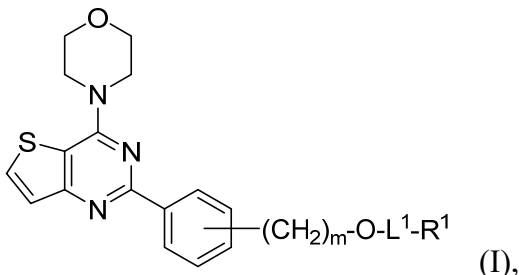


CLAIMS:

1. A compound having formula (I):



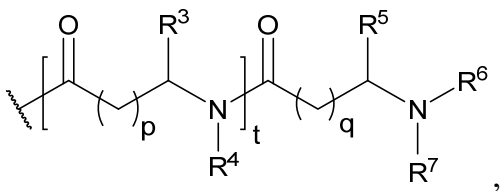
or a hydrate, solvate, and/or a pharmaceutically acceptable salt thereof,
wherein:

subscript m is an integer from 0 to 2; and

i) L^1 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)S-$, or $-C(O)NH-$; and

R^1 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-6} alkyl, or C_{6-10} aryl- C_{2-6} alkenyl;

ii) L^1-R^1 has the formula:



wherein

the wavy line indicates the attachment to the adjacent oxygen atom in formula (I);

subscript t is an integer from 0 to 1;

subscripts p and q are independently an integer from 0 to 2;

R^3 is hydrogen or a sidechain of a natural or unnatural amino acid and R^4 is hydrogen, or R^3 and R^4 are combined to be a sidechain of a cyclic amino acid;

R^5 is hydrogen or a sidechain of a natural or unnatural amino acid and R^6 is hydrogen, C_{1-6} alkyl, or C_{2-6} alkenyl, or R^5 and R^6 are combined to be a sidechain of a cyclic amino acid; and

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyl- $C(O)-$, or C_{2-6} alkenyl- $C(O)-$, or

R^5 is hydrogen or a sidechain of a natural or unnatural amino acid; and

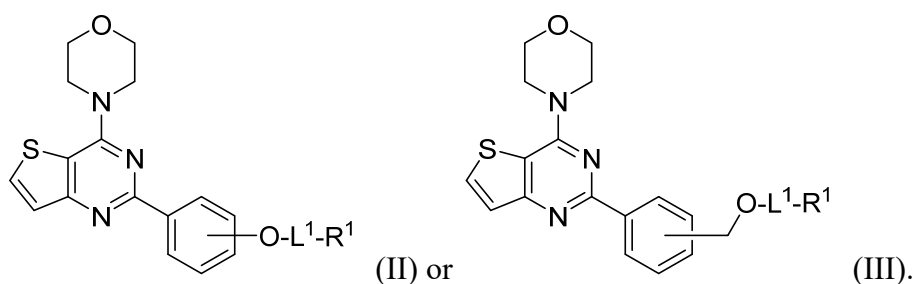
R⁶ and R⁷ are combined to form a 3-6 membered heterocycle, optionally having an additional 1-2 heteroatoms selected from O, S, and N as ring vertices; or

iii) L¹ is -C(O)-; and

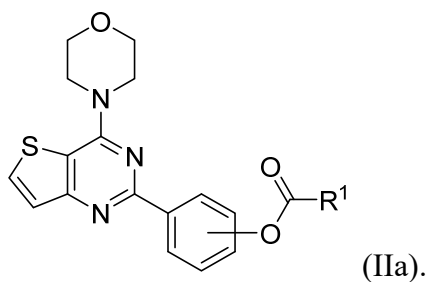
R¹ is an aliphatic chain of a saturated fatty acid having 8-18 carbon atoms or an unsaturated fatty acid having 10-18 carbon atoms.

2. The compound of claim 1, wherein subscript m is 0 or 1.

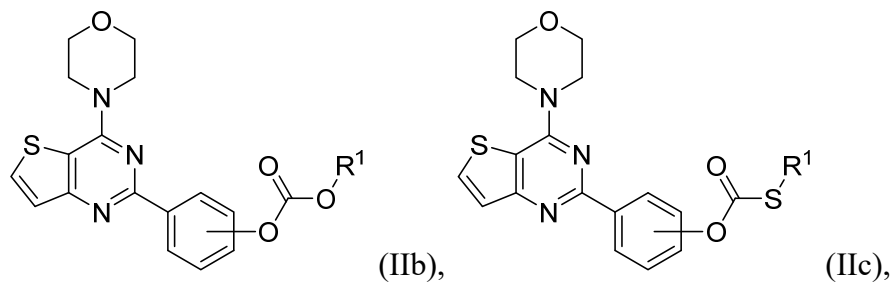
3. The compound of any one of claims 1-2, having formula (II) or (III):

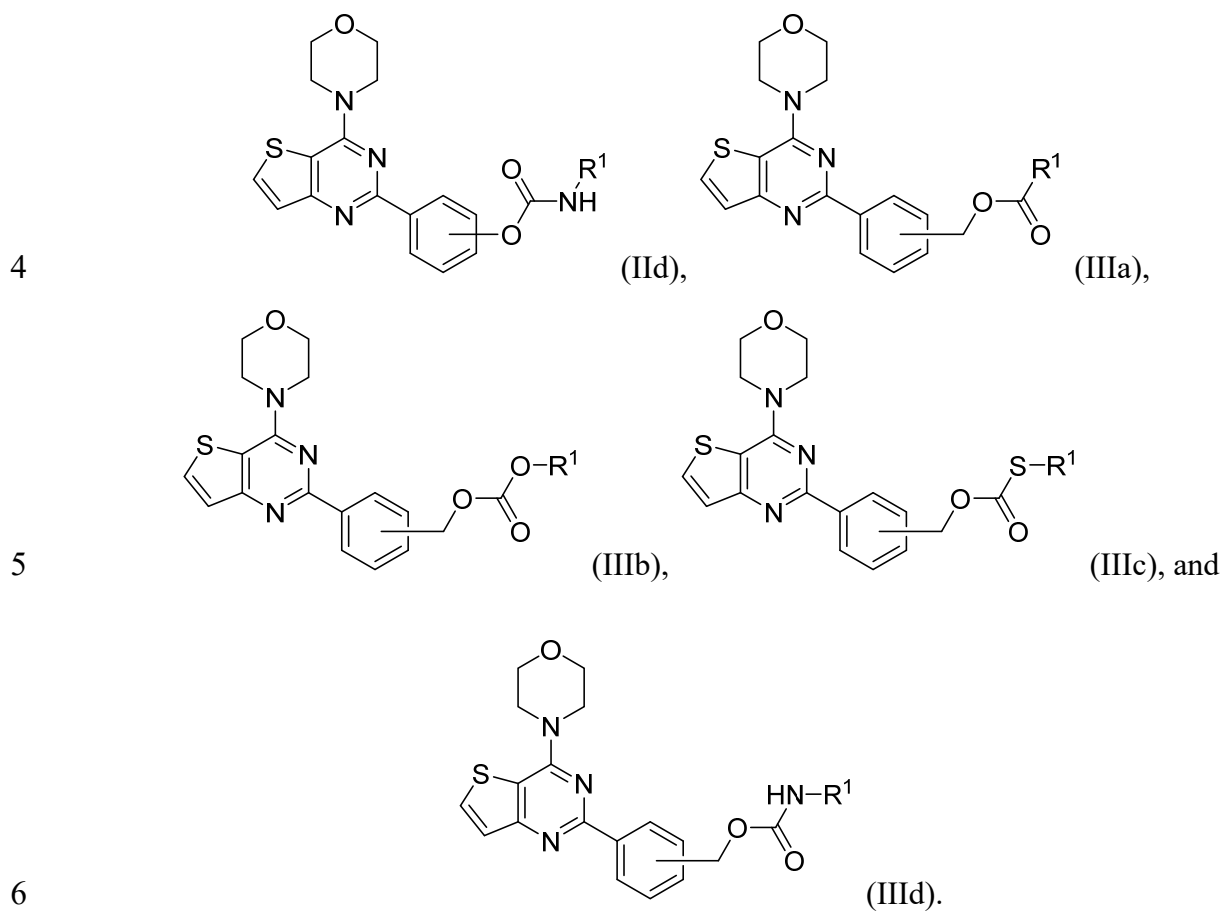


4. The compound of any one of claims 1-3, having formula (IIa):

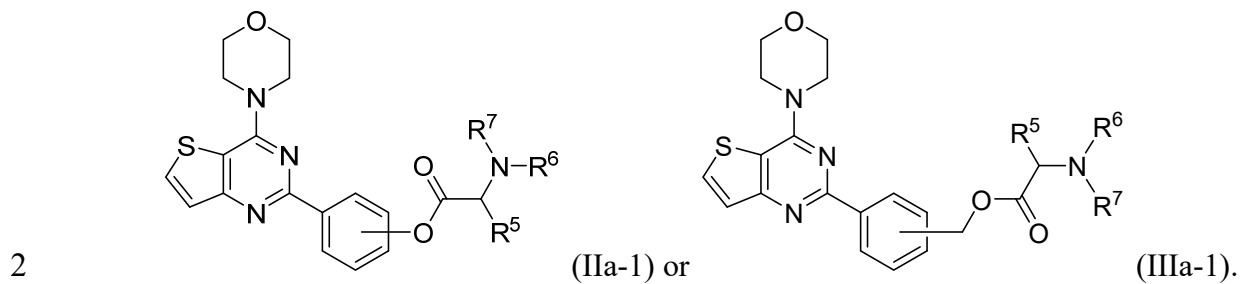


5. The compound of any one of claims 1-3, having the formula selected from the group consisting of:





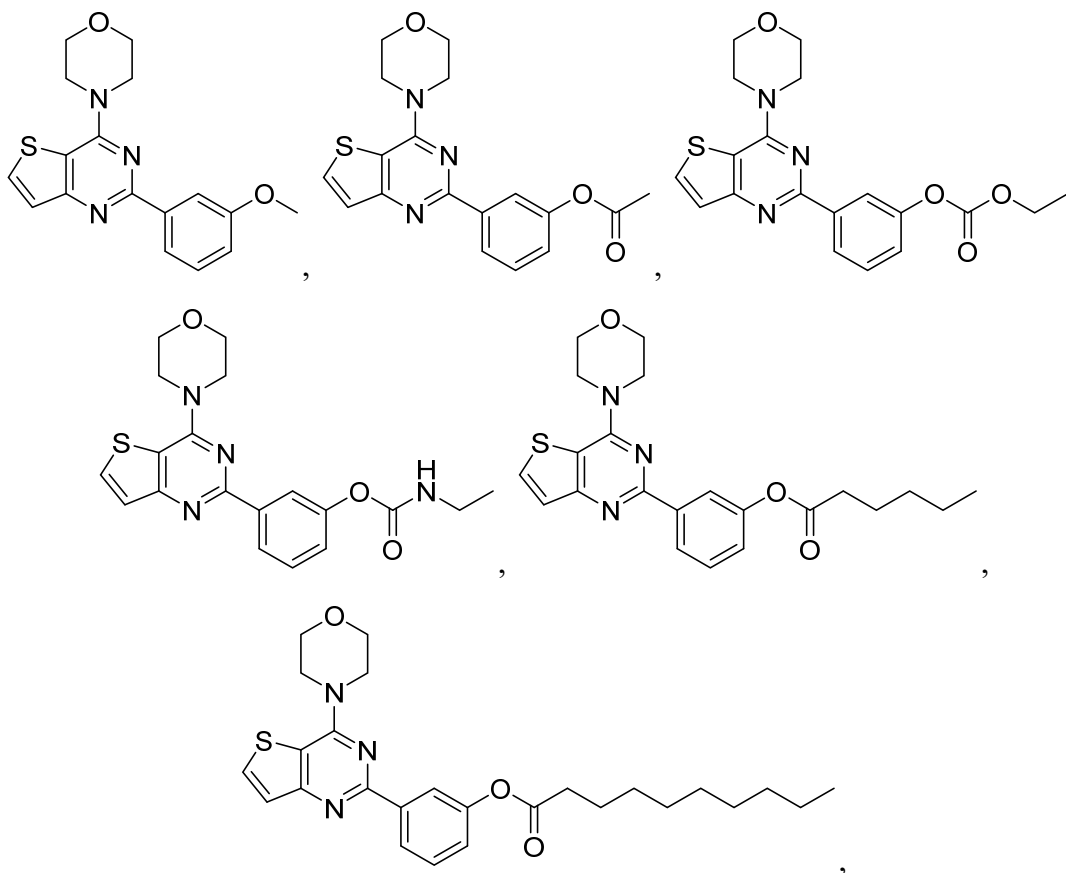
- 1 6. The compound of any one of claims 1-5, wherein R¹ is methyl or ethyl.
- 1 7. The compound of any one of claims 1-5, wherein R¹ is phenyl-CH=CH-.
- 1 8. The compound of any one of claims 1-4, wherein subscripts p and q are
- 2 each 0.
- 1 9. The compound of claim 8, having formula (IIa-1) or (IIIa-1):

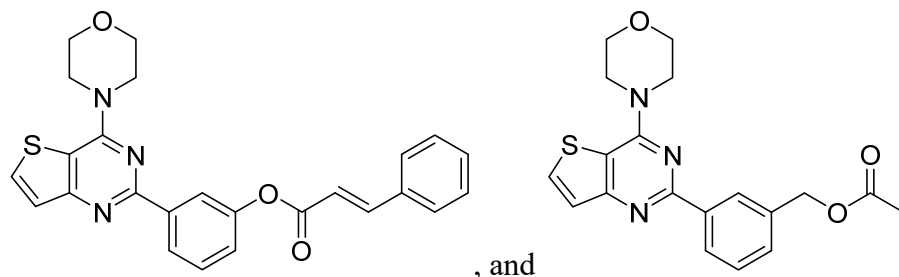
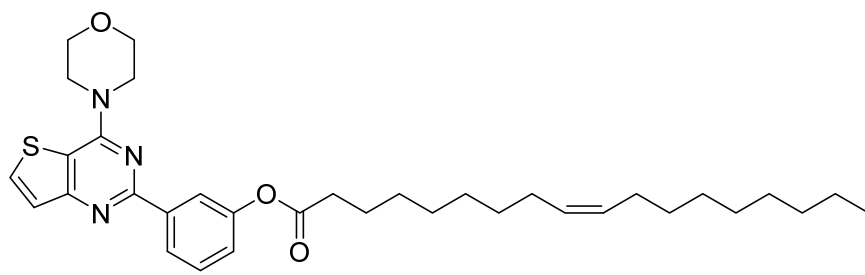


1 **10.** The compound of any one of claims 1-4, wherein the saturated fatty acid
2 having 8-18 carbon atoms is selected from the group consisting of caprylic acid, pelargonic acid,
3 capric acid, neodecanoic acid, undecylic acid, lauric acid, tridecylic acid, myristic acid,
4 pentadecylic acid, palmitic acid, margaric acid, stearic acid, and isostearic acid.

1 **11.** The compound of any one of claims 1-4, wherein the unsaturated fatty
2 acid having 10-18 carbon atoms is selected from the group consisting of caproleic acid, lauroleic
3 acid, myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid,
4 linoleic acid, alpha-linolenic acid, gamma-linolenic acid, columbinic acid, pinolenic acid, and
5 stearidonic acid.

1 **12.** The compound of claim 1, selected from the group consisting of:

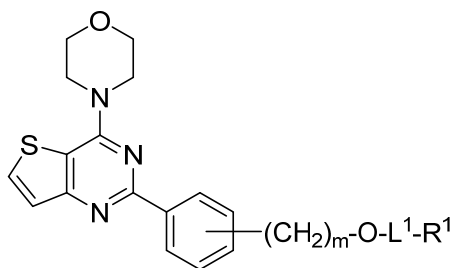




13. A topical formulation for the treatment of vascular malformations

comprising:

a) a compound having formula (I):



or a hydrate, solvate, and/or a pharmaceutically acceptable salt thereof;

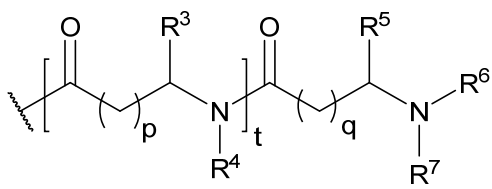
wherein:

subscript m is an integer from 0 to 2; and

i) L^1 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)S-$, or $-C(O)NH-$; and

R^1 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{6-10} aryl- C_{1-6} alkyl, or C_{6-10} aryl- C_{2-6} alkenyl;

ii) L^1-R^1 has the formula:



wherein

the wavy line indicates the attachment to the adjacent oxygen atom in formula (I);

subscript t is an integer from 0 to 1;

subscripts p and q are independently an integer from 0 to 2;

R³ is hydrogen or a sidechain of a natural or unnatural amino acid and R⁴ is hydrogen,
or R³ and R⁴ are combined to be a sidechain of a cyclic amino acid;

R⁵ is hydrogen or a sidechain of a natural or unnatural amino acid and R⁶ is hydrogen,
C₁₋₆ alkyl, or C₂₋₆ alkenyl, or R⁵ and R⁶ are combined to be a sidechain of a cyclic
amino acid; and

R⁷ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyl-C(O)-, or C₂₋₆ alkenyl-C(O)-, or

R⁵ is hydrogen or a sidechain of a natural or unnatural amino acid; and

R⁶ and R⁷ are combined to form a 3-6 membered heterocycle, optionally having an
additional 1-2 heteroatoms selected from O, S, and N as ring vertices; or

iii) L¹ is -C(O)-; and

R¹ is an aliphatic chain of a saturated fatty acid having 8-18 carbon atoms or an
unsaturated fatty acid having 10-18 carbon atoms; and

b) one or more topical excipients.

14. The topical formulation of claim 13, selected from the group consisting of
a lotion, a spray, an ointment, a cream, a gel, a paste, and a patch.

15. The topical formulation of claim 13, the one or more topical excipients are
selected from the group consisting of one or more solvents, one or more penetration enhancers,
one or more gelling agents, and combinations thereof.

16. The topical formulation of claim 15, wherein the one or more solvents or
penetration enhancers are selected from the group consisting of C₂₋₆ alcohol, a C₂₋₆ alkylene
glycol, a di-(C₂₋₆ alkylene) glycol, a polyethylene glycol, C₁₋₃ alkyl-(OCH₂CH₂)₁₋₅-OH, DMSO, a
fatty alcohol, a fatty acid, and a fatty ester.

17. The topical formulation of claim 15, wherein the one or more gelling
agents are selected from the group consisting of hydroxypropyl cellulose, Carbopols,
carboxymethyl cellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, magnesium aluminum

silicate (Veegum), methylcellulose, poloxamers (Pluronic), polyvinyl alcohol, sodium alginate, tragacanth, xanthan gum, and combinations thereof.

18. The topical formulation of claim 16, wherein the di-(C₂₋₆ alkylene) glycol is dipropylene glycol; the polyethylene glycol is PEG400; and/or the C₁₋₃ alkyl-(OCH₂CH₂)₁₋₅-OH is 2-(2-ethoxyethoxy)ethanol.

19. The topical formulation of claim 16, wherein the fatty alcohol is selected from capric alcohol, undecyl alcohol, lauryl alcohol, tridecyl alcohol, myristyl alcohol, pentadecyl alcohol, cetyl alcohol, palmitoleyl alcohol, heptadecyl alcohol, stearyl alcohol, oleyl alcohol, nonadecyl alcohol, arachidyl alcohol, heneicosyl alcohol, behenyl alcohol, erucyl alcohol, lignoceryl alcohol, and combinations thereof.

20. The topical formulation of claim 16, wherein the fatty acid is selected from the group consisting of neodecanoic acid, isostearic acid, caproic acid, lauroic acid, myristoleic acid, palmitoleic acid, oleic acid, linoleic acid, linolenic acid, and combinations thereof.

21. The topical formulation of claim 16, wherein the one or more solvents or penetration enhancers are selected from the group consisting of DMSO, oleic acid, oleyl alcohol, 2-(2-ethoxyethoxy)ethanol, dipropylene glycol, and PEG400.

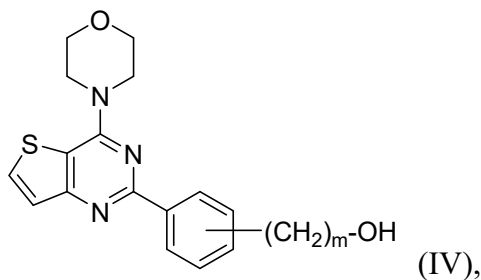
22. The topical formulation of claim 16, wherein DMSO, when present, is present in an amount of from 30% to 50%, from 20% to 50%, from 30% to 40%, from 20% to 40%, or from 20% to 30% by weight of the base formulation.

23. The topical formulation of claim 13, wherein the compound of formula (I) is in a salt-free form.

24. The topical formulation of any one of claims 13-23, wherein the compound of formula (I) is present in an amount of 0.05% to 15%, from 0.5% to 10%, from 1% to 10%, from 2% to 10%, from 5% to 10%, or from 2 to 5% by weight of the base formulation on a salt-free and anhydrous basis.

1 **25.** The topical formulation of any one of claims 13-24, wherein a relative
2 purity of the compound having formula (I) has a decrease of less than 10% over a period of 10
3 days at a temperature of 80°C or over a period of 6 months at a temperature of 40°C and relative
4 humidity of 75%.

1 **26.** The topical formulation of any one of claims 13-25, wherein a hydrolysis
2 of the compound having formula (I) to a corresponding compound having formula (IV):

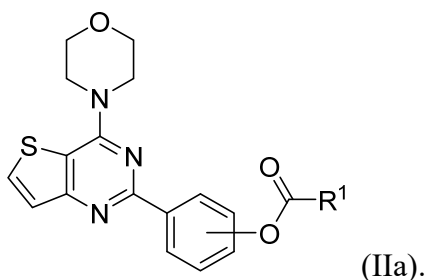


is less than 10% over a period of 10 days at a temperature of 80°C or over a period of 6 months
at a temperature of 40°C and a humidity of 75%, wherein subscript m is an integer from 0 to 2.

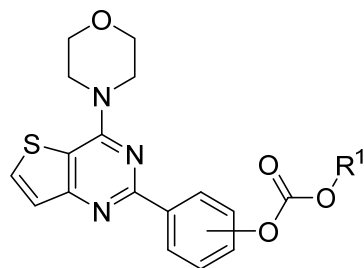
1 **27.** The topical formulation of any one of claims 13-26, wherein a skin flux of
2 the compound having formula (I) has an increase of greater than 2 fold as compared to a skin
3 flux of the corresponding compound having formula (IV) in the same topical formulation.

1 **28.** The topical formulation of any one of claims 13-27, wherein the skin flux
2 of the compound having formula (I) has an increase of from 2 to 5 fold, as compared to a skin
3 flux of the corresponding compound having formula (IV) in the same topical formulation.

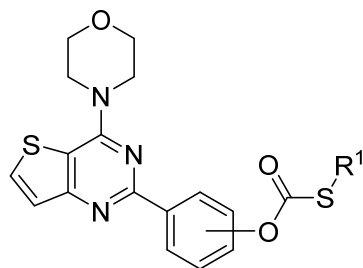
1 **29.** The topical formulation of any one of claims 13-28, the compound of
2 formula (I) is represented by formula (IIa):



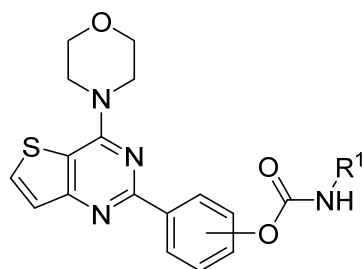
1 **30.** The topical formulation of any one of claims 13-28, the compound of
2 formula (I) is represented by the formula selected from the group consisting of:



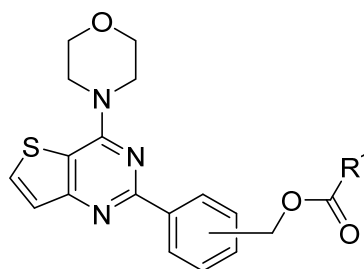
(IIb),



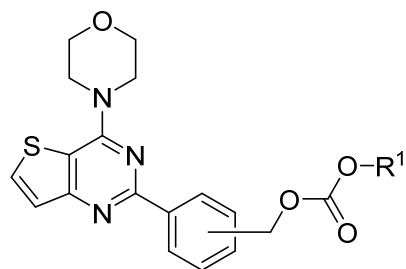
(IIc),



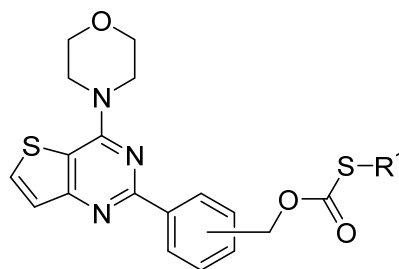
(IIId),



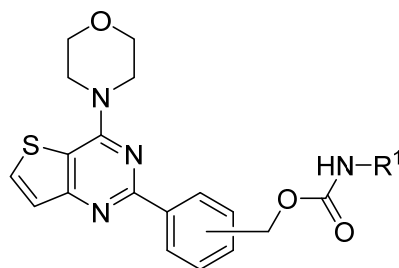
(IIIa),



(IIIb),

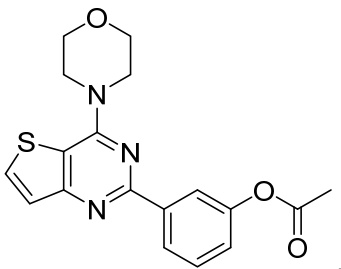


(IIIc), and



(IIId).

31. The topical formulation of any one of claims 13-29, the compound of formula (I) is represented by the formula:



32. Use of the compound of any one of claims 1-12, or the topical formulation of any one of claims 13-31 in the preparation of a medicament for treating a vascular malformation through inhibiting phosphoinositide-3-kinase (PI3K) in a subject.

33. The use of claim 32, wherein the vascular malformation is a venous malformation, an arterial malformation, an arteriovenous malformation, or a lymphatic malformation.

34. The use of claims 32 or 33, wherein the compound, topical formulation or medicament is to be administered topically.

35. The use of any one of claims 32-34, wherein the compound, topical formulation or medicament is to be administered as a lotion, a spray, an ointment, a cream, a gel, a paste, or a patch.

36. The use of any one of claims 32-35, wherein a conversion of the compound having formula (I) to a corresponding compound having formula (IV) after passing a skin is at least 50% over a period of 24 hours.