Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2520115 C 2012/10/02

(11)(21) 2 520 115

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2004/06/04
(87) Date publication PCT/PCT Publication Date: 2004/12/16
(45) Date de délivrance/Issue Date: 2012/10/02
(85) Entrée phase nationale/National Entry: 2005/09/23
(86) N° demande PCT/PCT Application No.: JP 2004/008165
(87) N° publication PCT/PCT Publication No.: 2004/108683
(30) Priorités/Priorities: 2003/06/06 (JP2003-161987);
2003/09/22 (JP2003-330627);
2003/12/03 (JP2003-404635);
2004/03/29 (JP2004-094931)

(51) Cl.Int./Int.Cl. *C07D 231/18* (2006.01),
A61K 31/415 (2006.01), *A61P 35/00* (2006.01),
A61P 7/00 (2006.01)

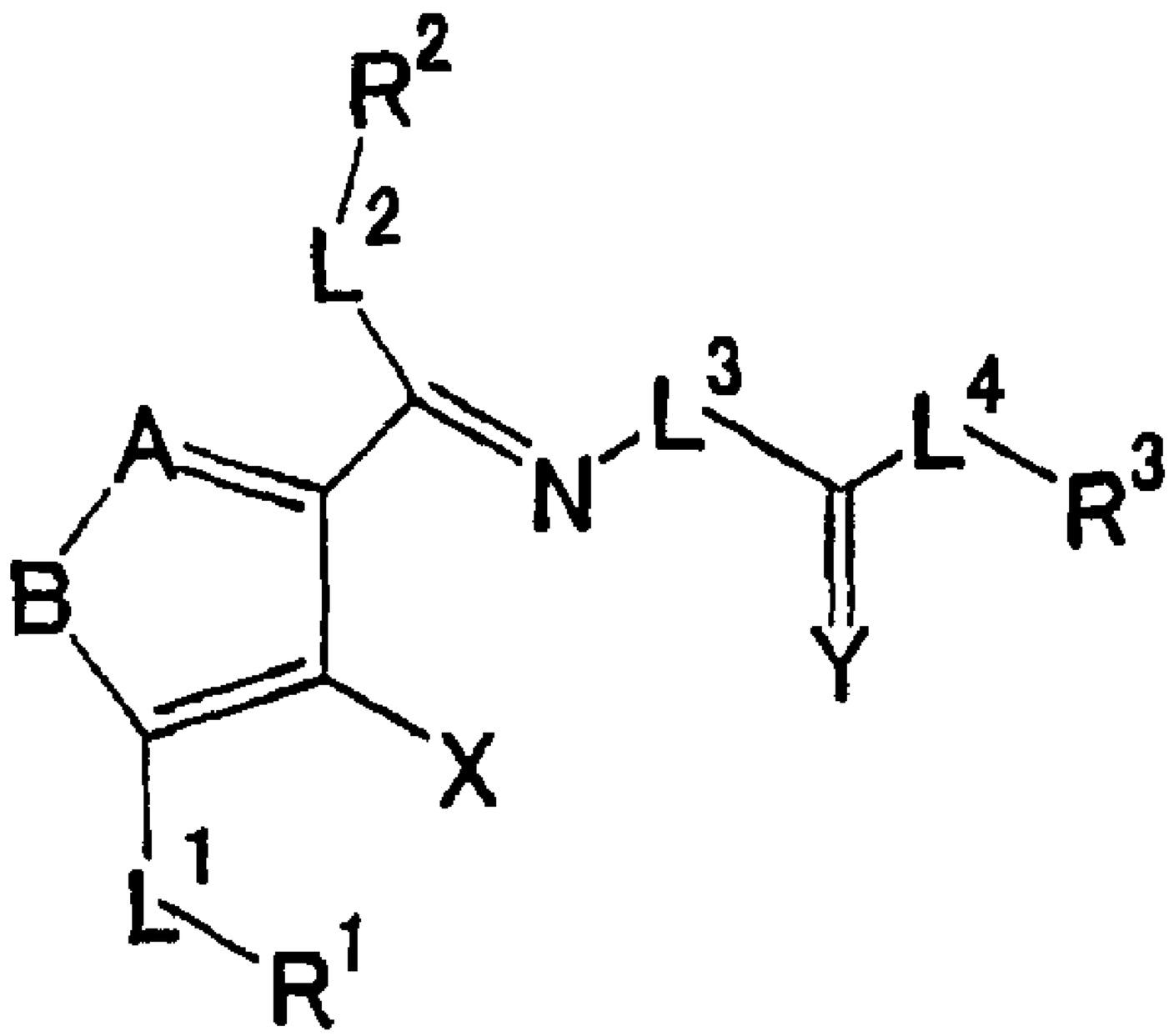
(72) Inventeurs/Inventors:
OWADA, SHINGO, JP;
IWAMOTO, SHUNSUKE, JP;
YANAGIHARA, KAZUFUMI, JP;
MIYAJI, KATSUAKI, JP;
NAKAMURA, TAKANORI, JP;
ISHIWATA, NORIHISA, JP;
HIROKAWA, YUTAKA, JP

(73) Propriétaire/Owner:
NISSAN CHEMICAL INDUSTRIES, LTD., JP

(74) Agent: SMART & BIGGAR

(54) Titre : UTILISATION DE COMPOSES HETEROARYLES A SUBSTITUTION 3-ALKYLIDENEHYDRAZINO EN TANT QU'ACTIVATEURS DU RECEPTEUR DE LA THROMBOPOIETINE

(54) Title: 3-ALKYLIDENEHYDRAZINO SUBSTITUTED HETEROARYL COMPOUNDS AS THROMBOPOIETIN RECEPTOR ACTIVATORS



(1)

(57) Abrégé/Abstract:
A compound represented by the formula (1): wherein A is a nitrogen atom or CR^4, B is an oxygen atom, a sulfur atom or NR^9 (provided that when A is a nitrogen atom, B is not NH), R^1 is a C^{2-14}; aryl group, L^1 is a bond, $CR^{10}R^{11}$, an oxygen atom, a sulfur

(11)(21) **2 520 115**

(13) **C**

(57) **Abrégé(suite)/Abstract(continued):**
atom or NR^{12}, X is OR^{13}, SR^{13} or $NR^{14}NR^{15}$, R^2 is a hydrogen atom, a formyl group, a C^{1-10}; alkyl group or the like, L^2 is a bond or the like, L^3 is a bond, $CR^{17}R^{18}$, an oxygen atom, a sulfur atom or NR^{19}, L^4 is a bond, $CR^{20}R^{21}$, an oxygen atom, a sulfur atom or NR^{22}, Y is an oxygen atom, a sulfur atom or NR^{23}, and R^3 is a C^{2-14}; aryl group, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108683 A1

(51) International Patent Classification[7]: C07D 231/18, 333/32, A61K 31/415, 31/381, A61P 7/00, 35/00

(21) International Application Number: PCT/JP2004/008165

(22) International Filing Date: 4 June 2004 (04.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2003-161987	6 June 2003 (06.06.2003)	JP
2003-330627	22 September 2003 (22.09.2003)	JP
2003-404635	3 December 2003 (03.12.2003)	JP
2004-094931	29 March 2004 (29.03.2004)	JP

(71) Applicant *(for all designated States except US)*: **NISSAN CHEMICAL INDUSTRIES, LTD.** [JP/JP]; 7-1, Kanda-Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 1010054 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **OWADA, Shingo** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Chemical Research Laboratories, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 2748507 (JP). **IWAMOTO, Shunsuke** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Chemical Research Laboratories, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 2748507 (JP). **YANAGIHARA, Kazufumi** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Chemical Research Laboratories, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 2748507 (JP). **MIYAJI, Katsuaki** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Chemical Research Laboratories, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 2748507 (JP). **NAKAMURA, Takanori** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Biological Research Laboratories, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 3490218 (JP). **ISHIWATA, Norihisa** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Biological Research Laboratories, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 3490218 (JP). **HIROKAWA, Yutaka** [JP/JP]; c/o Nissan Chemical Industries, Ltd., Chemical Research Laboratories, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 2748507 (JP).

(74) Agents: **SENMYO, Kenji** et al.; Torimoto Kogyo Bldg., 38, Kanda-Higashimatsushitacho, Chiyoda-ku, Tokyo 1010042 (JP).

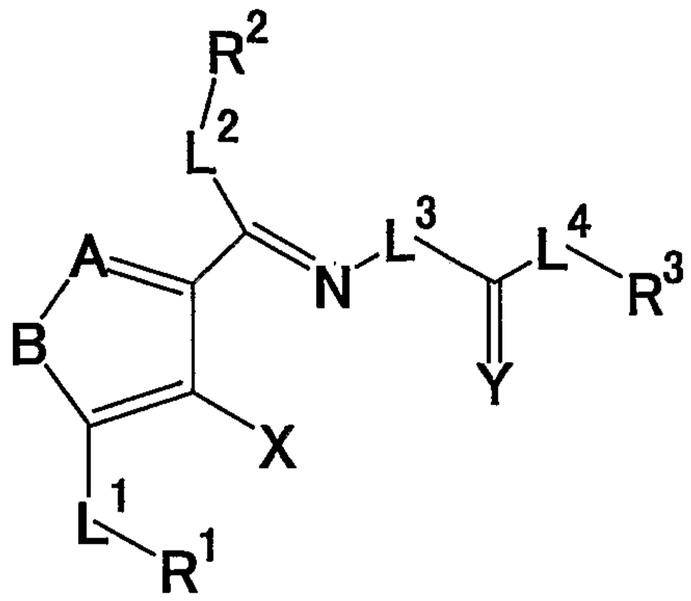
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 3-ALKYLIDENEHYDRAZINO SUBSTITUTED HETEROARYL COMPOUNDS AS THROMBOPOIETIN RECEPTOR ACTIVATORS



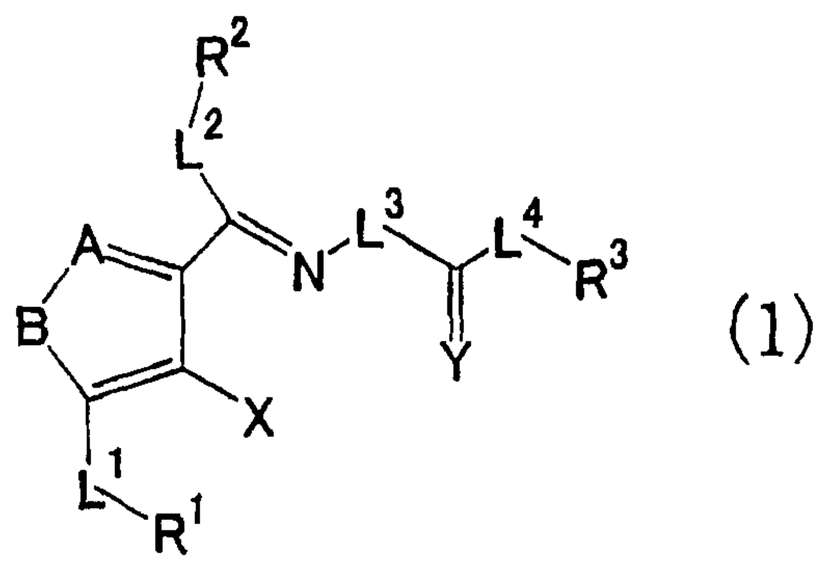
(1)

(57) Abstract: A compound represented by the formula (1): wherein A is a nitrogen atom or CR^4, B is an oxygen atom, a sulfur atom or NR^9 (provided that when A is a nitrogen atom, B is not NH), R^1 is a C^{2-14}; aryl group, L^1 is a bond, $CR^{10}R^{11}$, an oxygen atom, a sulfur atom or NR^{12}, X is OR^{13}, SR^{13} or $NR^{14}NR^{15}$, R^2 is a hydrogen atom, a formyl group, a C^{1-10}; alkyl group or the like, L^2 is a bond or the like, L^3 is a bond, $CR^{17}R^{18}$, an oxygen atom, a sulfur atom or NR^{19}, L^4 is a bond, $CR^{20}R^{21}$, an oxygen atom, a sulfur atom or NR^{22}, Y is an oxygen atom, a sulfur atom or NR^{23}, and R^3 is a C^{2-14}; aryl group, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

71416-328

CLAIMS:

1. A compound represented by the formula (1):



(1)

wherein A is a nitrogen atom or CR^4,

wherein R^4 is a hydrogen atom or a halogen atom;

when A is a nitrogen atom, B is NR^9,

wherein R^9 is a C_{1-10} alkyl group,

wherein the C_{1-10} alkyl group is unsubstituted or substituted with a phenyl group,

and when A is CR^4, B is a sulfur atom;

R^1 is a phenyl group,

wherein the phenyl group is substituted with one or more substituents selected from the group consisting of: halogen atoms, C_{1-10} alkyl groups and C_{1-10} alkoxy groups,

wherein the C_{1-10} alkyl groups and the C_{1-10} alkoxy groups is unsubstituted or substituted with one or more halogen atoms;

L^1 is a bond;

X is OH;

R^2 is a hydrogen atom or a C_{1-10} alkyl group;

L^2 is a bond;

L^3 is NH;

L^4 is a bond or NH;

Y is an oxygen atom or a sulfur atom; and

R^3 is a phenyl group or a thienyl group,

wherein the phenyl group and the thienyl group are substituted with one or more substituents independently represented by W^4,

wherein W^4 is a hydroxyl group, a halogen atom, a nitro group, a C_{1-10} alkylcarbonylamino group, SO_2R^{28}, COR^{28},

wherein R^{28} is a hydroxyl group, a C_{1-10} alkoxy group or $NR^{29}R^{30}$,

wherein R^{29} and R^{30} are independently a hydrogen atom or a C_{1-10} alkyl group

or a tetrazole group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

2. The compound according to claim 1, wherein;

A is a nitrogen atom;

B is NR^9, wherein R^9 is a methyl group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

3. The compound according to claim 1, wherein;

A is CR^4, wherein R^4 is a hydrogen atom;

B is a sulfur atom;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

4. The compound according to any one of claims 1 to 3, wherein;

L^4 is NH;

Y is a sulfur atom;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

5. The compound according to any one of claims 1 to 3, wherein;

L^4 is a bond;

Y is an oxygen atom;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

6. The compound according to any one of claims 1 to 5, wherein;

R^2 is a methyl group; and

R^3 is a phenyl group or a 2-thienyl group,

wherein the phenyl group and the 2-thienyl group is substituted with a substituent selected from the group consisting of: a carboxyl group, a methoxycarbonyl group and a tetrazole group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

71416-328

7. The compound according to claim 6, wherein;

R^3 is a phenyl group,

wherein the phenyl group is substituted with a carboxyl group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

8. The compound according claim 6, wherein;

R^3 is a 2-thienyl group,

wherein the 2-thienyl group is substituted with a carboxyl group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

9. The compound according to any one of claims 1 to 5, wherein;

R^2 is a methyl group; and

R^3 is a phenyl group or a 2-thienyl group,

wherein the phenyl group and the 2-thienyl group is substituted with a substituent selected from the group consisting of:

a carboxyl group and a methoxycarbonyl group;

and a substituent selected from the group consisting of:

a halogen atom, a nitro group, a hydroxyl group and a methylcarbonylamino group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

10. The compound according to claim 9, wherein;

R^3 is phenyl group,

wherein the phenyl group is substituted with a carboxyl group; and a substituent selected from the group consisting of:

a halogen atom, a nitro group and a hydroxyl group;

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

11. The compound according to any one of claims 1 to 10, wherein;

R^1 is a 3,4-dichlorophenyl, 4-tert-butylphenyl or 4-trifluoromethylphenyl,

a tautomer or pharmaceutically acceptable salt of the compound or a solvate thereof.

12. A thrombopoietin receptor activator which is a pharmaceutical preparation comprising the compound, tautomer, salt or solvate as defined in any one of claims 1 to 11, and

a pharmaceutically acceptable additive.

13. A pharmaceutical composition for preventing, treating or improving thrombocytopenia, which contains:

the compound, tautomer, salt or solvate as defined in any one of claims 1 to 11, and

a pharmaceutically acceptable additive.

14. A pharmaceutical composition for increasing platelets, which contains:

the compound, tautomer, salt or solvate as defined in any one of claims 1 to 11, and

a pharmaceutically acceptable additive.

15. A medicament containing:

the compound, tautomer, salt or solvate as defined in any one of claims 1 to 11, and

a pharmaceutically acceptable additive.

16. A pharmaceutical composition comprising:

the compound 4-{[(2-{1-[5-(3,4-dichlorophenyl)-4-hydroxy-1-methyl-1H-pyrazol-3-yl]ethylidene}hydrazino)carbonothioyl]amino}benzoic acid or a pharmaceutically acceptable salt thereof and

a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising:

the compound 4-[(2-{1-[5-(4-tert-butylphenyl)-4-hydroxy-1-methyl-1H-pyrazol-3-yl]ethylidene}hydrazine)carbonyl]benzoic acid or a pharmaceutically acceptable salt thereof and

a pharmaceutically acceptable carrier.

Fig. 1

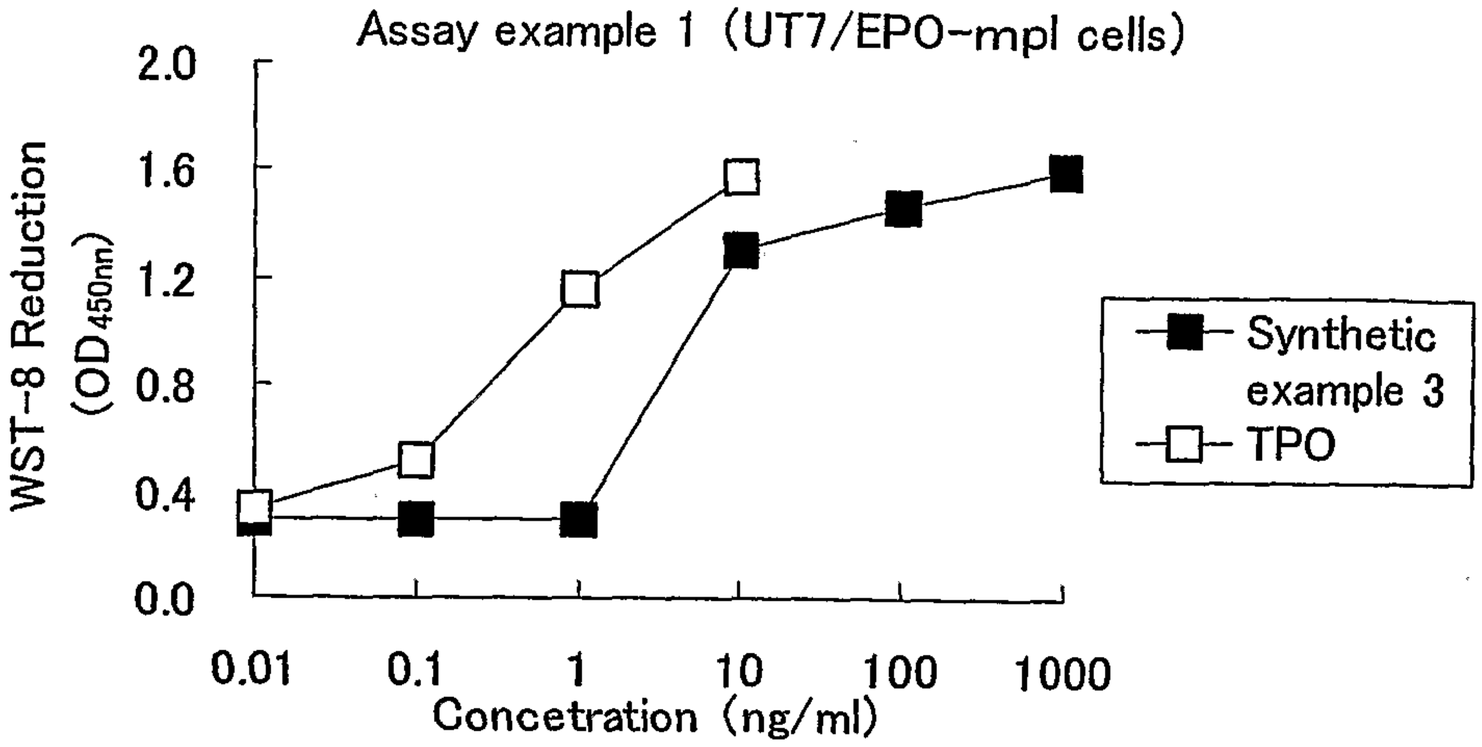
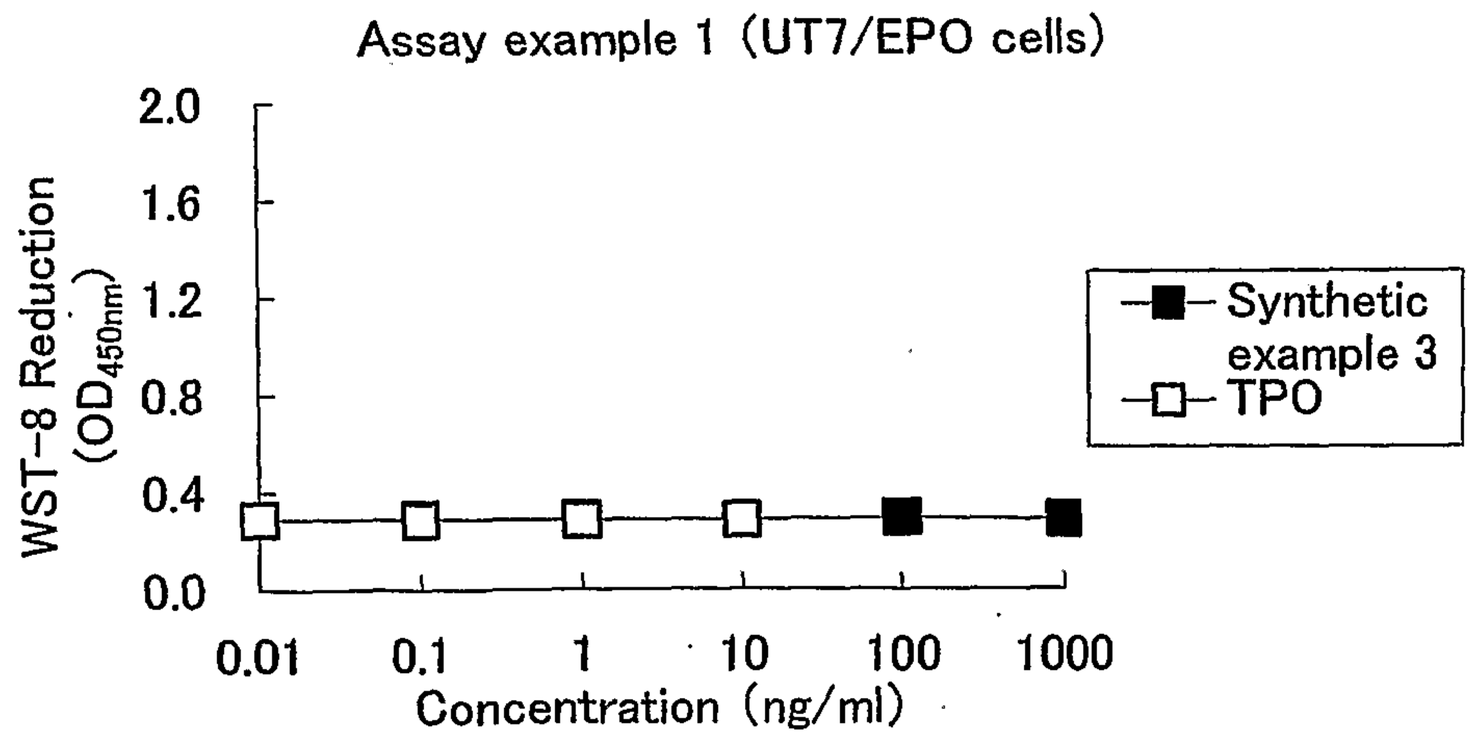
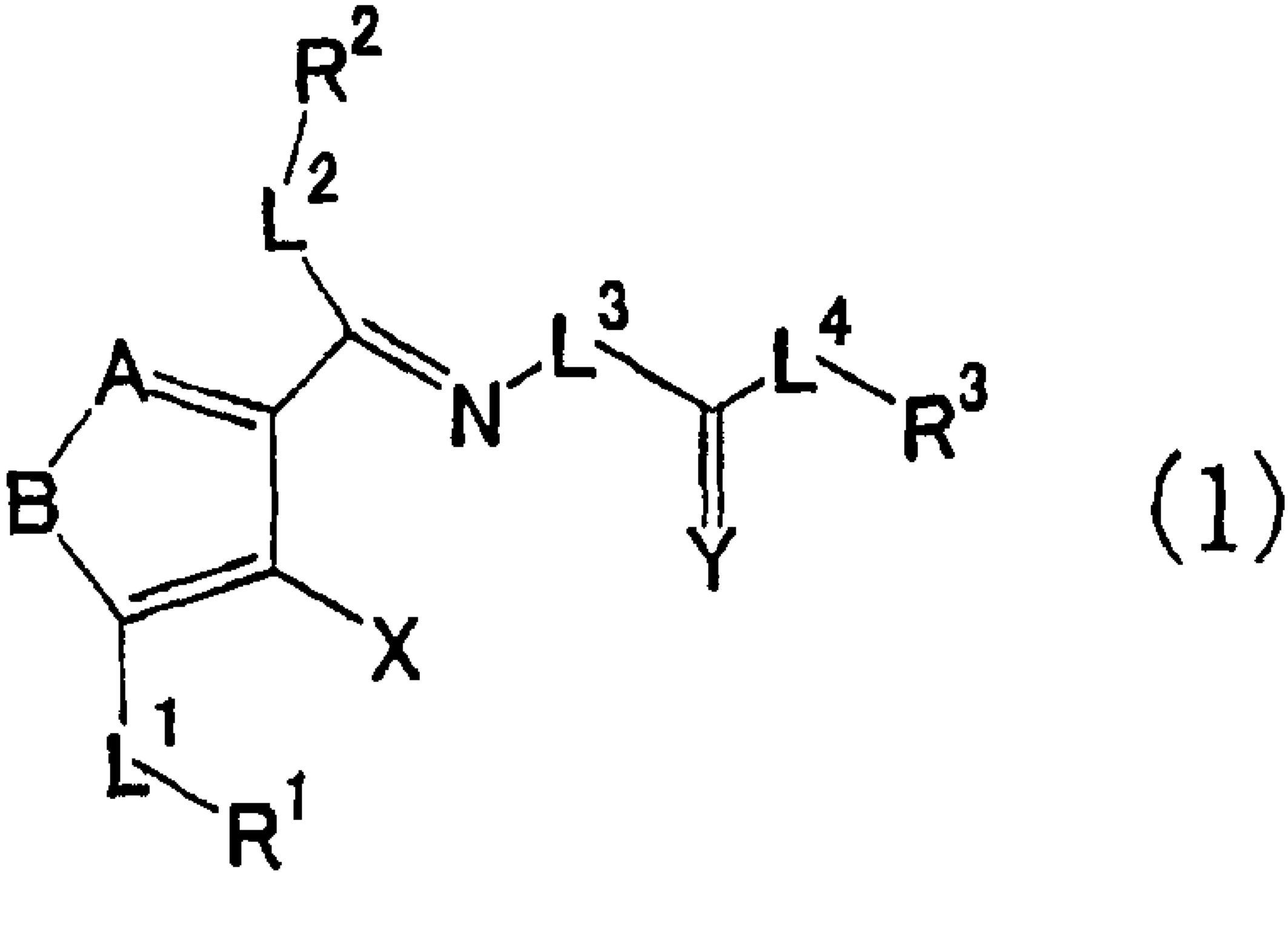

Assay example 1 (UT7/EPO-mpl cells)
WST-8 Reduction (OD450nm)
2.0
1.6
1.2
0.8
0.4
0.0
0.01
0.1
1
10
100
1000
Concetration (ng/ml)
Synthetic example 3
TPO

Fig. 2


Assay example 1 (UT7/EPO cells)
WST-8 Reduction (OD450nm)
2.0
1.6
1.2
0.8
0.4
0.0
0.01
0.1
1
10
100
1000
Concentration (ng/ml)
Synthetic example 3
TPO



(1)