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95035, US

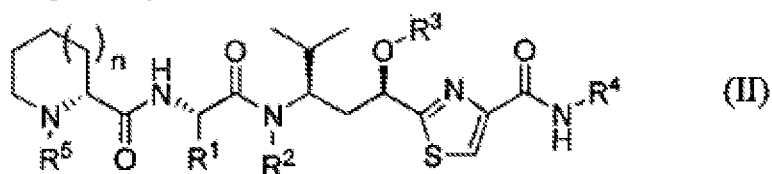
(74) Zastupnik: ZMP IP d.o.o., 10000 Zagreb, HR

(54) Naziv izuma: ANTIPROLIFERATIVNE TVARI, NJIHOVI KONJUGATI, METODE ZA NJIH I NJIHOVE
UPORABE

HR P20140976 T1

PATENTNI ZAHTEJEVI

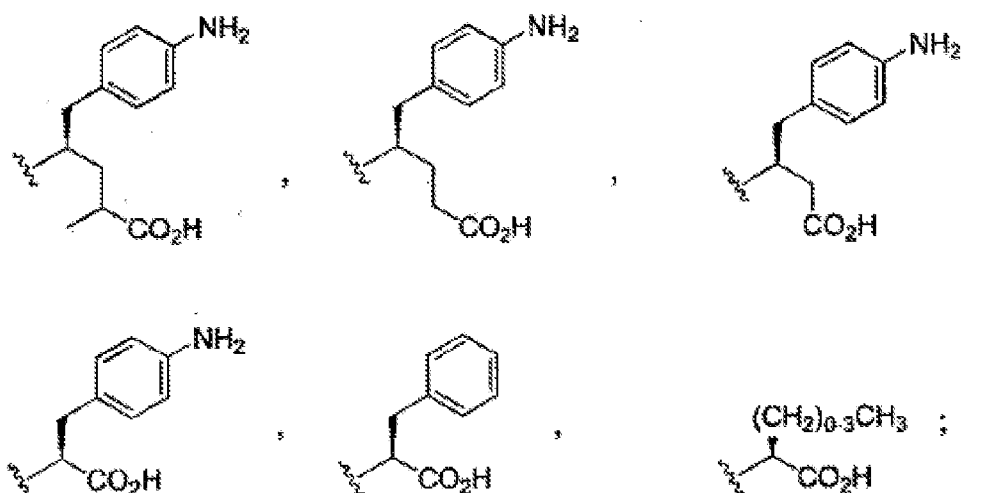
- 5 1. Tvar koja ima strukturu predstavljenu formulom (II)



gdje

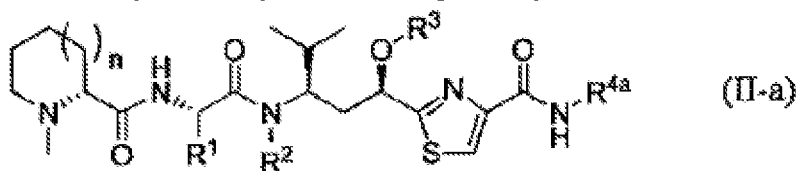
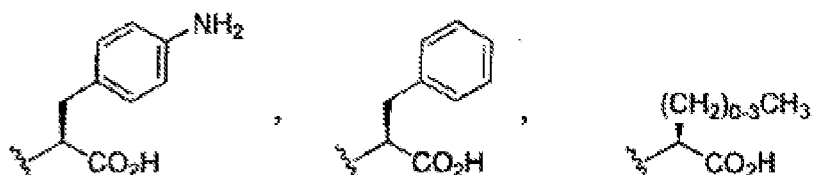
n je 0, 1, ili 2;

R¹, R² i R³ su nezavisno H, nesupstituirani ili supstituirani C₁-C₁₀ alkil, nesupstituirani ili supstituirani C₂-C₁₀ alkenil, nesupstituirani ili supstituirani C₂-C₁₀ alkinil, nesupstituirani ili supstituirani aril, nesupstituirani ili supstituirani heteroaril, nesupstituirani ili supstituirani (CH₂)₁₋₂O(C₁-C₁₀ alkil), nesupstituirani ili supstituirani (CH₂)₁₋₂O(C₁-C₁₀ alkenil), nesupstituirani ili supstituirani (CH₂)₁₋₂O(C₂-C₁₀ alkinil), (CH₂)₁₋₂OC(=O)(C₁-C₁₀ alkil), nesupstituirani ili supstituirani (CH₂)₁₋₂OC(=O)(C₂-C₁₀ alkenil), nesupstituirani ili supstituirani (CH₂)₁₋₂OC(=O)(C₂-C₁₀ alkinil), nesupstituirani ili supstituirani C(=O)(C₁-C₁₀ alkil), nesupstituirani ili supstituirani C(=O)(C₂-C₁₀ alkenil), nesupstituirani ili supstituirani C(=O)(C₂-C₁₀ alkinil), nesupstituirani ili supstituirani cikloalifat, nesupstituirani ili supstituirani heterocikloalifat, nesupstituirani ili supstituirani arilalkil, ili nesupstituirani ili supstituirani alkilaril;

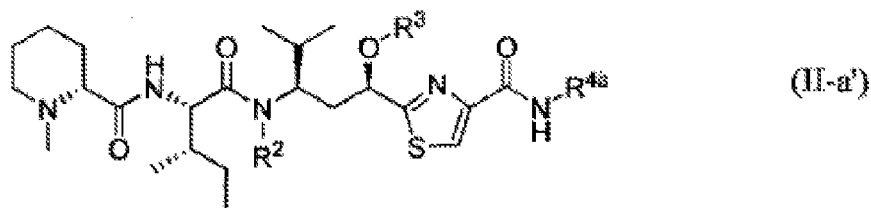
 $\mathbb{R}^4$ je

R⁵ je H, C₁-C₅ alkil, C₂-C₅ alkenil, C₂-C₅ alkinil, CO(C₁-C₅ alkil), CO(C₂-C₅ alkenil), CO(C₂-C₅ alkinil); ili njihov farmaceutski prihvatljivi ester, njihov farmaceutski prihvatljivi amid na karboksilnoj grupi R⁴ s α -amino grupom α -aminokiseline, ili njihova farmaceutski prihvatljiva sol.

2. Tvar u skladu s patentnim zahtjevom 1, koja ima strukturu predstavljenu formulom (II-a)

gdje je R^{4a} 

3. Tvar u skladu s patentnim zahtjevom 2, koja ima strukturu predstavljenu formulom (II-a')

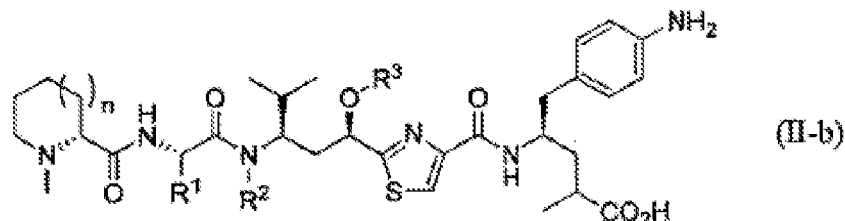


gdje

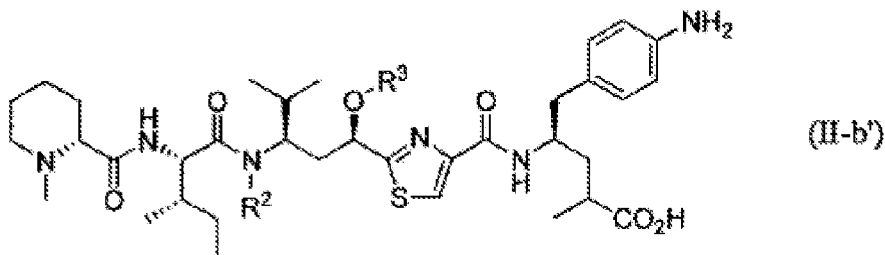
R^2 je H, C₁-C₅ alkil, C₂-C₅ alkenil, CH₂O(C₁-C₅ alkil), CH₂O(C₂-C₅ alkenil), CH₂O(C=O)(C₁-C₅ alkil), ili CH₂OC(=O)(C₂-C₅ alkenil); i

R^3 je H, C₁-C₅ alkil, C₂-C₅ alkenil, C(=O)C₁-C₅ alkil, ili C(=O)C₂-C₅ alkenil.

4. Tvar u skladu s patentnim zahtjevom 1, koja ima strukturu predstavljenu formulom (II-b)



5. Tvar u skladu s patentnim zahtjevom 4, koja ima strukturu predstavljenu formulom (II-b')

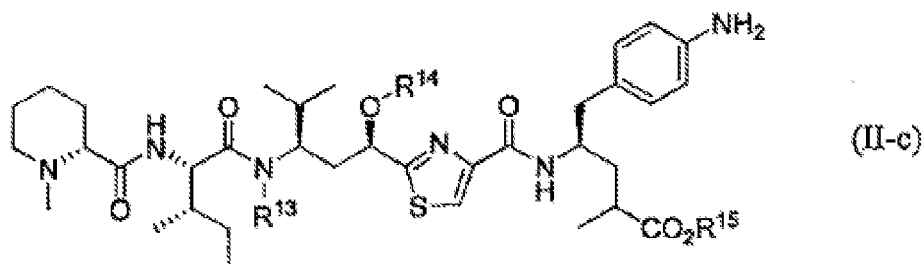


gdje

R^2 je H, C₁-C₅ alkil, C₂-C₅ alkenil, CH₂O(C₁-C₅ alkil), CH₂O(C₂-C₅ alkenil), CH₂O(C=O)(C₁-C₅ alkil), ili CH₂OC(=O)(C₂-C₅ alkenil); i

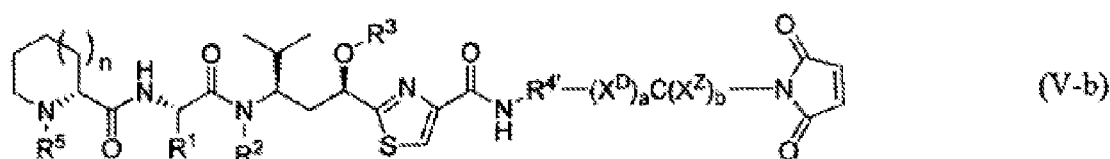
R^3 je H, C₁-C₅ alkil, C₂-C₅ alkenil, C(=O)C₁-C₅ alkil, ili C(=O)C₂-C₅ alkenil.

6. Tvar u skladu s patentnim zahtjevom 1, koja ima strukturu prema formuli (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (III-w), ili (III-y).
7. Tvar u skladu s patentnim zahtjevom 1, koja ima strukturu predstavljenu formulom (II-c)



gdje je R^{13} Me, n-Pr, CH₂OMe, ili CH₂OC(=O)CH₂CH(Me)₂; R^{14} je Me ili C(=O)Me; i R^{15} je H ili C₁-C₅ alkil.

8. Tvar molekula poveznik koja ima strukturu predstavljenu formulom (V-b)

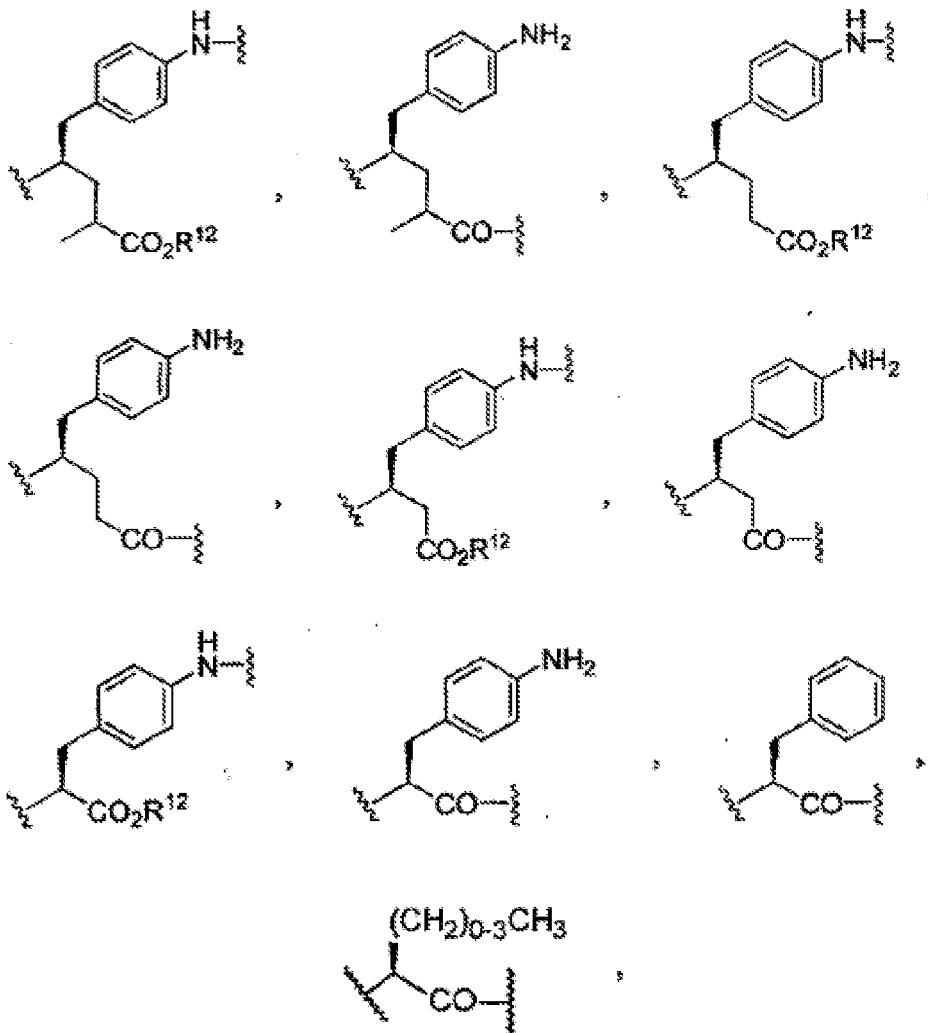


gdje

n je 0, 1, ili 2;

R^1 , R^2 i R^3 su nezavisno H, nesupstituirani ili supstituirani C₁-C₁₀ alkil, nesupstituirani ili supstituirani C₂-C₁₀ alkenil, nesupstituirani ili supstituirani C₂-C₁₀ alkinil, nesupstituirani ili supstituirani aril, nesupstituirani ili supstituirani heteroaril, nesupstituirani ili supstituirani (CH₂)₁₋₂O(C₁-C₁₀ alkil), nesupstituirani ili supstituirani

5

 $\mathbb{R}^4$ je

10

R⁵ je H, C₁-C₅ alkil, C₂-C₅ alkenil, C₂-C₅ alkinil, CO(C₁-C₅ alkil), CO(C₂-C₅ alkenil), ili CO(C₂-C₅ alkinil);

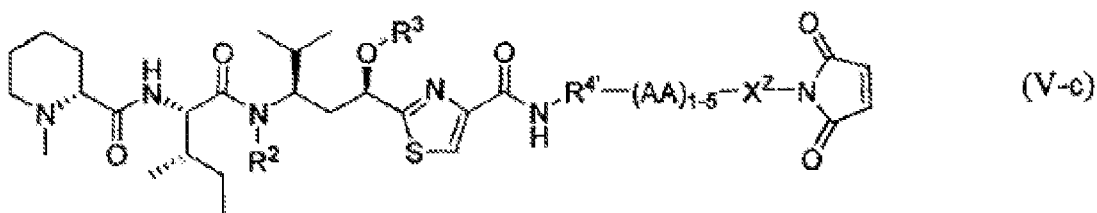
X^D i X^Z su razdjelne grupe;

C je grupa cijepanja; i

a i b su nezavisno 0 ili 1;

15

9. Tvar molekula poveznik u skladu s patentnim zahtjevom 8 koja ima strukturu predstavljenu formulom (V-c):

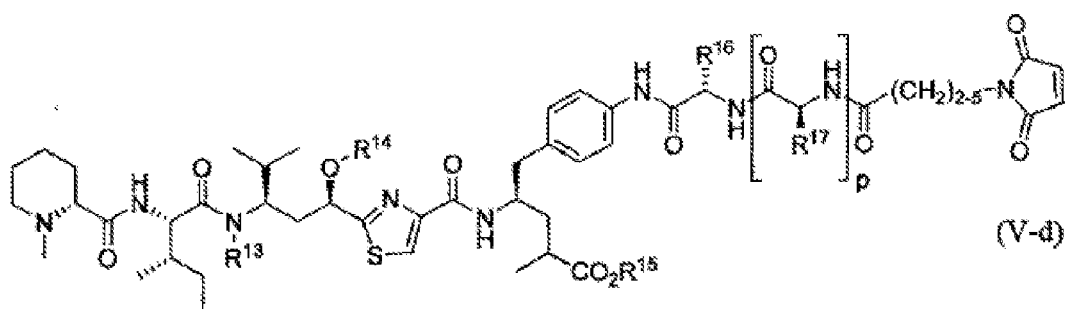


gdje su R^2 , R^3 i R^4 definirani u patentnom zahtjevu 8,

svaki AA je nezavisno prirodna aminokiselina, i

X^Z je $CH_2CH_2NHC(=O)(CH_2)_{2-5}$ ili $C(=O)(CH_2)_{2-5}$.

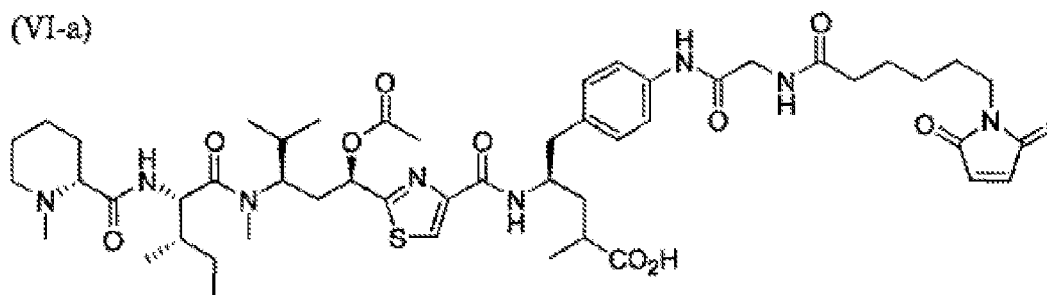
10. Tvar molekula poveznik u skladu s patentnim zahtjevom 9 koja ima strukturu predstavljenu formulom (V-d):



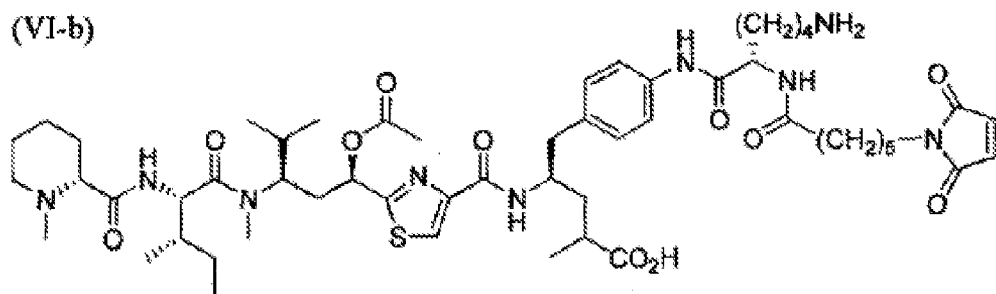
gdje je R^{13} Me, n-Pr, CH_2OMe , ili $CH_2OC(=O)CH_2CH(Me)_2$; R^{14} je Me ili $C(=O)Me$; R^{15} je H ili C_1-C_5 alkil; R^{16} je $(CH_2)_4NH_2$ ili $(CH_2)_3NHC(=O)NH_2$; R^{17} je $C(Me)_2$ ili Me; i p je 0 ili 1.

- 5 11. Tvar molekula poveznik u skladu s patentnim zahtjevom 8 koja ima strukturu predstavljenu bilo kojom od formula (VI-a) do (VI-t)

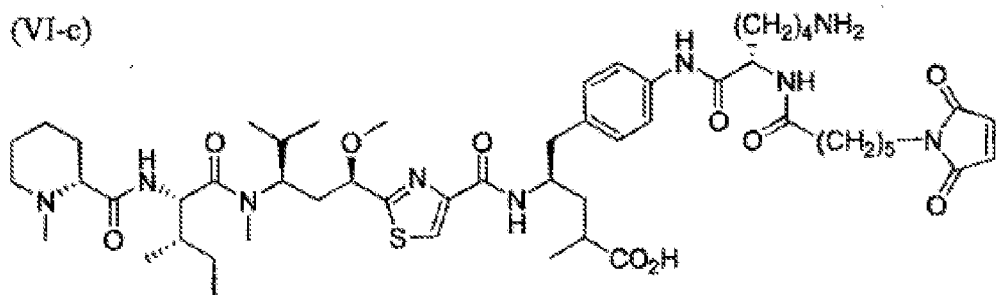
(VI-a)



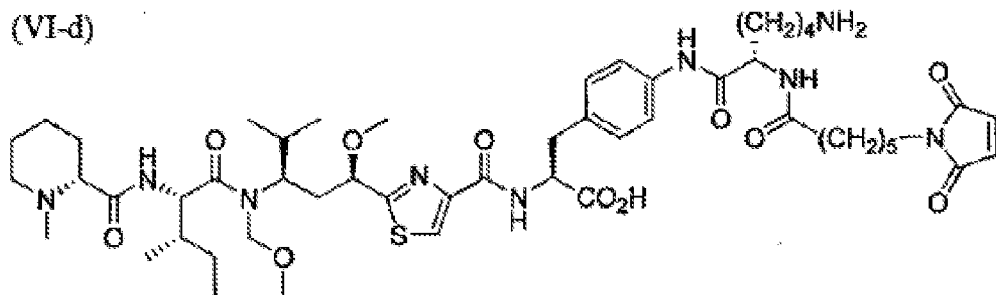
(VI-b)



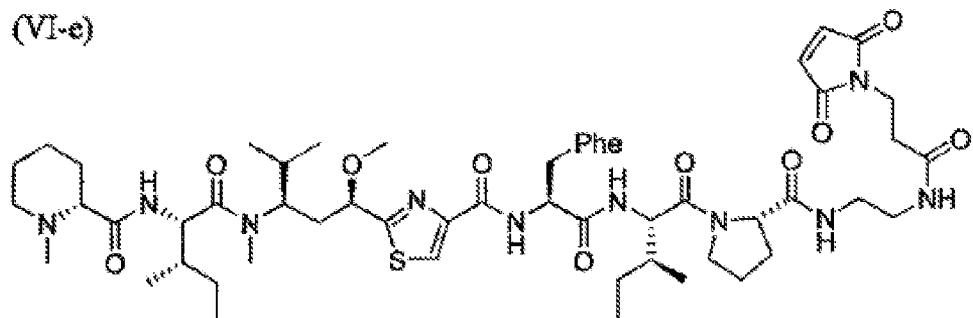
(VI-c)



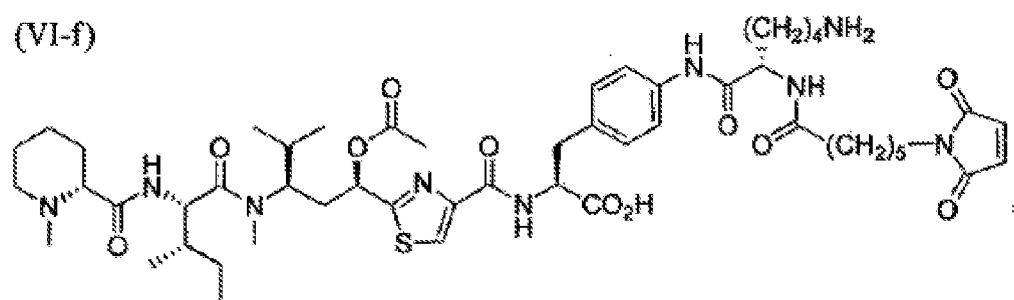
(VI-d)



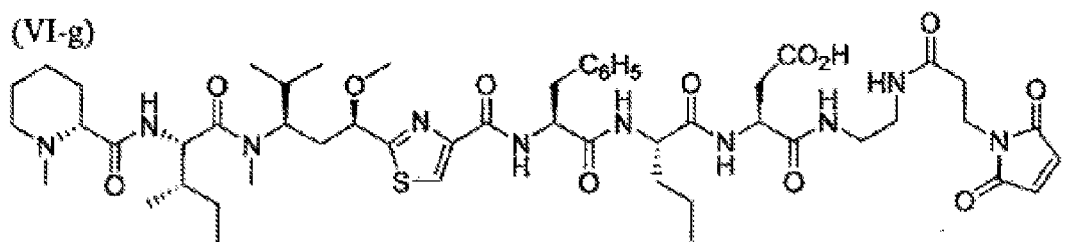
(VI-e)



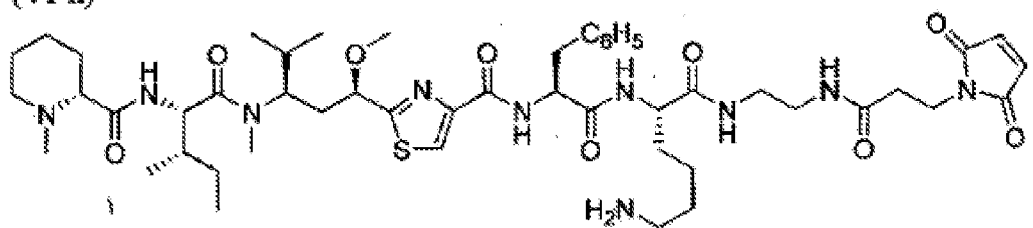
(VI-f)



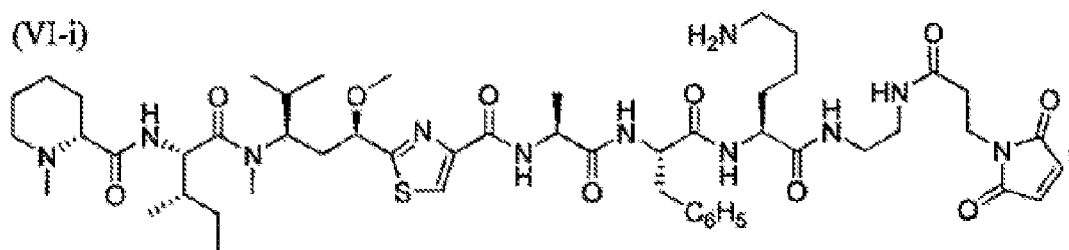
(VI-g)



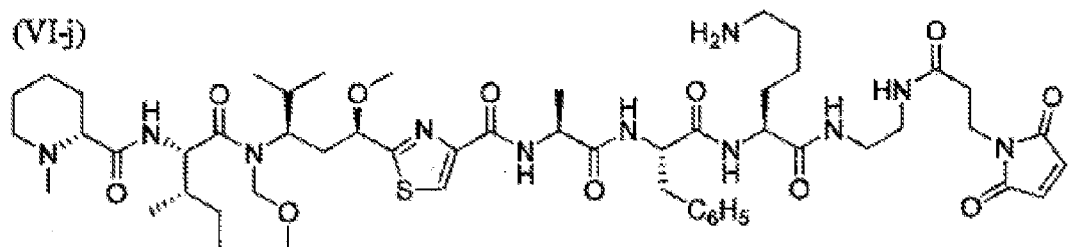
(VI-h)



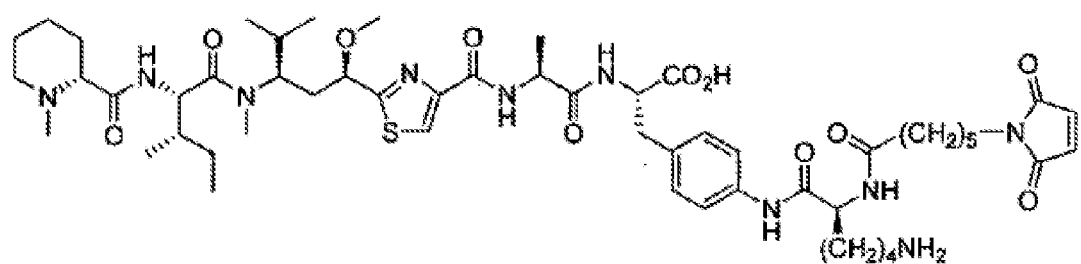
(VI-i)



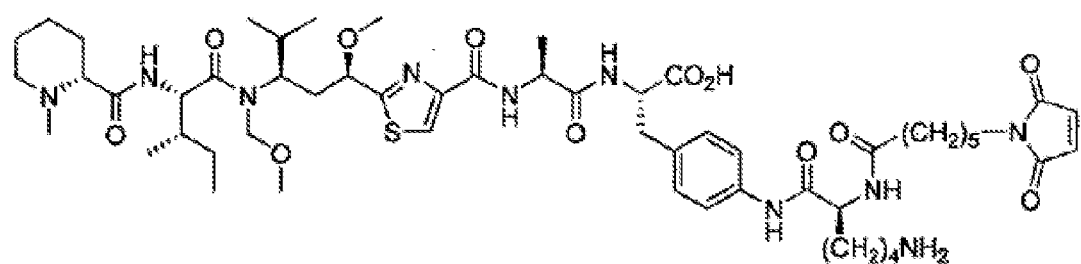
(VI-j)



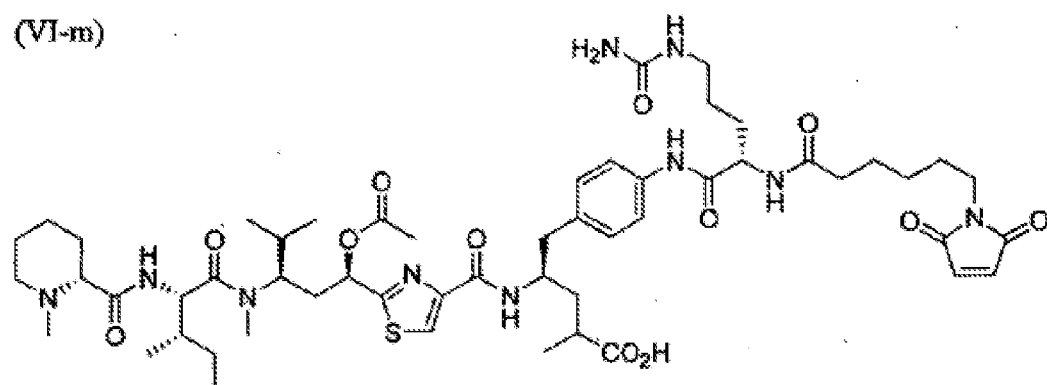
(VI-k)



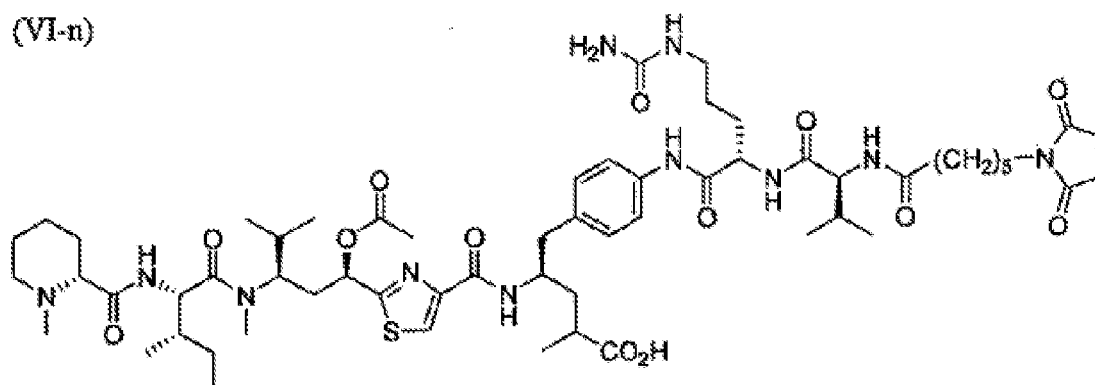
(VI-l)



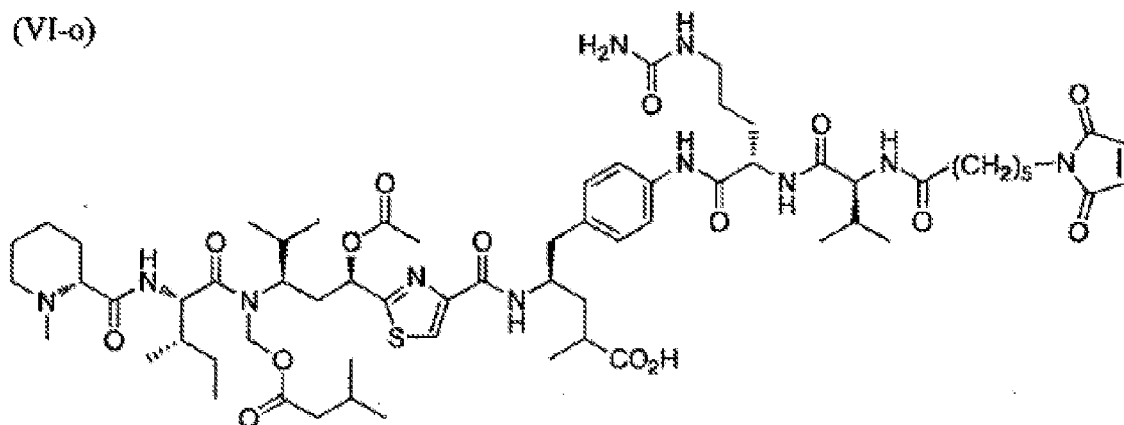
(VI-m)



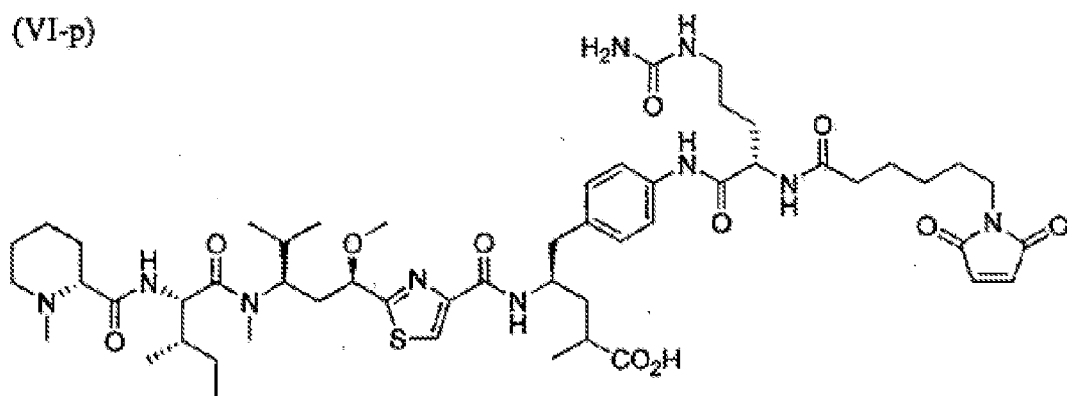
(VI-n)



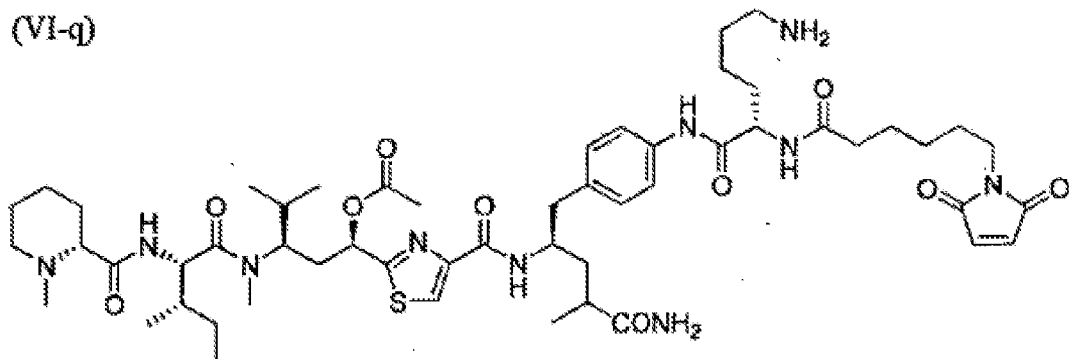
(VI-o)



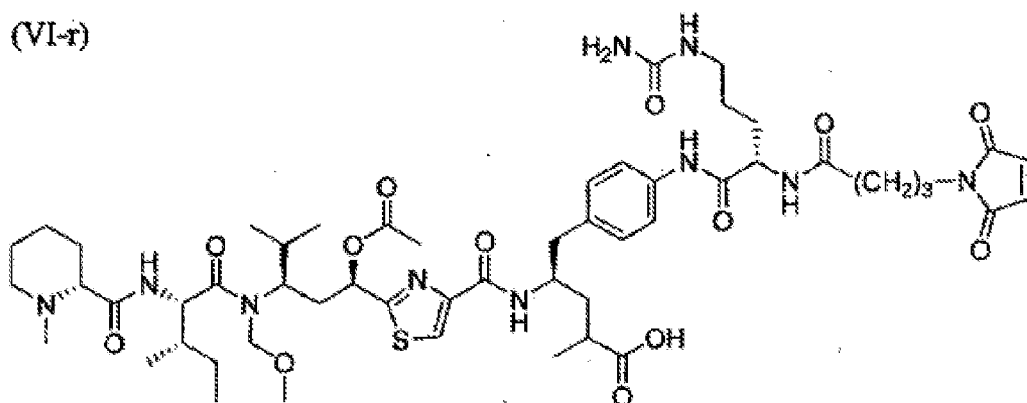
(VI-p)



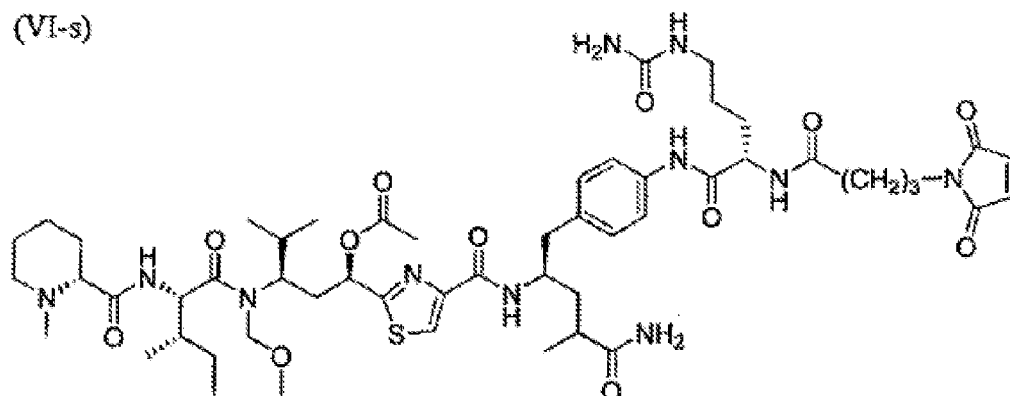
(VI-q)



(VI-r)

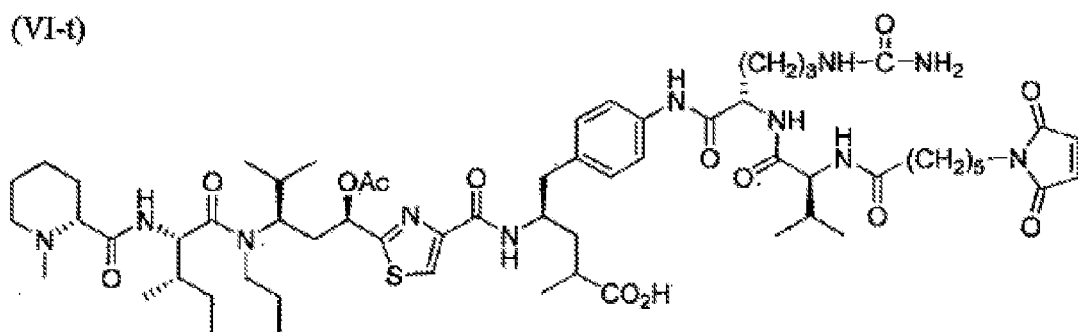


(VI-s)



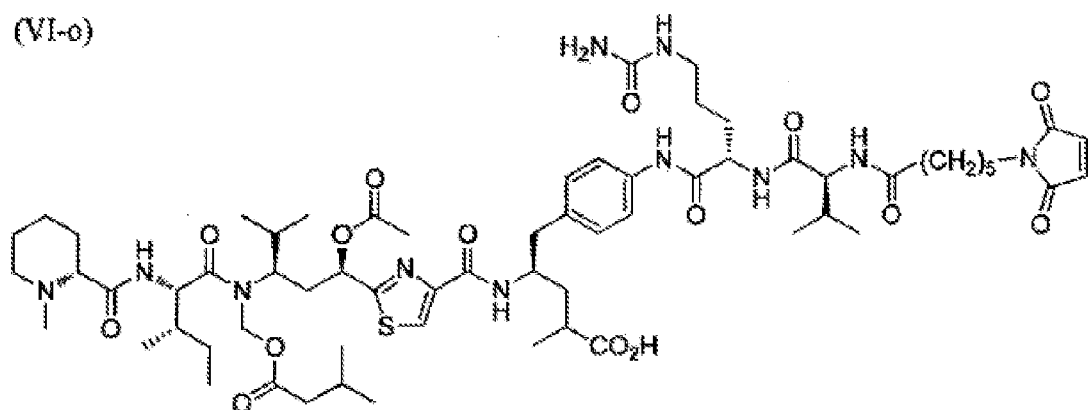
i

(VI-t)



12. Tvar molekula poveznik u skladu s patentnim zahtjevom 8 koja ima strukturu predstavljenu formulom (VI-o):

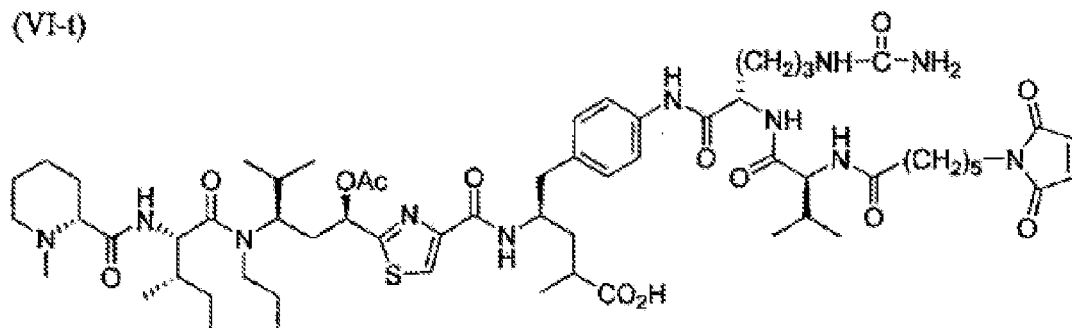
(VI-o)



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13. Tvar molekula poveznik u skladu s patentnim zahtjevom 8 koja ima strukturu predstavljenu formulom (VI-t):

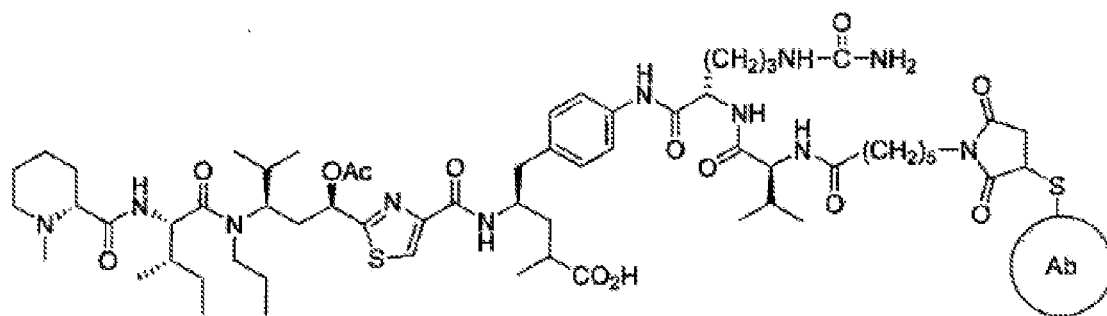
(VI-t)



14. Konjugat koji obuhvaća tvar molekule poveznika u skladu s bilo kojim od patentnih zahtjeva 8 do 13 konjugiranom s ligandom putem produkta nukleofilne adicije sulfhidrilne grupe liganda i maleimidne grupe tvari molekule poveznika, pri čemu je ligand odabran između protutijela, fragmenata protutijela i mimetika protutijela.

15. Tvar konjugat u skladu s patentnim zahtjevom 14, pri čemu tvar molekule poveznika ima strukturu predstavljenu sljedećom formulom:

10



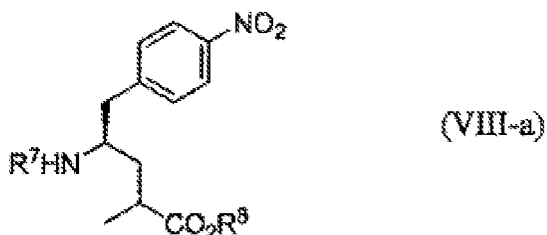
gdje Ab predstavlja ljudsko monoklonsko anti-mezotelijsko protutijelo 6A4 koje ima slijed varijabilne regije teškog lanca:

QVHVESGGGVVQPGRSLRLSCVASGITFRIYGMHWVRQAPGKGLEWVAVLWY
DGSHEYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAIYYCARDGDYYDSGS
PLDYWGQGTLVTVSS

i slijed varijabilne regije lakog lanca:

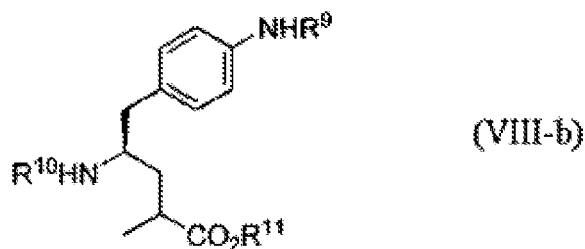
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT
GIPARFSGSGSGTDFLTITSSLEPEDFAVYYCQQRSNWPLTFGGGGTKVEIK

16. Tvar u skladu s bilo kojim od patentnih zahtjeva 1 do 7, ili konjugat u skladu s patentnim zahtjevom 14 ili patentnim zahtjevom 15, za uporabu u liječenju karcinoma.
17. Tvar koja ima strukturu u skladu s formulom (VIII-a)



gdje je R^7 H ili aminska zaštitna grupa i R^8 je H, C_1 - C_{10} alkil, C_2 - C_{10} alkenil, C_2 - C_{10} alkinil, aril, cikloalifat, alkilcikloalifat, arilalkil, ili alkilaril.

18. Tvar koja ima strukturu u skladu s formulom (VIII-b)



gdje su R^9 i R^{10} nezavisno H ili aminska zaštitna grupa i R^{11} je H, C_1 - C_{10} alkil, C_2 - C_{10} alkenil, C_2 - C_{10} alkinil, aril, cikloalifat, alkilcikloalifat, arilalkil, ili alkilaril.