



(19) REPUBLIKA HRVATSKA
DRŽAVNI ZAVOD ZA
INTELEKTUALNO VLASNIŠTVO

(10) Identifikator
dokumenta:



HR P20110657 T1

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(12) **PRIJEVOD PATENTNIH ZAHTJEVA
EUROPSKOG PATENTA**

(51) MKP:

C07K 16/24 (2006.01)
A61K 39/395 (2006.01)
G01N 33/53 (2006.01)

(46) Datum objave prijevoda patentnih zahtjeva: 31.10.2011.

(21) Broj predmeta: P20110657T

(22) Datum podnošenja zahtjeva u HR: 13.09.2011.

(86) Broj međunarodne prijave: PCT/GB2005001147
Datum podnošenja međunarodne prijave: 29.03.2005.

(96) Broj europske prijave patenta: EP 05733043.3
Datum podnošenja europske prijave patenta: 29.03.2005.

(87) Broj međunarodne objave: WO 2005095457
Datum međunarodne objave: 13.10.2005.

(97) Broj objave europske prijave patenta: EP 1730191 A2
Datum objave europske prijave patenta: 13.12.2006.

(97) Broj objave europskog patenta: EP 1730191 B1
Datum objave europskog patenta: 06.07.2011.

(31) Broj prve prijave: 0407197
0407193

(32) Datum podnošenja prve prijave: 30.03.2004.
30.03.2004.

(33) Država ili organizacija podnošenja prve prijave: GB
GB

(73) Nositelj patenta:

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(74) Zastupnik:

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(54) Naziv izuma: **IMUNOGLOBULIN KOJI SE VEŽE NA OSM**

HR P20110657 T1

PATENTNI ZAHTJEVI

- 5 1. Protutijelo, ili njegov antigenski vežući fragment, **naznačeno time** što se specifično veže na hOSM i sadrži sljedeće CDR-ove:
 CDRH1 sa SEQ.I.D.NO:1
 CDRH2 sa SEQ.I.D.NO:2
 CDRH3 sa SEQ.I.D.NO:3
 10 CDRL1 sa SEQ.I.D.NO:4
 CDRL2 sa SEQ.I.D.NO:5
 CDRL3 sa SEQ.I.D.NO:6.
2. Protutijelo, ili njegov antigenski vežući fragment, u skladu s patentnim zahtjevom 1, **naznačeno time** što terapijsko protutijelo, ili njegov antigenski vežući fragment, modulira međudjelovanje između OSM i gp130.
- 15 3. Protutijelo, ili njegov antigenski vežući fragment, u skladu s patentnim zahtjevima 1 ili 2, **naznačeno time** što protutijelo se bira iz skupine koju čine: cjelovito, kimerno, humanizirano, bispecifično, te heterokonjugirano.
4. Protutijelo u skladu s patentnim zahtjevom 3, **naznačeno time** što protutijelo je cjelovito protutijelo.
5. Protutijelo u skladu s patentnim zahtjevom 4, **naznačeno time** što cjelovito protutijelo je mišje, štakorsko, kuniće, primatsko ili ljudsko.
- 20 6. Protutijelo u skladu s patentnim zahtjevom 5, **naznačeno time** što cjelovito protutijelo je ljudsko.
7. Protutijelo u skladu s patentnim zahtjevom 3, **naznačeno time** što protutijelo je kimerno ili humanizirano.
8. Protutijelo u skladu s patentnim zahtjevom 7, **naznačeno time** što protutijelo je humanizirano.
9. Protutijelo u skladu s patentnim zahtjevom 8, **naznačeno time** što ostaci 28, 29, 30, 71 i 94 u okosnici ljudskog akceptorskog varijabilnog teškog lanca i položaji 49 i 71 u okosnici ljudskog akceptorskog varijabilnog lakog lanca su zamijenjeni odgovarajućim ostacima u okosnici donorskog protutijela, odakle je dobiven CDRH3.
- 25 10. Protutijelo u skladu s patentnim zahtjevom 9, **naznačeno time** što okosnica ljudskog teškog lanca sadrži sljedeće ostatke:

Položaj	Ostaci
28	S
29	L
30	T
71	K
94	K

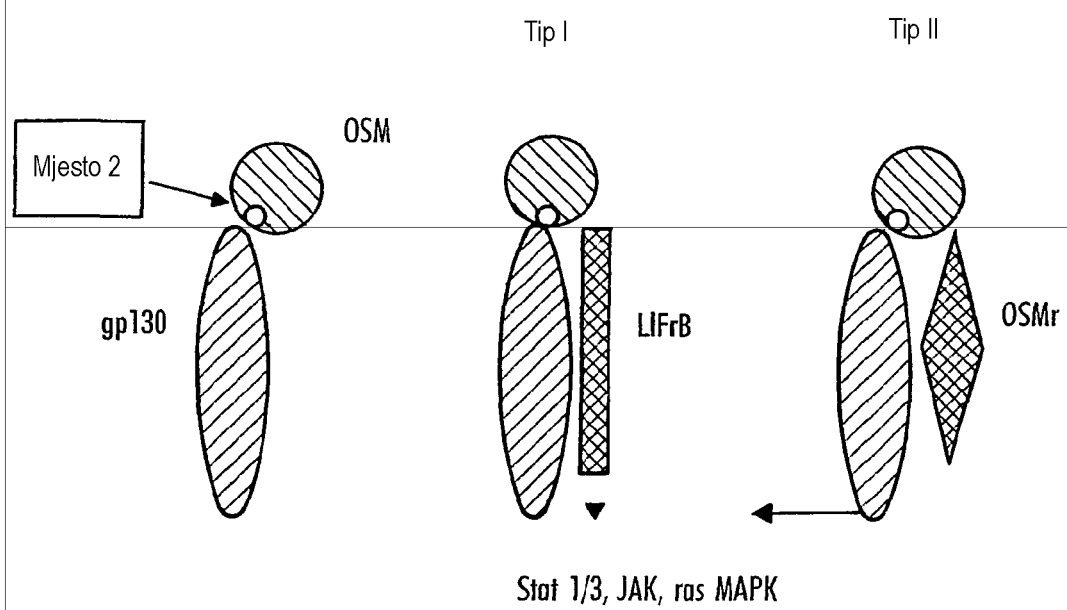
- 30 a ljudski laki lanac sadrži sljedeće ostatke:

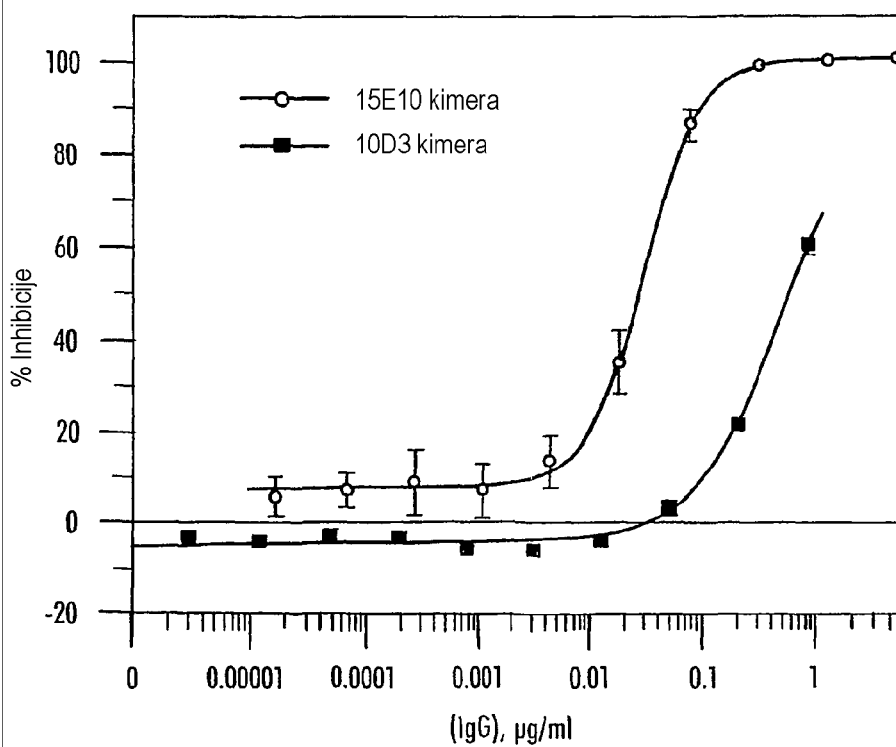
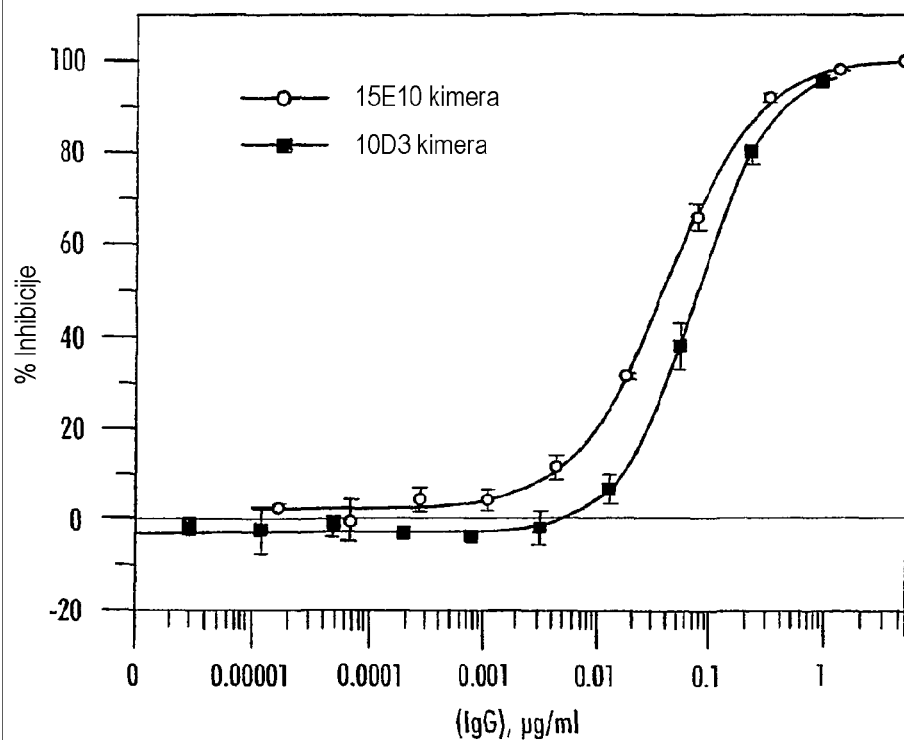
Položaj	Ostaci
49	E
71	Y

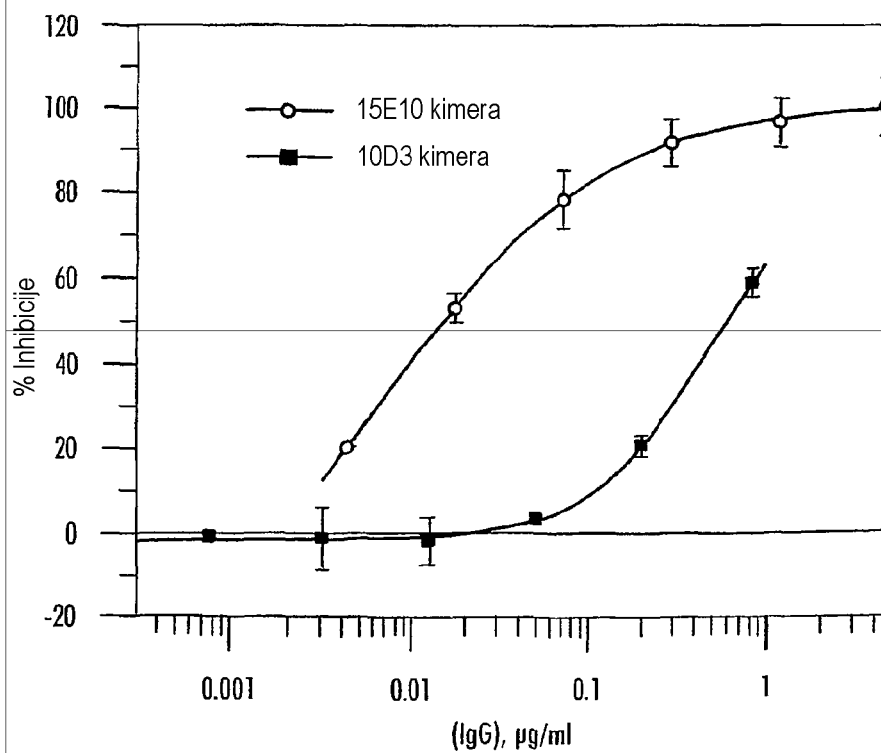
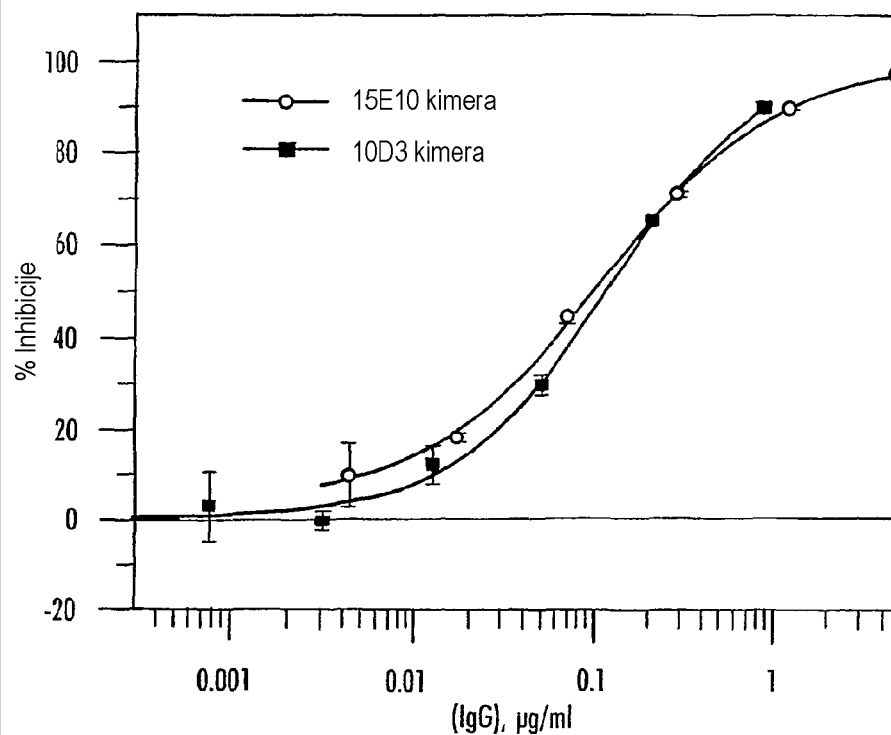
11. Protutijelo u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačeno time** što sadrži V_H domenu sa SEQ.I.D.NO:9 i V_L domenu sa SEQ.I.D.NO:10.
12. Protutijelo u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačeno time** što sadrži teški lanac sa SEQ.I.D.NO:11 i laki lanac sa SEQ.I.D.NO:12.
- 35 13. Protutijelo u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačeno time** što dodatno sadrži konstantno područje ljudskog teškog lanca, koje se bira iz skupine koju čine: IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, IgM.
14. Protutijelo u skladu s patentnim zahtjevom 13, **naznačeno time** što konstantno područje je IgG izotipa, primjerice IgG1 ili IgG4.
- 40 15. Protutijelo u skladu s patentnim zahtjevom 14, **naznačeno time** što konstantno područje je IgG1.
16. Protutijelo u skladu s patentnim zahtjevom 15, **naznačeno time** što konstantno područje je mutirano, kako bi se protutijelo učinilo nelitičkim.
17. Protutijelo, ili njegov antigenski vežući fragment, u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačeno time** što navedeno protutijelo, ili njegov antigenski vežući fragment, modulira međudjelovanje između Mjesta II u hOSM i gp130.
- 45 18. Protutijelo, ili njegov antigenski vežući fragment, u skladu s patentnim zahtjevom 17, **naznačeno time** što navedeno protutijelo inhibira navedeno međudjelovanje.
19. Protutijelo, ili njegov antigenski vežući fragment, u skladu s patentnim zahtjevom 18, **naznačeno time** što navedeno protutijelo blokira navedeno međudjelovanje.
- 50 20. Antigenski vežući fragment u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačen time** što se navedeni fragment bira iz skupine koju čine: Fab, Fab', Fd, F(ab)₂, ScFv.

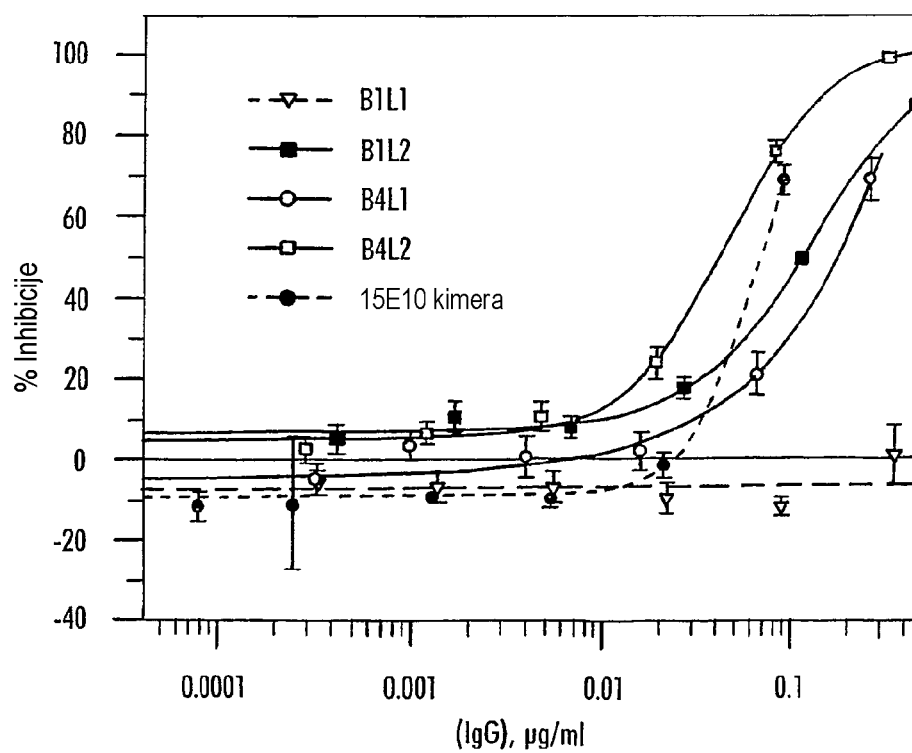
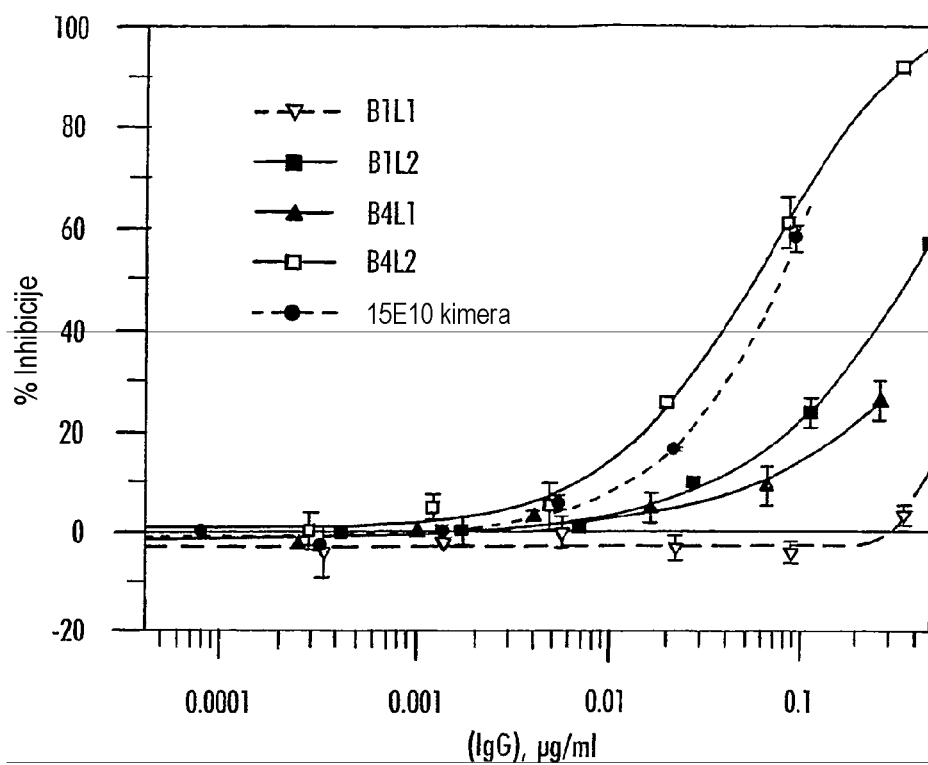
21. Farmaceutski pripravak, **naznačen time** što sadrži protutijelo, ili njegov antigenski vežući fragment, u skladu s bilo kojim od prethodnih patentnih zahtjeva.
22. Farmaceutski pripravak u skladu s patentnim zahtjevom 21, **naznačen time** što je namijenjen upotrebi u liječenju reumatoidnog artritisa i/ili osteoartritisa.
- 5 23. Farmaceutski pripravak u skladu s patentnim zahtjevom 21, **naznačen time** što je namijenjen upotrebi u liječenju COPD.
24. Farmaceutski pripravak u skladu s patentnim zahtjevom 21, **naznačen time** što je namijenjen upotrebi u liječenju psorijaze.
- 10 25. Farmaceutski pripravak u skladu s patentnim zahtjevom 21, **naznačen time** što je namijenjen upotrebi u liječenju ateroskleroze.
26. Upotreba protutijela, ili antigenski vežućeg fragmenta, u skladu s bilo kojim od patentnih zahtjeva 1 do 20, **naznačena time** što je navedeno protutijelo, ili antigenski vežući fragment, namijenjeno proizvodnji medikamenta za liječenje reumatoidnog artritisa, osteoartritisa, psorijaze, astme ili COPD.
- 15 27. Vektor (primjerice plazmid) koji kodira teški lanac i/ili laki lanac protutijela, ili antigenski vežućeg fragmenta, u skladu s bilo kojim od patentnih zahtjeva 1 do 20, **naznačen time** što, primjerice, navedeni vektor sadrži polinukleotid u skladu s bilo kojim od patentnih zahtjeva 28 do 31.
28. Polinukleotid koji kodira V_H domenu sa SEQ.I.D.NO:9, **naznačen time** što navedeni polinukleotid sadrži SEQ.I.D.NO:17.
- 20 29. Polinukleotid koji kodira V_L domenu sa SEQ.I.D.NO:10, **naznačen time** što navedeni polinukleotid sadrži SEQ.I.D.NO:18.
- 30 30. Polinukleotid koji kodira teški lanac sa SEQ.I.D.NO:11, **naznačen time** što navedeni polinukleotid sadrži SEQ.I.D.NO:19.
31. Polinukleotid koji kodira laki lanac sa SEQ.I.D.NO:12, **naznačen time** što navedeni polinukleotid sadrži SEQ.I.D.NO:20.
- 25 32. Stabilno transformirana ili transficirana rekombinantna stanica-domaćin, **naznačena time** što sadrži vektor u skladu s patentnim zahtjevom 27.
33. Stabilno transformirana ili transficirana rekombinantna stanica-domaćin, **naznačena time** što sadrži prvi vektor, koji sadrži polinukleotid sa SEQ.I.D.NO:17, i drugi vektor, koji sadrži polinukleotid sa SEQ.I.D.NO:18.
34. Stabilno transformirana ili transficirana rekombinantna stanica-domaćin, **naznačena time** što sadrži prvi vektor, koji sadrži polinukleotid sa SEQ.I.D.NO:19, i drugi vektor, koji sadrži polinukleotid sa SEQ.I.D.NO:20.
- 30 35. Stanica-domaćin u skladu s bilo kojim od patentnih zahtjeva 32 do 34, **naznačena time** što navedena stanica-domaćin je kralježnjačka stanica.
36. Stanica-domaćin u skladu s patentnim zahtjevom 35, **naznačena time** što navedena stanica je sisavačka.
37. Stanica-domaćin u skladu s patentnim zahtjevom 36, **naznačena time** što navedena stanica je CHO ili NS0.
- 35 38. Postupak proizvodnje protutijela, ili njegovog antigenski vežućeg fragmenta, **naznačen time** što se sastoji u koraku uzgajanja stanice-domaćina u skladu s bilo kojim od patentnih zahtjeva 32 do 34.
39. Protutijelo, ili njegov antigenski vežući fragment, u skladu s bilo kojim od prethodnih patentnih zahtjeva, **naznačeno time** što se, uz to što se može vezati na hOSM, može vezati i na cinomolgus OSM (cOSM).

Sl. 1

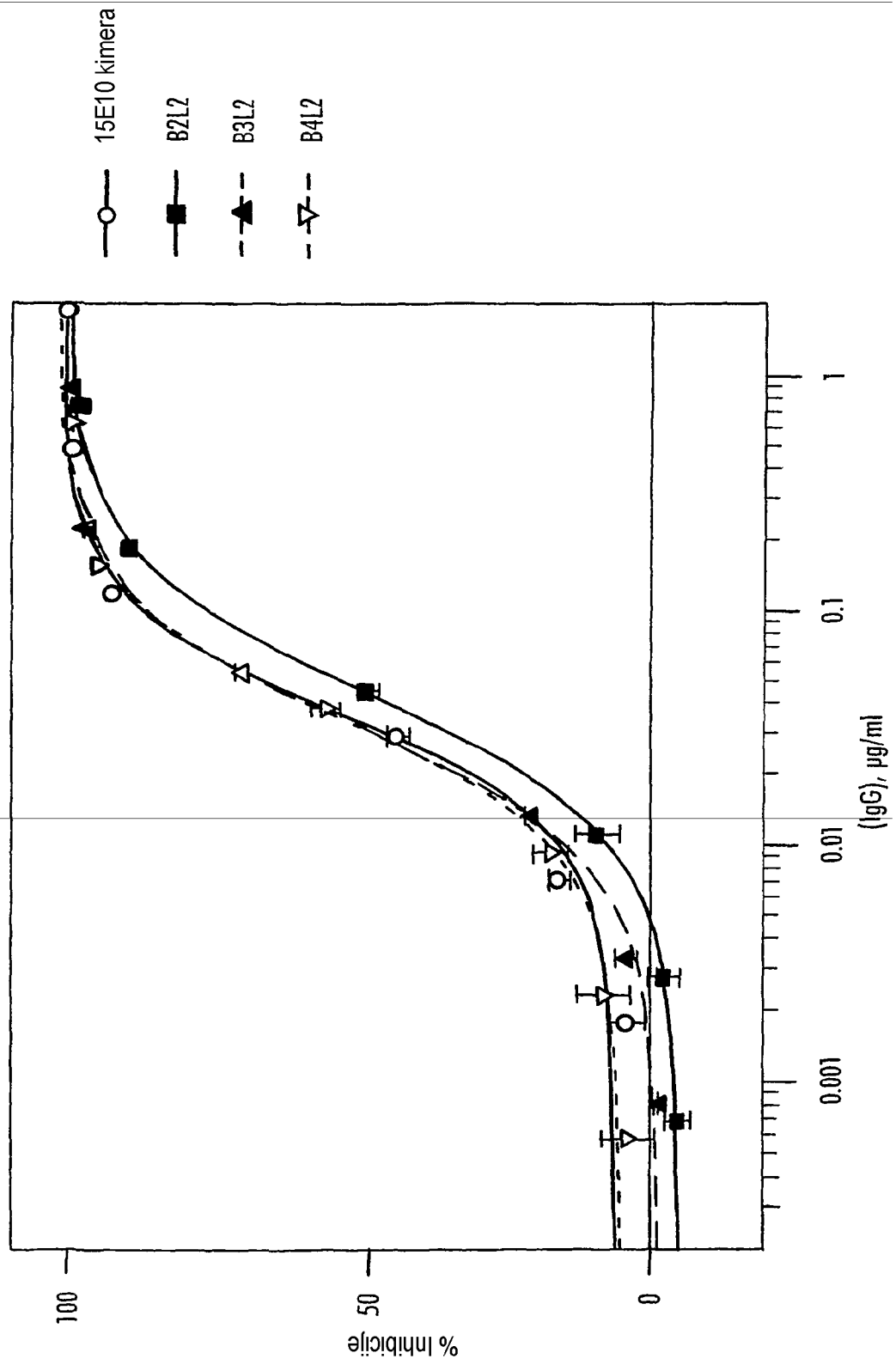


Sl. 2

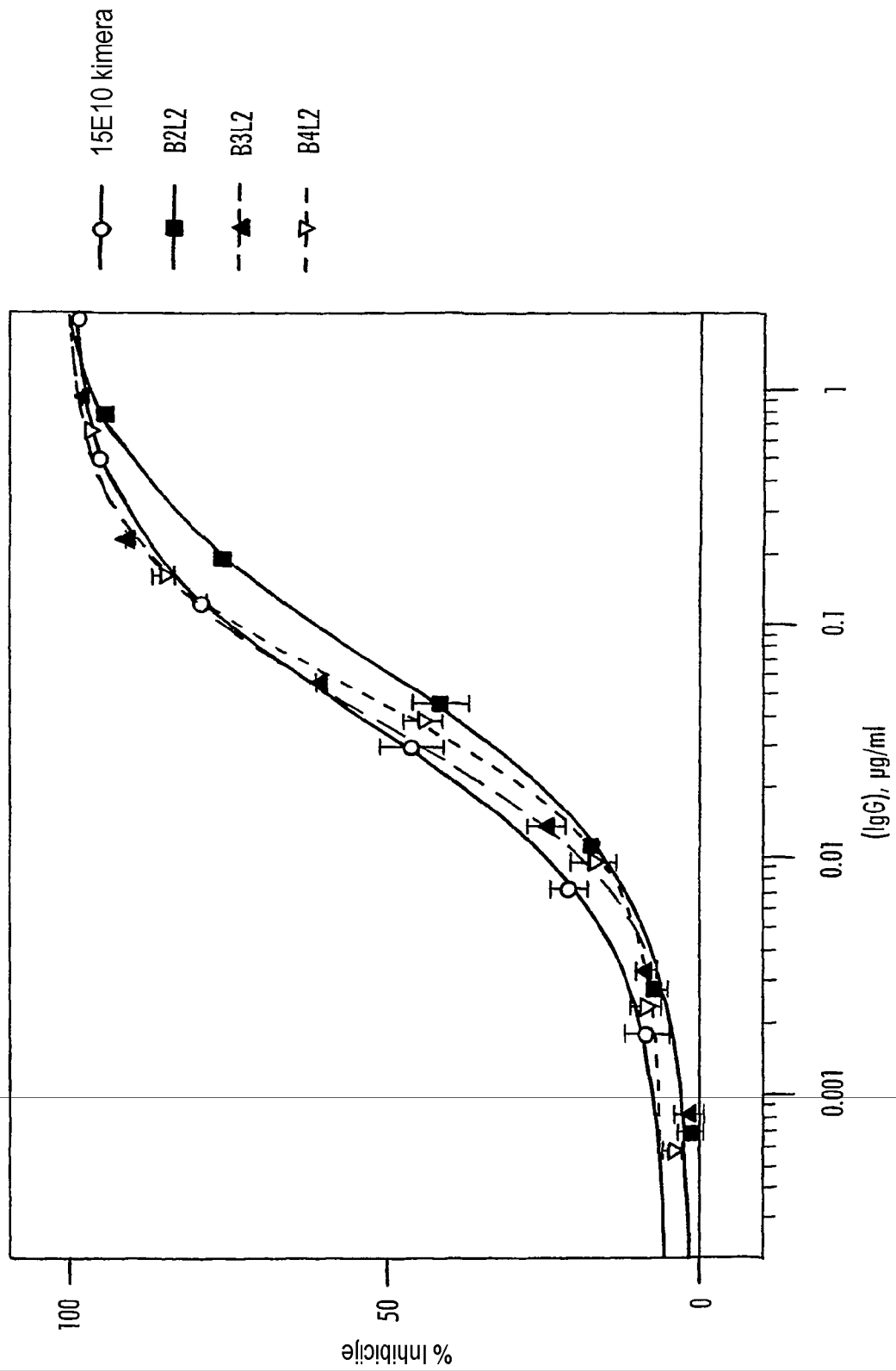
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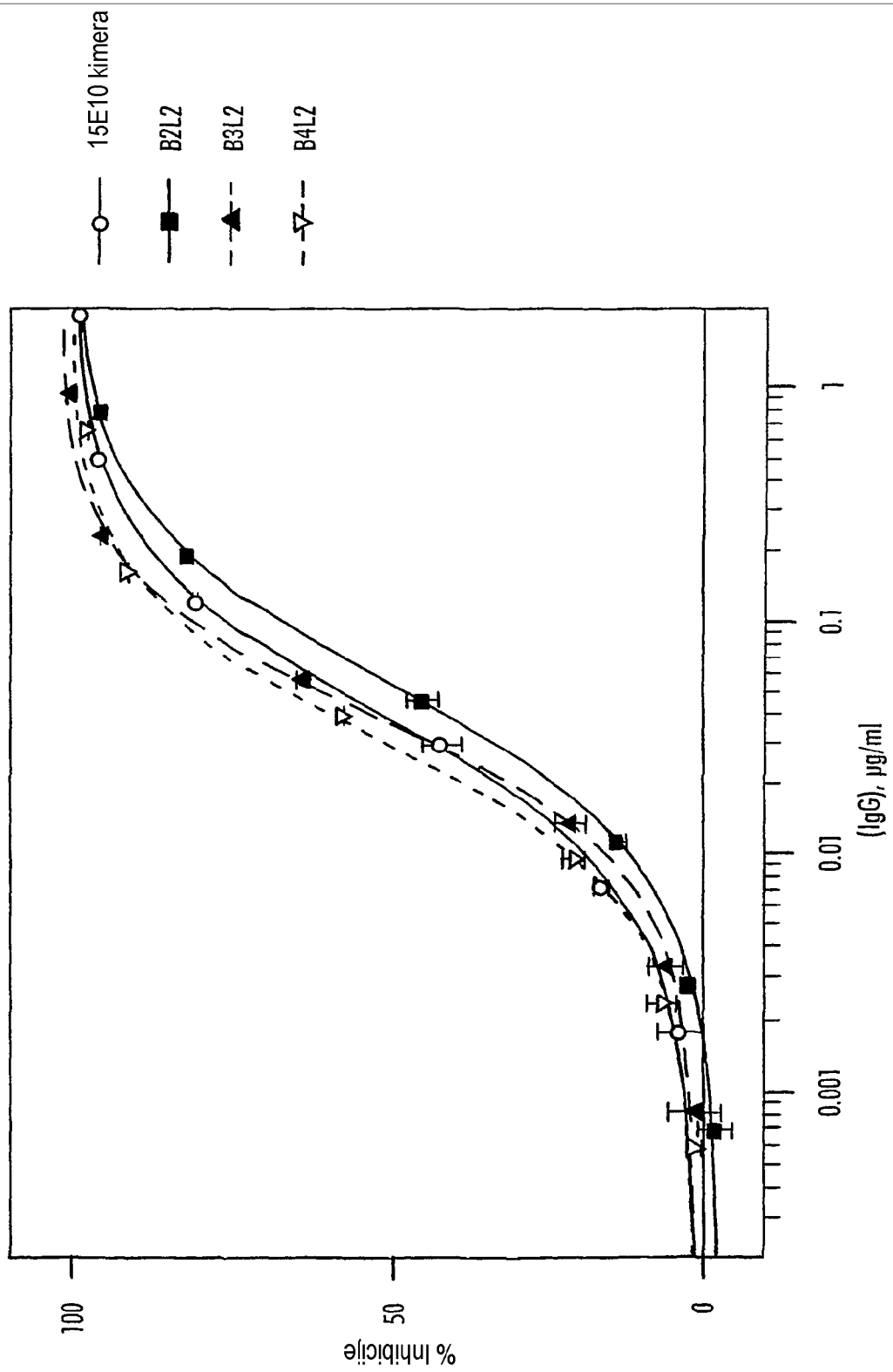
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SI. 5

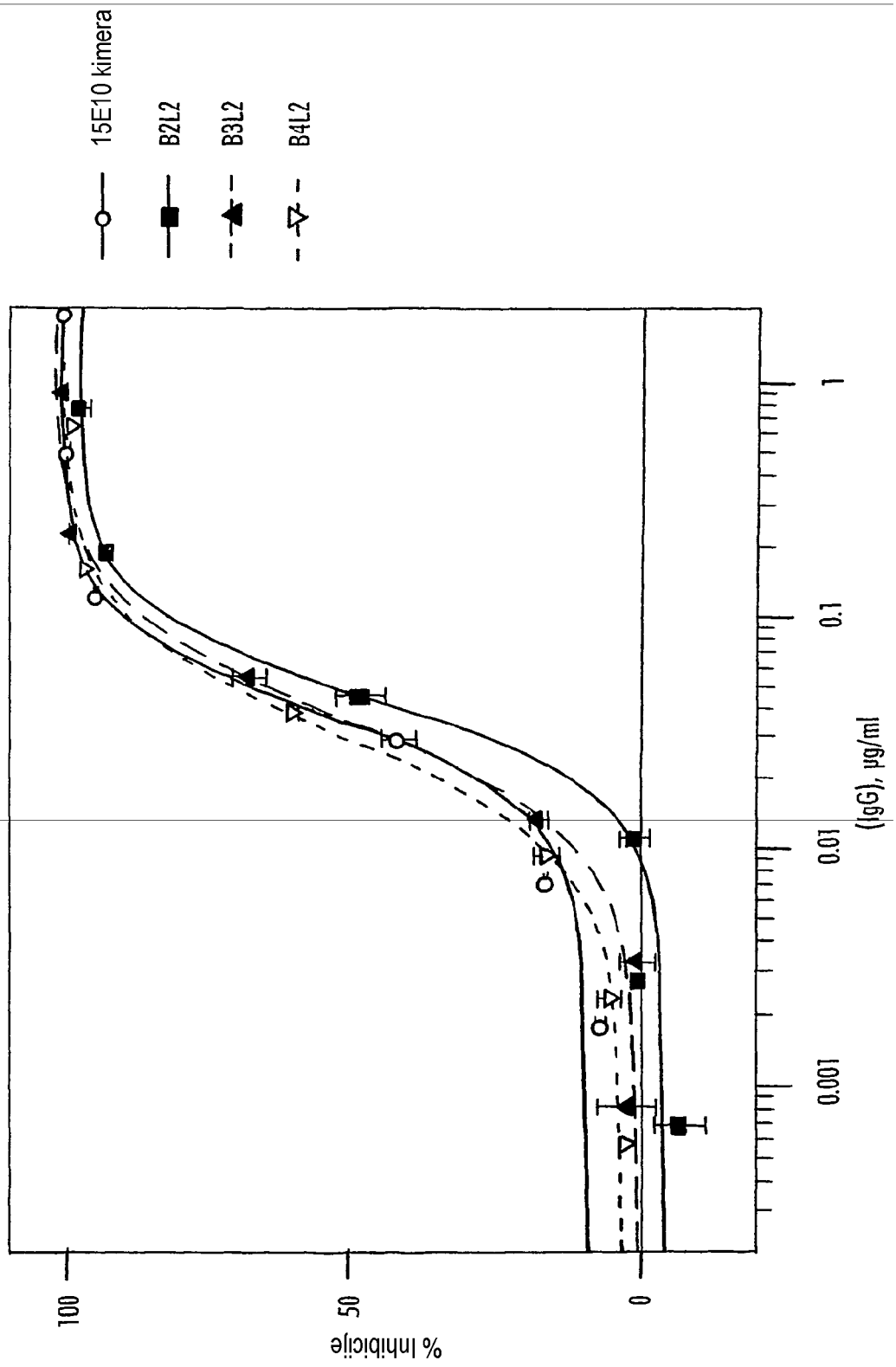


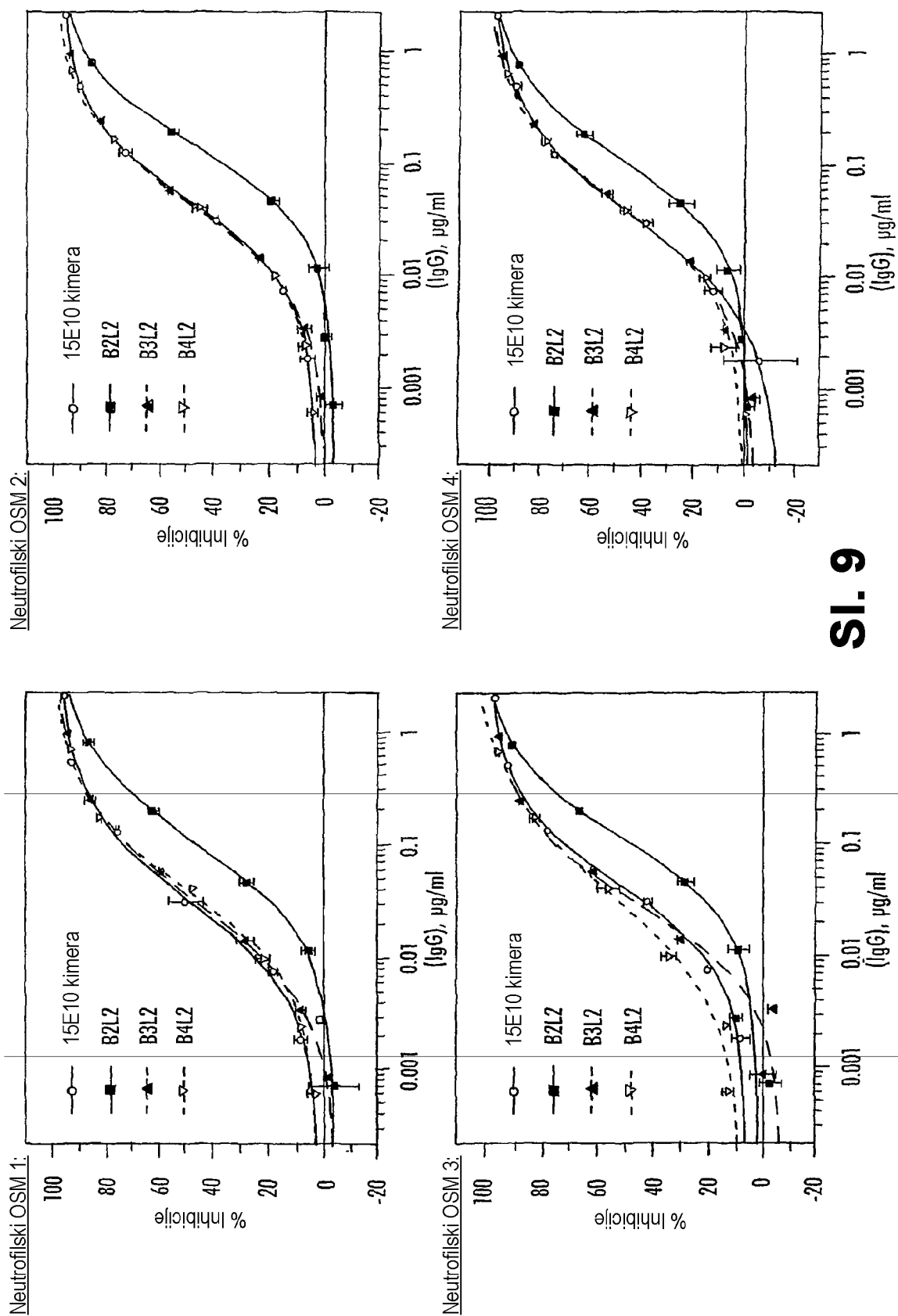
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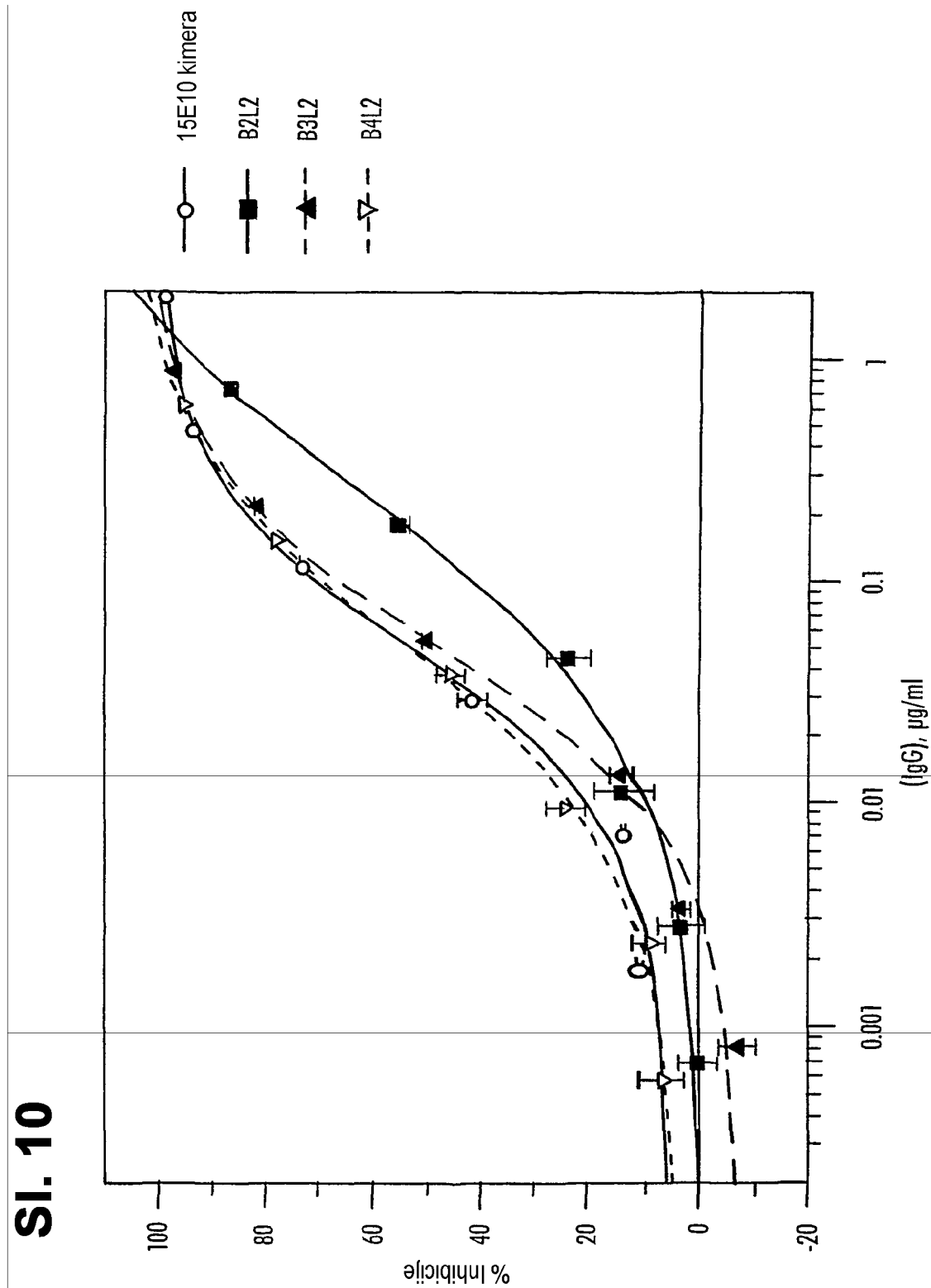


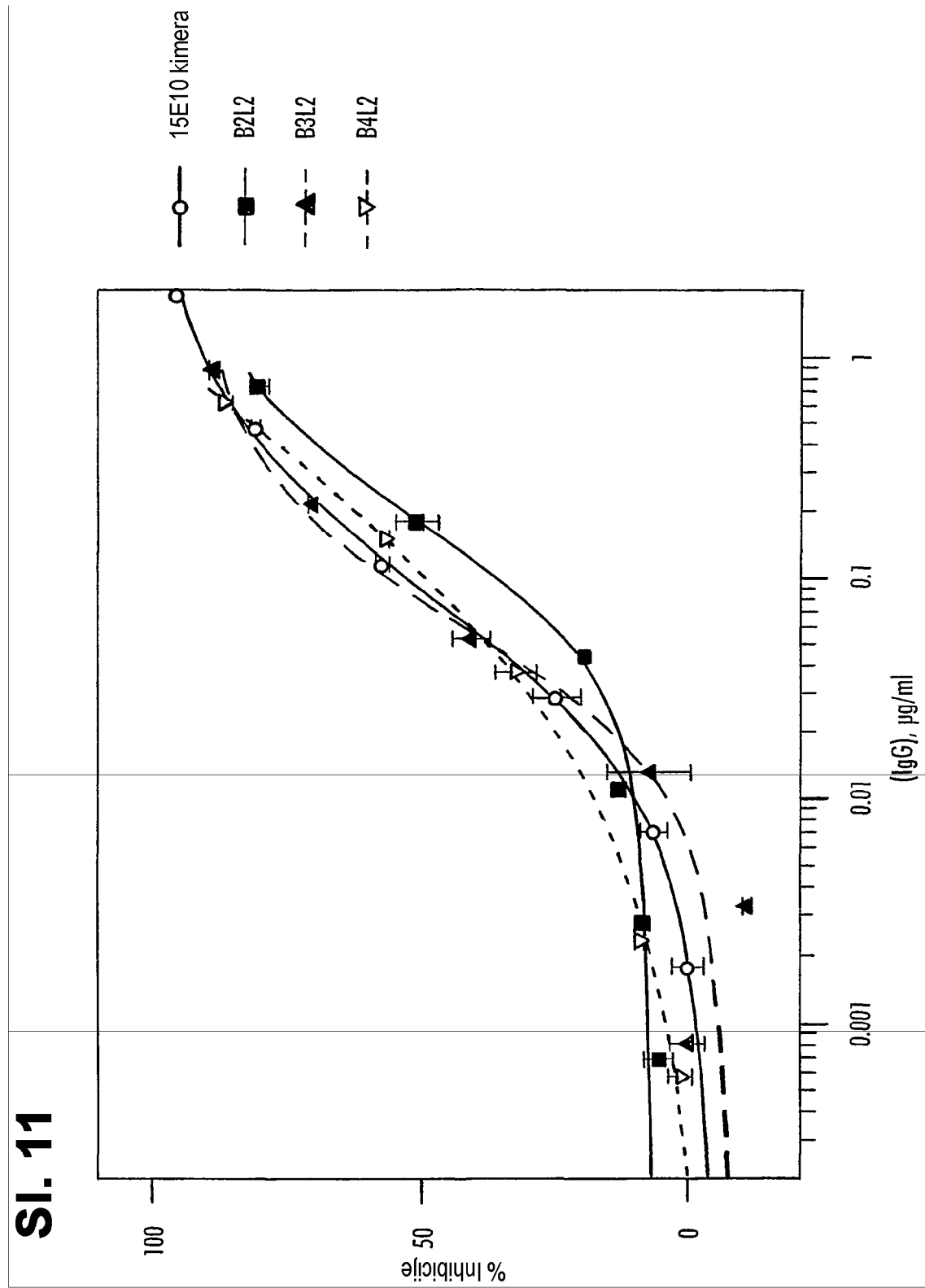
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SI. 8

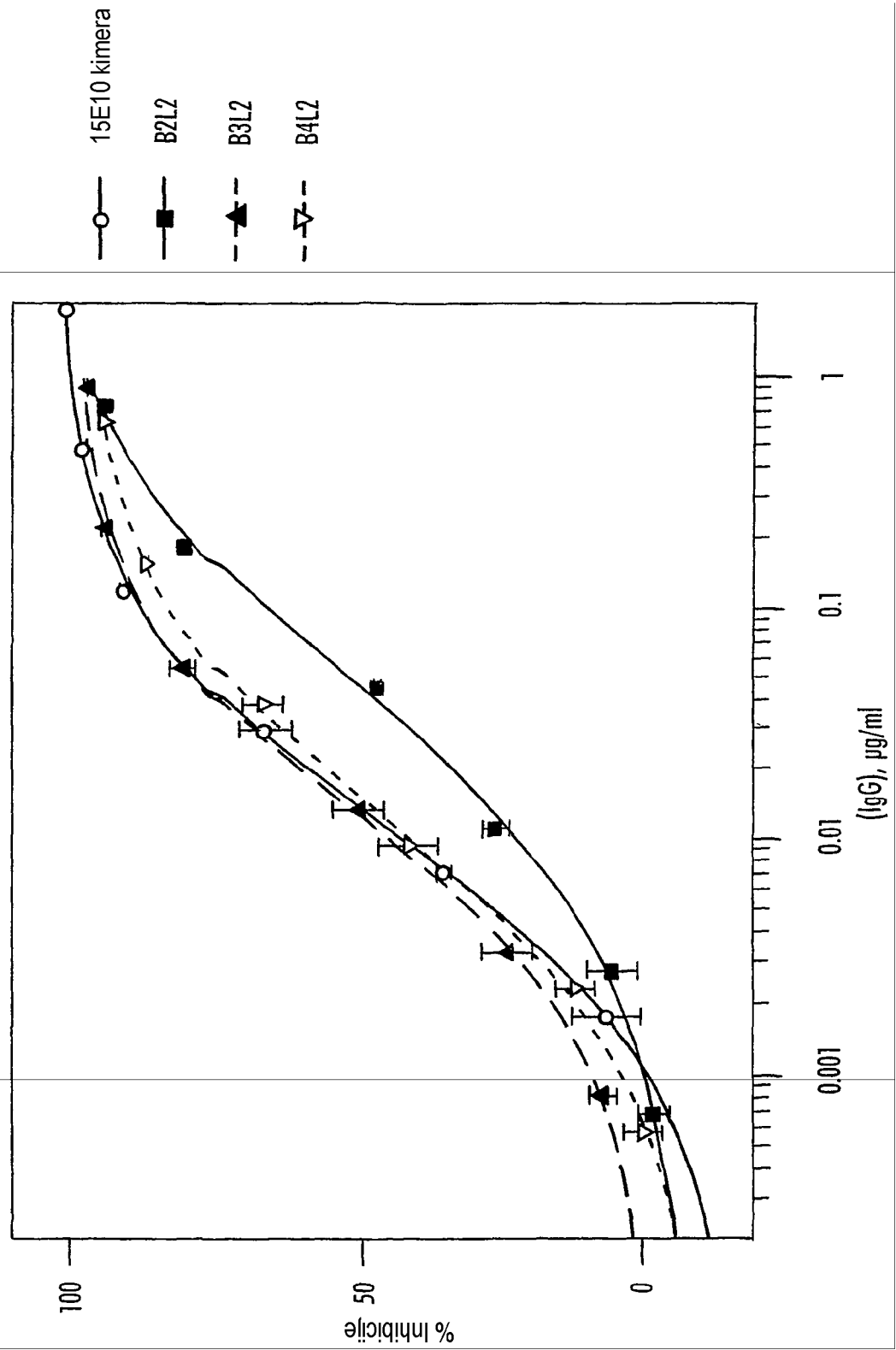


**SI. 9**

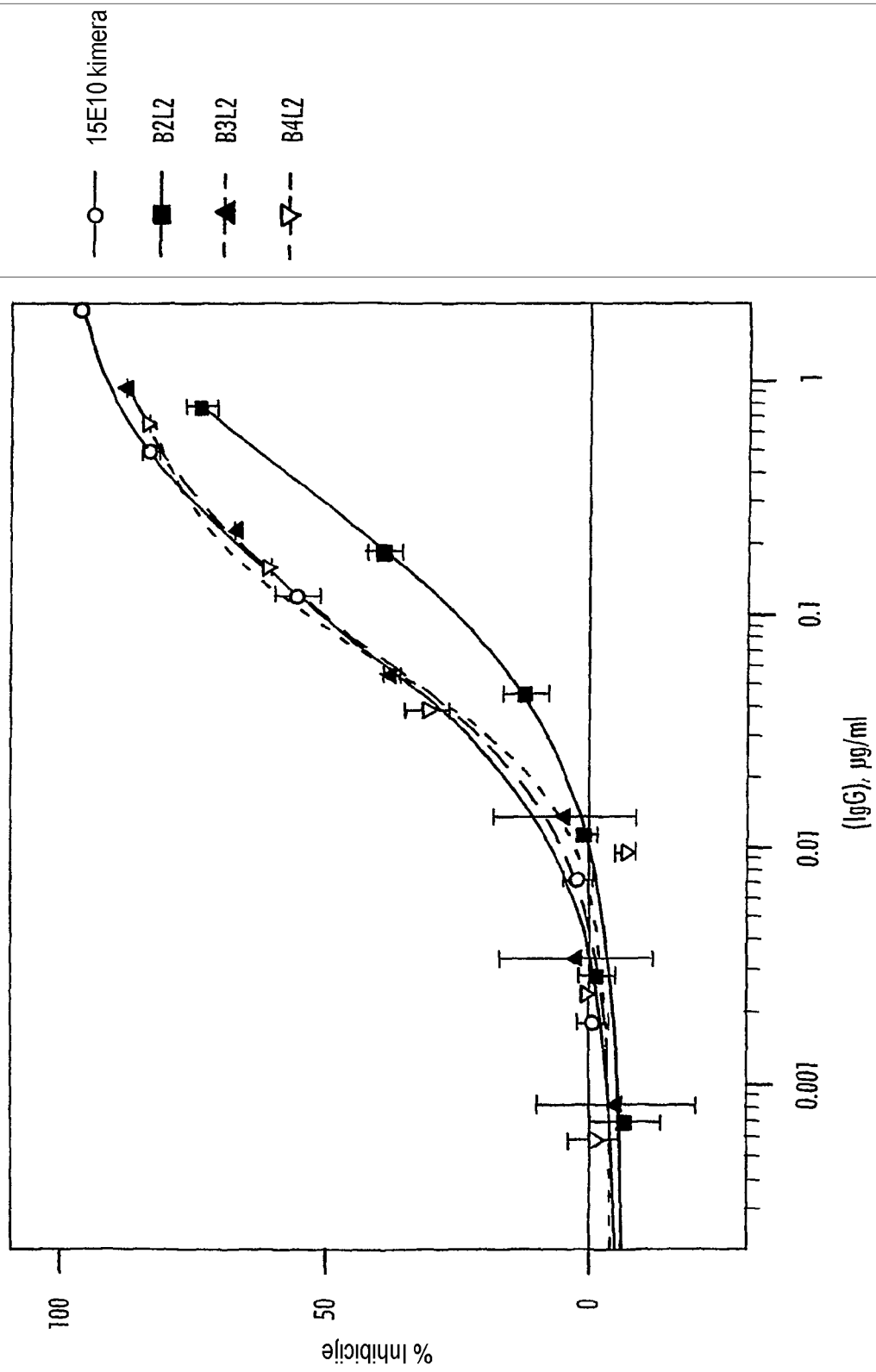


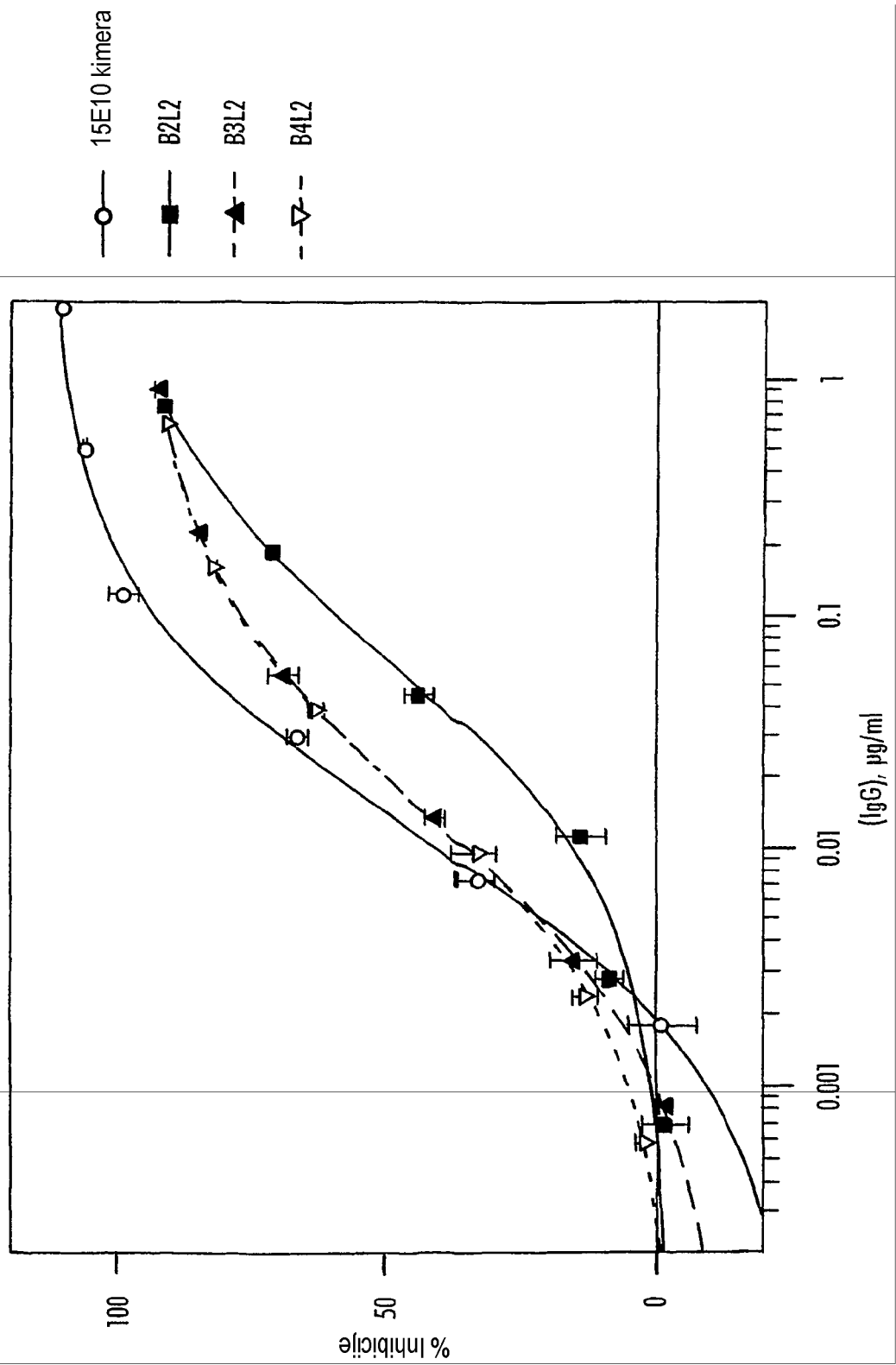


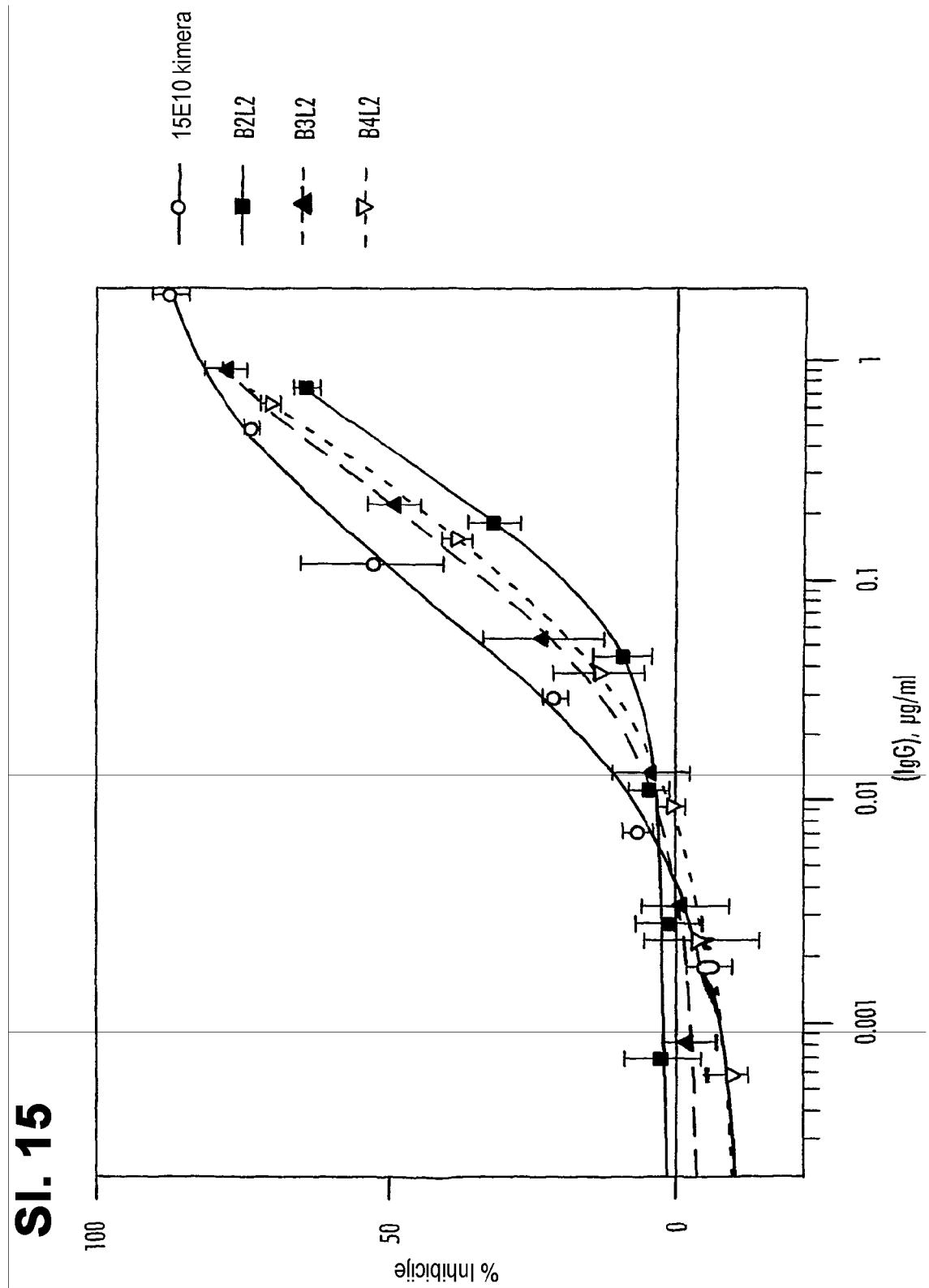
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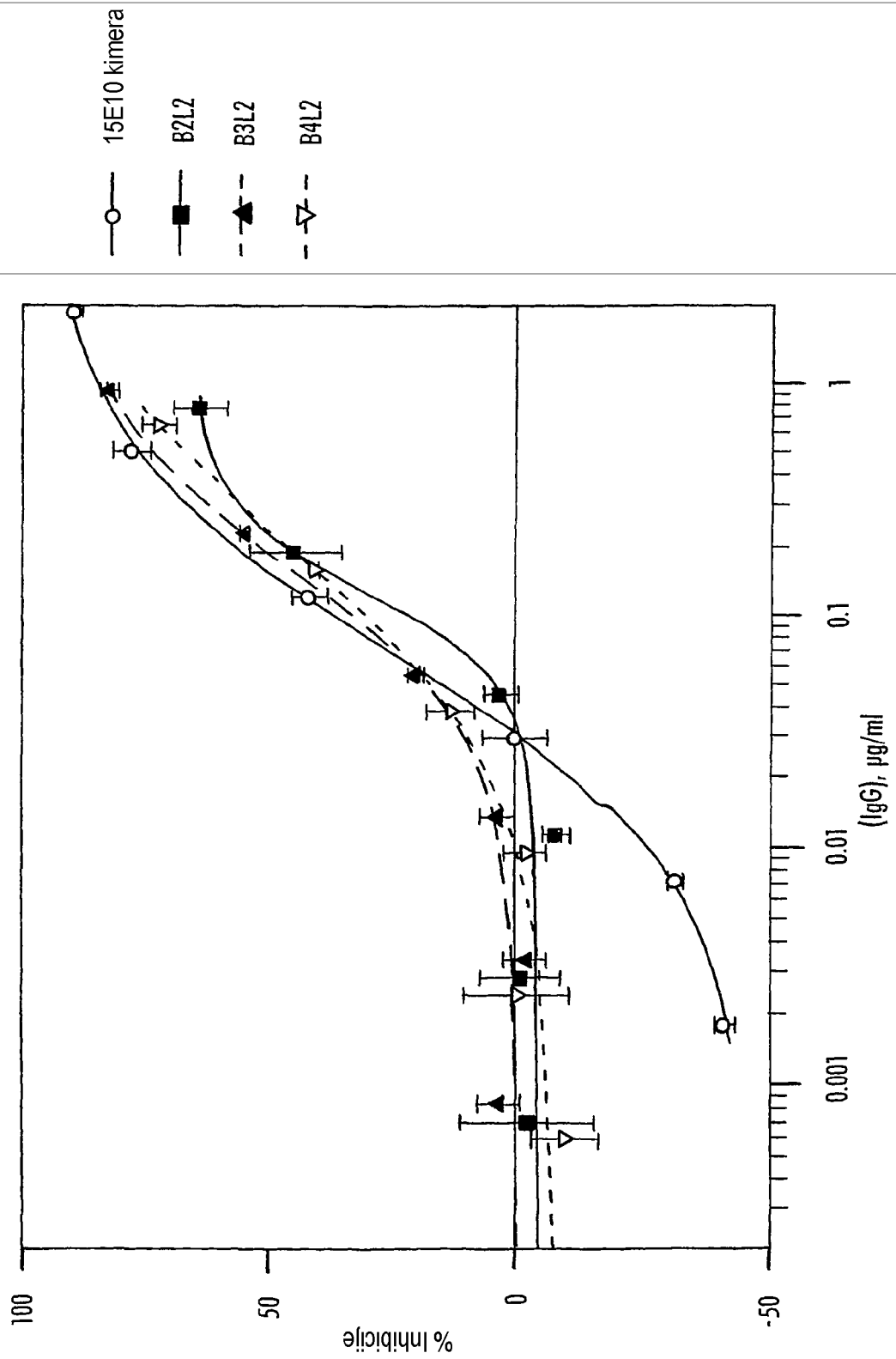
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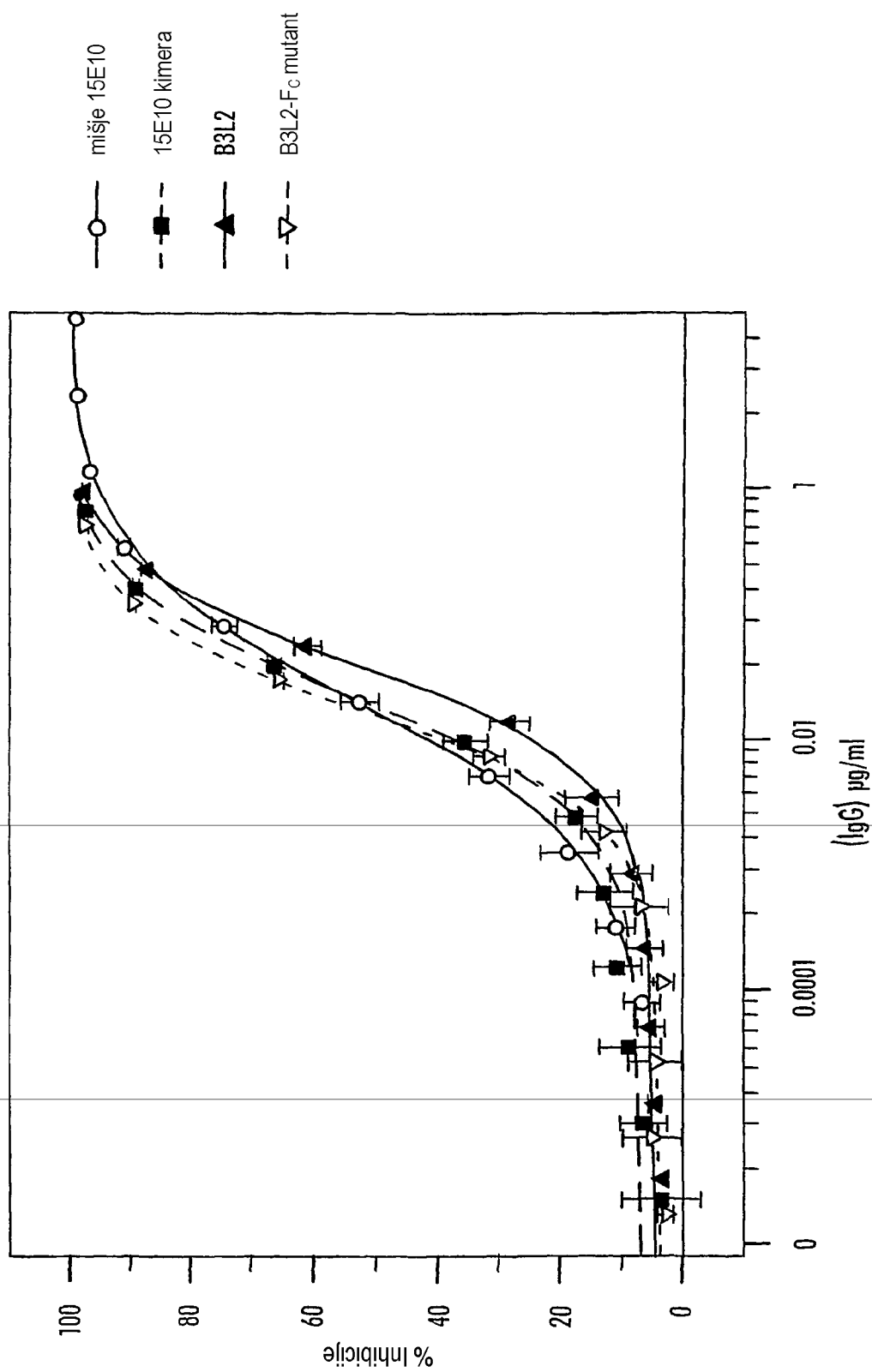
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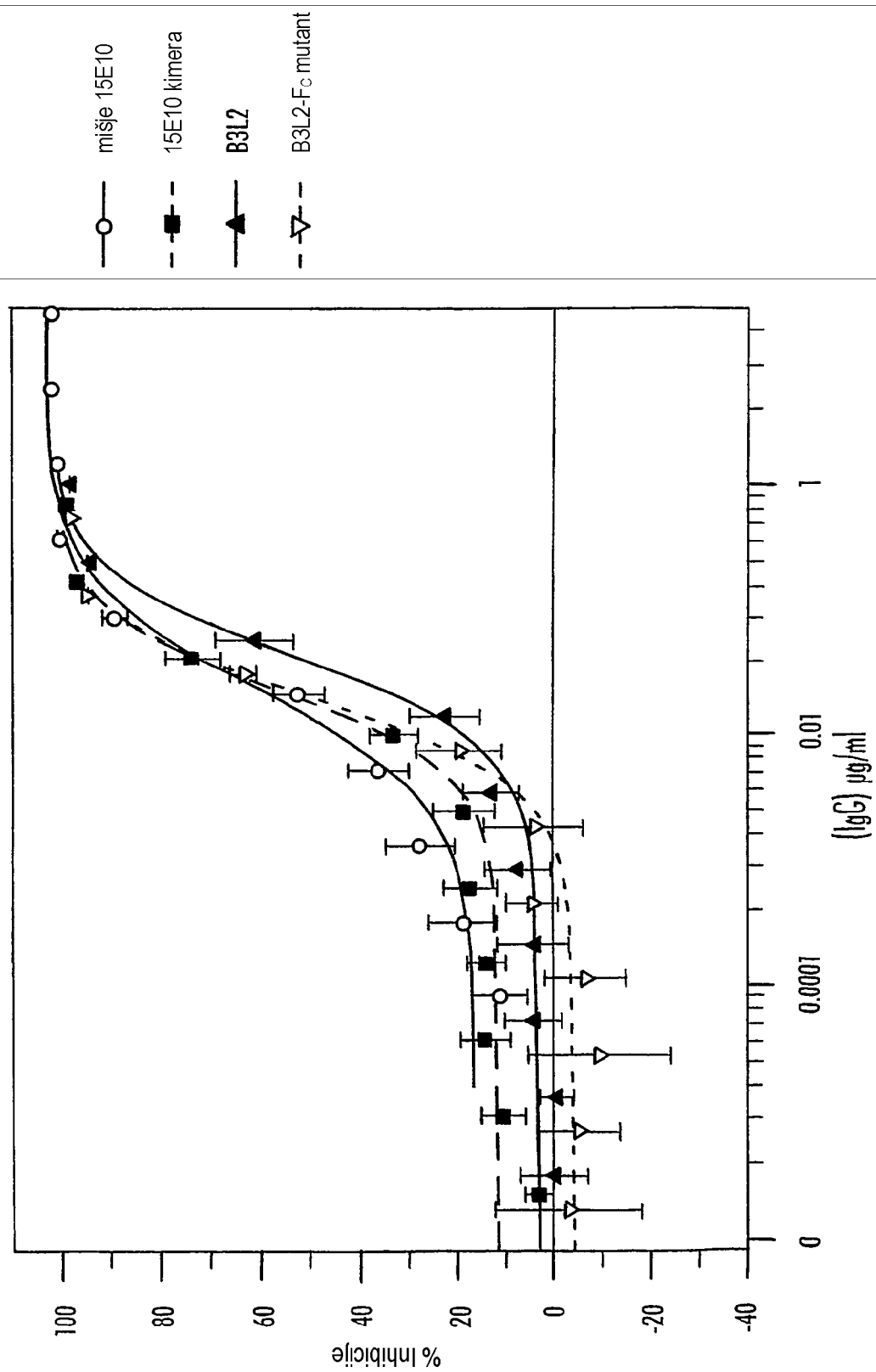
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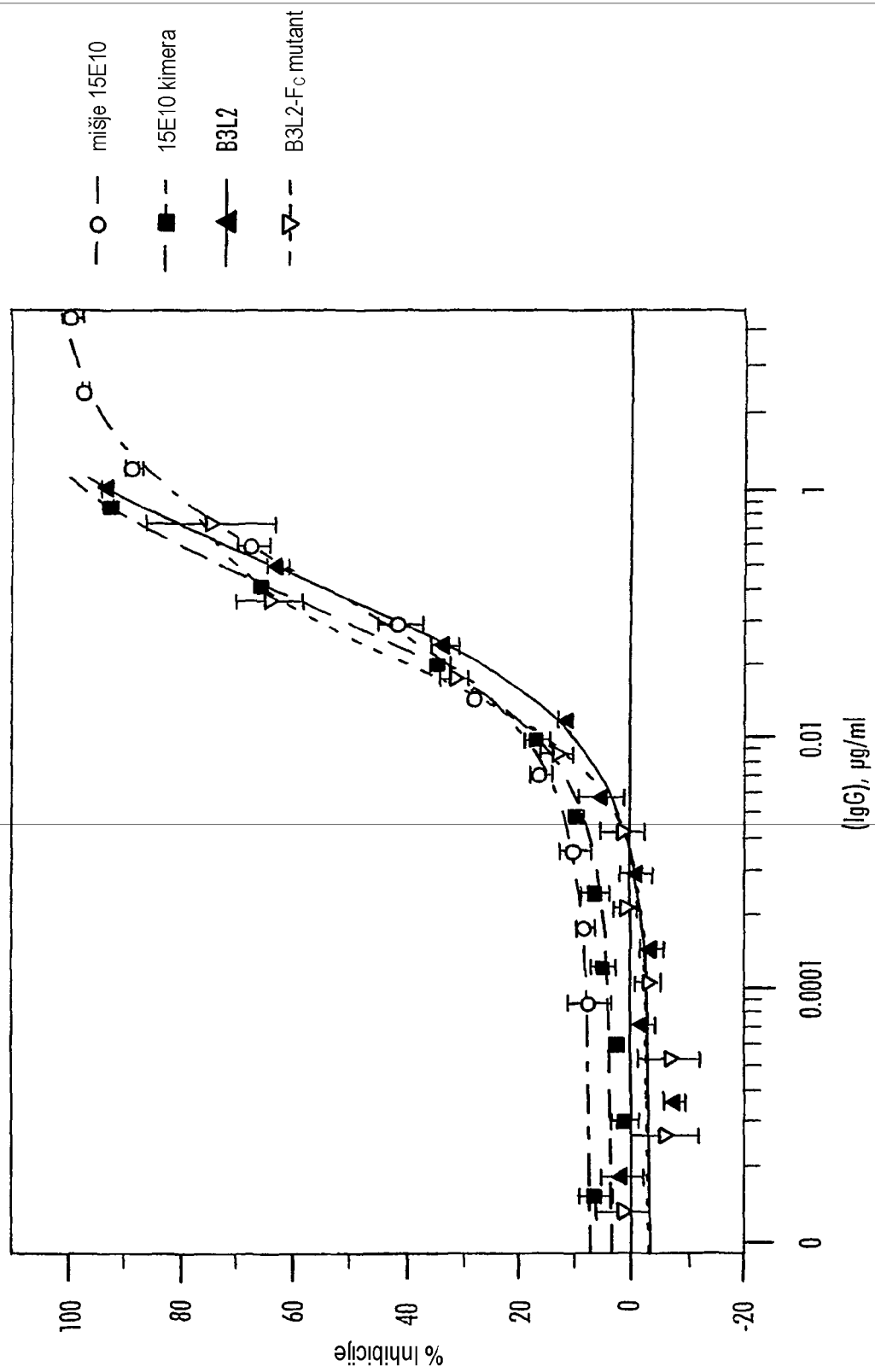


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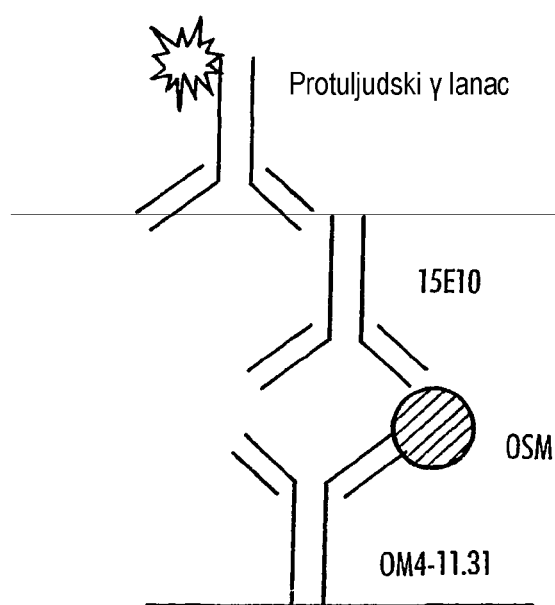


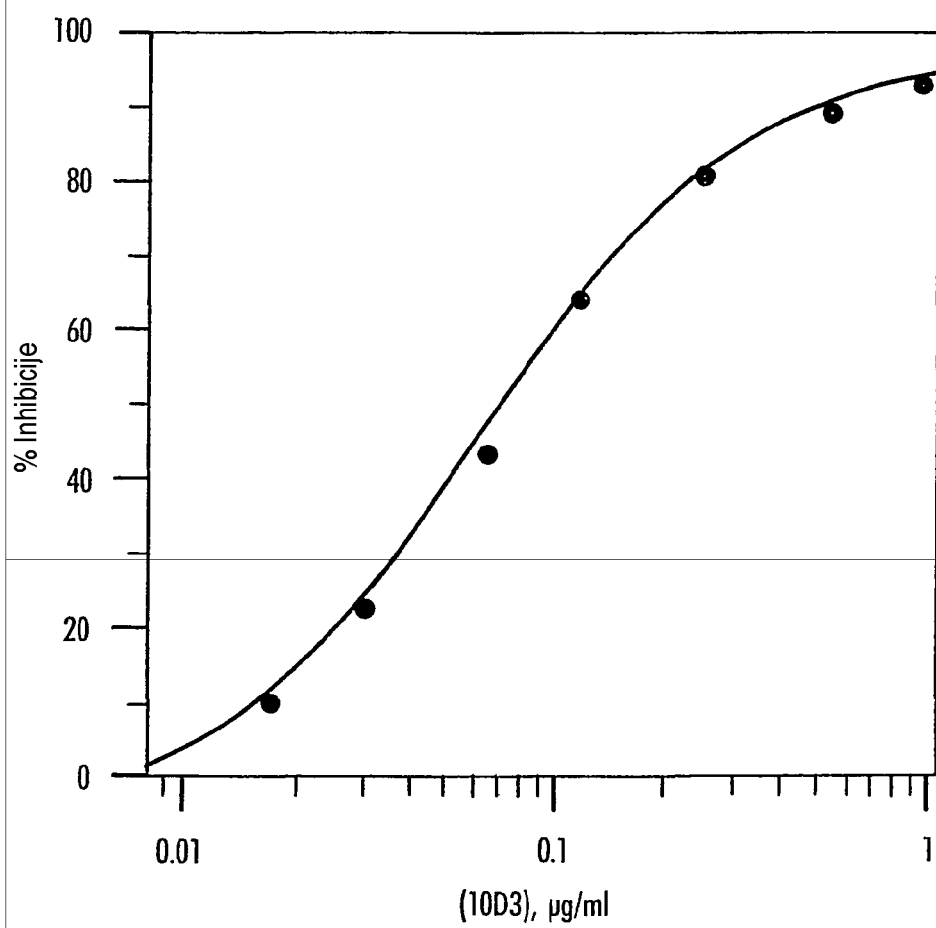
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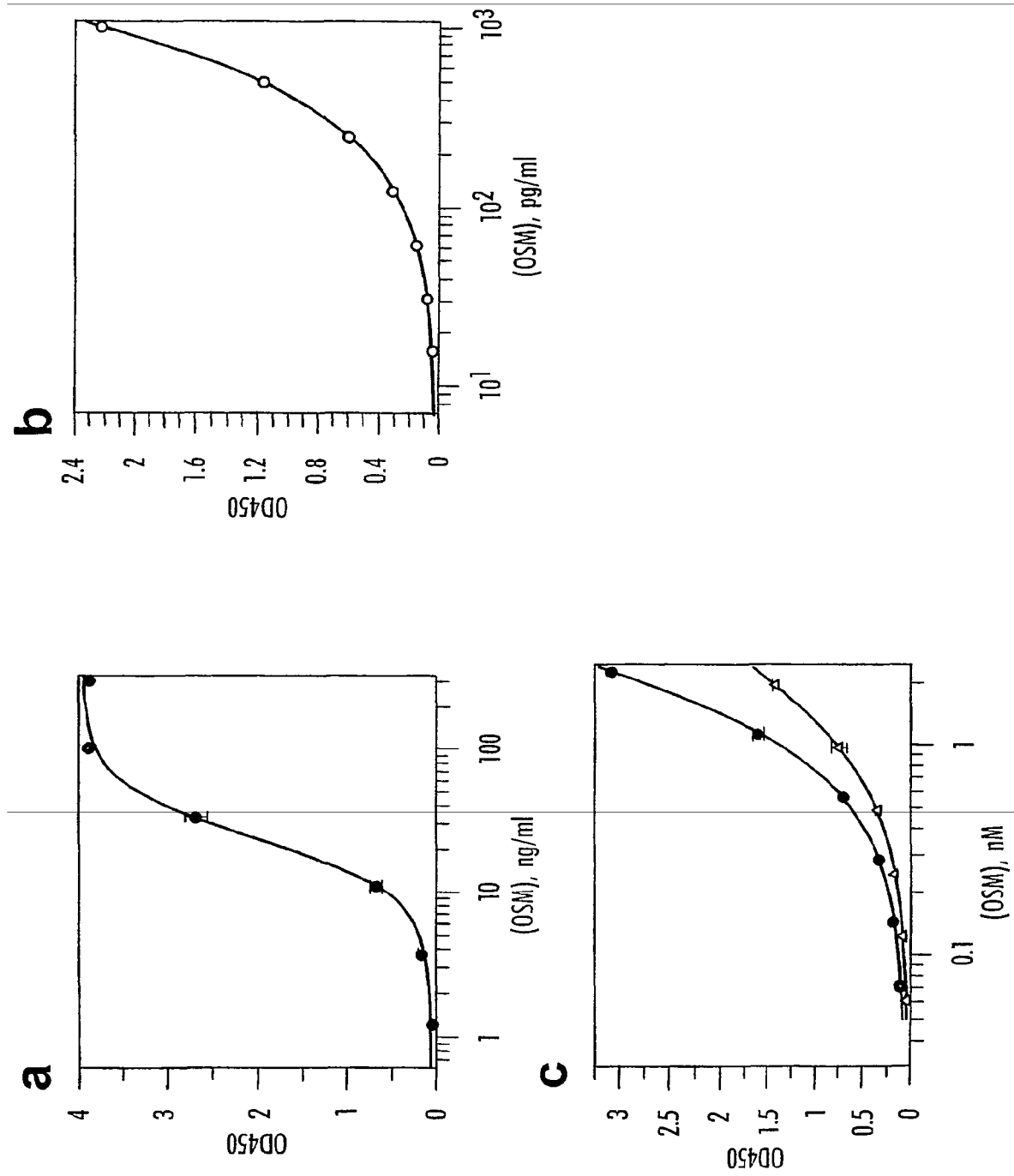
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Sl. 20

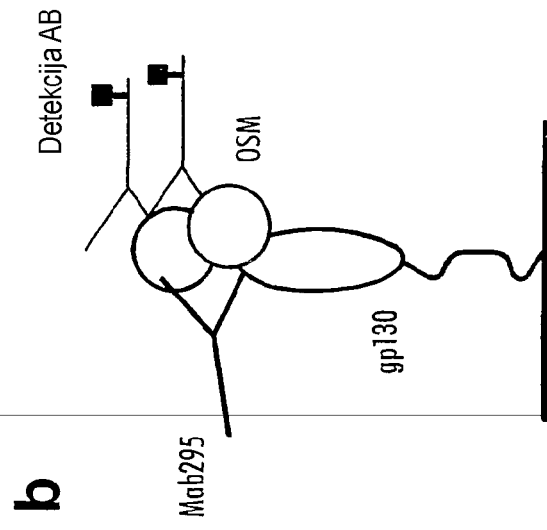
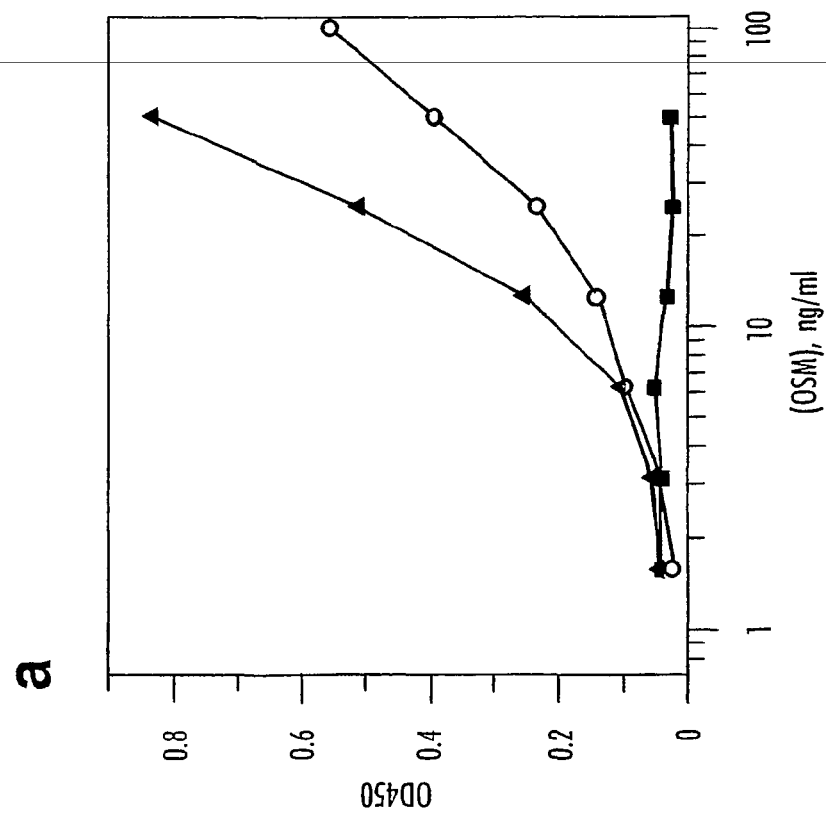


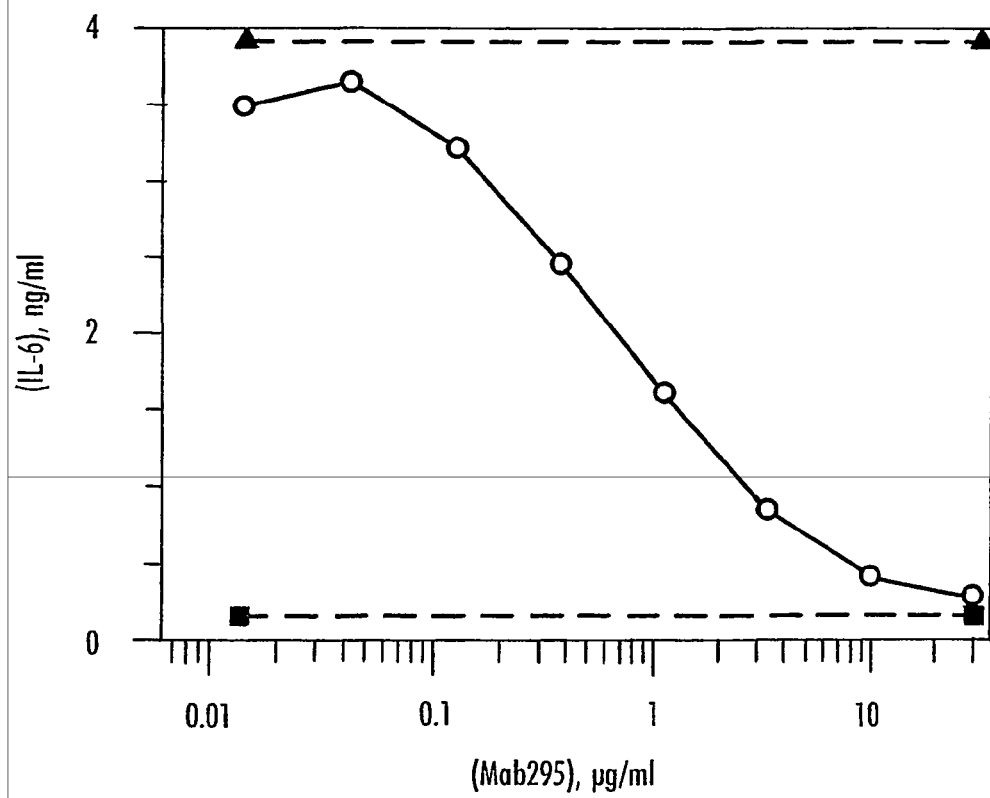
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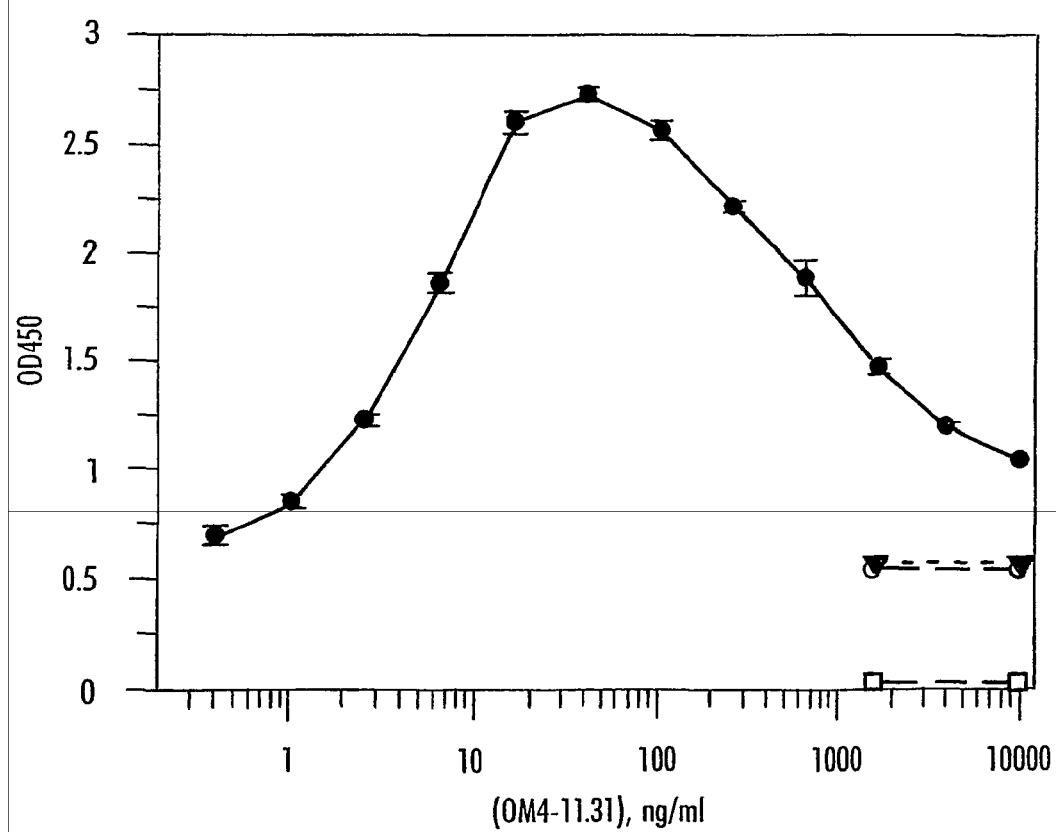
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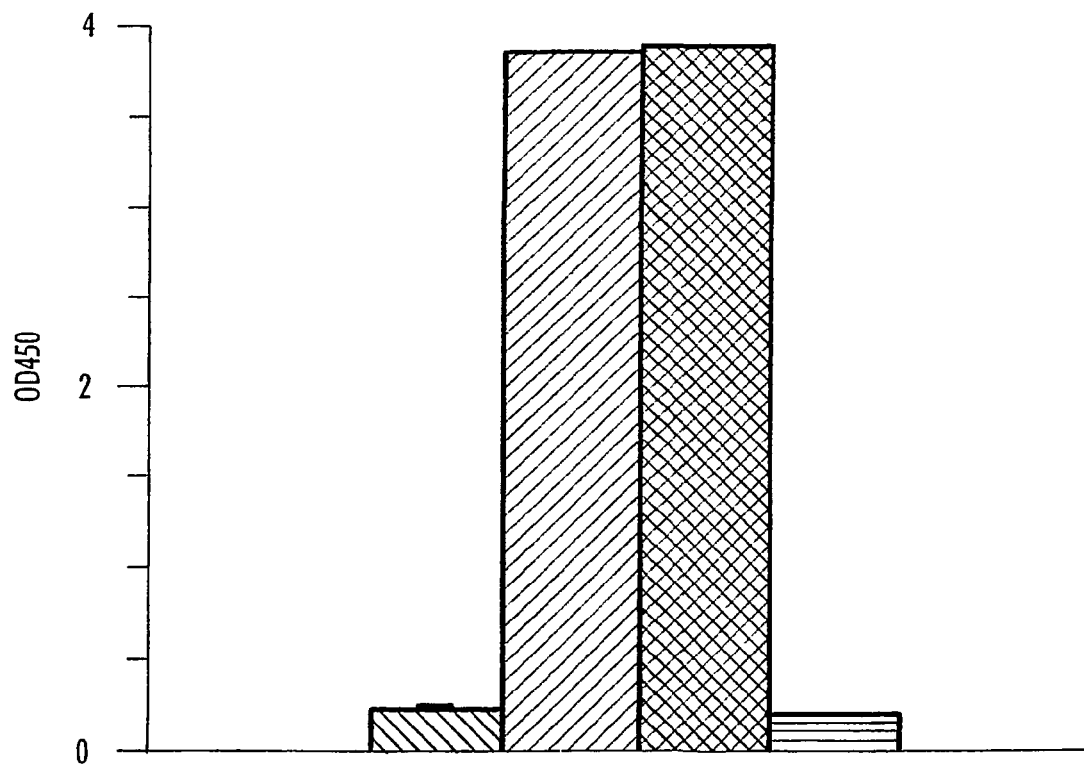
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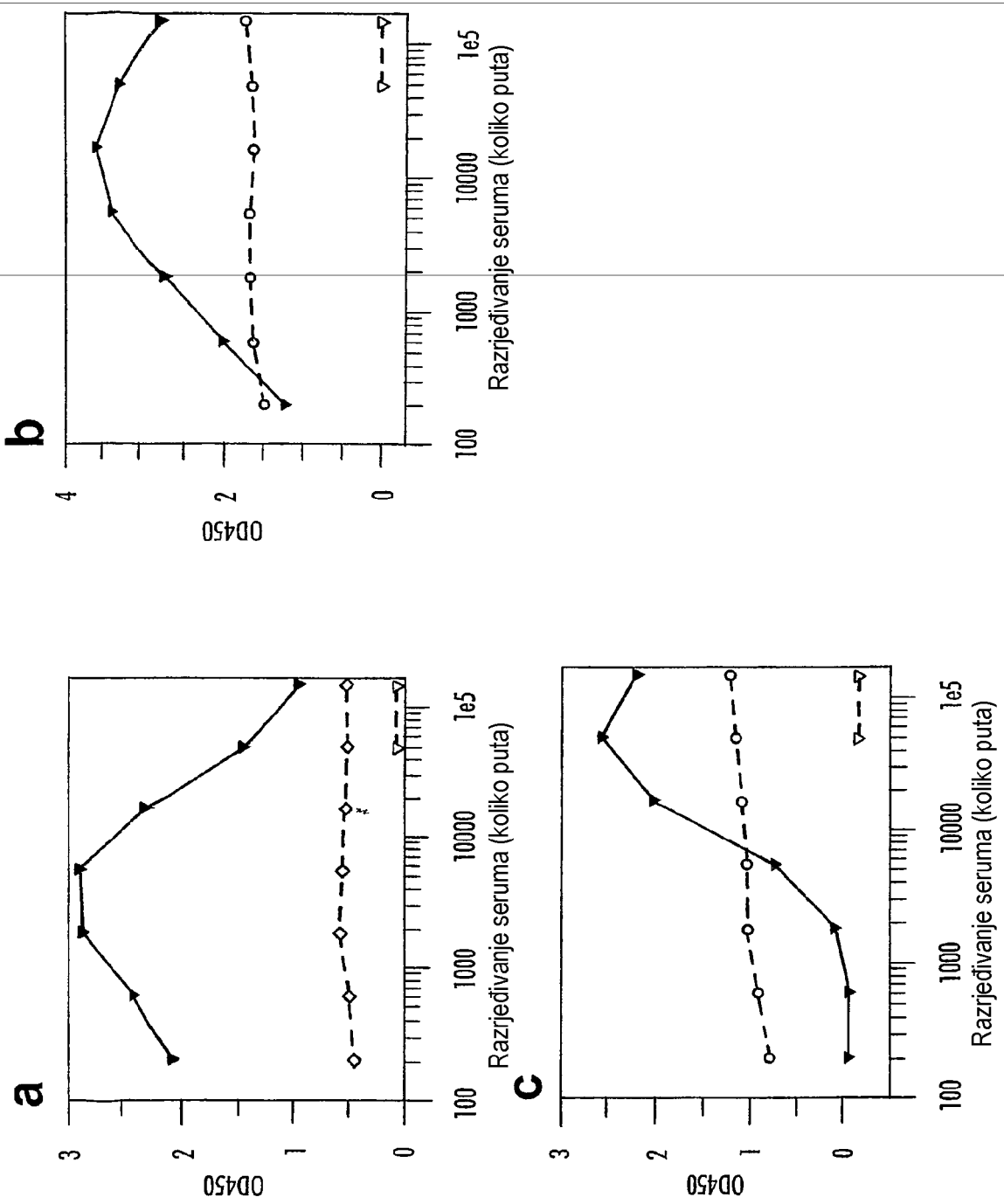
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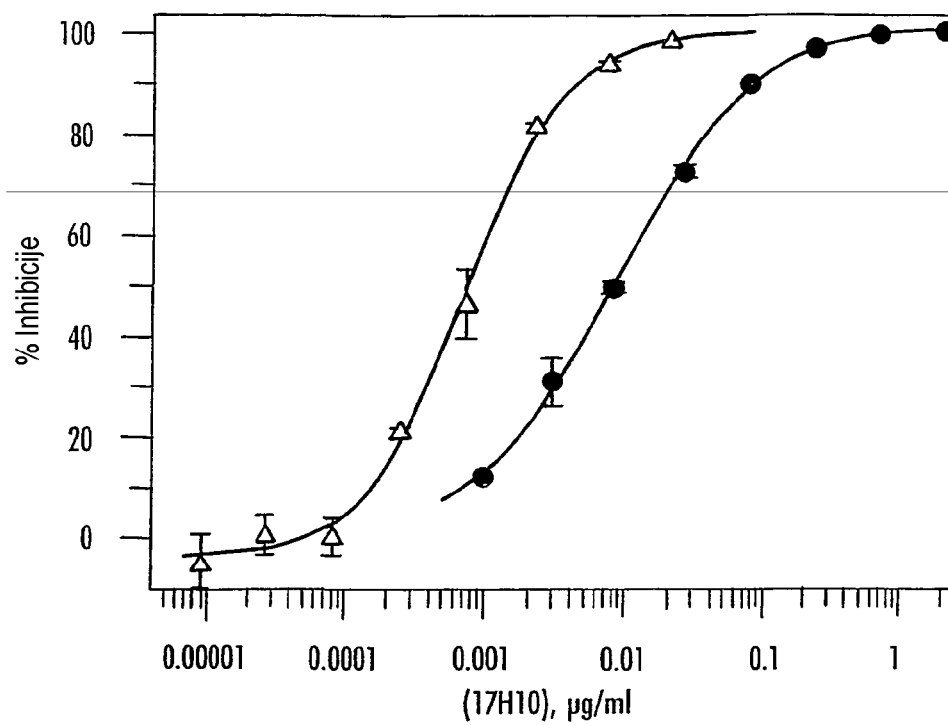
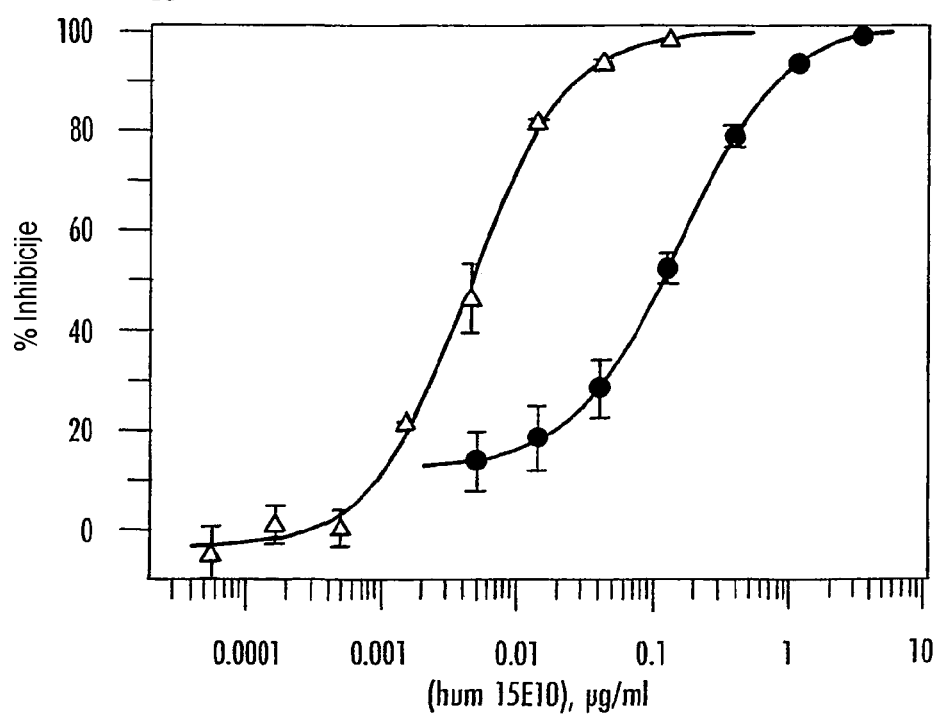
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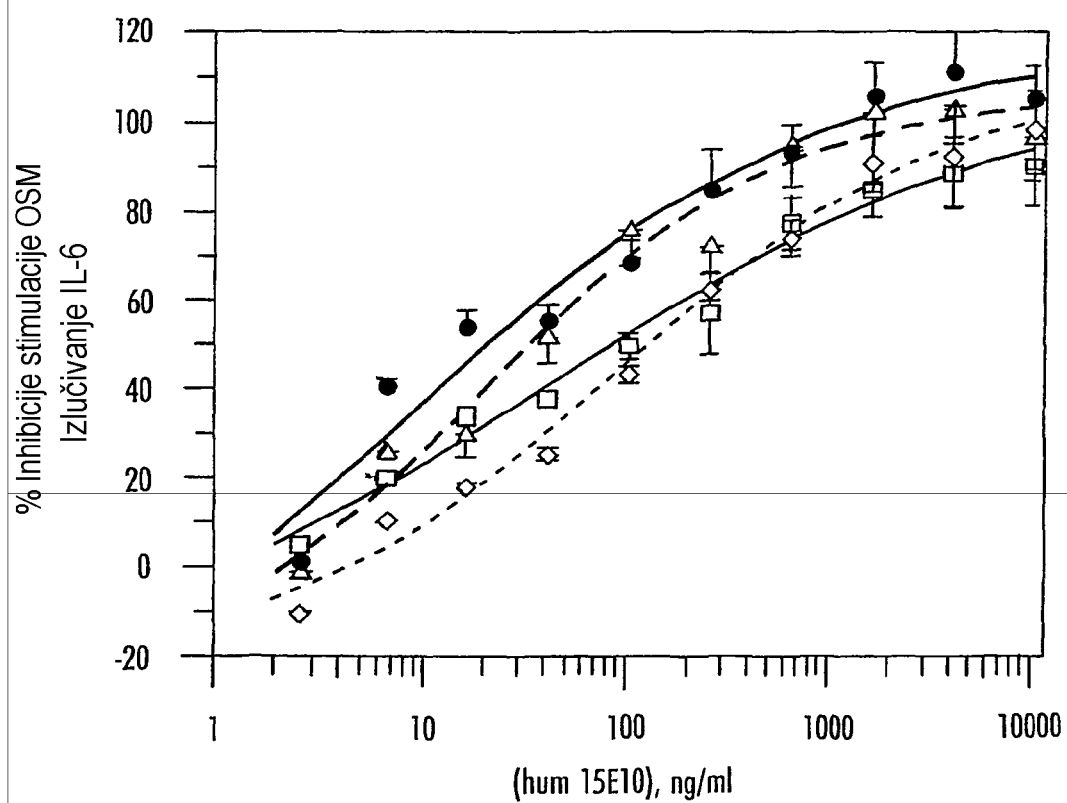
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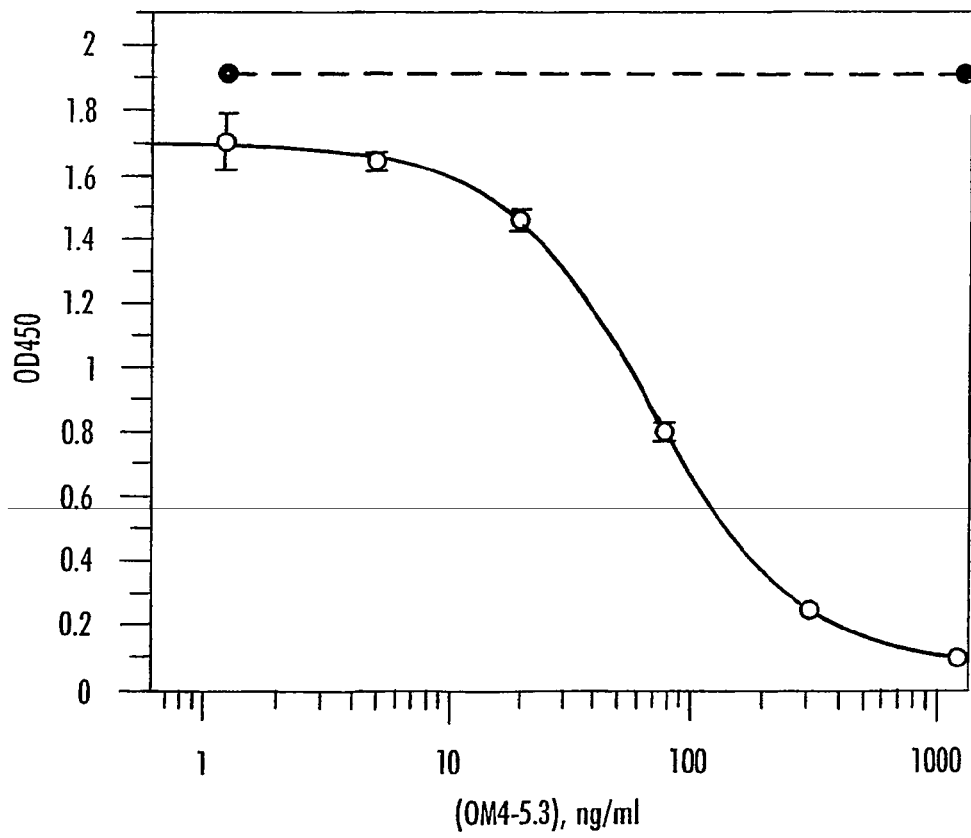


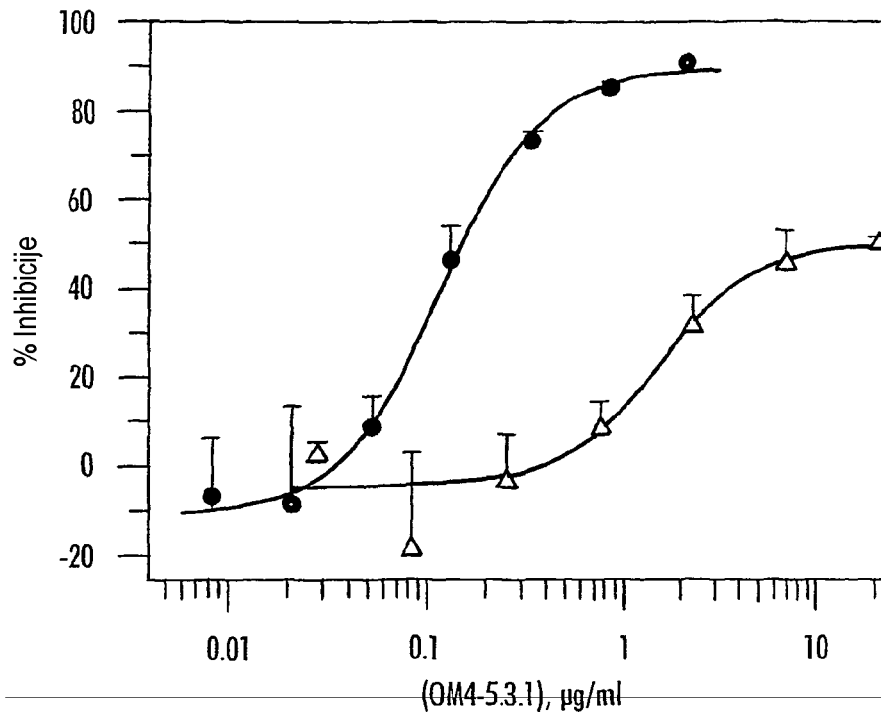
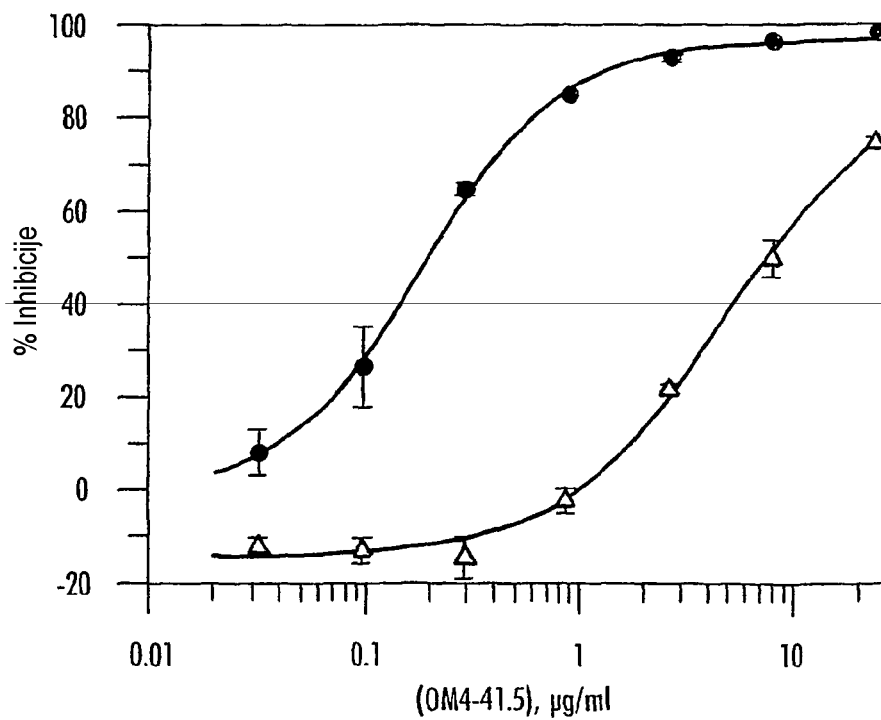
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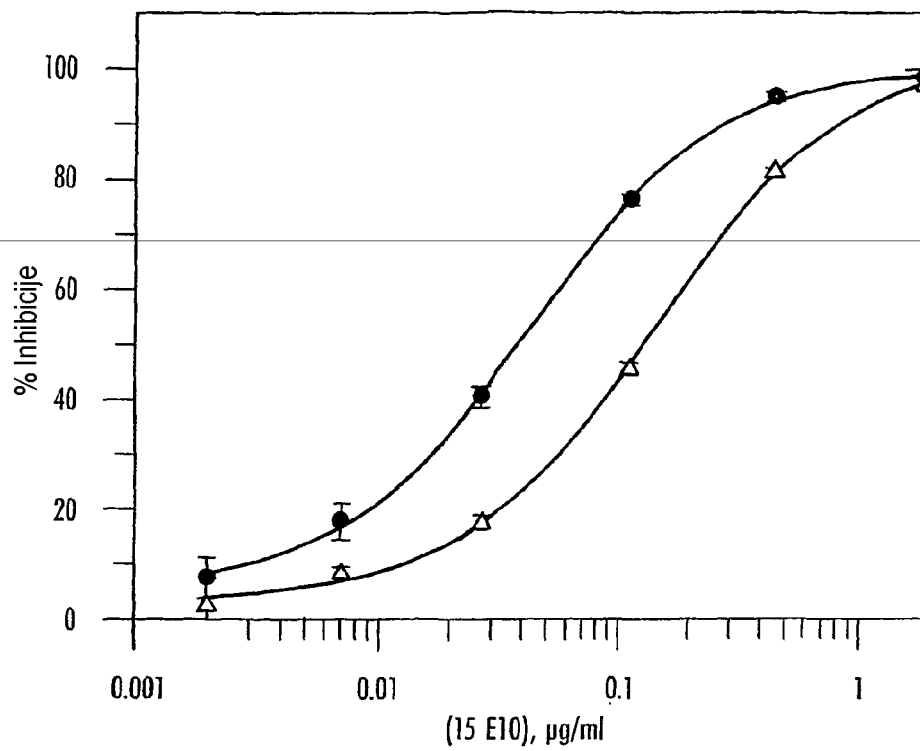
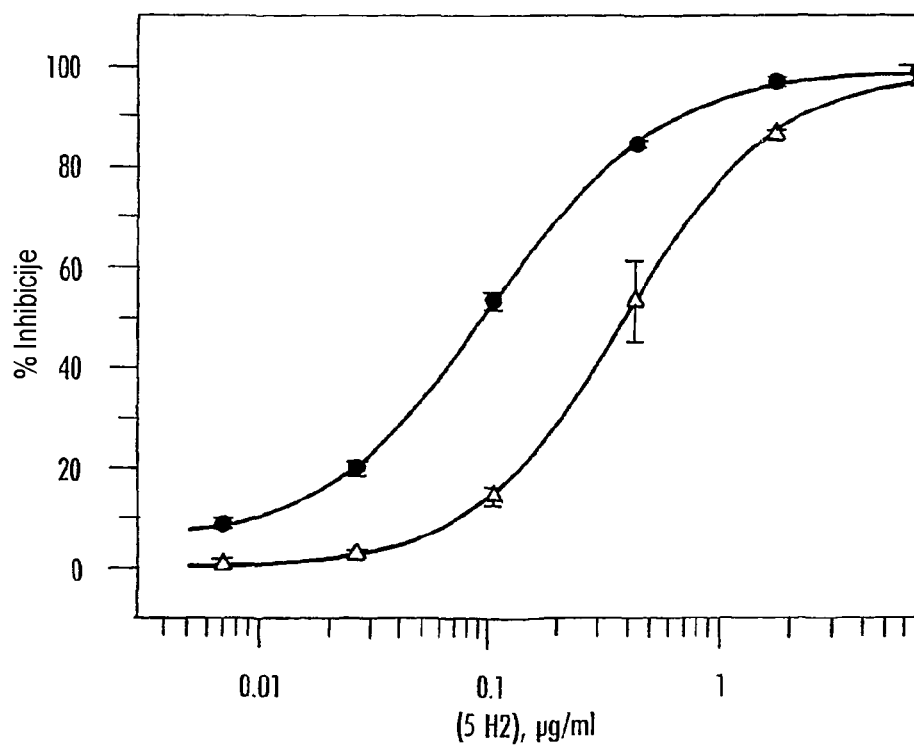


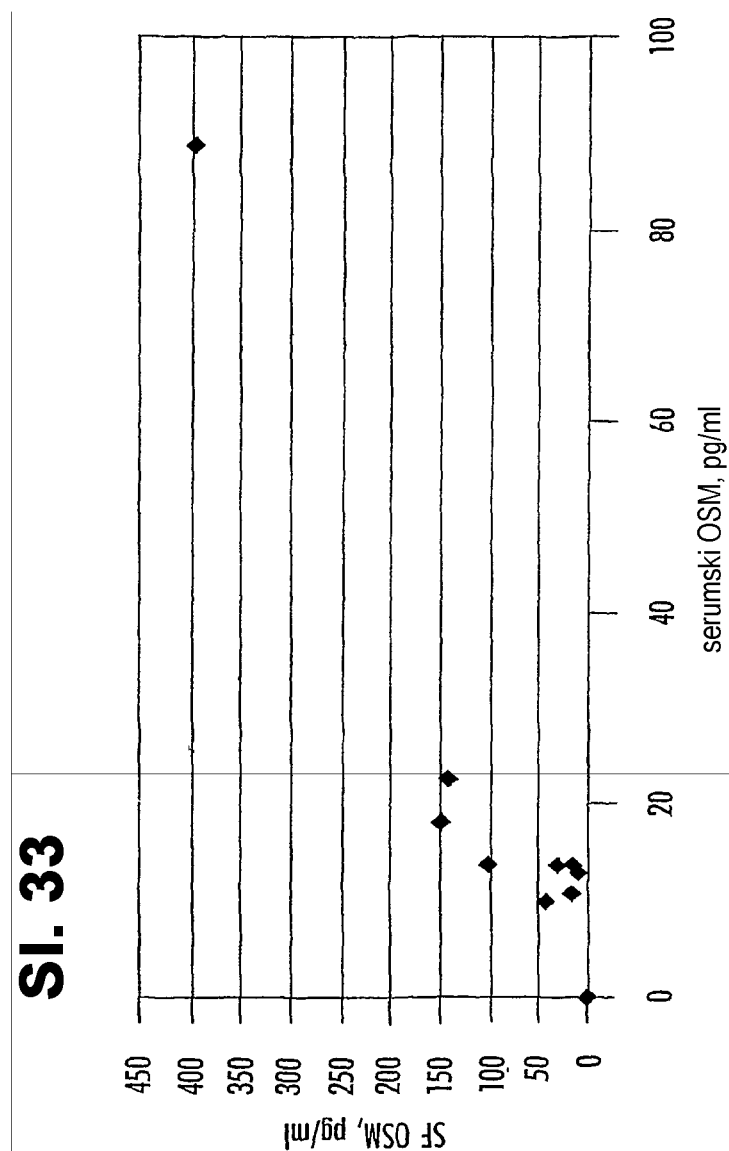
Sl. 28**a****b**

Sl. 29

SI. 30

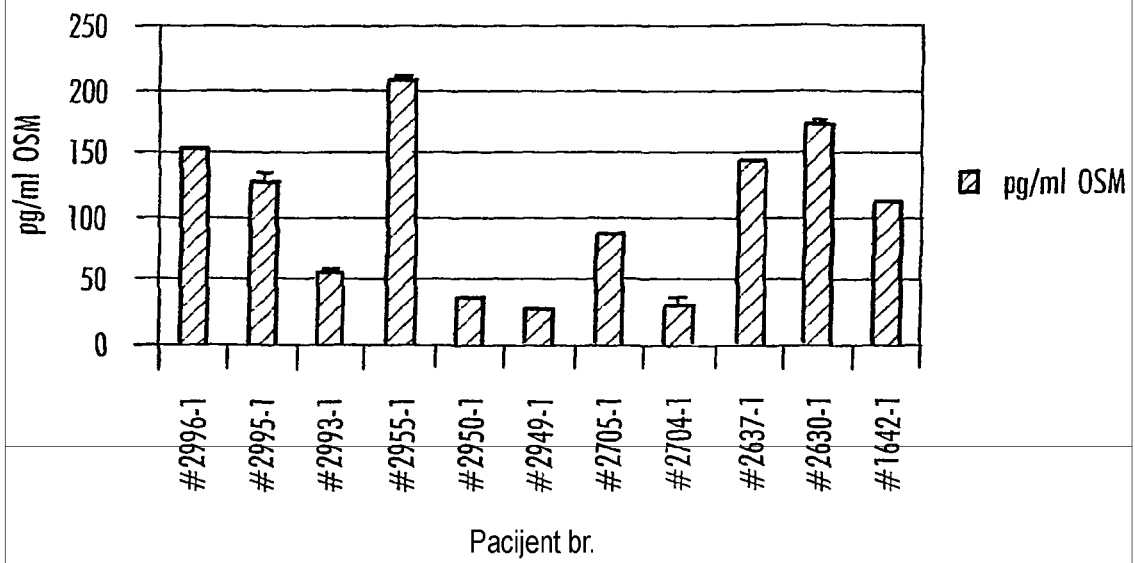
SI. 31**a****b**

Sl. 32**a****b**

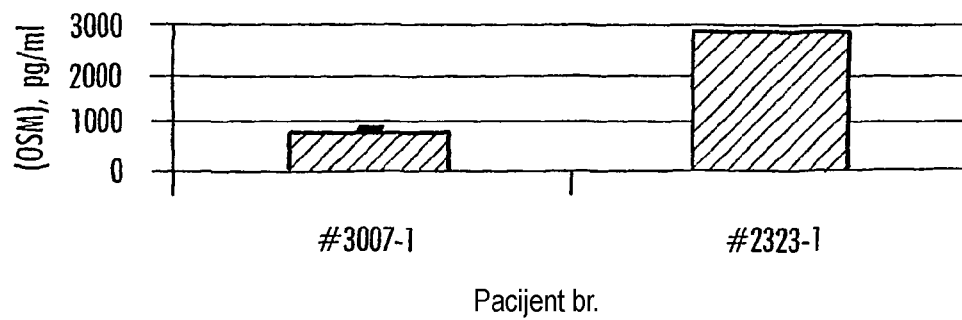


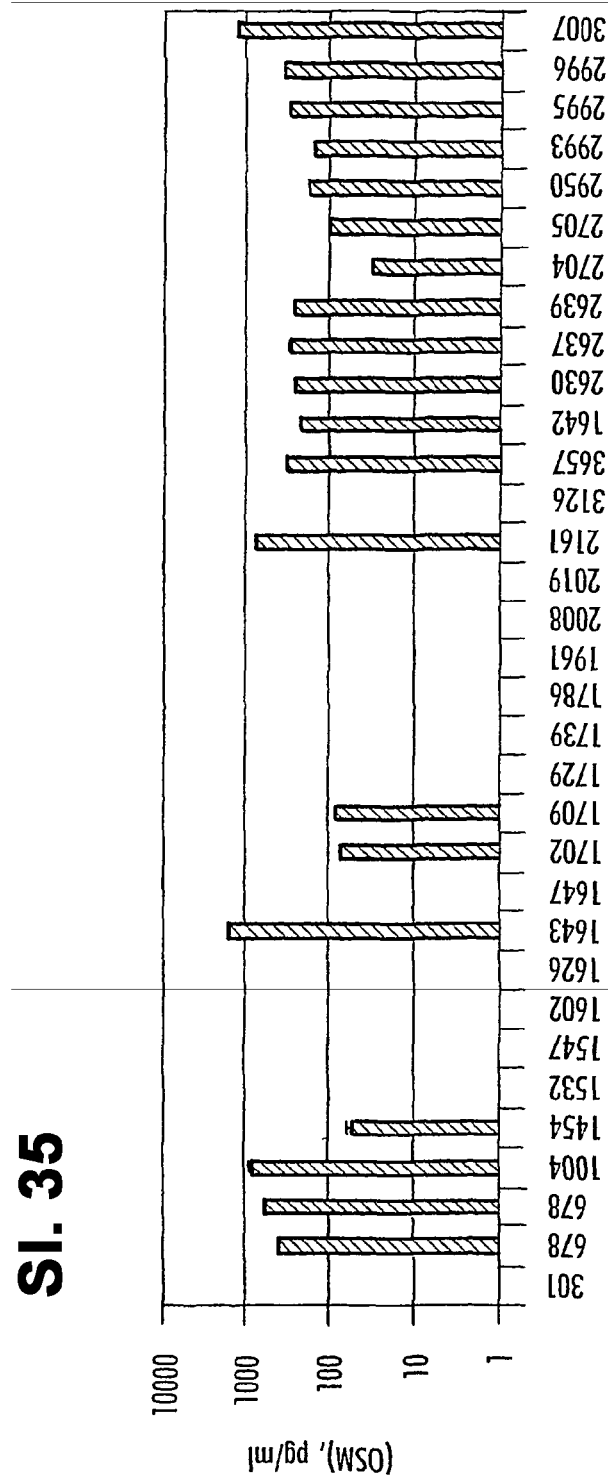
Sl. 34

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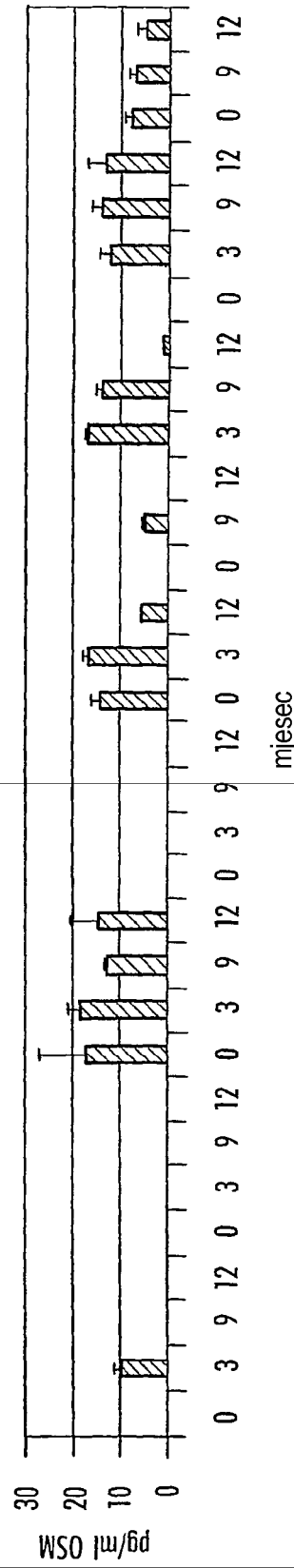


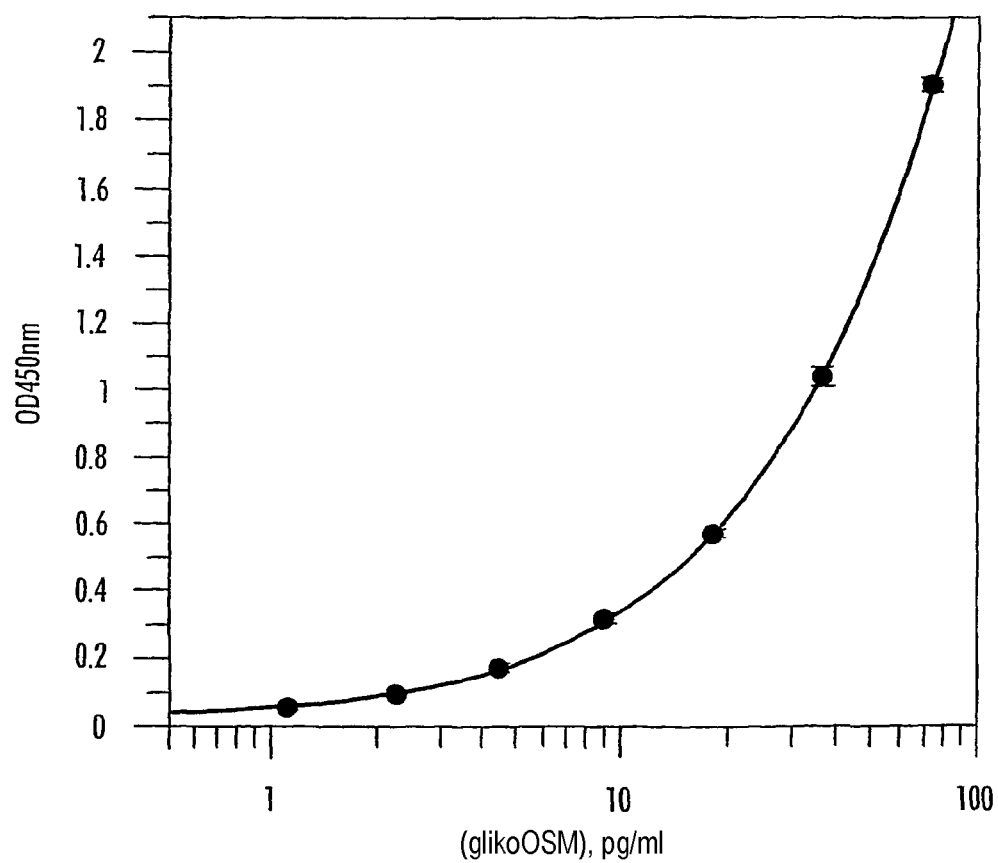
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Sl. 36



SI. 37

SPISAK SLJEDOVA

SEQ. I. D. NO: 1

NYGVH

SEQ. I. D. NO: 2

VIWRGGSTDYNAAFMS

SEQ. I. D. NO: 3

SPNSNFYWFYFDV

SEQ. I. D. NO: 4

SGSSSVSYMY

SEQ. I. D. NO: 5

DTSNLAS

SEQ. I. D. NO: 6

QQWSSYPPT

SEQ. I. D. NO: 7

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GRGTLVTVSS

SEQ. I. D. NO: 10

EIVLTQSPATLSPGERATLSCSGSSSVSYMYWYQQKPGQAPRLLIEDTSNLAS
GIPARFSGSGSGTDYTLTISNLEPEDFAVYYCQQWSSYPPTFGQGTKLEIK

SEQ. I. D. NO: 11

QVQLVESGGGVVQPGRSLRLSCAASGFSLTNYGVHWVRQAPGKGLEWVAVIWRGG
STDYNAAFMSRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAKSPNSNFYWFYFDVW
GRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTFSWNSGA
LTSQGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKEVP
KSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
VKENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPFENNYKRTTPFVLDSGSSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT
QKSLSLSPGK

SEQ. I. D. NO: 12

EIVLTQSPATLSPGERATLSCSGSSSVSYMYWYQQKPGQAPRLLIEDTSNLAS
GIPARFSGSGSGTDYTLTISNLEPEDFAVYYCQQWSSYPPTFGQGTKLEIKRTVA
APSVFI FPPSDEQLKSGTASVVCILNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ. I. D. NO: 15

CAGGTGCAACTGAAGCAGTCAGGACCTGGCCTAGTGCAGCCCTCACAGAGCCTGT
CCATAACCTGCACAGTCTCTGTTTCTCATTAATAATTATGGTGACACTGGGT
TCGCCAGTCTCCAGGAAAGGGTCTGGAGTGGCTGGGAGTGATATGGAGAGGTGGA
AGCACAGACTACAATGCAGCTTTCATGTCCAGACTGAGCATCACCAAGGACAAC

CCAGGAGCCAAGTTTCTTTAAATGAACAGTCTACAAGCTGATGACACTGCCAT
ATACTACTGTGCCAAAAGTCCGAATAGTAACTTTACTGGTATTTGATGTCTGG
GGCACAGGGACCACGGTCACCGTCTCCTCA

SEQ. I. D. NO:16

CAAATTGTTCTCAGCCAGTCTCCAACAATCATGTCTGCATCTCCAGGGGAGAAGG
TCACCATGACCTGCAGTGGCAGCTCAAGTGTAAGTTACATGTATTGGTACCAGGA
GAAGCCAGGATCCTCCCCAGACTCCTGATTGAAGACACATCCAACCTGGCTTCT
GGAGTCCCCTGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACA
TCAGCCGAATGGAGGCTGAAGATGCTGCCACTTATTACTGTCAACAGTGGAGTAG
TTATCCACCCACGTTCCGGCTCGGGGACAAAGTTGGAAATCAAA

SEQ. I. D. NO:17

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTCTCATTAACATAATTATGGTGTACACTGGGT
CCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTGATATGGAGAGGTGGA
AGCACAGACTACAATGCAGCTTTCATGTCCCGATTACCATCTCCAAGGACAATT
CCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGT
GTATTACTGTGCGAAAAGTCCGAATAGTAACTTTACTGGTATTTGATGTCTGG
GGCGTGGCACACTAGTCACAGTCTCCTCA

SEQ. I. D. NO:18

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCCTCCTGCAGTGGCAGCTCAAGTGTAAGTTACATGTATTGGTACCAACA
GAAACCTGGCCAGGCTCCAGGCTCCTCATCGAAGACACATCCAACCTGGCTTCT
GGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTACACTCTCACCA
TCAGCAACCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGTGGAGTAG
TTATCCACCCACGTTTGGCCAGGGGACCAAGCTGGAGATCAAA

SEQ. I. D. NO:19

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTCTCATTAACATAATTATGGTGTACACTGGGT
CCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTGATATGGAGAGGTGGA
AGCACAGACTACAATGCAGCTTTCATGTCCCGATTACCATCTCCAAGGACAATT
CCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGT
GTATTACTGTGCGAAAAGTCCGAATAGTAACTTTACTGGTATTTGATGTCTGG
GGCGTGGCACACTAGTCACAGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCT
TCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGACAGCGGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCC
CTGACCAGCGCGTGCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACT
CCTCAGCAGCGTGGTGCACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACT
CTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCC
AAATCTTGTGACAAAACCTCACACATGCCACCGTGGCCAGCACCTGAACTCCTGG
GGGGACCGTCACTCTTCTCTTCCCCCAAAACCAAGGACACCTCATGATCTC
CCGGACCCCTGAGGTGAGTGCCTGGTGGTGGACGTGAGCCACGAAGACCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC
CGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAAGCTCCTCACCCTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCC
CTCCAGCCCCCATCGAGAAAACCTCTCCAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCTTGCCTCCATCCCGGGATGAGCTGACCAAGAACCAAGGTGAG
CCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG
AGCAATGGGCAGCCGGAGAACTACAAGACCAGCCTCCCGTGTCTGGACTCCG
ACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA
GGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG
CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ. I. D. NO:20

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCCTCCTGCAGTGGCAGCTCAAGTGTAAGTTACATGTATTGGTACCAACA
GAAACCTGGCCAGGCTCCAGGCTCCTCATCGAAGACACATCCAACCTGGCTTCT
GGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTACACTCTCACCA

TCAGCAACCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGTGGAGTAG
TTATCCACCCACGTTTGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTGGCT
GCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACG
CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG
GAAGGTGGACAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAGAGCAG
GACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG
ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTC
GCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ. I. D. NO: 21

QVQLVESGGGVVQPGRSLRLSCAASGFSLTNYGVHWVRQAPGKGLEWVAVIWRG
GSTDYNAAFMRLTISKDNSKNTLYLQMNSLRAEDTAVYYCAKSPNSNFYWFYFD
VWGRGTLTVSS

SEQ. I. D. NO: 40

DYNMD

SEQ. I. D. NO: 41

DINPNNGGTILNQKFKD

SEQ. I. D. NO: 42

GIYYYGSHYFDY

SEQ. I. D. NO: 43

SATSSVSVMH

SEQ. I. D. NO: 44

DTSKLAS

SEQ. I. D. NO: 45

QQWSSNPLT

SEQ. I. D. NO: 46

EVQLQQSGPELVKPGASVKISCKASGYIFTDYNMDWVKQSHGKKLEWIGDINPNN
GGTIDNQKFKDKATLTVDKSSSTAYMELSLTSEDVAVYYCARGIYYYGSHYFDY
WGQGTTLTVSS

SEQ. I. D. NO: 47

QIVLTQSPAISASPGKVTMTCSATSSVSVMHWFQKKSGTSPKRWIYDTSKLAS
GVPTRFSGSGSTSYSLTISSMEAEDTATYYCQQWSSNPLTFGSGTKLELK

SEQ. I. D. NO: 48

EVQLVQSGAEVKKPGASVKVSCKASGYIFTDYNMDWVRQAPGQKLEWIGDINPNN
GGTIDNQKFKDRATLTVDKSTSTVYMESSLRSEDVAVYYCARGIYYYGSHYFDY
WGQGTTLTVSS

SEQ. I. D. NO: 49

EIVLTQSPSSLSASVGDRTITCSATSSVSVMHWFQKKPGKAPKRWIYDTSKLAS
GVPSRFSGSGSDTYTLTISSLQPEDFATYYCQQWSSNPLTFGGGTKVDIK

SEQ. I. D. NO: 50

EVQLVQSGAEVKKPGASVKVSCKASGYIFTDYNMDWVRQAPGQKLEWIGDINPNN
GGTIDNQKFKDRATLTVDKSTSTVYMESSLRSEDVAVYYCARGIYYYGSHYFDY
WGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE
PKSCDKHTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVRGFYFSDIAVEW
ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALAHNY
TQKSLSLSPGK

SEQ. I. D. NO: 51

EIVLTQSPSSLSASVGRVTITCSATSSVSVMHWFQKKPGKAPKRWIYDPSKLA
 GVPSRFGSGSGTDYTLTISSLPEDFATYYCQQWSSNPLTFGGGTHKVDIKRTVA
 APSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
 DSKDSTYLSLTSLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ. I. D. NO: 52

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGA
 AGATATCCTGCAAGGCCTCTGGATACATATTCAGTACTACAACATGGACTGGGT
 GAAGCAGAGCCATGGAAGAACTTGAGTGGATTGGAGATATTAATCCTAATAAT
 GGTGGTACTATCGACAACCAGAAGTTCAAGGACAAGGCCACATTGACTGTAGACA
 AGTCCTCCAGCACAGCCTACATGGAGCTCCGAGCCTGACATCTGAGGACACTGC
 AGTCTATTACTGTGCAAGAGGGATTATTACTACGGTAGTCACTACTTTGACTAT
 TGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

SEQ. I. D. NO: 53

CAAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCAC
 CATGACCTGCAGTGGCACCTCAAGTGTAAGTGTGATGCACTGGTTCCAGAAGAAGTCAG
 GTACCTCCCCCAAAGATGGATTTATGACACATCCAACTGGCTTCTGGAGTCCCTACT
 CGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGTAGCATGGAGGC
 TGAAGATACTGCCACTTATTACTGCCAGCAGTGGAGTAGTAACCCACTCACGTTCCGGTT
 CTGGGACCAAGCTGGAGCTGAAA

SEQ. I. D. NO: 54

GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGT
 TTCCTGCAAGGCATCTGGATACATATTCACCGACTACAACATGGACTGGGTGCGACAGG
 CCCCTGGACAAAACTTGAGTGGATTGGAGATATTAATCCTAATAATGGTGGTACTATC
 GACAACCAGAAGTTCAAGGACAGAGCCACCTTGACCGTAGACAAGTCCACGAGCACAGT
 CTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAG
 GGATTTATTACTACGGTAGTCACTACTTTGACTATTGGGGCCAGGGAACACTAGTCACA
 GTCTCCTCA

SEQ. I. D. NO: 55

GAAATTGTGTTGACGAGTCTCCATCCTCCCTGCTCTGCATCTGTTGGAGACAGAGTCAC
 CATCACTTGCAAGTGGCACCTCAAGTGTAAGTGTGATGCACTGGTTCCAGAAGAAACCAG
 GGAAAGCCCCAAGAGATGGATCTATGACACATCCAACTGGCTTCTGGGGTCCCATCA
 AGGTTCAAGTGGCAGTGGATCTGGGACAGATTACACTCTCACCATCAGCAGTCTGCAACC
 TGAAGATTTTGCAACTTATTACTGCCAGCAGTGGAGTAGTAACCCACTCACGTTCCGGC
 GAGGGACCAAGTGGATATCAAA

SEQ. I. D. NO: 56

GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGT
 TTCCTGCAAGGCATCTGGATACATATTCACCGACTACAACATGGACTGGGTGCGACAGG
 CCCCTGGACAAAACTTGAGTGGATTGGAGATATTAATCCTAATAATGGTGGTACTATC
 GACAACCAGAAGTTCAAGGACAGAGCCACCTTGACCGTAGACAAGTCCACGAGCACAGT
 CTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAG
 GGATTTATTACTACGGTAGTCACTACTTTGACTATTGGGGCCAGGGAACACTAGTCACA
 GTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCCTCCCCCTGGCACCCCTCCTCCAAGAG
 CACCTCTGGGGGCACAGCGGCCCTGGGCTGCCGTGGTCAAGGACTACTTCCCCGAACCGG
 TGACGGTGTGCTGGAACCTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCCGGCTGTC
 CTACAGTCCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
 GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACA
 AGAAAGTTGAGCCCCAATCTTGTGACAAAACACACATGCCACCGTGCCAGCACCT
 GAACTCCTGGGGGGACCGTCACTCTTCTCTTCCCCCAAAACCAAGGACACCCCTCAT
 GATCTCCCCGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTG
 AGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATTAATGCCAAGACAAAGCCG
 CGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAAGCTCCTCACCGTCTGCACCA
 GGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCC
 CCAATCGAGAAAACCACTCTCCAAGGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACC
 CTGCCCCCACTCCCGGGATGAGCTGACCAAGAACAGGTGAGCCTGACCTGCCTGGTCAA
 AGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCCGAGAACA

ACTACAAGACCACGCCTCCCGTGGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCCTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ. I. D. NO: 57

GAAATTGTGTTGACGCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACAGAGTCAC
CATCACTTGCAGTGCCACCTCAAGTGTAAGTGTGATGCATGCTGGTTCCAGAAGAAACCAG
GGAAAGCCCCCTAAGAGATGGATCTATGACACATCCAAACTGGCTTCTGGGGTCCCATCA
AGGTTTCAGTGGCAGTGGATCTGGGACAGATTACACTCTCACCATCAGCAGTCTGCAACC
TGAAGATTTTGCACCTTATTACTGCCAGCAGTGGAGTAGTAACCCACTCACGTTTCGGCG
GAGGGACCAAAGTGGATATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCG
CCATCTGATGAGCAGTTGAAATCTGGAACGTGCTCTGTGTGTGCTGCTGAATAACTT
CTATCCAGAGAGGGCCAAAGTACAGTGAAGGTGGACAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC
CTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ. I. D. NO: 61

QVQLVESGGGVVQPGKSLRLSCAASGFSLTNYGVHWVRQAPGKLEWVAVIWRG
GSTDYNAAFMSRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAKSPNSNFYWFYD
VWGRGTLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEFVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKHTHTCPPCPAPELAGAPSVFLEPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKLPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
EALHNHYTQKSLSLSPGK

SEQ. I. D. NO: 62

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCC'TG
AGACTCTCCTGTGCAGCGTCTGGATTCTCATTAACTAATTATGGTGTACACTGG
GTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTGATATGGAGAGGT
GGAAGCACAGACTACAATCAGAGCTTTCATGTCCCAGTTCACCATCTCCAAGGAC
AATPCCAAGAAGACAGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACAG
GCTGTGTATTA'FACTGTGCGAAAAGTCCGAATAGTAACCTTTACTGGTATTTTCGAT
GTCTGGGGCCGTGGCACACTAGTCACAGTCTCCTCAGCCTCCACCAAGGGCCCCA
TCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCC
CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAC
TCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCTCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGGACC
CAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAG
AAAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCCCAGCA
CCTGAACCTCGCGGGGGCACCGTCACTCTTCTCTTCCCCCAAACCCAAGGAC
ACCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGC
CACGAAGACCCGTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCTCACCGTCTTGACACAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAGCC
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTGAGCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC'TACAAGACC
ACGCTTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA