋₆
alkyl
wherein this group is C₁₋₆ alkyl
substituted by optionally substituted
heterocyclic group, as defined above
- 15 (11') -O-(CH₂)_p-COR^{a21}
wherein R^{a21} is C₁₋₆ alkylamino or optionally
substituted heterocyclic group (as defined
above) and p is 0 or an integer of 1 to 6,
- (12') -NR^{a22}R^{a23}
- 20 wherein R^{a22} and R^{a23} are each independently
(1'') hydrogen atom,
(2'') optionally substituted C₁₋₆ alkyl (as
defined above),
(3'') optionally substituted C₆₋₁₄ aryl (as
25 defined above)
(4'') optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl
(as defined above) or
(5'') optionally substituted heterocycle C₁₋₆
alkyl (as defined above),
- 30 (13') -NHCO-R^{a24}
wherein R^{a24} is optionally substituted C₁₋₆
alkyl (as defined above), optionally
substituted C₆₋₁₄ aryl (as defined above) or
optionally substituted heterocyclic group
(as defined above)
- 35 (14') -NHSO₂-R^{a25}
wherein R^{a25} is optionally substituted C₆₋₁₄

aryl or optionally substituted heterocyclic group (as defined above),

(15') $-\text{SO}_2-\text{R}^{\text{a}25}$

wherein $\text{R}^{\text{a}25}$ is as defined above, and

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(16') $-\text{SO}_2-\text{NHR}^{\text{a}26}$

wherein $\text{R}^{\text{a}26}$ is hydrogen atom, optionally substituted C_{6-14} aryl (as defined above), or optionally substituted heterocyclic group (as defined above),

10

(17') optionally substituted C_{6-14} aryl (as defined above),

(18') optionally substituted C_{3-8} cycloalkyl (as defined above),

15

(19') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above) or

(20') optionally substituted heterocyclic group (as defined above),

R^7 and R^8 are each independently

20

(1') hydrogen atom,

(2') halogen atom,

(3') nitro,

(4') cyano,

(5') optionally substituted C_{1-6} alkyl (as defined above),

25

(6') $-\text{OR}^{\text{a}27}$

wherein $\text{R}^{\text{a}27}$ is hydrogen atom or C_{1-6} alkyl,

(7') $-\text{COOR}^{\text{a}27}$

wherein $\text{R}^{\text{a}27}$ is as defined above,

(8') $-\text{CONR}^{\text{a}27}\text{R}^{\text{a}28}$

30

wherein $\text{R}^{\text{a}27}$ and $\text{R}^{\text{a}28}$ are each independently hydrogen atom or C_{1-6} alkyl,

(9') $-\text{C}(=\text{NR}^{\text{a}33})\text{NH}_2$

wherein $\text{R}^{\text{a}33}$ is hydrogen atom or C_{1-6} alkyl,

(10') $-\text{SO}_2\text{R}^{\text{a}32}$

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wherein $\text{R}^{\text{a}32}$ is hydrogen atom, C_{1-6} alkyl or C_{1-6} alkylamino,

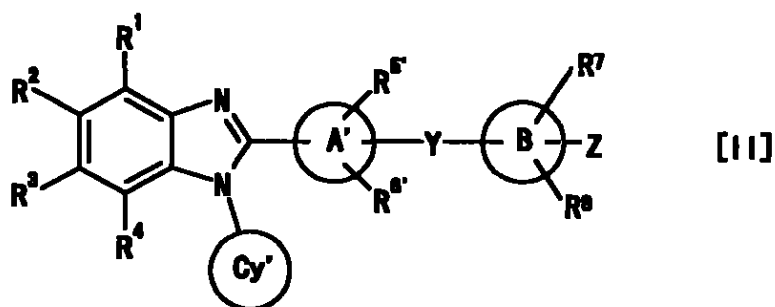
(11') $-\text{NR}^{\text{a}29}\text{R}^{\text{a}30}$

wherein $\text{R}^{\text{a}29}$ and $\text{R}^{\text{a}30}$ are each independently

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hydrogen atom, C₁₋₆ alkyl or C₁₋₆ alkanoyl, or
(12') optionally substituted heterocyclic group (as
defined above).

- (2) The therapeutic agent of (1) above, wherein at least one of R¹,
5 R², R³ and R⁴ is carboxyl, -COOR^{a1} (as defined above) or -CONR^{a2}R^{a3}
(as defined above).
(3) The therapeutic agent of (1) or (2) above, wherein the ring Cy
is cyclopentyl, cyclohexyl or cycloheptyl.
(4) The therapeutic agent of (1) to (3) above, wherein the ring A
10 is C₆₋₁₄ aryl.
(5) A benzimidazole compound of the following formula [II]



wherein

R¹, R², R³ and R⁴ are each independently,

- 15 (1) hydrogen atom,
(2) C₁₋₆ alkanoyl,
(3) carboxyl,
(4) cyano,
(5) nitro,
20 (6) C₁₋₆ alkyl optionally substituted by 1 to 3 substituent(s)
selected from the following group A,
group A; halogen atom, hydroxyl group, carboxyl, amino,
C₁₋₆ alkoxy carbonyl or C₁₋₆ alkylamino,
(7) -COOR^{a1}

25 wherein R^{a1} is optionally substituted C₁₋₆ alkyl (as
defined above) or C₆₋₁₄ aryl C₁₋₆ alkyl optionally
substituted by 1 to 5 substituent(s) selected from the
following group B,

30 group B; halogen atom, C₁₋₆ alkyl, cyano, nitro,
halogenated C₁₋₆ alkyl, C₁₋₆ alkanoyl,
-COOR^{b1}, -CONR^{b1}R^{b2}, -NR^{b1}R^{b2}, -NR^{b1}-COR^{b2}, -NHSO₂R^{b1},
-OR^{b1}, -SR^{b1}, -SO₂R^{b1} or -SO₂NR^{b1}R^{b2}

wherein R^{b1} and R^{b2} are each independently
hydrogen atom or C_{1-6} alkyl,

(8) $-\text{CONR}^{a2}\text{R}^{a3}$

5 wherein R^{a2} and R^{a3} are each independently hydrogen atom,
 C_{1-6} alkoxy or optionally substituted C_{1-6} alkyl (as
defined above),

(9) $-\text{C}(=\text{NR}^{a4})\text{NH}_2$

wherein R^{a4} is hydrogen atom or hydroxyl group,

(10) $-\text{NHR}^{a5}$

10 wherein R^{a5} is hydrogen atom, C_{1-6} alkanoyl or C_{1-6}
alkylsulfonyl,

(11) $-\text{OR}^{a6}$

wherein R^{a6} is hydrogen atom or optionally substituted
 C_{1-6} alkyl (as defined above),

15 (12) $-\text{SO}_2\text{R}^{a7}$

wherein R^{a7} is hydroxyl group, amino, C_{1-6} alkyl or C_{1-6}
alkylamino or

(13) $-\text{P}(=\text{O})(\text{OR}^{a31})_2$

20 wherein R^{a31} is hydrogen atom, optionally substituted C_{1-6}
alkyl (as defined above) or optionally substituted C_{6-14}
aryl C_{1-6} alkyl (as defined above),

ring Cy' is

(1) C_{3-8} cycloalkyl optionally substituted by 1 to 5
substituent(s) selected from the following group C,
25 group C; hydroxyl group, halogen atom, C_{1-6} alkyl or
 C_{1-6} alkoxy,

ring A' is a group selected from phenyl, pyridyl, pyrazinyl
pyrimidinyl, pyridazinyl, cyclohexyl or
cyclohexenyl,

30 $R^{5'}$ and $R^{6'}$ are each independently

(1) hydrogen atom,

(2) halogen atom,

(3) optionally substituted C_{1-6} alkyl (as defined above) or

(4) hydroxyl group,

35 Y is

(1) a single bond,

(2) C_{1-6} alkylene,

(3) C_{1-6} alkenylene,

(4) $-(CH_2)_m-O-(CH_2)_n-$,

(hereinafter m and n are each independently 0 or an integer of 1 to 6),

(5) $-CO-$,

5

(6) $-CO_2-(CH_2)_n-$,

(7) $-CONH-(CH_2)_n-NH-$,

(8) $-NHCO_2-$,

(9) $-NHCONH-$,

(10) $-O-(CH_2)_n-CO-$,

10

(11) $-O-(CH_2)_n-O-$,

(12) $-SO_2-$,

(13) $-(CH_2)_m-NR^{a12}-(CH_2)_n-$

wherein R^{a12} is

(1') hydrogen atom,

15

(2') optionally substituted C_{1-6} alkyl (as defined above),

(3') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(4') C_{6-14} aryl optionally substituted by 1 to 5

20

substituent(s) selected from the above group B,

(5') $-COR^{b5}$

wherein R^{b5} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above),

optionally substituted C_{6-14} aryl (as defined

25

above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(6') $-COOR^{b5}$ (R^{b5} is as defined above) or

(7') $-SO_2R^{b5}$ (R^{b5} is as defined above),

(14) $-NR^{a12}CO-$ (R^{a12} is as defined above),

30

(15) $-CONR^{a13}-(CH_2)_n-$

wherein R^{a13} is hydrogen atom, optionally

substituted C_{1-6} alkyl (as defined above) or

optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

35

(16) $-CONH-CHR^{a14}-$

wherein optionally substituted R^{a14} is C_{6-14} aryl (as defined above),

(17) $-O-(CH_2)_m-CR^{a15}R^{a16}-(CH_2)_n-$

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wherein R^{a15} and R^{a16} are each independently

(1') hydrogen atom,

(2') carboxyl,

(3') C_{1-6} alkyl,

5 (4') optionally substituted C_{6-14} aryl (as defined above)

(5') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(6') $-OR^{b6}$

wherein R^{b6} is C_{1-6} alkyl or C_{6-14} aryl C_{1-6} alkyl,

10 or

(7') $-NHR^{b7}$

wherein R^{b7} is hydrogen atom, C_{1-6} alkyl, C_{1-6} alkanoyl or C_{6-14} aryl C_{1-6} alkyloxycarbonyl,

15 (18) $-(CH_2)_n-NR^{a12}-CHR^{a15}-$ (R^{a12} and R^{a15} are each as defined above), or

(19) $-NR^{a17}SO_2-$

wherein R^{a17} is hydrogen atom or C_{1-6} alkyl,

ring B is

(1) C_{6-14} aryl,

20 (2) C_{3-8} cycloalkyl or

(3) heterocyclic group (as defined above),

Z is

(1) hydrogen atom,

(2) halogen atom,

25 (3) carbamoyl,

(4) cyano,

(5) nitro,

(6) C_{1-6} alkylamino,

(7) optionally substituted C_{1-6} alkyl (as defined above),

30 (8) $-COR^{a18}$,

wherein R^{a18} is optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl (as defined above),

(9) $-COOR^{a19}$

35 wherein R^{a19} is hydrogen atom, optionally substituted C_{1-6} alkyl (as defined above) or optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),

(10) $-OR^{a20}$

wherein R^{a20} is

- (1') hydrogen atom,
- (2') optionally substituted C_{1-6} alkyl (as defined above),
- (3') optionally substituted C_{2-6} alkenyl (as defined above),
- (4') C_{2-6} alkynyl optionally substituted by 1 to 3 substituent(s) selected from the above group A,
- (5') optionally substituted C_{6-14} aryl (as defined above),
- (6') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above),
- (7') optionally substituted heterocyclic group wherein this group is optionally substituted by 1 to 5 substituent(s) selected from the above group B, and has 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, or
- (8') optionally substituted heterocycle C_{1-6} alkyl wherein this group is C_{1-6} alkyl substituted by optionally substituted heterocyclic group (as defined above),

(11) $-O-(CH_2)_p-COR^{a21}$

wherein R^{a21} is C_{1-6} alkylamino or optionally substituted heterocyclic group (as defined above) and p is 0 or an integer of 1 to 6,

(12) $-NR^{a22}R^{a23}$

wherein R^{a22} and R^{a23} are each independently

- (1') hydrogen atom,
- (2') optionally substituted C_{1-6} alkyl (as defined above),
- (3') optionally substituted C_{6-14} aryl (as defined above),
- (4') optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above) or
- (5') optionally substituted heterocycle C_{1-6} alkyl (as defined above),

(13) -NHCO-R^{a24}

wherein R^{a24} is optionally substituted C_{1-6} alkyl (as defined above), optionally substituted C_{6-14} aryl (as defined above) or optionally substituted heterocyclic group (as defined above),

(14) $\text{-NHSO}_2\text{-R}^{a25}$

wherein R^{a25} is optionally substituted C_{6-14} aryl or optionally substituted heterocyclic group (as defined above),

(15) $\text{-SO}_2\text{-R}^{a25}$

wherein R^{a25} is as defined above, and

(16) $\text{-SO}_2\text{-NHR}^{a26}$

wherein R^{a26} is hydrogen atom, optionally substituted C_{6-14} aryl (as defined above) or optionally substituted heterocyclic group (as defined above),

(17) optionally substituted C_{6-14} aryl (as defined above),

(18) optionally substituted C_{3-8} cycloalkyl (as defined above),

(19) optionally substituted C_{6-14} aryl C_{1-6} alkyl (as defined above) or

(20) optionally substituted heterocyclic group (as defined above), and

R^7 and R^8 are each independently

(1) hydrogen atom,

(2) halogen atom,

(3) nitro,

(4) cyano,

(5) optionally substituted C_{1-6} alkyl (as defined above),

(6) -OR^{a27}

wherein R^{a27} is hydrogen atom or C_{1-6} alkyl,

(7) -COOR^{a27}

wherein R^{a27} is as defined above,

(8) $\text{-CONR}^{a27}\text{R}^{a28}$

wherein R^{a27} and R^{a28} are each independently hydrogen atom or C_{1-6} alkyl,

(9) $\text{-C(=NR}^{a33})\text{NH}_2$

wherein R^{a33} is hydrogen atom or C_{1-6} alkyl,

(10) $\text{-SO}_2\text{R}^{a32}$

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wherein R^{a32} is hydrogen atom, C_{1-6} alkyl or C_{1-6} alkylamino,

(11) $-NR^{a29}R^{a30}$

wherein R^{a29} and R^{a30} are each independently hydrogen atom, C_{1-6} alkyl or C_{1-6} alkanoyl, or

(12) optionally substituted heterocyclic group (as defined above),

or a pharmaceutically acceptable salt thereof.

(6) The benzimidazole compound of (5) above, wherein at least one of R^1 , R^2 , R^3 and R^4 is carboxyl or $-COOR^{a1}$ (as defined above), or a pharmaceutically acceptable salt thereof.

(7) The benzimidazole compound of (5) or (6) above, wherein the ring Cy' is cyclopentyl, cyclohexyl or cycloheptyl, or a pharmaceutically acceptable salt thereof.

(8) The benzimidazole compound of claims 5 to 7, wherein R^2 is carboxyl and R^1 , R^3 and R^4 are hydrogen atoms, or a pharmaceutically acceptable salt thereof.

(9) The benzimidazole compound of (5) to (8) above, wherein the ring A' is phenyl, or a pharmaceutically acceptable salt thereof.

(10) The benzimidazole compound of claims 5 to 9, wherein the Y is $-(CH_2)_m-O-(CH_2)_n-$, $-NHCO_2-$, $-CONH-CHR^{a14}-$, $-(CH_2)_m-NR^{a12}-(CH_2)_n-$, $-CONR^{a13}-(CH_2)_n-$, $-O-(CH_2)_m-CR^{a15}R^{a16}-(CH_2)_n-$ or $-(CH_2)_n-NR^{a12}-CHR^{a15}-$ (wherein each symbol is as defined above), or a pharmaceutically acceptable salt thereof.

(11) The benzimidazole compound of (5) to (10) above, wherein the Y is $-(CH_2)_m-O-(CH_2)_n-$ or $-O-(CH_2)_m-CR^{a15}R^{a16}-(CH_2)_n-$ (wherein each symbol is as defined above), or a pharmaceutically acceptable salt thereof.

(12) A pharmaceutical composition comprising a benzimidazole compound of (5) to (11) above, or a pharmaceutically acceptable salt thereof.

(13) A hepatitis C virus polymerase inhibitor comprising a benzimidazole compound of (1) to (11) above, or a pharmaceutically acceptable salt thereof.

(14) An anti-hepatitis C virus agent comprising a benzimidazole compound of (1) to (11) above, or a pharmaceutically acceptable salt thereof.

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(15) A therapeutic agent for hepatitis C comprising a benzimidazole compound of (5) to (11) above, or a pharmaceutically acceptable salt thereof.

5 The definitions of respective substituents and moieties used in the present specification are as follows.

The halogen atom is a fluorine atom, chlorine atom, bromine atom or iodine atom, preferably fluorine atom, chlorine atom or bromine atom.

10 Particularly preferably, the halogen atom is fluorine atom at R⁵, R^{5'}, R⁶, R^{6'} and Z, fluorine atom at the substituent at ring Cy and ring Cy', chlorine atom at R⁷ and R⁸ and fluorine atom or chlorine atom at the substituent of optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocyclic group, optionally substituted C₆₋₁₄ aryl
15 C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

The C₁₋₆ alkyl is straight chain or branched chain alkyl having 1 to 6 carbon atoms, and is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl and the like.

20 Preferably, it is straight chain or branched chain alkyl having 1 to 4 carbon atoms, and is particularly preferably methyl at R¹⁷ and substituent at R¹ and methyl or tert-butyl at the substituent of ring Cy, ring Cy', optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted
25 heterocyclic group, optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

The halogenated C₁₋₆ alkyl is the above-defined C₁₋₆ alkyl except that it is substituted by the above-defined halogen atom. Preferably, it is halogenated alkyl wherein the alkyl moiety
30 thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include fluoromethyl, difluoromethyl, trifluoromethyl, bromomethyl, chloromethyl, 1,2-dichloromethyl, 2,2-dichloromethyl, 2,2,2-trifluoroethyl and the like.

35 The halogenated C₁₋₆ alkyl is particularly preferably trifluoromethyl at the substituent of optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₈ cycloalkyl, optionally

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substituted heterocyclic group, optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

5 The C₁₋₆ alkylene is straight chain alkylene having 1 to 6 carbon atoms, and is exemplified by methylene, ethylene, trimethylene, tetramethylene, pentamethylene or hexamethylene.

The C₁₋₆ alkylene is preferably methylene or ethylene at Y.

The C₂₋₆ alkenylene is straight chain alkenylene having 2 to 6 carbon atoms, and is exemplified by vinylene, propenylene, 1-butenylene, 1,3-butadienylene and the like.

10 The C₂₋₆ alkenylene is preferably vinylene at Y.

The C₁₋₆ alkoxy is alkyloxy wherein the alkyl moiety thereof is the above-defined C₁₋₆ alkyl. Preferably, it is alkoxy wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include methoxy, 15 ethoxy, propoxy, isopropoxy, butoxy, isobutyloxy, tert-butyloxy, pentyloxy, hexyloxy and the like.

The C₁₋₆ alkoxy is particularly preferably methoxy at R^{a2}, R^{a3} and at the substituent of ring Cy, ring Cy', optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₈ cycloalkyl, 20 optionally substituted heterocyclic group, optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

The C₁₋₆ alkanoyl is alkylcarbonyl wherein the alkyl moiety thereof is the above-defined C₁₋₆ alkyl. Preferably, it is 25 alkanoyl wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include acetyl, propionyl, butyryl, isobutyryl, pivaloyl and the like.

The C₁₋₆ alkanoyl is particularly preferably acetyl at R¹, 30 R², R³, R⁴, R^{a5}, R^{a29}, R^{a30}, R^{b7} and at the substituent of optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocyclic group, optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

35 The C₁₋₆ alkoxycarbonyl is alkyloxycarbonyl wherein the alkoxy moiety thereof is the above-defined C₁₋₆ alkoxy. Preferably, it is alkoxycarbonyl wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms.

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Examples thereof include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropylloxycarbonyl, butoxycarbonyl, isobutylloxycarbonyl, tert-butylloxycarbonyl, pentylloxycarbonyl, hexylloxycarbonyl and the like.

5 The C₁₋₆ alkylamino is alkylamino or dialkylamino wherein the alkyl moiety thereof is the above-defined C₁₋₆ alkyl. Preferably, it is alkylamino or dialkylamino wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, 10 tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, methylethylamino, N-isopropyl-N-isobutylamino and the like.

15 The C₁₋₆ alkylamino is particularly preferably methylamino at R⁷ and R⁸, and particularly preferably dimethylamino at R¹⁹.

20 The C₁₋₆ alkanoylamino is alkylcarbonylamino wherein the alkanoyl moiety thereof is the above-defined C₁₋₆ alkanoyl. Preferably, it is alkoxycarbonyl wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include acetylamino, propionylamino, butyrylamino, isobutyrylamino, pivaloylamino and the like.

25 The C₁₋₆ alkylsulfonyl is alkylsulfonyl wherein the alkyl moiety thereof is the above-defined C₁₋₆ alkyl. Preferably, it is alkylsulfonyl wherein the alkyl moiety thereof is straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, hexylsulfonyl and the like.

30 The C₁₋₆ alkylsulfonyl is particularly preferably methylsulfonyl at R⁵ and at the substituent of optionally substituted C₆₋₁₄ aryl, optionally substituted C₃₋₆ cycloalkyl, optionally substituted heterocyclic group, optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl and optionally substituted heterocycle C₁₋₆ alkyl.

35 The C₆₋₁₄ aryl is aromatic hydrocarbon having 6 to 14 carbon atoms. Examples thereof include phenyl, naphthyl, anthryl, indenyl, azulenyl, fluorenyl, phenanthryl, pyrenyl and the like.

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The C₆₋₁₄ aryl is preferably phenyl or naphthyl, particularly preferably phenyl at the ring A, ring A' and ring B.

The C₃₋₈ cycloalkyl is saturated cycloalkyl having 3 to 8, preferably 5 to 7, carbon atoms. Examples thereof include
5 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The C₃₋₈ cycloalkenyl is cycloalkenyl having 3 to 8, preferably 5 to 7, carbon atoms and has partial double bond(s). Examples thereof include cyclopropenyl, cyclobutenyl,
10 cyclopentenyl, cyclopentadienyl, cyclohexenyl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl, cycloheptenyl and cyclooctenyl and the like, but do not include aryl (e.g., phenyl) or completely saturated cycloalkyl.

The C₃₋₈ cycloalkenyl is preferably cyclohexenyl at the ring
15 A.

The heterocyclic group has, as an atom constituting the ring, 1 to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, besides a carbon atom, and includes saturated ring and unsaturated ring, monocyclic ring and
20 fused ring having the number of ring atom constituting the ring of 3 to 14.

The heterocyclic group as a monocyclic ring includes, for example, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl,
25 tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl and the like.

Examples of the heterocyclic group as a fused ring include
30 quinolyl, isoquinolyl, quinazolinyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, 5,6,7,8-tetrahydroquinolyl, indolyl, benzimidazolyl, indolinyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl and the like.

Preferably, it is a heterocyclic group, which is a 5-
35 membered or a 6-membered monocyclic group. Examples thereof include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl,

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isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidyl, piperazinyl and the like.

5 The heterocyclic group is preferably pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl, which is an aromatic group, and particularly preferably pyridyl at the ring A and ring A'.

10 The heterocyclic group is particularly preferably pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thiadiazolyl, which is an aromatic group, at the ring B. More preferably it is thiazolyl.

15 The C₆₋₁₄ aryl C₁₋₆ alkyl is arylalkyl wherein the alkyl moiety thereof is the above-defined C₁₋₆ alkyl and the aryl moiety is the above-defined C₆₋₁₄ aryl. Preferably, it is arylalkyl wherein the alkyl moiety thereof is straight chain alkyl having 1 to 4 carbon atoms and the aryl moiety is phenyl. Examples thereof include benzyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl and the like.

20 The C₆₋₁₄ aryl C₁₋₆ alkyl is particularly preferably benzyl at R^{a8}.

25 The C₆₋₁₄ aryl C₁₋₆ alkyloxycarbonyl is arylalkyloxycarbonyl wherein the C₆₋₁₄ aryl C₁₋₆ alkyl moiety thereof is the above-defined C₆₋₁₄ aryl C₁₋₆ alkyl. Preferably, it is arylalkyloxycarbonyl wherein the alkyl moiety thereof is straight chain alkyl having 1 to 4 carbon atoms and the aryl moiety is phenyl. Examples thereof include benzyloxycarbonyl, phenethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 2-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl and the like.

30 The C₆₋₁₄ aryl C₁₋₆ alkyloxycarbonyl is particularly preferably benzyloxycarbonyl at R^{b7}.

35 The optionally substituted C₁₋₆ alkyl is the above-defined C₁₋₆ alkyl, preferably that wherein straight chain or branched chain alkyl having 1 to 4 carbon atoms is optionally substituted with 1 to 3 substituent(s), and includes unsubstituted alkyl. The substituent(s) is(are) selected from the above-defined halogen atom, hydroxyl group, carboxyl, the above-defined C₁₋₆ alkoxy carbonyl, amino and the above-defined C₁₋₆ alkylamino. Examples of optionally substituted C₁₋₆ alkyl include methyl,

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ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, neopentyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, 4-hydroxybutyl, 1-hydroxy-1-methylethyl, carboxymethyl, ethoxycarbonylmethyl, 2-ethoxycarbonylethyl, 2-dimethylaminoethyl and the like.

Preferably, the optionally substituted C₁₋₆ alkyl is methyl, 1-hydroxy-1-methylethyl, carboxymethyl or 2-dimethylaminoethyl at R¹, R², R³, R⁴, and R^{a12}, methyl or trifluoromethyl at R⁵, R^{5'}, R⁶ and R^{6'}, methyl or tert-butyl at R⁷ and R⁸, ethyl at R^{a1}, methyl, carboxymethyl or 2-dimethylaminoethyl at R^{a2} and R^{a3}, methyl or carboxymethyl at R^{a6}, methyl at R^{a8}, R^{a27} and R^{a28}, methyl, propyl, isopentyl or hydroxymethyl at R^{a20}, methyl or tert-butyl at R^{b1}, R^{b2}, R^{b3} and R^{b4} and methyl, tert-butyl or trifluoromethyl at Z.

It is particularly preferably, methyl at R⁷, R⁸ and R^{a27}.

The optionally substituted C₂₋₆ alkenyl is that wherein straight chain or branched chain alkenyl having 2 to 6 carbon atoms is optionally substituted by 1 to 3 substituent(s), and includes unsubstituted alkenyl. The substituent(s) is(are) selected from the above-defined halogen atom, hydroxyl group, carboxyl, the above-defined C₁₋₆ alkoxycarbonyl, amino and the above-defined C₁₋₆ alkylamino. Examples of optionally substituted C₂₋₆ alkenyl include vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 1,3-butadienyl, 2-isopentenyl, 3-isohexenyl, 4-methyl-3-pentenyl, 2-carboxylethenyl and the like.

The optionally substituted C₂₋₆ alkenyl is preferably 2-isopentenyl, 3-isohexenyl or 4-methyl-3-pentenyl at R^{a18}.

The optionally substituted C₂₋₆ alkynyl is that wherein straight chain or branched chain alkynyl having 2 to 6 carbon atoms is optionally substituted by 1 to 3 substituent(s), and includes unsubstituted alkynyl. The substituent(s) is(are) selected from the above-defined halogen atom, hydroxyl group, carboxyl, the above-defined C₁₋₆ alkoxycarbonyl, amino and the above-defined C₁₋₆ alkylamino. Examples thereof include ethynyl, 1-propynyl, 2-propynyl, 3-butyne and the like.

The optionally substituted C₂₋₆ alkynyl is preferably 2-propynyl at R^{a18}.

The optionally substituted C₆₋₁₄ aryl is that wherein the above-defined C₆₋₁₄ aryl is optionally substituted by 1 to 5

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substituent(s), and includes unsubstituted aryl. The substituent(s) is(are) selected from the above-defined halogen atom, the above-defined C₁₋₆ alkyl, the above-defined halogenated C₁₋₆ alkyl, the above-defined C₁₋₆ alkanoyl, cyano, nitro, -COOR^{b1},
5 -CONR^{b1}R^{b2}, -NR^{b1}R^{b2}, -NR^{b1}-COR^{b2}, -NHSO₂R^{b1}, -OR^{b1}, -SR^{b1}, -SO₂R^{b1} and -SO₂NR^{b1}R^{b2} (wherein R^{b1} and R^{b2} are each independently hydrogen atom or the above-defined C₁₋₆ alkyl).

Examples thereof include phenyl, naphthyl, anthryl, indenyl, azulenyl, fluorenyl, phenanthryl, pyrenyl, 3-fluorophenyl, 4-
10 fluorophenyl, 3,5-dichlorophenyl, pentafluorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-tert-butylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-acetylphenyl, 4-carboxylphenyl, 4-carbamoylphenyl, 4-aminophenyl, 4-dimethylaminophenyl, 4-acetylaminophenyl, 4-
15 (methylsulfonylamino)phenyl, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl, 4-mercaptophenyl, 4-methylsulfonylphenyl and 4-aminosulfonylphenyl.

The aryl moiety is preferably phenyl, the substituent here is preferably the above-defined halogen atom, the above-defined
20 C₁₋₆ alkyl or -OR^{b1}. More preferably, the substituent is the above-defined halogen atom. Particularly preferably, it is fluorine atom or chlorine atom.

Examples of optionally substituted C₆₋₁₄ aryl include phenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl or 4-methylphenyl
25 at R^{a12}, R^{a14}, R^{a15}, R^{a16}, R^{a18}, R^{a20}, R^{a22}, R^{a23}, R^{a24}, R^{a25} and R^{a26}, and phenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 3,5-dichlorophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 4-tert-butylphenyl, 4-nitrophenyl, 4-methoxyphenyl, 3,4,5-
30 trimethoxyphenyl, 4-carboxylphenyl, 4-carbamoylphenyl, 3,5-dichlorophenyl, 4-mercaptophenyl, 4-methylsulfonylphenyl or 4-acetylaminophenyl at Z. It is particularly preferably 3-fluorophenyl at R^{a15} and R^{a16}, and 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl or 4-chlorophenyl at Z.

35 The optionally substituted heterocyclic group is that wherein the above-defined heterocyclic group is optionally substituted by 1 to 5 substituent(s), and includes unsubstituted heterocyclic group. The substituent(s) is(are) selected from the

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above-defined halogen atom, the above-defined C₁₋₆ alkyl, the above-defined halogenated C₁₋₆ alkyl, the above-defined C₁₋₆ alkanoyl, cyano, nitro, -COOR^{b1}, -CONR^{b1}R^{b2}, -NR^{b1}R^{b2}, -NR^{b1}-COR^{b2}, -NHSO₂R^{b1}, -OR^{b1}, -SR^{b1}, -SO₂R^{b1} and -SO₂NR^{b1}R^{b2} wherein R^{b1} and R^{b2} are each independently hydrogen atom or the above-defined C₁₋₆ alkyl.

Examples thereof include 3-pyridyl, 4-pyridyl, 3-fluoropyridin-4-yl, 3-chloropyridin-4-yl, 4-chloropyridin-3-yl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, furyl, oxazolyl, 2-methyloxazol-4-yl, isoxazolyl, thiazolyl, 2-methylthiazol-4-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, isothiazolyl, thiadiazolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, piperidyl, N-methylpiperidin-4-yl, N-(tert-butoxycarbonyl)piperidin-4-yl, N-acetylpiperidin-4-yl, N-methylsulfonylpiperidin-4-yl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, 5,6,7,8-tetrahydroquinolyl, indolyl, benzimidazolyl, indolinyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl and the like.

The heterocyclic moiety is preferably a heterocyclic group which is a 5-membered or a 6-membered monocyclic group. Examples thereof include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidyl and piperazinyl, and the substituent here is preferably the above-defined halogen atom, the above-defined C₁₋₆ alkyl, the above-defined halogenated C₁₋₆ alkyl, the above-defined C₁₋₆ alkanoyl, -COOR^{b1}, -CONR^{b1}R^{b2} or -OR^{b1}.

Examples of optionally substituted heterocyclic group include preferably pyridyl, thiazolyl, piperidinyl or tetrahydropyranyl, and particularly preferably pyridyl or thiazolyl, at Z, R^{a19}, R^{a20}, R^{a22}, R^{a23} and R^{a24}. It is preferably tetrazolyl at R⁷ and R⁸.

The optionally substituted C₃₋₈ cycloalkyl is that wherein the above-defined C₃₋₈ cycloalkyl is optionally substituted by the 1 to 5 substituent(s) selected from hydroxyl group, the above-

defined halogen atom, the above-defined C₁₋₆ alkyl and the above-defined C₁₋₆ alkoxy, which may be unsubstituted. Examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 4-fluorocyclohexyl, 2-methylcyclopentyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 4,4-dimethylcyclohexyl, 3,5-dimethylcyclohexyl, 4-tert-butylcyclohexyl, 4-hydroxycyclohexyl, 4-methoxycyclohexyl and 2,3,4,5-pentafluorocyclohexyl.

The cycloalkyl moiety is preferably cyclopentyl or cyclohexyl, particularly preferably cyclohexyl.

At the ring Cy and ring Cy', the optionally substituted C₃₋₈ cycloalkyl is preferably cyclopentyl, cyclohexyl, 4-fluorocyclohexyl, 4-methylcyclohexyl, 4,4-dimethylcyclohexyl, 4-tert-butylcyclohexyl, 4-hydroxycyclohexyl or 4-methoxycyclohexyl, more preferably cyclopentyl or cyclohexyl, particularly preferably cyclohexyl. It is preferably cyclopentyl or cyclohexyl, particularly preferably cyclohexyl at Z.

The optionally substituted C₃₋₈ cycloalkenyl is that wherein the above-defined C₃₋₈ cycloalkenyl is optionally substituted by substituent(s) selected from hydroxyl group, the above-defined halogen atom, the above-defined C₁₋₆ alkyl and the above-defined C₁₋₆ alkoxy, which may be unsubstituted. Examples thereof include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, 4-fluoro-2-cyclohexenyl, 4-methyl-2-cyclohexenyl, 4-methyl-3-cyclohexenyl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl, cycloheptenyl and cyclooctenyl and the like, but do not include aryl (e.g., phenyl) or completely saturated cycloalkyl.

The optionally substituted C₃₋₈ cycloalkenyl is particularly preferably cyclohexenyl at the ring Cy.

The optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl is that wherein the above-defined C₆₋₁₄ aryl C₁₋₆ alkyl is optionally substituted by 1 to 5 substituent(s), and includes unsubstituted aryl. The substituent(s) is(are) selected from the above-defined halogen atom, the above-defined C₁₋₆ alkyl, the above-defined halogenated C₁₋₆ alkyl, the above-defined C₁₋₆ alkanoyl, cyano, nitro, -COOR^{b1}, -CONR^{b1}R^{b2}, -NR^{b1}R^{b2}, -NR^{b1}-COR^{b2}, -NHSO₂R^{b1}, -OR^{b1}, -SR^{b1}, -SO₂R^{b1} and -SO₂NR^{b1}R^{b2} wherein R^{b1} and R^{b2} are each independently hydrogen atom or the above-defined C₁₋₆ alkyl.

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Examples thereof include benzyl, 1-naphthylmethyl, 2-naphthylmethyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 3,5-dichlorophenylmethyl, pentafluorophenylmethyl, 4-chlorophenylmethyl, 4-methylphenylmethyl, 4-tert-butylphenylmethyl, 2-trifluoromethylphenylmethyl, 4-trifluoromethylphenylmethyl, 4-nitrophenylmethyl, 4-cyanophenylmethyl, 4-acetylphenylmethyl, 4-carboxyphenylmethyl, 4-carbamoylphenylmethyl, 4-aminophenylmethyl, 4-dimethylamino-phenylmethyl, 4-acetylaminophenylmethyl, 4-(methylsulfonylamino)-phenylmethyl, 4-methoxyphenylmethyl, 3,4,5-trimethoxyphenylmethyl, 4-mercaptophenylmethyl, 4-methylsulfonylphenylmethyl and 4-aminosulfonylphenylmethyl.

The aryl moiety is preferably phenyl, the alkyl moiety is preferably methylene or ethylene, and the substituent here is preferably the above-defined halogen atom, the above-defined C₁₋₆ alkyl or -OR^{b1}. More preferably, the substituent is the above-defined halogen atom.

The specific optionally substituted C₆₋₁₄ aryl C₁₋₆ alkyl at R^{a12}, R^{a13}, R^{a15}, R^{a16}, R^{a19}, R^{a22}, R^{a23}, R^{b6} and Z is preferably benzyl, phenethyl or 4-chlorophenylmethyl.

The optionally substituted heterocycle C₁₋₆ alkyl is that wherein the above-defined optionally substituted heterocyclic group substitutes on the above-defined C₁₋₆ alkyl.

Examples thereof include 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-fluoropyridin-4-ylmethyl, 3-chloropyridin-4-ylmethyl, 4-chloropyridin-3-ylmethyl, pyrrolylmethyl, imidazolylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 2-oxazolylmethyl, 5-isothiazolylmethyl, 2-methyloxazol-4-ylmethyl, 5-thiazolyl, 2-methylthiazol-4-ylmethyl, 2-methylthiazol-5-ylmethyl, 2,5-dimethylthiazol-4-ylmethyl, 2,4-dimethylthiazol-5-ylmethyl, 2-isothiazolylmethyl, 2-pyrrolinylmethyl, pyrrolidinylmethyl, piperidylmethyl, 4-piperidylmethyl, 1-methylpiperidin-4-ylmethyl, 1-(tert-butoxycarbonyl)piperidin-4-ylmethyl, 1-acetylpiperidin-4-ylmethyl, 1-methylsulfonylpiperidin-4-ylmethyl, piperazinylmethyl, morpholinomethyl, thiomorpholinylmethyl, 1-tetrahydropyranylmethyl, 2-quinolylmethyl, 1-isoquinolylmethyl and the like.

The heterocyclic moiety is preferably a heterocyclic group which is a 5-membered or 6-membered monocyclic group. Examples thereof include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,3,5-triazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, 5 tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidyl and piperazinyl. The substituent here is preferably the above-defined halogen atom, the above-defined C₁₋₆ alkyl, the above-defined halogenated C₁₋₆ alkyl, the above-defined C₁₋₆ alkanoyl, -COOR^{b1}, 10 -CONR^{b1}R^{b2} or -OR^{b1}, and the alkyl moiety thereof is preferably methylene or ethylene.

The alkyl moiety thereof is preferably straight chain alkyl having 1 to 4 carbon atoms.

Examples of optionally substituted heterocycle C₁₋₆ alkyl 15 preferably include 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-methylthiazol-5-ylmethyl, 1-methylpiperidin-4-ylmethyl, 1-(tert-butoxycarbonyl)piperidin-4-ylmethyl, 1-acetylpiperidin-4-ylmethyl, 1-methylsulfonylpiperidin-4-ylmethyl, piperazinylmethyl, 4-piperidylmethyl and tetrahydropyranyl at R^{a20}, 20 R^{a22} and R^{a23}, and more preferably, it is 4-pyridylmethyl.

R¹ and R⁴ are preferably hydrogen atom. R² is preferably carboxyl, -COOR^{a1} or -CONR^{a2}R^{a3} (each symbol is as defined above), particularly preferably carboxyl. R³ is preferably hydrogen atom or -OR^{a6} (R^{a6} is as defined above), particularly preferably 25 hydrogen atom.

The ring Cy is preferably cycloalkyl, the ring A is preferably aryl, and the ring B is preferably C₆₋₁₄ aryl or heterocyclic group.

Y is preferably -(CH₂)_m-O-(CH₂)_n-, -NHCO₂-, -CONH-CHR^{a14}-, 30 -(CH₂)_m-NR^{a12}-(CH₂)_n-, -CONR^{a13}-(CH₂)_n-, -O-(CH₂)_m-CR^{a15}R^{a16}-(CH₂)_n- or -(CH₂)_n-NR^{a12}-CHR^{a15}- (each symbol is as defined above), more preferably, -(CH₂)_m-O-(CH₂)_n- or -O-(CH₂)_m-CR^{a15}R^{a16}-(CH₂)_n-.

The l, m and n are preferably 0 or an integer of 1 to 4, particularly preferably 0, 1 or 2, at Y. In -(CH₂)_m-O-(CH₂)_n-, 35 m=n=0 or m=0 and n=1 is more preferable. In -O-(CH₂)_m-CR^{a15}R^{a16}-(CH₂)_n-, m=n=0 is more preferable.

It is preferable that either R^{a15} or R^{a16} at Y be hydrogen atom and the other be optionally substituted C₆₋₁₄ aryl.

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When ring A is phenyl, X or Y is preferably present at the para-position relative to imidazol-2-yl group. When ring B is phenyl, Z is preferably present at the meta- or para-position relative to Y. When ring B is thiazolyl, Z and Y are preferably substituted at the 4-position and the 5-position or at the 5-position and the 4-position, respectively.

Z is preferably halogen atom, $-OR^{a20}$ (the symbol is as defined above), optionally substituted C_{6-14} aryl or optionally substituted heterocyclic group, particularly preferably halogen atom, $-OR^{a20}$ or optionally substituted C_{6-14} aryl. R^{a20} is preferably C_{6-14} aryl, C_{6-14} aryl C_{1-6} alkyl, optionally substituted heterocyclic group or optionally substituted heterocycle C_{1-6} alkyl, particularly preferably optionally substituted heterocycle C_{1-6} alkyl.

With regard to R^5 and R^6 , one of them is preferably hydrogen atom and the other is halogen atom. Alternatively, the both are preferably hydrogen atoms.

It is preferable that either R^7 or R^8 be hydrogen atom and the other be halogen atom, optionally substituted alkyl or $-OR^{a27}$ (the symbol is as defined above), or the both are hydrogen atom. R^{a27} is preferably C_{1-6} alkyl.

The pharmaceutically acceptable salt may be any as long as it forms a non-toxic salt with a compound of the above-mentioned formula [I]. Such salt can be obtained by reacting the compound with an inorganic acid, such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like, or an organic acid, such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, benzyisulfonic acid and the like, or an inorganic base, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like, or an organic base, such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, cinchonine and the like, with an amino acid, such as lysine, arginine, alanine and the like. The present invention encompasses water-retaining product, hydrate and solvate of each compound.

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The compounds of the above-mentioned formula [I] have various isomers. For example, E compound and Z compound are present as geometric isomers, and when the compound has an asymmetric carbon, an enantiomer and a diastereomer are present due to the asymmetric carbon. A tautomer may be also present. The present invention encompasses all of these isomers and mixtures thereof.

The present invention also encompasses prodrug and metabolite of each compound.

10 A prodrug means a derivative of the compound of the present invention, which is capable of chemical or metabolic decomposition, which shows inherent efficacy by reverting to the original compound after administration to a body, and which includes salts and complexes without a covalent bond.

15 When the inventive compound is used as a pharmaceutical preparation, the inventive compound is generally admixed with pharmaceutically acceptable carriers, excipients, diluents, binders, disintegrators, stabilizers, preservatives, buffers, emulsifiers, aromatics, coloring agents, sweeteners, thickeners, 20 correctives, solubilizers, and other additives such as water, vegetable oil, alcohol such as ethanol, benzyl alcohol and the like, polyethylene glycol, glycerol triacetate, gelatin, lactose, carbohydrate such as starch and the like, magnesium stearate, talc, lanolin, petrolatum and the like, and prepared into a dosage form of tablets, pills, powders, granules, suppositories, injections, 25 eye drops, liquids, capsules, troches, aerosols, elixirs, suspensions, emulsions, syrups and the like, which can be administered systemically or topically and orally or parenterally.

While the dose varies depending on the age, body weight, 30 general condition, treatment effect, administration route and the like, it is from 0.1 mg to 1 g for an adult per dose, which is given one to several times a day.

The prophylaxis of hepatitis C means, for example, administration of a pharmaceutical agent to an individual found to 35 carry an HCV by a test and the like but without a symptom of hepatitis C, or to an individual who shows an improved disease state of hepatitis after a treatment of hepatitis C, but who still

carries an HCV and is associated with a risk of recurrence of hepatitis.

[Embodiment of the invention]

5 Examples of the production method of the compound to be used for the practice of the present invention are given in the following. However, the production method of the compound of the present invention is not limited to these examples.

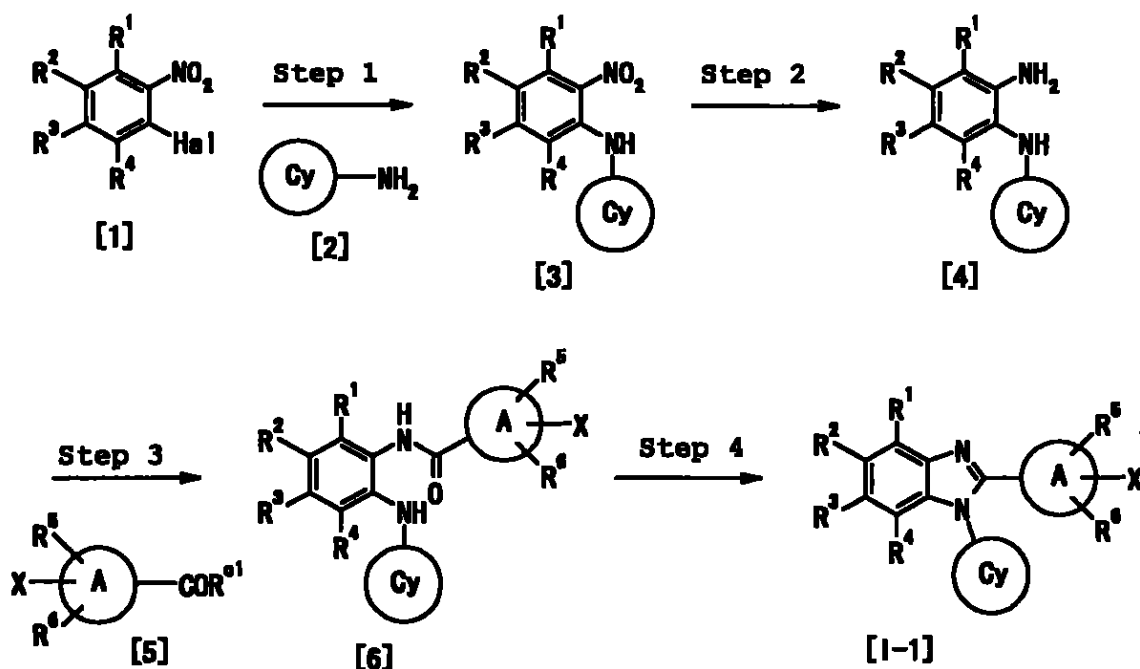
10 Even if no directly corresponding disclosure is found in the following Production Methods, the steps may be modified for efficient production of the compound, such as introduction of a protecting group into a functional group with deprotection in a subsequent step, and changing the order of Production Methods and steps.

15 The treatment after reaction in each step may be conventional ones, for which typical methods, such as isolation and purification, crystallization, recrystallization, silica gel chromatography, preparative HPLC and the like, can be appropriately selected and combined.

Production Method 1

20 In this Production Method, a benzimidazole compound is formed from a nitrobenzene compound.

Production Method 1-1



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wherein Hal is halogen atom, such as chlorine atom, bromine atom and the like, R^{cl} is halogen atom, such as chlorine atom, bromine atom and the like, or hydroxyl group, and other symbols are as defined above.

5 **Step 1**

 A compound [1] obtained by a conventional method or a commercially available compound [1] is reacted with amine compound [2] in a solvent such as N,N-dimethylformamide (DMF), acetonitrile, tetrahydrofuran (THF), toluene and the like in the presence or
10 absence of a base such as potassium carbonate, triethylamine, potassium t-butoxide and the like at room temperature or with heating to give compound [3].

Step 2

 The compound [3] is hydrogenated in a solvent such as
15 methanol, ethanol, THF, ethyl acetate, acetic acid, water and the like in the presence of a catalyst such as palladium carbon, palladium hydroxide, platinum oxide, Raney nickel and the like at room temperature or with heating to give compound [4]. In addition, compound [3] is reduced with a reducing agent such as
20 zinc, iron, tin(II) chloride, sodium sulfite and the like, or reacted with hydrazine in the presence of iron(III) chloride to give compound [4].

Step 3

 The compound [4] is condensed with carboxylic acid compound
25 [5] in a solvent such as DMF, acetonitrile, THF, chloroform, ethyl acetate, methylene chloride, toluene and the like using a condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diphenylphosphoryl azide and the like and, where necessary, adding N-
30 hydroxysuccinimide, 1-hydroxybenzotriazole and the like to give amide compound [6]. Alternatively, amide compound [6] can be obtained from compound [5] as follows. The carboxylic acid compound [5] is converted to an acid halide derived with thionyl chloride, oxalyl chloride and the like, or an active ester (e.g.,
35 mixed acid anhydride derived with ethyl chlorocarbonate and the like), which is then reacted in the presence of a base, such as triethylamine, potassium carbonate, pyridine and the like, or in

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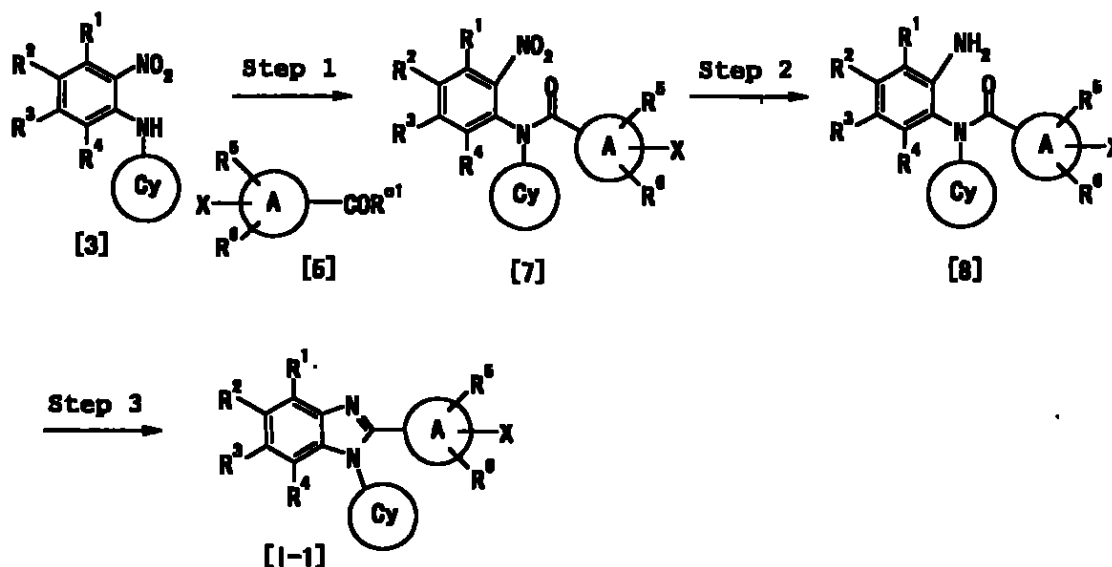
an amine solvent, such as pyridine and the like, to give amide compound [6].

Step 4

The compound [6] is heated in a solvent such as ethanol, methanol, toluene, DMF, chloroform and the like or without a solvent in the presence of an acid such as acetic acid, formic acid, hydrochloric acid, dilute sulfuric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid and the like, a halogenating agent such as zinc chloride, phosphorus oxychloride, thionyl chloride and the like or acid anhydride such as acetic anhydride and the like, to allow cyclization to give compound [I-1].

Production Method 1-2

This Production Method is an alternative method for producing compound [I-1].



wherein each symbol is as defined above.

Step 1

The compound [3] obtained in the same manner as in Step 1 of Production Method 1-1 is subjected to amide condensation with compound [5] in the same manner as in Step 3 of Production Method 1-1 to give compound [7].

Step 2

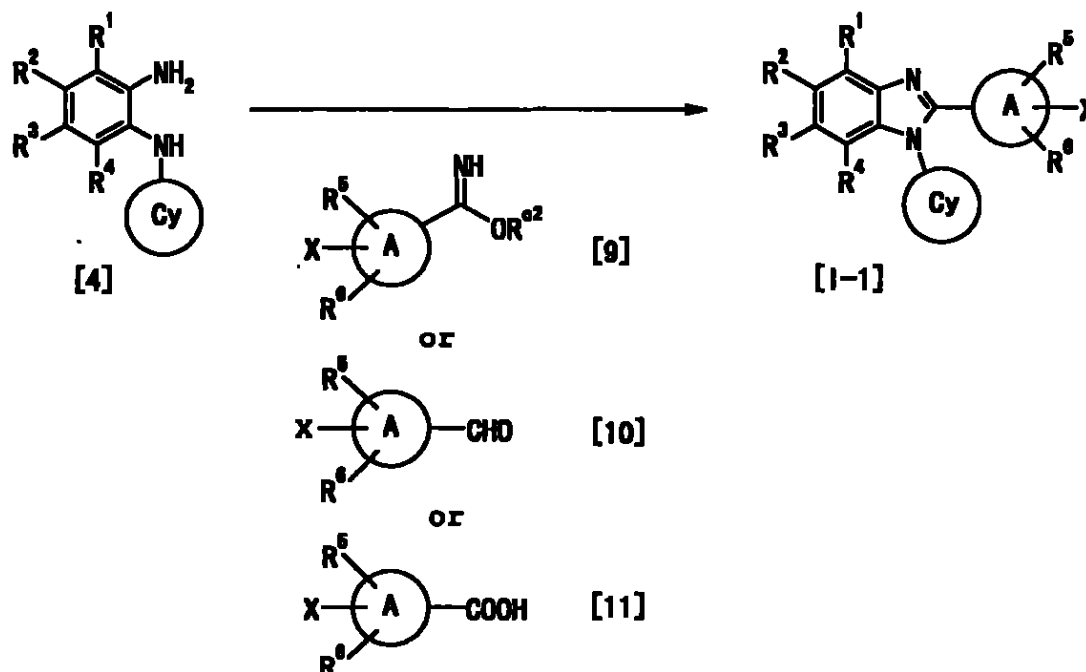
The compound [7] is reduced in the same manner as in Step 2 of Production Method 1-1 to give compound [8].

Step 3

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The compound [8] is subjected to cyclization in the same manner as in Step 4 of Production Method 1-1 to give compound [I-1].

Production Method 1-3



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wherein R^{62} is alkyl such as methyl, ethyl and the like, and other symbols are as defined above.

The compound [4] is reacted with imidate compound [9] in a solvent such as methanol, ethanol, acetic acid, DMF, THF, chloroform and the like at room temperature or with heating to give compound [I-1].

In addition, compound [4] may be reacted with aldehyde compound [10] in a solvent such as acetic acid, formic acid, acetonitrile, DMF, nitrobenzene, toluene and the like in the presence or absence of an oxidizing agent such as benzofuroxan, manganese dioxide, 2,3-dichloro-5,6-dicyano-p-benzoquinone, iodine, potassium ferricyanide and the like with heating to give compound [I-1].

Alternatively, compound [4] and carboxylic acid compound [11] may be heated to allow reaction in the presence of polyphosphoric acid, phosphoric acid, phosphorus oxychloride, hydrochloric acid and the like to give compound [I-1].

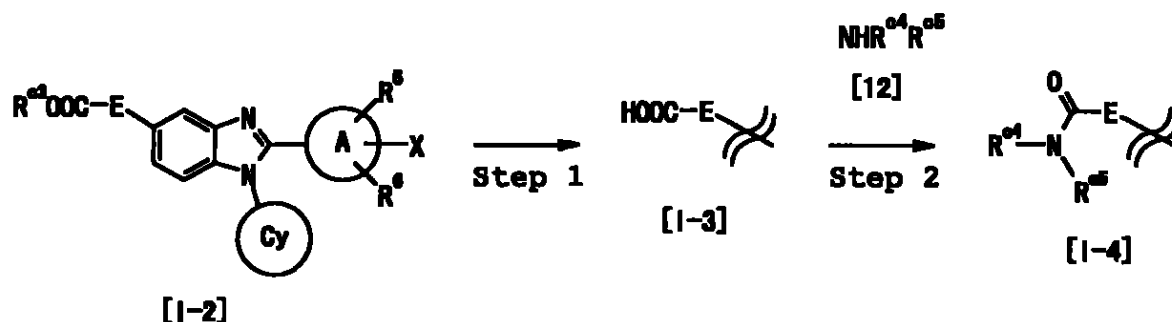
Production Method 2

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In this Production Method, conversion of the substituents (R^1 , R^2 , R^3 , R^4) on the benzene ring of benzimidazole is shown. While a method of converting R^2 when R^1 , R^3 and R^4 are hydrogen atoms is shown, this Production Method is applicable irrespective of the position of substitution.

Production Method 2-1

Conversion of carboxylic acid ester moiety to amide



wherein E is a single bond, $-(\text{CH}_2)_s-$, $-\text{O}-(\text{CH}_2)_s-$ or $-\text{NH}-(\text{CH}_2)_s-$ (wherein s is an integer of 1 to 6), R^{c3} , R^{c4} and R^{c5} are C_{1-6} alkyl, and other symbols are as defined above.

Step 1

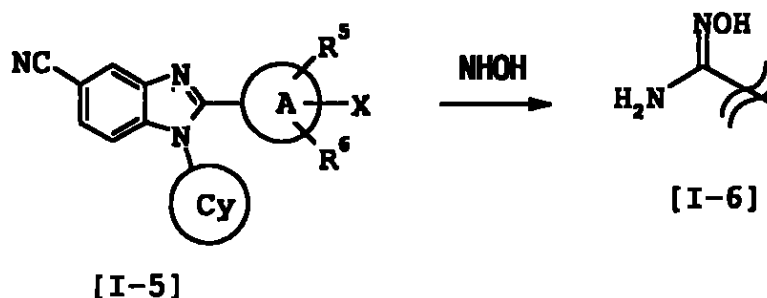
The compound [I-2] obtained in the same manner as in the above-mentioned Production Method is subjected to hydrolysis in a solvent such as methanol, ethanol, THF, dioxane and the like, or in a mixed solvent of these solvents and water under basic conditions with sodium hydroxide, potassium hydroxide, potassium carbonate, lithium hydroxide and the like or under acidic conditions with hydrochloric acid, sulfuric acid and the like to give compound [I-3].

Step 2

The compound [I-3] is reacted with compound [12] in the same manner as in Step 3 of Production Method 1-1 to give compound [I-4].

25 Production Method 2-2

Conversion of cyano group to substituted amidino group



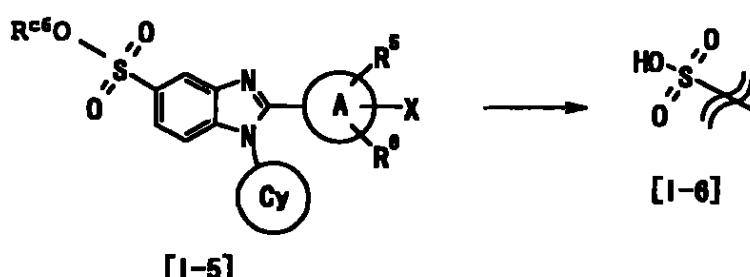
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wherein each symbol is as defined above.

The compound [I-5] obtained in the same manner as in the above-mentioned Production Method is reacted with hydroxylamine in a solvent such as water, methanol, ethanol, THF, DMF and the like to give compound [I-6]. When a salt of hydroxylamine such as hydrochloride and the like is used, the reaction is carried out in the presence of a base such as sodium hydrogencarbonate, sodium hydroxide, triethylamine and the like.

Production Method 2-3

10 Conversion of sulfonic acid ester moiety to sulfonic acid



wherein R^{c6} is C_{1-6} alkyl, and other symbols are as defined above.

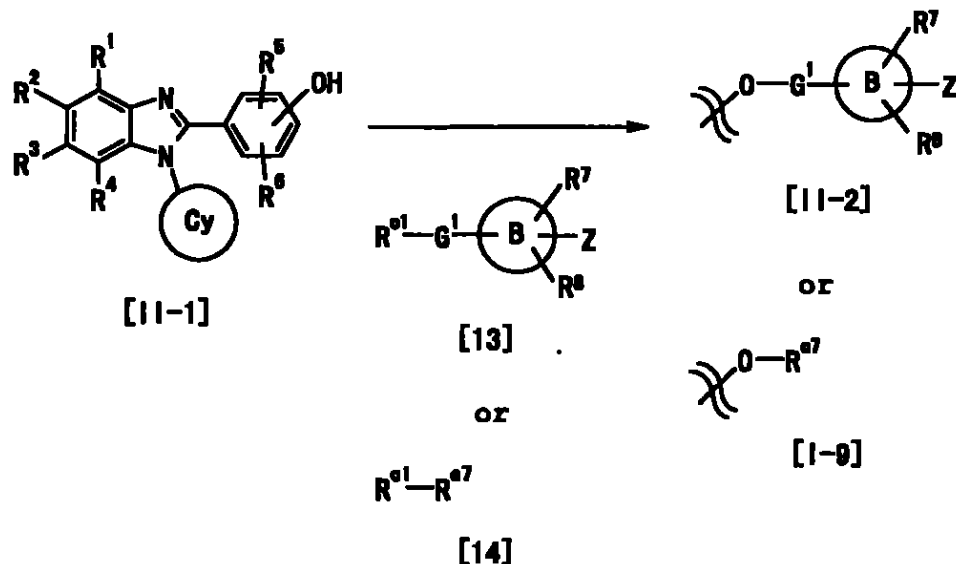
The compound [I-5] obtained in the same manner as in the above-mentioned Production Method is reacted with iodide salt such as sodium iodide, lithium iodide and the like, bromide salt such as sodium bromide, trimethylammonium bromide and the like, amine such as pyridine, trimethylamine, triazole and the like, phosphine such as triphenylphosphine and the like in a solvent such as DMF, dimethyl sulfoxide (DMSO), acetonitrile, methanol, ethanol, water and the like with heating to give compound [I-6].

Production Method 3

This Production Method relates to conversion of the substituent(s) on phenyl group at the 2-position of benzimidazole. This Production Method can be used even when phenyl is a different ring.

Production Method 3-1

Conversion of hydroxyl group to ether



wherein R^{q7} is optionally substituted alkyl corresponding to R^{q11}, G is a single bond, $^{*}-(\text{CH}_2)_n-$, $^{*}-(\text{CH}_2)_n-\text{O}-$, $^{*}-(\text{CH}_2)_n-\text{CO}-$ or $^{*}-(\text{CH}_2)_m-\text{CR}^{\text{q15}}\text{R}^{\text{q16}}-(\text{CH}_2)_n-$, wherein * show the side to be bonded to R^{q1}, and other symbols are as defined above.

When R^{q1} of compound [13] is halogen atom, compound [II-1] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [13] in a solvent such as DMF, DMSO, acetonitrile, ethanol, THF and the like in the presence of a base such as sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium ethoxide, potassium t-butoxide and the like at room temperature or with heating to give compound [II-2].

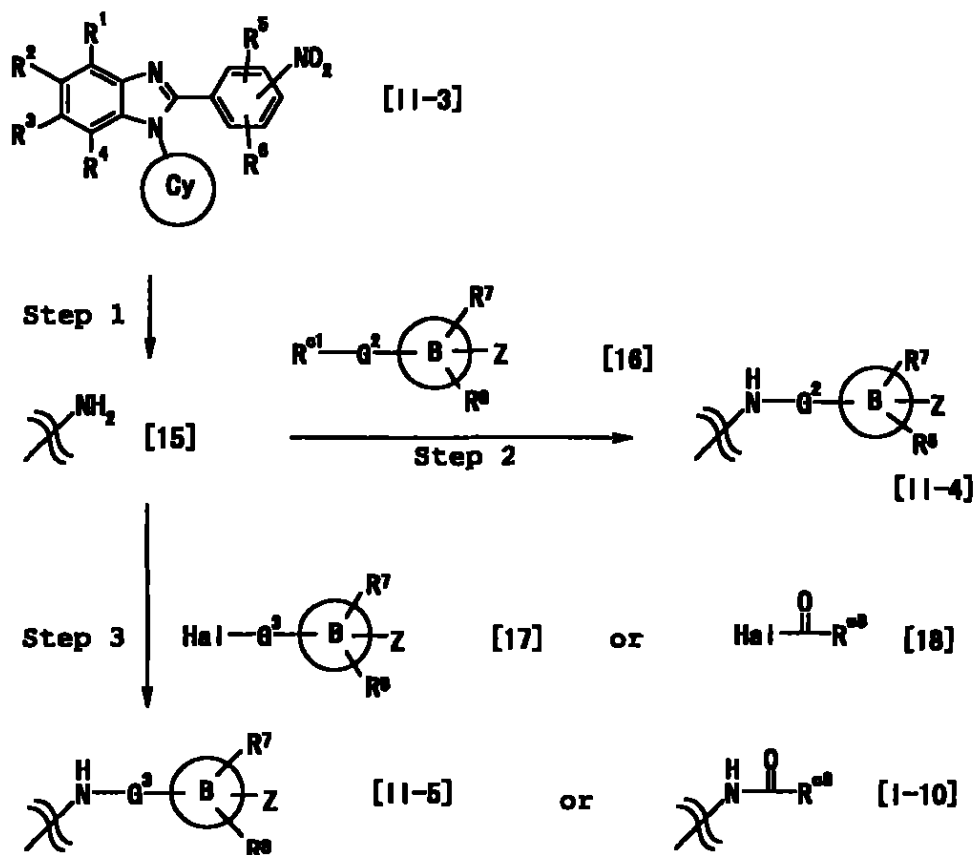
When R^{q1} of compound [13] is hydroxyl group, the hydroxyl group of compound [13] is converted to halogen atom with thionyl chloride, phosphorus tribromide, carbon tetrabromide - triphenylphosphine and the like and reacted with compound [II-1] by the aforementioned method to give compound [II-2]. In this case, compound [II-1] may be subjected to Mitsunobu reaction with compound [13] in a solvent such as DMF, acetonitrile, THF and the like using triphenylphosphine - diethyl azodicarboxylate and the like to give compound [II-2].

The compound [I-9] can be obtained in the same manner from compound [II-1] and compound [14].

Production Method 3-2

Conversion of nitro to substituted amino group

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wherein R^{c8} is C₁₋₆ alkyl, G² is $\text{---}(\text{CH}_2)_n\text{---}$ or $\text{---CHR}^{\text{a15}}\text{---}$, G³ is ---CO--- , $\text{---CO}_2\text{---}$, ---CONH--- or $\text{---SO}_2\text{---}$, and other symbols are as defined above.

Step 1

5 The nitro compound [II-3] obtained in the same manner as in the above-mentioned Production Method is reacted in the same manner as in Step 2 of Production Method 1-1 to give compound [15].

Step 2

10 The compound [15] is alkylated with compound [16] in the same manner as in Production Method 3-1 to give compound [II-4].

Step 3

When G³ of compound [II-4] is ---CO--- , $\text{---CO}_2\text{---}$ or ---CONH--- , compound [15] is acylated with compound [17] in the same manner as in Step 3 of Production Method 1-1 to give compound [II-5].

15 When G³ of compound [II-4] is $\text{---SO}_2\text{---}$, sulfonylation is conducted using sulfonyl halide instead of acid halide used in Step 3 of Production Method 1-1 to give compound [I-10].

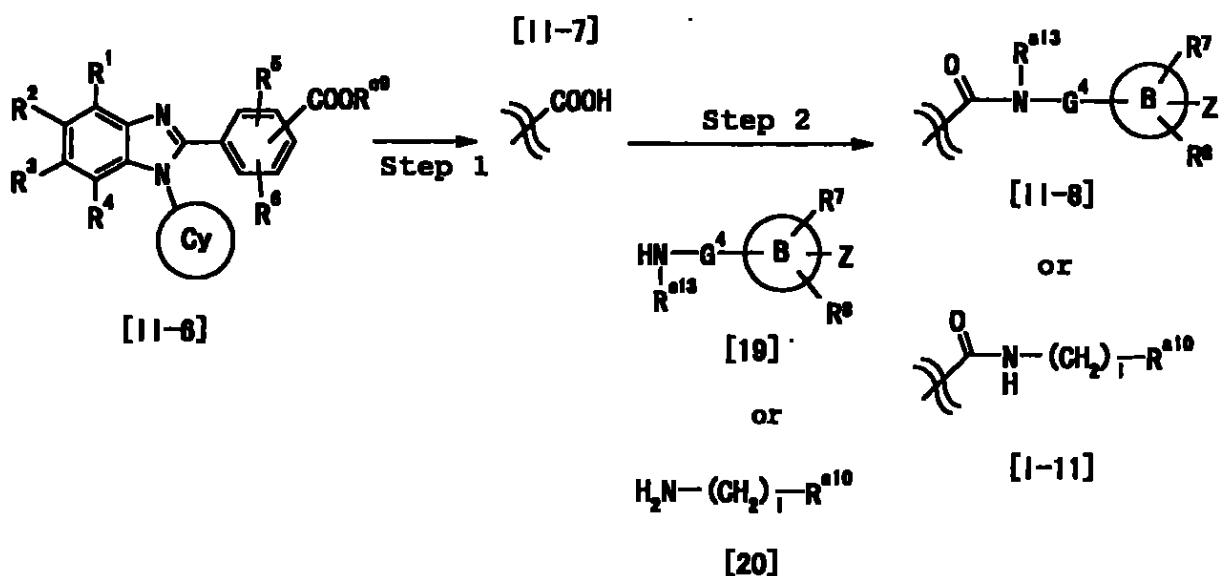
The compound [15] is acylated with compound [18] in the same manner as above to give compound [I-10].

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This Production Method is applied in the same manner as above to give disubstituted compounds (tertiary amine) of compound [II-4], compound [II-5] and compound [I-10].

Production Method 3-3

5 Conversion of carboxylic acid ester moiety to amide



wherein R^{G9} is C_{1-6} alkyl, G^4 is $\#-(CH_2)_n-R^{a10}$, $\#-(CH_2)_n-$, $\#-(CH_2)_n-NH-$ or $\#-CHR^{a14}$ -wherein $\#$ shows the side that is bounded to amine and other symbols are as defined above.

Step 1

The compound [II-6] obtained in the same manner as in the above-mentioned Production Method is reacted in the same manner as in Step 1 of Production Method 2-1 to give compound [II-7].

Step 2

The compound [II-7] is reacted with compound [19] in the same manner as in Step 2 of Production Method 2-1 to give compound [II-8].

The compound [I-11] is obtained from compound [II-7] and compound [20] in the same manner as above.

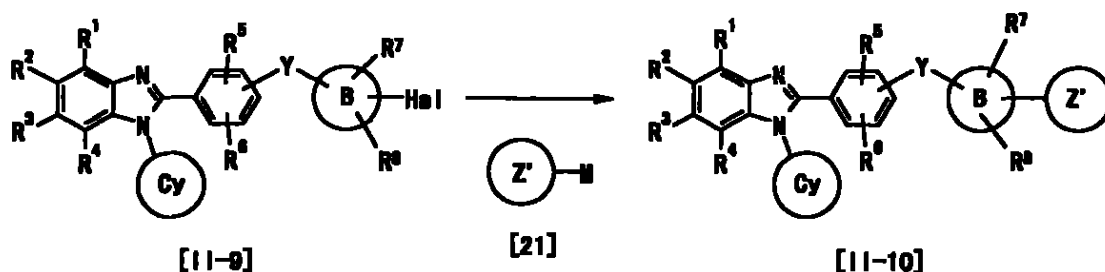
Production Method 4

In this Production Method, additional substituent(s) is(are) introduced into ring B on phenyl group that substitutes the 2-position of benzimidazole. This Production Method is applicable even when phenyl is a different ring.

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Production Method 4-1

Direct bonding of ring Z' to ring B

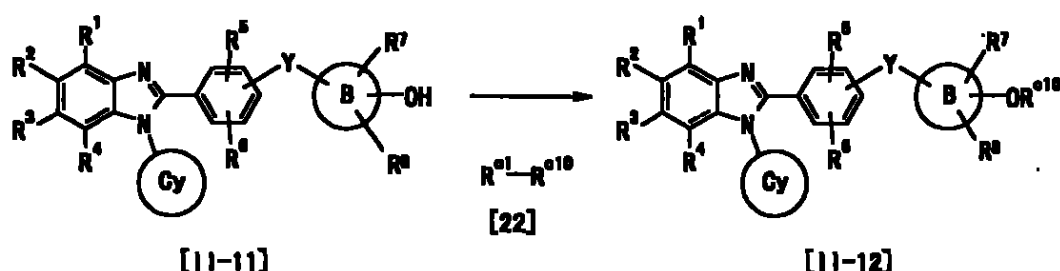


wherein ring Z'-M is aryl metal compound, ring Z' moiety is optionally substituted C₆₋₁₄ aryl or optionally substituted heterocyclic group corresponding to substituent Z, and the metal moiety is boron, zinc, tin or magnesium, and other symbols are as defined above.

The compound [II-9] obtained in the same manner as in the above-mentioned Production Method is reacted with aryl metal compound [21] in a solvent such as DMF, acetonitrile, 1,2-dimethoxyethane, THF, toluene, water and the like in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) dichloride, palladium acetate - triphenylphosphine and the like, a nickel catalyst such as nickel chloride, [1,3-bis(diphenylphosphino)propane]nickel(II) chloride and the like, and a base such as potassium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate, potassium phosphate, triethylamine and the like at room temperature or with heating, to give compound [II-10].

Production Method 4-2

Conversion of hydroxyl group to ether



wherein R^{a2} is -R^{a20} or -(CH₂)_p-COR^{a21} corresponding to substituent Z, and other symbols are as defined above.

The compound [II-11] obtained in the same manner as in the above-mentioned Production Method is reacted with compound [22] in

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the same manner as in Production Method 2-1 to give compound [II-12].

5 The compounds of the formulas [I] and [II], and production methods thereof of the present invention are explained in detail in the following by way of Examples. It is needless to say that the present invention is not limited by these Examples.

Example 1

Production of ethyl 1-cyclohexyl-2-[4-(3-bromophenoxy)phenyl]-benzimidazole-5-carboxylate

10 **Step 1: Production of ethyl 4-chloro-3-nitrobenzoate**

4-Chloro-3-nitrobenzoic acid (300 g) was dissolved in ethyl alcohol (1500 ml) and concentrated sulfuric acid (100 ml) was added with ice-cooling. The mixture was refluxed under heating for 7 hr. The reaction mixture was poured into ice-cold water and the precipitated crystals were collected by filtration to give the title compound (332 g, yield 97%).

¹H-NMR (300MHz, CDCl₃): 8.50(1H, d, J=2.1Hz), 8.16(1H, dd, J=8.4, 2.1Hz), 7.63(1H, d, J=8.4Hz), 4.43(2H, q, J=7.5Hz), 1.42(3H, t, J=7.5Hz)

20 **Step 2: Production of ethyl 4-cyclohexylamino-3-nitrobenzoate**

Ethyl 4-chloro-3-nitrobenzoate (330 g) obtained in the previous step was dissolved in acetonitrile (1500 ml), and cyclohexylamine (220 g) and triethylamine (195 g) were added. The mixture was refluxed under heating overnight. The reaction mixture was poured into ice-cold water and the precipitated crystals were collected by filtration to give the title compound (400 g, yield 94%).

25 ¹H-NMR (300MHz, CDCl₃): 8.87(1H, d, J=2.1Hz), 8.35-8.46(1H, m), 8.02(1H, dd, J=9.1, 2.1Hz), 6.87(1H, d, J=9.1Hz), 4.35(2H, q, J=7.1Hz), 3.65-3.50(1H, m), 2.14-1.29(10H, m), 1.38(3H, t, J=7.1Hz)

30 **Step 3: Production of ethyl 3-amino-4-cyclohexylaminobenzoate**

Ethyl 4-cyclohexylamino-3-nitrobenzoate (400 g) obtained in the previous step was dissolved in ethyl acetate (1500 ml) and ethyl alcohol (500 ml), and 7.5% palladium carbon (50% wet, 40 g) was added. The mixture was hydrogenated for 7 hr at atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. Diisopropyl ether was added

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to the residue and the precipitated crystals were collected by filtration to give the title compound (289 g, yield 80%).

¹H-NMR (300MHz, CDCl₃): 7.57(1H, dd, J=8.4, 1.9Hz), 7.41(1H, d, J=1.9Hz), 6.59(1H, d, J=8.4Hz), 4.30(2H, q, J=7.1Hz), 3.40-3.30(1H, m), 2.18-2.02(2H, m), 1.88-1.15(8H, m), 1.35(3H, t, J=7.1Hz)

Step 4: Production of ethyl 3-[4-(3-bromophenoxy)benzoyl]amino-4-cyclohexylaminobenzoate

4-(3-Bromophenoxy)benzoic acid (74 g) was dissolved in chloroform (500 ml), and oxalyl chloride (33 ml) and dimethylformamide (catalytic amount) were added. The mixture was stirred for 4 hr at room temperature. The reaction mixture was concentrated under reduced pressure and dissolved in dichloromethane (150 ml). The resulting solution was added dropwise to a solution of ethyl 3-amino-4-cyclohexylaminobenzoate (66 g) obtained in the previous step in dichloromethane (500 ml) and triethylamine (71 ml), and the mixture was stirred for 1 hr at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the residue for crystallization and the crystals were collected by filtration to give the title compound (129 g, yield 95%).

¹H-NMR (300MHz, CDCl₃): 8.00-7.78(4H, m), 7.66(1H, brs), 7.37-7.18(3H, m), 7.13-6.59(3H, m), 6.72(1H, d, J=8.7Hz), 4.50(1H, brs), 4.29(2H, q, J=7.2Hz), 3.36(1H, m), 2.12-1.96(2H, m), 1.83-1.56(3H, m), 1.47-1.12(5H, m), 1.37(3H, t, J=7.2Hz)

Step 5: Production of ethyl 2-[4-(3-bromophenoxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 3-[4-(3-bromophenoxy)benzoyl]amino-4-cyclohexylaminobenzoate (129 g) obtained in the previous step was suspended in acetic acid (600 ml) and the resulting suspension was refluxed under heating for 3 hr. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the precipitated crystals were collected by filtration to give the title compound (124 g, yield 99%).

¹H-NMR (300MHz, CDCl₃): 8.51(1H, d, J=1.5Hz), 8.00(1H, dd, J=8.4, 1.5Hz), 7.67(1H, d, J=8.4Hz), 7.63(2H, d, J=8.7Hz), 7.35-7.21(3H, m), 7.17(2H, d, J=8.7Hz), 7.14(1H, m), 4.42(2H, q, J=7.2Hz),

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675

4.38 (1H, m), 2.43-2.22 (2H, m), 2.07-1.87 (4H, m), 1.80 (1H, m),
1.42 (3H, t, J=7.2Hz), 1.40-1.27 (3H, m)

Example 2

5 Production of 2-[4-(3-bromophenoxy)phenyl]-1-cyclohexyl-
benzimidazole-5-carboxylic acid

Ethyl 2-[4-(3-bromophenoxy)phenyl]-1-cyclohexyl-
benzimidazole-5-carboxylate (1.0 g) obtained in Example 1 was
dissolved in tetrahydrofuran (10 ml) and ethyl alcohol (10 ml),
and 4N sodium hydroxide (10 ml) was added. The mixture was
10 refluxed under heating for 1 hr. The reaction mixture was
concentrated under reduced pressure and water was added to the
residue. The mixture was acidified with 6N hydrochloric acid and
the precipitated crystals were collected by filtration to give the
title compound (0.9 g, yield 96%).

15 melting point: 255-256°C

FAB-MS: 491 (MH+)

¹H-NMR (300MHz, DMSO-d₆): (12.75 (1H, brs), 8.24 (1H, s), 7.96 (1H, d,
J=8.7Hz), 7.86 (1H, d, J=8.7Hz), 7.71 (2H, d, J=8.6Hz), 7.47-7.34 (3H,
m), 7.24 (2H, d, J=8.6Hz), 7.20 (1H, m), 4.31 (1H, m), 2.38-2.18 (2H,
20 m), 2.02-1.79 (4H, m), 1.65 (1H, m), 1.44-1.20 (3H, m)

Example 3

Production of ethyl 1-cyclohexyl-2-(4-hydroxyphenyl)benzimidazole-
5-carboxylate

Ethyl 3-amino-4-cyclohexylaminobenzoate (130 g) obtained in
25 Example 1, Step 3, and methyl 4-hydroxybenzimidate hydrochloride
(139 g) were added to methyl alcohol (1500 ml), and the mixture
was refluxed under heating for 4 hr. The reaction mixture was
allowed to cool and the precipitated crystals were collected by
filtration to give the title compound (131 g, yield 72%).

30 ¹H-NMR (300MHz, CDCl₃): 10.02 (1H, brs), 8.21 (1H, d, J=1.4Hz),
7.93 (1H, d, J=8.6Hz), 7.83 (1H, dd, J=8.6, 1.4Hz), 7.48 (2H, d,
J=8.6Hz), 6.95 (2H, d, J=8.6Hz), 4.39-4.25 (1H, m), 4.33 (1H, q,
J=7.0Hz), 2.35-2.18 (2H, m), 1.98-1.79 (4H, m), 1.70- 1.60 (1H, m),
1.46-1.19 (3H, m), 1.35 (3H, t, J=7.0Hz)

35 Example 4

Production of ethyl 2-[4-(2-bromo-5-chlorobenzyloxy)phenyl]-1-
cyclohexylbenzimidazole-5-carboxylate

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2-Bromo-5-chlorobenzyl bromide prepared from 2-bromo-5-chlorotoluene (50 g), N-bromosuccinimide and N,N'-azobisisobutyronitrile, and ethyl 1-cyclohexyl-2-(4-hydroxyphenyl)benzimidazole-5-carboxylate (50 g) obtained in

5 Example 3 were suspended in dimethylformamide (300 ml). Potassium carbonate (38 g) was added and the mixture was stirred for 1 hr at 80°C with heating. The reaction mixture was allowed to cool and then added to a mixed solvent of water-ethyl acetate. The precipitated crystals were collected by filtration to give the

10 title compound (50 g, yield 64%).

¹H-NMR (300MHz, CDCl₃): 8.50 (1H, d, J=1.4Hz), 7.97 (1H, dd, J=8.6, 1.4Hz), 7.70-7.57 (5H, m), 7.20 (1H, dd, J=8.4, 2.5Hz), 7.14 (2H, d, J=8.7Hz), 5.17 (2H, s), 4.46-4.30 (1H, m), 4.41 (2H, q, J=7.1Hz), 2.40-2.20 (2H, m), 2.02-1.21 (8H, m), 1.42 (3H, t, J=7.1Hz)

15 **Example 5**

Production of ethyl 2-{4-[2-(4-chlorophenyl)-5-chlorobenzoyloxy]-phenyl}-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 2-[4-(2-bromo-5-chlorobenzoyloxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate (49 g) obtained in Example 4,

20 4-chlorophenylboronic acid (18 g) and tetrakis-(triphenylphosphine)palladium (10 g) were suspended in 1,2-dimethoxyethane (600 ml). Saturated aqueous sodium hydrogencarbonate solution (300 ml) was added and the mixture was refluxed under heating for 2 hr. Chloroform was added to the

25 reaction mixture. The organic layer was washed successively with saturated aqueous sodium hydrogencarbonate solution, water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (developing solvent,

30 chloroform:ethyl acetate = 97:3). Ethyl acetate and diisopropyl ether were added to the resulting oil for crystallization and the resulting crystals were collected by filtration to give the title compound (44 g, yield 85%).

¹H-NMR (300MHz, CDCl₃): 8.49 (1H, d, J=1.4Hz), 7.97 (1H, dd, J=8.6, 1.6Hz), 7.70-7.60 (2H, m), 7.55 (2H, d, J=8.7Hz), 4.95 (2H, s), 4.48-4.28 (1H, m), 4.40 (2H, m), 2.02-1.20 (8H, m), 1.41 (3H, t, J=7.1Hz)

35 **Example 6**

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Production of 2-{4-[2-(4-chlorophenyl)-5-chlorobenzyloxy]phenyl}-1-cyclohexylbenzimidazole-5-carboxylic acid

Ethyl 2-{4-[2-(4-chlorophenyl)-5-chlorobenzyloxy]phenyl}-1-cyclohexylbenzimidazole-5-carboxylate (43 g) obtained in Example 5 was treated in the same manner as in Example 2 to give the title compound (33 g, yield 76%).

melting point: 243-244°C

FAB-MS: 571(MH+)

¹H-NMR (300MHz, DMSO-d₆): 8.32(1H, s), 8.28(1H, d, J=8.9Hz), 8.05(1H, d, J=8.8Hz), 7.76-7.72(3H, m), 7.58-7.46(5H, m), 7.40(1H, d, J=8.3Hz), 7.24(2H, d, J=8.9Hz), 5.11(2H, s), 4.36(1H, m), 2.40-2.15(2H, m), 2.15-1.95(2H, m), 1.95-1.75(2H, m), 1.75-1.55(1H, m), 1.55-1.15(3H, m)

Example 7

Production of ethyl 2-[4-(2-bromo-5-methoxybenzyloxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 1-cyclohexyl-2-(4-hydroxyphenyl)benzimidazole-5-carboxylate obtained in Example 3 and 2-bromo-5-methoxybenzyl bromide were treated in the same manner as in Example 4 to give the title compound (59 g).

Example 8

Production of ethyl 2-{4-[2-(4-chlorophenyl)-5-methoxybenzyloxy]phenyl}-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 2-[4-(2-bromo-5-methoxybenzyloxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate obtained in Example 7 was treated in the same manner as in Example 5 to give the title compound (48 g, yield 77%).

¹H-NMR (300MHz, CDCl₃): 8.49(1H, d, J=1.4Hz), 7.97(1H, dd, J=8.6, 1.4Hz), 7.64(1H, d, J=8.6Hz), 7.54(2H, d, J=8.7Hz), 7.37(2H, d, J=8.6Hz), 7.31(2H, d, J=8.6Hz), 7.25(1H, d, J=8.4Hz), 7.19(1H, d, J=2.7Hz), 7.00(2H, d, J=8.7Hz), 6.97(1H, dd, J=8.4, 2.7Hz), 4.98(2H, s), 4.41(2H, q, J=7.1Hz), 4.42-4.29(1H, m), 3.88(3H, s), 2.40-2.20(2H, m), 2.01-1.88(4H, m), 1.83-1.73(1H, m), 1.42(3H, t, J=7.1Hz), 1.41-1.25(3H, m)

Example 9

Production of 2-{4-[2-(4-chlorophenyl)-5-methoxybenzyloxy]phenyl}-1-cyclohexylbenzimidazole-5-carboxylic acid

Ethyl 2-(4-[2-(4-chlorophenyl)-5-methoxybenzyloxy]phenyl)-1-cyclohexylbenzimidazole-5-carboxylate (52 g) obtained in Example 8 was treated in the same manner as in Example 2 to give the title compound (44 g, yield 89%).

5 melting point: 248-249°C

FAB-MS: 568 (MH⁺)

¹H-NMR (300MHz, DMSO-d₆): 8.20 (1H, s), 7.88 (1H, d, J=8.7Hz), 7.85 (1H, d, J=8.7Hz), 7.57 (d, 2H, J=8.6Hz), 7.46 (2H, d, J=8.6Hz), 7.44 (2H, d, J=8.6Hz), 7.29 (1H, d, J=8.5Hz), 7.24 (1H, d, J=2.6Hz), 10 7.11 (2H, d, J=8.6Hz), 7.06 (1H, dd, J=8.5, 2.6Hz), 5.04 (2H, s), 4.26 (1H, m), 3.83 (3H, s), 2.38-2.29 (2H, m)

Example 10

Production of ethyl 1-cyclohexyl-2-(4-[(E)-2-phenylvinyl]phenyl)-benzimidazole-5-carboxylate

15 Ethyl 3-amino-4-cyclohexylaminobenzoate (500 mg) obtained in Example 1, Step 3, was dissolved in methyl alcohol (6 ml) and trans-4-stilbenecarbaldehyde (397 mg) was added under ice-cooling. The mixture was stirred overnight at room temperature. The reaction mixture was ice-cooled and benzofuroxan (259 mg)
20 dissolved in acetonitrile (2 ml) was added. The mixture was stirred for 7 hr at 50°C. The reaction mixture was ice-cooled. After 1N sodium hydroxide was added, ethyl acetate was added and the mixture was extracted. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate,
25 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (developing solvent, n-hexane:ethyl acetate = 4:1) to give the title compound (540 mg, yield 63%).

¹H-NMR (300MHz, DMSO-d₆): 8.28 (1H, d, J=1.4Hz), 8.01 (1H, d, J=8.7Hz), 7.90-7.80 (3H, m), 7.75-7.65 (4H, m), 7.50-7.25 (5H, m), 4.35 (2H, q, J=7.0Hz), 4.31 (1H, m), 2.40-2.20 (2H, m), 2.00-1.80 (4H, m), 1.63 (1H, m), 1.40-1.20 (3H, m), 1.36 (3H, t, J=7.0Hz)

Example 11

35 Production of 1-cyclohexyl-2-(4-[(E)-2-phenylvinyl]phenyl)-benzimidazole-5-carboxylic acid

Ethyl 1-cyclohexyl-2-(4-[(E)-2-phenylvinyl]phenyl)-benzimidazole-5-carboxylate (127 mg) obtained in Example 10 was

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treated in the same manner as in Example 2 to give the title compound (116 mg, yield 97%).

melting point: not lower than 300°C

FAB-MS: 423 (MH+)

5 ¹H-NMR (300MHz, DMSO-d₆): 8.25 (1H, s), 7.96-7.29 (13H, m), 4.33 (1H, brt), 2.41-2.23 (2H, m), 2.03-1.78 (4H, m), 1.71-1.59 (1H, m), 1.49-1.20 (3H, m)

Example 12

10 Production of 2-(4-benzyloxyphenyl)-1-cyclopentylbenzimidazole-5-carboxylic acid

In the same manner as in Examples 1 and 2, the title compound (700 mg) was obtained.

FAB-MS: 413 (MH+)

15 ¹H-NMR (300MHz, CDCl₃): 8.60 (1H, s), 8.04 (1H, d, J=9.0Hz), 7.63 (2H, d, J=8.4Hz), 7.51-7.32 (6H, m), 7.14 (2H, d, J=9.0Hz), 5.16 (2H, s), 5.03-4.89 (1H, m), 2.41-1.63 (8H, m)

Example 13

Production of 1-cyclopentyl-2-(4-benzyloxyphenyl)benzimidazole-5-carboxamide

20 2-(4-Benzyloxyphenyl)-1-cyclopentylbenzimidazole-5-carboxylic acid (700 mg) obtained in Example 12 was dissolved in dimethylformamide (10 ml), and ammonium chloride (108 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (390 mg), 1-hydroxybenzotriazole (275 mg) and triethylamine (0.3 ml) were
25 added. The mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogencarbonate, water and saturated brine, dried over anhydrous magnesium sulfate,
30 and concentrated under reduced pressure. Ethyl acetate and diisopropyl ether were added to the residue for crystallization and the crystals were collected by filtration to give the title compound (571 mg, yield 81%).

melting point: 232-233°C

35 FAB-MS: 412 (MH+)

¹H-NMR (300MHz, CDCl₃): 8.23 (1H, d, J=1.5Hz), 7.86 (1H, dd, J=8.5, 1.5Hz), 7.65-7.30 (8H, m), 7.13 (2H, d, J=8.8Hz), 5.16 (2H, s), 4.93 (1H, quint, J=8.8Hz), 2.40-1.60 (8H, m)

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Example 14

Production of 2-(4-benzyloxyphenyl)-5-cyano-1-cyclopentylbenzimidazole

In the same manner as in Example 1, the title compound (400 mg) was obtained.

FAB-MS: 394 (MH⁺)

¹H-NMR (300MHz, CDCl₃): 8.11 (1H, s), 7.68-7.30 (9H, m), 7.13 (2H, s), 5.16 (2H, s), 4.94 (1H, quint, J=8.9Hz), 2.35-1.60 (8H, m)

Example 15

Production of 2-(4-benzyloxyphenyl)-1-cyclopentylbenzimidazole-5-carboxamide oxime

2-(4-Benzyloxyphenyl)-5-cyano-1-cyclopentylbenzimidazole (400 mg) obtained in Example 14 was suspended in ethyl alcohol (3 ml) and water (1.5 ml), and hydroxylamine hydrochloride (141 mg) and sodium hydrogencarbonate (170 mg) were added. The mixture was refluxed under heating overnight. The reaction mixture was allowed to cool and the precipitated crystals were collected by filtration to give the title compound (312 mg, yield 71%).

melting point: 225-226°C

FAB-MS: 456 (MH⁺)

¹H-NMR (300MHz, DMSO-d₆): 8.20 (1H, s), 7.50-7.31 (9H, m), 7.12 (2H, d, J=8.7Hz), 5.15 (2H, s), 4.94 (1H, quint, J=8.7Hz), 3.61 (3H, s), 3.40 (3H, s), 2.41-1.42 (8H, m)

Example 16

Production of ethyl 1-cyclohexyl-2-(4-[(4-(4-fluorophenyl)-2-methyl-5-thiazolyl)methoxy]phenyl)benzimidazole-5-carboxylate
Step 1: Production of 4-(4-fluorophenyl)-5-hydroxymethyl-2-methylthiazole

Ethyl 4-(4-fluorophenyl)-2-methyl-5-thiazolecarboxylate (59 g) prepared by a known method (Chem. Pharm. Bull., 43(6), 947, 1995) was dissolved in tetrahydrofuran (700 ml). Lithium aluminum hydride (13 g) was added under ice-cooling and the mixture was stirred for 30 min. Water (13 ml), 15% sodium hydroxide (13 ml) and water (39 ml) were added successively to the reaction mixture, and the precipitated insoluble materials were filtered off. The filtrate was concentrated under reduced pressure to give the title compound (37 g, yield 71%).

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¹H-NMR (300MHz, CDCl₃): 7.60 (2H, dd, J=8.7, 6.6Hz), 7.11 (2H, t, J=8.7Hz), 4.80 (2H, s), 2.70 (3H, s)

Step 2: Production of 5-chloromethyl-4-(4-fluorophenyl)-2-methylthiazole

5 4-(4-Fluorophenyl)-5-hydroxymethyl-2-methylthiazole (37 g) obtained in the previous step was dissolved in chloroform (500 ml), and thionyl chloride (24 ml) and pyridine (2 ml) were added. The mixture was stirred for 3 hr at room temperature. The reaction mixture was poured into ice-cold water. The mixture was extracted
10 with chloroform, and washed with water and saturated brine. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure to give the title compound (29 g, yield 76%).

15 ¹H-NMR (300MHz, CDCl₃): 7.67 (2H, dd, J=8.8, 5.4Hz), 7.16 (2H, t, J=8.7Hz), 4.79 (2H, s), 2.73 (3H, s)

Step 3: Production of ethyl 1-cyclohexyl-2-(4-[(4-(4-fluorophenyl)-2-methyl-5-thiazolyl)methoxy]phenyl)benzimidazole-5-carboxylate

20 5-Chloromethyl-4-(4-fluorophenyl)-2-methylthiazole (28 g) obtained in the previous step and ethyl 1-cyclohexyl-2-(4-hydroxyphenyl)benzimidazole-5-carboxylate (36 g) obtained in Example 3 were treated in the same manner as in Example 4 to give the title compound (61 g, yield 100%).

APCI-MS: 570 (MH⁺)

25 ¹H-NMR (300MHz, DMSO-d₆): 8.25 (1H, d, J=1.5Hz), 7.97 (1H, d, J=8.7Hz), 7.86 (1H, dd, J=8.6, 1.6Hz), 7.74 (2H, dd, J=8.8, 5.5Hz), 7.62 (2H, d, J=8.7Hz), 7.33 (2H, t, J=8.9Hz), 7.22 (2H, t, J=8.9Hz), 5.41 (2H, s), 4.34 (2H, q, J=7.1Hz), 4.31 (1H, m), 2.71 (3H, s), 2.40-2.15 (2H, m), 2.05-1.75 (4H, m), 1.55-1.15 (3H, m), 1.36 (3H, t,
30 J=7.1Hz)

Example 17

Production of 1-cyclohexyl-2-(4-[(4-(4-fluorophenyl)-2-methyl-5-thiazolyl)methoxy]phenyl)benzimidazole-5-carboxylic acid

35 Ethyl 1-cyclohexyl-2-(4-[(4-(4-fluorophenyl)-2-methyl-5-thiazolyl)methoxy]phenyl)benzimidazole-5-carboxylate (60 g) obtained in Example 16 was treated in the same manner as in Example 2 to give the title compound (39g, yield 69%).

melting point: 196-198°C

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FAB-MS: 542 (MH⁺)

¹H-NMR (300MHz, DMSO-d₆): 13.1 (1H, brs), 8.34 (1H, s), 8.29 (1H, d, J=8.8Hz), 8.06 (1H, d, J=8.7Hz), 7.80-7.72 (4H, m), 7.36-7.31 (4H, m), 5.46 (2H, s), 4.38 (1H, m), 2.72 (3H, s), 2.45-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m)

Example 18

Production of ethyl 1-cyclohexyl-2-(2-fluoro-4-hydroxyphenyl)-benzimidazole-5-carboxylate

In the same manner as in Example 3, the title compound (50 g) was obtained.

Example 19

Production of ethyl 2-(4-[bis(3-fluorophenyl)methoxy]-2-fluorophenyl)-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 1-cyclohexyl-2-(2-fluoro-4-hydroxyphenyl)-benzimidazole-5-carboxylate (50 g) obtained in Example 18 and 3,3'-difluorobenzhydryl chloride (34 g) were treated in the same manner as in Example 4 to give the title compound (76 g, yield 99%).

FAB-MS: 585 (MH⁺)

¹H-NMR (300MHz, DMSO-d₆): 8.24 (1H, d, J=1.4Hz), 7.98 (1H, d, J=8.7Hz), 7.88 (1H, d, J=8.7Hz), 7.56 (1H, t, J=8.6Hz), 7.50-7.40 (6H, m), 6.82 (1H, s), 4.34 (2H, q, J=7.1Hz), 3.95 (1H, m), 2.20-2.10 (2H, m), 1.90-1.80 (4H, m), 1.6 (1H, m), 1.35 (3H, t, J=7.2Hz), 1.30-1.20 (3H, m)

Example 20

Production of 2-(4-(bis[3-fluorophenyl]methoxy)-2-fluorophenyl)-1-cyclohexylbenzimidazole-5-carboxylic acid

Ethyl 2-(4-[bis(3-fluorophenyl)methoxy]-2-fluorophenyl)-1-cyclohexylbenzimidazole-5-carboxylate (75 g) obtained in Example 19 was treated in the same manner as in Example 2 to give the title compound (48 g, yield 62%).

melting point: 242-243°C

FAB-MS: 557 (MH⁺)

¹H-NMR (300MHz, DMSO-d₆): 8.29 (1H, s), 8.16 (1H, d, J=8.8Hz), 7.99 (1H, d, J=8.7Hz), 7.66 (1H, t, J=8.7Hz), 7.51-7.40 (6H, m), 7.30 (1H, d, J=12.1Hz), 7.20-7.14 (3H, m), 6.88 (1H, s), 4.07 (1H, m), 2.40-2.10 (2H, m), 2.00-1.75 (4H, m), 1.70-1.55 (1H, m), 1.50-1.15 (3H, m)

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Example 21

Production of ethyl 1-cyclopentyl-2-(4-nitrophenyl)benzimidazole-5-carboxylate

In the same manner as in Example 1, the title compound (12 g) was obtained.

Example 22

Production of ethyl 1-cyclopentyl-2-(4-aminophenyl)benzimidazole-5-carboxylate

Ethyl 1-cyclopentyl-2-(4-nitrophenyl)benzimidazole-5-carboxylate (12 g) obtained in Example 21 was dissolved in tetrahydrofuran (200 ml) and ethyl alcohol (50 ml), 7.5% palladium carbon (50% wet, 1 g) was added. The mixture was hydrogenated for 1 hr at atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. Tetrahydrofuran was added to the residue to allow crystallization and the crystals were collected by filtration to give the title compound (11 g, yield 98%).

¹H-NMR (300MHz, CDCl₃): 8.49(1H, d, J=1.3Hz), 7.95(1H, dd, J=8.5, 1.3Hz), 7.50-7.40(3H, m), 6.79(2H, d, J=4.6Hz), 4.97(1H, quint, J=8.9Hz), 4.40(2H, q, J=7.1Hz), 3.74(2H, brs), 2.40-1.60(8H, m), 1.41(3H, t, J=7.1Hz)

Example 23

Production of ethyl 2-(4-benzoylaminophenyl)-1-cyclopentylbenzimidazole-5-carboxylate

Ethyl 1-cyclopentyl-2-(4-aminophenyl)benzimidazole-5-carboxylate (300 mg) obtained in Example 22 was dissolved in pyridine (3 ml) and chloroform (3 ml), and benzoyl chloride (127 mg) was added. The mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure and water was added to the residue to allow crystallization. The crystals were collected by filtration to give the title compound (403 mg, yield 100%).

¹H-NMR (300MHz, CDCl₃): 8.58(1H, s), 8.00(1H, d, J=9.0Hz), 7.84(2H, d, J=7.5Hz), 7.60-7.40(6H, m), 7.14(2H, d, J=7.5Hz), 4.84(1H, quint, J=8.7Hz), 4.41(2H, q, J=7.5Hz), 2.20-1.30(8H, m), 1.41(3H, t, J=7.5Hz)

Example 24

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Production of 2-(4-benzoylamino-phenyl)-1-cyclopentylbenzimidazole-5-carboxylic acid

Ethyl 2-(4-benzoylamino-phenyl)-1-cyclopentylbenzimidazole-5-carboxylate (200 mg) obtained in Example 23 was treated in the same manner as in Example 2 to give the title compound (131 mg, yield 70%).

melting point: not lower than 300°C

FAB-MS: 426 (MH+)

¹H-NMR (300MHz, DMSO-d₆): 10.75 (1H, s), 8.35 (1H, s), 8.15 and 7.85 (4H, ABq, J=8.9Hz), 8.10-7.98 (4H, m), 7.70-7.55 (3H, m), 5.02 (1H, quint, J=8.7Hz), 2.36-2.15 (4H, m), 2.14-1.95 (2H, m), 1.80-1.62 (2H, m)

Example 25

Production of ethyl 2-[4-[3-(3-chlorophenyl)phenoxy]phenyl]-1-cyclohexylbenzimidazole-5-carboxylate

Ethyl 2-[4-(3-bromophenoxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate (65 g) obtained in Example 1 and 3-chlorophenylboronic acid (23 g) were treated in the same manner as in Example 5 to give the title compound (59 g, yield 85%).

¹H-NMR (300MHz, CDCl₃): 8.51 (1H, d, J=1.8Hz), 7.99 (1H, dd, J=8.7, 1.8Hz), 7.71-7.55 (4H, m), 7.51-7.43 (2H, m), 7.43-7.27 (4H, m), 7.19 (1H, d, J=8.4Hz), 7.12 (1H, m), 4.41 (2H, q, J=7.2Hz), 4.39 (1H, m), 2.42-2.22 (2H, m), 2.03-1.87 (4H, m), 1.79 (1H, m), 1.42 (3H, t, J=7.2Hz), 1.39-1.29 (3H, m)

Example 26

Production of 2-[4-[3-(3-chlorophenyl)phenoxy]phenyl]-1-cyclohexylbenzimidazole-5-carboxylic acid

Ethyl 2-[4-[3-(3-chlorophenyl)phenoxy]phenyl]-1-cyclohexylbenzimidazole-5-carboxylate (59 g) obtained in Example 25 was treated in the same manner as in Example 2 to give the title compound (43 g, yield 76%).

melting point: 253-254°C

FAB-MS: 523 (MH+)

¹H-NMR (300MHz, DMSO-d₆): 12.82 (1H, brs), 8.24 (1H, d, J=1.3Hz), 7.98 (1H, d, J=8.7Hz), 7.89 (1H, dd, J=8.7, 1.3Hz), 7.78 (1H, s), 7.72 (2H, d, J=9.7Hz), 7.70 (1H, m), 7.64-7.42 (5H, m), 7.25 (2H, d,

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at
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J=8.7Hz), 7.20(1H, m), 4.33(1H, m), 2.39-2.17(2H, m), 2.00-1.76(4H, m), 1.65(1H, m), 1.50-1.22(3H, m)

Example 27

Production of ethyl 2-[4-(3-acetoxyphenyloxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate

In the same manner as in Example 1, the title compound (87 g) was obtained.

Example 28

Production of ethyl 1-cyclohexyl-2-[4-(3-hydroxyphenyloxy)phenyl]benzimidazole-5-carboxylate

Ethyl 2-[4-(3-acetoxyphenyloxy)phenyl]-1-cyclohexylbenzimidazole-5-carboxylate (87 g) obtained in Example 27 was dissolved in methyl alcohol (250 ml) and tetrahydrofuran (250 ml), and potassium carbonate (31 g) was added. The mixture was stirred for 30 min at room temperature. The insoluble materials were filtered off and the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was neutralized with 2N hydrochloric acid. The precipitated crystals were collected by filtration to give the title compound (78 g, yield 97%).

¹H-NMR (300MHz, DMSO-d₆): 9.71(1H, s), 7.98(1H, d, J=8.7Hz), 7.87(1H, d, J=8.7Hz), 7.68(2H, d, J=8.6Hz), 7.24(1H, t, J=8.1Hz), 7.18(2H, d, J=8.6Hz), 6.63(1H, d, J=8.1Hz), 6.57(1H, d, J=8.1Hz), 6.51(1H, s), 4.38-4.23(1H, m), 4.35(2H, q, J=6.9Hz), 2.36-2.18(2H, m), 1.99-1.78(4H, m), 1.71-1.59(1H, m), 1.45-1.20(3H, m), 1.36(3H, t, J=6.9Hz)

Example 29

Production of ethyl 1-cyclohexyl-2-[4-[3-(4-pyridylmethoxy)phenyloxy]phenyl]benzimidazole-5-carboxylate

Ethyl 1-cyclohexyl-2-[4-(3-hydroxyphenyloxy)phenyl]benzimidazole-5-carboxylate (78 g) obtained in Example 28 was suspended in dimethylformamide (800 ml), and sodium hydride (60% oil, 14 g) was added under ice-cooling. The mixture was stirred for 1 hr at room temperature. After the reaction mixture was ice-cooled, 4-chloromethylpyridine hydrochloride (29 g) was added and the mixture was stirred for 30 min. The mixture was then stirred overnight at room temperature. Water was added to the reaction mixture and the precipitated crystals were collected by filtration.

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The resulting crystals were recrystallized from ethyl alcohol to give the title compound (77 g, yield 82%).

¹H-NMR (300MHz, CDCl₃): 8.63(2H, d, J=6.0Hz), 8.51(1H, s), 7.99(1H, d, J=8.7Hz), 7.66(2H, d, J=8.7Hz), 7.62(2H, d, J=8.7Hz), 7.36(2H, d, J=8.7Hz), 7.31(1H, t, J=8.2Hz), 7.26(1H, s), 7.16(2H, d, J=8.7Hz), 6.79-6.70(3H, m), 5.09(2H, s), 4.47-4.31(1H, m), 4.42(2H, q, J=7.0Hz), 2.42-2.22(2H, m), 2.04-1.71(5H, m), 1.45-1.25(3H, m), 1.42(3H, t, J=7.0Hz)

Example 30

10 Production of 1-cyclohexyl-2-(4-[3-(4-pyridylmethoxy)phenyloxy]-phenyl)benzimidazole-5-carboxylic acid

Ethyl 1-cyclohexyl-2-(4-[3-(4-pyridylmethoxy)phenyloxy]-phenyl)benzimidazole-5-carboxylate (60 g) obtained in Example 29 was treated in the same manner as in Example 2 to give the title
15 compound (54 g, yield 75%).

melting point: 235-237°C

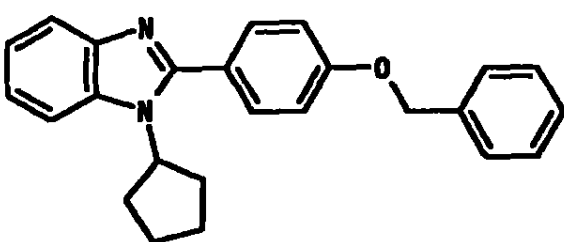
FAB-MS: 520 (MH⁺)

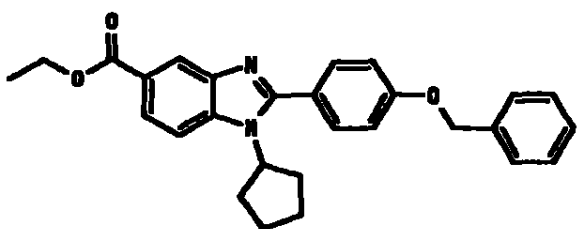
¹H-NMR (300MHz, DMSO-d₆): 8.58(2H, d, J=6.0Hz), 8.23(1H, s), 7.96 and 7.86(2H, ABq, J=8.7Hz), 7.68 and 7.17(4H, A'B'q, J=8.7Hz),
20 7.44(2H, d, J=8.7Hz), 7.39(1H, t, J=8.3Hz), 6.90(1H, d, J=8.1Hz), 6.84(1H, s), 6.75(1H, d, J=8.1Hz), 5.22(2H, s), 4.40-4.22(1H, m), 2.40-2.19(2H, m), 2.00-1.80(4H, m)

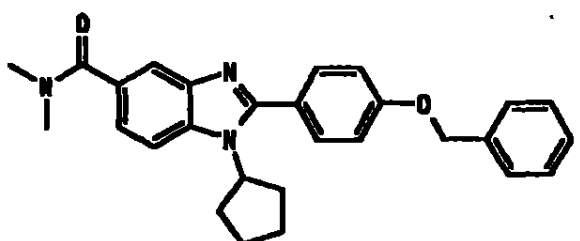
The compounds of Examples 31 to 232 were obtained in the
25 same manner as in Examples 1 to 30 or by other conventional method employed as necessary. The chemical structures and properties are shown in Tables 1 to 70.

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Table 1

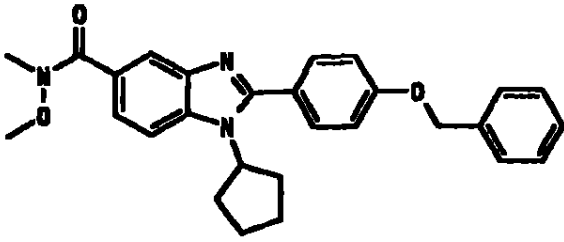
Example No.	31	1H NMR (δ) ppm
		300MHz, CDCl ₃ 7.81 (2H, d, J=6.6Hz), 7.60 (2H, d, J=8.8Hz), 7.51-7.21 (8H, m), 7.11 (2H, d, J=8.8Hz), 5.15 (2H, s), 4.93 (1H, quint, J=8.8Hz), 2.36-2.32 (2H, m), 2.09-2.04 (3H, m), 1.75-1.68 (3H, m).
Purity	> 90% (NMR)	
MS	369 (M+1)	

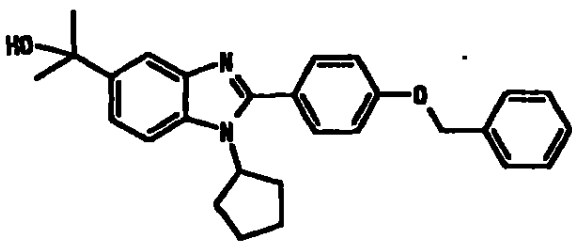
Example No.	32	1H NMR (δ) ppm
		300MHz, CDCl ₃ 8.51 (1H, d, J=1.5Hz), 7.98 (1H, d, J=8.4Hz), 7.61 (2H, d, J=8.7Hz), 7.56-7.10 (6H, m), 7.12 (2H, d, J=8.7Hz), 5.15 (2H, s), 4.94 (1H, quint, J=9.3Hz), 4.41 (2H, q, J=7.5Hz), 2.40-1.50 (8H, m), 1.41 (3H, t, J=7.5Hz)
Purity	> 90% (NMR)	
MS	441 (M+1)	

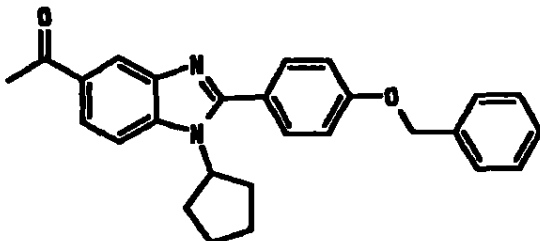
Example No.	33	1H NMR (δ) ppm
		300MHz, CDCl ₃ 7.84 (1H, s), 7.61 (2H, d, J=9.0Hz), 7.58-7.30 (7H, m), 7.12 (2H, d, J=9.0Hz), 5.15 (2H, s), 4.94 (1H, quint, J=8.7Hz), 3.10 (6H, brs), 2.40-1.50 (8H, m)
Purity	> 90% (NMR)	
MS	440 (M+1)	

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Table 2

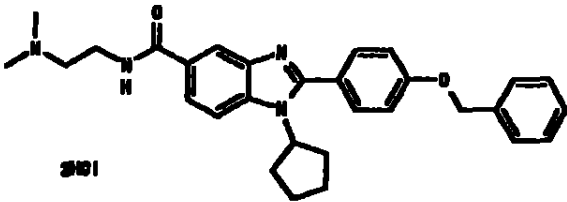
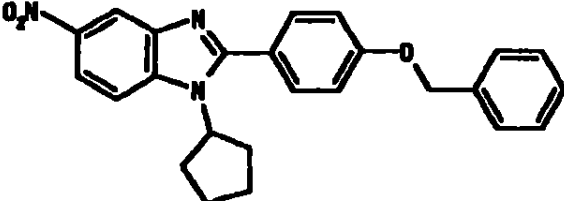
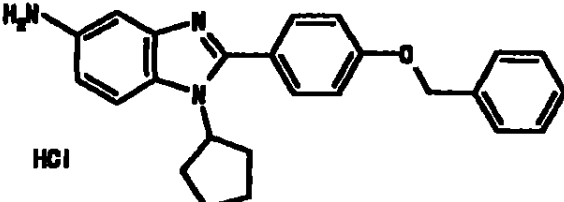
Example No.	34	1H NMR (δ) ppm
		300MHz, CDC13 8.20 (1H, s), 7.50-7.31 (9H, m), 7.12 (2H, d, J=8.7Hz), 5.15 (2H, s), 4.94 (1H, quint, J=8.7Hz), 3.61 (3H, s), 3.40 (3H, s), 2.41-1.42 (8H, m)
Purity	> 90% (NMR)	
MS	456 (M+1)	

Example No.	35	1H NMR (δ) ppm
		300MHz, CDC13 7.91 (1H, s), 7.59 (2H, d, J=8.7Hz), 7.49-7.30 (7H, m), 7.11 (2H, d, J=8.8Hz), 5.15 (2H, s), 4.19 (1H, quint, J=8.8Hz), 2.41-2.22 (2H, m), 2.13-1.49 (14H, m)
Purity	> 90% (NMR)	
MS	427 (M+1)	

Example No.	36	1H NMR (δ) ppm
		300MHz, CDC13 8.40 (1H, d, J=1.4Hz), 7.95 (1H, dd, J=8.6, 1.4Hz), 7.61 (2H, d, J=8.7Hz), 7.57-7.30 (6H, m), 7.13 (2H, d, J=8.7Hz), 5.16 (2H, s), 4.95 (1H, quint, J=8.8Hz), 2.64 (3H, s), 2.40-1.54 (8H, m)
Purity	> 90% (NMR)	
MS	411 (M+1)	

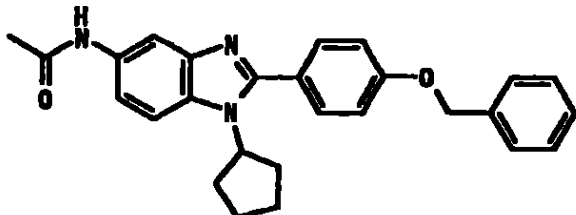
689

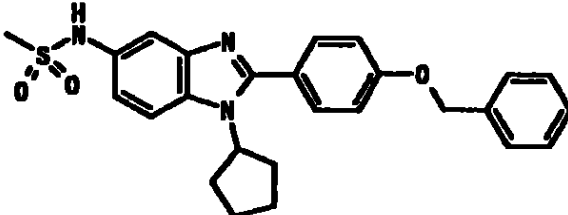
Table 3

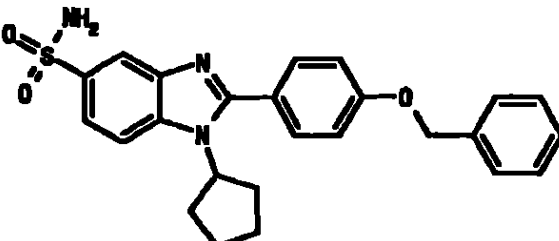
Example No.	37	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.47 (1H, brs.), 9.15 (1H, brs), 8.40 (1H, s), 8.07 (1H, d, J=9.0Hz), 7.93 (1H, d, J=8.7Hz), 7.77 (2H, d, J=8.7Hz), 7.55-7.29 (7H, m), 5.26 (2H, s), 4.93 (1H, quint, J=9.0Hz), 3.77-3.63 (2H, m), 3.39-3.23 (2H, m), 2.84 (6H, d, J=4.8Hz), 2.32-1.60 (8H, m)
Purity	> 90% (NMR)	
MS	483 (M+1)	
Example No.	38	1H NMR (δ) ppm
		300MHz, CDCl3 8.69 (1H, s), 8.19 (1H, d, J=9.0Hz), 7.62 (2H, d, J=8.7Hz), 7.54 (1H, d, J=9.0Hz), 7.48-7.36 (5H, m), 7.15 (2H, d, J=8.7Hz), 5.17 (2H, s), 4.98 (1H, quint, J=9.0Hz), 2.27-2.07 (6H, m), 1.82-1.78 (2H, m)
Purity	> 90% (NMR)	
MS	414 (M+1)	
Example No.	39	1H NMR (δ) ppm
		300MHz, DMSO-d6 7.84 (1H, d, J=9.0Hz), 7.79 (2H, d, J=8.7Hz), 7.52-7.33 (8H, m), 7.26 (1H, d, J=9.0Hz), 5.27 (2H, s), 4.92 (1H, quint, J=9.3Hz), 2.19-1.70 (8H, m)
Purity	> 90% (NMR)	
MS	384 (M+1)	

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Table 4

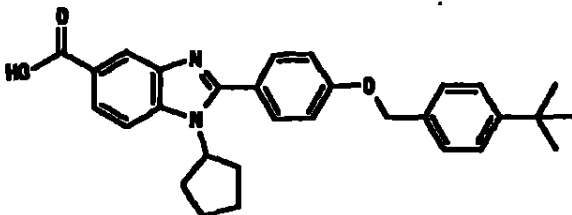
Example No.	40	1H NMR (δ) ppm
		300MHz, CDCl ₃ 7.72 (1H, s), 7.60-7.35 (10H, m), 7.10 (2H, d, J=8.7Hz), 5.14 (2H, s), 4.90 (1H, quint, J=8.8Hz), 2.29-2.19 (2H, m), 2.19 (3H, s), 2.19-1.74 (6H, m).
Purity	> 90% (NMR)	
MS	426 (M+1)	

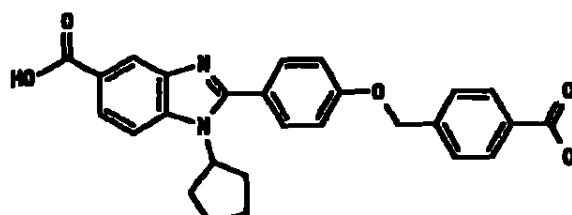
Example No.	41	1H NMR (δ) ppm
		300MHz, CDCl ₃ 7.66 (1H, s), 7.61 (2H, d, J=8.8Hz), 7.50-7.28 (7H, m), 7.12 (2H, d, J=8.8Hz), 6.86 (1H, brs), 5.15 (2H, s), 4.94 (1H, quint, J=8.8Hz), 2.97 (3H, s), 2.29-1.76 (8H, m).
Purity	> 90% (NMR)	
MS	462 (M+1)	

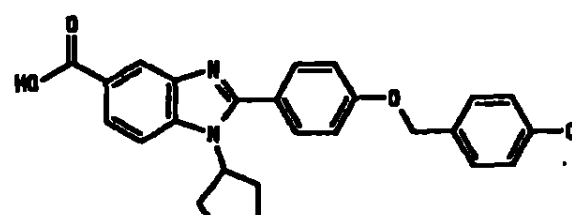
Example No.	42	1H NMR (δ) ppm
		300MHz, DMSO 8.11 (1H, s), 7.81 (1H, d, J=8.4Hz), 7.72 (1H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz), 7.51 (2H, m), 7.43 (2H, m), 7.37 (1H, m), 7.29 (2H, s), 7.23 (2H, d, J=8.4Hz), 5.22 (2H, s), 4.89 (1H, quintet, J=9.2Hz), 2.2-2.0 (6H, m), 1.7 (2H, m).
Purity	> 90% (NMR)	
MS	448 (M+)	

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 691

Table 5

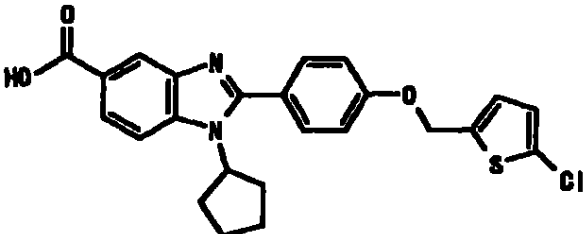
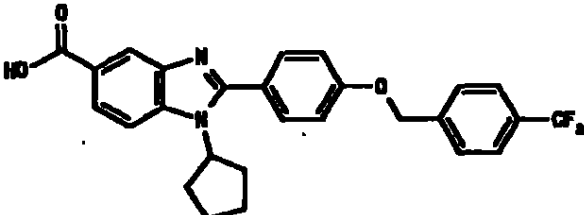
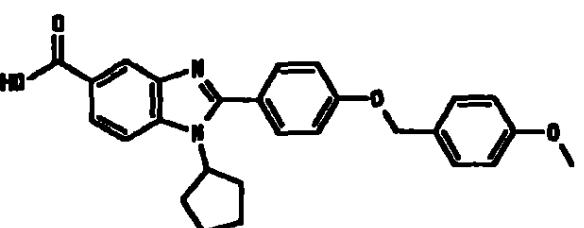
Example No.	43	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.08 (1H, d, J=9.0 Hz), 7.99 (1H, d, J=9.0 Hz), 7.47-7.41 (4H, m), 7.33 (2H, d, J=8.4 Hz), 5.22 (2H, s), 4.96 (1H, quint, J=9.0 Hz), 2.25-1.60 (8H, m), 1.30 (9H, s)
Purity	> 90% (NMR)	
MS	469 (M+1)	

Example No.	44	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.9 (2H, brs), 8.25 (1H, s), 8.00 (2H, d, J=7.8 Hz), 7.90 (1H, d, J=8.4 Hz), 7.74 (1H, d, J=8.7 Hz), 7.67 (2H, d, J=9.0 Hz), 7.62 (2H, d, J=8.1 Hz), 7.24 (2H, d, J=8.4 Hz), 5.32 (2H, s), 4.88 (1H, quint, J=9.0 Hz), 2.25-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	457 (M+1)	

Example No.	45	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.4 (1H, brs), 8.32 (1H, s), 8.06 (1H, d, J=8.7 Hz), 7.97 (1H, d, J=8.7 Hz), 7.79 (2H, d, J=8.8 Hz), 7.56-7.48 (4H, m), 7.33 (2H, d, J=8.8 Hz), 5.27 (2H, s), 4.95 (1H, quint, J=8.9 Hz), 2.30-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	447 (M+1)	

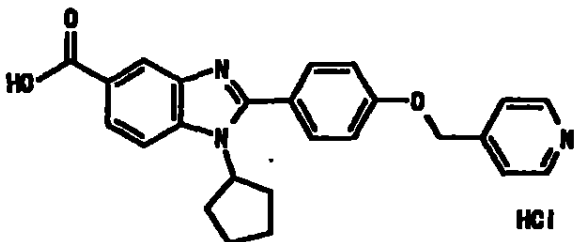
80
418
692

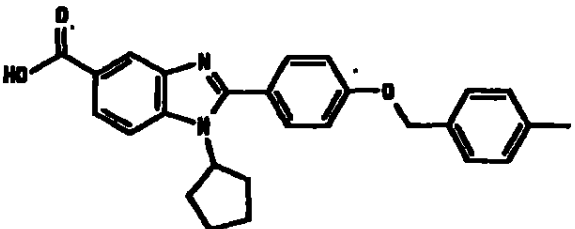
Table 6

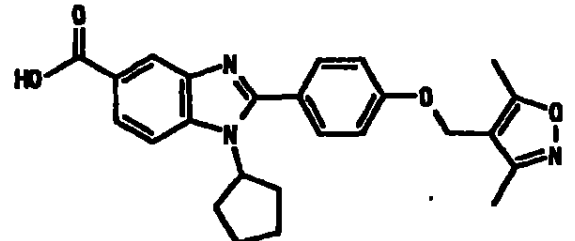
Example No.	46	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.07 (1H, d, J=8.7Hz), 7.98 (1H, d, J=8.7Hz), 7.80 (2H, d, J=8.4Hz), 7.34 (2H, d, J=8.4Hz), 7.19 (1H, d, J=3.6Hz), 7.09 (1H, d, J=3.6Hz), 5.41 (2H, s), 4.95 (1H, quint, J=8.7Hz), 2.30-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	453 (M+1)	
Example No.	47	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.07 (1H, d, J=8.4Hz), 7.98 (1H, d, J=9.0Hz), 7.82-7.72 (6H, m), 7.35 (2H, d, J=9.0Hz), 5.40 (2H, s), 4.95 (1H, quint, J=8.7Hz), 2.35-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	481 (M+1)	
Example No.	48	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.88 (1H, d, J=8.4Hz), 7.70 (1H, d, J=8.4Hz), 7.64 (2H, d, J=8.4Hz), 7.43 (2H, d, J=8.4Hz), 7.20 (2H, d, J=8.4Hz), 6.98 (2H, d, J=8.4Hz), 5.13 (2H, s), 4.88 (1H, quint, J=8.7Hz), 3.77 (3H, s), 2.35-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	443 (M+1)	

87
914
693

Table 7

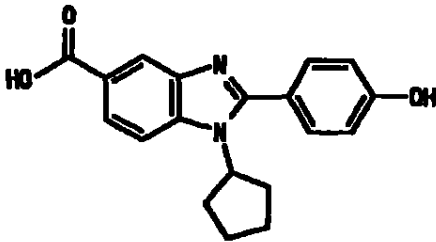
Example No.	49	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.93 (2H, d, J=6.6Hz), 8.35 (1H, s), 8.06-8.04 (3H, m), 7.97 (1H, d, J=8.7Hz), 7.83 (2H, d, J=8.7Hz), 7.38 (2H, d, J=8.7Hz), 5.61 (2H, s), 4.94 (1H, quint, J=8.7Hz), 2.40-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	414 (M+1)	

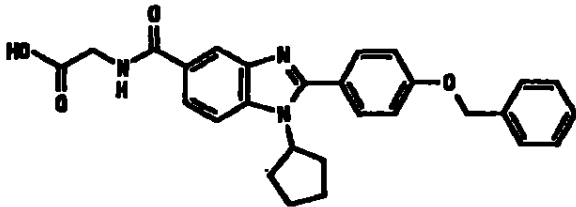
Example No.	50	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.08 (1H, d, J=8.7Hz), 7.99 (1H, d, J=9.0Hz), 7.78 (2H, d, J=8.4Hz), 7.39 (2H, d, J=8.1Hz), 7.32 (2H, d, J=8.7Hz), 7.23 (2H, d, J=7.8Hz), 5.22 (2H, s), 4.96 (1H, quint, J=9.0Hz), 2.32 (3H, s), 2.30-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	427 (M+1)	

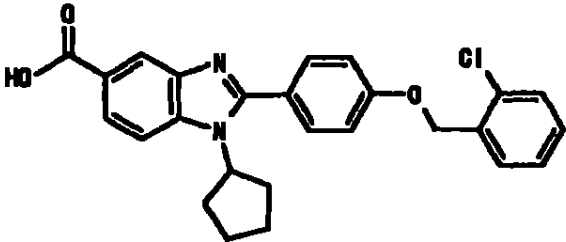
Example No.	51	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.03 (1H, d, J=9.0Hz), 7.93 (1H, d, J=9.0Hz), 7.77 (2H, d, J=8.4Hz), 7.31 (2H, d, J=8.7Hz), 5.07 (2H, s), 4.94 (1H, quint, J=8.7Hz), 2.45 (3H, s), 2.26 (3H, s), 2.26-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	432 (M+1)	

82
694

Table 8

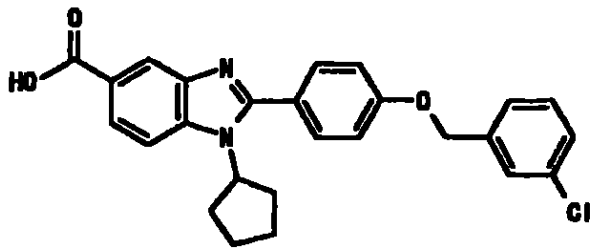
Example No.	52	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.7 (1H, brs), 10.0 (1H, s), 8.22 (1H, s), 7.87 (1H, d, J=8.6Hz), 7.69 (1H, d, J=8.6Hz), 7.53 (2H, d, J=8.6Hz), 6.96 (2H, d, J=8.6Hz), 4.89 (1H, quint, J=9.0Hz), 2.30-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	323 (M+1)	

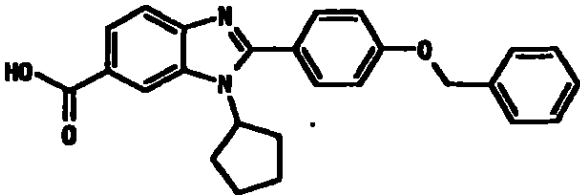
Example No.	53	1H NMR (δ) ppm
		300MHz, DMSO-d6 9.18 (1H, t, J=5.6Hz), 8.34 (1H, s), 8.04 (1H, d, J=9.6Hz), 7.98 (1H, d, J=8.7Hz), 7.80 (2H, d, J=8.7Hz), 7.52-7.32 (7H, m), 5.27 (2H, s), 4.95 (1H, quint, J=9.0Hz), 3.99 (2H, d, J=5.7Hz), 2.40-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	470 (M+1)	

Example No.	54	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.05 (1H, d, J=8.7Hz), 7.95 (1H, d, J=8.7Hz), 7.80 (2H, d, J=8.4Hz), 7.67 (1H, t, J=4.5Hz), 7.56 (1H, t, J=4.5Hz), 7.45-7.42 (2H, m), 7.35 (2H, d, J=8.4Hz), 5.31 (2H, s), 4.96 (1H, quint, J=9.0Hz), 2.30-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	447 (M+1)	

83
421
695

Table 9

Example No.	55	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.78 (1H, br s), 8.24 (1H, s), 7.88 and 7.72 (2H, ABq, J=8.6Hz), 7.66 and 7.23 (4H, A'B'q, J=8.6Hz), 7.58 (1H, s), 7.48-7.42 (3H, m), 5.24 (1H, s), 4.88 (1H, quint, J=8.8Hz), 2.30-1.91 (6H, m), 1.78-1.60 (2H, m)
Purity	> 90% (NMR)	
MS	447 (M+1)	

Example No.	56	1H NMR (δ) ppm
		300MHz, DMSO 12.89 (1H, broad), 8.18 (1H, s), 7.87 (1H, d, J=8.4Hz), 7.74 (1H, d, J=9.2Hz), 7.67 (2H, d, J=8.8Hz), 7.52 (2H, m), 7.45 (2H, m), 7.38 (1H, m), 7.23 (2H, d, J=8.8Hz), 5.22 (2H, s), 4.94 (1H, quintet, J=8.9Hz), 2.16 (4H, m), 1.98 (2H, m), 1.73 (2H, m).
Purity	> 90% (NMR)	
MS	413 (M+)	

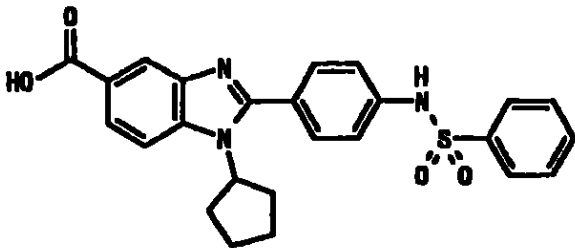
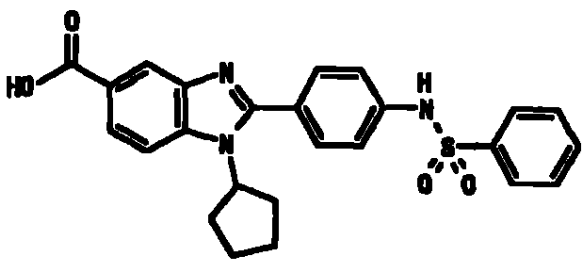
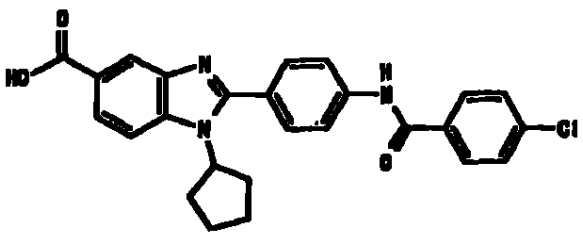
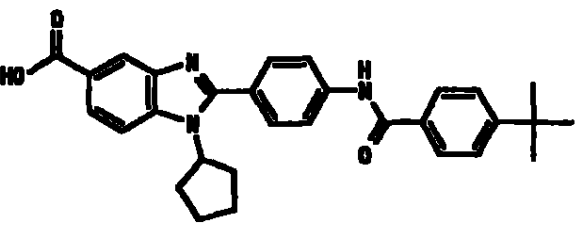
Example No.	57	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.99 (1H, s), 8.26 (1H, s), 8.01-7.86 (4H, m), 7.69-7.59 (5H, m), 7.38 (2H, d, J=8.7Hz), 4.86 (1H, quint, J=8.7Hz), 2.12-1.90 (6H, m), 1.72-1.59 (2H, m)
Purity	> 90% (NMR)	
MS	462 (M+1)	

Table 10

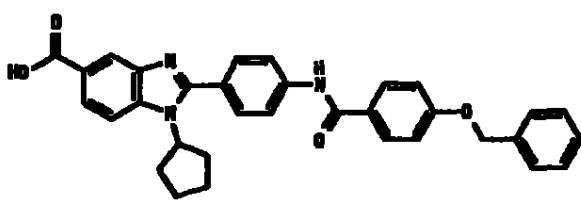
Example No.	58	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.78 (1H, s), 10.69 (1H, s), 8.26-7.72 (9H, m), 4.92 (1H, quint, J=9.0Hz), 2.34-1.70 (6H, m), 1.75-1.61 (2H, m)
Purity	> 90% (NMR)	
MS	494 (M+1)	

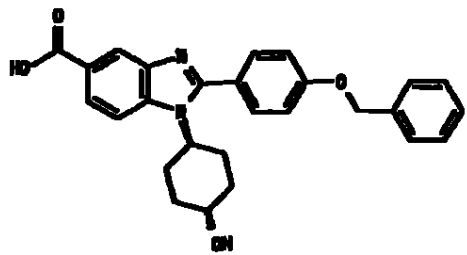
Example No.	59	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.82 (1H, s), 8.34 (1H, s), 8 .14 and 7.84 (4H, ABq, J=8.4H z), 8.06 and 7.66 (4H, A'B'q, J=8.6Hz), 8.06-7.98 (4H, m) , 5.01 (1H, quint, J=9.3Hz), 2.35-2.15 (4H, m), 2.11-1.9 6 (2H, m), 1.80-1.62 (2H, m)
Purity	> 90% (NMR)	
MS	460 (M+1)	

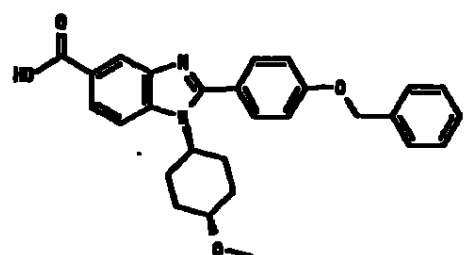
Example No.	60	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.61 (1H, s), 8.32 (1H, s), 8 .12 and 7.81 (4H, ABq, J=8.9H z), 8.03 and 7.93 (2H, A'B'q, J=8.7Hz), 7.95 and 7.59 (4H, A''B''q, J=8.4Hz), 4.99 (1H, q uint, J=9.0Hz), 2.33-2.12 (4H, m), 2.10-1.93 (2H, m), 1. 80-1.63 (2H, m), 1.34 (9H, m)
Purity	> 90% (NMR)	
MS	482 (M+1)	

697

Table 11

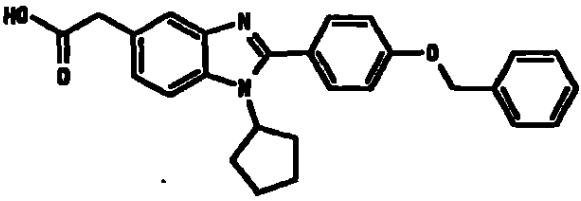
Example No.	61	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.6 (1H, s), 8.34 (1H, s), 8.13 (2H, d, J=8.7Hz), 8.09-7.98 (4H, m), 7.82 (2H, d, J=8.7Hz), 7.50-7.35 (5H, m), 7.20-7.17 (2H, d, J=9.0Hz), 5.24 (2H, s), 5.01 (1H, quint, J=9.3Hz), 2.40-1.60 (8H, m).
Purity	> 90% (NMR)	
MS	532 (M+1)	

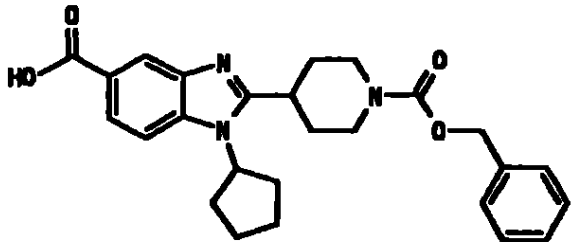
Example No.	62	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.26 (1H, d, J=8.7Hz), 8.04 (1H, d, J=8.7Hz), 7.77 (2H, d, J=8.4Hz), 7.52 (2H, d, J=6.9Hz), 7.46-7.39 (5H, m), 5.28 (2H, s), 4.38 (1H, m), 3.71 (1H, m), 2.60-2.15 (2H, m), 2.04-1.96 (4H, m), 1.30-1.20 (2H, m).
Purity	> 90% (NMR)	
MS	443 (m+1)	

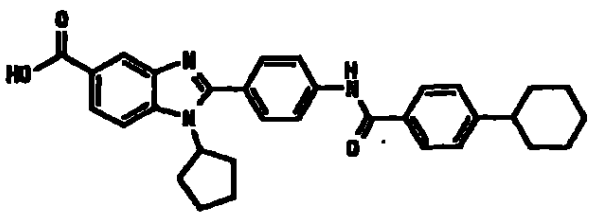
Example No.	63	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, s), 8.14 (1H, d, J=8.7Hz), 7.96 (1H, d, J=8.4Hz), 7.71 (2H, d, J=9.0Hz), 7.51 (2H, d, J=6.9Hz), 7.46-7.37 (3H, m), 7.30 (2H, d, J=8.4Hz), 5.25 (3H, s), 4.39 (1H, m), 3.44 (1H, m), 3.27 (3H, s), 2.60-1.95 (6H, m), 1.25-1.05 (2H, m).
Purity	約 90% (NMR)	
MS	457 (M+1)	

86
698

Table 12

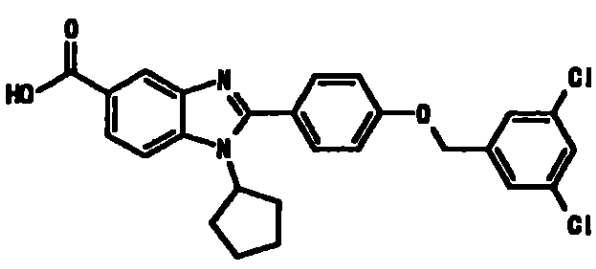
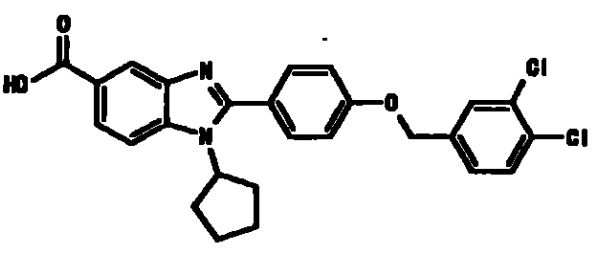
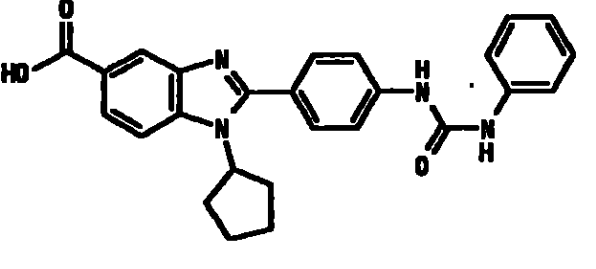
Example No.	64	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.25 (1H, brs), 7.70-7.30 (9H, m), 7.20 (2H, d, J=8.7Hz), 7.14 (1H, d, J=8.4Hz), 5.20 (2H, s), 4.84 (1H, quint, J=6.0Hz), 3.66 (2H, s), 2.30-1.51 (8H, m)
Purity	> 90% (NMR)	
MS	427 (M+1)	

Example No.	65	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.64 (1H, brs), 8.13 (1H, s), 7.80 (1H, d, J=7.2Hz), 7.59 (1H, d, J=8.7Hz), 7.48-7.30 (5H, m), 5.11 (2H, s), 5.03 (1H, quint, J=8.7Hz), 4.20-4.05 (2H, m), 3.45-3.90 (3H, m), 2.15-1.60 (12H, m)
Purity	> 90% (NMR)	
MS	448 (M+1)	

Example No.	66	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.59 (1H, s), 8.31 (1H, s), 8.10 (2H, d, J=8.6Hz), 8.03 (1H, d, J=8.7Hz), 8.00-7.85 (3H, m), 7.80 (2H, d, J=8.6Hz), 7.41 (2H, d, J=8.2Hz), 4.98 (1H, quint, J=8.8Hz), 2.71-1.10 (19H, m)
Purity	> 90% (NMR)	
MS	508 (M+1)	

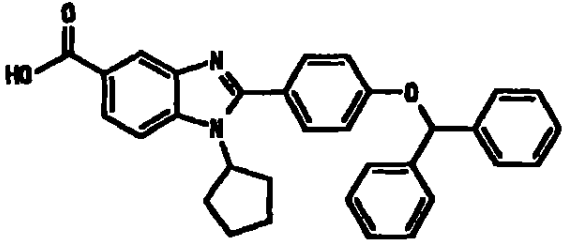
87
95
699

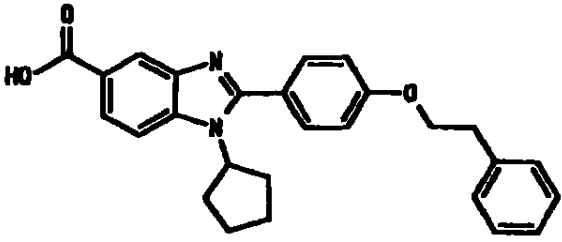
Table 13

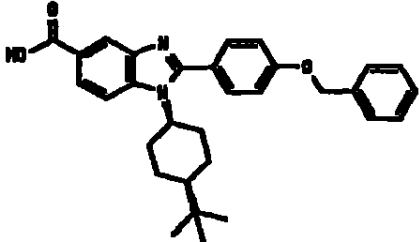
Example No.	67	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.81 (1H, brs), 8.42 (1H, s), 7.90 (1H, d, J=8.5Hz), 7.80-7.52 (6H, m), 7.44 (2H, d, J=8.6Hz), 5.25 (2H, s), 4.88 (1H, quint, J=8.8Hz), 2.30-1.52 (8H, m)
Purity	> 90% (NMR)	
MS	481 (M+1)	
Example No.	68	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, d, J=1.4Hz), 8.05 (1H, d, J=8.6Hz), 7.96 (1H, d, J=8.6Hz), 8.86-8.61 (4H, m), 7.51 (1H, d, J=6.3Hz), 7.33 (2H, d, J=8.8Hz), 5.28 (2H, s), 4.94 (1H, quint, J=8.8Hz), 2.31-1.60 (8H, m)
Purity	> 90% (NMR)	
MS	481 (M+1)	
Example No.	69	1H NMR (δ) ppm
		300MHz, DMSO-d6 9.88 (1H, s), 9.42 (1H, s), 8.32 (1H, s), 8.09 and 8.02 (2H, ABq, J=9.0Hz), 7.81 and 7.78 (4H, A'B'q, J=9.2Hz), 7.50 (2H, d, J=7.8Hz), 7.31 (2H, t, J=7.8Hz), 7.00 (1H, t, J=7.8Hz), 5.03 (1H, quint, J=8.7Hz), 2.31-2.17 (4H, m), 2.13-1.96 (2H, m), 1.83-1.64 (2H, m)
Purity	> 90% (NMR)	
MS	441 (M+1)	

88
700

Table 14

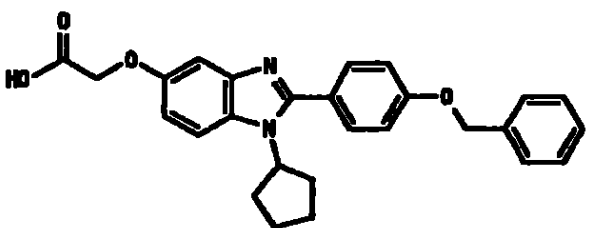
Example No.	70	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, d, J=1.2Hz), 8.04 (1H, d, J=8.7Hz), 7.94 (1H, d, J=8.7Hz), 7.72 (2H, d, J=8.7Hz), 7.60-7.20 (12H, m), 6.74 (1H, s), 4.92 (1H, quint, J=8.9Hz), 2.30-1.58 (8H, m)
Purity	> 90% (NMR)	
MS	489 (M+1)	

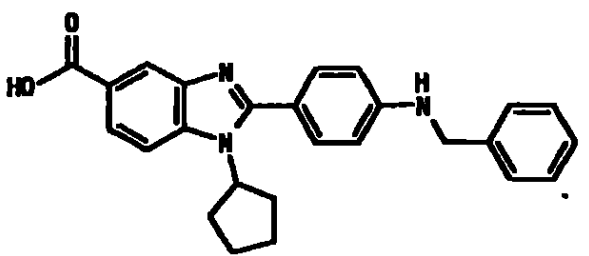
Example No.	71	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.05 (1H, d, J=8.7Hz), 7.97 (1H, d, J=8.7Hz), 7.76 (2H, d, J=8.6Hz), 7.44-7.19 (7H, m), 4.94 (1H, quint, J=8.8Hz), 4.35 (2H, t, J=6.7Hz), 3.10 (2H, t, J=6.7Hz), 2.32-1.60 (8H, m)
Purity	> 90% (NMR)	
MS	427 (M+1)	

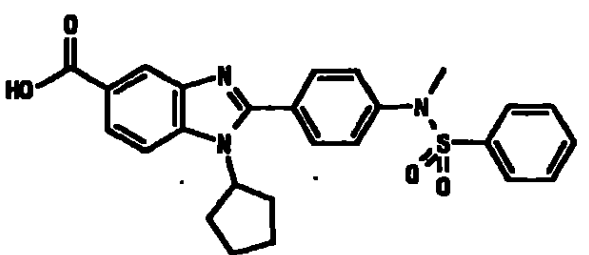
Example No.	72	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.30 (1H, s), 8.25 (1H, d, J=8.7Hz), 8.03 (1H, d, J=9.0Hz), 7.75 (2H, d, J=8.7Hz), 7.51 (2H, d, J=7.2Hz), 7.46-7.33 (5H, m), 5.27 (2H, s), 4.36 (1H, m), 2.50-2.25 (2H, m), 2.15-2.00 (2H, m), 1.95-1.85 (2H, m), 1.35 (1H, m), 1.20-1.10 (2H, m), 0.87 (9H, s)
Purity	> 90% (NMR)	
MS	483 (M+1)	

89
701

Table 15

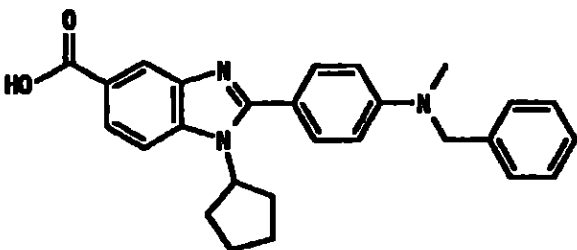
Example No.	73	1H NMR (δ) ppm
		300MHz, DMSO-d6 7.59 (2H, d, J=8.4Hz), 7.52-7.35 (6H, m), 7.20 (2H, d, J=8.7Hz), 7.14 (1H, d, J=2.1Hz), 6.90 (1H, dd, J=9.0, 2.4Hz), 5.21 (2H, s), 4.83 (1H, quint, J=8.7Hz), 4.70 (2H, s), 2.30-1.90 (6H, m), 1.75-1.55 (2H, m).
Purity	> 90% (NMR)	
MS	443 (M+1)	

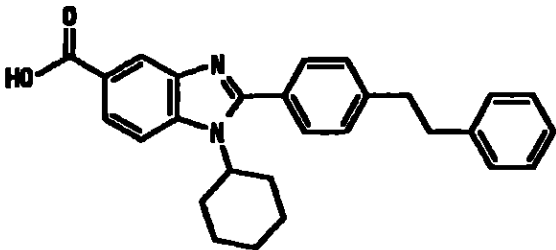
Example No.	74	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, s), 8.06 and 7.97 (2H, ABq, J=8.7Hz), 7.57 and 6.86 (4H, A'B'q, J=8.9Hz), 7.42-7.26 (5H, m), 5.04 (1H, quint, J=9.0Hz), 4.42 (2H, s), 2.32-1.94 (6H, m), 1.80-1.62 (2H, m)
Purity	> 90% (NMR)	
MS	412 (M+1)	

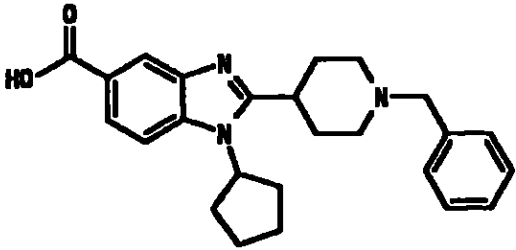
Example No.	75	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.80 (1H, s), 8.26 (1H, s), 7.90 (1H, d, J=9.2Hz), 7.76-7.60 (8H, m), 7.35 (2H, d, J=8.4Hz), 4.84 (1H, quint, J=8.8Hz), 3.23 (3H, s), 2.32-1.90 (6H, m), 1.78-1.61 (2H, m)
Purity	> 90% (NMR)	
MS	476 (M+1)	

92
93
762

Table 16

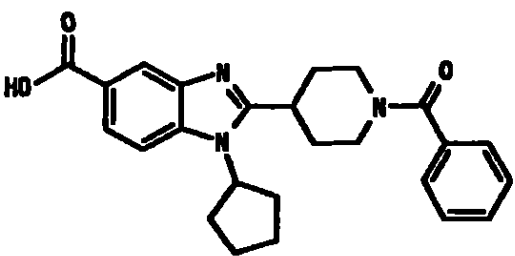
Example No.	76	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.29 (1H, s), 8.07 and 7.49 (2H, ABq, J=8.7Hz), 7.66 and 7.00 (4H, A'B'q, J=7.7Hz), 7.39-7.24 (5H, m), 5.05 (1H, quint, J=8.8Hz), 4.76 (2H, s), 3.21 (3H, s), 2.35-1.92 (6H, m), 1.81-1.62 (2H, m)
Purity	> 90% (NMR)	
MS	426 (M+1)	

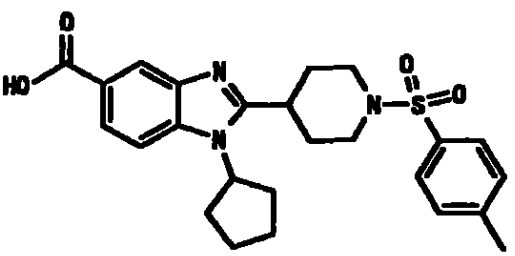
Example No.	77	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 7.87 (1H, s), 7.56 and 7.43 (4H, ABq, J=8.1Hz), 7.34-7.16 (5H, m), 4.25 (1H, brt, J=12.5Hz), 3.06-2.92 (4H, m), 2.41-2.17 (2H, m), 1.96-1.77 (4H, m), 1.72-1.58 (1H, m), 1.48-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	425 (M+1)	

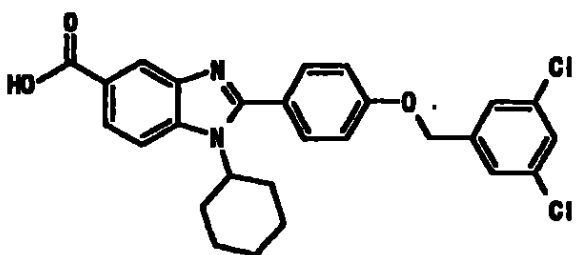
Example No.	78	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.14 (1H, s), 7.79 (1H, d, J=9.0Hz), 7.57 (1H, d, J=8.7Hz), 7.40-7.20 (5H, m), 4.89 (1H, quint, J=8.7Hz), 3.54 (2H, s), 3.19-2.90 (3H, m), 2.23-1.69 (14H, m)
Purity	> 90% (NMR)	
MS	404 (M+1)	

91
729
203

Table 17

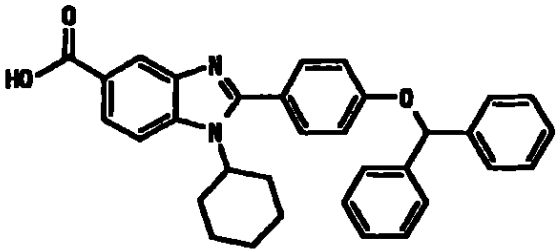
Example No.	79	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.15 (1H, s), 7.81 (1H, d, J=8.4Hz), 7.59 (1H, d, J=9.0Hz), 7.50-7.38 (5H, m), 5.05 (1H, quint, J=9.0Hz), 3.85-2.95 (3H, m), 2.20-1.65 (14H, m)
Purity	> 90% (NMR)	
MS	418 (M+1)	

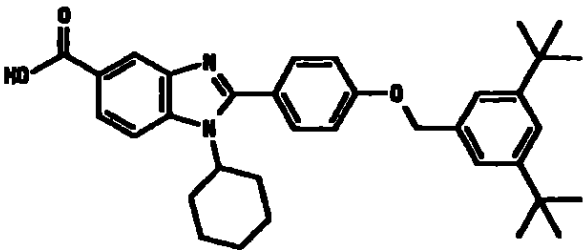
Example No.	80	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.17 (1H, m), 7.84 (1H, d, J=8.4Hz), 7.78-7.62 (3H, m), 7.49 (2H, d, J=8.1Hz), 5.05-4.91 (1H, m), 3.80-3.70 (2H, m), 3.30-3.12 (1H, m), 2.48-2.31 (5H, m), 2.15-1.60 (12H, m)
Purity	> 90% (NMR)	
MS	468 (M+1)	

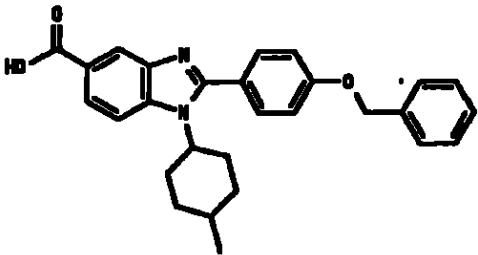
Example No.	81	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, brs), 8.21 (1H, d, J=1.4Hz), 7.49 (1H, d, J=8.6Hz), 7.85 (1H, dd, J=8.6, 1.4Hz), 7.70-7.55 (5H, m), 7.23 (2H, d, J=8.7Hz), 5.25 (2H, s), 4.36-4.15 (1H, m), 2.39-2.18 (2H, m), 2.00-1.78 (4H, m), 1.70-1.57 (1H, m), 1.48-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	495 (M+1)	

92
93
104

Table 18

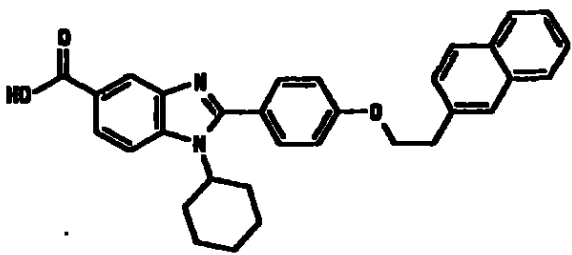
Example No.	82	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, s), 8.22 (1H, d, J=8.7Hz), 8.02 (1H, d, J=8.7Hz), 7.69 (2H, d, J=8.7Hz), 7.60-7.50 (4H, m), 7.45-7.25 (8H, m), 6.75 (1H, s), 4.21-4.23 (1H, m), 2.39-2.18 (2H, m), 2.10-1.78 (4H, m), 1.70-1.15 (4H, m)
Purity	> 90% (NMR)	
MS	503 (M+1)	

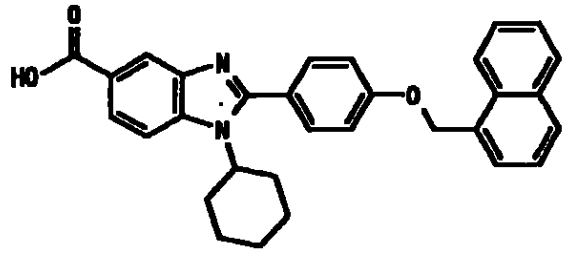
Example No.	83	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.2 (1H, brs), 8.30 (1H, s), 8.23 (1H, d, J=8.8Hz), 8.02 (1H, d, J=8.7Hz), 7.74 (2H, d, J=8.6Hz), 7.40-7.33 (5H, m), 5.22 (2H, s), 4.36 (1H, m), 2.50-1.40 (10H, m), 1.31 (18H, s).
Purity	> 90% (NMR)	
MS	539 (M+1)	

Example No.	84	1H NMR (δ) ppm
		mixture of isomers (cis:trans=3:1) 300MHz, DMSO-d6 8.30 (1H, s), 8.20-7.95 (2H, m), 7.72 (2H, d, J=8.4Hz), 7.52-7.29 (7H, m), 5.25 (2H, s), 4.34, 3.40 (1H, m), 2.50-2.20 (2H, m), 2.05-1.50 (6H, m), 1.14, 0.90 (3H, d, J=6.9, 6.3Hz), 1.09 (1H, m).
Purity	> 90% (NMR)	
MS	441 (M+1)	

93
931
765

Table 19

Example No.	85	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.25 (1H, s), 8.14-7.83 (6H, m), 7.77-7.44 (5H, m), 7.21 (2H, d, J=7.8Hz), 4.44 (2H, brt), 4.31 (1H, brt), 3.56 (2H, brt), 2.20-2.16 (2H, m), 2.00-1.74 (4H, m), 1.70-1.55 (1H, m), 1.45-1.14 (3H, m)
Purity	> 90% (NMR)	
MS	491 (M+1)	

Example No.	86	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.23 (1H, s), 8.15 (1H, d, J=7.6Hz), 8.02-7.53 (10H, m), 7.32 (2H, d, J=8.7Hz), 5.68 (2H, s), 4.32 (1H, brt, J=12.2Hz), 2.41-2.20 (2H, m), 2.01-1.78 (4H, m), 1.71-1.56 (1H, m), 1.50-1.16 (3H, m)
Purity	> 90% (NMR)	
MS	477 (M+1)	

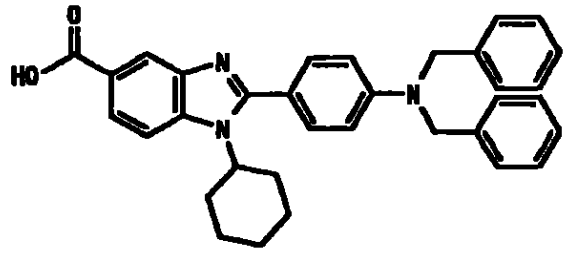
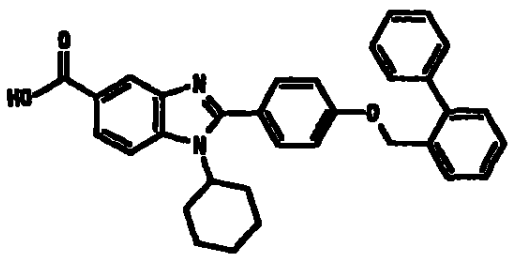
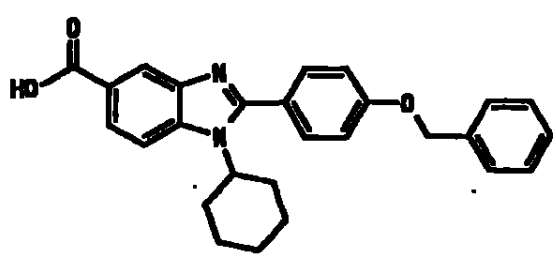
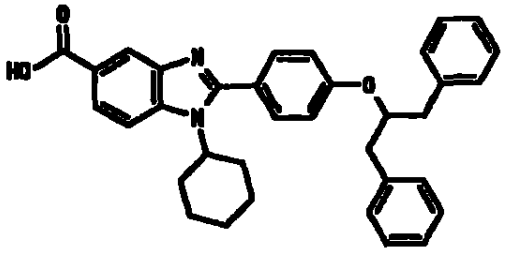
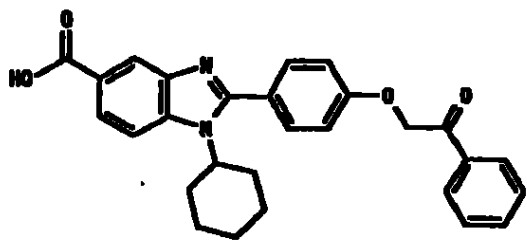
Example No.	87	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, brs), 8.16 (1H, s), 7.91 and 7.82 (2H, ABq, J=8.5Hz), 7.44 and 6.86 (4H, A' B' q, J=8.6Hz), 7.39-7.26 (10H, m), 4.82 (2H, s), 4.35 (1H, brt, J=12.2Hz), 2.35-2.16 (2H, m), 1.97-1.75 (4H, m), 1.69-1.56 (1H, m), 1.45-1.16 (3H, m)
Purity	> 90% (NMR)	
MS	516 (M+1)	

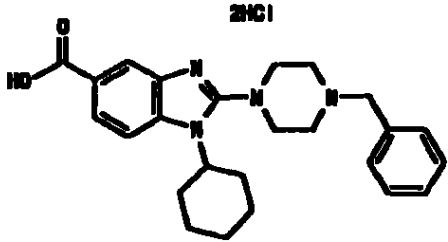
Table 20

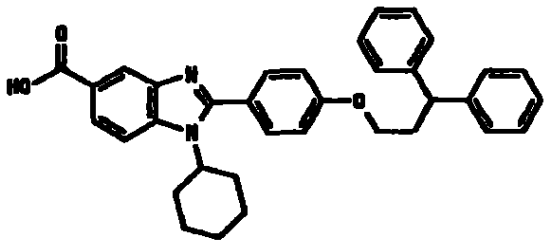
Example No.	88	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.26 and 8.06 (2H, ABq, J=8.9Hz), 7.73 and 7.22 (4H, A'B'q, J=8.7Hz), 7.50-7.36 (8H, m), 5.10 (2H, s), 4.37 (1H, brt, J=12.2Hz), 2.38-2.28 (2H, m), 2.10-1.80 (4H, m), 1.70-1.56 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	503 (M+1)	
Example No.	89	1H NMR (δ) ppm
		
Purity	91% (HPLC)	
MS		
Example No.	90	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.40-8.20 (2H, m), 8.04 (1H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz), 7.50-7.10 (12H, m), 5.08 (1H, m), 4.33 (1H, m), 3.00 (4H, m), 2.50-1.10 (10H, m)
Purity	> 90% (NMR)	
MS	531 (M+1)	

95
93
707

Table 21

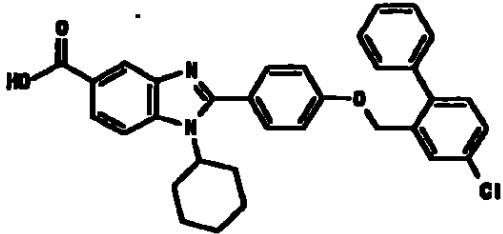
Example No.	91	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.27 (1H, d, J=8.7Hz), 8.08-8.03 (3H, m), 7.77-7.58 (5H, m), 7.31 (2H, d, J=8.7Hz), 5.81 (2H, s), 4.40 (1H, m), 2.50-1.20 (10H, m).
Purity	約90% (NMR)	
MS	455 (M+1)	

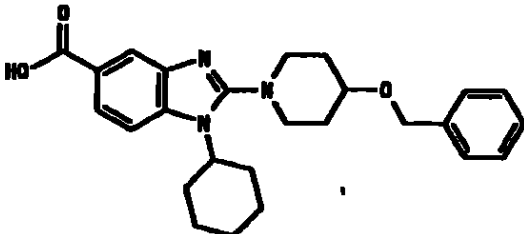
Example No.	92	1H NMR (δ) ppm
		300MHz, DMSO-d6 11.8 (1H, brs), 8.07 (1H, s), 7.89 (1H, d, J=8.7Hz), 7.84 (1H, d, J=8.4Hz), 7.69 (2H, m), 7.48 (3H, m), 4.42 (2H, s), 4.11 (1H, m), 3.73 (4H, m), 3.40 (4H, m), 2.40-1.40 (10H, m).
Purity	>90% (NMR)	
MS	419 (M+1)	

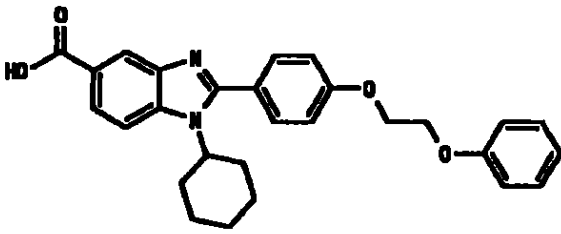
Example No.	93	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.28 (1H, d, J=8.9Hz), 8.05 (1H, d, J=8.7Hz), 7.72 (2H, d, J=8.7Hz), 7.38 (4H, d, J=7.2Hz), 7.31 (4H, t, J=7.3Hz), 7.21-7.17 (4H, m), 4.37 (1H, m), 4.26 (1H, t, J=7.9Hz), 4.01 (2H, t, J=6.2Hz), 2.57 (2H, m), 2.50-2.20 (2H, m), 2.10-2.00 (2H, m), 2.00-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m).
Purity	>90% (NMR)	
MS	531 (M+1)	

96
131
108

Table 22

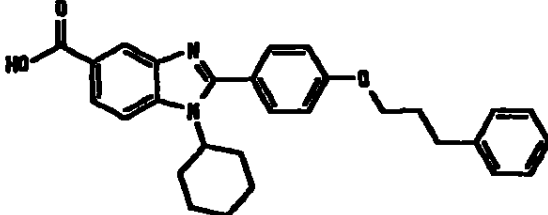
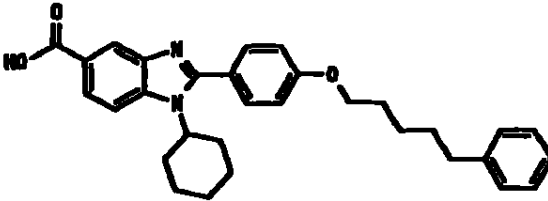
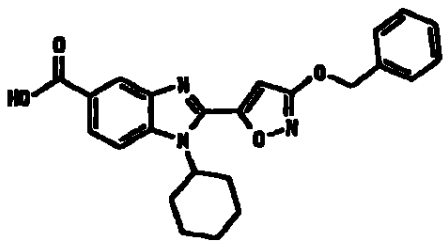
Example No.	94	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.27 (1H, d, J=9.0Hz), 8.05 (1H, d, J=8.7Hz), 7.75-7.70 (3H, m), 7.56 (1H, d, J=8.4Hz), 7.55-7.35 (6H, m), 7.22 (2H, d, J=8.7Hz), 5.11 (2H, s), 4.36 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m).
Purity	> 90% (NMR)	
MS	537 (M+1)	

Example No.	95	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.9 (1H, brs), 8.02 (1H, s), 7.82 (2H, m), 7.40-7.25 (5H, m), 4.58 (2H, s), 4.09 (1H, m), 3.71 (1H, m), 3.49 (2H, m), 3.21 (2H, m), 2.35-1.30 (14H, m).
Purity	> 90% (NMR)	
MS	434 (M+1)	

Example No.	96	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, d, J=1.3Hz), 8.27 (1H, d, J=8.8Hz), 8.05 (1H, d, J=8.8Hz), 7.76 (2H, d, J=8.7Hz), 7.40-7.25 (4H, m), 7.06-6.90 (3H, m), 4.53-4.26 (5H, m), 2.40-2.18 (2H, m), 2.12-1.56 (5H, m), 1.50-1.19 (3H, m).
Purity	> 90% (NMR)	
MS	457 (M+1)	

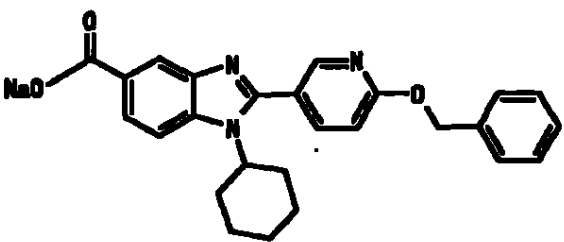
91
92
709

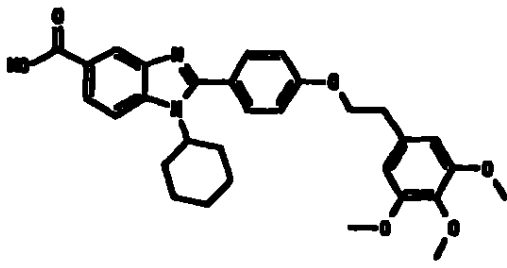
Table 23

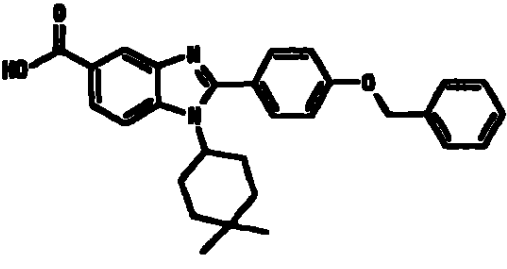
Example No.	97	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, d, J=1.3Hz), 8.29 (1H, d, J=8.8Hz), 8.05 (1H, dd, J=8.8, 1.3Hz), 8.42 (2H, d, J=8.8Hz), 7.37-7.16 (7H, m), 4.48-4.30 (1H, m), 4.12 (2H, t, J=6.2Hz), 2.83-2.70 (2H, m), 2.40-1.50 (9H, m), 1.59-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	455 (M+1)	
Example No.	98	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.28 (1H, d, J=1.3Hz), 8.21 (1H, d, J=8.8Hz), 8.01 (1H, d, J=10.1Hz), 7.70 (2H, d, J=8.7Hz), 7.33-7.12 (7H, m), 4.44-4.28 (1H, m), 4.10 (2H, t, J=6.3Hz), 2.62 (2H, t, J=7.4Hz), 2.39-2.15 (2H, m), 2.10-1.18 (14H, m)
Purity	> 90% (NMR)	
MS	483 (M+1)	
Example No.	99	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.93 (1H, brs), 8.30 (1H, d, J=1.4Hz), 8.04 (1H, d, J=8.7Hz), 7.92 (1H, dd, J=8.7, 1.4Hz), 7.59-7.34 (5H, m), 7.07 (1H, s), 5.38 (2H, s), 4.78-4.60 (1H, m), 2.32-2.14 (2H, m), 2.03-1.28 (8H, m)
Purity	> 90% (NMR)	
MS	418 (M+1)	

48
22
716

Table 24

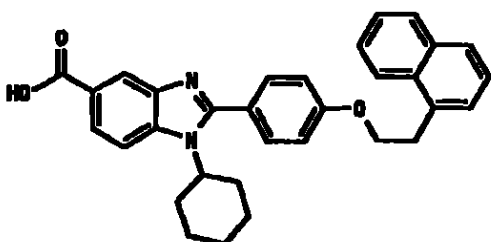
Example No.	100	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.46 (1H, d, J=2.1Hz), 8.16 (1H, s), 8.00 (1H, dd, J=8.5, 2.1Hz), 7.87 (1H, d, J=8.5Hz), 7.68 (1H, d, J=8.5Hz), 7.55-7.30 (5H, m), 7.08 (1H, d, J=8.5Hz), 5.45 (2H, s), 4.25-4.08 (1H, m), 2.39-2.18 (2H, m), 2.00-1.75 (4H, m), 1.70-1.55 (1H, m), 1.45-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	427 (M+1)	

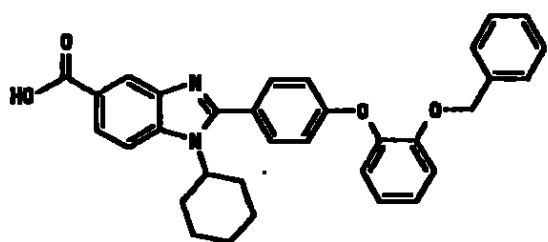
Example No.	101	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

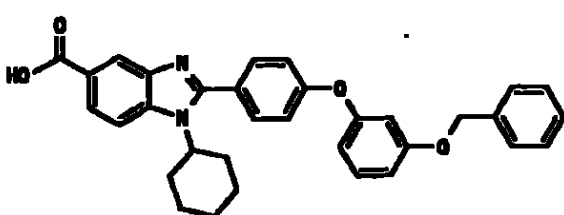
Example No.	102	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

99
932
711

Table 25

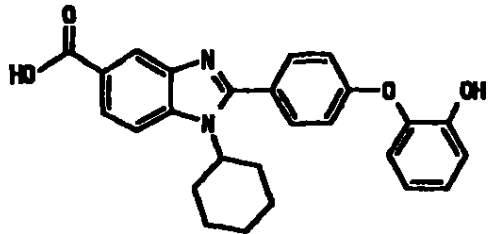
Example No.	103	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.79 (1H, brs), 8.22 (2H, s), 8.02-7.78 (4H, m), 7.63-7.42 (6H, m), 7.20-7.09 (2H, m), 4.43 (2H, s), 4.27 (1H, brt, J=12.2Hz), 3.59 (2H, s), 2.39-2.15 (2H, m), 1.98-1.72 (4H, m), 1.68-1.59 (1H, m), 1.43-1.12 (3H, m)
Purity	> 90% (NMR)	
MS	491 (M+1)	

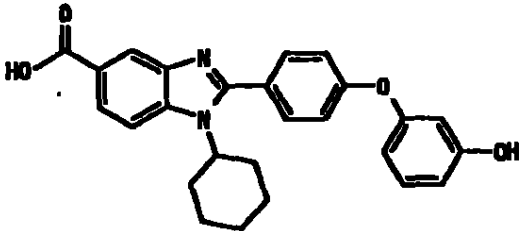
Example No.	104	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.23 (1H, s), 7.94 and 7.86 (2H, ABq, J=8.6Hz), 7.64 and 7.05 (4H, A'B'q, J=8.7Hz), 7.32-7.09 (9H, m), 5.13 (2H, s), 4.28 (1H, brt, J=12.2Hz), 2.36-2.19 (2H, m), 1.95-1.77 (4H, m), 1.66-1.56 (1H, m), 1.46-1.10 (3H, m)
Purity	> 90% (NMR)	
MS	519 (M+1)	

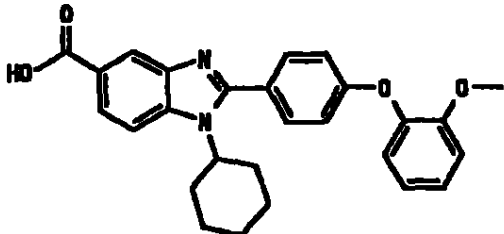
Example No.	105	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.94 and 7.87 (2H, ABq, J=8.6Hz), 7.68 and 7.17 (4H, A'B'q, J=8.7Hz), 7.46-7.33 (6H, m), 6.93 and 6.75 (2H, A'B'q, J=8.2Hz), 6.82 (1H, s), 5.13 (2H, s), 4.30 (1H, brt, J=12.2Hz), 2.39-2.18 (2H, m), 1.98-1.77 (4H, m), 1.71-1.59 (1H, m), 1.48-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	519 (M+1)	

212

Table 26

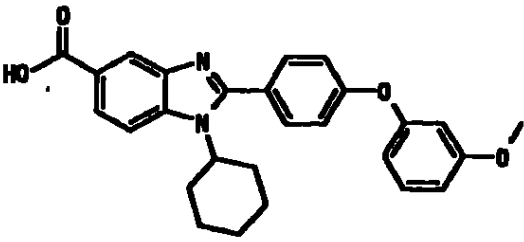
Example No.	106	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.89 (1H, brs), 9.73 (1H, s), 8.24 (1H, s), 8.03 and 7.91 (2H, ABq, J=8.7Hz), 7.66 and 7.04 (4H, A' B' q, J=8.7Hz), 7.16-7.03 (3H, m), 6.89 (2H, t, J=9.2Hz), 4.33 (1H, brt, J=12.2Hz), 2.40-2.18 (2H, m), 2.00-1.78 (4H, m), 1.70-1.58 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	429 (M+1)	

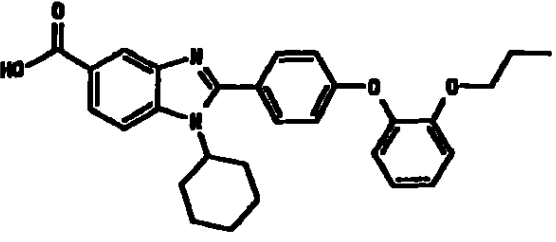
Example No.	107	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.98 (1H, brs), 9.82 (1H, brs), 8.27 (1H, s), 8.09 and 7.94 (2H, ABq, J=8.7Hz), 7.74 and 7.22 (4H, A' B' q, J=8.7Hz), 7.28-7.22 (1H, m), 6.67-6.54 (3H, m), 4.35 (1H, brt, J=12.2Hz), 2.40-2.20 (2H, m), 2.05-1.80 (4H, m), 1.72-1.59 (1H, m), 1.50-1.21 (3H, m)
Purity	> 90% (NMR)	
MS	429 (M+1)	

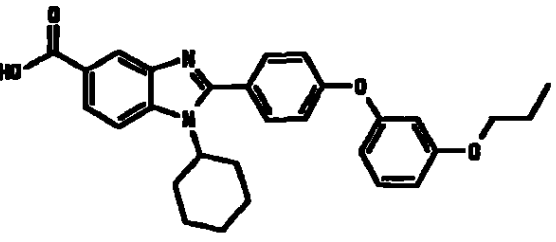
Example No.	108	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, s), 8.01 and 7.90 (2H, ABq, J=8.7Hz), 7.65 and 7.03 (4H, A' B' q, J=8.7Hz), 7.32-7.20 (3H, m), 7.08-7.03 (1H, m), 4.32 (1H, brt, J=12.2Hz), 3.77 (3H, s), 2.36-2.20 (2H, m), 2.00-1.78 (4H, m), 1.71-1.59 (1H, m), 1.44-1.11 (3H, m)
Purity	> 90% (NMR)	
MS	443 (M+1)	

101
459
713

Table 27

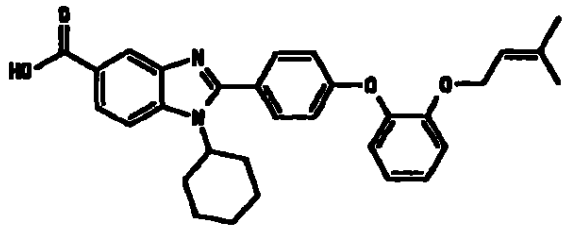
Example No.	109	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.24 (1H, s), 7.96 and 7.87 (2H, ABq, J=9.0 Hz), 7.69 and 7.19 (4H, A'B'q, J=8.6 Hz), 7.37 (1H, t, J=7.1 Hz), 6.84-6.70 (3H, m), 4.31 (1H, brt, J=12.2 Hz), 3.78 (3H, s), 2.39-2.20 (2H, m), 1.98-1.78 (4H, m), 1.76-1.60 (1H, m), 1.48-1.13 (3H, m)
Purity	> 90% (NMR)	
MS	443 (M+1)	

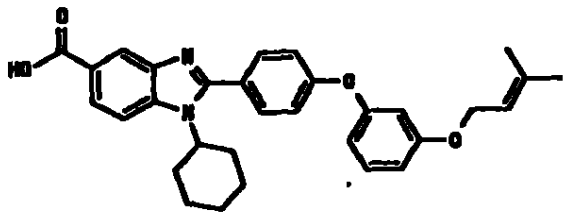
Example No.	110	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.26 and 8.04 (2H, ABq, J=8.8 Hz), 7.75 and 7.71 (4H, A'B'q, J=8.8 Hz), 7.32-7.03 (4H, m), 4.34 (1H, brt, J=12.2 Hz), 3.94 (2H, t, J=6.3 Hz), 2.40-2.19 (2H, m), 2.11-1.81 (4H, m), 1.72-1.16 (6H, m), 0.71 (3H, t, J=7.3 Hz)
Purity	> 90% (NMR)	
MS	471 (M+1)	

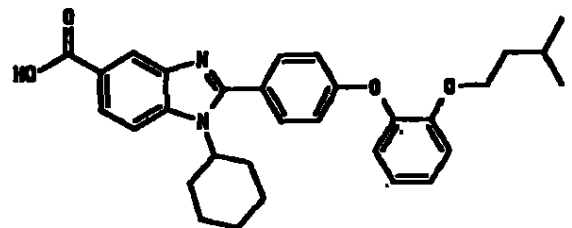
Example No.	111	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.22 (1H, s), 7.91 and 7.87 (2H, ABq, J=8.7 Hz), 7.68 and 7.18 (4H, A'B'q, J=8.7 Hz), 7.35 (1H, t, J=8.5 Hz), 6.80 (1H, d, J=9.0 Hz), 6.72-6.68 (2H, m), 4.30 (1H, brt, J=12.2 Hz), 3.94 (2H, t, J=6.5 Hz), 2.39-2.18 (2H, m), 1.97-1.58 (7H, m), 1.45-1.20 (3H, m), 0.97 (3H, t, J=7.4 Hz)
Purity	> 90% (NMR)	
MS	471 (M+1)	

102
240
714

Table 28

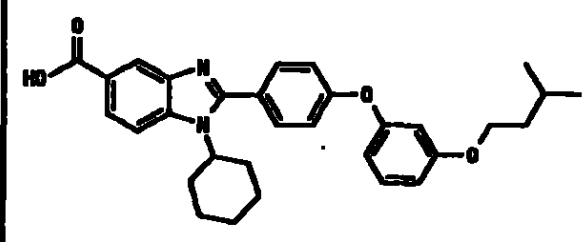
Example No.	112	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.73 (1H, s), 8.22 (1H, s), 7.94 and 7.85 (2H, ABq, J=9.3 Hz), 7.61 and 7.01 (4H, A' B' q, J=8.6 Hz), 7.25-7.00 (4H, m), 5.25 (2H, brs), 4.55 (2H, d, J=6.6 Hz), 4.29 (1H, brt, J=12.2 Hz), 2.38-2.18 (2H, m), 1.96-1.78 (4H, m), 1.70-1.56 (1H, m), 1.67 (3H, s), 1.60 (3H, s), 1.48-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	497 (M+1)	

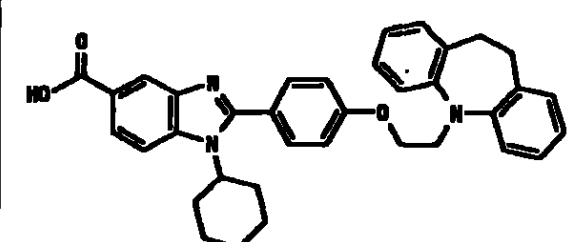
Example No.	113	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.23 (1H, s), 7.95 and 7.86 (2H, ABq, J=8.9 Hz), 7.69 and 7.18 (4H, A' B' q, J=8.9 Hz), 7.35 (1H, t, J=8.3 Hz), 6.81-6.69 (3H, m), 5.41 (2H, brs), 4.54 (2H, d, J=6.6 Hz), 4.31 (1H, brt, J=12.2 Hz), 2.41-2.18 (2H, m), 1.98-1.76 (4H, m), 1.73 (3H, s), 1.70-1.58 (1H, m), 1.68 (3H, s), 1.45-1.17 (3H, m)
Purity	> 90% (NMR)	
MS	497 (M+1)	

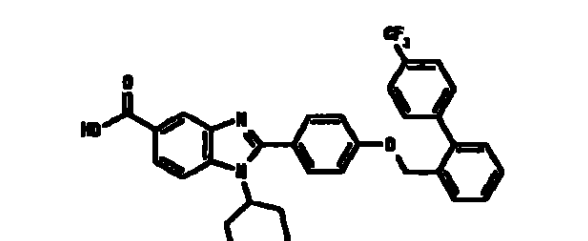
Example No.	114	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.73 (1H, s), 8.22 (1H, s), 7.94 and 7.85 (2H, ABq, J=8.4 Hz), 7.60 and 6.99 (4H, A' B' q, J=8.6 Hz), 7.29-7.00 (4H, m), 4.29 (1H, brt, J=12.2 Hz), 3.99 (2H, t, J=6.3 Hz), 2.41-2.20 (2H, m), 1.95-1.76 (4H, m), 1.70-1.14 (7H, m), 0.76 (3H, d, J=6.6 Hz)
Purity	> 90% (NMR)	
MS	499 (M+1)	

103
94
715

Table 29

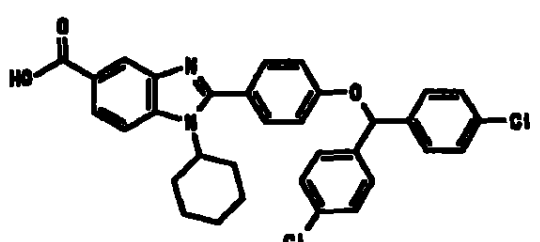
Example No.	115	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.93 and 7.87 (2H, ABq, J=8.6Hz), 7.69 and 7.19 (4H, A'B'q, J=8.6Hz), 7.35 (1H, t, J=7.8Hz), 6.82-6.69 (3H, m), 4.30 (1H, brt, J=12.2Hz), 4.00 (2H, t, J=6.9Hz), 2.38-2.20 (2H, m), 1.97-1.54 (8H, m), 1.47-1.20 (3H, m), 0.93 (6H, d, J=6.6Hz)
Purity	> 90% (NMR)	
MS	499 (M+1)	

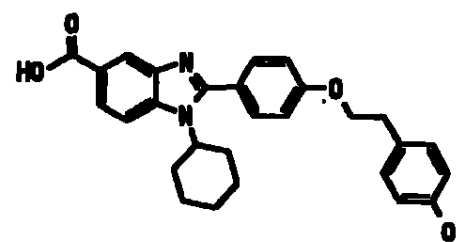
Example No.	116	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.30 (1H, s), 8.25 (1H, d, J=8.9Hz), 8.03 (1H, d, J=8.8Hz), 7.68 (2H, d, J=8.8Hz), 7.24 (2H, d, J=7.2Hz), 7.19-7.10 (6H, m), 6.94 (2H, t, J=7.2Hz), 4.34 (1H, m), 4.19 (4H, brs), 3.10 (4H, brs), 2.40-2.15 (2H, m), 2.10-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m).
Purity	> 90% (NMR)	
MS	557 (M+1)	

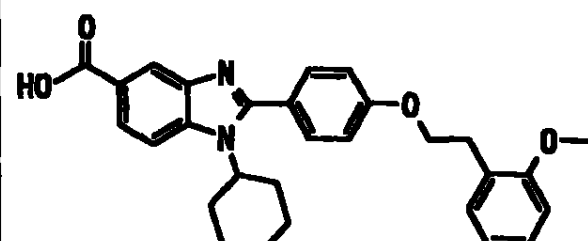
Example No.	117	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.8 (1H, brs), 8.22 (1H, s), 7.98 (1H, d, J=8.7Hz), 7.87 (1H, d, J=8.6Hz), 7.80 (2H, d, J=8.2Hz), 7.72-7.67 (3H, m), 7.59 (2H, d, J=8.7Hz), 7.54-7.51 (2H, m), 7.42-7.41 (1H, m), 7.11 (2H, d, J=8.8Hz), 5.09 (2H, s), 4.27 (1H, m), 2.40-2.15 (2H, m), 2.00-1.75 (4H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	571 (M+1)	

104
216

Table 30

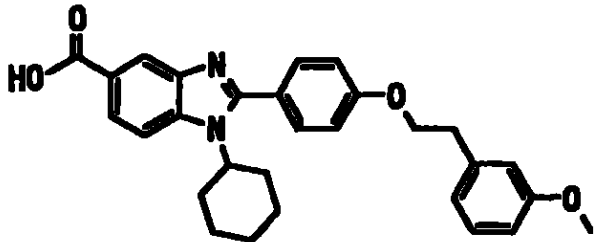
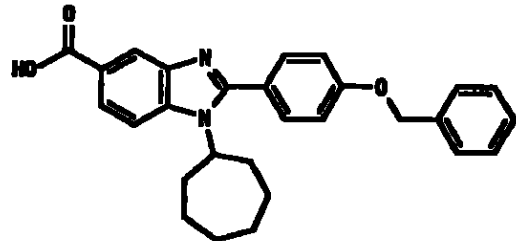
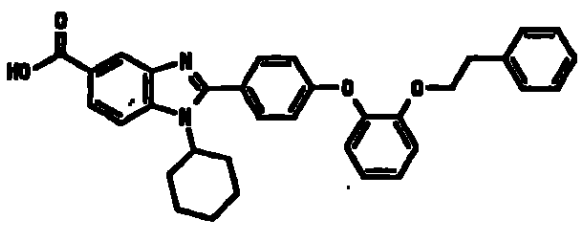
Example No.	118	1H NMR(δ) ppm
		300MHz, DMSO-d6 13.3 (1H, brs), 8.30 (1H, s), 8.25 (1H, d, J=8.9Hz), 8.04 (1H, d, J=8.7Hz), 7.72 (2H, d, J=8.8Hz), 7.57 (4H, d, J=8.6Hz), 7.47 (4H, d, J=8.6Hz), 7.33 (2H, d, J=8.9Hz), 6.84 (1H, s), 4.33 (1H, m), 2.45-2.10 (2H, m), 2.10-1.95 (2H, m), 1.95-1.70 (2H, m), 1.70-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	571 (M+1)	

Example No.	119	1H NMR(δ) ppm
		
Purity	> 90% (NMR)	
MS		

Example No.	120	1H NMR(δ) ppm
		
Purity	> 90% (NMR)	
MS		

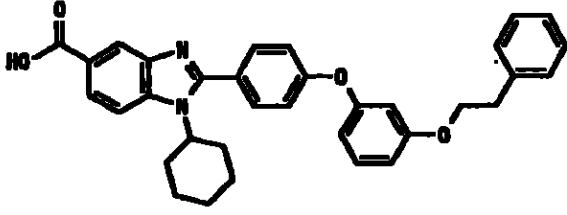
105
413
717

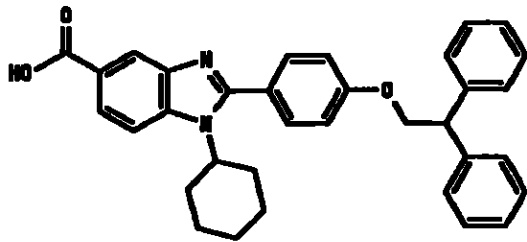
Table 31

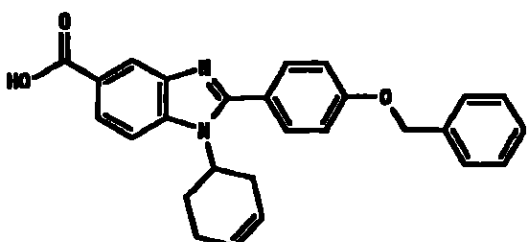
Example No.	121	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		
Example No.	122	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.8 (1H, brs), 8.22 (1H, s), 7.87 (2H, m), 7.62 (2H, d, J=8 .1Hz), 7.60-7.20 (7H, m), 5. 23 (2H, s), 4.46 (1H, m), 2.50 -2.30 (2H, m), 1.70-1.40 (10 H, m).
Purity	> 90% (NMR)	
MS	441(M+1)	
Example No.	123	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, s), 7.97 (1H, d, J=9 .0Hz), 7.87 (1H, d, J=8.4Hz) , 7.65 (2H, d, J=8.7Hz), 7.40 -7.05 (9H, m), 7.03 (2H, d, J= 8.4Hz), 4.31 (1H, m), 4.18 (2 H, t, J=6.6Hz), 2.81 (2H, t, J =6.3Hz), 2.40-2.20 (2H, m), 2.00-1.70 (4H, m), 1.70-1.5 0 (1H, m), 1.50-1.05 (3H, m).
Purity	> 90% (NMR)	
MS	533(M+1)	

105
44
718

Table 32

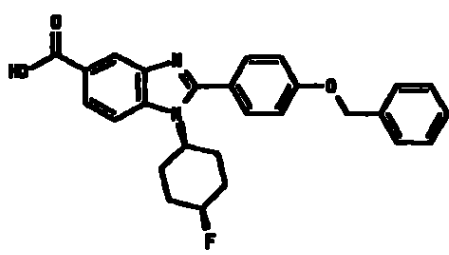
Example No.	124	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.1 (1H, brs), 8.29 (1H, s), 8.17 (1H, d, J=8.7Hz), 7.99 (1H, d, J=8.7Hz), 7.77 (2H, d, J=8.7Hz), 7.40-7.20 (8H, m), 6.84 (1H, d, J=9.3Hz), 6.75-6.72 (2H, m), 4.36 (1H, m), 4.22 (2H, t, J=6.8Hz), 3.04 (2H, t, J=6.7Hz), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	533 (M+1)	

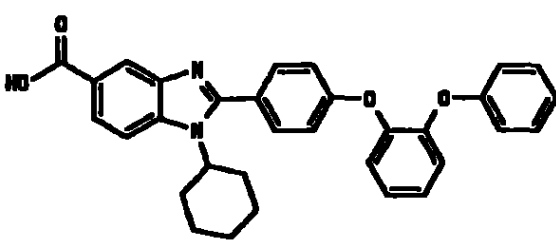
Example No.	125	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.28 (1H, d, J=8.7Hz), 8.05 (1H, d, J=9.0Hz), 7.73 (2H, d, J=9.0Hz), 7.43 (4H, d, J=7.2Hz), 7.36-7.20 (8H, m), 4.74 (2H, d, J=7.5Hz), 4.57 (1H, t, J=7.5Hz), 4.38 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.85 (2H, m), 1.85-1.55 (1H, m), 1.55-1.20 (3H, m).
Purity	> 90% (NMR)	
MS	517 (M+1)	

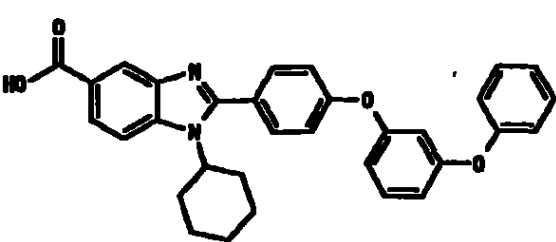
Example No.	126	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.14 (1H, d, J=8.7Hz), 8.03 (1H, d, J=8.7Hz), 7.77 (2H, d, J=9.0Hz), 7.52-7.31 (7H, m), 5.74 (2H, m), 5.26 (2H, s), 4.61 (1H, m), 2.96 (1H, m), 2.60-2.10 (5H, m).
Purity	> 90% (NMR)	
MS	425 (M+1)	

107
219

Table 33

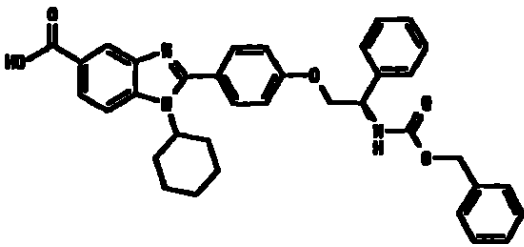
Example No.	127	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.2 (1H, brs), 8.33 (1H, s), 8.12 (1H, d, J=8.7Hz), 7.96 (1H, d, J=8.8Hz), 7.79 (2H, d, J=8.7Hz), 7.52-7.32 (7H, m), 5.26 (2H, s), 4.92 (1H, d, J=49.4Hz), 4.57 (1H, m), 2.65-2.35 (2H, m), 2.25-1.50 (6H, m).
Purity	> 90% (NMR)	
MS	445 (M+1)	

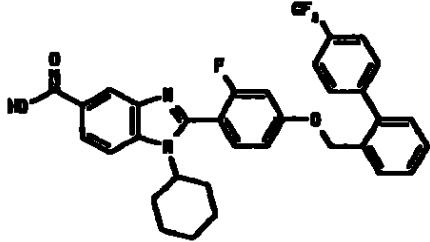
Example No.	128	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 7.92 and 7.85 (2H, ABq, J=8.6Hz), 7.61 and 7.06 (4H, A'B'q, J=8.6Hz), 7.36-6.91 (9H, m), 4.24 (1H, brt, J=12.2Hz), 2.35-2.15 (2H, m), 1.95-1.75 (4H, m), 1.70-1.58 (1H, m), 1.48-1.14 (3H, m)
Purity	> 90% (NMR)	
MS	505 (M+1)	

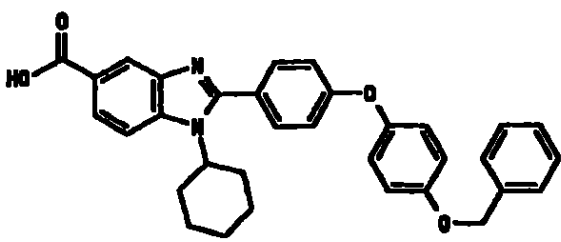
Example No.	129	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 7.92 and 7.86 (2H, ABq, J=8.6Hz), 7.69 and 7.22 (4H, A'B'q, J=8.6Hz), 7.52-7.39 (1H, m), 7.47 and 7.41 (2H, A'B'q, J=8.1Hz), 6.91 (1H, d, J=8.0Hz), 6.89 (1H, d, J=8.2Hz), 6.75 (1H, s), 4.36-4.18 (1H, m), 2.38-2.17 (2H, m), 1.95-1.76 (4H, m), 1.70-1.59 (1H, m), 1.44-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	505 (M+1)	

106
226
720

Table 34

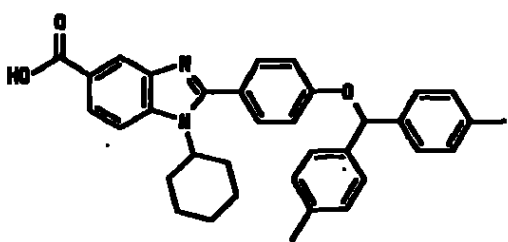
Example No.	130	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, s), 7.69 (2H, d, J=8.6Hz), 7.49-7.21 (1H, m), 5.08 and 5.03 (2H, ABq, J=12.6 Hz), 5.07-4.99 (1H, m), 4.26 (2H, d, J=6.6Hz), 2.40-2.18 (2H, m), 2.04-1.77 (4H, m), 1.70-1.58 (1H, m), 1.48-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	590 (M+1)	

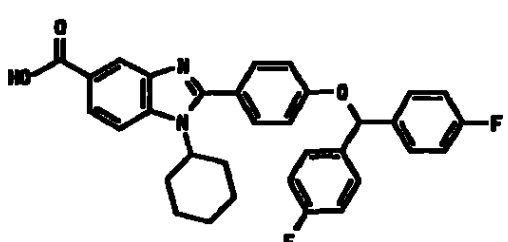
Example No.	131	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.29 (1H, s), 8.11 (1H, d, J=9.0Hz), 7.96 (1H, d, J=8.4Hz), 7.80 (2H, d, J=8.1Hz), 7.72-7.41 (7H, m), 7.12 (1H, d, J=12.6Hz), 7.01 (1H, d, J=8.4Hz), 5.12 (2H, s), 4.06 (1H, m), 2.35-2.10 (2H, m), 2.00-1.75 (4H, m), 1.75-1.55 (1H, m), 1.60-1.20 (3H, m).
Purity	> 90% (NMR)	
MS	589 (M+1)	

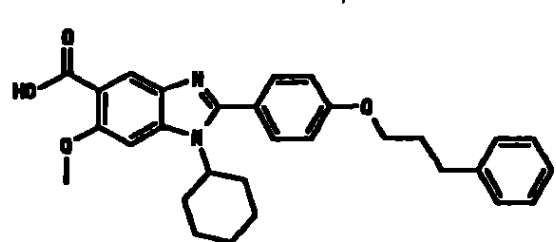
Example No.	132	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.8 (1H, brs), 8.23 (1H, s), 7.97 (1H, d, J=8.7Hz), 7.87 (1H, d, J=8.6Hz), 7.66 (2H, d, J=8.6Hz), 7.49-7.33 (5H, m), 7.17-7.05 (6H, m), 5.12 (2H, s), 4.31 (1H, m), 2.40-2.15 (2H, m), 2.05-1.20 (8H, m).
Purity	> 90% (NMR)	
MS	519 (M+1)	

107
94
221

Table 35

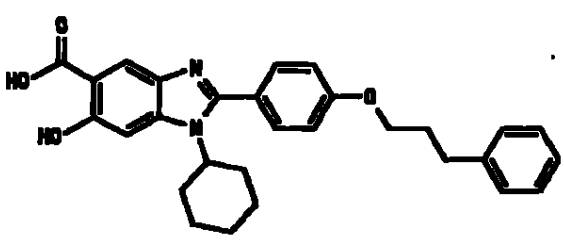
Example No.	133	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.57 (1H, s), 8.01 (1H, d, J=8.7Hz), 7.66 (1H, d, J=8.7Hz), 7.51 (2H, d, J=8.7Hz), 7.31 (4H, d, J=8.0Hz), 7.16 (4H, d, J=8.0Hz), 7.09 (2H, d, J=8.7Hz), 6.26 (1H, s), 4.37 (1H, m), 2.41-2.28 (2H, m), 2.33 (6H, s), 2.03-1.84 (4H, m), 1.77 (1H, m), 1.45-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	531 (M+1)	

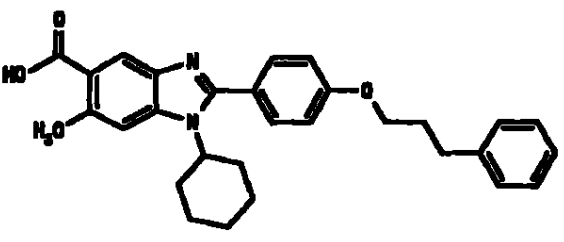
Example No.	134	1H NMR (δ) ppm
		8.59 (1H, d, J=1.5Hz), 8.02 (1H, dd, J=8.7, 1.5Hz), 7.68 (1H, d, J=8.7Hz), 7.54 (2H, d, J=8.8Hz), 7.39 (4H, dd, J=8.7, 5.3Hz), 7.08 (4H, d, J=8.7Hz), 7.05 (2H, d, J=8.8Hz), 6.29 (1H, s), 4.36 (1H, m), 2.43-2.19 (2H, m), 2.04-1.85 (4H, m), 1.78 (1H, m), 1.45-1.23 (3H, m)
Purity	> 90% (NMR)	
MS	539 (M+1)	

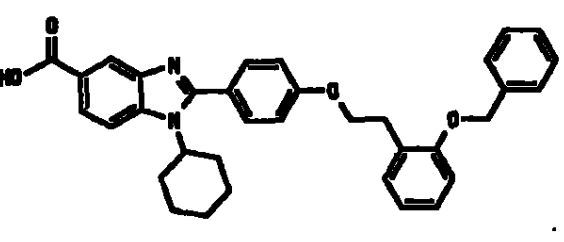
Example No.	135	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.34 (1H, brs), 7.93 (1H, s), 7.55 (1H, d, J=8.6Hz), 7.33-7.15 (6H, m), 7.11 (2H, d, J=8.6Hz), 4.30-4.20 (1H, m), 4.07 (2H, t, J=6.3Hz), 3.93 (3H, s), 2.78 (2H, t, J=7.4Hz), 2.35-2.19 (2H, m), 2.12-2.00 (2H, m), 1.91-1.79 (4H, m), 1.69-1.60 (1H, m), 1.47-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	485 (M+1)	

140
222

Table 36

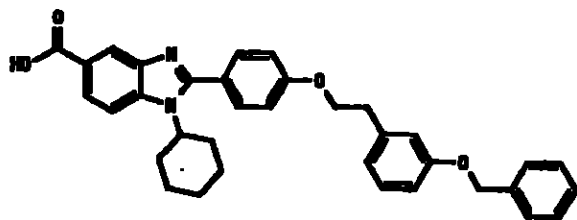
Example No.	136	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.13 (1H, s), 7.65 (2H, d, J=8.7Hz), 7.63 (1H, s), 7.35-7.12 (7H, m), 4.35-4.20 (1H, m), 4.10 (1H, t, J=6.3Hz), 2.78 (2H, t, J=7.5Hz), 2.33-1.78 (8H, m), 1.70-1.16 (4H, m)
Purity	> 90% (NMR)	
MS	471 (M+1)	

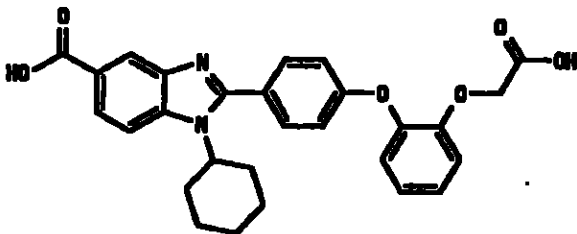
Example No.	137	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, s), 8.11 (1H, s), 7.76 (2H, d, J=9.0Hz), 7.37-7.16 (7H, m), 4.43-4.30 (1H, m), 4.13 (2H, t, J=6.3Hz), 2.84-2.68 (5H, m), 2.42-2.22 (2H, m), 2.18-1.80 (6H, m), 1.70-1.20 (4H, m)
Purity	> 90% (NMR)	
MS	469 (M+1)	

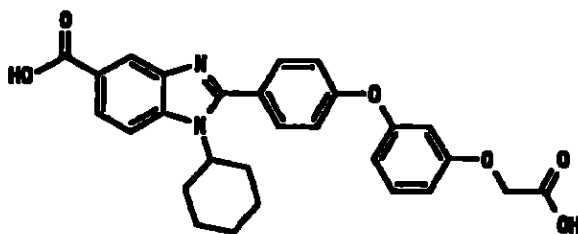
Example No.	138	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

H1 924
 923

Table 37

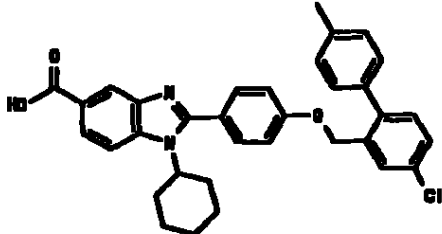
Example No.	139	1H NMR(δ) ppm
		
Purity	> 90% (NMR)	
MS		

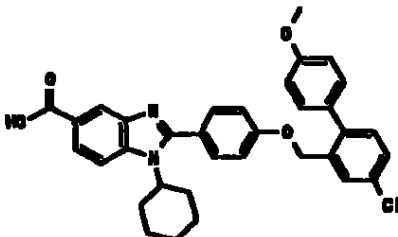
Example No.	140	1H NMR(δ) ppm
		
Purity	> 90% (NMR)	
MS		

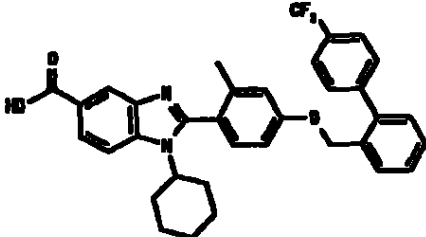
Example No.	141	1H NMR(δ) ppm
		
Purity	> 90% (NMR)	
MS		

142
924

Table 38

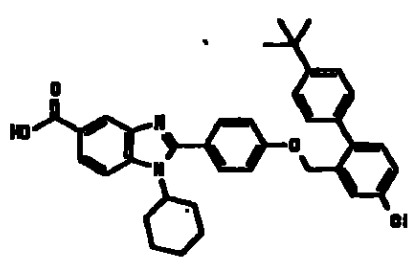
Example No.	142	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.27 (1H, d, J=8.7Hz), 8.05 (1H, d, J=9.0Hz), 7.76-7.72 (3H, m), 7.54 (1H, d, J=8.4Hz), 7.39-7.22 (7H, m), 5.11 (1H, s), 4.36 (1H, m), 2.35 (3H, s), 2.35-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	551 (M+1)	

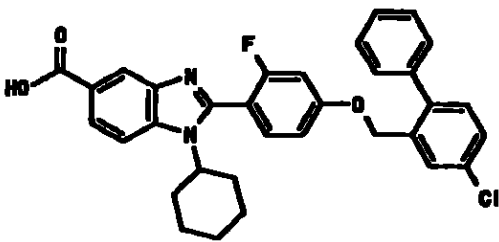
Example No.	143	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.1 (1H, brs), 8.30 (1H, s), 8.24 (1H, d, J=8.8Hz), 8.03 (1H, d, J=8.7Hz), 7.74-7.71 (3H, m), 7.52 (1H, d, J=8.3Hz), 7.40-7.36 (3H, m), 7.23 (2H, d, J=8.8Hz), 7.01 (2H, d, J=8.7Hz), 5.11 (2H, s), 4.35 (1H, m), 3.79 (3H, s), 2.45-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	567 (M+1)	

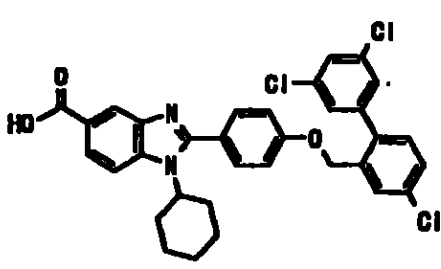
Example No.	144	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.0 (1H, brs), 8.31 (1H, s), 8.23 (1H, d, J=8.7Hz), 8.04 (1H, d, J=8.7Hz), 7.80 (2H, d, J=8.3Hz), 7.70-7.66 (3H, m), 7.55-7.40 (4H, m), 7.03-6.95 (2H, m), 5.08 (2H, s), 4.03 (1H, m), 2.40-2.15 (2H, m), 2.18 (3H, s), 2.05-1.70 (4H, m), 1.70-1.50 (1H, m), 1.50-1.10 (3H, m).
Purity	> 90% (NMR)	
MS	585 (M+1)	

13
23
725

Table 39

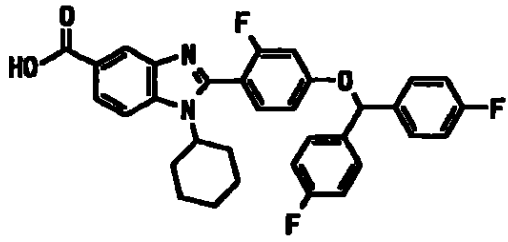
Example No.	145	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.23 (1H, d, J=8.8Hz), 8.02 (1H, d, J=8.7Hz), 7.73-7.71 (3H, m), 7.54 (1H, d, J=8.3Hz), 7.48 (2H, d, J=8.4Hz), 7.41-7.37 (3H, m), 7.22 (2H, d, J=8.7Hz), 5.13 (2H, s), 4.34 (1H, m), 2.40-2.20 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.70-1.55 (1H, m), 1.50-1.15 (3H, m), 1.31 (9H, s).
Purity	> 90% (NMR)	
MS	593 (M+1)	

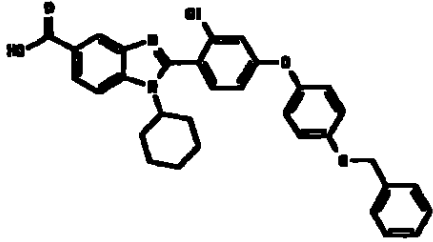
Example No.	146	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.29 (1H, s), 8.13 (1H, d, J=8.7Hz), 7.97 (1H, d, J=8.6Hz), 7.76 (1H, d, J=2.1Hz), 7.63 (1H, t, J=8.5Hz), 7.57 (1H, d, J=8.2), 7.55-7.35 (6H, m), 7.15 (1H, d, J=12.1Hz), 7.02 (1H, d, J=8.6Hz), 5.10 (2H, s), 4.07 (1H, m), 2.35-2.10 (2H, m), 2.00-1.70 (4H, m), 1.70-1.55 (1H, m), 1.50-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	555 (M+1)	

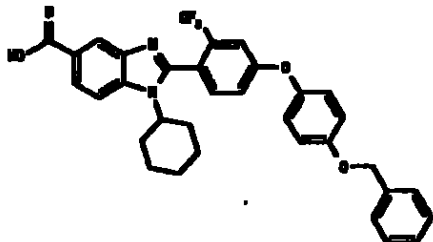
Example No.	147	1H NMR (δ) ppm
		300MHz, CDCl3 8.61 (1H, s), 8.04 (1H, d, J=8.7Hz), 7.69 (1H, d, J=8.7Hz), 7.66 (1H, d, J=2.4Hz), 7.59 (2H, d, J=8.7Hz), 7.42 (1H, d, J=8.0), 7.38 (1H, t, J=1.8Hz), 7.28 (2H, d, J=1.8Hz), 7.26 (1H, d, J=8.0Hz), 7.03 (2H, d, J=8.7Hz), 4.94 (2H, s), 4.37 (1H, m), 2.43-2.21 (2H, m), 2.17-1.86 (4H, m), 1.79 (1H, m), 1.43-1.26 (3H, m).
Purity	> 90% (NMR)	
MS	605 (M+1)	

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Table 40

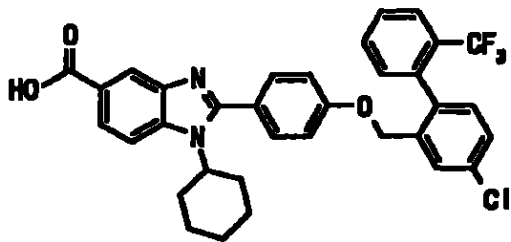
Example No.	148	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (s, 1H), 7.89 (1H, d, J=8.7Hz), 7.87 (1H, d, J=8.7Hz), 7.63-7.46 (5H, m), 7.30-7.12 (5H, m), 7.08 (1H, d, J=11.0Hz), 6.81 (1H, s), 3.92 (1H, m), 2.15-2.06 (2H, m), 1.89-1.72 (4H, m), 1.61 (1H, m), 1.42-1.09 (3H, m).
Purity	> 90% (NMR)	
MS	557 (M+1)	

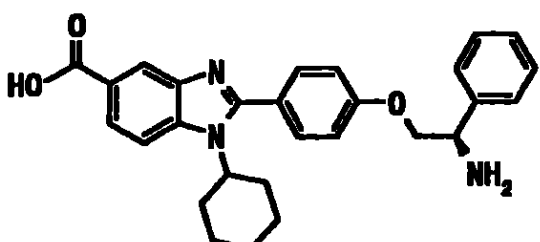
Example No.	149	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, d, J=1.5Hz), 7.96 (1H, d, J=9.0Hz), 7.88 (1H, dd, J=9.0, 1.5Hz), 7.58 (1H, d, J=8.7Hz), 7.50-7.30 (5H, m), 7.22-7.00 (6H, m), 5.13 (2H, s), 3.98-3.80 (1H, s), 2.36-1.10 (10H, m)
Purity	> 90% (NMR)	
MS	553 (M+1)	

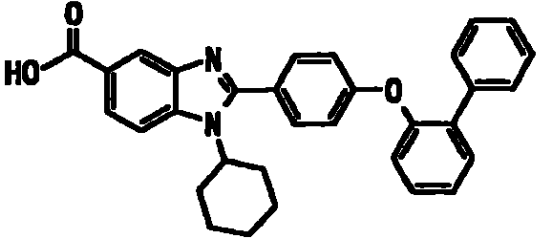
Example No.	150	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 8.95 (1H, d, J=8.4Hz), 7.88 (1H, d, J=8.7Hz), 7.66 (1H, d, J=8.4Hz), 7.52-7.28 (7H, m), 7.23 (2H, d, J=9.3Hz), 7.14 (2H, d, J=8.7Hz), 5.14 (2H, s), 3.90-3.72 (1H, m), 2.20-1.10 (10H, m)
Purity	> 90% (NMR)	
MS	587 (M+1)	

115
453
727

Table 41

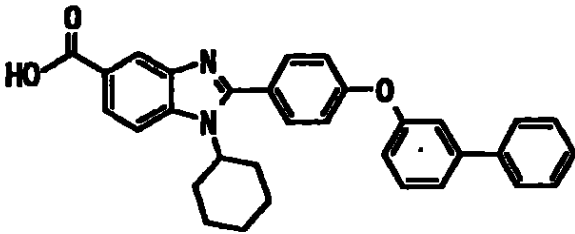
Example No.	151	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.18 (1H, s), 7.92-7.78 (3H, m), 7.78-7.58 (3H, m), 7.58-7.44 (4H, m), 7.29 (1H, d, J=8.2Hz), 7.01 (2H, d, J=8.7Hz), 4.88 (1H, d, J=11.8Hz), 4.80 (1H, d, J=11.8Hz), 4.22 (1H, m), 2.37-2.16 (2H, m), 1.95-1.75 (4H, m), 1.64 (1H, m), 1.48-1.14 (3H, m).
Purity	> 90% (NMR)	
MS	605 (M+1)	

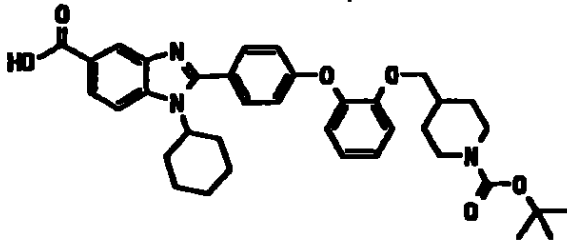
Example No.	152	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (2H, m), 7.99-7.80 (2H, m), 7.63-7.08 (9H, m), 4.20-3.98 (4H, m), 2.20-2.15 (2H, m), 1.95-1.74 (4H, m), 1.70-1.54 (1H, m), 1.44-1.14 (3H, m)
Purity	> 90% (NMR)	
MS	456 (M+1)	

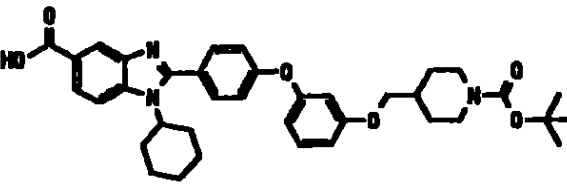
Example No.	153	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.20 (1H, s), 8.93 and 7.83 (2H, ABq, J=8.7Hz), 7.86-7.21 (11H, m), 7.03 (2H, d, J=8.7Hz), 4.20 (1H, brt, J=12.2Hz), 2.32-2.13 (2H, m), 1.92-1.74 (4H, m), 1.69-1.58 (1H, m), 1.45-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	489 (M+1)	

110
951
728

Table 42

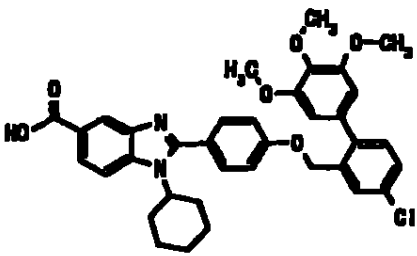
Example No.	154	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.94 and 7.86 (2H, ABq, J=8.6Hz), 7.72-7.16 (13H, m), 5.25 (2H, brs), 4.55 (2H, d, J=6.6Hz), 4.31 (1H, brt, J=12.2Hz), 2.37-2.18 (2H, m), 1.98-1.77 (4H, m), 1.70-1.58 (1H, m), 1.48-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	489 (M+1)	

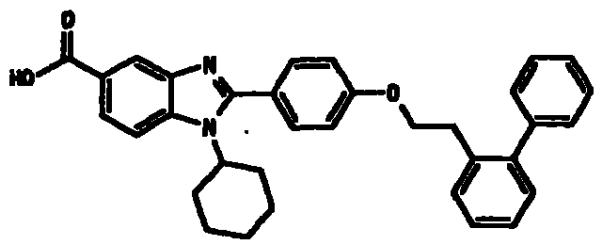
Example No.	155	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 7.85 and 7.61 (2H, ABq, J=8.7Hz), 7.61 and 6.99 (4H, A' B' q, J=8.7Hz), 7.28-7.18 (1H, m), 7.25 (2H, d, J=7.5Hz), 7.07-6.99 (1H, m), 4.30 (1H, brt, J=12.2Hz), 3.83 (2H, d, J=6.0Hz), 3.82-3.72 (1H, m), 2.68-2.49 (2H, m), 2.39-2.21 (2H, m), 1.95-1.80 (4H, m), 1.79-1.60 (2H, m), 1.46-1.22 (5H, m), 1.30 (9H, s), 1.00-0.82 (2H, m)
Purity	> 90% (NMR)	
MS	626 (M+1)	

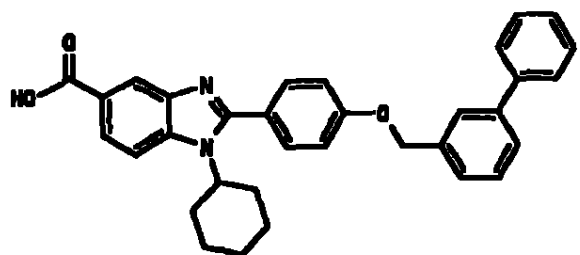
Example No.	156	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.22 (1H, s), 7.92 and 7.86 (2H, ABq, J=8.7Hz), 7.68 and 7.18 (4H, A' B' q, J=8.7Hz), 7.35 (1H, t, J=8.5Hz), 6.80 (1H, d, J=8.3Hz), 6.72-6.70 (2H, m), 4.30 (1H, brt, J=12.2Hz), 3.99 (2H, brd, J=12.0Hz), 3.85 (2H, d, J=6.3Hz), 2.82-2.62 (2H, m), 2.38-2.20 (2H, m), 1.99-1.59 (8H, m), 1.42-1.03 (5H, m), 1.39 (9H, s)
Purity	> 90% (NMR)	
MS	626 (M+1)	

117
729

Table 43

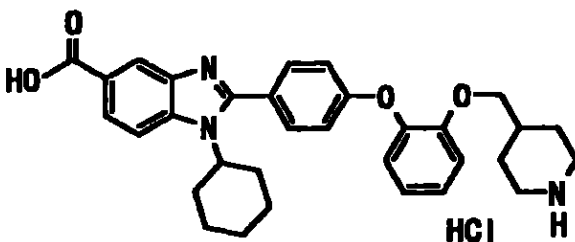
Example No.	157	¹ H NMR (δ) ppm
		300MHz, DMSO-d ₆ 12.78 (1H, brs), 8.22 (1H, s), 7.96 (1H, d, J=8.6Hz), 7.86 (1H, d, J=8.6Hz), 7.75 (1H, d, J=2.2Hz), 7.60 (2H, d, J=8. 4Hz), 7.55 (1H, dd, J=8.3, 2. 2Hz), 7.48 (1H, d, J=8.3Hz), 7.18 (2H, d, J=8.4Hz), 6.73 (2H, s), 5.08 (2H, s), 4.23 (1H, m), 3.68 (9H, s), 2.37-2.17 (2H, m), 1.99-1.79 (4H, m), 1.65 (1H, s), 1.49-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	627 (M+1)	

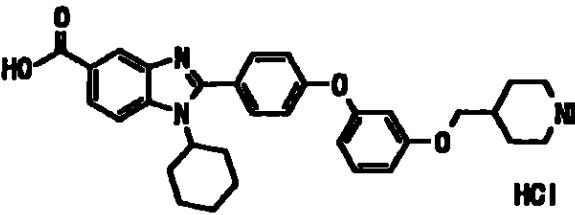
Example No.	158	¹ H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

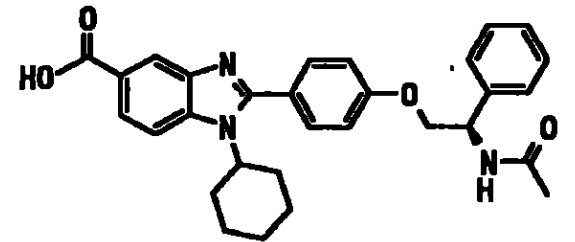
Example No.	159	¹ H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

730

Table 44

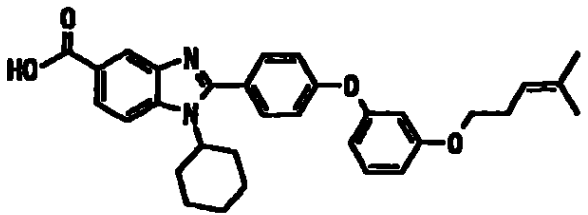
Example No.	160	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.90 (1H, brs), 8.59 (1H, brs), 8.33 (1H, s), 8.18 and 8.00 (2H, ABq, J=8.5Hz), 7.73 and 7.10 (4H, A' B' q, J=8.5Hz), 7.32-7.05 (4H, m), 4.35 (1H, brt, J=12.2Hz), 3.86 (2H, d, J=6.3Hz), 3.25-3.08 (2H, m), 2.85-2.66 (2H, m), 2.40-2.28 (2H, m), 2.07-1.14 (15H, m)
Purity	> 90% (NMR)	
MS	526 (M+1)	

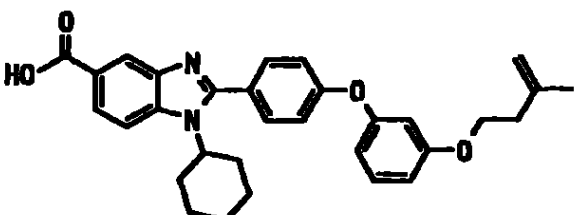
Example No.	161	1H NMR (δ) ppm
		300MHz, DMSO-d6 9.05 (1H, brs), 8.76 (1H, brs), 8.31 (1H, s), 8.19 and 8.00 (2H, ABq, J=8.3Hz), 7.79 and 7.25 (4H, A' B' q, J=8.3Hz), 7.39 (1H, brs), 6.86-6.74 (4H, m), 4.37 (1H, brt, J=12.2Hz), 3.89 (2H, d, J=5.0Hz), 3.35-3.18 (2H, m), 2.98-2.75 (2H, m), 2.38-2.17 (2H, m), 2.16-1.15 (15H, m)
Purity	> 90% (NMR)	
MS	526 (M+1)	

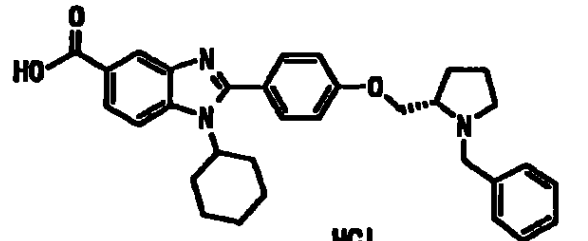
Example No.	162	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.87 (1H, brs), 8.58 (1H, d, J=6.0Hz), 8.23 (1H, s), 7.99 and 7.80 (2H, ABq, J=8.6Hz), 7.61 and 7.18 (4H, A' B' q, J=8.0Hz), 7.45-7.30 (5H, m), 5.29 (1H, brs), 4.26 (1H, brt, J=12.2Hz), 2.37-2.11 (2H, m), 2.00-1.71 (4H, m), 1.92 (3H, s), 1.70-1.52 (1H, m), 1.45-1.11 (3H, m)
Purity	> 90% (NMR)	
MS	498 (M+1)	

109
231

Table 45

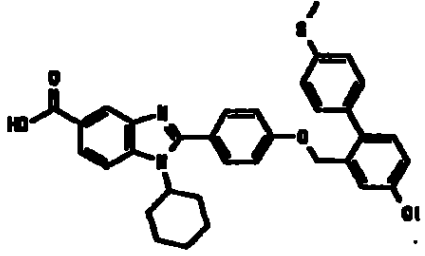
Example No.	163	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.95 and 7.86 (2H, ABq, J=8.6Hz), 7.69 and 7.18 (4H, A'B'q, J=8.6Hz), 7.35 (1H, t, J=8.6Hz), 6.80 (1H, d, J=7.5Hz), 6.72-6.69 (2H, m), 5.20 (1H, t, J=3.7Hz), 4.31 (1H, brt, J=12.2Hz), 3.95 (2H, t, J=6.8Hz), 2.49-2.19 (4H, m), 1.97-1.76 (4H, m), 1.68 (3H, s), 1.67-1.54 (1H, m), 1.61 (3H, s), 1.45-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	511 (M+1)	

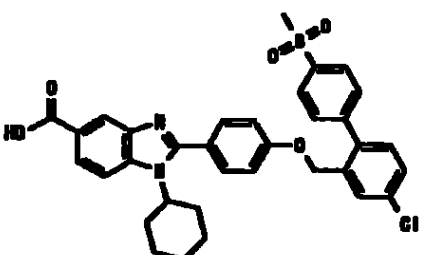
Example No.	164	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.20 (1H, s), 7.87 (2H, s), 7.68 and 7.18 (4H, ABq, J=8.7Hz), 7.35 (1H, t, J=7.9Hz), 6.81 (1H, d, J=9.4Hz), 6.72 (1H, s), 6.71 (1H, d, J=6.8Hz), 4.80 (2H, s), 4.29 (1H, brt, J=12.2Hz), 4.10 (1H, t, J=6.7Hz), 2.43 (1H, t, J=6.7Hz), 2.39-2.19 (2H, m), 1.97-1.78 (4H, m), 1.76 (3H, s), 1.70-1.56 (1H, m), 1.43-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	497 (M+1)	

Example No.	165	1H NMR (δ) ppm
 HCl		300MHz, DMSO-d6 11.21 (1H, brs), 8.33 (1H, s), 8.25 (1H, d, J=8.6Hz), 8.04 (1H, d, J=8.6Hz), 7.78 (2H, d, J=8.7Hz), 7.70-7.67 (2H, m), 7.55-7.42 (3H, m), 7.27 (2H, d, J=8.7Hz), 4.73-4.30 (5H, m), 4.20-3.97 (1H, m), 3.42-3.10 (2H, m), 2.45-1.23 (4H, m)
Purity	> 90% (NMR)	
MS		

120
732

Table 46

Example No.	166	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.27 (1H, s), 8.13 (1H, d, J=8.4Hz), 7.97 (1H, d, J=9.0Hz), 7.73 (1H, d, J=1.8Hz), 7.68 (2H, d, J=8.4Hz), 7.54 (1H, d, J=8.4, 2.1Hz), 7.41-7.31 (5H, m), 7.19 (2H, d, J=8.4Hz), 5.10 (2H, s), 4.32 (1H, m), 2.50 (3H, s), 2.40-2.15 (2H, m), 2.10-1.75 (4H, m), 1.75-1.55 (1H, m), 1.55-1.10 (3H, m).
Purity	> 90% (NMR)	
MS	583 (M+1)	

Example No.	167	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.25 (1H, s), 8.09 (1H, d, J=8.4Hz), 8.00 (2H, d, J=8.4Hz), 7.94 (1H, d, J=8.7Hz), 7.80 (1H, d, J=2.1Hz), 7.73 (2H, d, J=8.1Hz), 7.65 (2H, d, J=8.7Hz), 7.60 (1H, dd, J=8.1, 2.1Hz), 7.44 (1H, d, J=8.1Hz), 7.16 (2H, d, J=8.7Hz), 5.13 (2H, s), 4.30 (1H, m), 3.26 (3H, s), 2.40-1.15 (2H, m), 2.05-1.75 (4H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	615 (M+1)	

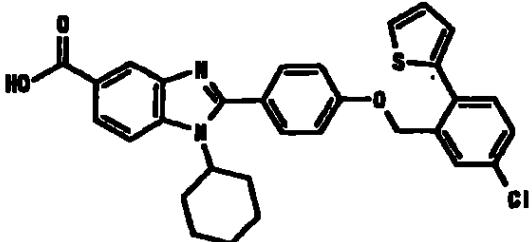
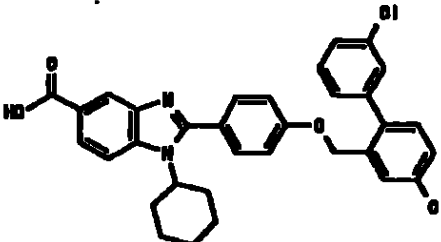
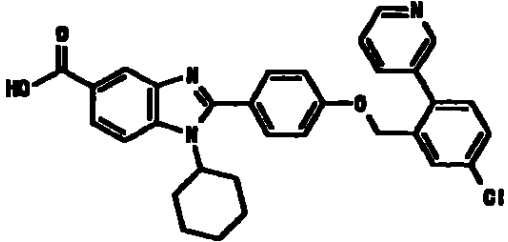
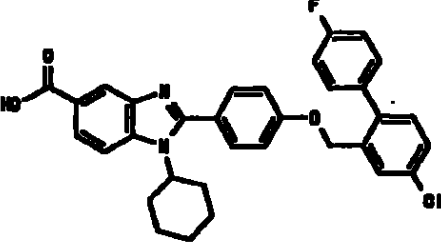
Example No.	168	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.1 (1H, brs), 8.32 (1H, s), 8.28 (1H, d, J=8.8Hz), 8.05 (1H, d, J=8.7Hz), 7.80-7.75 (3H, m), 7.69 (1H, d, J=4.1Hz), 7.57 (2H, m), 7.34-7.29 (3H, m), 7.20-7.15 (1H, m), 5.24 (2H, s), 4.39 (1H, m), 2.45-2.20 (2H, m), 2.20-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	543 (M+1)	

Table 47

Example No.	169	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.26 (1H, d, J=8.7Hz), 8.05 (1H, d, J=8.7Hz), 7.78-7.71 (3H, m), 7.59-7.41 (6H, m), 7.23 (2H, d, J=9.0Hz), 5.11 (2H, s), 4.35 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	571 (M+1)	

Example No.	170	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.7 (1H, brs), 8.66 (1H, s), 8.61 (1H, m), 8.21 (1H, s), 7.92-7.79 (4H, m), 7.61-7.56 (3H, m), 7.50-7.43 (2H, m), 7.10 (2H, d, J=8.7Hz), 5.09 (2H, s), 4.26 (1H, m), 2.40-2.15 (2H, m), 2.00-1.75 (4H, m), 1.75-1.55 (1H, m), 1.50-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	538 (M+1)	

Example No.	171	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.31 (1H, s), 8.25 (1H, d, J=8.7Hz), 8.04 (1H, d, J=8.7Hz), 7.74-7.71 (3H, m), 7.57-7.46 (3H, m), 7.39 (1H, d, J=8.1Hz), 7.31-7.21 (4H, m), 5.11 (2H, s), 4.35 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	555 (M+1)	

122
d6

734

Table 48

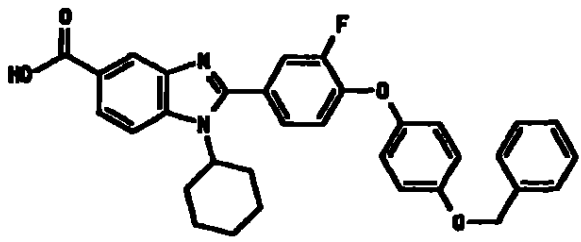
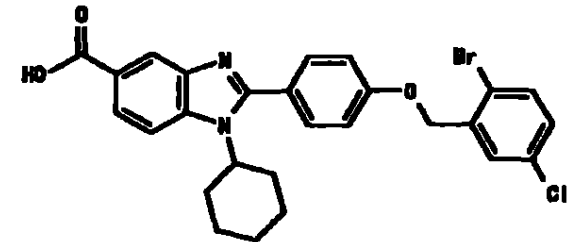
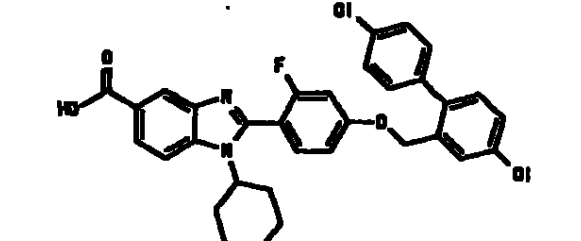
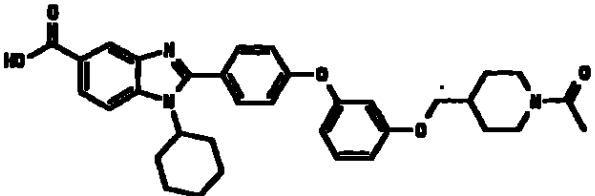
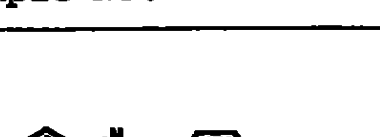
Example No.	172	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, s), 7.99 (1H, d, J=8.7Hz), 7.88 (1H, d, J=10.5Hz), 7.70 (1H, dd, J=11.4, 1.8Hz), 7.48-7.32 (6H, m), 7.17-7.09 (5H, m), 5.12 (2H, s), 4.30 (1H, m), 2.40-2.15 (2H, m), 2.05-1.75 (4H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	537 (M+1)	
Example No.	173	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.29 (1H, d, J=8.7Hz), 8.06 (1H, d, J=8.7Hz), 7.82-7.74 (4H, m), 7.45 (1H, dd, J=8.4, 3.0Hz), 7.39 (2H, d, J=8.7Hz), 5.28 (2H, s), 4.40 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m)
Purity	> 90% (NMR)	
MS	540 (M+1)	
Example No.	174	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.80 (1H, brs), 8.26 (1H, s), 8.01 (1H, d, J=8.7Hz), 7.85 (1H, d, J=8.7Hz), 7.80-7.70 (1H, m), 7.60-7.36 (7H, m), 7.18-6.91 (2H, m), 5.09 (2H, s), 4.11-3.90 (1H, m), 2.32-1.18 (14H, m)
Purity	> 90% (NMR)	
MS	590 (M+1)	

Table 49

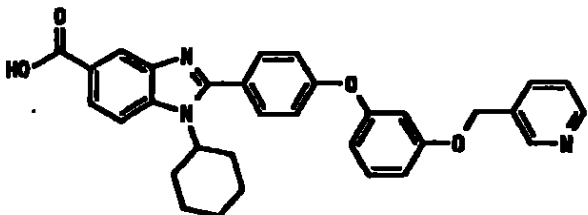
Example No.	175	¹ H NMR (δ) ppm 300MHz, DMSO-d ₆ 12.75 (1H, s), 8.21 (1H, s), 7.94 and 7.85 (2H, ABq, J=8.7 Hz), 7.61 and 7.00 (4H, A' B' q, J=8.5 Hz), 7.31-6.91 (2H, m), 7.25 (2H, d, J=7.7 Hz), 5.41 (2H, brs), 4.54 (2H, d, J=6.6 Hz), 4.35-4.14 (2H, m), 2.49-2.15 (3H, m), 1.95-1.55 (5H, m), 1.50-1.13 (5H, m), 1.10-0.77 (2H, m)
Purity	> 90% (NMR)	
MS	568 (M+1)	

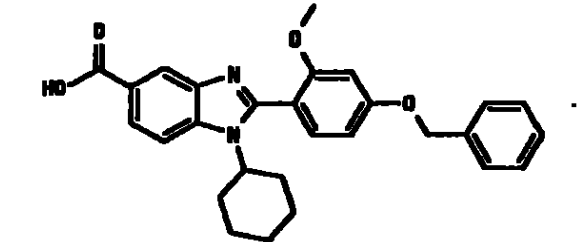
Example No.	176	¹ H NMR (δ) ppm
		300MHz, DMSO-d ₆ 8. 24 (1H, s), 7. 97and7. 87 (2 H, ABq, J=8. 6Hz), 7. 69and7. 19 (4H, A' B' q, J=8. 6Hz), 7. 35 (1H, t, J=8. 1Hz), 6. 81 (1H, d, J=9. 2Hz), 6. 72 (1H, s), 6. 71 (1H, d, J=6. 5Hz), 4. 48-4. 20 (2H, m), 3. 95-3. 75 (3H, m), 3. 03 (1H, t, J=12. 3Hz), 2. 60-2. 40 (1H, m), 2. 39-2. 15 (2 H, m), 2. 07-1. 58 (6H, m), 1. 99 (3H, s), 1. 50-1. 00 (5H, m)
Purity	> 90% (NMR)	
MS	568 (M+1)	

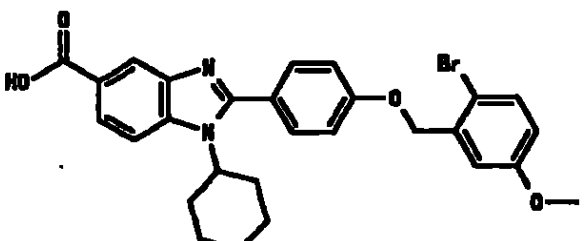
Example No.	177	¹ H NMR (δ) ppm
		300MHz, DMSO-d ₆ 12.76 (1H, s), 8.23 (1H, s), 7.96 and 7.86 (2H, ABq, J=8.6 Hz), 7.69 and 7.20 (4H, A'B'q, J=8.6 Hz), 7.39 (1H, t, J=8.2 Hz), 6.86 (1H, d, J=8.3 Hz), 6.81 (1H, s), 6.76 (1H, d, J=8.0 Hz), 4.83 (2H, s), 4.31 (1H, brt, J=12.2 Hz), 2.39-2.19 (2H, m), 1.99-1.79 (4H, m), 1.70-1.58 (1H, m), 1.48-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	467 (M+1)	

124
852
736

Table 50

Example No.	178	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.85 (1H, s), 8.75 (1H, s), 8.63 (2H, d, J=3.8Hz), 8.25 (1H, s), 8.04-8.01 (2H, m), 8.02 and 7.90 (2H, ABq, J=8.6Hz), 7.72 and 7.20 (4H, A'B'q, J=8.6Hz), 7.57 (2H, dd, J=7.8, 5.0Hz), 7.40 (1H, t, J=8.2Hz), 6.93 (1H, d, J=8.2Hz), 6.87 (1H, s), 6.77 (1H, d, J=8.2Hz), 5.23 (2H, s), 4.33 (1H, br t, J=12.2Hz), 2.40-2.18 (2H, m), 2.00-1.55 (5H, m), 1.50-1.15 (2H, m)
Purity	> 90% (NMR)	
MS	520 (M+1)	

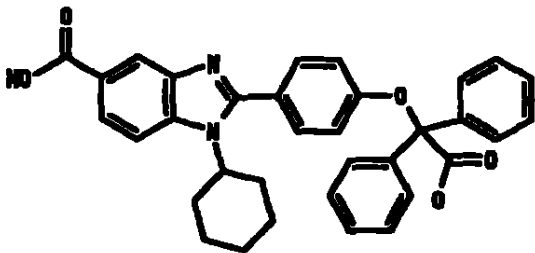
Example No.	179	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.29 (1H, d, J=9.0Hz), 8.06 (1H, d, J=8.7Hz), 7.61 (1H, d, J=8.4Hz), 7.58-7.32 (5H, m), 6.98 (1H, d, J=2.1Hz), 6.93 (1H, dd, J=8.7, 2.1Hz), 5.27 (2H, s), 4.16-4.00 (1H, m), 3.87 (3H, s), 2.20-2.12 (2H, m), 2.02-1.98 (4H, m), 1.70-1.60 (1H, m), 1.52-1.10 (3H, m)
Purity	> 90% (NMR)	
MS	457 (M+1)	

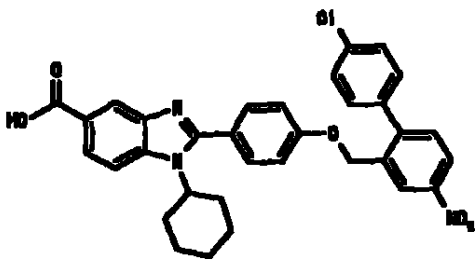
Example No.	180	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 7.91 (1H, d, J=8.6Hz), 7.85 (1H, d, J=8.6Hz), 7.63 (2H, d, J=8.4Hz), 7.60 (1H, d, J=9.0Hz), 7.25 (2H, d, J=8.4Hz), 7.23 (1H, d, J=3.0Hz), 6.95 (1H, dd, J=9.0, 3.0Hz), 5.19 (2H, s), 4.30 (1H, m), 3.78 (3H, s), 2.40-2.19 (2H, m), 2.00-1.87 (4H, m), 1.66 (1H, m), 1.49-1.18 (3H, m)
Purity	> 90% (NMR)	
MS	536 (M+1)	

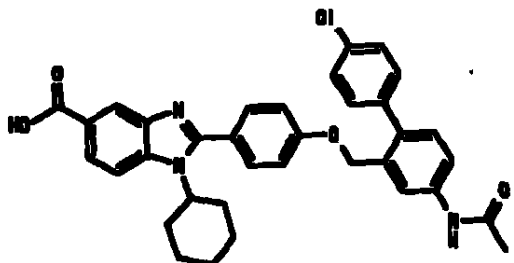
125
263

737

Table 51

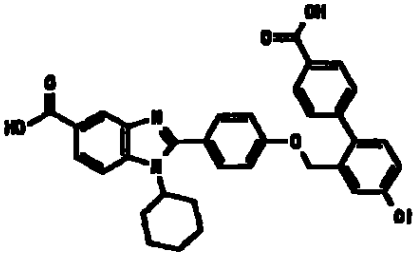
Example No.	181	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.19 (1H, s), 7.95 (1H, d, J=8.7Hz), 7.86 (1H, d, J=8.7Hz), 7.65 (4H, d, J=7.4Hz), 7.47 (2H, d, J=8.7Hz), 7.44-7.27 (6H, m), 6.99 (2H, d, J=8.7Hz), 4.20 (1H, m), 2.34-2.12 (2H, m), 1.98-1.75 (4H, m), 1.64 (1H, m), 1.46-1.13 (3H, m).
Purity	> 90% (NMR)	
MS	547 (M+1)	

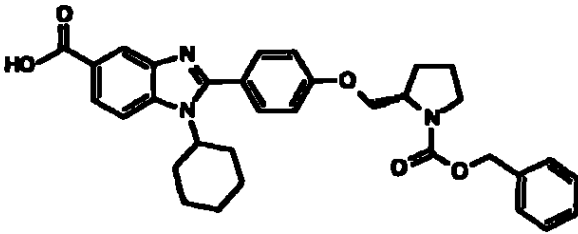
Example No.	182	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

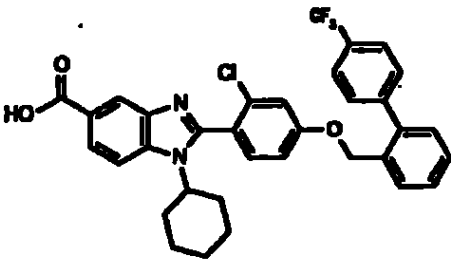
Example No.	183	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

128
 738

Table 52

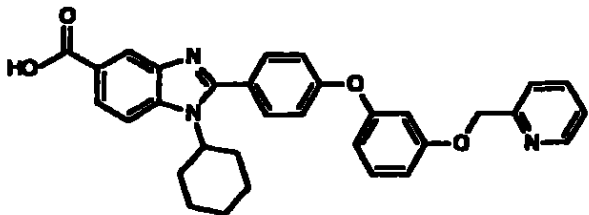
Example No.	184	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.2 (2H, brs), 8.30 (1H, s), 8.26 (1H, d, J=8.8Hz), 8.04 (1H, d, J=8.8Hz), 8.00 (2H, d, J=8.2Hz), 7.79 (1H, s), 7.73 (2H, d, J=8.7Hz), 7.61-7.56 (3H, m), 7.44 (1H, d, J=8.3Hz), 7.23 (2H, d, J=8.8Hz), 5.13 (2H, s), 4.35 (1H, m), 2.45-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (1H, m), 1.75-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	581 (M+1)	

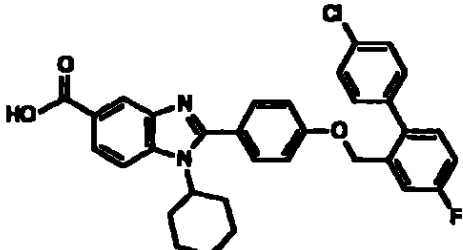
Example No.	185	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.30 (1H, m), 8.24 (1H, d, J=9.0Hz), 8.03 (1H, d, J=9.0Hz), 7.79-7.10 (9H, m), 5.20-5.07 (2H, m), 4.43-4.04 (4H, m), 3.50-3.36 (2H, m), 2.40-1.19 (14H, m)
Purity	> 90% (NMR)	
MS	554 (M+1)	

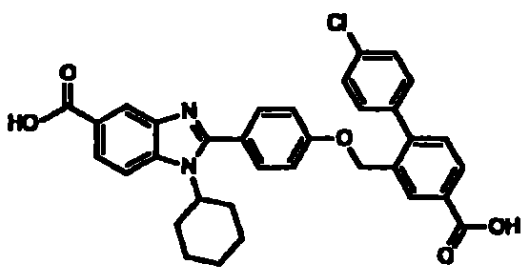
Example No.	186	1H NMR (δ) ppm
		(DMSO-d6) δ : 8.29 (1H, brs), 8.10 (1H, d, J=8.4Hz), 7.97 (1H, d, J=8.4Hz), 7.79 (2H, d, J=8.4Hz), 7.74-7.67 (1H, m), 7.68 (2H, d, J=8.4Hz), 7.61 (1H, d, J=8.4Hz), 7.57-7.50 (2H, m), 7.46-7.39 (1H, m), 7.29 (1H, d, J=2.4Hz), 7.11 (1H, dd, J=2.4, 8.4Hz), 5.12 (2H, s), 3.99-3.84 (1H, m), 2.35-1.72 (6H, m), 1.68-1.55 (1H, m), 1.42-1.10 (3H, m)
Purity	> 90% (NMR)	
MS	605 (M+1)	

123
20
739

Table 53

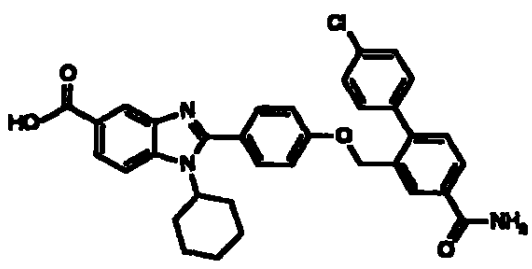
Example No.	187	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.76 (1H, s), 8.57 (1H, d, J=4.4Hz), 8.23 (1H, s), 7.96 and 7.86 (2H, ABq, J=8.2Hz), 7.87-7.82 (1H, m), 7.68 and 7.12 (4H, A'B'q, J=8.6Hz), 7.53 (2H, d, J=7.8Hz), 7.37 (1H, t, J=8.3Hz), 7.36-7.33 (1H, m), 6.90 (1H, d, J=8.3Hz), 6.83 (1H, s), 6.74 (1H, d, J=8.0Hz), 5.20 (2H, s), 4.31 (1H, br t, J=12.2Hz), 2.35-2.19 (2H, m), 1.99-1.57 (5H, m), 1.45-1.20 (2H, m)
Purity	> 90% (NMR)	
MS	520 (M+1)	

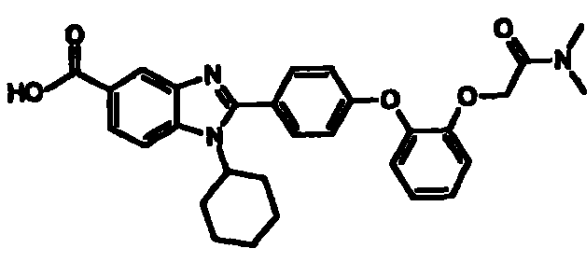
Example No.	188	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.77 (1H, brs), 8.21 (1H, d, J=1.4Hz), 7.92 (1H, d, J=8.7Hz), 7.88 (1H, dd, J=8.7, 1.4Hz), 7.57 (2H, d, J=8.7Hz), 7.57-7.27 (7H, m), 7.11 (2H, d, J=8.7Hz), 5.07 (2H, s), 4.26 (1H, m), 2.36-2.16 (2H, m), 1.98-1.75 (4H, m), 1.64 (1H, m), 1.49-1.17 (3H, m).
Purity	> 90% (NMR)	
MS	555 (M+1)	

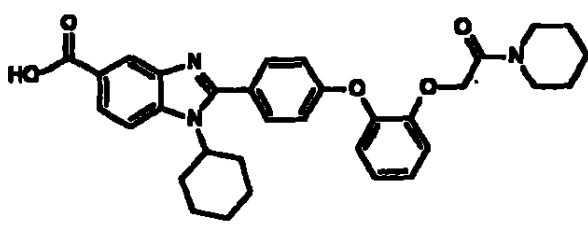
Example No.	189	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.30-8.20 (2H, m), 8.10-7.98 (2H, m), 7.74 (2H, d, J=9.0Hz), 7.60-7.46 (5H, m), 7.24 (2H, d, J=9.0Hz), 5.19 (2H, s), 4.44-4.30 (1H, m), 2.40-2.20 (2H, m), 2.12-1.78 (4H, m), 1.72-1.58 (4H, m)
Purity	> 90% (NMR)	
MS	581 (M+1)	

128
966
740

Table 54

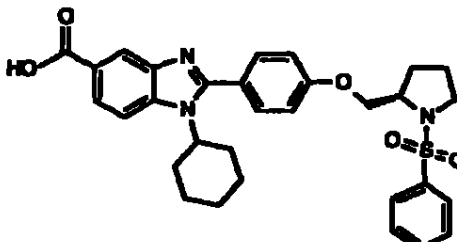
Example No.	190	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.36-7.90 (5H, m), 7.74 (2H, d, J=8.6Hz), 7.60-7.40 (5H, m), 7.25 (2H, d, J=8.7Hz), 5.14 (2H, s), 4.45-4.28 (1H, m), 2.40-2.15 (4H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	580 (M+1)	

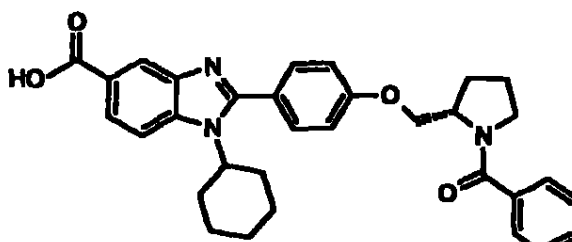
Example No.	191	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

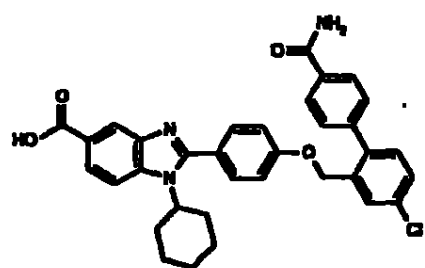
Example No.	192	1H NMR (δ) ppm
		
Purity	> 90% (NMR)	
MS		

129
241

Table 55

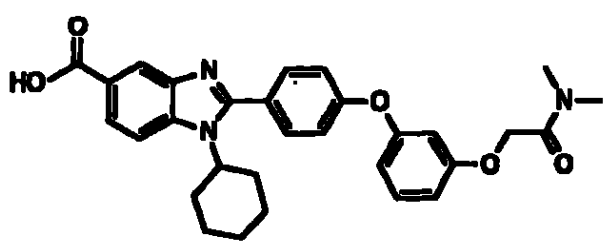
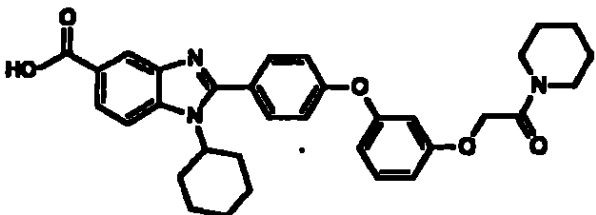
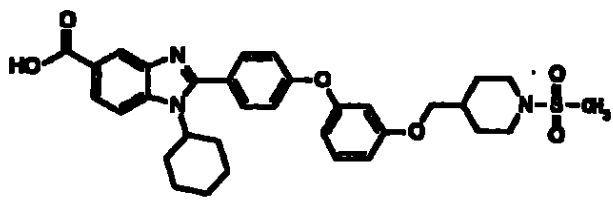
Example No.	193	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.00 (1H, brs), 8.29 (1H, d, J=1.4Hz), 8.15 (1H, d, J=8.8Hz), 7.97 (1H, dd, J=1.4Hz, 8.8Hz), 7.89 (2H, d, J=8.8Hz), 7.80-7.60 (5H, m), 7.25 (2H, d, J=8.8Hz), 4.47-3.90 (4H, m), 3.20-3.10 (2H, m), 2.41-1.22 (14H, m)
Purity	> 90% (NMR)	
MS	560 (M+1)	

Example No.	194	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.80 (1H, brs), 8.23 (1H, s), 7.97 (1H, d, J=8.5Hz), 7.87 (1H, d, J=8.5Hz), 7.70-7.17 (9H, m), 4.60-4.13 (4H, m), 3.72-3.40 (2H, m), 2.40-1.15 (14H, m)
Purity	> 90% (NMR)	
MS	524 (M+1)	

Example No.	195	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.25 (1H, s), 8.09-7.92 (5H, m), 7.77 (1H, s), 7.65 (2H, d, J=8.4Hz), 7.59-7.51 (3H, m), 7.43 (2H, d, J=8.4Hz), 7.17 (2H, d, J=8.7Hz), 5.10 (2H, s), 4.30 (1H, m), 2.40-2.15 (2H, m), 2.10-1.75 (4H, m), 1.75-1.55 (1H, m), 1.55-1.10 (3H, m)
Purity	> 90% (NMR)	
MS	580 (M+1)	

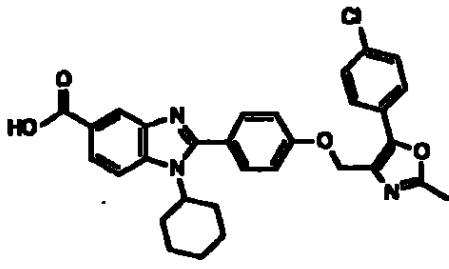
130
463
742

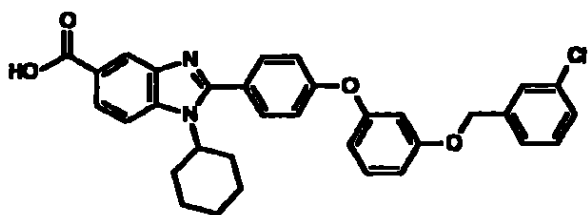
Table 56

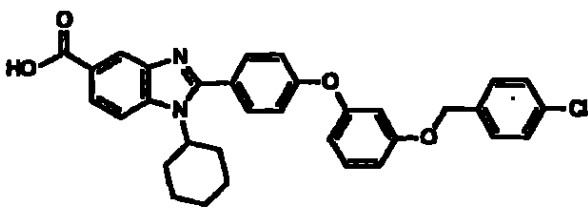
Example No.	196	1H NMR (δ) ppm
		
Purity > 90% (NMR)		
MS		
Example No.	197	1H NMR (δ) ppm
		
Purity > 90% (NMR)		
MS		
Example No.	198	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.23 (1H, d, J=4.4Hz), 7.95 and 7.86 (2H, AB q, J=8.6Hz), 7.69 and 7.19 (4H, A'B' q, J=8.6Hz), 7.36 (1H, t, J=7.8Hz), 6.82 (1H, d, J=9.3Hz), 6.73 (1H, s), 6.71 (1H, d, J=7.2Hz), 4.30 (1H, brt, J=12.2Hz), 3.89 (2H, d, J=6.0Hz), 3.59 (2H, d, J=11.7Hz), 2.85 (3H, s), 2.73 (2H, t, J=10.5Hz), 2.41-2.20 (2H, m), 1.98-1.59 (8H, m), 1.46-1.18 (6H, m)
Purity > 90% (NMR)		
MS 604 (M+1)		

131
269
743

Table 57

Example No.	199	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 (1H, s), 8.30 (1H, d, J=8.9Hz), 8.06 (1H, d, J=8.7Hz), 7.79 (2H, d, J=8.7Hz), 7.70 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.7Hz), 7.39 (2H, d, J=8.8Hz), 5.28 (2H, s), 4.39 (1H, m), 2.50-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	542 (M+1)	

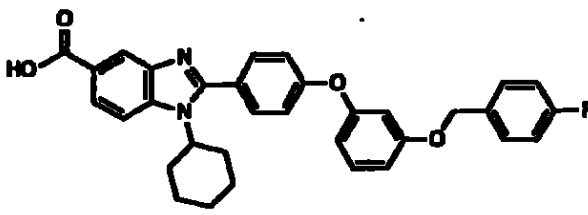
Example No.	200	1H NMR (δ) ppm
		(DMSO-d6) δ : 8.23 (1H, s), 7.96 (1H, d, J=8.6Hz), 7.86 (1H, d, J=8.6Hz), 7.69 (2H, d, J=8.4Hz), 7.52 (1H, s), 7.50-7.30 (4H, m), 7.18 (2H, d, J=8.4Hz), 6.90 (1H, d, J=8.3Hz), 6.84 (1H, s), 6.74 (1H, d, J=8.3Hz), 5.15 (2H, s), 4.39-4.21 (1H, m), 2.39-2.18 (2H, m), 1.99-1.80 (4H, m), 1.71-1.59 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	553 (M+1)	

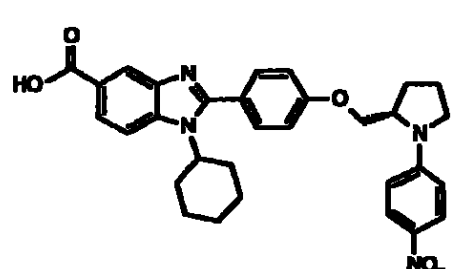
Example No.	201	1H NMR (δ) ppm
		(DMSO-d6) δ : 8.26 (1H, s), 8.06 (1H, d, J=8.7Hz), 7.92 (1H, d, J=8.7Hz), 7.72 (2H, d, J=8.7Hz), 7.47 (4H, s), 7.38 (1H, t, J=8.2Hz), 7.20 (2H, d, J=8.7Hz), 6.90 (1H, d, J=8.2Hz), 6.83 (1H, s), 6.74 (1H, d, J=8.2Hz), 5.14 (2H, s), 2.40-2.19 (2H, m), 2.04-1.78 (4H, m), 1.71-1.60 (1H, m), 1.50-1.21 (3H, m)
Purity	> 90% (NMR)	
MS	553 (M+1)	

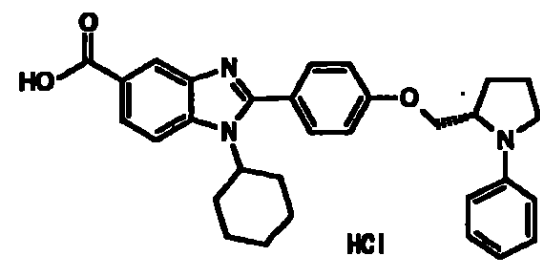
132
98

744

Table 58

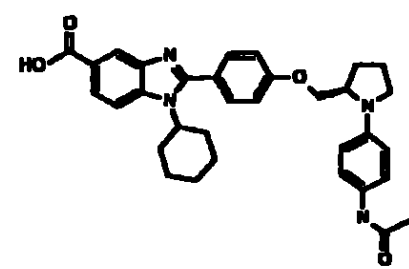
Example No.	202	1H NMR (δ) ppm
		(DMSO-d6) δ : 12.81 (1H, brs), 8.24 (1H, s), 7.99 (1H, d, J=8.7Hz), 7.87 (1H, d, J=8.7Hz), 7.69 (2H, d, J=8.6Hz), 7.53-7.47 (2H, m), 7.38 (1H, t, J=8.2Hz), 7.26-7.16 (4H, m), 6.89 (1H, d, J=8.2Hz), 6.82 (1H, s), 6.73 (1H, d, J=8.2Hz), 6.11 (2H, s), 4.40-4.21 (1H, m), 2.40-2.17 (2H, m), 2.01-1.77 (4H, m), 1.71-1.59 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	537 (M+1)	

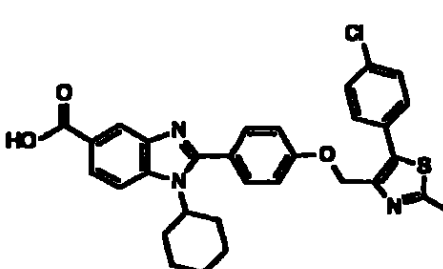
Example No.	203	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.74 (1H, brs), 8.21 (1H, s), 8.08 (2H, d, J=9.0Hz), 7.93 (1H, d, J=8.7Hz), 7.85 (2H, d, J=8.7Hz), 7.58 (2H, d, J=8.7Hz), 7.13 (2H, d, J=8.7Hz), 6.83 (2H, d, J=9.0Hz), 4.50-4.08 (4H, m), 3.68-3.30 (2H, m), 2.40-1.23 (14H, m)
Purity	> 90% (NMR)	
MS	541 (M+1)	

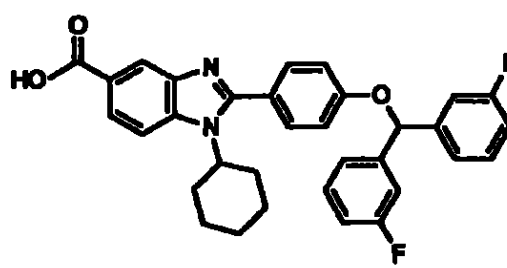
Example No.	204	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.39-8.28 (2H, m), 8.08 (1H, d, J=8.8Hz), 7.76 (2H, d, J=8.7Hz), 7.29 (2H, d, J=8.7Hz), 7.25-7.13 (2H, m), 6.80-6.60 (3H, m), 4.46-3.98 (4H, m), 3.51-3.42 (1H, m), 3.20-3.04 (1H, m), 2.39-1.20 (14H, m)
Purity	> 90% (NMR)	
MS		

183
994
745

Table 59

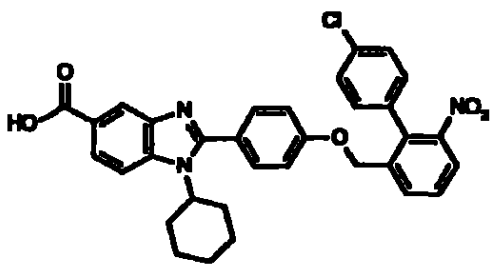
Example No.	205	1H NMR (δ) ppm
		300MHz, DMSO-d6 9.59 (1H, brs), 8.23 (1H, s), 8.04 (1H, d, J=8.4Hz), 7.90 (1H, d, J=8.4Hz), 7.62 (2H, d, J=8.7Hz), 7.39 (2H, 2H, d, J=8.7Hz) 7.18 (2H, d, J=8.7Hz), 6.63 (2H, d, J=8.7Hz), 3.95-3.37 (4H, m), 3.51-3.40 (1H, m), 3.17-3.02 (1H, m), 2.39-1.18 (17H, m)
Purity	> 90% (NMR)	
MS	553 (M+1)	

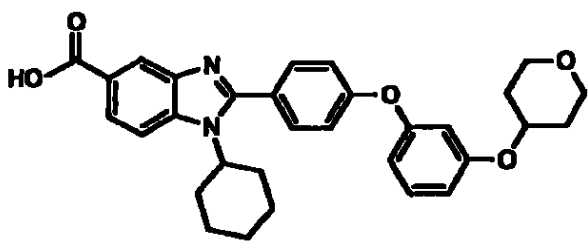
Example No.	206	1H NMR (δ) ppm
		300MHz, DMSO-d6 13.1 (1H, brs), 8.33 (1H, s), 8.29 (1H, d, J=8.8Hz), 8.06 (1H, d, J=8.7Hz), 7.77 (2H, d, J=8.7Hz), 7.59-7.52 (4H, m), 7.35 (2H, d, J=8.8Hz), 5.19 (2H, s), 4.39 (1H, m), 2.71 (3H, s), 2.45-2.20 (2H, m), 2.20-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	558 (M+1)	

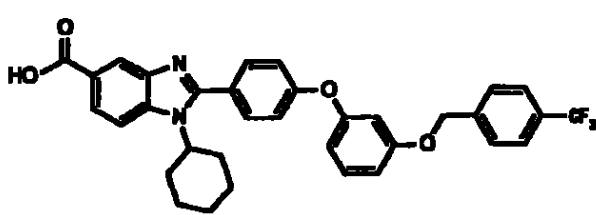
Example No.	207	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.29 (1H, s), 8.26 (1H, d, J=8.8Hz), 8.04 (1H, d, J=8.7Hz), 7.73 (2H, d, J=8.8Hz), 7.50-7.41 (6H, m), 7.36 (2H, d, J=8.8Hz), 7.18-7.13 (2H, m), 6.84 (1H, s), 4.33 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	539 (M+1)	

1324
246

Table 60

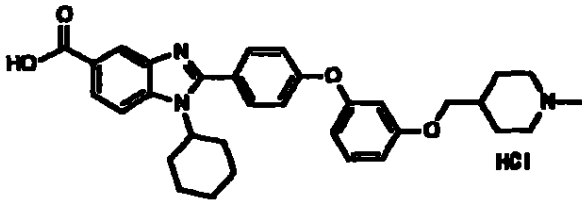
Example No.	208	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.32 (1H, s), 8.27 (1H, d, J=9.0Hz), 8.07-8.00 (3H, m), 7.79-7.70 (3H, m), 7.51 (2H, d, J=8.1Hz), 7.40 (2H, d, J=8.4Hz), 7.18 (2H, d, J=8.7Hz), 4.99 (2H, s), 4.34 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	582 (M+1)	

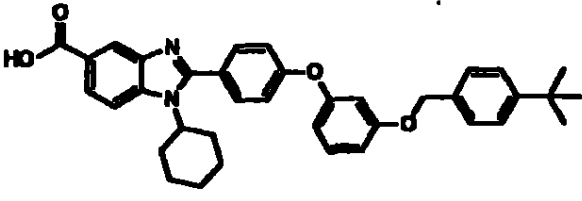
Example No.	209	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.24 (1H, d, J=4.4Hz), 7.98 and 7.88 (2H, ABq, J=8.6Hz), 7.70 and 7.19 (4H, A'B'q, J=8.4Hz), 7.35 (1H, t, J=8.4Hz), 6.86 (1H, d, J=8.1Hz), 6.79 (1H, s), 6.71 (1H, d, J=8.1Hz), 4.65-4.53 (1H, m), 4.31 (1H, brt, J=12.2Hz), 3.88-3.78 (2H, m), 3.48 (2H, t, J=9.0Hz), 2.39-2.19 (2H, m), 1.02-1.71 (6H, m), 1.70-1.50 (3H, m), 1.46-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	513 (M+1)	

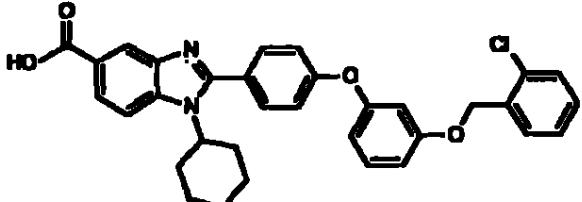
Example No.	210	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, s), 8.23 (1H, s), 7.96 and 7.87 (2H, ABq, J=8.7Hz), 7.84-7.66 (6H, m), 7.38 (1H, t, J=8.4Hz), 7.18 (2H, d, J=8.4Hz), 6.91 (1H, d, J=9.0Hz), 6.84 (1H, s), 6.74 (1H, d, J=8.1Hz), 5.26 (2H, s), 4.31 (1H, brt, J=12.2Hz), 2.40-2.20 (2H, m), 1.99-1.76 (4H, m), 1.69-1.58 (1H, m), 1.45-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	587 (M+1)	

125
223
747

Table 61

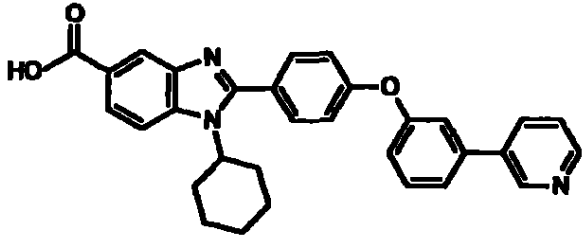
Example No.	211	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.29 (1H, s), 8.15 and 7.47 (2H, ABq, J=9.0Hz), 7.77 and 7.24 (4H, ABq, J=8.9Hz), 7.39 (1H, t, J=7.8Hz), 6.84 (1H, d, J=9.3Hz), 6.76 (1H, s), 6.75 (1H, d, J=9.5Hz), 4.36 (1H, brt, J=12.2Hz), 3.89 (2H, d, J=6.0Hz), 3.42 (2H, d, J=10.8Hz), 3.04-2.88 (2H, m), 2.78-2.60 (1H, m), 2.71 (2H, d, J=4.8Hz), 2.38-2.20 (2H, m), 2.07-1.80 (7H, m), 1.70-1.20 (5H, m)
Purity	> 90% (NMR)	
MS	540 (M+1)	

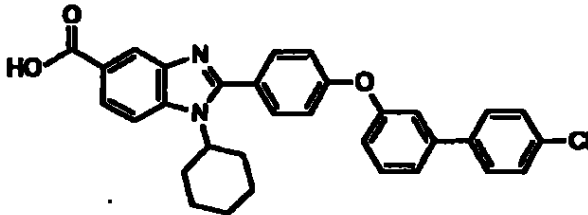
Example No.	212	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.22 (1H, s), 7.93 and 7.87 (2H, ABq, J=8.6Hz), 7.68 and 7.17 (4H, A' B' q, J=8.7Hz), 7.43-7.33 (5H, m), 6.87 (1H, d, J=8.1Hz), 7.18 (2H, d, J=8.4Hz), 6.91 (1H, d, J=9.0Hz), 6.81 (1H, s), 6.72 (1H, d, J=8.0Hz), 5.08 (2H, s), 4.36 (1H, brt, J=12.2Hz), 2.37-2.20 (2H, m), 1.98-1.78 (4H, m), 1.69-1.60 (1H, m), 1.41-1.21 (3H, m), 1.28 (9H, s)
Purity	> 90% (NMR)	
MS	575 (M+1)	

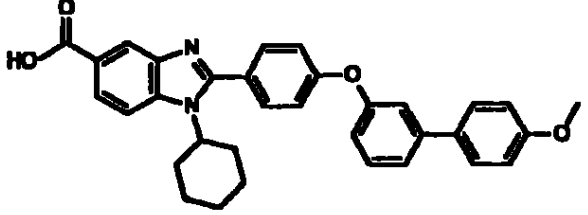
Example No.	213	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.95 and 7.86 (2H, ABq, J=8.4Hz), 7.69 and 7.19 (4H, A' B' q, J=8.7Hz), 7.62-7.36 (5H, m), 6.90 (1H, d, J=8.1Hz), 6.84 (1H, s), 6.76 (1H, d, J=8.1Hz), 5.19 (2H, s), 4.31 (1H, brt, J=12.2Hz), 2.40-2.19 (2H, m), 1.99-1.76 (4H, m), 1.68-1.55 (1H, m), 1.50-1.18 (3H, m)
Purity	> 90% (NMR)	
MS	553 (M+1)	

136
248

Table 62

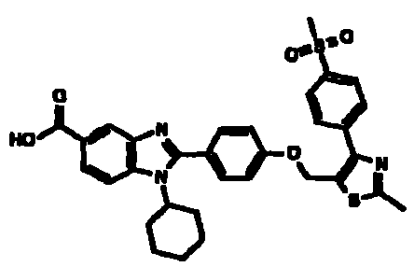
Example No.	214	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.94 (1H, d, J=2.1Hz), 8.60 (1H, dd, J=4.8, 1.5Hz), 8.23 (1H, d, J=1.5Hz), 8.12 (1H, dt, J=8.1, 2.1Hz), 7.93 (1H, d, J=8.7Hz), 7.87 (1H, dd, J=8.7, 1.5Hz), 7.70 (1H, d, J=8.7Hz), 7.67-7.54 (3H, m), 7.50 (1H, dd, J=8.1, 4.8Hz), 7.25 (2H, d, J=8.7Hz), 7.21 (1H, m), 4.31 (1H, m), 2.38-2.19 (2H, m), 2.00-1.78 (4H, m), 1.66 (1H, m), 1.48-1.22 (3H, m).
Purity	> 90% (NMR)	
MS	490 (M+1)	

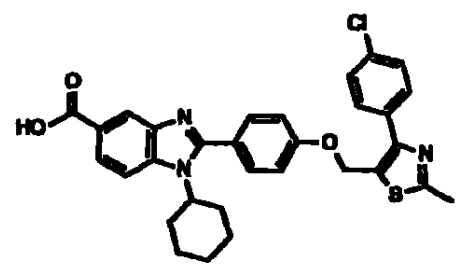
Example No.	215	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.75 (1H, brs), 8.23 (1H, s), 7.95 (1H, d, J=8.7Hz), 7.86 (1H, d, J=8.7Hz), 7.73 (2H, d, J=8.4Hz), 7.71 (2H, d, J=8.4Hz), 7.63-7.39 (2H, m), 7.52 (2H, d, J=8.4Hz), 7.24 (2H, d, J=8.4Hz), 7.18 (1H, m), 4.31 (1H, m), 2.39-2.20 (2H, m), 2.00-1.76 (4H, m), 1.65 (1H, m), 1.49-1.18 (3H, m).
Purity	> 90% (NMR)	
MS	523 (M+1)	

Example No.	216	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.77 (1H, s), 8.23 (1H, d, J=1.4Hz), 7.95 (1H, d, J=8.6Hz), 7.86 (1H, dd, J=8.6, 1.4Hz), 7.70 (2H, d, J=8.7Hz), 7.64 (2H, d, J=8.8Hz), 7.56-7.48 (2H, m), 7.40 (1H, s), 7.23 (2H, d, J=8.7Hz), 7.10 (1H, m), 7.03 (2H, d, J=8.8Hz), 4.31 (1H, m), 3.80 (3H, s), 2.48-2.20 (2H, m), 2.00-1.88 (4H, m), 1.66 (1H, m), 1.50-1.21 (3H, m).
Purity	> 90% (NMR)	
MS	519 (M+1)	

137
249

Table 63

Example No.	217	¹ H NMR (δ) ppm
		(DMSO-d ₆) δ : 12.80 (1H, brs), 8.23 (1H, s), 8.04 (1H, d, J=8.6Hz), 7.96 (3H, d, J=8.6Hz), 7.86 (1H, d, J=8.7Hz), 7.63 (2H, d, J=8.6Hz), 7.25 (2H, d, J=8.6Hz), 5.50 (2H, s), 4.36-4.21 (1H, m), 3.27 (3H, s), 2.74 (3H, s), 2.40-2.19 (2H, m), 1.99-1.79 (4H, m), 1.71-1.60 (1H, m), 1.49-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	602 (M+1)	

Example No.	218	¹ H NMR (δ) ppm
		300MHz, DMSO-d ₆ 12.9 (1H, brs), 8.25 (1H, s), 8.04 (1H, d, J=8.7Hz), 7.91 (1H, d, J=8.6Hz), 7.72 (2H, d, J=8.5Hz), 7.67 (2H, d, J=8.7Hz), 7.56 (2H, d, J=8.5Hz), 7.26 (2H, d, J=8.7Hz), 5.45 (2H, s), 4.31 (1H, m), 2.71 (3H, s), 2.40-2.15 (2H, m), 2.05-1.80 (4H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	558 (M+1)	

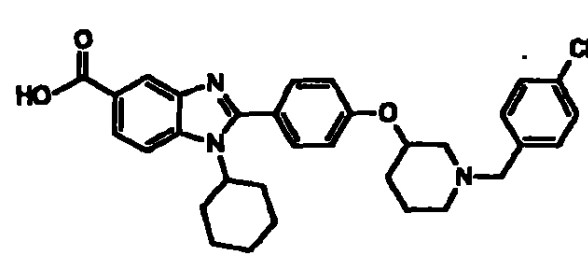
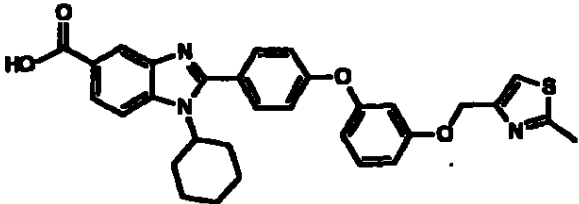
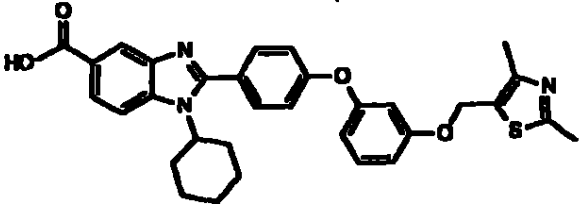
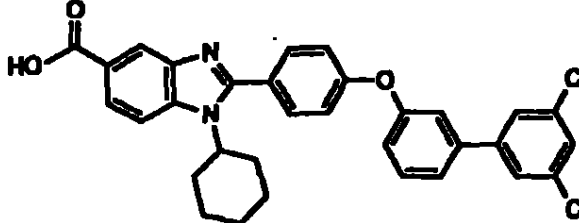
Example No.	219	¹ H NMR (δ) ppm
		300MHz, DMSO-d ₆ 8.21 (1H, d, J=1.5Hz), 7.93 (1H, d, J=9.0Hz), 7.84 (1H, dd, J=9.0, 1.5Hz), 7.56 (2H, d, J=8.7Hz), 7.42-7.30 (4H, m), 7.12 (2H, d, J=8.7Hz), 4.53 (1H, brs), 4.36-4.20 (1H, m), 3.55 (2H, brs), 3.00-2.90 (1H, m), 2.70-2.58 (1H, m), 2.40-1.10 (18H, m)
Purity	> 90% (NMR)	
MS	544 (M+1)	

Table 64

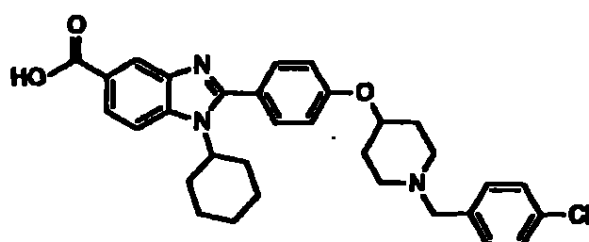
Example No.	220	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.76 (1H, s), 8.23 (1H, s), 7.96 and 7.87 (2H, ABq, J=8.9 Hz), 7.69 and 7.19 (4H, A' B' q, J=8.6 Hz), 7.55 (1H, s), 7.37 (1H, t, J=8.1 Hz), 6.91 (1H, d, J=7.8 Hz), 6.85 (1H, s), 6.74 (1H, d, J=7.5 Hz), 5.13 (2H, s), 4.31 (1H, brt, J=12.2 Hz), 2.65 (3H, s), 2.41-2.20 (2H, m), 2.00-1.74 (4H, m), 1.70-1.59 (1H, m), 1.58-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	540 (M+1)	

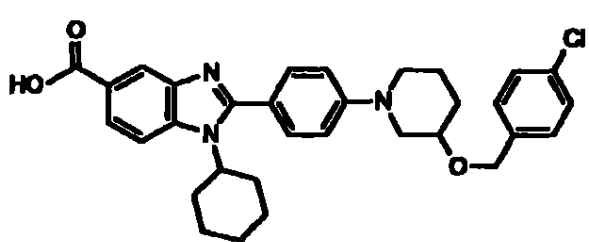
Example No.	221	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.23 (1H, s), 7.96 and 7.86 (2H, ABq, J=8.6 Hz), 7.69 and 7.18 (4H, A' B' q, J=8.7 Hz), 7.37 (1H, t, J=8.2 Hz), 6.87 (1H, d, J=8.2 Hz), 6.82 (1H, s), 6.75 (1H, d, J=8.0 Hz), 5.24 (2H, s), 4.32 (1H, brt, J=12.2 Hz), 2.58 (3H, s), 2.38-2.20 (2H, m), 2.30 (3H, s), 2.00-1.79 (4H, m), 1.70-1.59 (1H, m), 1.44-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	554 (M+1)	

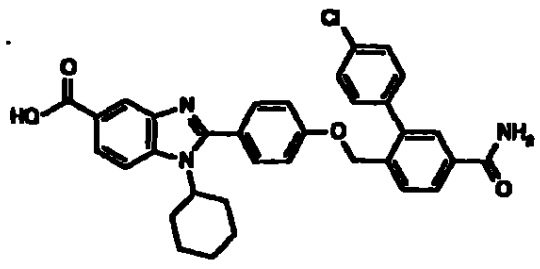
Example No.	222	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.88 (1H, brs), 8.25 (s, 1H), 8.07-7.57 (11H, m), 7.26 (2H, d, J=8.7 Hz), 7.24 (1H, m), 4.34 (1H, m), 2.30-2.20 (2H, m), 2.03-1.78 (4H, m), 1.64 (1H, m), 1.49-1.19 (3H, m).
Purity	> 90% (NMR)	
MS	557 (M+1)	

139
251

Table 65

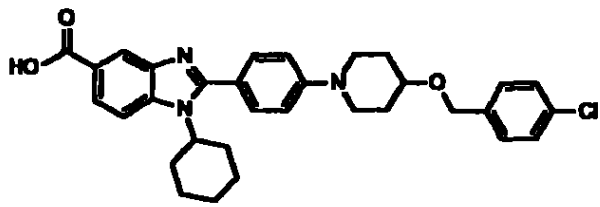
Example No.	223	1H NMR (δ) ppm
		300MHz, DMSO-d6 10.96 (1H, brs), 8.21 (1H, d, J=1.4Hz), 7.93 (1H, d, J=8.7 Hz), 7.84 (1H, dd, J=8.7, 1.4 Hz), 7.76-7.40 (7H, m), 7.18 (2H, d, J=8.0Hz), 4.24-4.16 (2H, m), 2.40-1.12 (18H, m)
Purity	> 90% (NMR)	
MS	544 (M+1)	

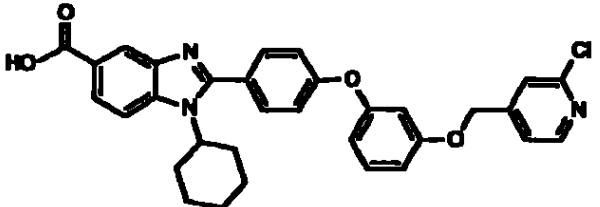
Example No.	224	1H NMR (δ) ppm
		(DMSO-d6) δ : 8.22 (1H, s), 8.07 (1H, d, J=8.4Hz), 7.92 (1H, d, J=8.4Hz), 7.54 (2H, d, J=8.7Hz), 7.40 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.4Hz), 7.14 (2H, d, J=8.7Hz), 4.61 (2H, s), 4.48-4.32 (1H, m), 3.82 (1H, brd, J=12.3Hz), 3.65-3.47 (2H, m), 3.10 (brdd, J=8.4, 12.3Hz), 2.40-2.20 (2H, m), 2.09-1.76 (6H, m), 1.71-1.16 (6H, m)
Purity	> 90% (NMR)	
MS	544 (M+1)	

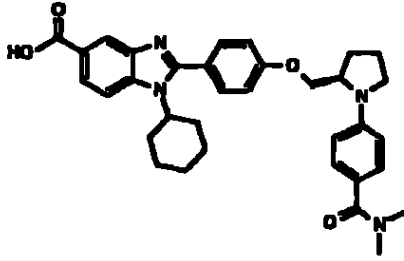
Example No.	225	1H NMR (δ) ppm
		(DMSO-d6) δ : 12.83 (1H, brs), 8.21 (1H, s), 8.10 (1H, brs), 7.01-7.91 (2H, m), 7.89-7.82 (2H, m), 7.75 (1H, d, J=8.0Hz), 7.59 (2H, d, J=8.7Hz), 7.53 (4H, s), 7.46 (1H, brs), 7.12 (2H, d, J=8.7Hz), 7.23 (2H, s), 4.35-4.17 (1H, m), 2.38-2.20 (2H, m), 1.99-1.79 (4H, m), 1.71-1.59 (1H, m), 1.48-1.18 (3H, m)
Purity	> 90% (NMR)	
MS	580 (M+1)	

140
752

Table 66

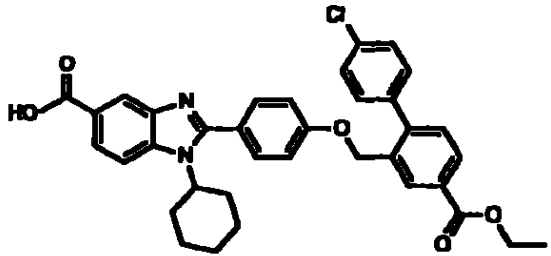
Example No.	226	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.33 and 8.08 (2H, ABq, J=8.7 Hz), 8.31 (1H, m), 7.66 and 7.26 (4H, A'B'q, J=9.2 Hz), 7.42 and 7.39 (4H, A''B''q, J=8.7 Hz), 4.57 (2H, s), 4.50 (1H, br t, J=12.2 Hz), 3.85-3.62 (3H, m), 3.28-3.16 (2H, m), 2.42-2.23 (2H, m), 2.14-1.81 (6H, m), 1.72-1.25 (6H, m)
Purity	> 90% (NMR)	
MS	544 (M+1)	

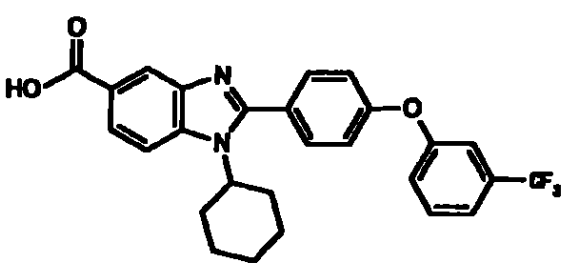
Example No.	227	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.43 (1H, d, J=5.0 Hz), 8.23 (1H, s), 7.96 and 7.86 (2H, ABq, J=8.6 Hz), 7.69 and 7.18 (4H, A'B'q, J=8.6 Hz), 7.57 (1H, s), 7.47 (1H, d, J=5.0 Hz), 7.40 (2H, t, J=8.2 Hz), 6.91 (1H, d, J=8.3 Hz), 6.85 (1H, s), 6.77 (1H, d, J=7.9 Hz), 5.25 (2H, s), 4.31 (1H, br t, J=12.2 Hz), 2.40-2.19 (2H, m), 1.99-1.75 (4H, m), 1.73-1.57 (1H, m), 1.49-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	554 (M+1)	

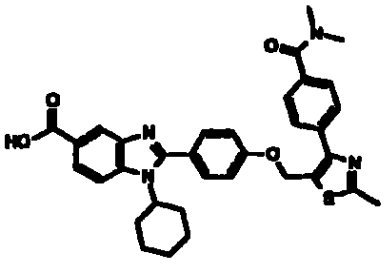
Example No.	228	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.80 (1H, brs), 8.22 (1H, s), 7.94 (1H, d, J=8.6 Hz), 7.87 (1H, d, J=8.6 Hz), 7.60 (2H, d, J=8.7 Hz), 7.32 (2H, d, J=8.7 Hz), 7.17 (2H, d, J=8.7 Hz), 6.70 (2H, d, J=8.7 Hz), 4.35-3.97 (4H, m), 3.62-3.11 (2H, m), 2.96 (6H, s), 2.39-1.12 (4H, m)
Purity	> 90% (NMR)	
MS	567 (M+1)	

1419
753

Table 67

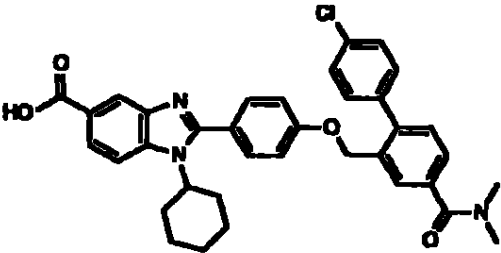
Example No.	229	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.25 (1H, s), 8.20 (1H, s), 8.04 (1H, dd, J=8.1, 1.8 Hz), 7.92 (1H, d, J=8.1 Hz), 7.84 (1H, d, J=9.9 Hz), 7.62-7.50 (7H, m), 7.12 (2H, d, J=8.7 Hz), 5.14 (2H, s), 4.36 (2H, q, J=6.9 Hz), 4.30-4.20 (1H, m), 2.38-2.18 (2H, m), 1.98-1.18 (8H, m), 1.35 (3H, t, J=6.9 Hz)
Purity	> 90% (NMR)	
MS	608 (M+1)	

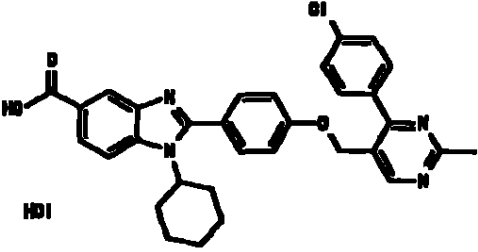
Example No.	230	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.35 (1H, s), 8.27 (1H, d, J=8.7 Hz), 8.05 (1H, d, J=9.0 Hz), 7.87 (2H, d, J=8.7 Hz), 7.74 (1H, t, J=8.1 Hz), 7.64 (1H, d, J=7.8 Hz), 7.59-7.50 (2H, m), 7.36 (2H, d, J=8.7 Hz), 4.39 (1H, m), 2.40-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.20 (3H, m).
Purity	about 90% (NMR)	
MS	481 (M+1)	

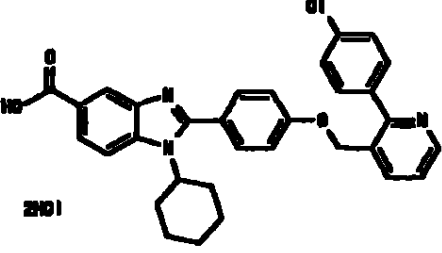
Example No.	231	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.78 (1H, brs), 8.23 (1H, d, J=1.5 Hz), 7.96 (1H, d, J=8.7 Hz), 7.87 (1H, dd, J=8.7, 1.5 Hz), 7.75 (2H, d, J=8.4 Hz), 7.63 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 5.47 (2H, s), 4.29 (1H, m), 2.97 (6H, brs), 2.72 (3H, s), 2.39-2.16 (2H, m), 2.00-1.78 (4H, m), 1.71-1.59 (1H, m), 1.49-1.17 (3H, m).
Purity	about 90% (NMR)	
MS	595 (M+1)	

143
20
754

Table 68

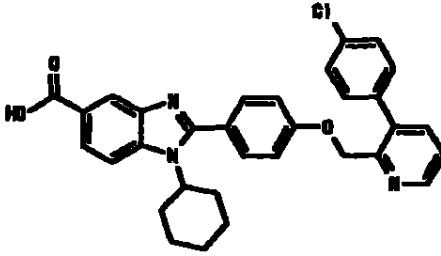
Example No.	232	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.8 (1H, brs), 8.22 (1H, s), 7.96 (1H, d, J=8.7Hz), 7.86 (1H, d, J=8.6Hz), 7.70 (1H, s), 7.59 (2H, d, J=8.7Hz), 7.53-7.50 (5H, m), 7.42 (1H, d, J=7.9Hz), 7.12 (2H, d, J=8.7Hz), 5.11 (2H, s), 4.27 (1H, m), 3.01 (3H, brs), 2.97 (3H, brs), 2.40-2.15 (2H, m), 2.00-1.75 (4H, m), 1.75-1.55 (1H, m), 1.50-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	608 (M+1)	

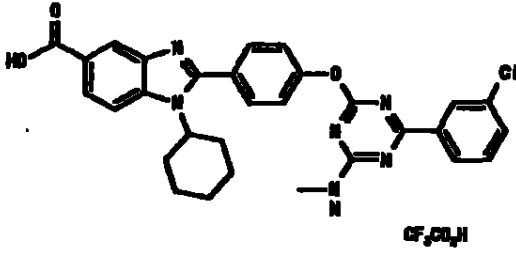
Example No.	233	1H NMR (δ) ppm
		DMSO-d6 13.20 (1H, brs), 8.99 (1H, s), 8.32 (1H, s), 8.25 (1H, d, J=8.8Hz), 8.04 (1H, d, J=8.6Hz), 7.79-7.74 (4H, m), 7.60 (2H, d, J=8.5Hz), 7.30 (2H, d, J=8.7Hz), 5.26 (2H, s), 4.36 (1H, m), 2.72 (3H, s), 2.50-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	553 (M+1-HCl)	

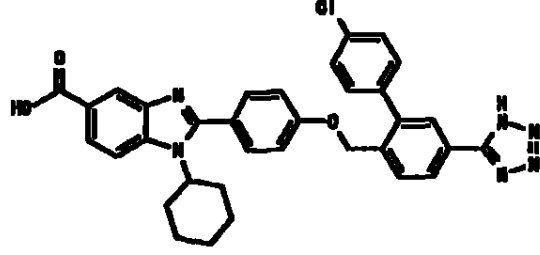
Example No.	234	1H NMR (δ) ppm
		DMSO-d6 8.77 (1H, d, J=3.6Hz), 8.36-8.26 (3H, m), 8.08 (1H, d, J=8.8Hz), 7.79 (2H, d, J=8.7Hz), 7.72-7.64 (3H, m), 7.58 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.7Hz), 5.26 (2H, s), 4.38 (1H, m), 2.50-2.15 (2H, m), 2.15-1.95 (2H, m), 1.95-1.75 (2H, m), 1.75-1.55 (1H, m), 1.55-1.15 (3H, m).
Purity	> 90% (NMR)	
MS	538 (M+1-2HCl)	

143
288
755

Table 69

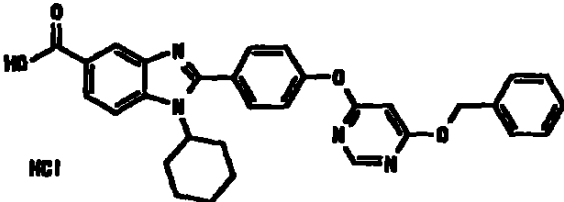
Example No.	235	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.74 (1H, brs), 8.67 (1H, dd, J=3.1, 1.6Hz), 8.21 (1H, d, J=1.6Hz), 7.93 (1H, d, J=8.6Hz), 7.90-7.80 (2H, m), 7.60-7.50 (7H, m), 7.09 (2H, d, J=8.7Hz), 5.16 (2H, s), 4.26 (1H, m), 2.40-2.20 (2H, m), 2.00-1.60 (5H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	APCI-MS 538 (M+1)	

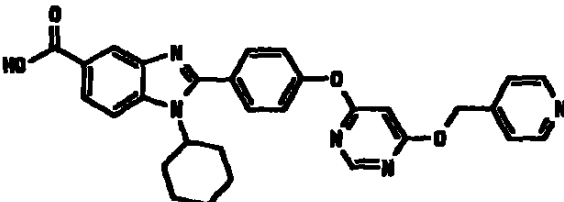
Example No.	236	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.40-7.40 (11H, m), 2.95, 2.81 (3H, each d, J=4.7Hz), 2.40-2.20 (2H, m), 2.10-1.80 (4H, m), 1.70-1.60 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	APCI-MS 555 (M+1)	

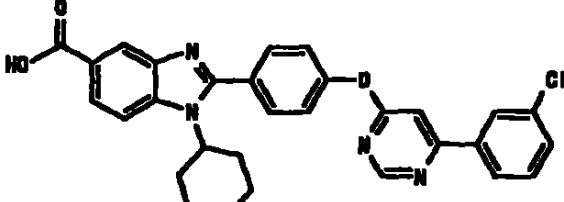
Example No.	237	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.21 (1H, s), 8.15 (1H, d, J=9.5Hz), 8.02 (1H, s), 8.00-7.80 (3H, m), 7.70-7.50 (6H, m), 7.12 (2H, d, J=8.7Hz), 5.16 (2H, s), 4.28 (1H, m), 2.40-2.20 (2H, m), 2.00-1.80 (4H, m), 1.65 (1H, m), 1.50-1.20 (3H, m)
Purity	> 90% (NMR)	
MS	FAB-MS 605 (M+1)	

147
98
756

Table 70

Example No.	238	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.80 (1H, brs), 8.54 (1H, s), 8.25 (1H, s), 7.98 and 7.88 (2H, Abq, J=8.6Hz), 7.76 (2H, d, J=8.6Hz), 7.53-7.31 (3H, m), 6.61 (1H, s), 5.46 (2H, s), 4.32 (1H, brt), 2.40-2.20 (2H, m), 2.02-1.79 (4H, m), 1.69-1.59 (1H, m), 1.48-1.19 (3H, m)
Purity	> 90% (NMR)	
MS	APCI-MS 521 (M+1)	

Example No.	239	1H NMR (δ) ppm
		300MHz, DMSO-d6 12.79 (1H, brs), 8.60 (2H, d, J=1.5Hz), 8.53 (1H, s), 8.25 (1H, s), 7.98 and 7.85 (2H, ABq, J=9.4Hz), 7.76 (2H, d, J=9.0Hz), 7.44 (4H, d, J=6.5Hz), 6.69 (1H, s), 5.53 (2H, s), 4.32 (1H, brt), 2.40-2.19 (2H, m), 2.03-1.82 (4H, m), 1.72-1.61 (1H, m), 1.42-1.22 (3H, m)
Purity	> 90% (NMR)	
MS	APCI-MS 522 (M+1)	

Example No.	240	1H NMR (δ) ppm
		300MHz, DMSO-d6 8.90 (1H, s), 8.32 (1H, s), 8.28 (1H, s), 8.25 (1H, d, J=8.3Hz), 8.05 (1H, d, J=8.8Hz), 7.96 (1H, s), 7.93 (1H, d, J=8.8Hz), 7.83 (1H, d, J=8.4Hz), 7.68-7.59 (2H, m), 7.54 (2H, d, J=8.8Hz), 4.37 (1H, brt), 2.30 (2H, m), 2.00 (2H, m), 1.88 (2H, m), 1.67 (1H, m), 1.5-1.2 (3H, m)
Purity	> 90% (NMR)	
MS	APCI-MS 525 (M+1)	

145
757

The evaluation of the HCV polymerase inhibitory activity of the compound of the present invention is explained in the following. This polymerase is an enzyme coded for by the non-structural protein region called NS5B on the RNA gene of HCV (EMBO J., 15:12-22, 1996).

Experimental Example [I]

1) Preparation of enzyme (HCV polymerase)

Using, as a template, a cDNA clone corresponding to the full length RNA gene of HCV BK strain obtained from the blood of a patient with hepatitis C, a region encoding NS5B (591 amino acids; J Virol 1991 Mar, 65(3), 1105-13) was amplified by PCR. The objective gene was prepared by adding a 6 His tag (base pair encoding 6 continuous histidine (His)) to the 5' end thereof and transformed to *Escherichia coli*. The *Escherichia coli* capable of producing the objective protein was cultured. The obtained cells were suspended in a buffer solution containing a surfactant and crushed in a microfluidizer. The supernatant was obtained by centrifugation and applied to various column chromatographies (poly[U]-Sephadex, Sephacryl S-200, mono-S (Pharmacia)), inclusive of metal chelate chromatography, to give a standard enzyme product.

11) Synthesis of substrate RNA

Using a synthetic primer designed based on the sequence of HCV genomic 3' untranslated region, a DNA fragment (148 bp) containing polyU and 3'X sequence was entirely synthesized and cloned into plasmid pBluescript SK II(+) (Stratagene). The cDNA encoding full length NS5B, which was prepared in 1) above, was digested with restriction enzyme KpnI to give a cDNA fragment containing the nucleotide sequence of from the restriction enzyme cleavage site to the termination codon. This cDNA fragment was inserted into the upstream of 3' untranslated region of the DNA in pBluescript SK II(+) and ligated. The about 450 bp inserted DNA sequence was used as a template in the preparation of substrate RNA. This plasmid was cleaved immediately after the 3'X sequence, linearized and purified by phenol-chloroform treatment and ethanol precipitation to give DNA.

RNA was synthesized (37°C, 3 hr) by run-off method using this purified DNA as a template, a promoter of pBluescript SK

440
258

II(+), MEGAscript RNA synthesis kit (Ambion) and T7 RNA polymerase. DNaseI was added and the mixture was incubated for 1 hr. The template DNA was removed by decomposition to give a crude RNA product. This product was treated with phenol-chloroform and purified by ethanol precipitation to give the objective substrate RNA.

This RNA was applied to formaldehyde denaturation agarose gel electrophoresis to confirm the quality thereof and preserved at -80°C.

iii) Assay of enzyme (HCV polymerase) inhibitory activity

A test substance (compound of the present invention) and a reaction mixture (30 µl) having the following composition were reacted at 25°C for 90 min.

10% Trichloroacetic acid at 4°C and 1% sodium pyrophosphate solution (150 µl) were added to this reaction mixture to stop the reaction. The reaction mixture was left standing in ice for 15 min to insolubilize RNA. This RNA was trapped on a glass filter (Whatman GF/C and the like) upon filtration by suction. This filter was washed with a solution containing 1% trichloroacetic acid and 0.1% sodium pyrophosphate, washed with 90% ethanol and dried. A liquid scintillation cocktail (Packard) was added and the radioactivity of RNA synthesized by the enzyme reaction was measured on a liquid scintillation counter.

The HCV polymerase inhibitory activity (IC₅₀) of the compound of the present invention was calculated from the values of radioactivity of the enzyme reaction with and without the test substance.

The results are shown in Tables 71 - 75.

Reaction mixture : HCV polymerase (5 µg/ml) obtained in i), substrate RNA (10 µg/ml) obtained in ii), ATP (50 µM), GTP (50 µM), CTP (50 µM), UTP (2 µM), [5,6-³H]UTP (46 Ci/mmol (Amersham), 1.5 µCi) 20 mM Tris-HCl (pH 7.5), EDTA (1 mM), MgCl₂ (5 mM), NaCl (50 mM), DTT (1 mM), BSA (0.01%)

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259

Table 71

Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]	Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]
2	0.079	67	0.26
6	0.034	68	0.28
9	0.019	70	0.19
11	0.53	71	0.62
12	0.60	77	0.51
17	0.047	81	0.18
20	0.042	82	0.097
26	0.033	83	0.52
30	0.052	85	0.17
43	0.58	86	0.13
44	0.95	87	0.80
45	0.40	88	0.092
46	0.47	89	0.34
47	0.54	90	0.20
48	0.44	91	0.53
49	0.94	93	0.16
50	0.54	94	0.084
51	1.0	96	0.25
54	0.56	97	0.16
55	0.36	98	0.30

48
48
760

Table 72

Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]	Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]
99	0.53	120	0.16
100	0.78	121	0.19
101	0.14	122	0.51
103	0.17	123	0.10
104	0.073	124	0.091
105	0.076	125	0.12
106	0.40	128	0.14
107	0.11	129	0.12
108	0.21	130	0.16
109	0.11	131	0.046
110	0.24	132	0.055
111	0.14	133	0.12
112	0.11	134	0.071
113	0.071	139	0.26
114	0.56	140	0.11
115	0.17	141	0.43
116	0.37	142	0.055
117	0.075	143	0.053
118	0.14	144	0.19
119	0.13	145	0.088

149
261

Table 73

Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]	Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]
146	0.043	167	0.033
147	0.31	168	0.078
148	0.038	169	0.15
149	0.15	170	0.048
150	0.24	171	0.050
151	0.20	172	0.10
153	0.19	173	0.14
154	0.076	174	0.030
155	0.53	175	0.29
156	0.23	176	0.053
157	0.16	177	0.077
158	0.11	178	0.052
159	0.13	179	0.63
160	0.24	180	0.11
161	0.062	181	0.71
162	0.43	182	0.021
163	0.15	183	0.017
164	0.16	184	0.018
165	0.58	185	0.11
166	0.055	186	0.37

150
762

Table 74

Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]	Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]
187	0.056	207	0.081
188	0.038	208	0.039
189	0.017	209	0.12
190	0.020	210	0.31
191	0.43	211	0.059
192	0.22	212	0.23
193	0.13	213	0.10
194	0.52	214	0.059
195	0.023	215	0.078
196	0.20	216	0.084
197	0.11	217	0.058
198	0.044	218	0.033
199	0.11	219	0.13
200	0.10	220	0.073
201	0.14	221	0.058
202	0.095	222	0.041
203	0.063	223	0.21
204	0.16	225	0.014
205	0.077	227	0.045
206	0.05	228	0.18

187
987
763.

Table 75

Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]	Ex. No.	HCV polymerase inhibitory activity IC ₅₀ [μM]
229	0.022	235	0.036
230	0.17	236	0.075
231	0.073	237	0.015
232	0.015	238	0.19
233	0.028	239	0.17
234	0.022	240	0.055

152
eqd
764

Formulation Example is given in the following. This example is merely for the purpose of exemplification and does not limit the invention.

Formulation Example

- | | | |
|---|-----------------------------------|------|
| 5 | (a) compound of Example 1 | 10 g |
| | (b) lactose | 50 g |
| | (c) corn starch | 15 g |
| | (d) sodium carboxymethylcellulose | 44 g |
| | (e) magnesium stearate | 1 g |

- 10 The entire amounts of (a), (b) and (c) and 30 g of (d) are kneaded with water, dried in vacuo and granulated. The obtained granules are mixed with 14 g of (d) and 1 g of (e) and processed into tablets with a tableting machine to give 1000 tablets each containing 10 mg of (a).

- 15 **[Effect of the Invention]**

As is evident from the above-mentioned results, the compound of the present invention shows a high inhibitory activity against HCV polymerase.

- 20 Therefore, the compound of the present invention can provide a pharmaceutical agent effective for the prophylaxis or treatment of hepatitis C, based on the anti-HCV effect afforded by the HCV polymerase inhibitory activity. Its high inhibitory activity specific to HCV polymerase suggests the possibility of the compound being a pharmaceutical agent with slight side effects,
- 25 which can be used safely for humans.

Ver-folios 499 + 500 → 791

183
94t
→ 765

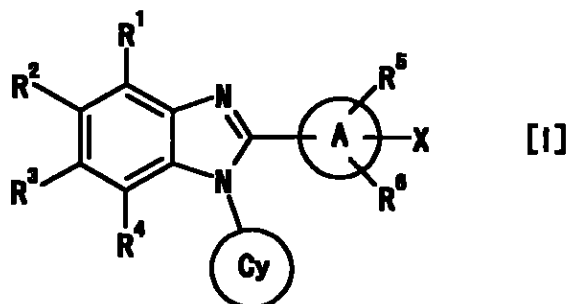
791

【Document】 Abstract

【Summary】

【Solving Means】 To provide a therapeutic agent and a prophylactic agent effective against hepatitis C, which shows an anti-HCV action by HCV polymerase inhibitory activity.

5 【Solving Means】 The benzimidazole compound of the following formula [I]



10 wherein each symbol is as defined in the specification, a pharmaceutically acceptable salt thereof, and a therapeutic agent for hepatitis C, which contains this compound.

【Main Drawing】 None