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(54) Title **POLYSACCHARIDE ANTIGEN-GLYCOLIPID CONJUGATE VACCINES**

(56) References Cited:

WO-A1-2010/083728
WO-A2-2006/027685

Patentkrav

1. Forbindelse med den generelle formelen (I):

$$A[L\text{-}CH\text{-}CA]_p \qquad (I)$$

hvori

A representerer et karbohydrat-antigen med 1 til 10 000 karbohydratmonomerer, og karbohydrat-antigenet tilhører klassen polysakkarider, hvori karbohydrat-antigenets karbohydrat-monomer eventuelt er modifisert til å bære amid-, karbonat-, karbamat-, karbonyl-, tiokarbonyl-, karboksy-, tiokarboksy-, ester-, tioester-, eter-, epoksy-, hydroksyalkyl-, alkylenyl-, fenylen-, alkenyl-, imino-, imid-, isourea-, tiokarbamat-, tiourea- og/eller ureaenheter,

p er et antall rester -L-CH-CA som er bundet til karbohydrat-antigen A, og

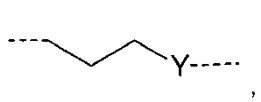
p er et heltall definert som følger:

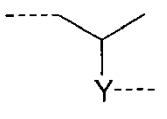
p er 1 eller 2		dersom u er 1
p er 1, 2, 3 eller 4		dersom u er 2
p er 1, 2, 3, 4, 5 eller 6.		dersom u er 3
p er 1, 2, 3, 4, 5, 6, 7 eller 8		dersom u er 4
$1 \leq p \leq 10$	dersom	$5 \leq u \leq 10$
$2 \leq p \leq 50$	dersom	$11 \leq u \leq 100$
$20 \leq p \leq 200$	dersom	$101 \leq u \leq 1000$
$50 \leq p \leq 400$	dersom	$1001 \leq u \leq 10000$

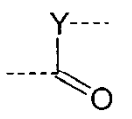
u er antall karbohydrat-monomerer til karbohydrat-antigen A

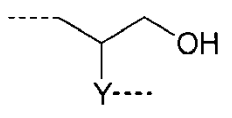
L representerer $-L^1-L^2-$, $-L^2-$, $-L^2-L^3-$ eller $-L^1-L^2-L^3-$;

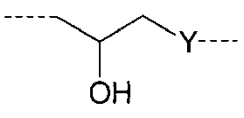
L^1 representerer én av de følgende restene:

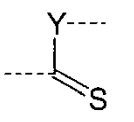


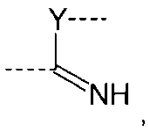


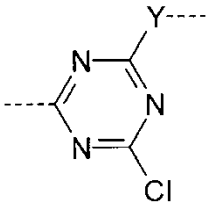


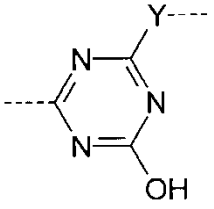


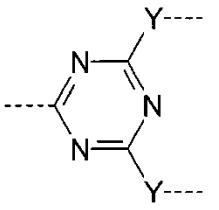


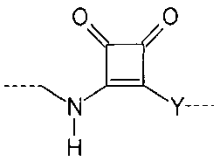


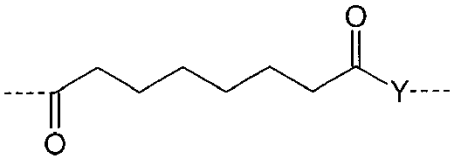

Y
NH

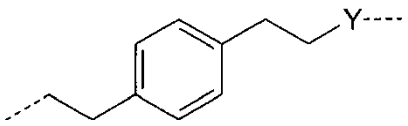

Y
N
N
N
Cl

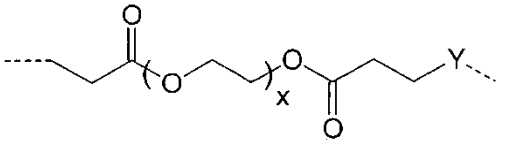

Y
N
N
N
OH

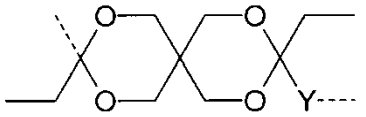

Y
N
N
N
Y

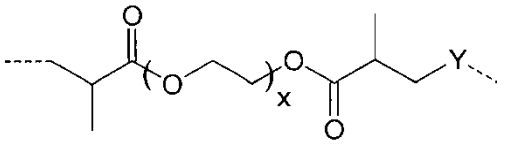

O
O
N
H
Y

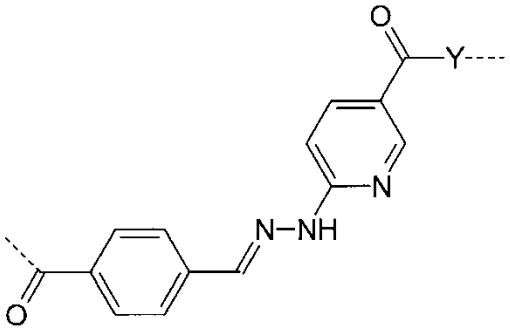

O
Y
O

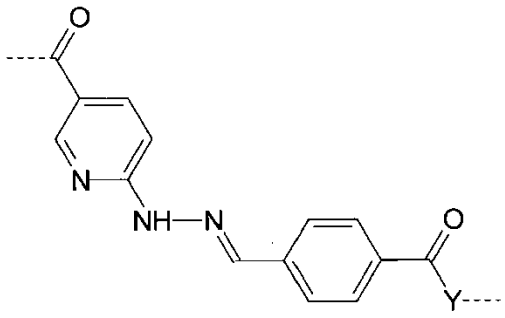

Y

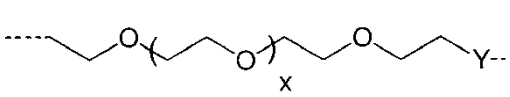

O
O
O
x
O
Y

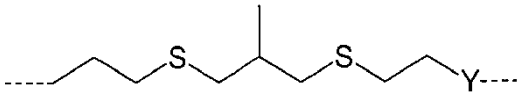

O
O
O
O
Y

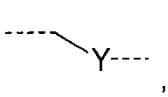

O
O
O
x
O
Y

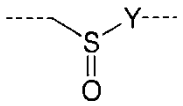

O
Y
N
N–NH
O

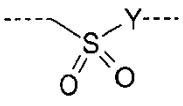

O
N
NH–N
O
Y

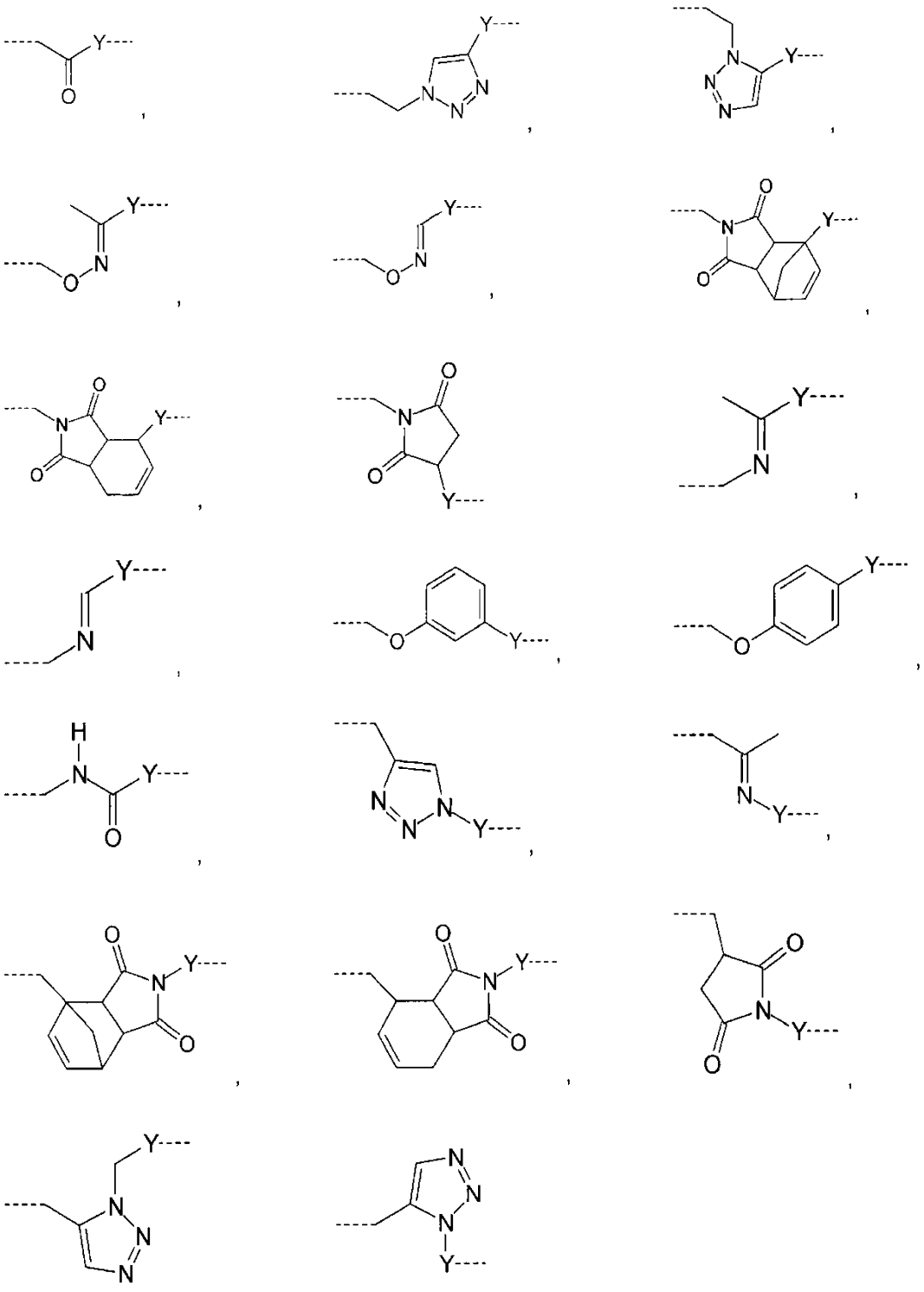

O
O
x
O
Y


S
S
Y


Y


Y
S
O


Y
S
O
O



hvori x er et heltall fra 1 til 60;

Y representerer en binding, -O-, -S-; -S-S-;

L^2 representerer $-CH_2-$, $-C_2H_4-$, $-C_3H_6-$, $-C_4H_8-$, $-C_5H_{10}-$, $-C_6H_{12}-$, $-C_7H_{14}-$, $-C_8H_{16}-$, $-C_9H_{18}-$, $-C_{10}H_{20}-$, $-CH(CH_3)-$, $-C[(CH_3)_2]-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$, $-CH(CH_3)-C_2H_4-$, $-CH_2-CH(CH_3)-CH_2-$, $-C_2H_4-CH(CH_3)-$, $-CH_2-C[(CH_3)_2]-$, $-C[(CH_3)_2]-CH_2-$, $-CH(CH_3)-CH(CH_3)-$, $-C[(C_2H_5)(CH_3)]-$, $-CH(C_3H_7)-$, $-(CH_2-CH_2-$

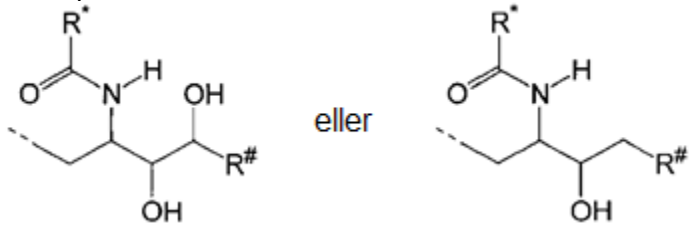
O)$_n$-CH_2-CH_2-, -CO-CH_2-, -CO-C_2H_4-, -CO-C_3H_6-, -CO-C_4H_8-, -CO-C_5H_{10}-, -CO-C_6H_{12}-, -CO-C_7H_{14}-, -CO-C_8H_{16}-, -CO-C_9H_{18}-, -CO-$C_{10}H_{20}$-, -CO-$CH(CH_3)$-, -CO-$C[(CH_3)_2]$-, -CO-CH_2-$CH(CH_3)$-, -CO-$CH(CH_3)$-CH_2-, -CO-$CH(CH_3)$-C_2H_4-, -CO-CH_2-$CH(CH_3)$-CH_2-, -CO-C_2H_4-$CH(CH_3)$-, -CO-CH_2-$C[(CH_3)_2]$-, -CO-$C[(CH_3)_2]$-CH_2-, -CO-$CH(CH_3)$-$CH(CH_3)$-, -CO-$C[(C_2H_5)(CH_3)]$-, -CO-$CH(C_3H_7)$-, -CO-(CH_2-CH_2-O)$_n$-CH_2-CH_2-;

n representerer et heltall fra 1 til 60;

L^3 representerer -CO-, -O-CO-, -NH-CO-, -NH(C=NH)-, -SO_2-, -O-SO_2-, -NH-, -NH-CO-CH_2-;

CH representerer et monosakkarid, et disakkarid eller et trisakkarid;

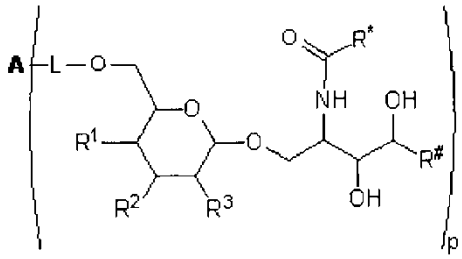
CA representerer



R* og $R^{\#}$ representerer uavhengig av hverandre en lineær eller forgrenet eller syklisk, substituert eller usubstituert, mettet eller umettet karbonrest bestående av 1 til 30 karbonatomer;

og tautomerer og farmasøytisk aksekptable salter derav.

2. Forbindelse ifølge krav 1 med den generelle formelen (II):



(II)

hvori

A, L og p har samme betydning som definert i krav 1;

R^1, R^2, R^3 representerer uavhengig av hverandre:

-H, -OH, -OCH_3, -OC_2H_5, -OC_3H_7, -O-SO_2-CH_3, -O-SO_2-C_2H_5, -O-SO_2-C_3H_7, -O-$COOCH_3$, -$NHCOCH_3$, -NH_2;

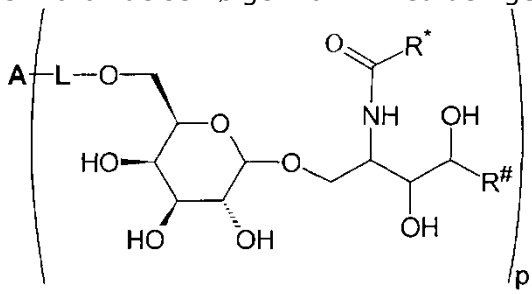
R* og $R^{\#}$ representerer uavhengig av hverandre:

-CH_3, -(CH_2)$_r$-CH_3, -$CH(OH)$-(CH_2)$_s$-CH_3, -$CH{=}CH$-CH_3, -$CH{=}CH$-(CH_2)$_t$-CH_3, -$CH(OH)$-(CH_2)$_v$-$CH(CH_3)_2$, -$CH(OH)$-(CH_2)$_w$-$CH(CH_3)$-CH_2-CH_3, -(CH_2)$_a$-$CH{=}CH$-

$(CH_2)_b$-CH_3, -$(CH_2)_c$-CH=CH-$(CH_2)_d$-CH=CH-$(CH_2)_e$-CH_3, -$(CH_2)_f$-CH=CH-$(CH_2)_g$-CH=CH-$(CH_2)_h$-CH=CH-$(CH_2)_i$-CH_3, -$(CH_2)_j$-CH=CH-$(CH_2)_k$-CH=CH-$(CH_2)_l$-CH=CH-$(CH_2)_o$-CH=CH-$(CH_2)_q$-CH_3,

hvori a, b, c, d, e, f, g, h, i, j, k, I, o, q er heltall fra 1 til 26 på betingelse av at: (a+b) ≤ 27; (c+d+e) ≤ 25; (f+g+h+i) ≤ 23; (j+k+l+o+q) ≤ 21; og hvori r er et heltall fra 1 til 29, s er et heltall fra 1 til 28, t er et heltall fra 1 til 27, v er et heltall fra 1 til 26, w is et heltall fra 1 til 26.

3. Forbindelse ifølge krav 1 med den generelle formelen (XIV):



(XIV)

hvori

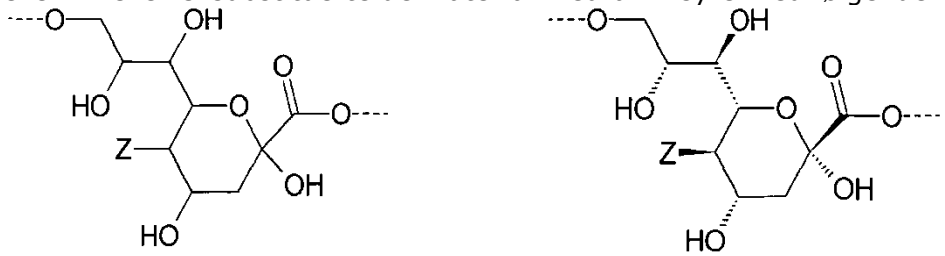
A, L, R^*, $R^\#$ og p har samme betydning som definert i krav 1.

4. Forbindelse ifølge et hvilket som helst av kravene 1 - 3, hvori karbohydratantigenets karbohydratmonomerer tilhører gruppen av karbohydrater omfattende:

α-D-ribopyranose, α-D-arabinopyranose, α-D-xylopyranose, α-D-lyksopyranose, α-D-allopyranose, α-D-altropyranose, α-D-glukopyranose, α-D-mannpyranose, α-D-glukopyranose, α-D-idopyranose, α-D-galaktopyranose, α-D-talopyranose, α-D-psikopyranose, α-D-fruktopyranose, α-D-sorbopyranose, α-D-tagatopyranose, α-D-ribofuranose, α-D-arabinofuranose, α-D-xylofuranose, α-D-lyksofuranose, α-D-Allofuranose, α-D-Altrofuranose, α-D-glukofuranose, α-D-Mannofuranose, α-D-gulofuranose, α-D-idofuranose, α-D-galaktofuranose, α-D-talofuranose, α-D-psikofuranose, α-D-fruktofuranose, α-D-sorbofuranose, α-D-tagatofuranose, α-D-xylulofuranose, α-D-ribulofuranose, α-D-treofuranose, α-D-rhamnopyranose, α-D-erytrofuranose, α-D-glukosamin, α-D-glukopyranuronsyre, β-D-ribopyranose, β-D-arabinopyranose, β-D-xylopyranose, β-D-lyksopyranose, β-D-allopyranose, β-D-altropyranose, β-D-glukopyranose, β-D-mannpyranose, β-D-glukopyranose, β-D-idopyranose, β-D-galaktopyranose, β-D-talopyranose, β-D-psikopyranose, β-D-fruktopyranose, β-D-sorbopyranose, β-D-tagatopyranose, β-D-ribofuranose, β-D-arabinofuranose, β-D-xylofuranose, β-D-lyksofuranose, β-D-rhamnopyranose, β-D-allofuranose, β-D-altrofuranose, β-D-

glukofuranose, β-D-mannofuranose, β-D-gulofuranose, β-D-idofuranose, β-D-galaktofuranose, β-D-talofuranose, β-D-psikofuranose, β-D-fruktofuranose, β-D-sorbofuranose, β-D-tagatofuranose, β-D-xylulofuranose, β-D-ribulofuranose, β-D-treofuranose, β-D-erytrofuranose, β-D-glukosamin, β-D-glukopyranuronsyre, α-L-ribopyranose, α-L-arabinopyranose, α-L-xylopyranose, α-L-lyksopyranose, α-L-allopyranose, α-L-altropyranose, α-L-glukopyranose, α-L-mannopyranose, α-L-glukopyranose, α-L-idopyranose, α-L-galaktopyranose, α-L-talopyranose, α-L-psikopyranose, α-L-fruktopyranose, α-L-sorbopyranose, α-L-tagatopyranose, α-L-rhamnopyranose, α-L-ribofuranose, α-L-arabinofuranose, α-L-xylofuranose, α-L-lyksofuranose, α-L-Allofuranose, α-L-Altrofuranose, α-L-glukofuranose, α-L-Mannofuranose, α-L-gulofuranose, α-L-idofuranose, α-L-galaktofuranose, α-L-talofuranose, α-L-psikofuranose, α-L-fruktofuranose, α-L-sorbofuranose, α-L-tagatofuranose, α-L-xylulofuranose, α-L-ribulofuranose, α-L-treofuranose, α-L-erytrofuranose, α-L-glukosamin, α-L-glukopyranuronsyre, β-L-ribopyranose, β-L-arabinopyranose, β-L-xylopyranose, β-L-lyksopyranose, β-L-allopyranose, β-L-altropyranose, β-L-glukopyranose, β-L-mannopyranose, β-L-glukopyranose, β-L-idopyranose, β-L-galaktopyranose, β-L-talopyranose, β-L-psikopyranose, β-L-fruktopyranose, β-L-sorbopyranose, β-L-tagatopyranose, β-L-ribofuranose, β-L-arabinofuranose, β-L-xylofuranose, β-L-lyksofuranose, β-L-allofuranose, β-L-altrofuranose, β-L-glukofuranose, β-L-mannofuranose, β-L-gulofuranose, β-L-idofuranose, β-L-galaktofuranose, β-L-talofuranose, β-L-psikofuranose, β-L-fruktofuranose, β-L-sorbofuranose, β-L-tagatofuranose, β-L-xylulofuranose, β-L-ribulofuranose, β-L-treofuranose, β-L-erytrofuranose, β-L-glukosamin, β-L-glukopyranuronsyre, β-L-rhamnopyranose,

eller N- eller O-substituerte derivater av neuraminsyre med følgende formel:



hvori Z representerer $-NH_2$, -NHAc, eller -OH. ;

5. Forbindelse ifølge et hvilket som helst av kravene 1 - 4, hvori CH-enhetens karbohydrat-monomerer tilhører gruppen av karbohydrater omfattende:
α-D-ribopyranose, α-D-arabinopyranose, α-D-xylopyranose, α-D-lyksopyranose, α-D-allopyranose, α-D-altropyranose, α-D-glukopyranose, α-D-mannpyranose, α-D-glukopyranose, α-D-idopyranose, α-D-galaktopyranose, α-D-talopyranose,

α-D-psikopyranose, α-D-fruktopyranose, α-D-sorbopyranose, α-D-tagatopyranose, α-D-ribofuranose, α-D-arabinofuranose, α-D-xylofuranose, α-D-lyksofuranose, α-D-Allofuranose, α-D-Altrofuranose, α-D-glukofuranose, α-D-Mannofuranose, α-D-gulofuranose, α-D-idofuranose, α-D-galaktofuranose, α-D-talofuranose, α-D-psikofuranose, α-D-fruktofuranose, α-D-sorbofuranose, α-D-tagatofuranose, α-D-xylulofuranose, α-D-ribulofuranose, α-D-treofuranose, α-D-erytrofuranose, α-D-glukosamin, α-D-glukopyranuronsyre, α-D-rhamnopyranose, β-D-ribopyranose,

β-D-arabinopyranose, β-D-xylopyranose, β-D-lyksopyranose, β-D-allopyranose, β-D-altropyranose, β-D-glukopyranose, β-D-mannpyranose, β-D-glukopyranose, β-D-idopyranose, β-D-galaktopyranose, β-D-talopyranose, β-D-psikopyranose, β-D-fruktopyranose, β-D-sorbopyranose, β-D-tagatopyranose, β-D-ribofuranose, β-D-arabinofuranose, β-D-xylofuranose, β-D-lyksofuranose, β-D-allofuranose, β-D-altrofuranose, β-D-glukofuranose, β-D-mannofuranose, β-D-gulofuranose, β-D-idofuranose, β-D-galaktofuranose, β-D-talofuranose, β-D-psikofuranose, P-D-fruktofuranose, β-D-sorbofuranose, β-D-tagatofuranose, β-D-xylulofuranose, β-D-ribulofuranose, β-D-treofuranose, β-D-erytrofuranose, β-D-rhamnopyranose, β-D-glukosamin, β-D-glukopyranuronsyre, α-L-ribopyranose, α-L-arabinopyranose, α-L-xylopyranose, α-L-lyksopyranose, α-L-allopyranose, α-L-altropyranose, α-L-glukopyranose, α-L-mannopyranose, α-L-glukopyranose, α-L-idopyranose, α-L-galaktopyranose, α-L-talopyranose, α-L-psikopyranose, α-L-fruktopyranose, α-L-sorbopyranose, α-L-tagatopyranose, α-L-ribofuranose, α-L-arabinofuranose, α-L-xylofuranose, α-L-lyksofuranose, α-L-Allofuranose, α-L-Altrofuranose, α-L-glukofuranose, α-L-Mannofuranose, α-L-gulofuranose, α-L-idofuranose, α-L-galaktofuranose, α-L-talofuranose, α-L-psikofuranose, α-L-fruktofuranose, α-L-sorbofuranose, α-L-tagatofuranose, α-L-xylulofuranose, α-L-ribulofuranose, α-L-rhamnopyranose α-L-treofuranose, α-L-erytrofuranose, α-L-glukosamin, α-L-glukopyranuronsyre, β-L-ribopyranose, β-L-arabinopyranose, β-L-xylopyranose, β-L-lyksopyranose, β-L-allopyranose, β-L-altropyranose, β-L-glukopyranose, β-L-mannpyranose, β-L-glukopyranose, β-L-idopyranose, β-L-galaktopyranose, β-L-talopyranose, β-L-psikopyranose, β-L-fruktopyranose, β-L-sorbopyranose, β-L-tagatopyranose, β-L-ribofuranose, β-L-arabinofuranose, β-L-xylofuranose, β-L-lyksofuranose, β-L-allofuranose, β-L-altrofuranose, β-L-glukofuranose, β-L-mannofuranose, β-L-gulofuranose, β-L-idofuranose, β-L-galaktofuranose, β-L-talofuranose, β-L-psikofuranose, β-L-fruktofuranose, β-L-sorbofuranose, β-L-tagatofuranose, β-L-xylulofuranose, β-L-ribulofuranose, β-L-

treofuranose, β-L-erytrofuranose, β-L-glukosamin, β-L-glukopyranuronsyre, β-L-rhamnopyranose.

6. Forbindelse ifølge hvilke som helst av kravene 1 - 5, hvori sakkarid-antigen-A er et bakterielt kapselsakkarid, et sakkarid til et virusglykoprotein, et sakkarid-antigen til sporozoer eller parasitter, et sakkarid-antigen til patogene sopper eller et sakkarid-antigen som er spesifikt for kreftceller.

7. Forbindelse ifølge hvilke som helst av kravene 1 - 6 for bruk som farmasøytisk aktivt middel i medisin eller for bruk i vaksinasjon mot infeksjonssykdommer.

8. Forbindelse ifølge krav 7, hvori infeksjonssykdommen er forårsaket av et patogen valgt fra gruppen omfattende:
Allochromatium vinosum, Acinetobacter baumanii, Bacillus anthracis, Campylobacter jejuni, Clostridium spp., Citrobacter spp., Escherichia coli, Enterobacter spp., Enterococcus faecalis., Enterococcus faecium, Francisella tularensis, Haemophilus influenzae, Helicobacter pylori, Klebsiella spp., Listeria monocytogenes, Moraxella catharralis, Mycobacterium tuberculosis, Neisseria meningitidis, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella spp., Serratia spp., Shigella spp., Stenotrophomonas maltophilia, Staphyloccocus aureus, Staphyloccocus epidermidis, Streptococcus pneunmoniae, Streptococcus pyogenes, Streptococcus agalactiae, Yersina pestis, Yersina enterocolitica,
infuensavirus, humant immunsviktvirus ("HIV"), herpes simplex-virus ("HSV", type 1 eller 2), humant papillomavirus ("HPV", type 16 eller 18), humant cytomegalovirus ("HCMV") eller humant hepatitt B- eller C-virus ("HBV", Type B; "HCV", type C).

9. Forbindelse ifølge krav 6, hvori det bakterielle kapselsakkaridet tilhører bakterier valgt fra:
Allochromatium vinosum, Acinetobacter baumanii, Bacillus anthracis, Campylobacter jejuni, Clostridium spp., Citrobacter spp., Escherichia coli, Enterobacter spp., Enterococcus faecalis., Enterococcus faecium, Francisella tularensis, Haemophilus influenzae, Helicobacter pylori, Klebsiella spp., Listeria monocytogenes, Moraxella catharralis, Mycobacterium tuberculosis, Neisseria meningitidis, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella spp., Serratia spp., Shigella spp.,

Stenotrophomonas maltophilia, Staphyloccocus aureus, Staphyloccocus epidermidis, Streptococcus pneunmoniae, Streptococcus pyogenes, Streptococcus agalactiae, Yersina pestis og Yersina enterocolitica.

10. Forbindelse ifølge krav 6, hvori sakkaridet til virale glykoproteiner tilhører virus valgt fra:
Adenovirus, ebolavirus, Epstein-Barr-virus, flavivirus, FSME-virus, influensavirus, hantavirus, humant immunsviktvirus ("HIV"), herpes simplex virus ("HSV", type 1 eller 2), humant herpesvirus 6 (HHV-6), humant papillomavirus ("HPV", type 16 eller 18), humant cytomegalovirus ("HCMV"), humant hepatitt B- eller C-virus ("HBV", Type B; "HCV", type C), lassavirus, lyssavirus (EBL 1 eller EBL 2), marburgvirus, norovirus, parvo-virus B19, pestvirus, poliovirus, rhinovirus, rotaviruses, SARS-assosiert coronavirus, varicella-zoster-virus.

11. Forbindelse ifølge krav 6, hvori sakkarid-antigenet til sporozoer eller parasitter tilhører sporozoer eller parasitter valgt fra:
Babesia, Balantidium, Besnoitia, Blastocystis, Coccidia, Cryptosporidium, Cytauxzoon, Cyclospora, Dientamoeba, Eimeria, Entamoeba, Enterocytozoon, Enzephalitozoon, Eperythrozoon, Giardia, Hammondia, Isospora, Leishmania, Microsporidia, Naegleria, Plasmodium, Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi, Pneumocystis, Schistosoma, Sarcocystis, Theileria, Trichinella, Toxoplasma, Trichomonas, Trypanosoma, Unicaria, Cestoda, Dipylidium, Dranunculus, Echinococcus, Fasciola, Fasciolopsis, Taenia, Ancylostoma, Ascaris, Brugia, Enterobius, Loa loa, Mansonella, Necator, Oncocerca, Strongyloides, Strongylus, Toxocara, Toxascaris, Trichuris eller Wucheria.

12. Forbindelse ifølge krav 6, hvori sakkarid-antigenet til sopp tilhører sopper valgt fra:
Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton interdigitale, T. schönleinii, T. verrucosum, T. violaceum, T. tonsurans, Trichophyton spp., M. canis, Candida albicans, C. guillermondii, C. krusei, C. parapsilosis, C. tropicalis, C. glabrata, Candida spp., Microsporum spp., Microsporum canis, Microsporum audonii, Microsporum gypseum, M. ferrugineum, Trichosporum beigelii, Trichosporum inkiin, Aspergillus niger, Alternaria, Acremonium, Fusarium eller Scopulariopsis.

13. Forbindelse ifølge krav 6, hvori sakkarid-antigenet som er spesifikt for kreftceller tilhører gruppen av kreft valgt fra:
blærekreft, brystkreft, tykktarmskreft og rektal kreft, endometriekreft, nyrekreft, leukemi, lungekreftmelanom, non-Hodkins lymfom, pankreaskreft, prostatakreft, skjoldbruskkjertelkreft.

14. Forbindelse ifølge hvilke som helst av kravene 1 - 6, hvori gjennomsnittsforholdet mellom karbohydrat-antigen A og glykolipid (L-CH-CA) er mellom 1:4 og 1:100 (n/n).

15. Vaksineformulering omfattende én forbindelse eller en blanding av ulike forbindelser ifølge et hvilket som helst av kravene 1 - 14.