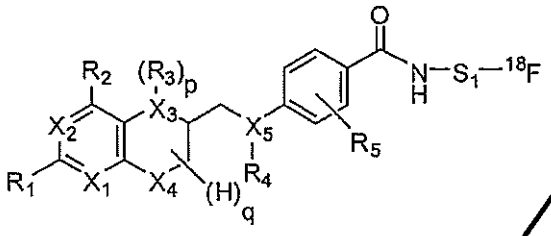
Claims

1. A method of synthesis of a ^{18}F-labeled compound of general formula III



III

wherein

X_1 to X_5 are independently of each other C or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R' is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl, nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, (C1-C12 alkylamino)carbonyl,

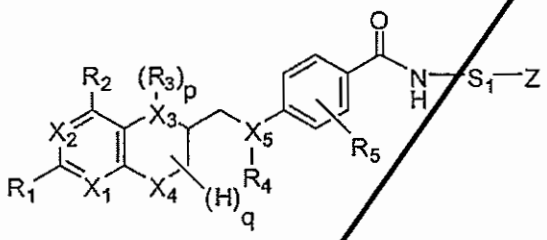
S_1 is a straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-, -CH=CH-, -C≡C-, -S-, $-SO_3R'$-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or

2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

p is 0, 1 or 2, and

q has a value of 1 to 7,

comprising the steps of (a) providing a precursor of formula IV,



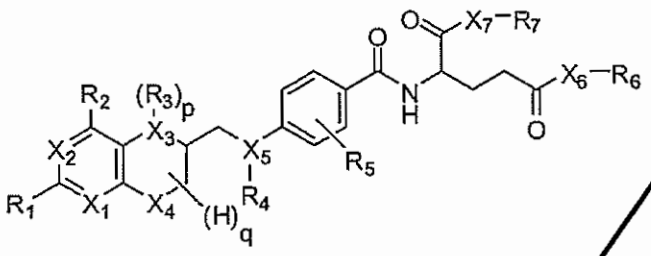
IV

wherein Z is a leaving group, and X_1 to X_5, R_1 to R_5, S_1, p, and q are defined as hereinabove, and (b) subjecting said precursor to direct radiolabeling with ^{18}F.

2. A method according to claim 1, wherein ^{18}F in step (b) is activated by phase transfer catalysts such as tetrabutylamonium carbonate or aminopolyethers (e.g. Kryptofix® 2.2.2) in combination with potassium carbonate or oxalate.

3. A method according to claim 1, wherein Z is selected from Hal, NO_2, diazonium salts, sulfonate esters, including mesylate, tosylate, pentafluorobenzoate, triflate, iodonium salts, dialkyl/-aryl silanes, and silanols.

4. A method according to any preceding claim, wherein the obtained compound has the formula V



V

wherein

X_6, X_7 are independently of each other C, N or O,

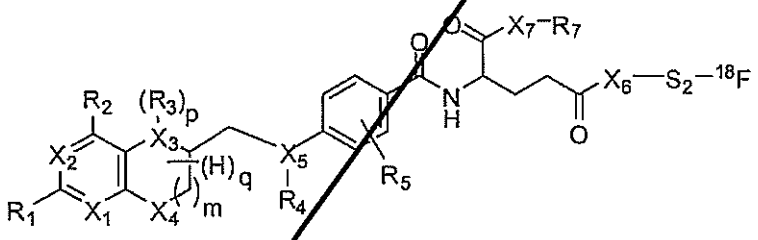
R_6, R_7 are independently of each other H, straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal or NO_2, or a group $-S_2-{}^{18}F$, wherein S_2 is straight chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-, -CH=CH-, -C≡C-, -S-, $-SO_3R'-$, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

with the proviso that at least one of R_6 and R_7 is a group $-S_2-{}^{18}F$, and

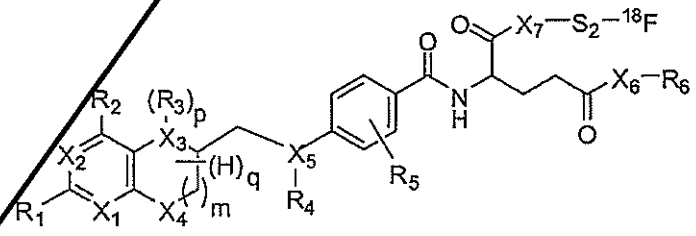
X_1 to X_5, R_1 to R_5, p and q, are as defined in claim 1.

5. A method according to claim 4, wherein S_2 is straight chain or branched C1-C8 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

6. A method according to any preceding claim, wherein the obtained compound has the formulae VI or VIa,



VI



VIa

wherein

X_1 to X_5 are independently of each other C or N,

X_6, X_7 are independently of each other C, O or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-

C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R′ is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl, nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, and (C1-C12 alkylamino)carbonyl,

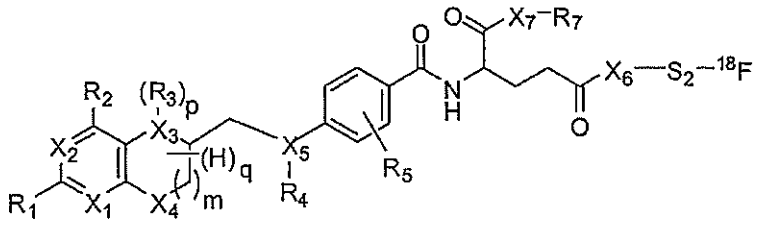
R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2,

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR′-, -N=, -NR′-CO-, -CO-NR′-, -NR′-CO-O-, -O-CO-NR′-, -NR′-CO-NR′-, -CH=CH-, -C≡C-, -S-, -SO_3R′-, -PR′-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR′, or COOR′, wherein R′ represents H or C1-C6 alkyl, or a combination thereof,

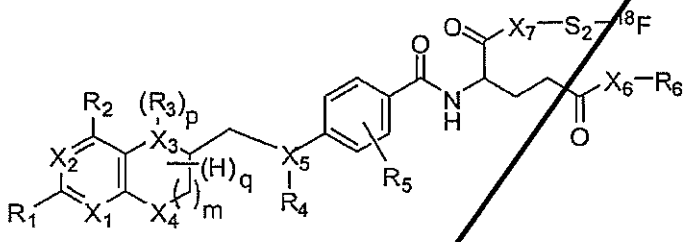
p is 0, 1 or 2, and

q has a value of 1 to 7.

7. A method of synthesis according to claim 1 of a ^{18}F-labeled compound of general formulae VI or VIa,



VI



VIa

wherein

X_1 to X_5 are independently of each other C or N,

X_6, X_7 are independently of each other C, O or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R' is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl, nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, and (C1-C12 alkylamino)carbonyl,

R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substi-

tuted by at least one CN, Hal, or NO_2,

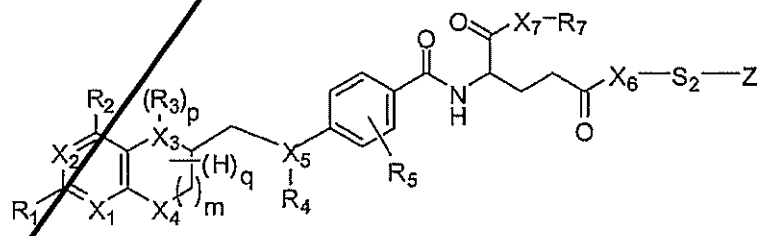
S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-,-CH=CH-, -C≡C-, -S-, $-SO_3R'$-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

p is 0, 1 or 2, and

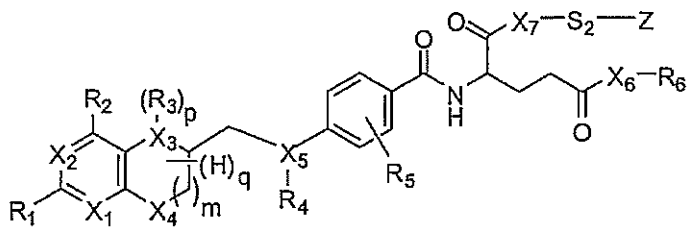
q has a value of 1 to 7,

comprising the steps of

(a) providing a precursor of formulae VII or VIIa,



VII

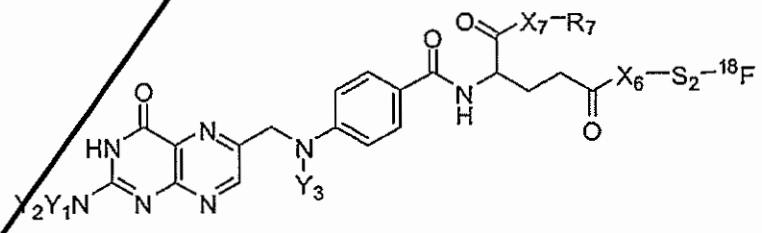


VIIa

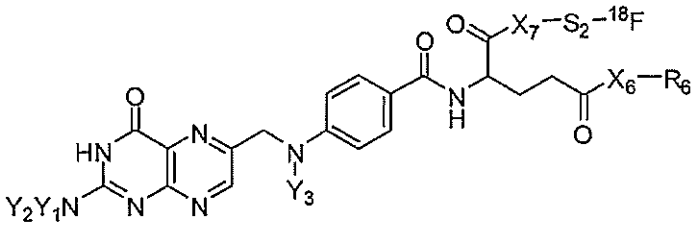
wherein Z is a leaving group, and X_1 to X_7, R_1 to R_7, S_2, p, and q are defined as hereinabove,
and (b) subjecting said precursor to direct radiolabeling with ^{18}F.

8. A method according to claims 6 or 7, wherein S_2 is straight chain or branched C1-C8 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

9. A method according to any preceding claim, wherein the obtained compound has the formulae VIII or VIIIa,



VIII



VIIIa

wherein,

X_6, X_7 are independently of each other C, N or O,

Y_1, Y_2 are independently of each other selected from H, straight chain or branched C_1-C_6 alkyl,

Y_3 is selected from H, formyl, nitroso, straight chain or branched C_1-C_{12} alkyl,

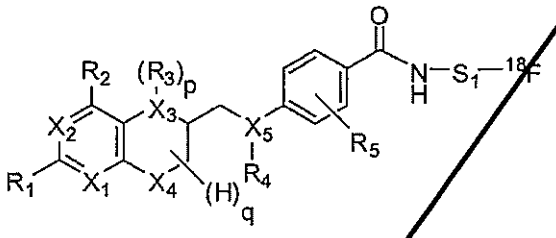
R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-,-CH=CH-, -C≡C-, -S-, -SO_3R'-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

10. A method according to claim 9, wherein S_2 is straight-

chain or branched C1-C8 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, or a five- or six-membered aromatic ring, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

11. A compound according to formula III



III

wherein

X_1 to X_5 are independently of each other C or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R' is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl, nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, (C1-C12 alkylamino)carbonyl,

S_1 is a straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-

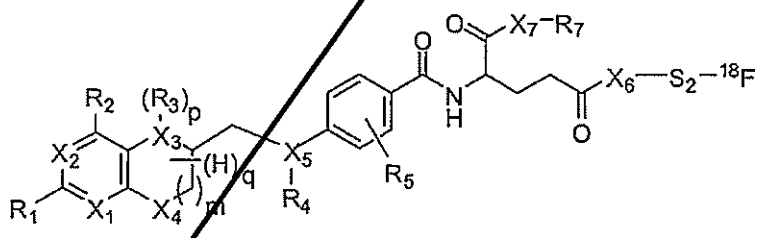
, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-,-CH=CH-, -C≡C-, -S-, -SO_3R'-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

p is 0, 1 or 2, and

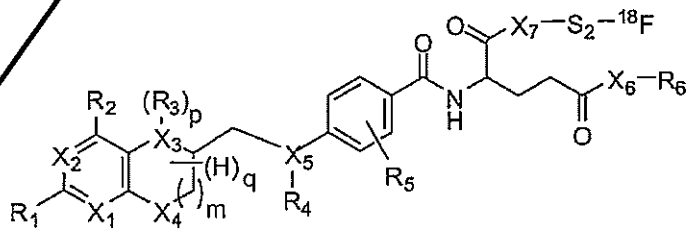
q has a value of 1 to 7,

with the proviso that S_1 does not represent benzyl para-substituted with ^{18}F.

12. A compound according to claim 11 having formulae VI or VIa,



VI



VIa

wherein

X_1 to X_5 are independently of each other C or N,

X_6, X_7 are independently of each other C, O or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R' is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl, nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, and (C1-C12 alkylamino)carbonyl,

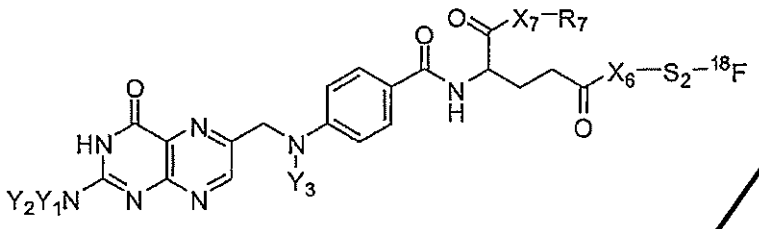
R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2,

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-CO-NR'-, -NR'-CO-NR'-, -CH=CH-, -C≡C-, -S-, -SO_3R'-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

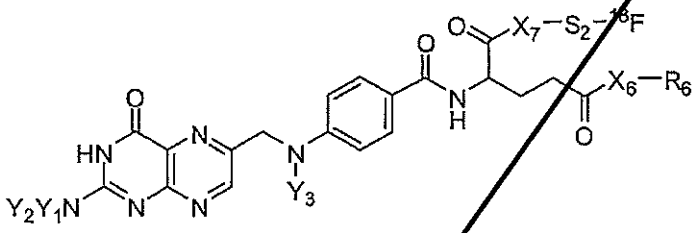
p is 0, 1 or 2, and

q has a value of 1 to 7.

13. A compound according to claim 11 having formulae VIII or VIIIa,



VIII



VIIIa

wherein,

X_6, X_7 are independently of each other C, N or O,

Y_1, Y_2 are independently of each other selected from H, straight chain or branched C_1-C_6 alkyl,

Y_3 is selected from H, formyl, nitroso, straight chain or branched C_1-C_{12} alkyl,

R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, -NR'-, -N=, -NR'-CO-, -CO-NR'-, -NR'-CO-O-, -O-

CO-NR'-, -NR'-CO-NR'-,-CH=CH-, -C≡C-, -S-, -SO_3R'-, -PR'-, or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

14. Use of a compound according to anyone of claims 11 to 13 for diagnostic imaging of a cell or population of cells expressing a folate-receptor in vitro or in vivo.

15. Use of a compound according to anyone of claims 11 to 13 for convenient and effective administration to a subject in need for diagnostic imaging.

16. Method for diagnostic imaging of a cell or population of cells expressing a folate-receptor, said method comprising the steps of administering at least one compound according to anyone of claims 11 to 13 in a diagnostic imaging amount, and obtaining a diagnostic image of said cell or population of cells.

17. Method according to claim 16, wherein the diagnostic imaging is performed of a cell or population of cells expressing a folate-receptor in vitro or in vivo.

18. Method for in vitro detection of a cell expressing the folate receptor in a tissue sample which includes contacting said tissue sample with a compound according to anyone of claims 11 to 13 in effective amounts and for sufficient time and conditions to allow binding to occur

and detecting such binding by PET imaging.

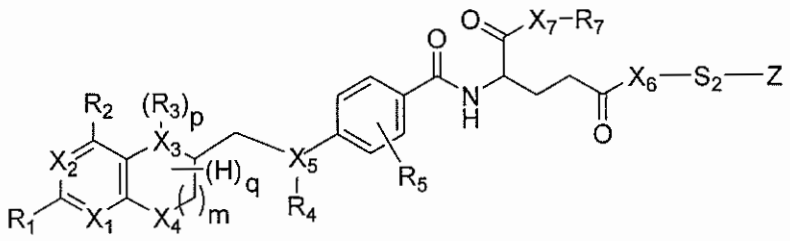
19. Method of diagnostic imaging or monitoring a subject comprising the steps of (i) administering at least one compound according to anyone of claims 11 to 13 in a diagnostic imaging amount, and (ii) performing diagnostic imaging using PET by detecting a signal from said at least one compound.

20. Method of monitoring therapy of cancer or inflammatory and autoimmune diseases in a subject comprising the steps of (i) administering to a subject in need thereof at least one compound according to anyone of claims 11 to 13 in a diagnostic imaging amount in combination with a therapeutically active, and (ii) performing diagnostic imaging using PET by detecting a signal from said at least one compound to follow the course of therapy of cancer or inflammatory and autoimmune diseases.

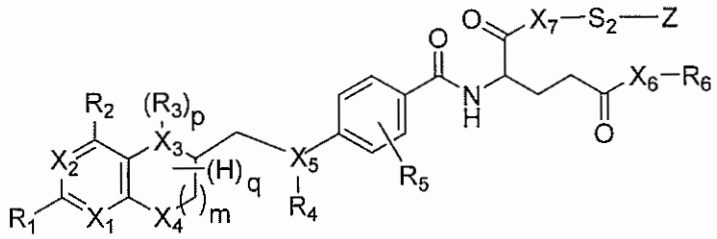
21. Method of claims 19 or 20 used in combination with any other methods of diagnosis or therapy of cancer or inflammatory and autoimmune diseases.

Claims

1. A method of direct radiolabeling of the glutamate moiety of a folate compound with ^{18}F comprising the step of reacting a compound of formulae VII or VIIa with ^{18}F,



VII



VIIa

wherein

X_1 to X_5 are N,

X_6, X_7 are independently of each other O or N,

R_1, R_2 are independently of each other H, Hal, -OR', -NHR', C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, or (C1-C12 alkylamino)carbonyl, wherein R' is H or C1-C6 alkyl,

R_3, R_4 are independently of each other H, formyl, iminomethyl,

nitroso, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, halosubstituted C1-C12 alkanoyl,

R_5 is H, CN, Hal, NO_2, C1-C12 alkyl, C1-C12 alkoxy, C1-C12 alkanoyl, C2-C12 alkenyl, C2-C12 alkynyl, (C1-C12 alkoxy)carbonyl, and (C1-C12 alkylamino)carbonyl,

R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2,

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-; or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof,

m is 1,

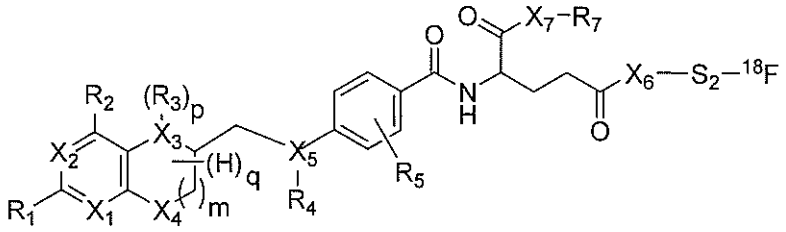
p is 0, 1 or 2,

q has a value of 1 to 7,

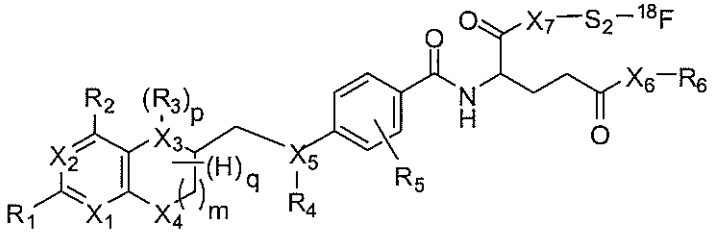
Z is a leaving group, and

wherein ^{18}F is activated by phase transfer catalysts such as tetrabutylamonium carbonate or aminopolyethers (e.g. Kryptofix© 2.2.2) in combination with potassium carbonate or oxalate,

to obtain a ^{18}F-labeled compound of general formulae VI or VIa,



VI



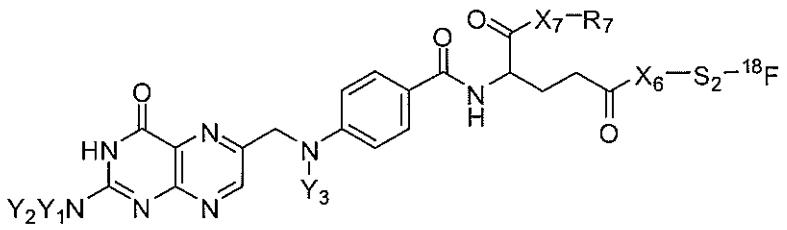
VIa.

2. A method according to claim 1, wherein ^{18}F is activated with Kryptofix® 2.2.2 in a polar solvent selected from acetonitrile, acetone, 1,4-dioxane, tetrahydrofuran (THF), N-methylpyrrolidinone (NMP), di-methoxyethane (DME), dimethylacetamide (DMA), N,N-dimethylformamide (DMF), dimethytsulfoxide (DMS), hexa-methylphosphoramide (HMPA) and mixtures thereof.

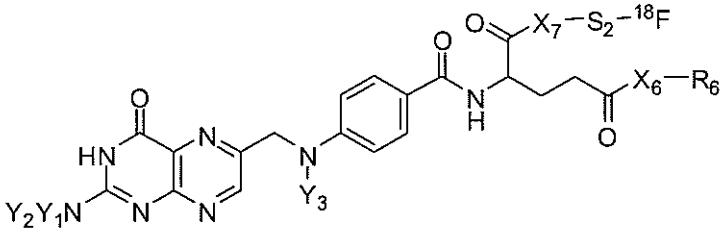
3. A method according to claims 1 or 2, wherein Z is selected from Hal, NO_2, diazonium salts, sulfonate esters, including mesylate, tosylate, pentafluorobenzoate, triflate, iodonium salts, dialkyl/-aryl silanes, and silanols.

4. A method according to any preceding claim, wherein S_2 is straight chain or branched C1-C6 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2

5. A method according to any preceding claim, wherein the obtained compound has the formulae VIII or VIIIa,



VIII



VIIIa

wherein,

X_6, X_7 are independently of each other N or O,

Y_1, Y_2 are independently of each other selected from H, straight chain or branched C_1-C_4 alkyl,

Y_3 is selected from H, formyl, nitroso, straight chain or branched C_1-C_{12} alkyl,

R_6, R_7 are independently of each other H or straight chain or branched C_1-C_{12} alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2, and

S_2 is straight-chain or branched C1-C12 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or

NO_2, and wherein one or more of the non-adjacent CH_2 groups may independently be replaced by -O-; or a five- or six-membered aromatic ring having 0, 1 or 2 heteroatoms, which is unsubstituted or substituted with CN, Hal, NO_2, COR', or COOR', wherein R' represents H or C1-C6 alkyl, or a combination thereof.

6. A method according to claim 5, wherein S_2 is straight-chain or branched C1-C6 alkyl, which is unsubstituted or substituted by at least one CN, Hal, or NO_2.