

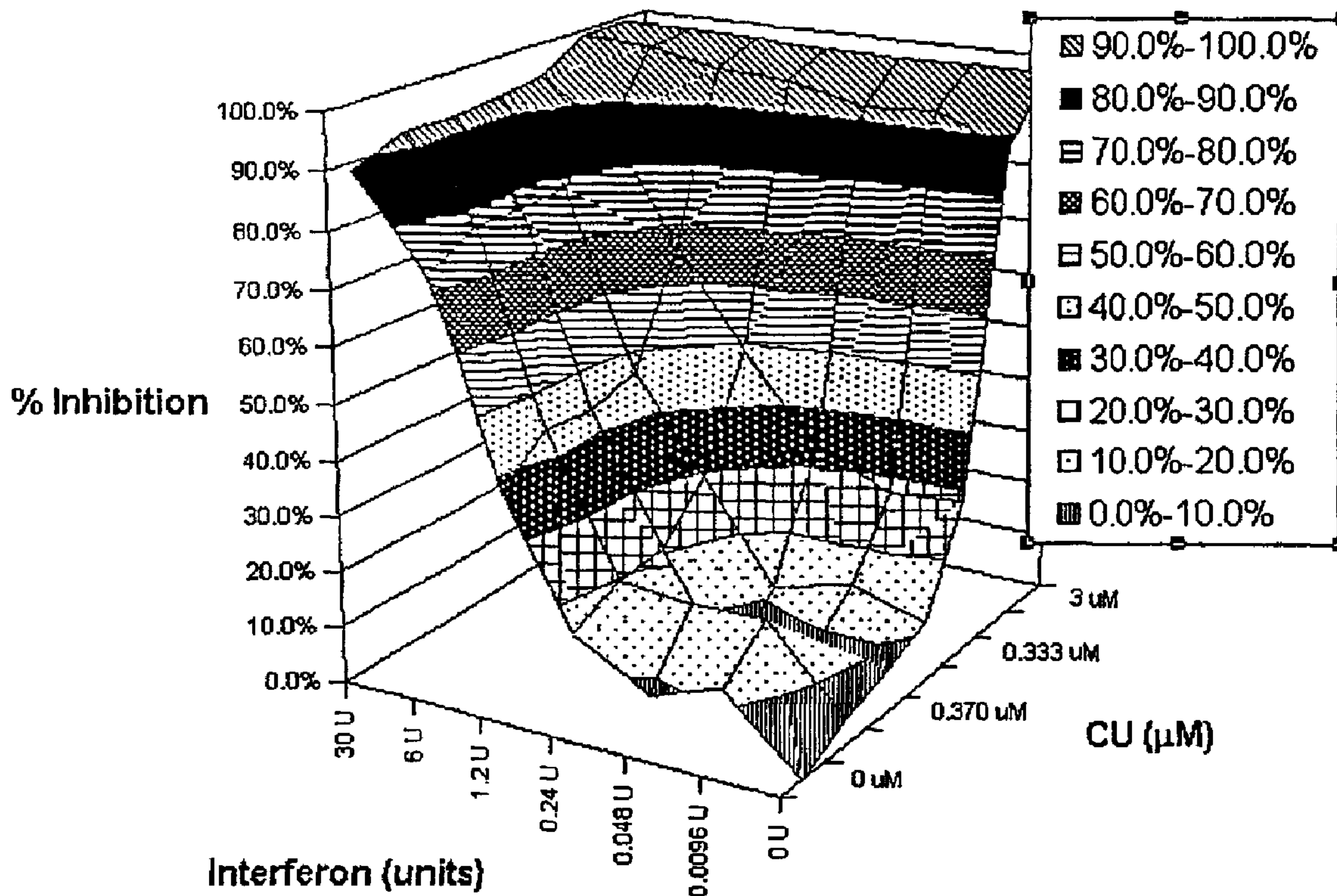


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(54) Titre : INHIBITEURS PEPTIDOMIMETIQUES DE PROTEASE  
 (54) Title: PEPTIDOMIMETIC PROTEASE INHIBITORS

**Combination treatment with Interferon alpha-2B and Compound CU**



(57) Abrégé/Abstract:

The present invention relates to peptidomimetic compounds useful as protease inhibitors (1), particularly as serine protease inhibitors and more particularly as hepatitis C NS3 protease inhibitors; intermediates thereto; their preparation including novel

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(57) **Abrégé(suite)/Abstract(continued)**:

stereoselective processes to intermediates. The invention is also directed to pharmaceutical compositions and to methods for using the compounds for inhibiting HCV protease or treating a patient suffering from an HCV infection or physiological condition related to the infection. Also provided are pharmaceutical combinations comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti HCV activity and a pharmaceutically acceptable carrier, and methods for treating or preventing a HCV infection in a patient using the compositions. The present invention is also directed to a kit or pharmaceutical pack for treating or preventing HCV infection in a patient.

**ABSTRACT**

The present invention relates to peptidomimetic compounds useful as protease inhibitors (1), particularly as serine protease inhibitors and more particularly as hepatitis C NS3 protease inhibitors; intermediates thereto; their preparation including novel stereoselective processes to intermediates. The invention is also directed to pharmaceutical compositions and to methods for using the compounds for inhibiting HCV protease or treating a patient suffering from an HCV infection or physiological condition related to the infection. Also provided are pharmaceutical combinations comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti HCV activity and a pharmaceutically acceptable carrier, and methods for treating or preventing a HCV infection in a patient using the compositions. The present invention is also directed to a kit or pharmaceutical pack for treating or preventing HCV infection in a patient.

## SEQUENCE LISTING

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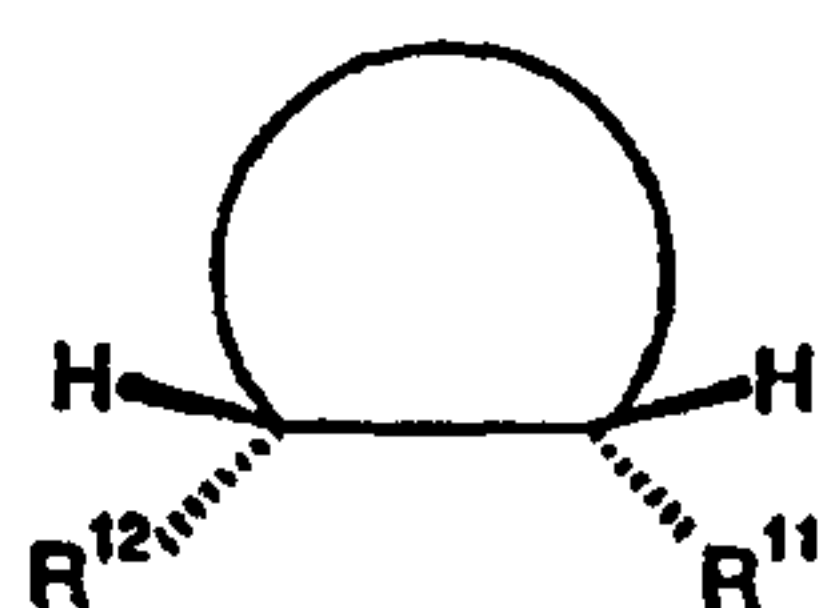
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## CLAIMS:

1. A compound of formula 24



10

wherein:



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

$R^{11}$  is  $-\text{CO}_2R^{13}$ ;

15

$R^{12}$  is an iminic glycinimide derivative adduct; and

$R^{13}$  is acid protecting group or optionally substituted aliphatic group.

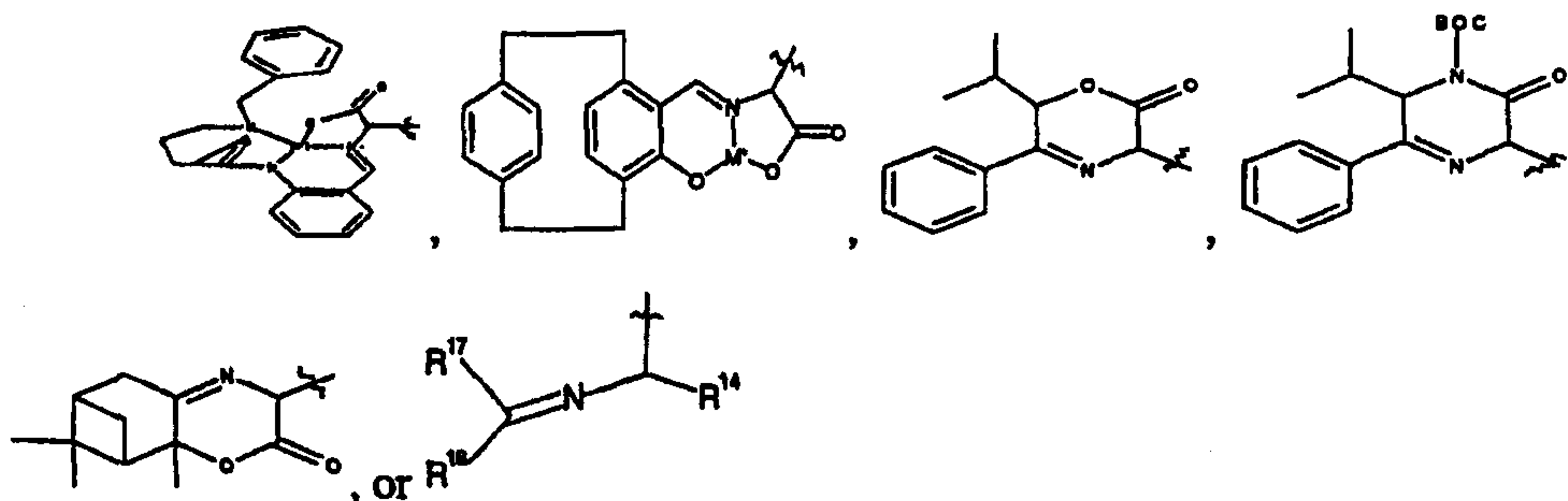
2. A compound of claim 1 wherein:

optionally substituted cycloalkyl means a non-aromatic mono- or multicyclic ring system of 3 to 10 carbon atoms optionally substituted with one or more ring group substituents;

20 optionally substituted fused arylcycloalkyl means a fused arylcycloalkyl optionally substituted with one or more ring group substituents;

optionally substituted aliphatic group are alkyl, alkenyl, or alkynyl optionally substituted with an aliphatic group substituent;

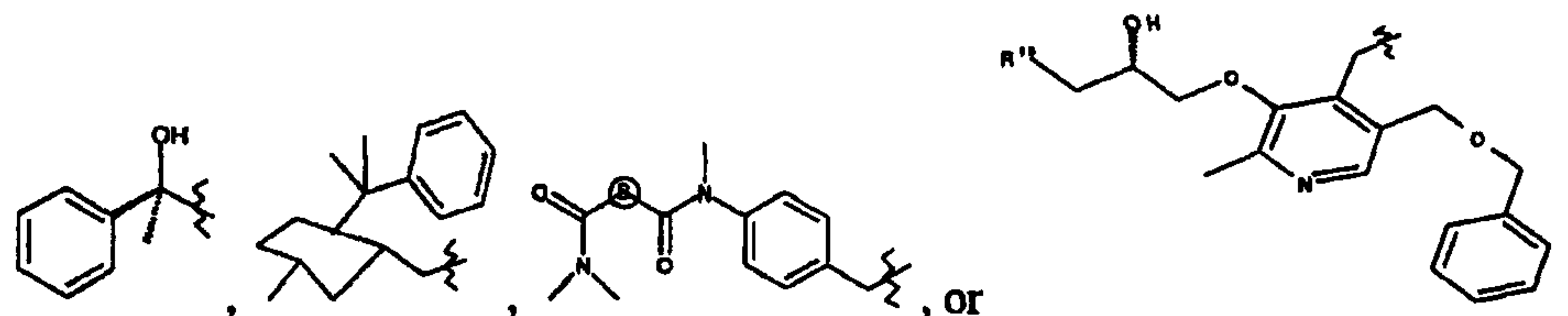
an iminic glycinimide derivative adduct is a compound selected from the group consisting of



wherein:

$R^{16}$  is an acid protecting group, optionally substituted aryl, or optionally substituted  
5 aliphatic group;

$R^{17}$  is optionally substituted aryl, optionally substituted aliphatic group,



$R^{18}$  is hydrogen, alkyl, or alkylthio; or optionally substituted aryl;

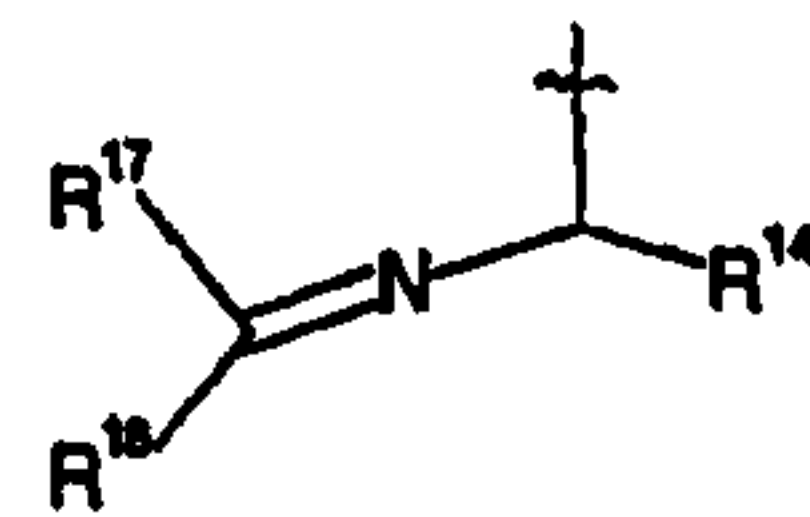
10 wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring  
systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy,  
acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo  
analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy,  
15 heteroaroyloxy, halo, nitro, cyano, carboxy (acid),  $-C(O)-NHOH$ ,  $-C(O)-CH_2OH$ ,  $-C(O)-$   
 $CH_2SH$ ,  $-C(O)-NH-CN$ , sulpho, phosphono, alkylsulphonylcarbonyl, tetrazolyl,  
arylsulphonylcarbonyl, N-methoxycarbonyl, heteroarylsulphonylcarbonyl,  
3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or  
hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl,  
20 alkoxy carbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl,  
alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl,  
cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio,  
heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol,  $Y^1Y^2N-$ ,  $Y^1Y^2NC(O)-$ ,  
 $Y^1Y^2NC(O)O$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ , wherein  $Y^1$ ,  $Y^2$  and  $Y^3$  are  
25 independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is  $Y^1Y^2N-$ ,  
then one of  $Y^1$  and  $Y^2$  may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl,

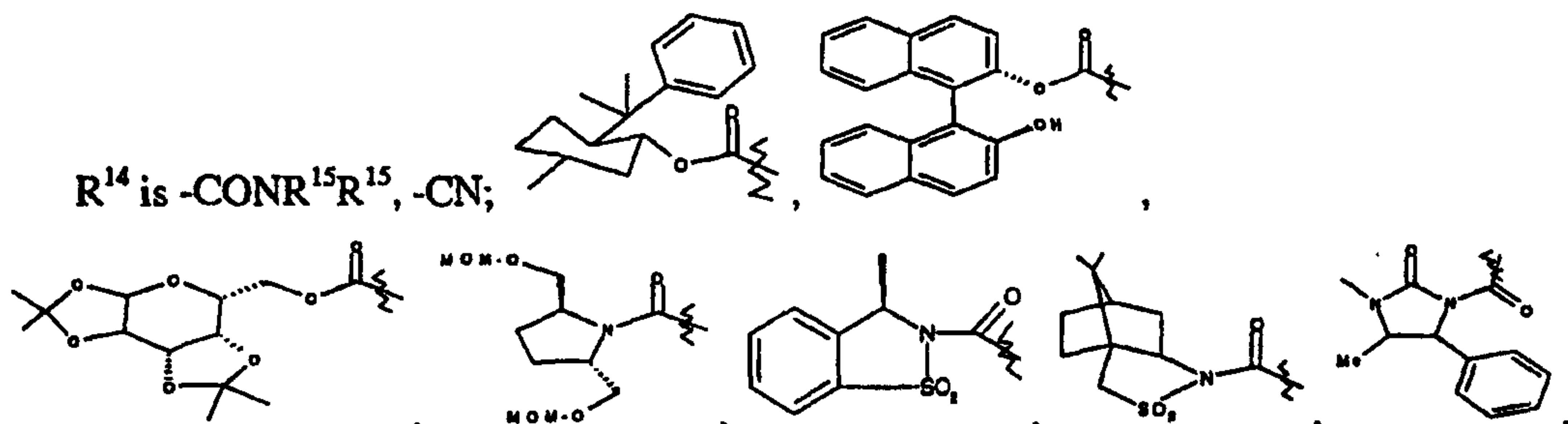
- cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, as defined herein and the other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered
- 5 azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene ( $H_2C=$ ), oxo ( $O=$ ) and thioxo ( $S=$ ); and
- aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclyl carbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyle or its thioxo analogue, acyloxy, cyclyl carbonyloxy, aroyloxy, heteroaroyleoxy, halo, nitro, cyano, carboxy (acid),  $-C(O)-NHOH$ ,  $-C(O)-CH_2OH$ ,  $-C(O)-CH_2SH$ ,  $-C(O)-NH-CN$ , sulpho, phosphono, alkylsulphonyl carbamoyl, tetrazolyl, arylsulphonyl carbamoyl, N-methoxycarbamoyl, heteroarylsulphonyl carbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene ( $H_2C=$ ), oxo ( $O=$ ), thioxo ( $S=$ ),  $Y^1Y^2N-$ ,  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$ ,  $Y^1Y^2NSO_2-$ , or  $Y^3SO_2NY^1-$  wherein  $R^2$  is as defined herein,  $Y^1$  and  $Y^2$  are independently hydrogen, alkyl, aryl or heteroaryl, and  $Y^3$  is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is  $Y^1Y^2N-$ , then one of  $Y^1$  and  $Y^2$  may be acyl, cyclyl carbonyl, aroyl, heteroaroyle, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, as defined herein and the other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl; and aryl means an aromatic monocyclic or multicyclic ring system of 6 to 14 carbon atoms.
- 30 3. A compound according to claims 1 or 2 where  $R^{11}$  is  $-CO_2R^{13}$ .
4. A compound according to any one of claims 2 or 3 where  $R^{13}$  is an optionally substituted aliphatic group.
5. A compound according to any one of claims 2 to 4 where  $R^{13}$  is an alkyl group.
6. A compound according to any one of claims 3 to 5 where  $R^{13}$  is lower alkyl.

7. A compound according to any one of claims 1 to 6 where R<sup>13</sup> is methyl.

8. A compound according to any one of claims 1 to 7 where R<sup>12</sup> is  
wherein:



R<sup>14</sup> is -CONR<sup>15</sup>R<sup>15</sup>, -CN;

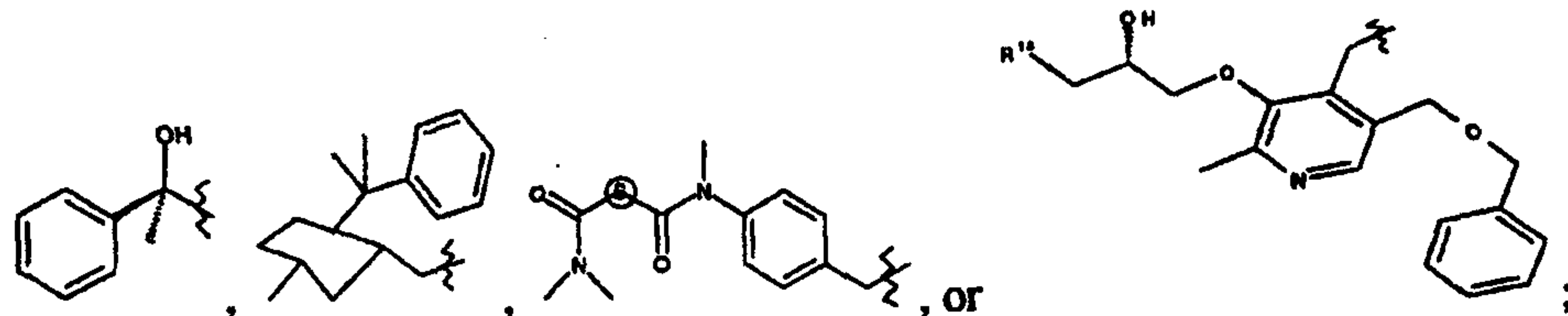


or -CO<sub>2</sub>R<sup>16</sup>;

R<sup>15</sup> is optionally substituted aliphatic group;

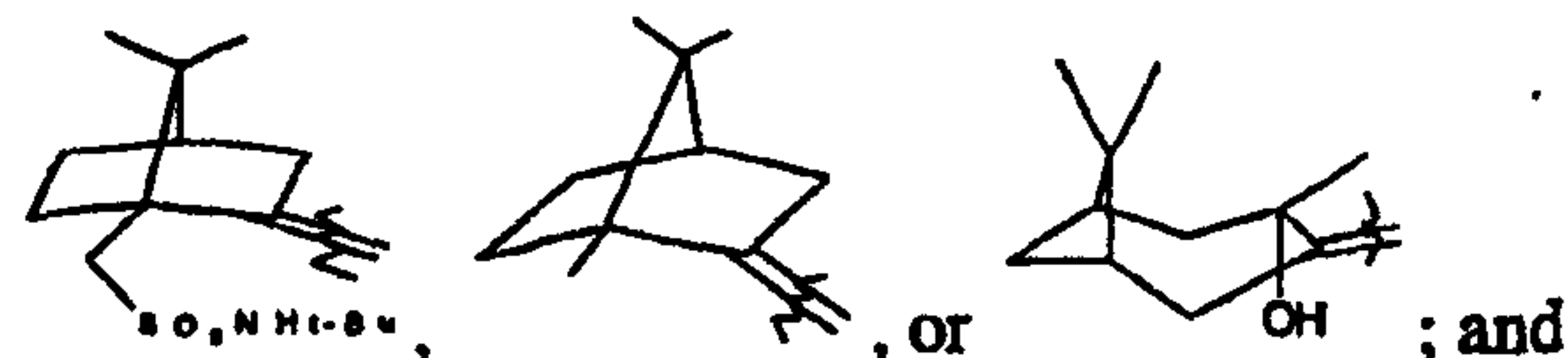
R<sup>16</sup> is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

R<sup>17</sup> is optionally substituted aryl, optionally substituted aliphatic group,



R<sup>18</sup> is hydrogen, alkyl, or alkylthio; or optionally substituted aryl;

R<sup>17</sup> and R<sup>18</sup> taken together with the carbon to which R<sup>17</sup> and R<sup>18</sup> are attached



Ⓢ is a solid phase.

9. A compound according to claim 8 where R<sup>14</sup> is -CO<sub>2</sub>R<sup>16</sup>.

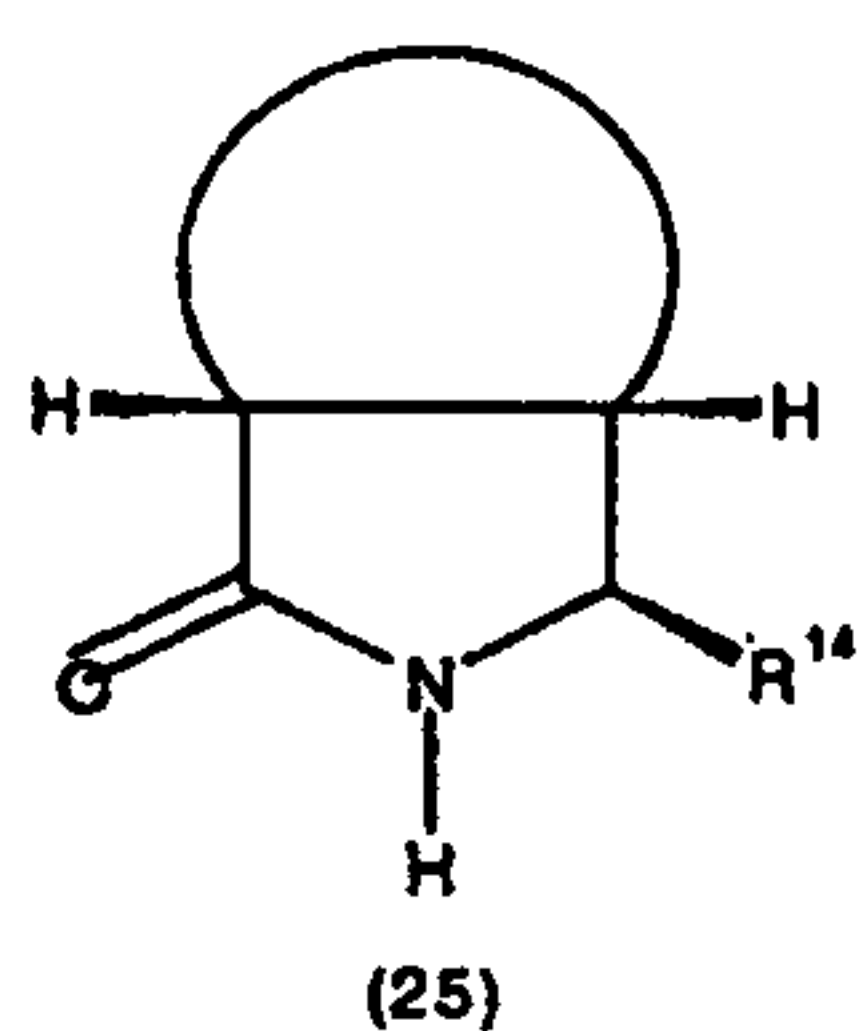
10. A compound according to claim 8 or 9 where R<sup>16</sup> is optionally substituted aliphatic.

11. A compound according to any one of claims 8 to 10 where R<sup>16</sup> is alkyl.

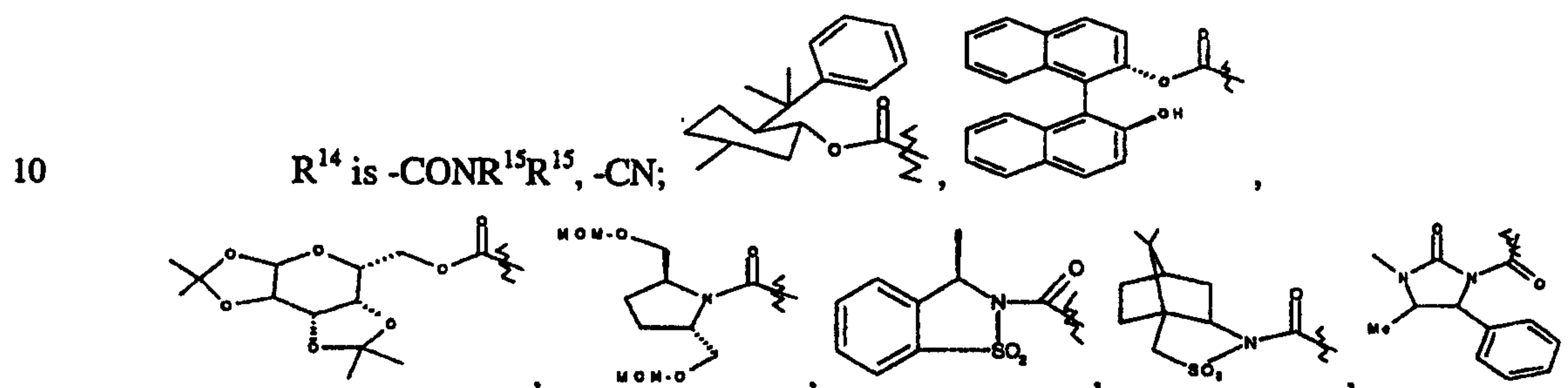
12. A compound according to any one of claims 8 to 11 where R<sup>16</sup> is lower alkyl.

13. A compound according to any one of claims 8 to 12 where R<sup>16</sup> is t-Bu.

14. A compound according to any one of claims 8 to 13 where  $R^{17}$  is optionally substituted aryl.
15. A compound according to any one of claims 8 to 14 where  $R^{17}$  is phenyl.
16. A compound according to any one of claims 8 to 15 where  $R^{18}$  is optionally substituted aryl.
17. A compound according to any one of claims 8 to 16 where  $R^{18}$  is phenyl.
18. A compound of formula 25



wherein:



or  $-\text{CO}_2\text{R}^{16}$ ;

$R^{15}$  is optionally substituted aliphatic group; and

15  $R^{16}$  is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

19. A compound according to Claim 18 wherein:
- optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;
- optionally substituted aryl means an aromatic monocyclic or multicyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;
- 20 wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cycloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy,

25

heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyle, tetrazolyl, arylsulphonylcarbamoyle, N-methoxycarbamoyle, heteroarylsulphonylcarbamoyle, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or

5 hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y<sup>1</sup>Y<sup>2</sup>N-, Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, wherein Y<sup>1</sup>, Y<sup>2</sup> and Y<sup>3</sup> are

10 independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>N-, then one of Y<sup>1</sup> and Y<sup>2</sup> may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y<sup>1</sup> and Y<sup>2</sup> is as defined previously, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, Y<sup>1</sup> and Y<sup>2</sup> may also be taken together

15 with the N atom through which Y<sup>1</sup> and Y<sup>2</sup> are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the "ring group substituents" further include, methylene (H<sub>2</sub>C=), oxo (O=) and thioxo (S=); and

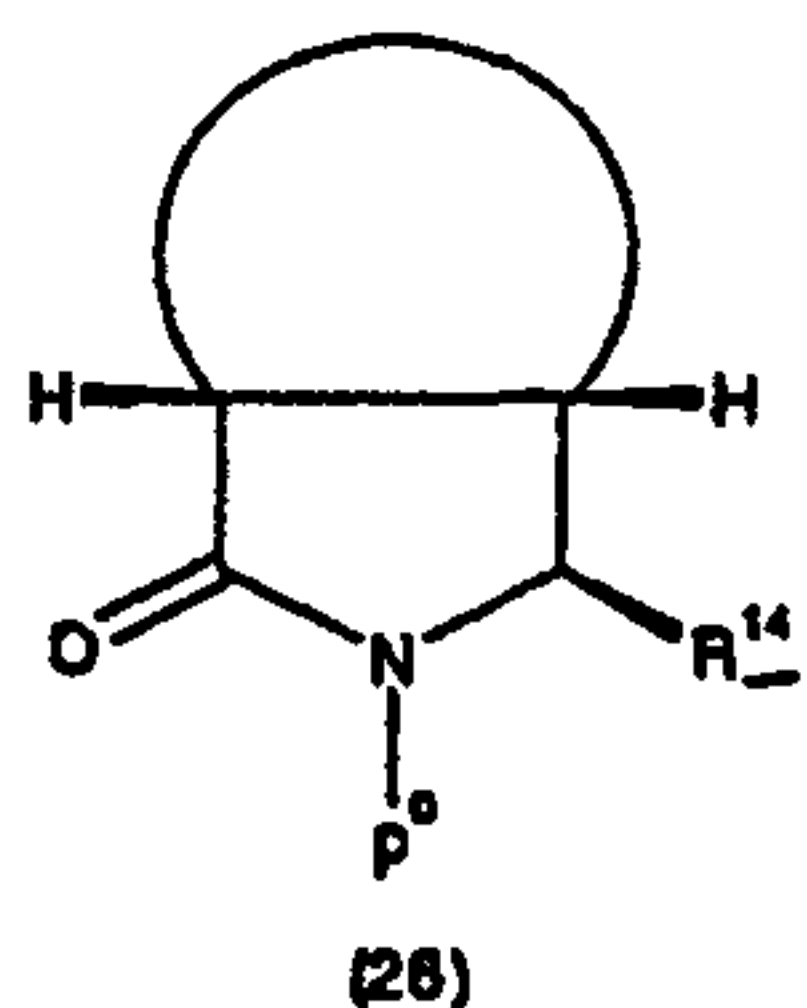
20 aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyle, tetrazolyl, arylsulphonylcarbamoyle, N-methoxycarbamoyle,

25 heteroarylsulphonylcarbamoyle, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio,

30 arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H<sub>2</sub>C=), oxo (O=), thioxo (S=), Y<sup>1</sup>Y<sup>2</sup>N-, Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>-, Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, or Y<sup>3</sup>SO<sub>2</sub>NY<sup>1</sup>- wherein R<sup>2</sup> is as defined herein, Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen,

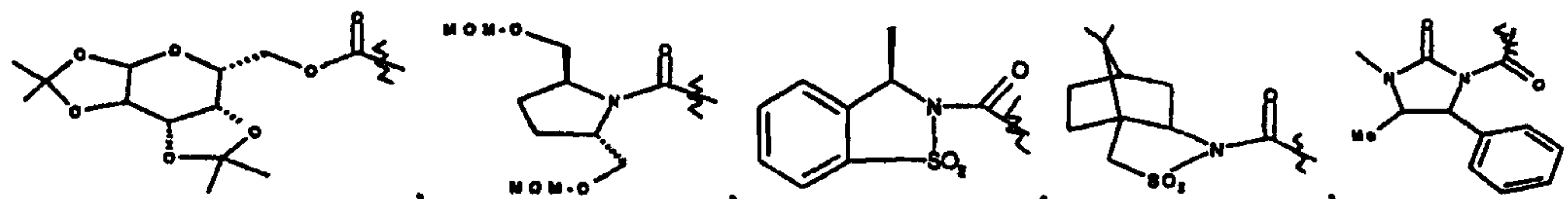
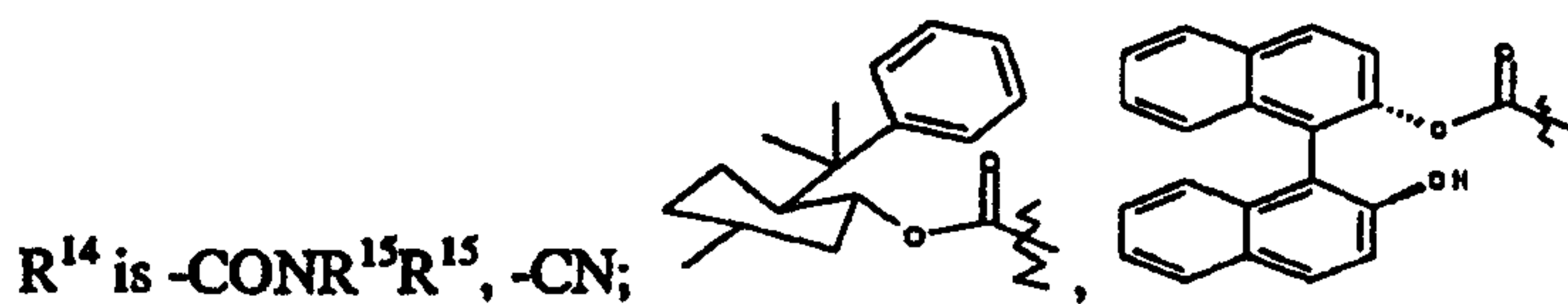
alkyl, aryl or heteroaryl, and  $Y^3$  is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is  $Y^1Y^2N-$ , then one of  $Y^1$  and  $Y^2$  may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, as defined herein and the other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl.

20. A compound according to claims 18 or 19 where  $R^{14}$  is  $-CO_2R^{16}$ .
21. A compound according to any one of claims 18 to 20 where  $R^{16}$  is optionally substituted aliphatic.
22. A compound according to any one of claims 18 to 21 where  $R^{16}$  is alkyl.
23. A compound according to any one of claims 18 to 22 where  $R^{16}$  is lower alkyl.
24. A compound according to any one of claims 18 to 23 where  $R^{16}$  is t-Bu.
25. A compound of formula 26



wherein:

$p^O$  is amide protecting group;



or  $-CO_2R^{16}$ ;

$R^{15}$  is optionally substituted aliphatic group; and

$R^{16}$  is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

26. A compound according to Claim 25 wherein:

optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

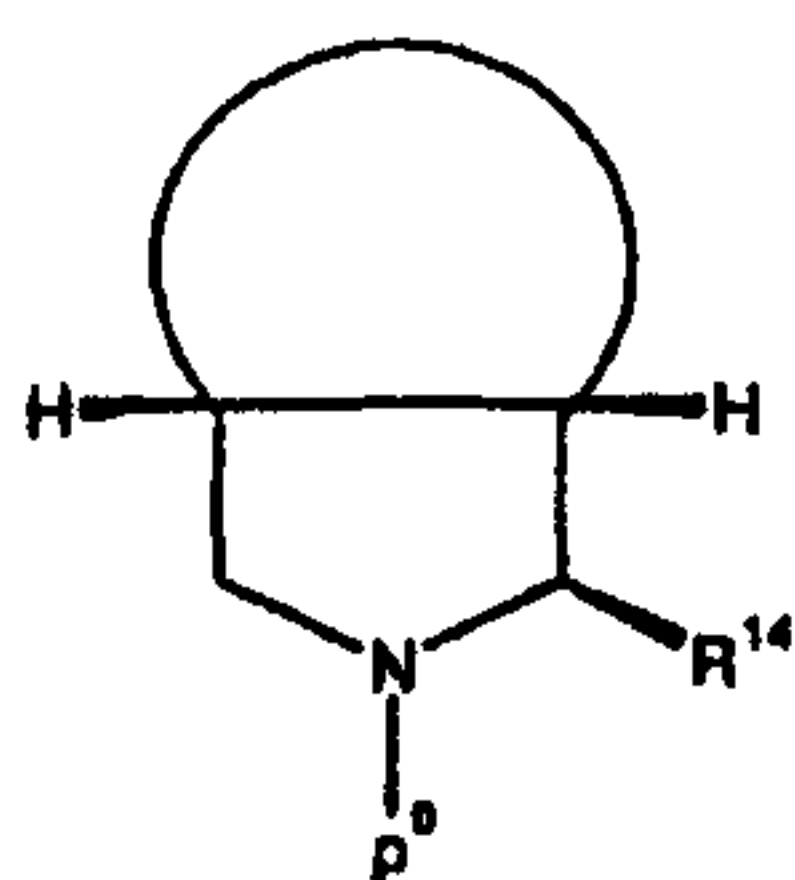
optionally substituted aryl means an aromatic monocyclic or mylticyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;

5 wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazoly, alkoxy-carbonyl, cyclyloxy-carbonyl, aryloxy-carbonyl, heteroaryloxy-carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y<sup>1</sup>Y<sup>2</sup>N-, Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, wherein Y<sup>1</sup>, Y<sup>2</sup> and Y<sup>3</sup> are independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>N-, then one of Y<sup>1</sup> and Y<sup>2</sup> may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy-carbonyl, cyclyloxy-carbonyl, aryloxy-carbonyl or heteroaryloxy-carbonyl, as defined herein and the other of Y<sup>1</sup> and Y<sup>2</sup> is as defined previously, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, Y<sup>1</sup> and Y<sup>2</sup> may also be taken together with the N atom through which Y<sup>1</sup> and Y<sup>2</sup> are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene (H<sub>2</sub>C=), oxo (O=) and thioxo (S=); and

aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl,

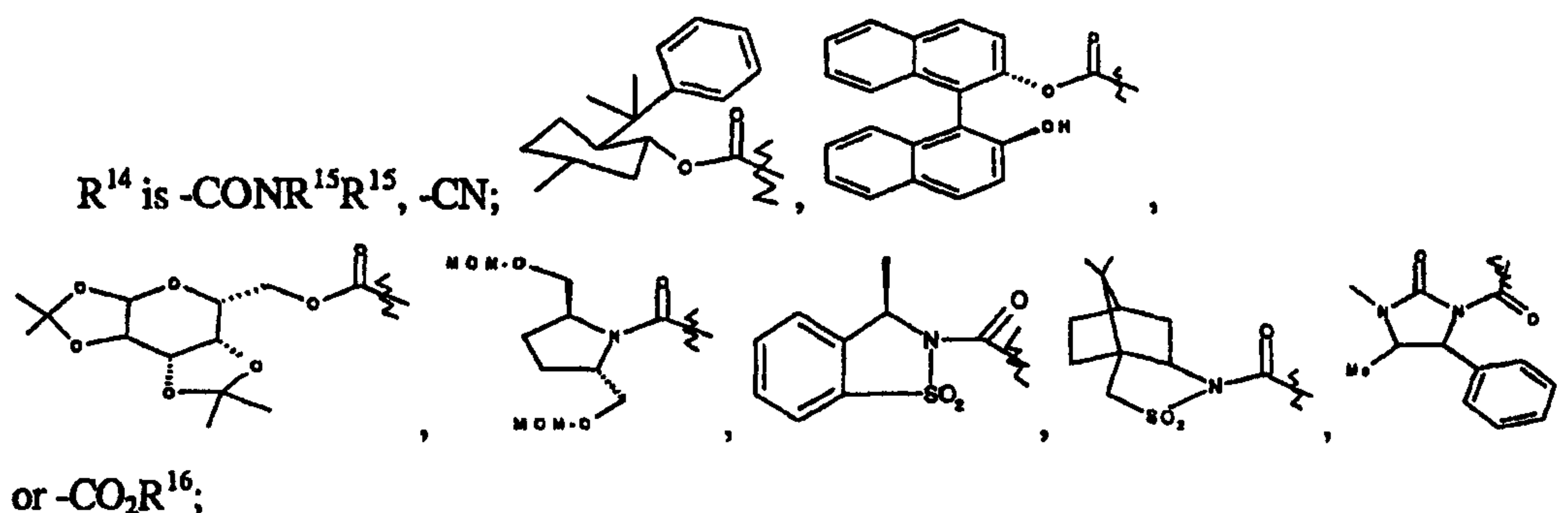
- tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl,  
heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-  
oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl,  
3-hydroxy-1-methylpyrazolyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl,  
5 heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl,  
alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio,  
arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H<sub>2</sub>C=), oxo  
(O=), thioxo (S=), Y<sup>1</sup>Y<sup>2</sup>N-, Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>-, Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-,  
or Y<sup>3</sup>SO<sub>2</sub>NY<sup>1</sup>- wherein R<sup>2</sup> is as defined herein, Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen,  
10 alkyl, aryl or heteroaryl, and Y<sup>3</sup> is alkyl, cycloalkyl aryl or heteroaryl, or for where the  
substituent is Y<sup>1</sup>Y<sup>2</sup>N-, then one of Y<sup>1</sup> and Y<sup>2</sup> may be acyl, cyclyl carbonyl, aroyl,  
heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or  
heteroaryloxy carbonyl, as defined herein and the other of Y<sup>1</sup> and Y<sup>2</sup> is as defined  
previously, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>-  
15 or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, Y<sup>1</sup> and Y<sup>2</sup> may also be taken together with the N atom through which Y<sup>1</sup>  
and Y<sup>2</sup> are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl.
27. A compound according to claim 25 or 26 where R<sup>14</sup> is -CO<sub>2</sub>R<sup>16</sup>.
28. A compound according to any one of claims 25 to 27 where R<sup>16</sup> is optionally  
substituted aliphatic.
- 20 29. A compound according to any one of claims 25 to 28 where R<sup>16</sup> is alkyl.
30. A compound according to any one of claims 25 to 29 where R<sup>16</sup> is lower alkyl.
31. A compound according to any one of claims 25 to 30 where R<sup>16</sup> is t-Bu.
32. A compound according to any one of claims 25 to 31 where p<sup>0</sup> is selected from the  
group consisting of BOC, CBz, and -CO<sub>2</sub>alkyl.
- 25 33. A compound according to claim 32 where p<sup>0</sup> is BOC.
34. A compound of formula 27



(27)

wherein:

p<sup>0</sup> is amide protecting group;



$R^{15}$  is optionally substituted aliphatic group; and

5  $R^{16}$  is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

35. A compound according to Claim 34 wherein:

optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

10 optionally substituted aryl means an aromatic monocyclic or multicyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;

wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, 15 acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid),  $-\text{C}(\text{O})-\text{NHOH}$ ,  $-\text{C}(\text{O})-\text{CH}_2\text{OH}$ ,  $-\text{C}(\text{O})-\text{CH}_2\text{SH}$ ,  $-\text{C}(\text{O})-\text{NH}-\text{CN}$ , sulpho, phosphono, alkylsulphonylcarbamoyle, tetrazolyl, arylsulphonylcarbamoyle, N-methoxycarbamoyle, heteroarylsulphonylcarbamoyle, 20 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol,  $\text{Y}^1\text{Y}^2\text{N}-$ ,  $\text{Y}^1\text{Y}^2\text{NC}(\text{O})-$ ,  $\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{O}$ ,  $\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{NY}^3-$  or  $\text{Y}^1\text{Y}^2\text{NSO}_2-$ , wherein  $\text{Y}^1$ ,  $\text{Y}^2$  and  $\text{Y}^3$  are 25 independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is  $\text{Y}^1\text{Y}^2\text{N}-$ , then one of  $\text{Y}^1$  and  $\text{Y}^2$  may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the

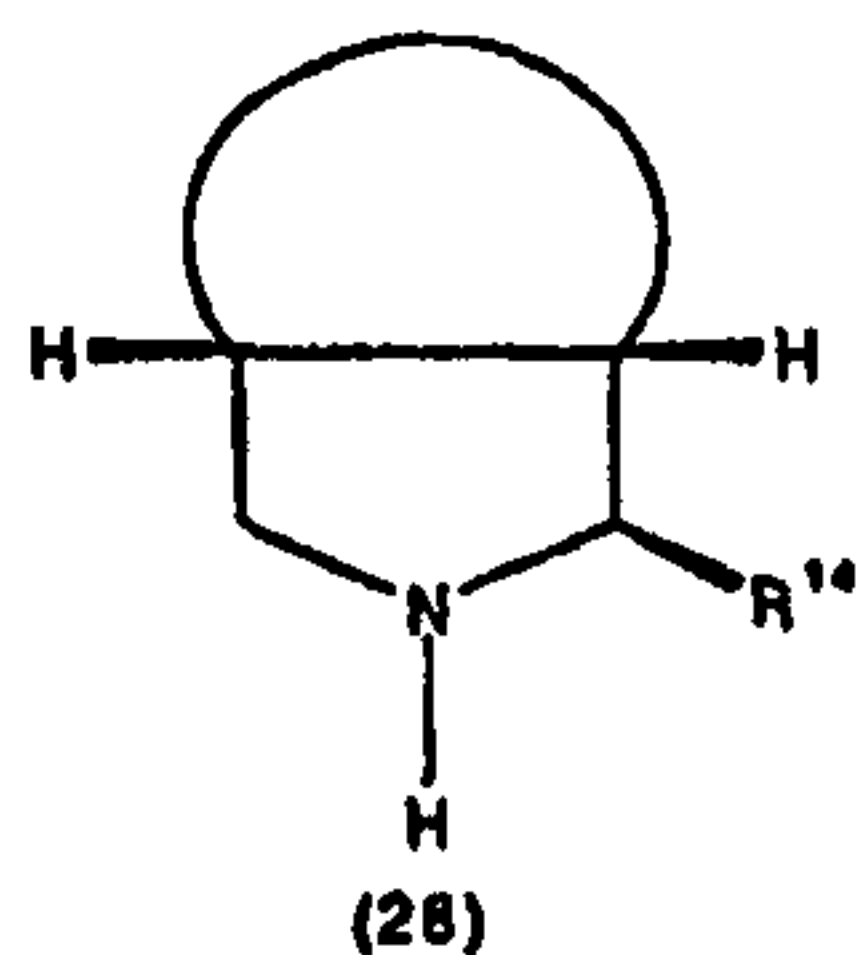
- other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene ( $H_2C=$ ), oxo ( $O=$ ) and thioxo ( $S=$ ); and
- aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid),  $-C(O)-NHOH$ ,  $-C(O)-CH_2OH$ ,  $-C(O)-CH_2SH$ ,  $-C(O)-NH-CN$ , sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene ( $H_2C=$ ), oxo ( $O=$ ), thioxo ( $S=$ ),  $Y^1Y^2N-$ ,  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$ ,  $Y^1Y^2NSO_2-$ , or  $Y^3SO_2NY^1-$  wherein  $R^2$  is as defined herein,  $Y^1$  and  $Y^2$  are independently hydrogen, alkyl, aryl or heteroaryl, and  $Y^3$  is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is  $Y^1Y^2N-$ , then one of  $Y^1$  and  $Y^2$  may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl.
36. A compound according to any one of claims 34 to 35 where  $R^{14}$  is  $-CO_2R^{16}$ .
37. A compound according to any one of claims 34 to 36 where  $R^{16}$  is optionally substituted aliphatic.
38. A compound according to any one of claims 34 to 37 where  $R^{16}$  is alkyl.
39. A compound according to any one of claims 34 to 38 where  $R^{16}$  is lower alkyl.
40. A compound according to any one of claims 34 to 39 where  $R^{16}$  is t-Bu.

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41. A compound according to any one of claims 34 to 40 where  $p^0$  is selected from the group consisting of BOC, CBz, and  $-\text{CO}_2\text{alkyl}$ .

42. A compound according to claim 41 where  $p^0$  is BOC.

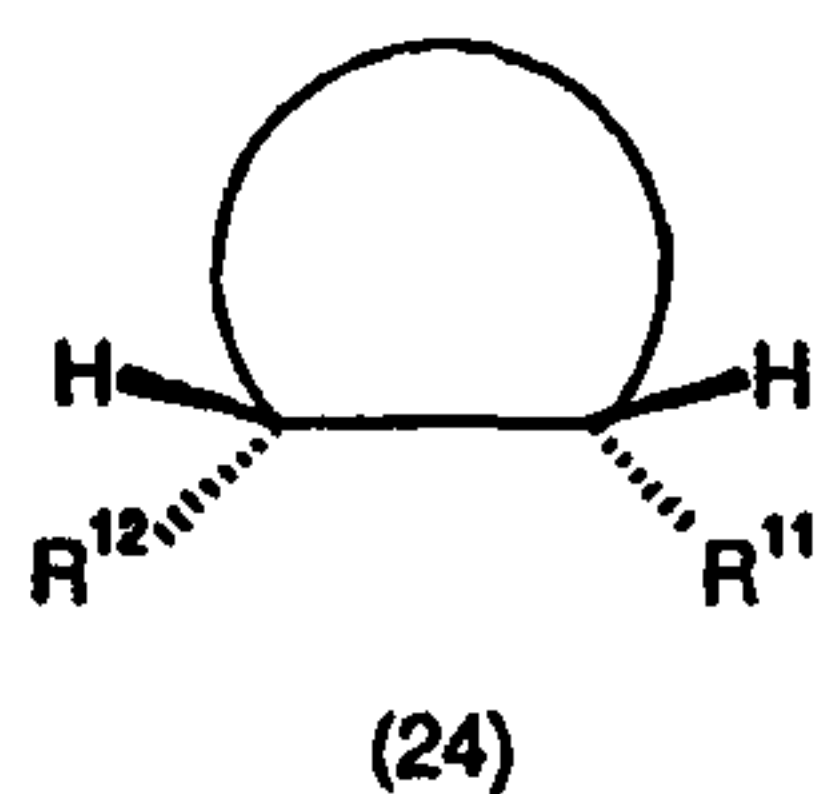
43. A process for preparing a chiral bicycloprolinate compound of formula 28



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comprising the steps of:

(a) cleaving and cyclizing a compound of formula 24



10

wherein:



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

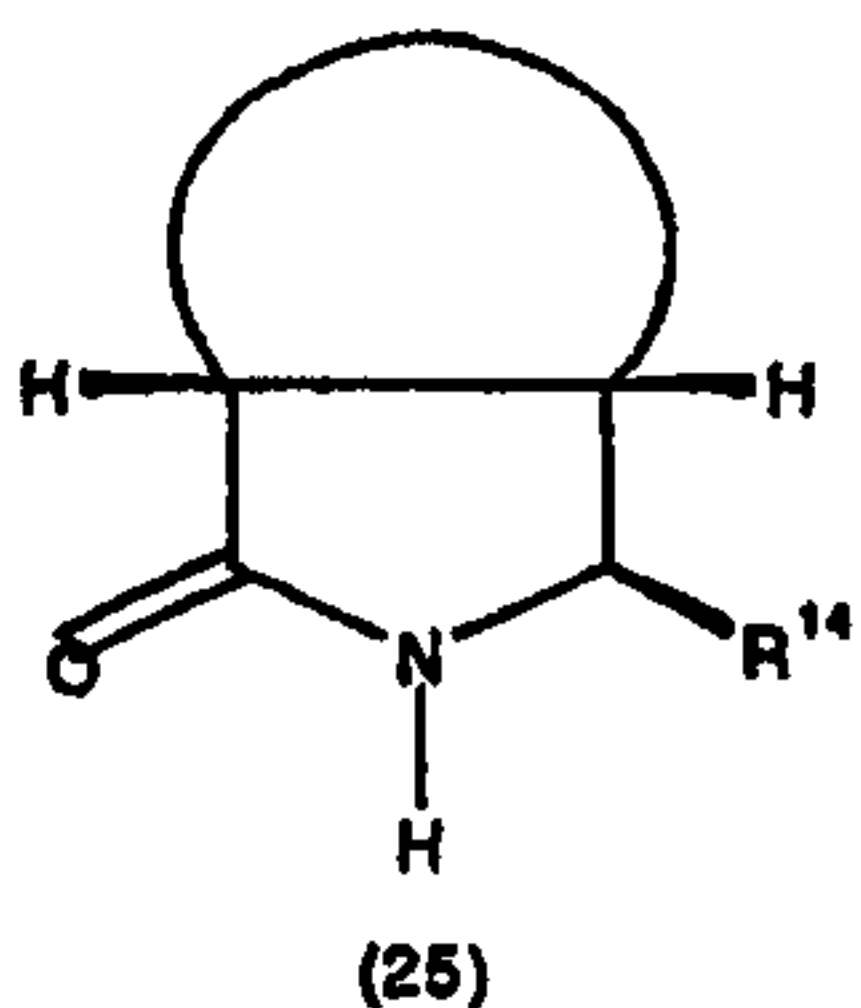
$R^{11}$  is  $-\text{CO}_2R^{13}$ ;

$R^{12}$  is an iminic glycinimide derivative adduct;

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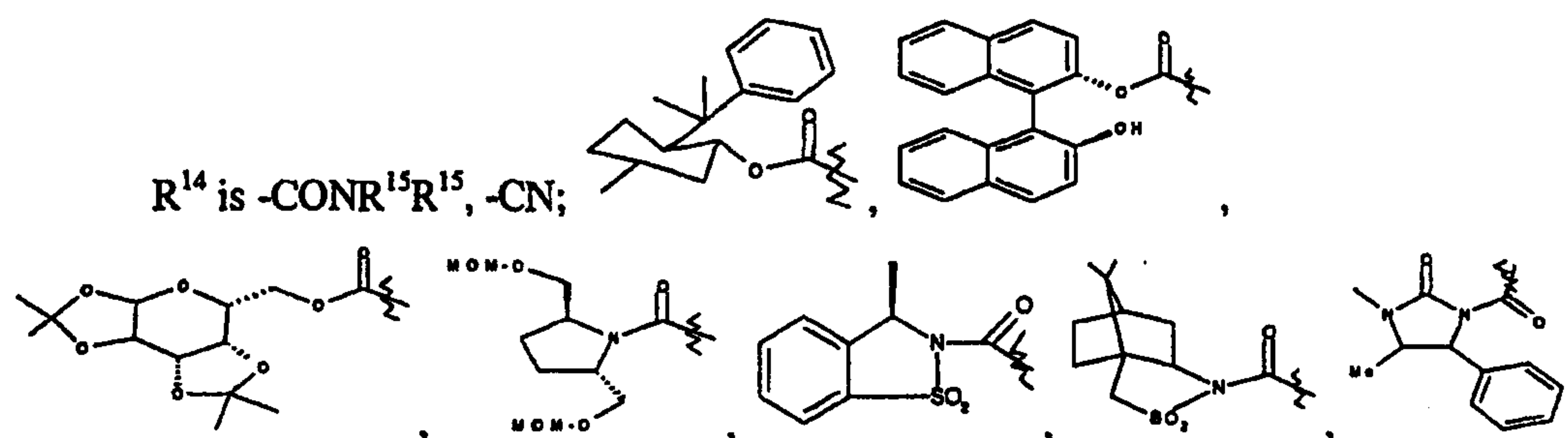
$R^{13}$  is acid protecting group or optionally substituted aliphatic group;

under cleaving and cyclizing conditions to form a compound of formula 25



wherein:

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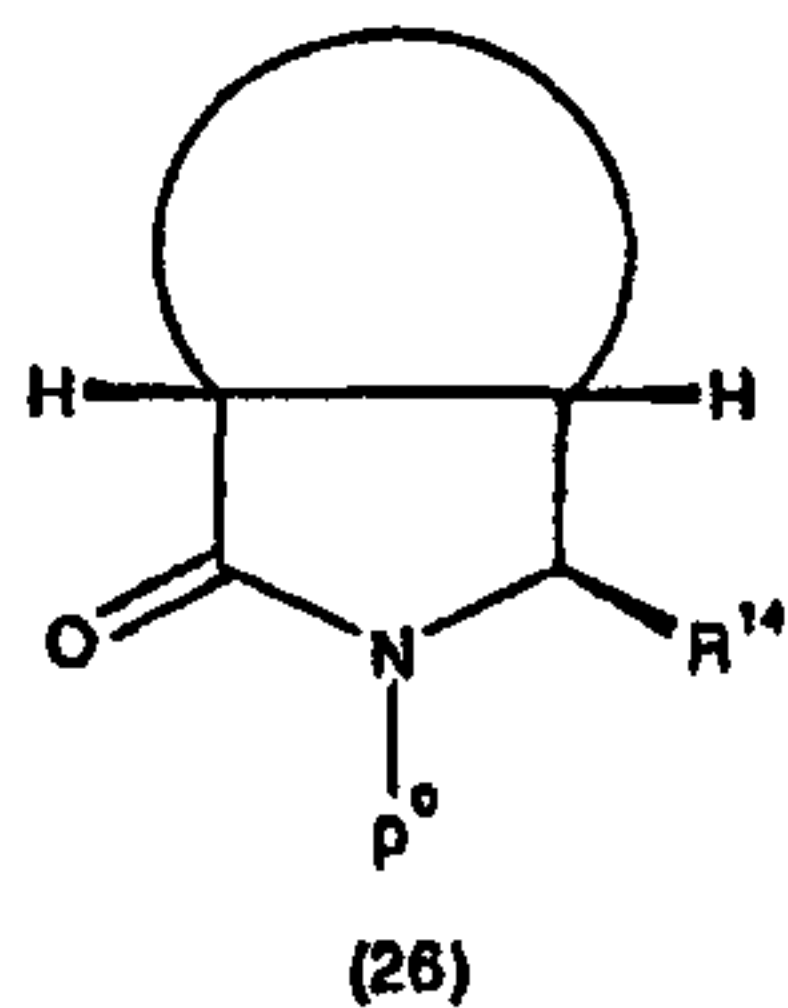


or  $-\text{CO}_2\text{R}^{16}$ ;

$R^{15}$  is optionally substituted aliphatic group;

5  $R^{16}$  is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group; and

(b) protecting the nitrogen of the lactam moiety in the compound of formula 25 with an amide protecting group to form a compound of formula 26

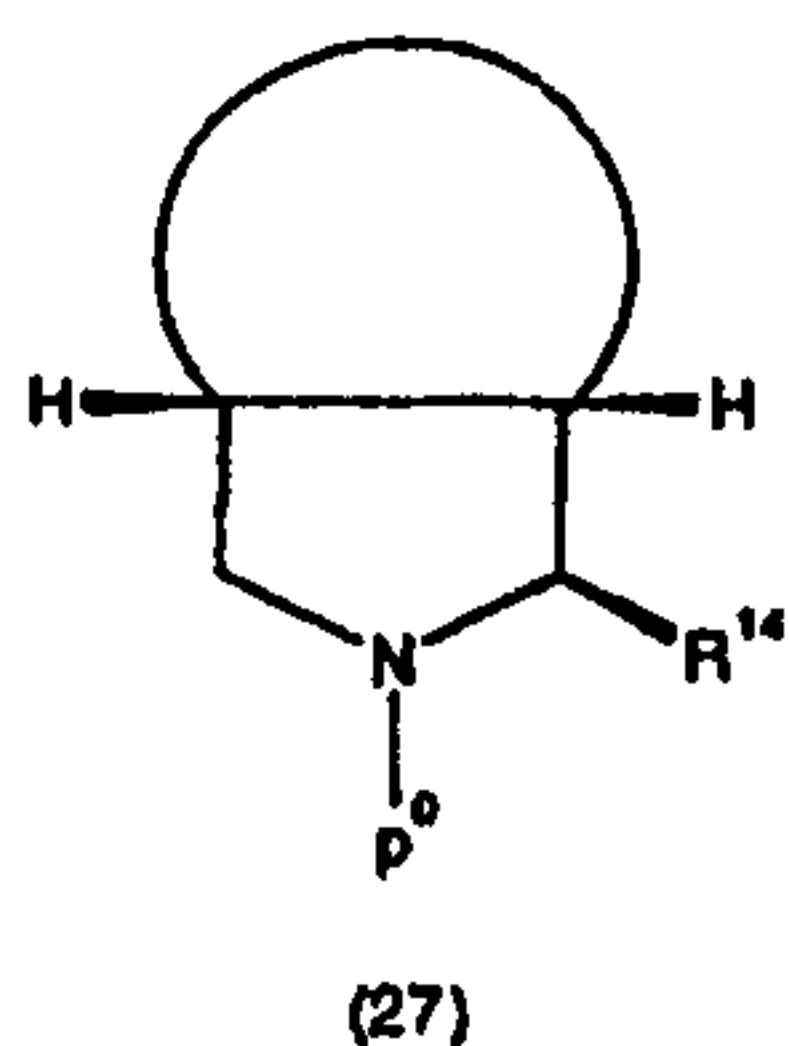


10 wherein:

$p^O$  is amide protecting group;

$R^{14}$  is as described herein; and

(c) reducing the compound of formula 26 under reducing conditions to form a compound of formula 27

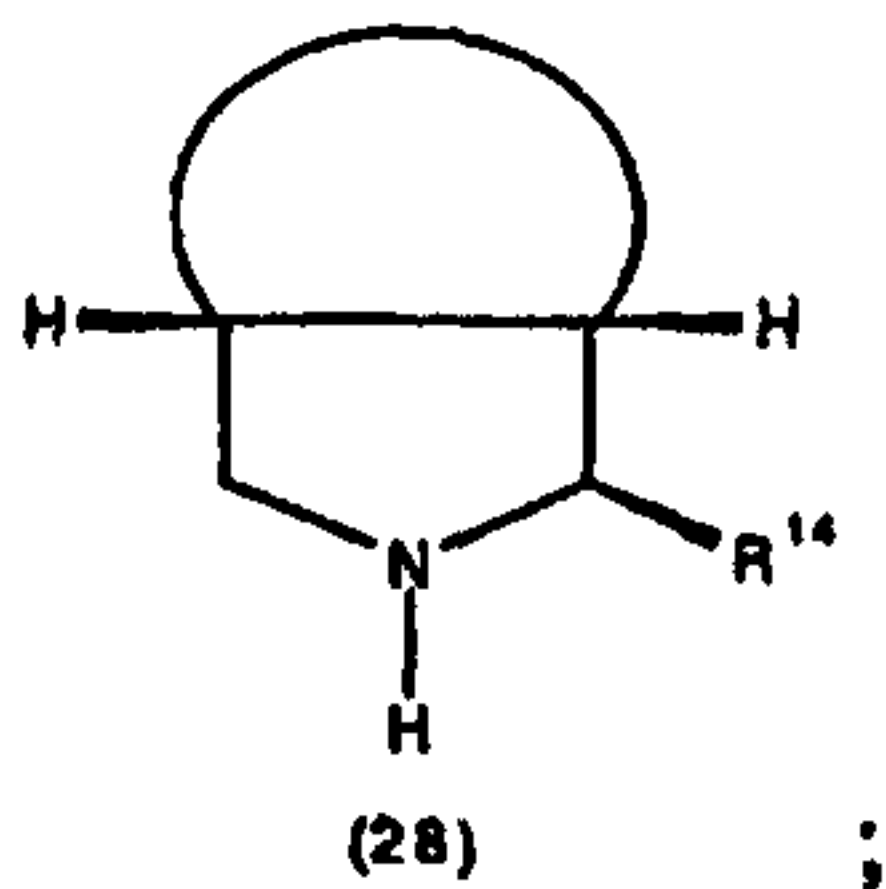


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wherein:

$p^O$  and  $R^{14}$  are as described herein; and

(d) deprotecting the compound of formula 27 under deprotecting conditions to form a compound of formula 28



wherein:

$R^{14}$  is as described herein.

44. A compound according to Claim 43 wherein:

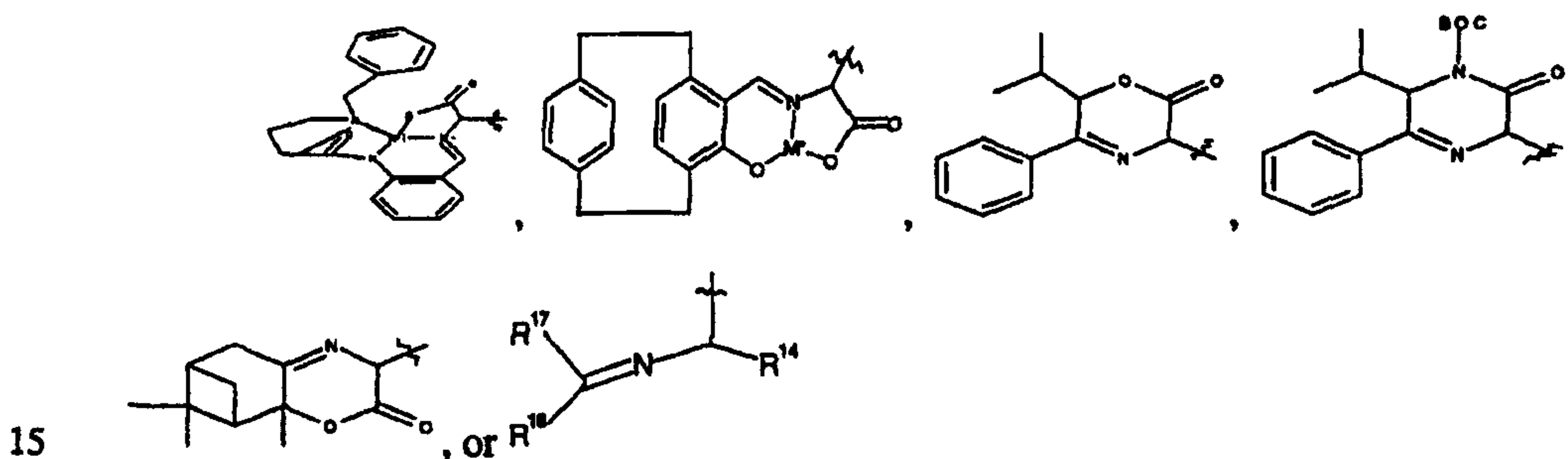
5 optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

optionally substituted aryl means an aromatic monocyclic or multicyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;

10 optionally substituted cycloalkyl means a non-aromatic mono- or multicyclic ring system of 3 to 10 carbon atoms optionally substituted with one or more ring group substituents;

optionally substituted fused arylcycloalkyl means a fused arylcycloalkyl optionally substituted with one or more ring group substituents;

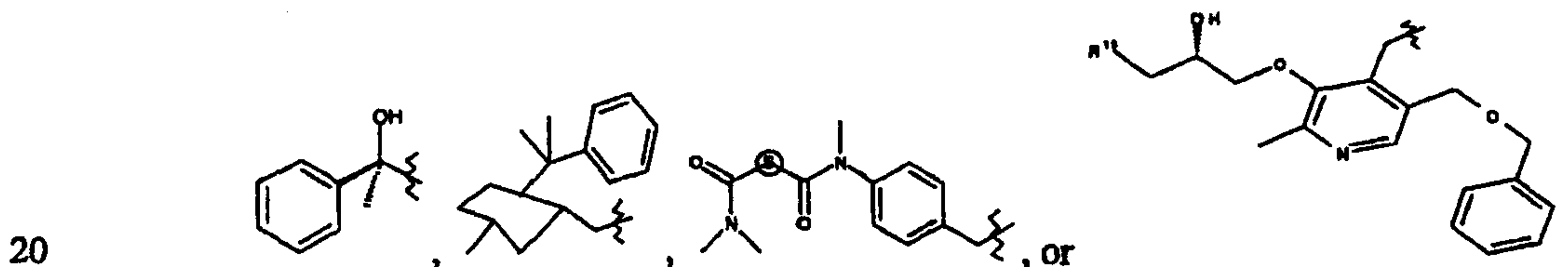
an iminic glycinimide derivative adduct is a compound selected from the group consisting of



wherein:

$R^{16}$  is an acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

$R^{17}$  is optionally substituted aryl, optionally substituted aliphatic group,



$R^{18}$  is hydrogen, alkyl, or alkylthio; or optionally substituted aryl;

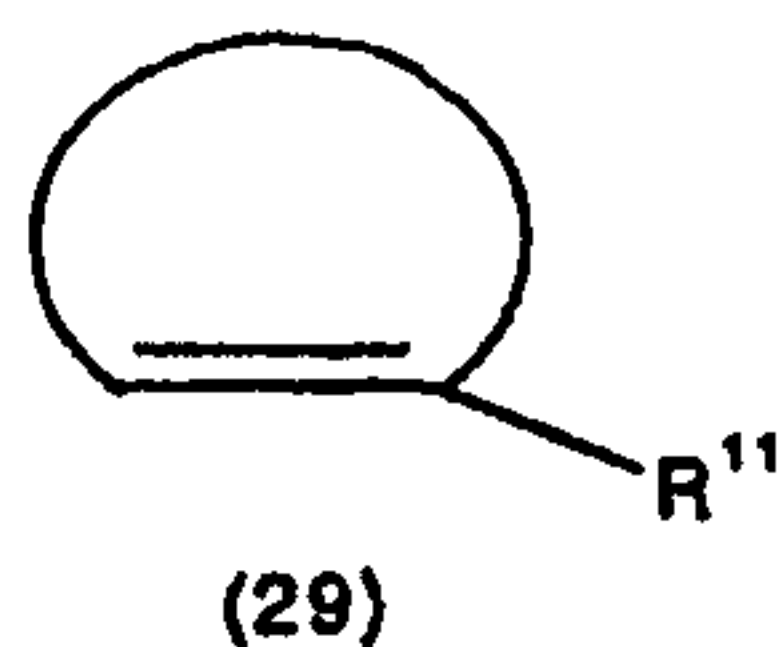
wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y<sup>1</sup>Y<sup>2</sup>N-, Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, wherein Y<sup>1</sup>, Y<sup>2</sup> and Y<sup>3</sup> are independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>N-, then one of Y<sup>1</sup> and Y<sup>2</sup> may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, as defined herein and the other of Y<sup>1</sup> and Y<sup>2</sup> is as defined previously, or for where the substituent is Y<sup>1</sup>Y<sup>2</sup>NC(O)-, Y<sup>1</sup>Y<sup>2</sup>NC(O)O-, Y<sup>1</sup>Y<sup>2</sup>NC(O)NY<sup>3</sup>- or Y<sup>1</sup>Y<sup>2</sup>NSO<sub>2</sub>-, Y<sup>1</sup> and Y<sup>2</sup> may also be taken together with the N atom through which Y<sup>1</sup> and Y<sup>2</sup> are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene (H<sub>2</sub>C=), oxo (O=) and thioxo (S=); and

aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH<sub>2</sub>OH, -C(O)-CH<sub>2</sub>SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl,

alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene ( $H_2C=$ ), oxo ( $O=$ ), thioxo ( $S=$ ),  $Y^1Y^2N-$ ,  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$ ,  $Y^1Y^2NSO_2-$ , or  $Y^3SO_2NY^1-$  wherein  $R^2$  is as defined herein,  $Y^1$  and  $Y^2$  are independently hydrogen, alkyl, aryl or heteroaryl, and  $Y^3$  is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is  $Y^1Y^2N-$ , then one of  $Y^1$  and  $Y^2$  may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, as defined herein and the other of  $Y^1$  and  $Y^2$  is as defined previously, or for where the substituent is  $Y^1Y^2NC(O)-$ ,  $Y^1Y^2NC(O)O-$ ,  $Y^1Y^2NC(O)NY^3-$  or  $Y^1Y^2NSO_2-$ ,  $Y^1$  and  $Y^2$  may also be taken together with the N atom through which  $Y^1$  and  $Y^2$  are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl.

45. The process of claim 44 further comprising the step wherein the compound of formula 24 is prepared by effecting a Michael addition with an iminic glycinimide compound on a compound of formula 29



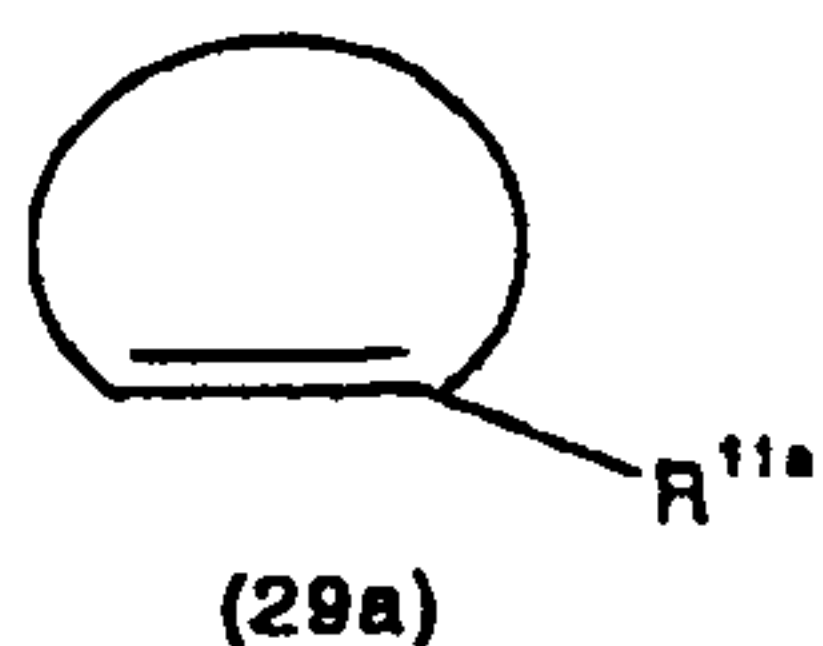
wherein:



is optionally substituted cycloalkenyl or optionally substituted fused arylcycloalkenyl;

wherein:

the compound of formula 29 may be prepared by esterifying a compound of formula 29a



wherein:

$R^{11a}$  is  $-CHO$ ,  $-COR^{15}$ ,  $-C\equiv N$ , or  $-CONR^{15}R^{15}$ .

46. The process of claim 45 wherein the process is carried out at a temperature between  $0^\circ C$  and  $-78^\circ C$ .

47. The process of claim 46 wherein the process is carried out at  $-60^\circ$ .

48. The process of claim 47 wherein the process is catalyzed by a chiral phase transfer catalyst.
49. The process of claim 47 wherein the process is catalyzed by a nonchiral phase transfer catalyst.
- 5 50. The process of any one of claims 43 to 49 wherein the protecting group is BOC.
51. The process of claim 50 wherein the iminic glycinimide is (N-diphenylmethylene)-glycine tert-butyl ester.
52. The process of claim 50 wherein the compound of formula 29 is 1-carboxy-1-cyclopentene methyl ester.

Figure 1.

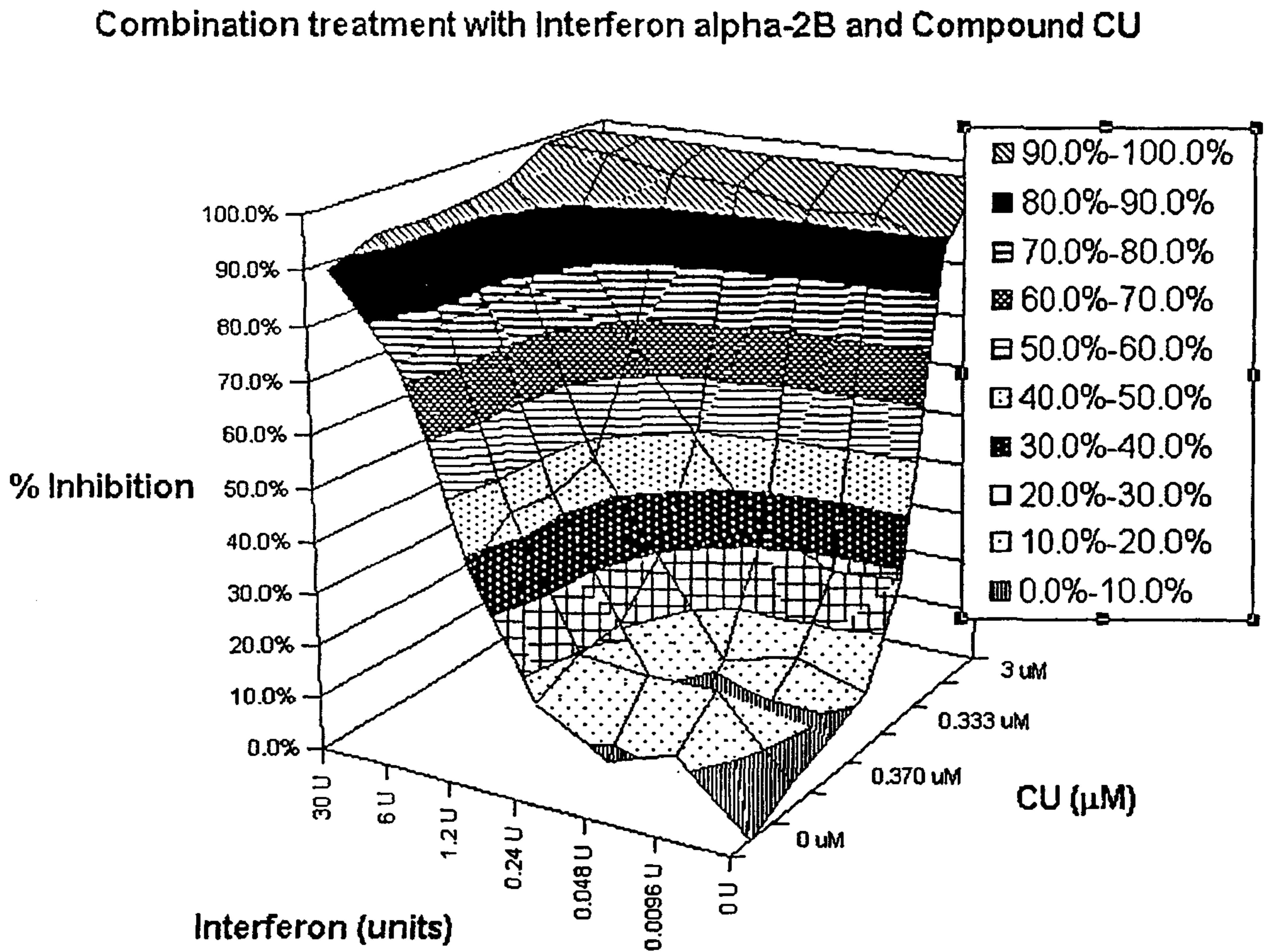


Fig 2.

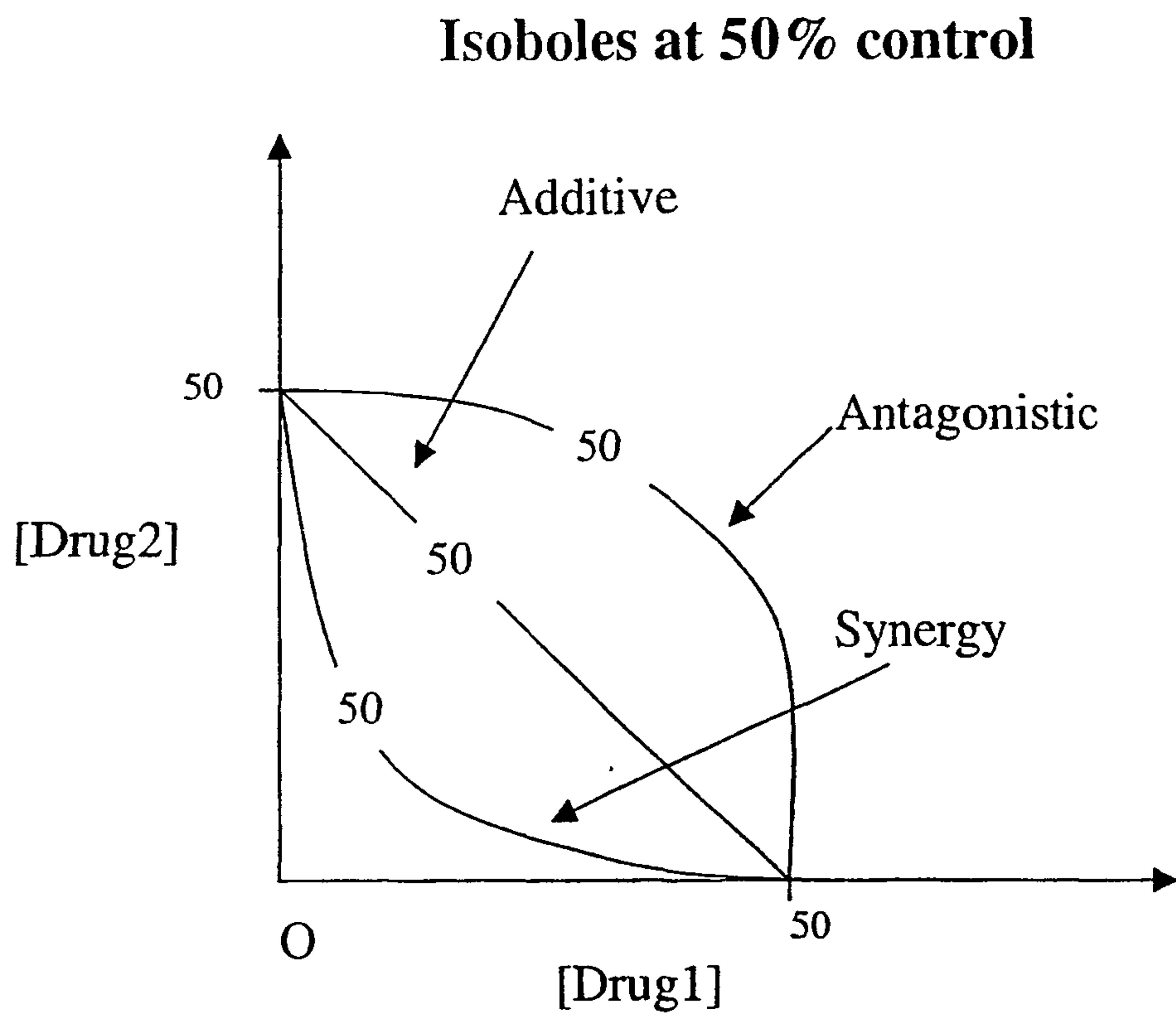


Fig. 3.

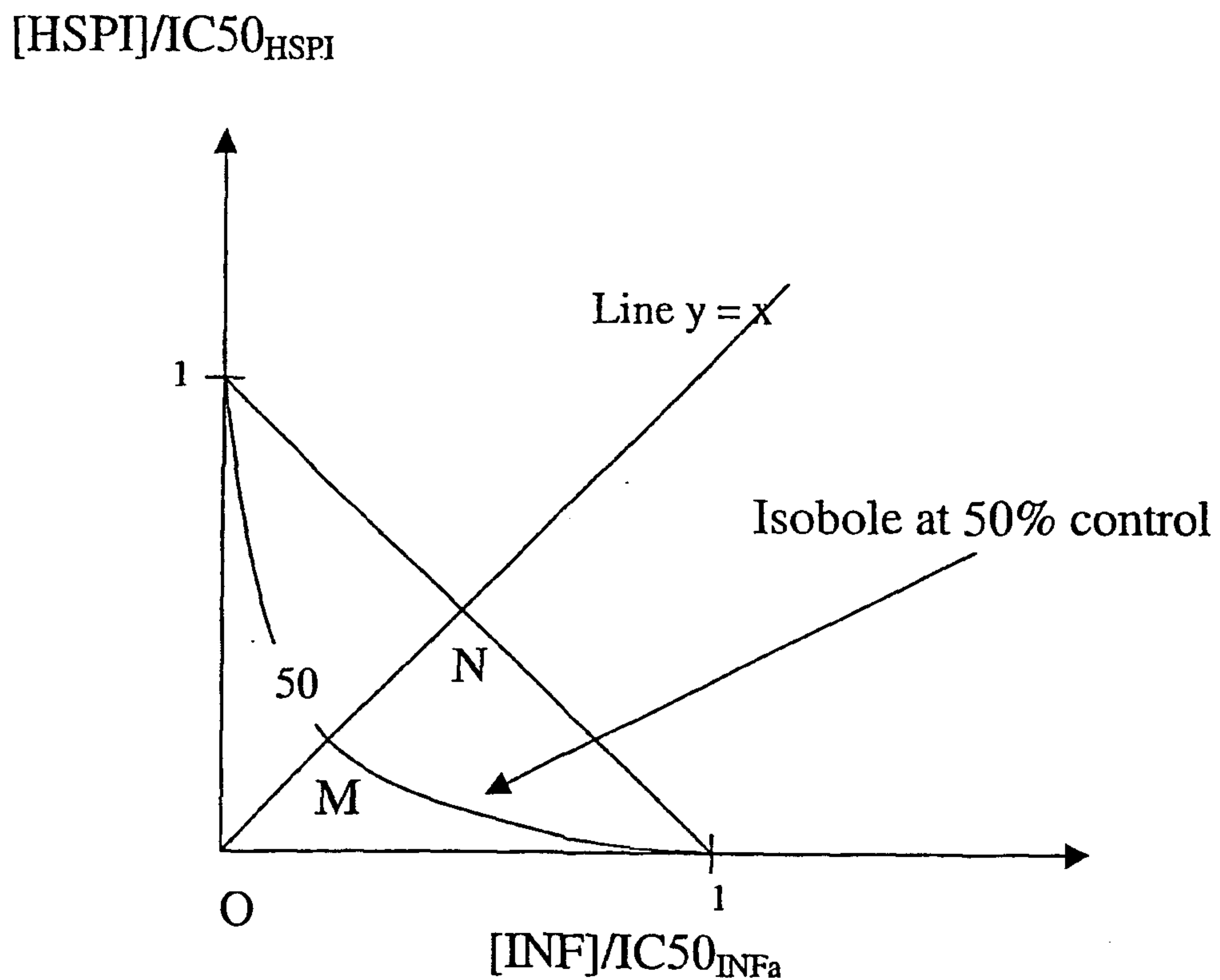


Fig. 4.

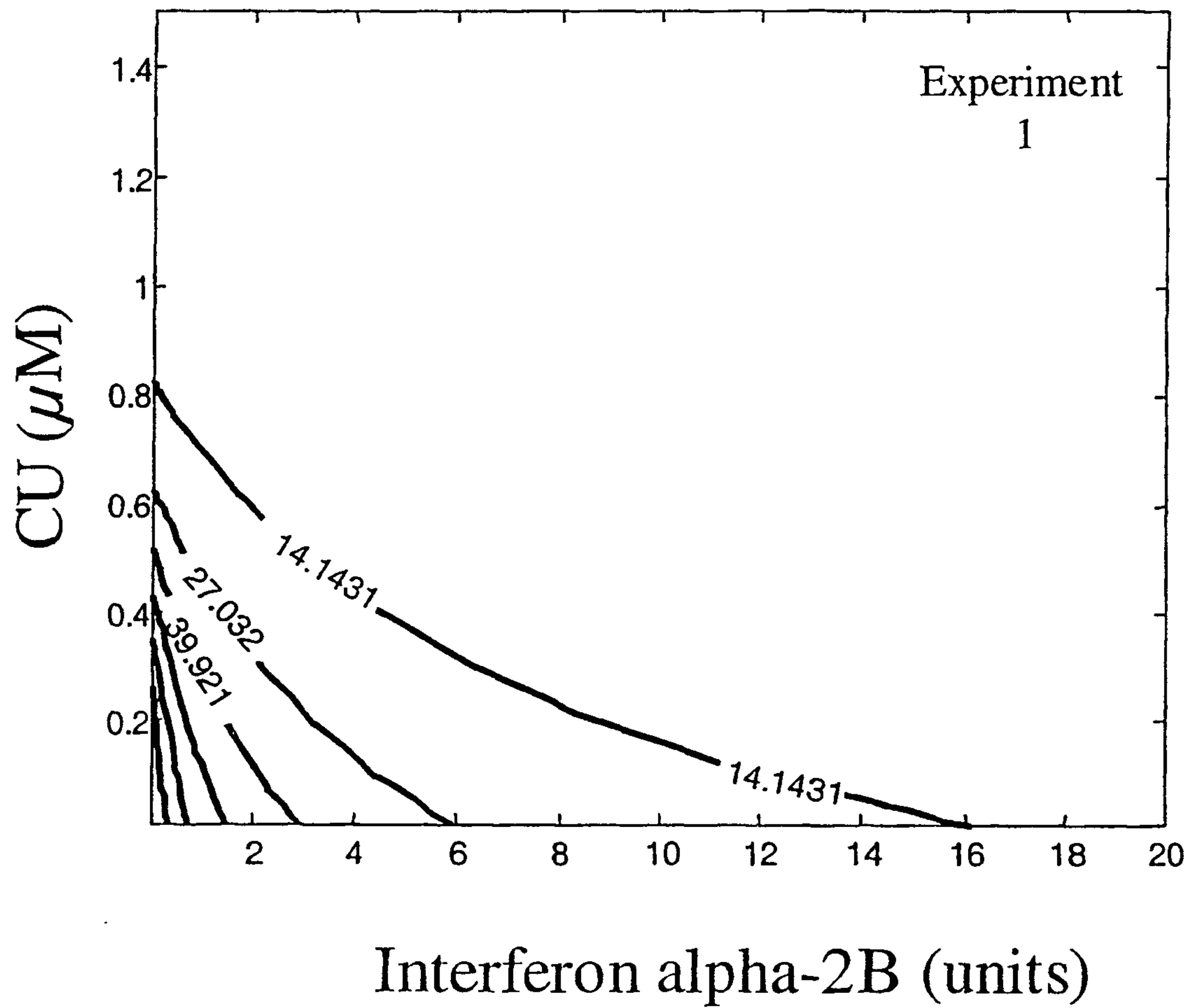


Fig. 5

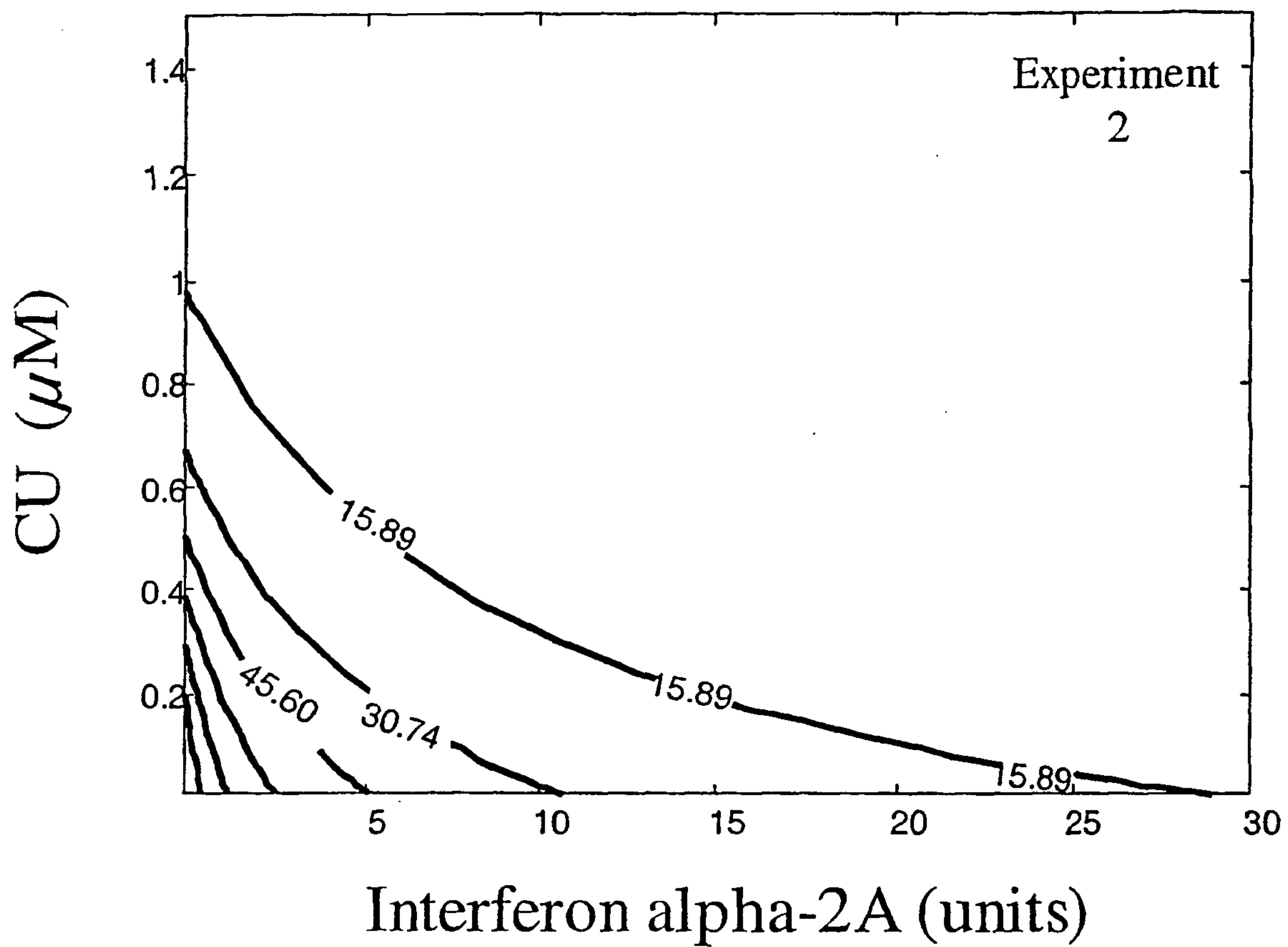


Fig. 6

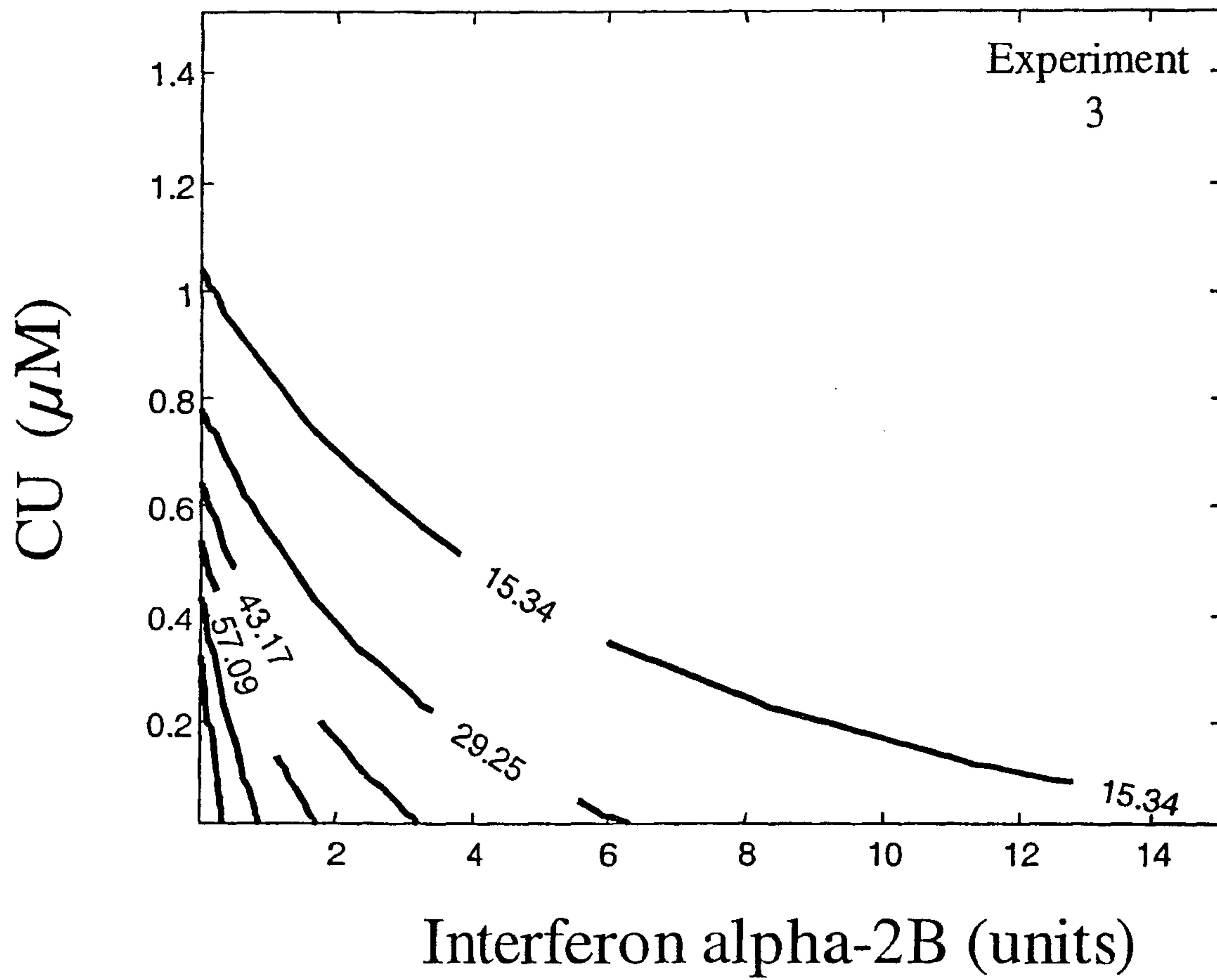


Fig. 7

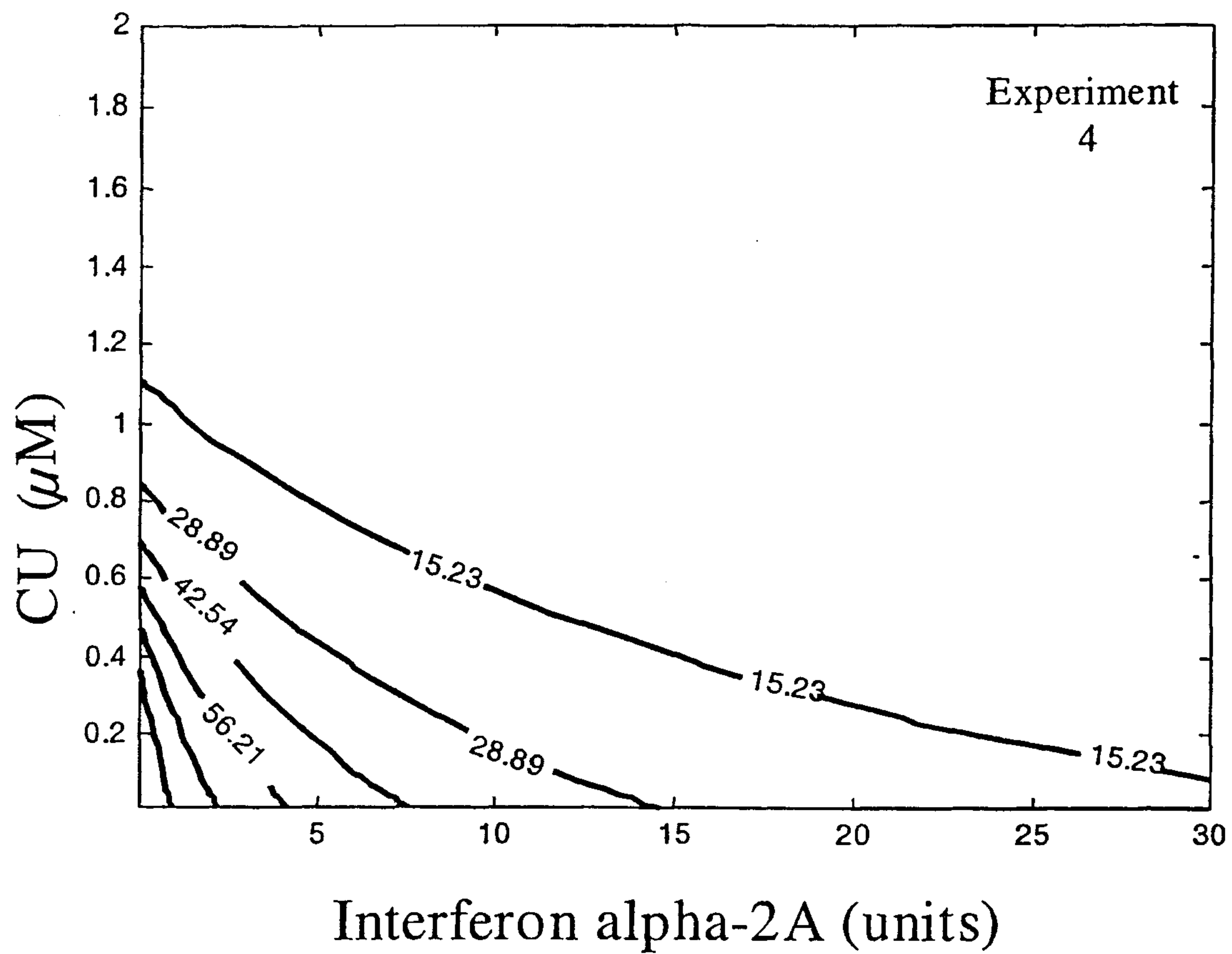


Fig. 8.

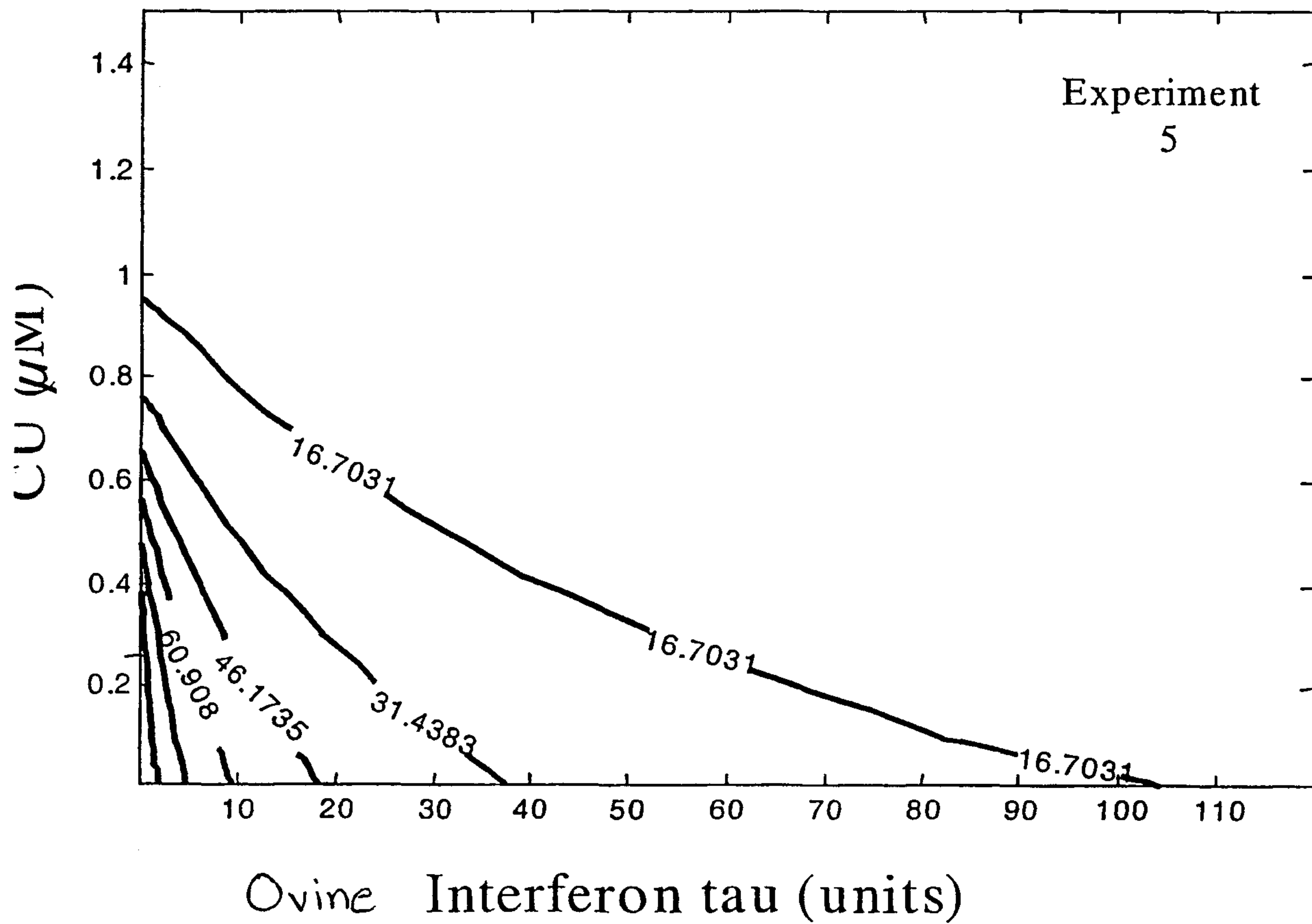


Fig 9.

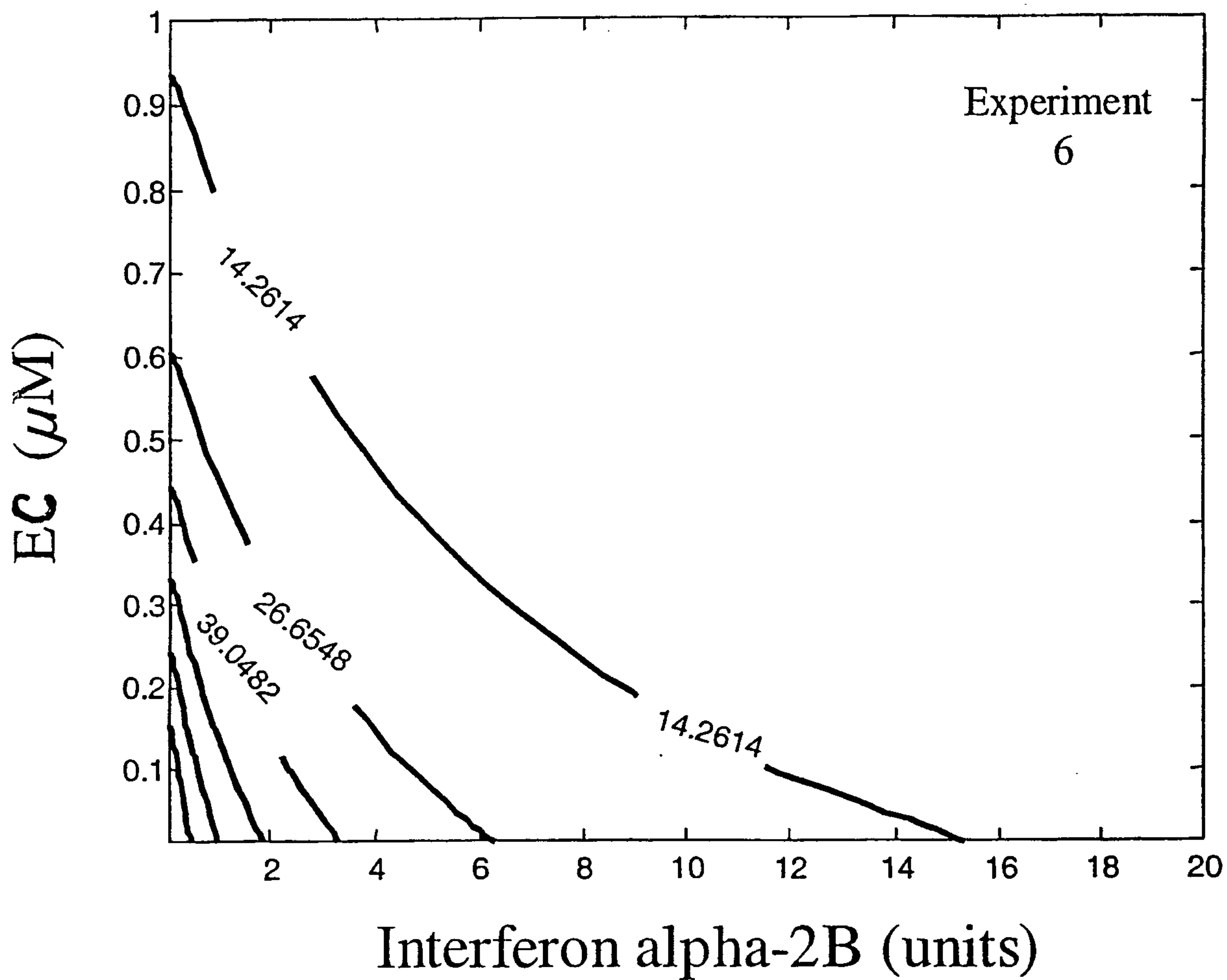


Fig. 10.

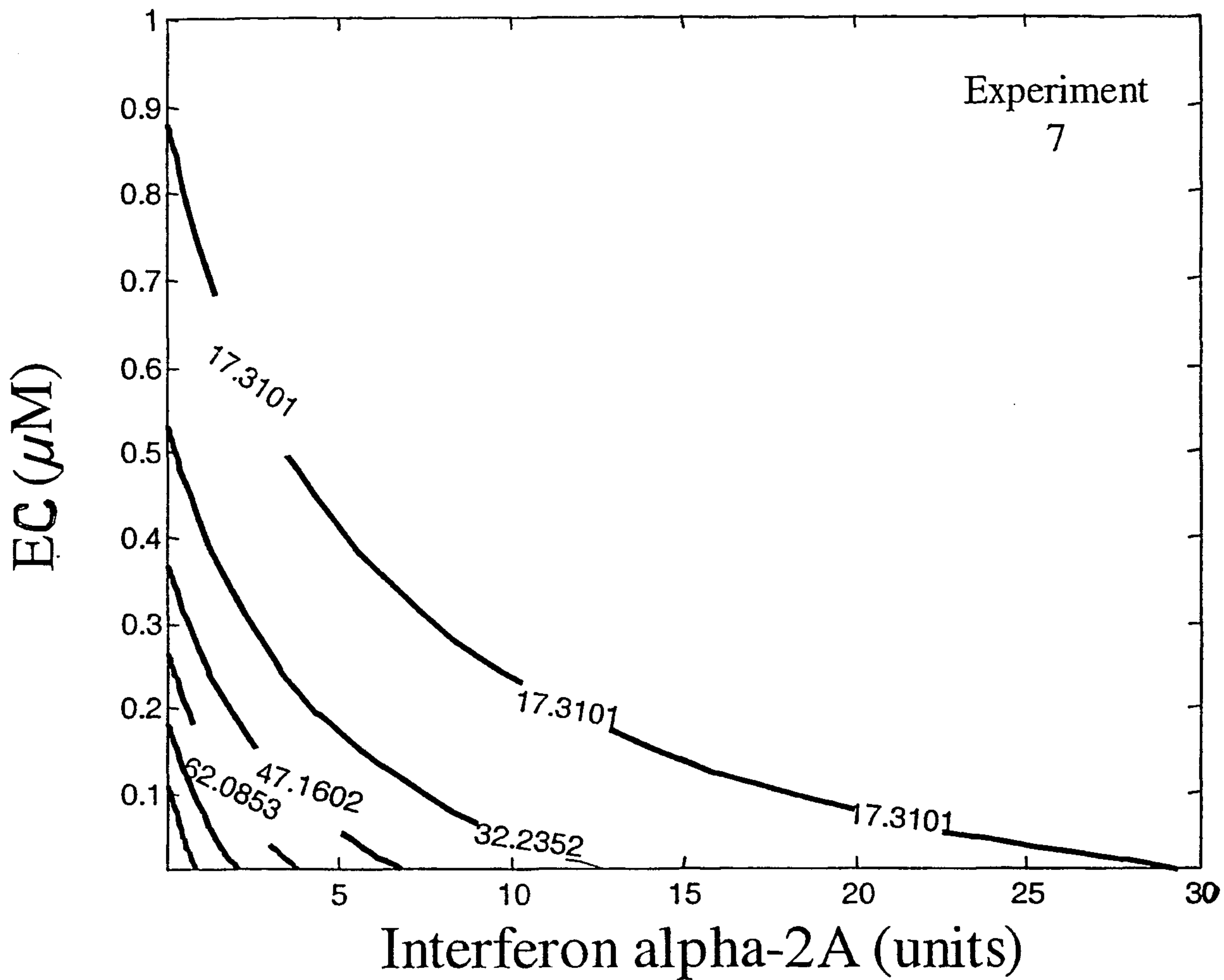


Fig 11.

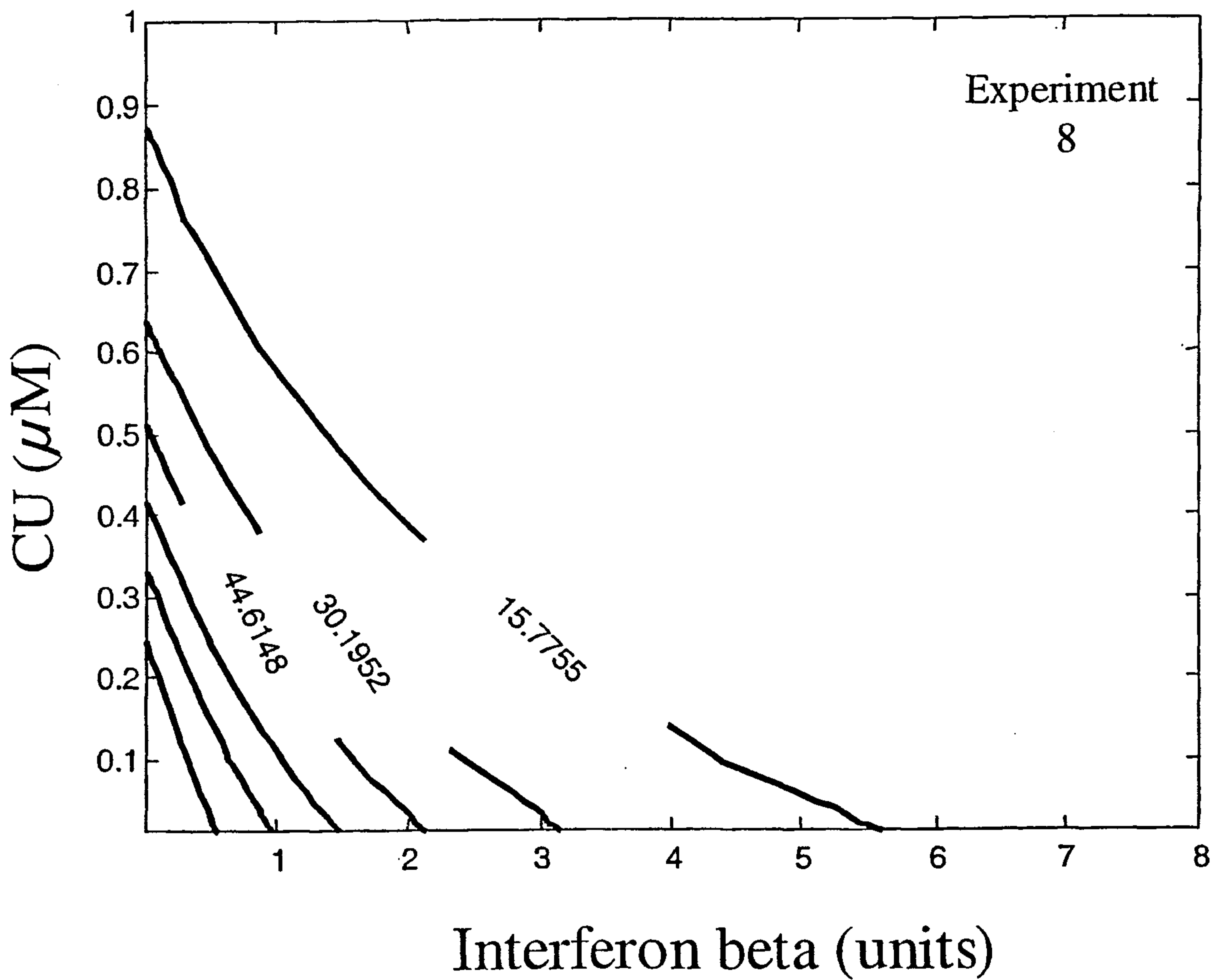


Fig. 12.

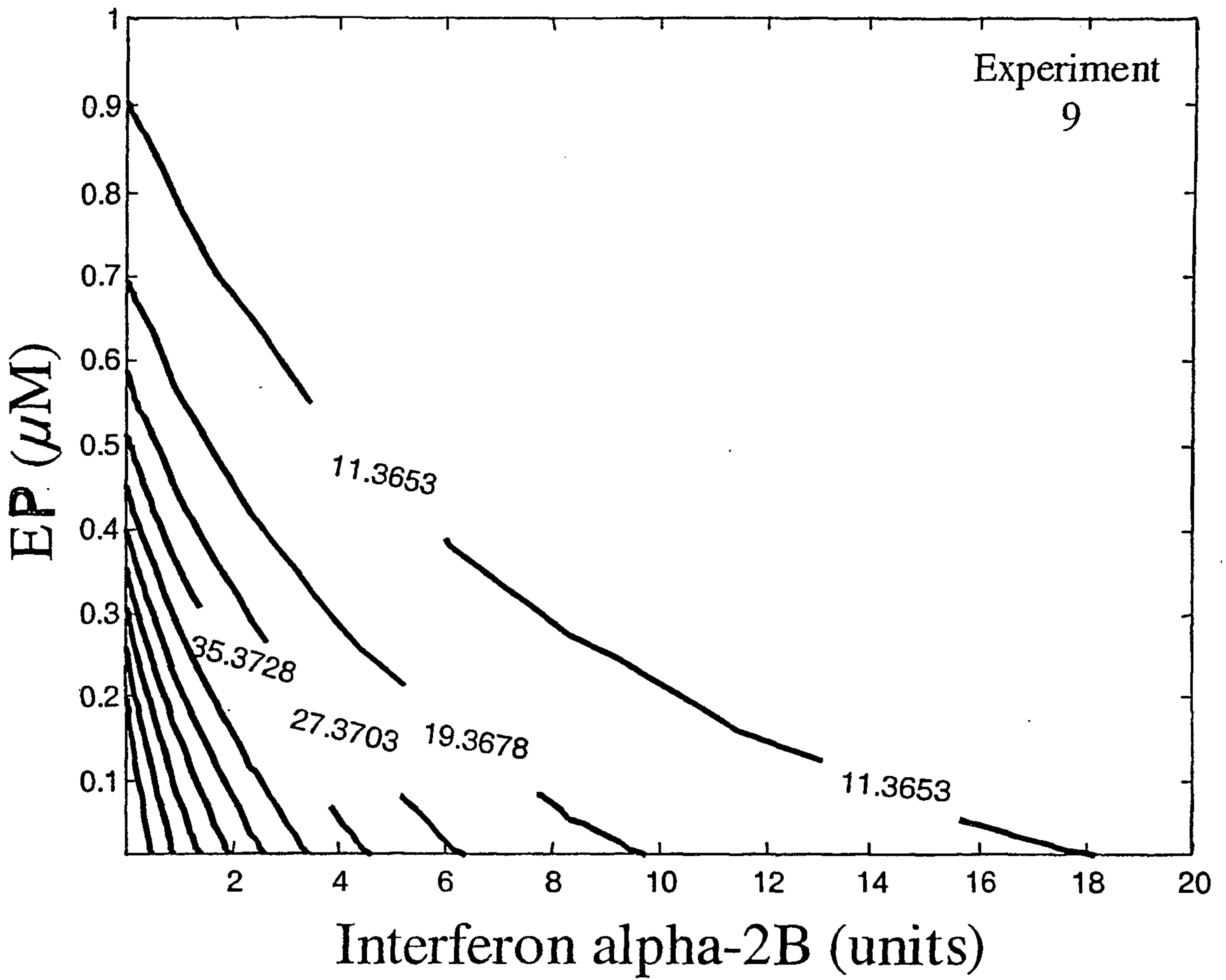


Fig 13.

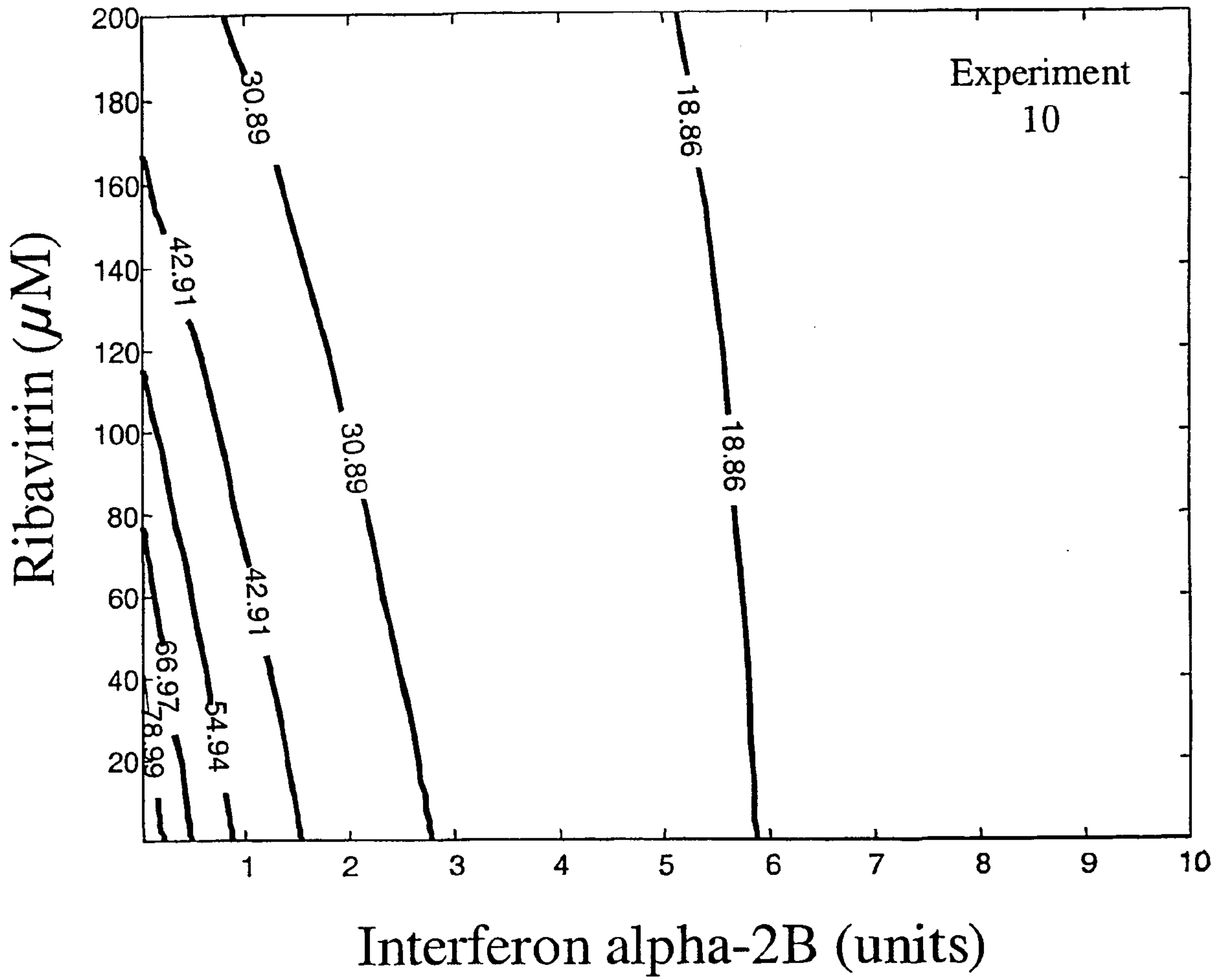
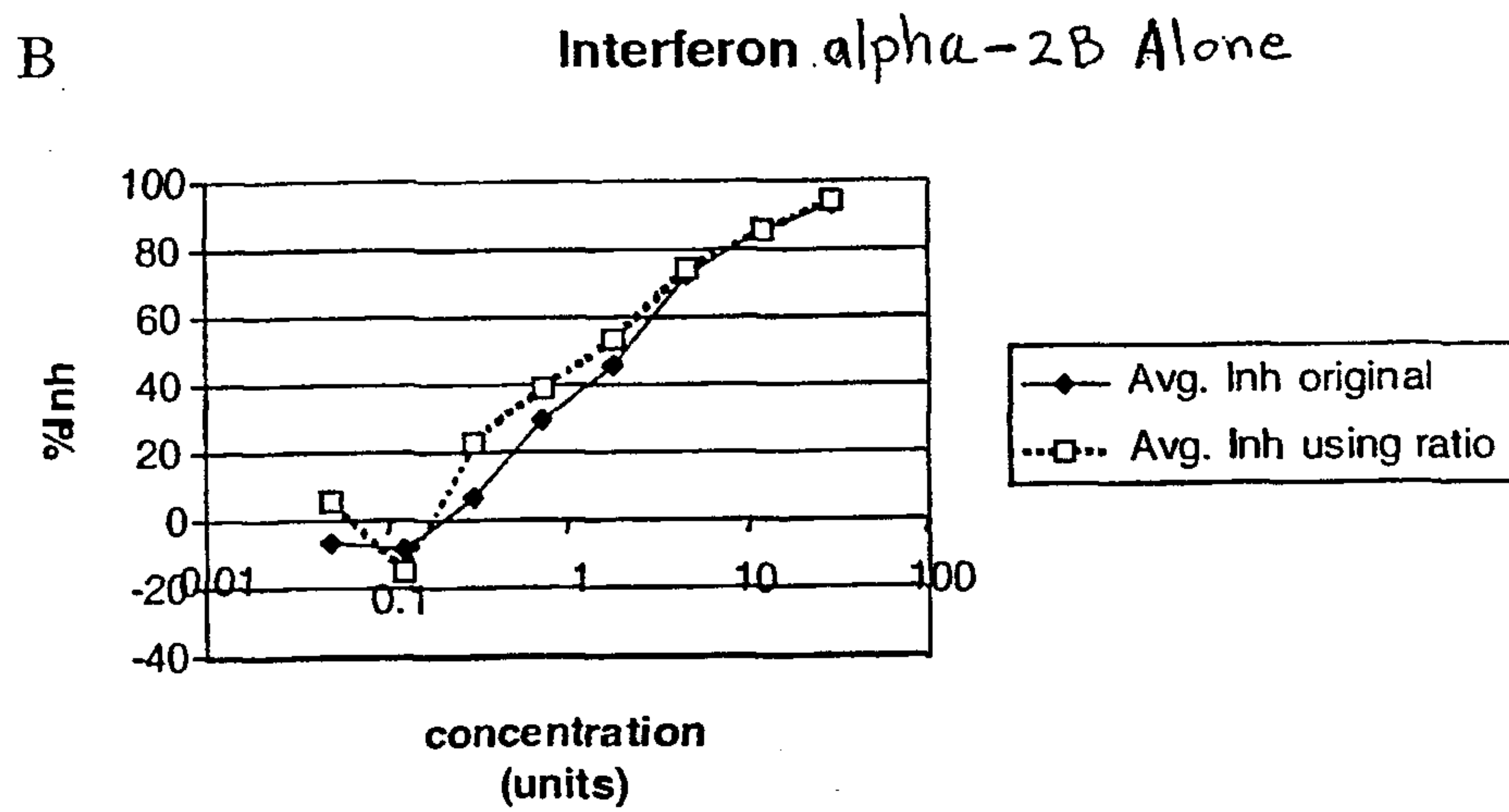
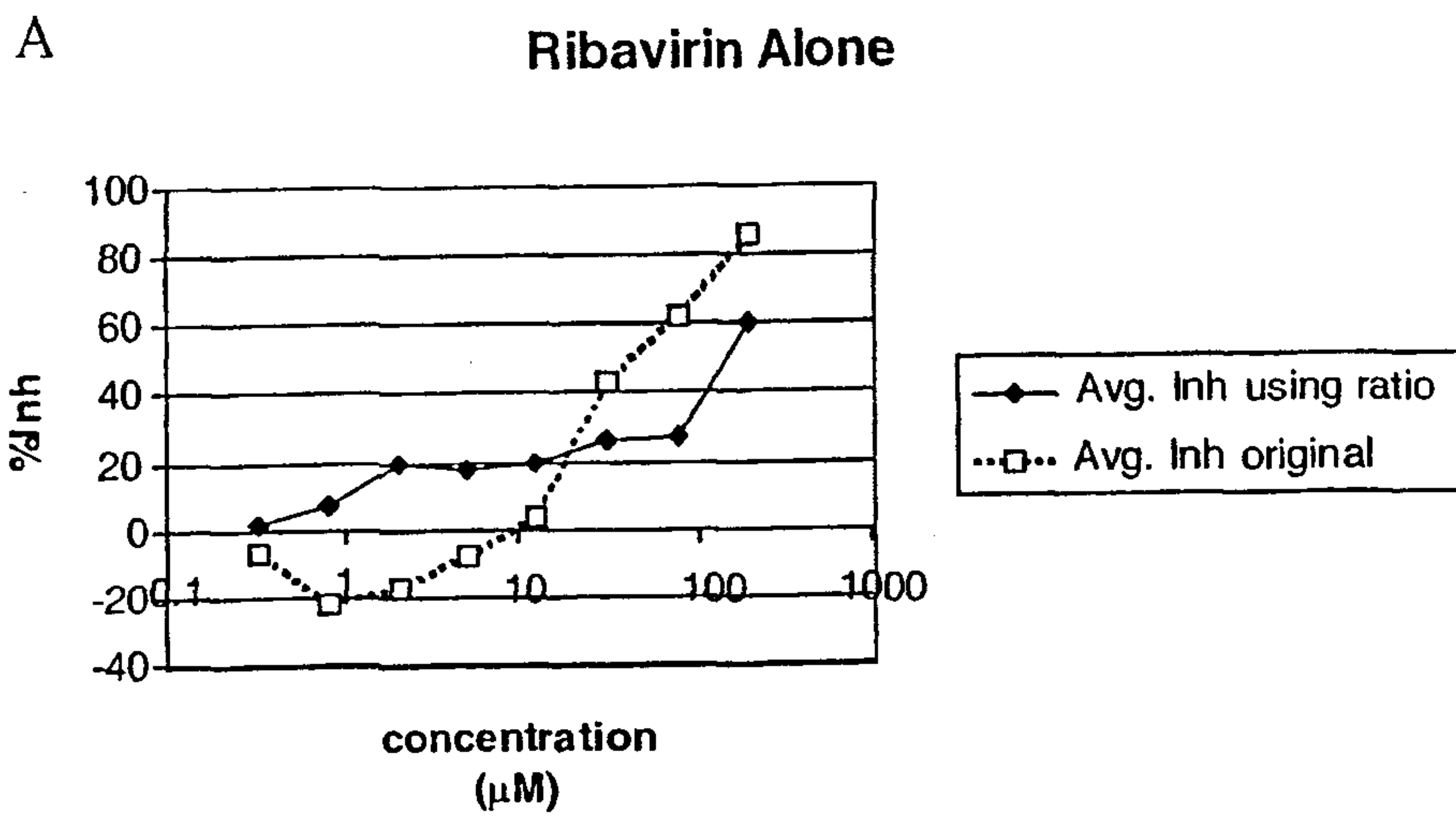


Fig. 14



# Combination treatment with Interferon alpha-2B and Compound CU

