cause of diseases. Thus, in some cases, it is assumed that ubiquitination of the target protein does not induce degradation of the target protein.

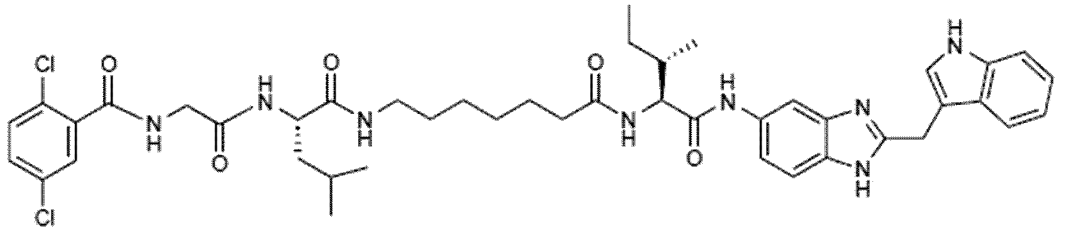
In view of the above circumstances, an object of the present disclosure is to provide a Ras protein-degradation inducing molecule capable of inducing degradation of a Ras protein, and a pharmaceutical composition including the Ras protein-degradation inducing molecule.

Means for Solving the Problems

In one aspect, there is provided a Ras protein-degradation inducing molecule, wherein the Ras protein-degradation inducing molecule is a conjugate of a Ras protein affinity molecule that is capable of binding to a Ras protein, and a protein-degradation inducing tag that is capable of binding to a 26S proteasome and does not inhibit degradation of a protein by the 26S proteasome; and the Ras protein-degradation inducing molecule is capable of inducing degradation of the Ras protein, with the proviso that the conjugate excludes a fusion protein.

In another aspect, there is provided a pharmaceutical composition comprising the Ras protein-degradation inducing molecule as described herein.

In yet another aspect, there is provided a compound represented by the following formula:



.

Specific means for achieving the above object include the following embodiments.

<1> A Ras protein-degradation inducing molecule being a conjugate of a Ras protein affinity molecule that has an affinity with a Ras protein, and a protein-degradation inducing tag that has an affinity with a protease and does not inhibit degradation of a protein by the protease; and being capable of inducing degradation of a Ras protein.

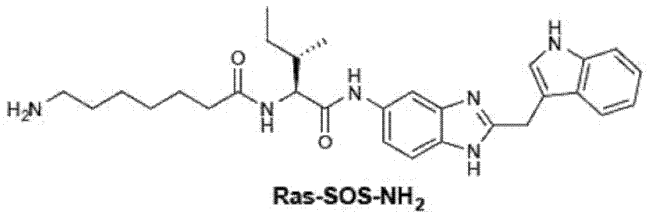
<2> The Ras protein-degradation inducing molecule according to <1>, in which the Ras protein-degradation inducing molecule is capable of inducing degradation of the Ras protein in a ubiquitin-independent manner.

<3> The Ras protein-degradation inducing molecule according to <1> or <2>, in which the protein-degradation inducing tag has a structure where a protease inhibitory activity of a protease inhibitor is inactivated.

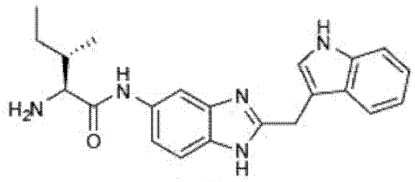
<4> The Ras protein-degradation inducing molecule

molecule.

Ras-SOS-NH_2 represented by the following formula was used as the Ras protein affinity molecule. Ras-SOS-NH_2 is a compound obtained by reacting an amino group of Ras-SOS represented by the following formula with H_2N-$(CH_2)_6$-COOH.



Ras-SOS-NH_2



Ras-SOS

Ras-SOS is Compound 12 described in the document by Sun, Q. et al. (Sun, Q. et al., Angew. Chem. Int. Ed., 2012, 51, 6140-6143) (see No. 22 in Table 4). When a SOS protein is bound to the Ras protein, GDP bound to the Ras protein is replaced with GTP, and the Ras protein is activated. It is known that Ras-SOS is bound to the Ras protein to inhibit the interaction between the Ras protein and the SOS protein, thus inhibiting the activation of the Ras protein. Furthermore, it is known that Ras-SOS is bound to not only a wild-type K-Ras protein but also a G12D mutant and a G12V mutant K-Ras protein.

It is noted that Ras-SOS and Ras-SOS-NH_2 were synthesized according to the method described in the document by Sun, Q. et.al.

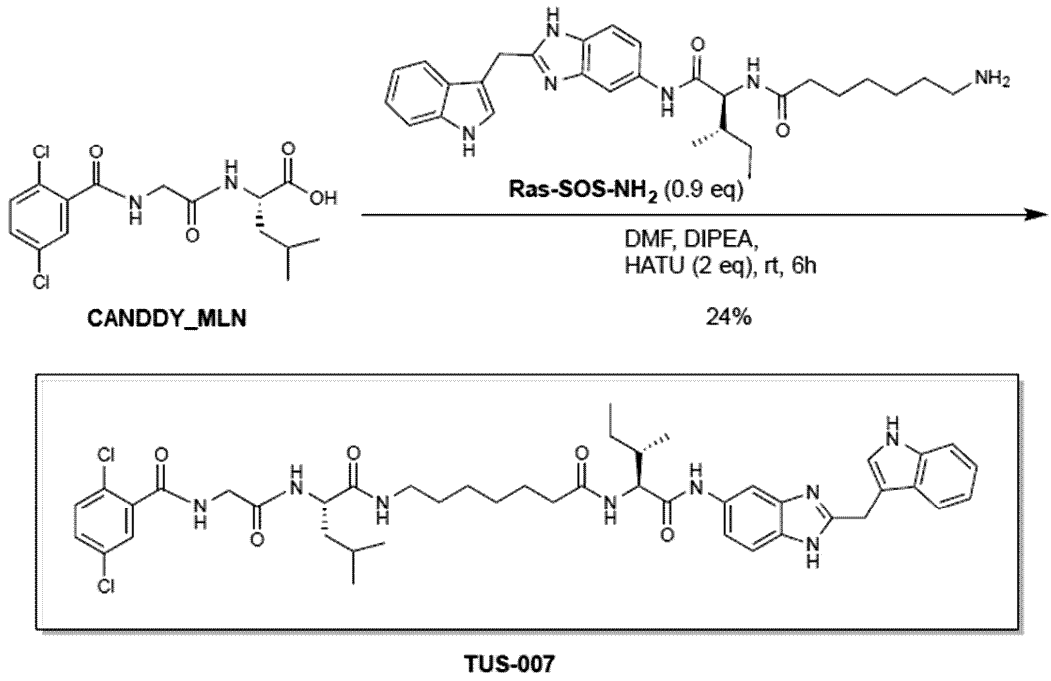
Furthermore, as the protein-degradation inducing tag, a

acetate/hexane (= 4/1). After being dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. Separation and purification treatment was performed by silica gel chromatography (hexane/chloroform = 1/1 to 0/1, gradient) to obtain a compound S3 (244.2 mg, 0.58 mmol, 76%).

Next, the compound S3 (240.8 mg, 0.58 mmol) was charged into an eggplant flask, and 5 mL of dichloromethane was added. This was stirred at room temperature for 5 minutes, and then 5 mL of TFA was added, and stirred at room temperature for 1 hour. After evaporating the solvent under reduced pressure, vacuum drying was performed to obtain CANDDY_MLN (214.7 mg, 0.59 mmol, 100%).

(Synthesis of TUS-007)

TUS-007 was synthesized according to the following synthesis scheme.



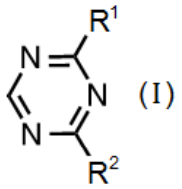
CANDDY_MLN (52.4 mg, 0.15 mmol, 1 eq) and separately synthesized Ras-SOS-NH_2 (62.4 mg, 0.12 mmol, 0.9 eq) were

CLAIMS

1. A Ras protein-degradation inducing molecule, wherein the Ras protein-degradation inducing molecule is a conjugate of a Ras protein affinity molecule that is capable of binding to a Ras protein, and a protein-degradation inducing tag that is capable of binding to a 26S proteasome and does not inhibit degradation of a protein by the 26S proteasome; and the Ras protein-degradation inducing molecule is capable of inducing degradation of the Ras protein, with the proviso that the conjugate excludes a fusion protein.

2. The Ras protein-degradation inducing molecule according to claim 1, wherein the Ras protein-degradation inducing molecule is capable of inducing degradation of the Ras protein in a ubiquitin-independent manner.

3. The Ras protein-degradation inducing molecule according to claim 1 or 2, wherein the protein-degradation inducing tag has a structure represented by the formula (I), or has a structure where a proteasome inhibitory activity of a proteasome inhibitor is inactivated, or has a structure of a proteasome activator:



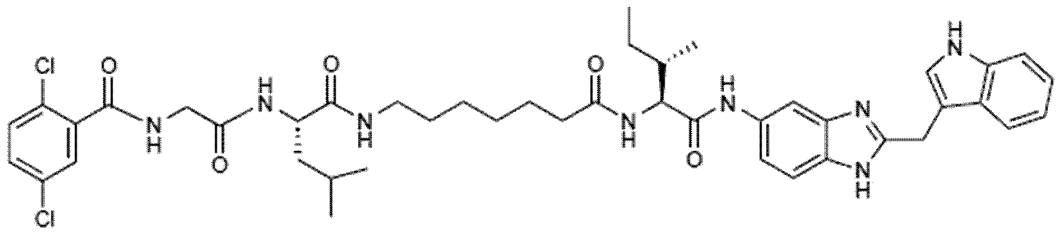
(I)

wherein R^1 and R^2 each independently represent a hydrocarbon

group having 1 to 20 carbon atoms, an alkoxy group having 1 to 20 carbon atoms, an aryloxy group having 6 to 20 carbon atoms, a hydroxy group, a carboxy group, an amino group, or a halogen group.

4. The Ras protein-degradation inducing molecule according to claim 3, wherein the proteasome inhibitory activity is an inhibitory activity against at least one selected from a caspase-like activity, a trypsin-like activity, and a chymotrypsin-like activity.

5. The Ras protein-degradation inducing molecule according to any one of claims 1 to 4, wherein the Ras protein-degradation inducing molecule is represented by the following formula:



7. A pharmaceutical composition comprising the Ras protein-degradation inducing molecule according to any one of claims 1 to 6.

8. The pharmaceutical composition according to claim 7, wherein the pharmaceutical composition is used for preventing or treating a Ras protein-mediated disease or condition, wherein the Ras protein-mediated disease or condition is a cancer, an immune disease, an infection, a neurological disease, a RAS/MAPK syndrome, cirrhosis, chronic hepatitis, or a memory impairment.

9. The pharmaceutical composition according to claim 8, wherein the Ras protein-mediated disease or condition is a cancer.

10. A compound represented by the following formula:

