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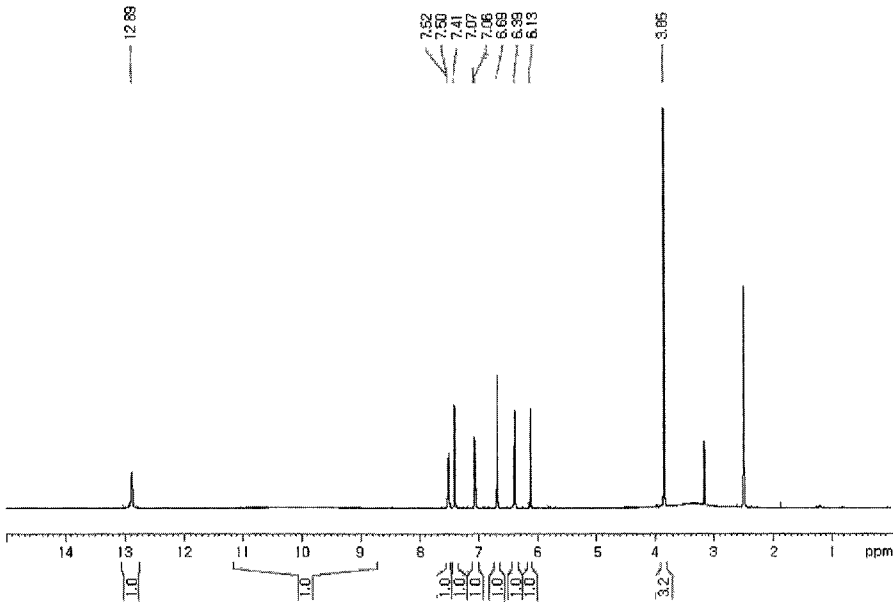
[Continued on next page]

(54) Title: C-KIT ACTIVATION INHIBITOR, SKIN WHITENING COMPOUND AND COMPOSITION FOR SKIN WHITENING CONTAINING THE SAME



(57) Abstract: Disclosed are a c-Kit activation inhibitor, a skin whitening compound and a composition for skin whitening comprising the skin whitening compound as an active ingredient. The c-Kit activation inhibitor of the present invention is a flavone derivative selected from the group consisting of the compounds represented by Formulas 1 to 10. The flavone derivative inhibits activity of the c-Kit associated with melanin synthesis, melanocyte differentiation and maturity, etc. Accordingly, the above-mentioned flavone derivatives are useful as skin whitening compound, and the cosmetic compositions comprising the flavone derivatives as an active ingredient can be highly effectively used for skin whitening, for example treating melasma, freckles, etc.

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C-KIT ACTIVATION INHIBITOR, SKIN WHITENING COMPOUND AND COMPOSITION FOR SKIN WHITENING CONTAINING THE SAME

TECHNICAL FIELD

The present invention relates to an activation inhibitor of c-Kit associated with melanin synthesis, melanocyte differentiation and maturity, etc., a skin whitening compound having skin whitening effect such as treatment of melasma or freckles, and a composition for skin whitening comprising the skin whitening compound as an active ingredient.

BACKGROUND ART

It has been known that c-Kit, which is a receptor belonging to a class III receptor tyrosine kinase (RTK), is associated with survival, proliferation and differentiation of melanocyte. The number of the melanocyte is increased in skins when the skins are exposed to UV rays. In this reaction, the c-Kit plays an important role. It was confirmed that increased stem cell factors (SCFs) in a hair follicle 'niche,' which generates and differentiates melanocyte, grow and differentiate melanocyte to migrate out of the niche in the case of a K14 (keratin promoter)-steel factor transgenic mouse, and that mice have white hair and white skin if the mice are treated with ACK2 which is an antibody against c-Kit in an embryonic step (Nature 416, 854-860, 2002).

Form the beginning, there have been many more attempts to study c-Kit as a target of an anti-cancer drug than as a whitening compound. Imatinib (Gleevec, STI-571, Novatis, East Hanover, NJ, USA) has been widely known as an anti-cancer

drug for treating leukemia, which targets Bcr-Abl kinase. However, it was revealed that a level of melanin pigment is decreased in skins of 6 patients who receive a prescription of imatinib, indicating that the imatinib inhibits activity of c-Kit in addition to the Bcr-Abl. Accordingly, it might be seen that SCF/c-Kit plays an essential role in growing and sustaining human melanocyte (Cancer 98, 2483-7, 2003).

Meanwhile, it was reported that SCF, which is a ligand of c-kit, is more excessively expressed in a lesion region of melasma than a normal skin region (Korean J. Dermatol. 2005; 43 (8): 1046-1052), and that SCF is excessively expressed in excessive melanotic conditions such as UVB-melanosis, lentigo senilis, dermatofibroma and Caffe aure macule (Pigment Cell Research 17:96-110. 2004).

If c-Kit is activated, the activated c-Kit activates MAP kinase, and the activated MAP kinase sequentially phosphorylates a microphthalmia-associated transcription factor (Mitf), which is a helix-loop-helix/leucine zipper protein, into an activated state. The activated Mitf stimulates transcription of melanin-synthesizing enzymes such as tyrosinase, Tyrp-2, etc. to synthesize melanin pigment. SCF, secreted from keratinocyte when exposed to UV-rays, stimulates differentiation of precursor melanocyte into mature melanocyte harboring c-Kit, and also stimulates synthesis of melanin pigment by stimulating transcription of enzymes associated with the melanin synthesis.

As described above, the c-Kit is mainly associated with a signal transduction system which stimulates synthesis of melanin by UV-rays. Accordingly, if it is possible to inhibit the c-Kit activity, differentiation and maturity of the melanocyte may be inhibited, in addition to the anti-cancer effect.

Generally, many persons hope to have a white and soft skin, but if melanin is excessively synthesized in their skins, they have a dark skin tone, and also have melasma, freckles, etc. Accordingly, if the synthesis of melanin pigment in skin is inhibited, a skin tone may be brightened to thereby whiten skin, and cutaneous hyperpigmentation such as melasma, freckles, lentigo senilis, dermatofibroma, Caffe aure macule etc., which are caused by UV-rays, hormones and other genetic factors, may be treated to thereby whiten skin.

Accordingly, conventional compounds such as hydroquinone, ascorbic acid, kojic acid and glutathione, which have an inhibitory activity on tyrosinase, were mixed with skin-applicable compositions such as ointment or cosmetics, and then the resultant compositions were used in the art to whiten skin, for example to treat melasma and freckles. However, it was confirmed that the hydroquinone has some whitening effect, but it is used in an extremely low amount due to severe irritation to skin. Also, the ascorbic acid has a problem that smells and colors of an ascorbic acid-containing cosmetic composition are easily changed due to its susceptibility to oxidation. Meanwhile, thiol compounds such as glutathione, cysteine, etc. have an inherent disgusted smell and a transdermal delivery-related problem, and their glycosides and derivatives are also difficult to use as mixing ingredients due to its high polarity.

DISCLOSURE OF INVENTION

[Technical Problem]

Therefore, one object of the present invention is to provide a c-Kit activation inhibitor capable of inhibiting activity of c-Kit associated with melanin synthesis,

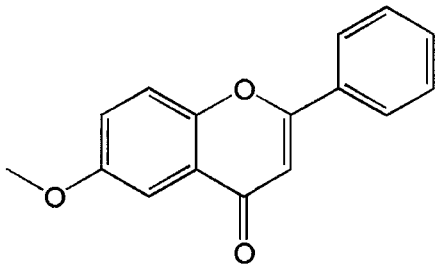
anti-cancer activity, etc.

In addition, another object of the present invention is to provide a skin whitening compound and a composition for skin whitening being able to be safely used without any side effect on skin and having an excellent inhibitory effect on pigmentation.

[Technical Solution]

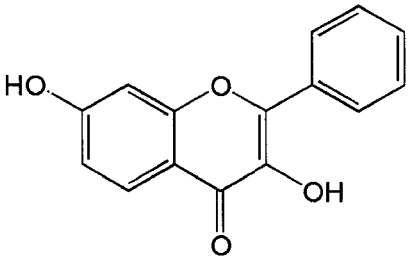
In order to accomplish the first object, the present invention provides a c-Kit activation inhibitor which is a flavone derivative selected from the group consisting of compounds represented by the following Formulas 1 to 10.

[Formula 1]



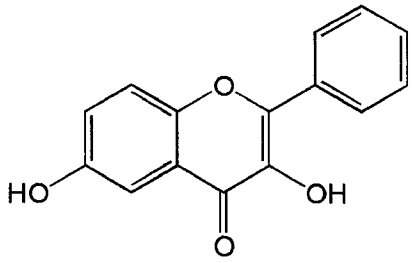
6-methoxyflavone

[Formula 2]



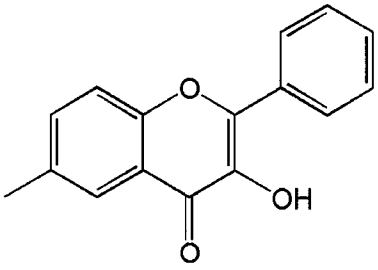
3,7-dihydroxyflavone

[Formula 3]



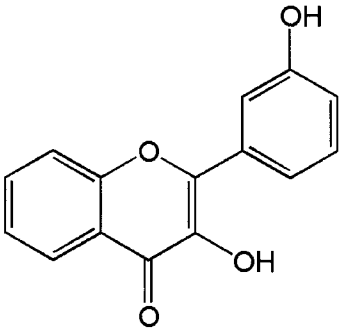
3,6-dihydroxyflavone

[Formula **4]**



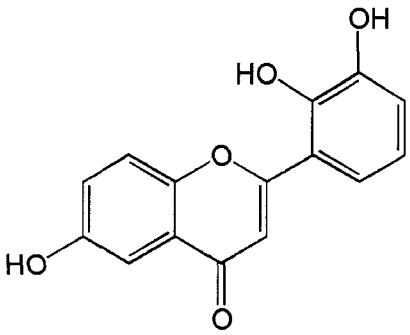
3-hydroxy-6-m ethylflavone

[Formula **5]**



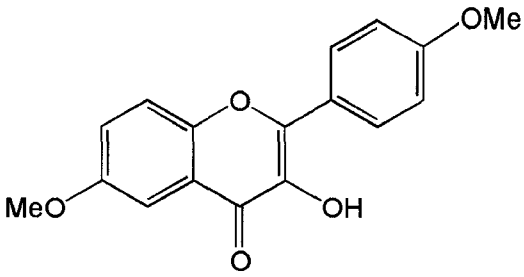
3,3'-dihydroxyf lavone

[Formula **6]**



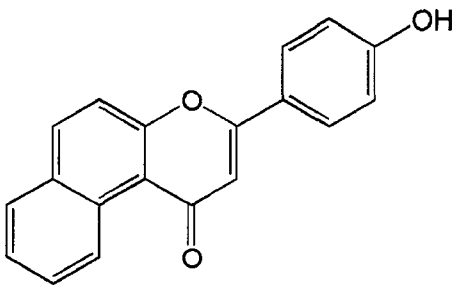
6,2',3'-trihydroxyflavone

[Formula **7]**



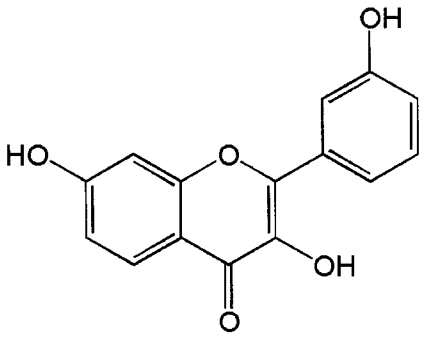
6,4'-dimethoxy-3-hydroxyflavone

[Formula **8]**



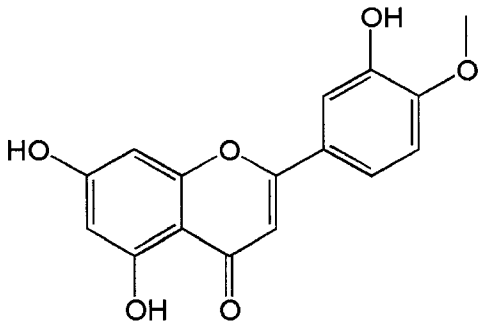
4'-hydroxy-beta-naphthof lavone

[Formula 9]



3,7,3'-trihydroxyflavone

[Formula 10]



diosmetin

In addition, the present invention provides a skin whitening compound, one flavone derivative, selected from the group consisting of compounds represented by the Formulas 1 to 10, and a composition for skin whitening comprising any of the compounds as an active ingredient.

In the composition for skin whitening, a content of the flavone derivatives preferably ranges from 0.000001 to 10 % by weight, based on the total weight of the composition, and these flavone derivatives can be added to various formulations such as skin, lotion, cream, foundation, essence, gel, pack, foam cleansing, soap, ointment, etc. to give a skin whitening effect.

Hereinafter, the present invention will be described in more detail.

The present invention provides a c-Kit inhibitor, one flavone derivative, selected from the group consisting of 6-methoxyflavone (6-methoxy-2-phenyl-4H-chromen-4-one, $C_{16}H_{12}O_3$, CAS No. 26964-24-9) of Formula 1, 3,7-dihydroxyflavone ($C_{15}H_{10}O_4$, CAS NO. 492-00-2) of Formula 2, 3,6-Dihydroxyflavone ($C_{15}H_{10}O_4$, CAS No. 08238-41-1) of Formula 3, 3-hydroxy-6-methylflavone (6-methyl-3-hydroxyflavone, $C_{16}H_{12}O_3$, CAS No. 6971-18-2) of Formula 4, 3,3'-dihydroxyflavone ($C_{15}H_{10}O_4$, CAS No. 55977-09-8) of Formula 5, 6,2',3'-trihydroxyflavone ($C_{15}Hi_0O_5$, CAS No. 108238-47-7) of Formula 6, 6,4'-dimethoxy-3-hydroxyfiavone ($C_{17}H_{14}O_5$, CAS No. 93176-02-4) of Formula 7, 4'-hydroxy-β-naphthoflavone ($C_{19}H_{12}O_3$, CAS No. 98166-72-4) of Formula 8, 3,7,3'-trihydroxyflavone ($C_{15}H_{10}Os$) of Formula 9 and diosmetin (5,7-dihydroxy-2-(3-hydroxy-4-methoxy-phenyl)-chromen-4-one, $C_{16}H_{12}O_6$, CAS No. 520-34-3) of Formula 10.

In particular, the diosmetin of Formula 10 is a compound that has been reported as an ingredient of plants including Acacia farnesiana, Achillea asiatica, Arnica longifolia, Artemisia rutifolia, Artemisia vulgaris, Caleriana chionophila, Capsella bursa-pastoris, Citrus limon, Cnidium monnieri, Cyperus alopecuroides, Gentiana barbata, Hieracium compositum, Lnaria macroura, Mentha spicata, Origaganum vulgare, Pedalium murex, Petroselinum crispum, Rosmarinus officinalis, Salvia candidissima, Salvia nutans, Salvia reptans, Soroseris hookeriana, Stemodia viscose, Tanacetum vulgare, Toddalia floribunda, Thymbra capitata, Thymus hirtus, Thymus vulgaris, Verbena bipinnatifida, Valeriana cardamines, Valeriana eriophylla, Valeriana

fedtschenkoi, Valeriana laxiflora, Vicia truncatula, Xanthorrhoea hastile durch and Xanthorrhoea hastila. It has been known that the diosmetin has an anti-bacterial effect (Planta Medica, 70 (6), 2004, 509-514), and anti-allergic effect (Bioorg. Med. Chem, 10 (10), 2002, 3123-3128), anti-inflammation effect (J. haram. Pharmacol., 50 (9), 1998, 1069-1074), etc.

The inventors have studied about compounds that can inhibit the activity of the c-KIT associated with melanin synthesis, melanocyte differentiation and maturity, etc., and have found that the above-mentioned flavone derivatives show a very potent inhibitory effect on the c-Kit, on which the present invention is based.

That is to say, the above-mentioned flavone derivatives inhibit the activity of the c-Kit, and therefore they can be used as multifunctional skin whitening compounds that inhibit synthesis of enzymes associated with melanocyte differentiation and maturity and melanin synthesis, as well as an anti-cancer effect. Particularly, the c-Kit activation inhibitor such as the above-mentioned flavone derivatives can be useful to attain an excellent skin whitening effect even if it is used in a small amount since it acts at the beginning of signal transduction for the melanin synthesis.

In the present invention, the term "skin whitening effect " is generally intended to include effects of improving undesirable conditions associated with the skin colors, for example treating melasma and freckles, improving lentigo senilis, dermatofibroma, and cutaneous hyperpigmentation, as well as an effect of making skin whiter.

The above-mentioned flavone derivatives of Formulas 1 to 10 are commercially available. However, it is more preferable to use an extract of *Chrysanthemum morifolium* {*Chrysanthemum morifolium* petals) as the diosmetin of Formula 10. A

method for extracting diosmetin from *Chrysanthemum morifolium* will be illustrated as described below, but the scope of the present invention is not limited to the subject to be extracted or the extraction methods as described in the present invention.

Chrysanthemum morifolium, commercially available as a medicinal herb, was purchased, ground into small pieces, and the ground substance was extracted with 5-20 times volume of methanol at 50-100 ℃ for 1-5 hours in an extractor having a reflux cooler. The residue was extracted through a filter cloth using the same method, and then the remaining extract was filtered once or more. The resultant extracts were collected, concentrated under a reduced pressure, and then freeze-dried or spray-dried to obtain a dry extract. In order to confirm the presence of an active ingredient in the methanol extract of the *Chrysanthemum morifolium*, the methanol extract was suspended in 10 times volume of water, and fractionated with an equivalent amount of hexane to remove non-polar compounds, and the remaining aqueous layer was then fractionated with an equivalent amount of butanol solvent to obtain a butanol fraction of the *Chrysanthemum morifolium*. An active ingredient was separated from the resultant butanol fraction of the *Chrysanthemum morifolium* with a silica gel column chromatography using mixed chloroform/methanol solvent mixture as an eluent, and the obtained active ingredient was purified using a preparative HPLC under the same conditions. The purified active ingredient was confirmed to be diosmetin using nuclear magnetic resonance (NMR) and mass spectrometry (Mass).

In order to give a skin whitening effect, the above-mentioned pure flavone derivatives of Formulas 1 to 10 or the diosmetin extracts can be added in an effective amount to various compositions such as an ointment and cosmetic products including a

skin, a lotion, a cream, a foundation, an essence, a gel, a pack, a foam cleansing, a soap, etc., and the flavone derivatives or the diosmetin extracts can be used alone or in combination thereof.

In consideration of a skin whitening effect and economical efficiency, an amount of the added flavone derivatives preferably ranges from 0.000001 to 10 % by weight, more preferably from 0.0001 to 1 % by weight, based on the total weight of the composition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing a H^1-NMR spectrum of diosmetin extracted and purified according to one embodiment of the present invention.

FIG. 2 is a graph showing a C^{13} NMR spectrum of diosmetin extracted and purified according to one embodiment of the present invention.

FIG. 3 is a graph showing a mass spectrometry spectrum of diosmetin extracted and purified according to one embodiment of the present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

Hereinafter, preferred embodiments of the present invention will be described in detail referring to the accompanying drawings. However, the description proposed herein is just a preferable example for the purpose of illustrations only, not intended to limit the scope of the invention, so it should be understood that other equivalents and modifications could be made thereto without departing from the spirit and scope of the invention. The preferred embodiments of the present invention will be described in

detail for the purpose of better understandings, as apparent to those skilled in the art.

Evaluation of Flavone Derivatives of Formulas 1 to 9

The commercially available flavone derivative compounds of Formulas 1 to 9 were purchased and used. Each of the flavone derivative compounds was adjusted to a final concentration of 1 uM and added to each well of a 384-well plate, and c-Kit RTK and ATP were also added to each well of the 384-well plate, and then subject to a primary reaction at a room temperature. Then, biotinylated-poly[Glu:Tyr] (4:1) as a substrate was added, and then subject to a secondary enzyme reaction.

A capture buffer containing donor beads coated with streptavidin and acceptor beads to which antibody (P-Tyr-100) binds was added, and then subject to a tertiary reaction to bind to the substrate. Phosphorylation levels of the substrates were determined by measuring AlphaScreen signal using a Fusion™ microplate analyzer. Also, their inhibitory effects were compared using Tyrphostin A51 known as c-Kit inhibitor in the prior art.

In order to measure the AlphaScreen signal to an accurate level, each test sample was tested three times. Here, in order to determine inhibition by c-Kit, DMSO was used as a positive control instead of the test samples, and DMSO and a buffer were used instead of the test samples and the enzyme as a positive control, respectively.

The inhibition (%) on c-Kit was calculated from the detected signal according to the following Equation 1. The results are listed in the following Table 1.

Equation 1

Inhibition (%) = (Mean Value of Test Samples - Mean Value of Negative Control) /

(Mean Value of Positive Control - Mean Value of Negative Control) X 100

Table 1

Test Samples	Inhibition (%)
6-methoxyflavone (Formula 1)	45
3,7-dihydroxyflavone (Formula 2)	51
3,6-dihydroxyflavone (Formula 3)	44
3-hydroxy-6-methylflavone (Formula 4)	51
3,3'-dihydroxyflavone (Formula 5)	70
6,2'3'-trihydroxyflavone (Formula 6)	37
6,4'-dimethoxy-3-hydroxyflavone (Formula 7)	56
4'-hydroxy-β-naphthoflavone (Formula 8)	47
3,7,3'-trihydroxyflavone (Formula 9)	65
Tyrphostin A51 14.8 uM	80

As listed in Table 1, it was revealed that the flavone derivative compounds of Formulas 1 to 9 exhibit a potent inhibitory activity on the c-Kit in a lower concentration than the Tyrphostin A51 known as the c-Kit activation inhibitor.

On the basis of compositions and their contents as listed in the following Table 2, some of the above-mentioned flavone derivative compounds were added to a cream, and then evaluated for a whitening effect.

Table 2

Components (% by weight)	Preparative Examples			Comparative Example 1
	1	2	3	
6-Methoxyflavone (Formula 1)	0.5	-	-	-
3,3'-dihydroxyflavone (Formula 5)	-	0.5	-	-

6,4'-dimethoxy-3-hydroxyflavone (Formula 7)	-	-	0.5	-
Stearic acid	1.50	1.50	1.50	1.50
Cetanol	1.0	1.0	1.0	1.0
Potassium hydroxide	0.7	0.7	0.7	0.7
Glycerin	5.0	5.0	5.0	5.0
Propylene glycol	3.0	3.0	3.0	3.0
Preservative	Proper Amount	Proper Amount	Proper Amount	Proper Amount
Perfume	Proper Amount	Proper Amount	Proper Amount	Proper Amount
Purified water	the Balance	the Balance	the Balance	the Balance

In order to inspect skin whitening effects of the creams produced on the basis of the above-mentioned compositions, tests on inhibition of pigmentation and treatment of melasma were carried out, as follows.

Test of Inhibitory Effect on Pigmentation

20 healthy men and women were selected, and aluminum foil having two grooved lines, each having 6 holes with a diameter of 7 mm, was attached to both forearms of their arms. Then, the forearms were irradiated with a radiation intensity of 60 mJ/cm^2 using a IOOOW ORIEL solar simulator located at a distance of 10 cm from the arms. Before the irradiation, sites to be irradiated were washed thoroughly with an aqueous 70 % ethanol solution. The base compositions prepared according to Preparative example 1-3 and Comparative example 1 were applied in pairs to the same grooved lines two times daily during a period from 3 days before the irradiation to 3 weeks after the irradiation.

Pigmentation rates on the base compositions of the preparative examples and the comparative examples were evaluated with the naked eye, and then the base compositions of the preparative examples were evaluated in two level, namely to be effective and not to be effective, compared to the base compositions of the comparative examples. The results are listed in the following Table 3.

Table 3

Test Materials	Effective (Heads)	Not Effective (Heads)
Preparative example 1	14	6
Preparative example 2	10	10
Preparative example 3	11	9

As listed in Table 3, it was revealed that the flavone derivative-containing creams of Preparative examples 1-3 have a whitening effect but no side effect in at least 10 of the 20 subjects.

Test of Effect on Treatment of Melasma

10 healthy women having melasma were selected, and then the base composition prepared according to Preparative example 1 was applied to their faces with melasma two times daily for three weeks.

After the experiment was completed, medical specialists valuated pigmentations with the naked eye, and the subjects to be tested evaluated treatment of melasma on the basis of their subjective judgments, and therefore the cream of Preparative example 1 was evaluated in two level, namely to be effective and not to be effective on the treatment of melasma. The results are listed in the following Table 4.

Table 4

	Effective (Head)	Not Effective (Head)
Judgment by Experts	6	4
Subjective Judgment by Subjects	7	3

As listed in Table 4, it was revealed that the 6-Methoxyflavone-containing cream prepared according to Preparative examples 1 has an effect on the treatment of melasma but no side effect in at least 6 of the 10 subjects.

Preparation and Evaluation of Diosmetin Extract of Formula 10

Example 1

Dry *Chrysanthemum morifolium* commercially available as a medicinal herb was purchased and ground into small pieces, and 10 kg of the ground substance was heated to 70 ℃ for 3 hours in an extractor provided with a reflux cooler and extracted with 150L of methanol. The resultant extract was filtered through a filter cloth, and the remaining extract was then filtered once or more. The resultant extracts were collected and concentrated under a reduced pressure to obtain 1.2 kg of a dry extract.

Example 2

1 kg of the *Chrysanthemum morifolium* methanol extract prepared in Example 1 was suspended in 1OL of water and fractionated with 1OL of hexane solvent three times to remove a hexane fraction. Then, the remaining aqueous layer was fractionated with 1OL of butanol solvent three times to obtain a butanol fraction. The butanol fraction was concentrated under a reduced pressure to obtain 125 g of a dry substance.

Example 3

1 kg of the *Chrysanthemum morifolium* methanol extract prepared in Example 1 was suspended in 1OL of water and fractionated with 1OL of ethylacetate solvent three times to obtain an ethylacetate fraction. Then, the ethylacetate fraction was concentrated under a reduced pressure to obtain 230 g of a dry substance.

Example 4

100 g of the soluble *Chrysanthemum morifolium* butanol fraction prepared in Example 2 was subject to silica gel column chromatography using mixed chloroform/methanol solvent as an eluent to obtain an active fraction. Then, the resultant active fraction was purified with preparative HPLC to obtain 1.2 g of an active ingredient. The purified active ingredient was confirmed to be diosmetin, represented by Formula 10, through nuclear magnetic resonance (NMR) and mass spectrometry (Mass) (see FIGs. 1 to 3), as follows.

Molecular Formula: $C_{16}H_{12}O_6$

Molecular Weight: 300.27

Melting Point: 260-264℃

UV (λax, nm) (MeOH): 272, 342

IH-NMR (DMSO-d6) σ: 3H (6.69,s), 6H (6.13,s), 8H (6.39,s), 2H (7.41,S), 5'H (7.06,d,8.6Hz), 6'H (7.51,d,8.6Hz), 5-OH (12.89,br), 7-OH (lO.O.br), 4'-OMe (3.85,s)

Inhibitory Effect on c-Kit Activity

Each concentrations of the methanol extract of Example 1 and the soluble

butanol fraction of Example 2 were adjusted to 20 ug/ml, and a final concentration of the diosmetin of Example 4 were adjusted to 0.3 uM, and then evaluated in the same manner as the evaluation method of the above-mentioned flavone derivative compounds of Formulas 1 to 9. The results are listed in the following Table 5.

Table 5

Test Samples	Inhibition (%)
Methanol Extract (Example 1) 20 ug/ml	33.3
Soluble Butanol Fraction (Example 2) 20 ug/ml	45.1
Diosmetin (Example 4) 0.3 uM	83.1
Tyrphostin A51 14.8 uM	100.0

As listed in Table 5, it was revealed that the test samples of Examples 1 and 2, which are the diosmetin-containing crude extracts, have a high inhibitory effect on c-Kit, and the test sample of Example 4, which is the purified diosmetin, has an excellent inhibitory effect on c-Kit activity, which is comparable to that of Tyrphostin A51 known as the c-Kit activation inhibitor.

Evaluation of Whitening Effect

In order to evaluate a whitening effect of the diosmetin-containing cosmetics, creams were prepared on the basis of compositions and their contents listed in the following Table 2.

Table 6

Component (% by weight)	Preparative example 4	Comparative example 2
Diosmetin (Example 4)	0.5	-
Stearic acid	15.0	15.0
Cetanol	1.0	1.0

Potassium hydroxide	0.7	0.7
Glycerin	5.0	5.0
Propylene glycol	3.0	3.0
Preservative	Proper Amount	Proper Amount
Perfume	Proper Amount	Proper Amount
Purified water	the Balance	the Balance

The creams prepared as listed in Table 6 were evaluated for an inhibitory effect on pigmentation in the same manner as in the above-mentioned Preparative examples 1-3. The results are listed in the following Table 7.

Table 7

Tested Material	Effective (Head)	Not Effective (Head)
Preparative example 4	14	6

As listed in Table 7, it was revealed that the diosmetin-containing cream of Preparative example 4 has a whitening effect but no side effect on skin in 14 of the 20 subjects.

Effect on Treatment of Melasma

10 healthy women having melasma were selected, and then the base composition prepared according to Preparative example 4 was applied to their faces with melasma two times daily for three weeks.

After the experiment was completed, medical specialists valuated pigmentations with the naked eye, and the subjects to be tested evaluated treatment of melasma on the basis of their subjective judgments, and therefore the cream of Preparative example 4 was evaluated in two level, namely to be effective and not to be effective on the

treatment of melasma. The results are listed in the following Table 8.

Table 8

	Effective (Heads)	Not Effective (Heads)
Judgment by Experts	5	5
Subjective Judgment by Subjects	7	3

As shown in the Table 8, it was revealed that the diosmetin-containing cream prepared according to the preparative example 4 shows an effect on the treatment of melasma in 7 of 10 subjects.

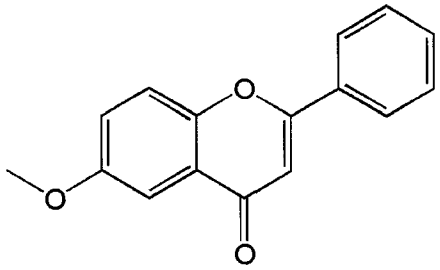
INDUSTRIAL APPLICABILITY

As described above, the flavone derivatives of the present invention are effective c-Kit activation inhibitors. Particularly, the above-mentioned flavone derivatives have no side effect on skin, and inhibit melanin synthesis, and differentiation and maturity of melanocyte, and therefore the composition containing the flavone derivatives the as active ingredients can be highly effectively used to treat melasma and freckles, improve cutaneous hyperpigmentations such as lentigo senilis, dermatofibroma, Caffe aure macule, etc. and attain a skin whitening effect.

What is claimed is:

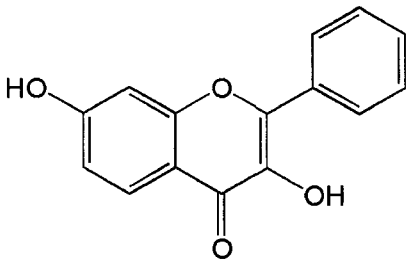
1. A c-Kit activation inhibitor which is a flavone derivative selected from the group consisting of the following Formulas 1 to 10.

Formula 1



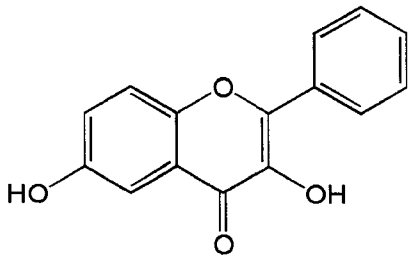
6-methoxyflavone

Formula **2**



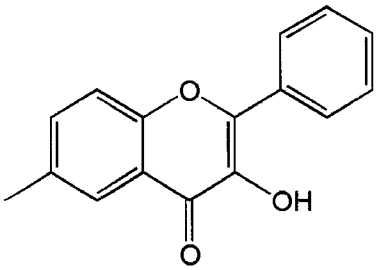
3,7-dihydroxyflavone

Formula **3**



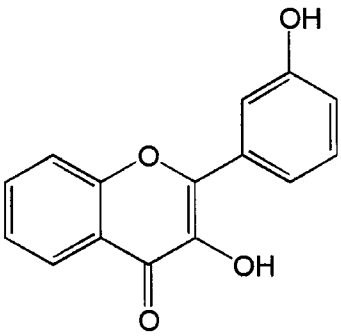
3,6-dihydroxyflavone

Formula **4**



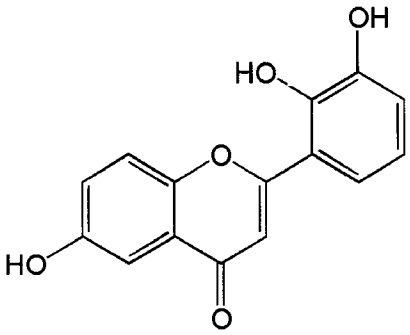
3-hydroxy-6-methylflavone

Formula **5**



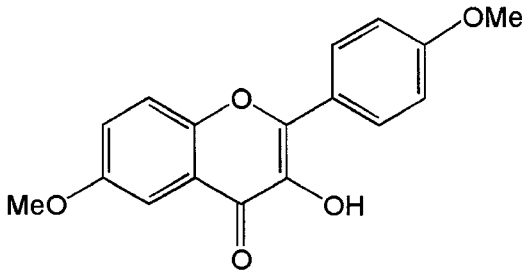
3,3'-dihydroxyf lavone

Formula **6**



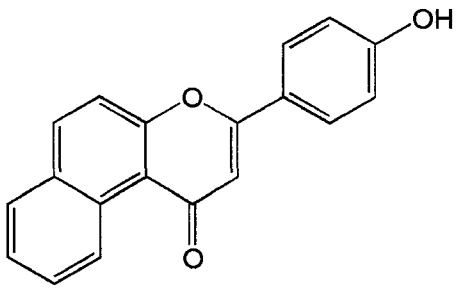
6,2',3'-trihydroxyf lavone

Formula **7**



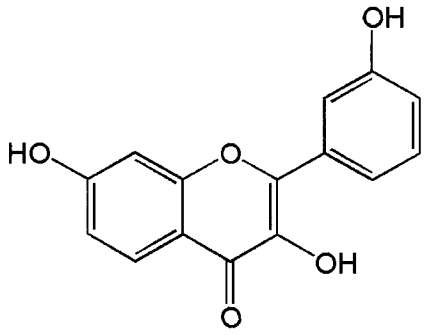
6,4'-dimethoxy-3-hydroxyflavone

Formula **8**



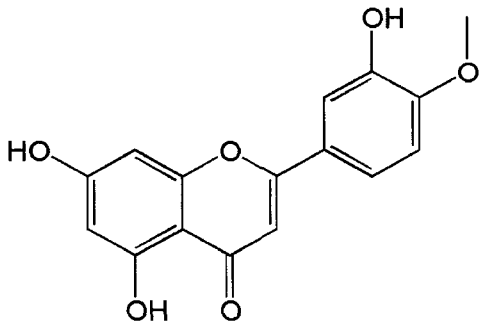
4'-hydroxy-beta-naphthof lavone

Formula **9**



3,7,3'-trihydroxyflavone

Formula 10

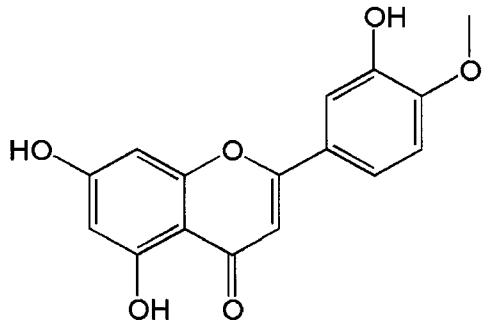


diosmetin

2. A composition for skin whitening comprising, as an active ingredient, at least one flavone derivative selected from the group consisting of the compounds represented by the Formulas 1 to 10 as defined in Claim 1.

3. A composition for skin whitening comprising a compound of the following Formula 10 as an active ingredient.

Formula 10



diosmetin

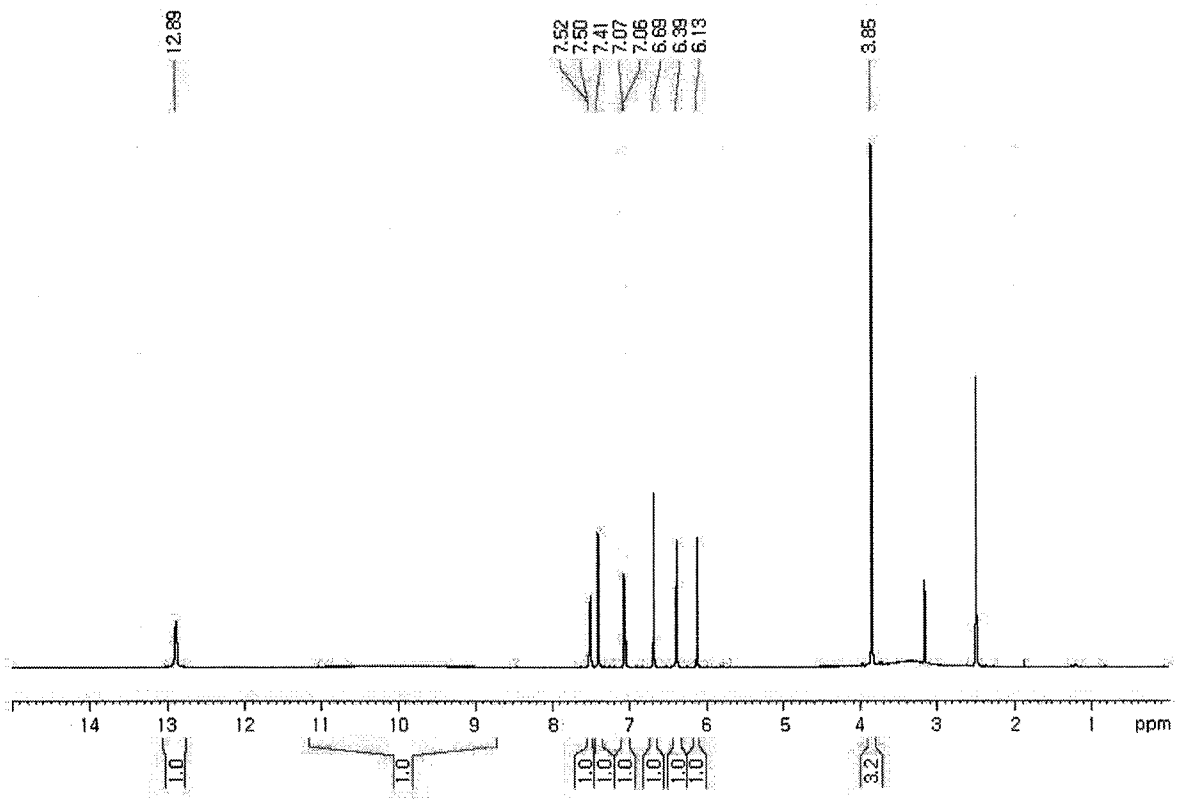
4. A composition for skin whitening comprising a *Chrysanthemum morifolium* {*Chrysanthemum morifolium* petals) extract as an active ingredient.

5. The composition for skin whitening according to any one of claims 2 to 4, wherein the skin whitening is the treatment of melasma or cutaneous hyperpigmentation.

6. The composition for skin whitening according to any one of claims 2 to 4, wherein a content of the flavone derivative ranges from 0.000001 to 10 % by weight, based on the total weight of the composition.

7. The composition for skin whitening according to any one of claims 2 to 4, wherein the composition for skin whitening is one formulation selected from the group consisting of skin, lotion, cream, foundation, essence, gel, pack, foam cleansing, soap and ointment.

FIG. 1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7.50
7.41
7.07
7.06
6.89
6.39
6.13
3.85
14
13
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9
8
7
6
5
4
3
2
1
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1.0
1.0
1.0
1.0
3.2

FIG. 2

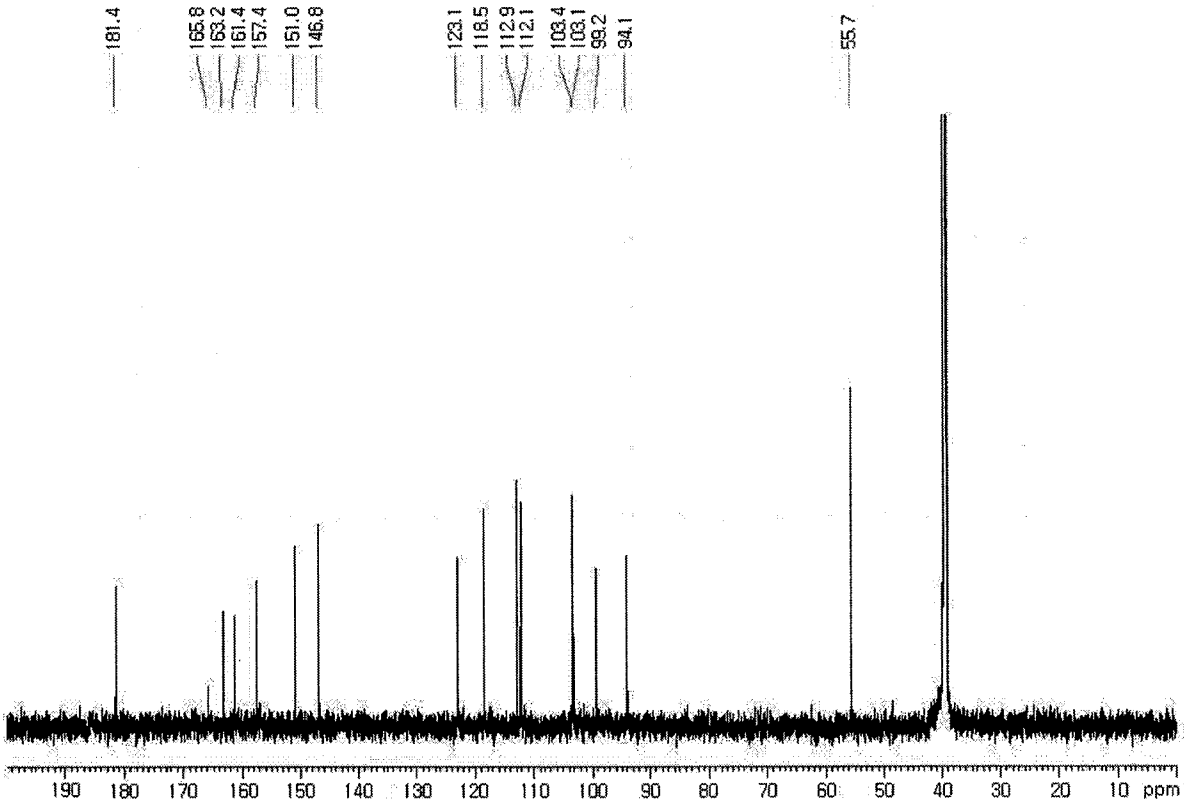
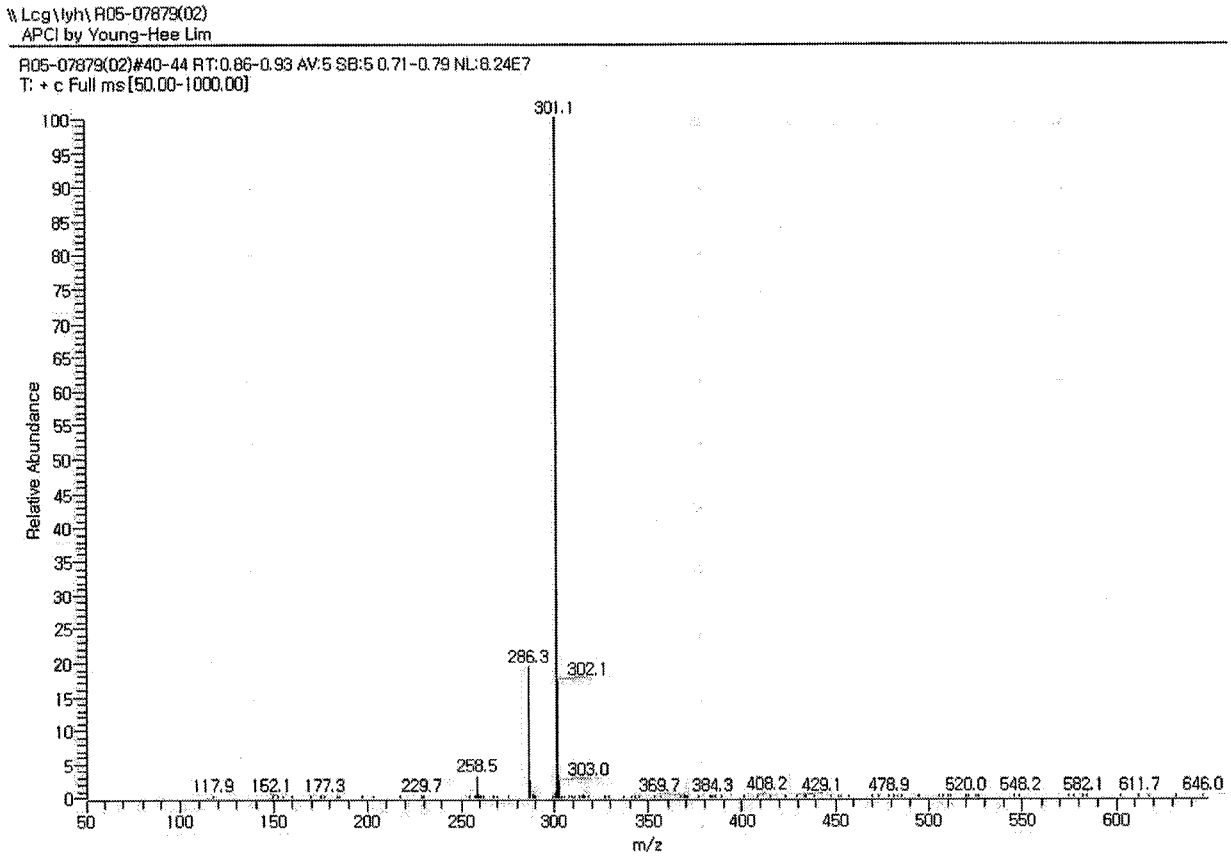

181.4
165.8
163.2
161.4
157.4
151.0
146.8
123.1
118.5
112.9
112.1
103.4
103.1
99.2
94.1
55.7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

FIG. 3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302.1
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303.0
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384.3
408.2
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548.2
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611.7
646.0

INTERNATIONAL SEARCH REPORT

International application No
PCT/KR2007/000227

A. CLASSIFICATION OF SUBJECT MATTER

A61K 8/49(2006.01)1, A61Q 19/02(2006.01)1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC8 A61K, A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
STN(Registry, Caplus)
eKIPASS, Pubmed (Chrysanthemum moπfolium, skin whitening, c-kit activation inhibitor)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category'*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	JP 57-35506 A (SANSHO SEIYAKU KK) 26 February 1982 See the compound of formula (I) and page 66, line 8	2, 3, 5-7
X	KR 10-2005-0030821 A (HANBUL COSMETICS) 31 March 2005 See the compound of formula 1 and claim 2	2, 3, 5-7
A	KR 10-2005-0001899 A (KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY) 07 January 2005 See the whole document	1-7

☐ Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 MARCH 2007 (26 03 2007)	26 MARCH 2007 (26.03.2007)

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Republic of Korea
Facsimile No 82-42-472-7140

Authorized officer
LEE, Mi Jeong
Telephone No 82-42-481-5601

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/KR2007/000227

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 57-35506 A	26.02.1982	None	
KR 10-2005-0030821 A	31.03.2005	None	
KR 10-2005-0001899 A	07.01.2005	None	