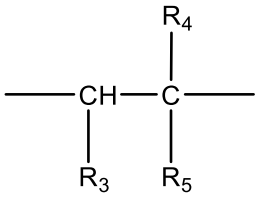
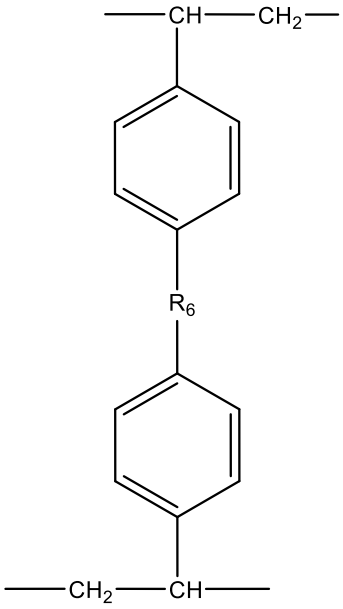
We claim:

1. A solid-phase synthesis carrier, wherein, the solid-phase synthesis carrier is a copolymer comprising repeating structural units represented by formula (I), formula (II), formula (III), and formula (IV) in its skeleton:



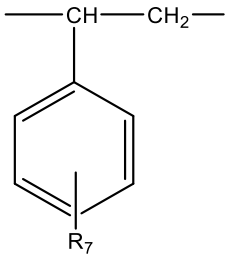
(I)

wherein, R_3 is selected from the groups consisting of -H, -CN and $-CH_2-CN$; R_4 is -H or $-CH_3$; and R_5 is selected from the groups consisting of -CN, $-CH_2-CN$, $-COOCH_3$ and $-CONH_2$;



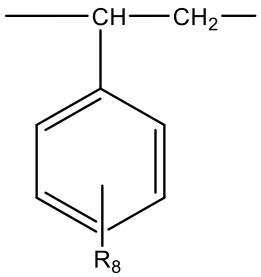
(II)

wherein, R_6 is $-(CH_2)_x-$, x is 2;



(III)

R_7 is selected from the groups consisting of –H, $CH_3(CH_2)_z$ - or $CH_3(CH_2)_ZO$-, wherein z is an integer 0-4, $(CH_3)_2CH$-, $(CH_3)_2CH(CH_2)$-, $(CH_3)_2CH(CH_2)_2$-, $(CH_3)_3C$-, $CH_3CH_2CH(CH_3)$-, $CH_3CH_2C(CH_3)_2$-, and $CH_3CH_2CH_2CH(CH_3)$-;



(IV)

R_8 is selected from the groups consisting of -OH, $-CH_2OH$, $-NH_2$, $-CH_2NH_2$, $-CHCOOC-C_6H_4-OH$, $-CHCOOCCH_2-C_6H_4-OH$, $-(CH_2)_4OOC-C_6H_4-OH$, $-(CH_2)_4OOCCH_2-C_6H_4-OH$, $-COO-C_6H_4-OH$ and $-CH_2COO-C_6H_4-OH$,

wherein the solid-phase synthesis carrier has a content of hydroxyl group or amino group of 100-1000 μmol/g,

the solid-phase synthesis carrier has a particle size in a range of 35-200 μm; and

the solid-phase synthesis carrier has an average pore diameter of 10-200nm.

2. The solid-phase synthesis carrier according to claim 1, wherein the carrier has a content of hydroxyl group or amino group of 400-700 μmol/g.

3. The solid-phase synthesis carrier according to claim 1, wherein the carrier has a particle size in a range of 50-100 μm.

4. The solid-phase synthesis carrier according to claim 1, wherein the carrier has an average pore diameter of 40-100nm.

5. A method for preparing a solid-phase synthesis carrier, wherein the method comprises the following steps of:

A. preparing an aqueous phase and an oil phase, respectively; the aqueous phase

comprising water, a dispersant and an inorganic salt; the oil phase comprising: a cross-linking monomer, a monovinyl compound, a functional monomer, a modified monomer, a pore-forming agent and an initiator, wherein the cross-linking monomer, the monovinyl compound, the functional monomer and the modified monomer are monomers capable of polymerization;

the cross-linking monomer is 1,2-di(4-vinylphenyl)ethane;

the monovinyl compound is styrene, unsubstituted or substituted with C1-C5 alkyl or alkoxy on its benzene ring;

the functional monomer is selected from the group consisting of 4-hydroxystyrene, 4-hydroxymethyl styrene, 4-acetoxy styrene, benzoyloxy styrene, 4-amino styrene, 4-aminomethyl styrene, 4-(4-bromobutyl) styrene, p-chloromethyl styrene, methyl 4-vinylbenzoate, and 4-ethenylbenzeneacetic acid ethyl ester;

the modified monomer is selected from the group consisting of acrylonitrile, methacrylonitrile, fumaronitrile, 1,4-dicyano-2-butene, methyl methacrylate and acrylamide;

the pore-forming agent is an organic solvent or a surfactant which is not polymerizable and insoluble or slightly soluble in water; and

the dispersant is a water-soluble polymer which selected from the group consisting of polyvinyl alcohol, hydroxyethyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, sodium polyacrylate and polyvinylpyrrolidone; and

B. adding the oil phase to the aqueous phase, stirring and heating to carry out polymerization reaction, and removing the pore-forming agent after the polymerization reaction is completed, obtaining a porous polymer resin;

the porous polymer resin is capable of undergoing a further reaction to obtain a solid-phase synthesis carrier containing a hydroxyl group or an amino group as functional groups,

wherein the solid-phase synthesis carrier has a content of hydroxyl group or amino group of 100-1000 μmol/g;

the solid-phase synthesis carrier has a particle size in a range of 35-200 μm; and

the solid-phase synthesis carrier has an average pore diameter of 10-200nm.

6. The method according to claim 5, wherein the initiator is an organic peroxide or an

azo compound.

7. The method according to claim 6, wherein the initiator is selected from the group consisting of benzoyl peroxide, lauroyl peroxide, tert butyl peroxy-2-ethylhexanoate, 2,2'-azobis(2-methylpropionitrile), 2,2'-azobis(2-methylbutyronitrile) and 2,2'-azobis(2,4-dimethyl)valeronitrile.

8. The method according to claim 5, wherein the pore-forming agent is selected from the group consisting of benzene, toluene, ethylbenzene; hexane, heptane, octane, dodecane, isooctane, isododecane and cyclohexane; chloroform, chlorobenzene; ethyl acetate, butyl acetate, dibutyl phthalate; hexanol, cyclohexanol, octanol, isooctanol, decanol, dodecanol; sorbitan trioleate, polyoxyethylene sorbitol beeswax derivative, sorbitan tristearate, polyoxyethylene sorbitol hexastearate, ethylene glycol fatty acid ester, propylene glycol fatty acid ester, propylene glycol monostearate, sorbitan sesquioleate, polyoxyethylene sorbitol oleate, monostearin, lanolin hydroxylated, sorbitol monooleate and propylene glycol laurate, and any combination thereof.

9. The method according to claim 5, wherein,

the dispersant is present in an amount of 0.1-5% by weight in the aqueous phase, and the inorganic salt is present in an amount of 20% by weight or lower in the aqueous phase;

a weight ratio of the oil phase to the aqueous phase is 1:3-1:20;

the monovinyl compound in the oil phase accounts for 45-95% by weight based on a total weight of the monomers;

the cross-linking monomer in the oil phase accounts for 2.9-20% by weight based on a total weight of the monomers;

the functional monomers in the oil phase accounts for 2-20% by weight based on a total weight of the monomers;

the modified monomer in the oil phase accounts for 0.1-15% by weight based on a total weight of the monomers; and

the pore-forming agent in the oil phase accounts for 15-130% by weight based on a total weight of the monomers.

10. The method according to claim 9, wherein,

the monovinyl compound in the oil phase accounts for 62-86% by weight based on a total weight of the monomers;

the cross-linking monomer in the oil phase accounts for 7-13% by weight based on a total weight of the monomers;

the functional monomers in the oil phase accounts for 5-15% by weight based on a total weight of the monomers;

the modified monomer in the oil phase accounts for 2-10% by weight based on a total weight of the monomers; and

the pore-forming agent in the oil phase accounts for 30-110% by weight based on a total weight of the monomers.

11. The method according to claim 5, wherein the polymerization is carried out at a temperature of 50-90 ℃.

12. The method according to claim 11, wherein the polymerization is carried out at a temperature of 70-85 ℃.

13. The method according to any one of claims 5-12, comprising the following steps of:

adding a certain amount of purified water into a reactor, adding the dispersant in an amount which is 0.1-5% by weight of the aqueous phase and the inorganic salt in an amount which is not more than 20% by weight of the aqueous phase, and dissolving to obtain an aqueous phase;

weighing out the monovinyl compound, cross-linking monomer, functional monomer, modified monomer, pore-forming agent and initiator according to a weight ratio of the oil phase to the aqueous phase being1:3-1:20;, wherein, the monovinyl compound accounts for 45-95% of the total weight of the monomers, the cross-linking monomer accounts for 2.9-20% of the total weight of the monomers, the functional monomer accounts for 2-20% of the total weight of the monomers, and the modified monomer accounts for 0.1-15% of the total weight of the monomers,

the pore-forming agent accounts for 15-130% of the total weight of monomers, and mixing well to obtain an oil phase;

adding the oil phase into the reactor, stirring and heating up to 50-90 ℃ to carry out reaction; removing the pore-forming agent after the reaction is completed, and screening and collecting the resin with appropriate particle size, and vacuum drying to obtain a porous polymer resin; and

carrying out a further reaction with the resin to obtain a solid-phase synthesis carrier having amino group or hydroxyl group.

14. The method according to claim 13, comprising the following steps of:

adding a certain amount of purified water into a reactor, adding the dispersant in an amount which is 0.1-5% by weight of the aqueous phase and the inorganic salt in an amount which is not more than 20% by weight of the aqueous phase, and dissolving to obtain an aqueous phase;

weighing out the monovinyl compound, cross-linking monomer, functional monomer, modified monomer, pore-forming agent and initiator according to a weight ratio of the oil phase to the aqueous phase being 1:3-1:20;, wherein, the monovinyl compound accounts for 62-86% of the total weight of the monomers, the cross-linking monomer accounts for 7-13% of the total weight of the monomers, the functional monomer accounts for 5-15% of the total weight of the monomers, and the modified monomer accounts for 2-10% of the total weight of the monomers, the pore-forming agent accounts for 30-110% of the total weight of monomers, and mixing well to obtain an oil phase;

adding the oil phase into the reactor, stirring and heating up to 70-85 ℃ to carry out reaction; removing the pore-forming agent after the reaction is completed, and screening and collecting the resin with appropriate particle size, and vacuum drying to obtain a porous polymer resin; and

carrying out a further reaction with the resin to obtain a solid-phase synthesis carrier having amino group or hydroxyl group.

15. The method according to any one of claims 5-14, comprising the following steps of:

adding 2L of purified water, 20g of polyvinyl alcohol and 30g of sodium chloride into a 3L reactor equipped with a condenser, an agitator and a thermometer, and dissolving to obtain an aqueous phase;

weighing out 108.8g of styrene, 14g of 1,2-di (4-vinylphenyl) ethane, 12.2g of p-chloromethyl styrene, 5g of fumaronitrile, 6g of sorbitol trioleate, 40g of isooctanol, 20g of isododecane and 2.5g of benzoyl peroxide, and mixing well to obtain an oil phase;

adding the oil phase into the reactor, stirring, and heating up to 80 ℃ to carry out polymerization for 6h; washing with hot water after the polymerization is completed, removing the pore-forming agent by ethanol reflux extraction, screening and collecting the resin a particle size of 50-100 μm and vacuum drying to obtain a polymer porous resin with a chlorine content of 565μmol/g;

adding 50g of the polymer porous resin and 500ml of N,N-dimethylformamide into a 1L reactor equipped with a condenser, an agitator and a thermometer, and stirring; then adding 30g of potassium phthalate and heating up to 95 ℃ to carry out reaction for 16 hours; cooling to room temperature after the reaction is completed, washing twice with N,N-dimethylformamide, washing to neutral with purified water, washing three times with absolute ethanol, and filtering and drying the resin; adding 200g of absolute ethanol and 50g of hydrazine hydrate into the reactor, heating up to 75 ℃ and reacting for 16 hours; thereafter washing three times with ethanol/purified water solution with a volume ratio of 50:50, washing to neutral with purified water, washing three times with absolute ethanol, and filtering and drying, adding 200g of absolute ethanol and 50g of concentrated hydrochloric acid to the reactor, heating up to 60 ℃ and reacting for 6h, thereafter cooling to room temperature, washing to neutral with water, and then vacuum drying to obtain a solid-phase synthesis carrier having an amino content of 554 μmol/g and an average pore diameter of 54nm measured by mercury intrusion method.

16. The method according to any one of claims 5-14, comprising the following steps of:

adding 2L of purified water, 20g of polyvinyl alcohol and 30g of sodium chloride into a 3L reactor equipped with a condenser, an agitator and a thermometer, and dissolving to obtain an aqueous phase;

weighing out 107.7g of styrene, 12.8g of 1,2-di (4-vinylphenyl) ethane, 12.5g of 4-acetoxystyrene, 7g of fumaronitrile, 10g of sorbitol trioleate, 42g of isooctanol, 21g of isododecane and 2.5g of benzoyl peroxide, and mixing well to obtain an oil phase;

adding the oil phase into the reactor, stirring, and heating up to 78℃ to carry out polymerization for 6h; washing with hot water after the polymerization is completed, removing the pore-forming agent by ethanol reflux extraction, screening and collecting the resin a particle size of 50-100 μm and vacuum drying to obtain a polymer porous resin;

adding 50g of the polymer porous resin and 300ml of acetonitrile into a 1L reactor equipped with a condenser, an agitator and a thermometer, and stirring; then adding 7.5ml of hydrazine hydrate slowly and reacting for 3h at room temperature, washing to neutral with water, and then vacuum drying to obtain a solid-phase synthesis carrier having a hydroxyl content of 538μmol/g and an average pore diameter of 58nm measured by mercury intrusion method.

17. Use of the solid-phase synthesis carrier of claim 1 and the solid-phase synthesis carrier prepared via the method according to any one of claims 5-16 in the solid-phase synthesis of oligonucleotides.