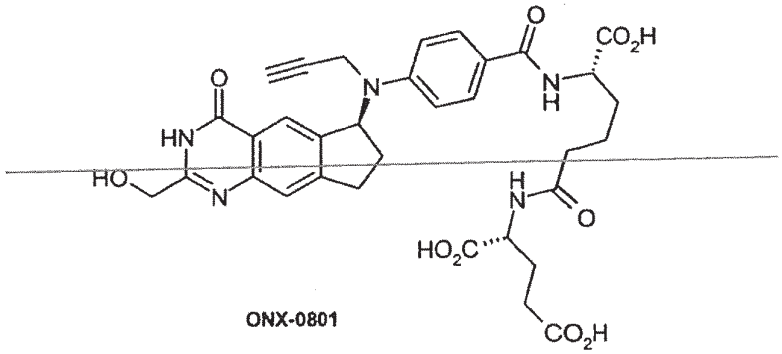
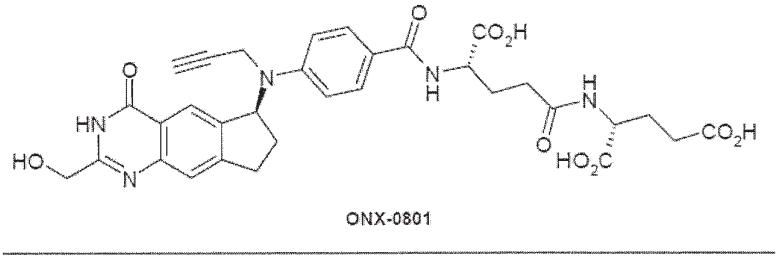
In some embodiments a compound obtainable by the methods of the invention is *N*-{*N*-{4-[*N*-((6*S*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclo-penta[g]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino]benzoyl}-L-γ-glutamyl}-D-glutamic acid (ONX-0801).





The present invention also provides certain compounds, useful as intermediates in the synthesis of cyclopentaquinazolines *via* the methods of the invention, and methods for their preparation.

These compounds may include the following:

5-(*t*-butoxyacetamido)-6-bromoindan-1-one;
5-(benzyloxyacetamido)-6-cyanoindan-1-one;
5-(*t*-butoxyacetamido)-6-cyanoindan-1-one;
6-aminocarbonyl-5-(benzyloxyacetamido)indan-1-one;
6-aminocarbonyl-5-(*t*-butoxyacetamido)indan-1-one;
2-(benzylyoxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
2-(hydroxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
2-(*t*-butoxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
2-(*t*-butyldimethylsiloxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R,S)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(*R*)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(*S*)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R,S)-2-(*t*-butoxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(*R*)-2-(*t*-butoxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;

9. A process according to any one of claims 1 to 8, wherein (c) hydrolysis of the nitrile group produced in step (b) comprises conversion of the 6-nitrile produced in the cyanation step to an amide.

10. A process according to claim 9, wherein hydrolysis comprises treatment with acid.

11. A process according to claim 10, wherein hydrolysis comprises treatment with formic acid in the presence of magnesium sulfate.

12. A process according to claim 9, wherein hydrolysis comprises treatment with hydrogen peroxide.

13. A process according to claim 12, wherein hydrolysis comprises treatment with hydrogen peroxide and potassium carbonate in aqueous ethanol.

14. A process according to any one of claims 1 to 13, wherein (d) cyclisation of a 5-(*N*-acylamino)-6-amidoindanone to form a cyclopentaquinazoline ring system comprises treatment of said 5-(*N*-acylamino)-6-amidoindanone with a base.

15. A process according to claim 14, wherein the base is a solution of an alkali metal alkoxide in a C_{1-4} alkyl alcohol.

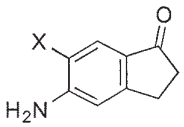
16. A process according to claim 15, wherein the base is a solution of an alkali metal alkoxide in the corresponding alcohol.

17. A process according to any one of claims 1 to 13, wherein (d) cyclisation of a 5-(*N*-acylamino)-6-amidoindanone to form a cyclopentaquinazoline ring system occurs spontaneously during step (c) hydrolysis of the nitrile group.

18. A process according to claim 17, wherein steps (c) and (d) comprise sequential addition of hydrogen peroxide and aqueous sodium or potassium hydroxide to a mixture of the 5-acylamino-6-cyanoindan-1-one in an aqueous alcohol, the mixture then being allowed to warm and spontaneously exotherm, to form a cyclopentaquinazoline ring system.

19. A process to according to any one of claims 15 to 18, further comprising purification of the crude cyclopentaquinazoline produced by crystallization of the material from an isopropanol/hexanes mixture.

62. A process according to any one of claims 1 to 61 wherein the 5-amino-6-haloindanone is a compound of general formula:



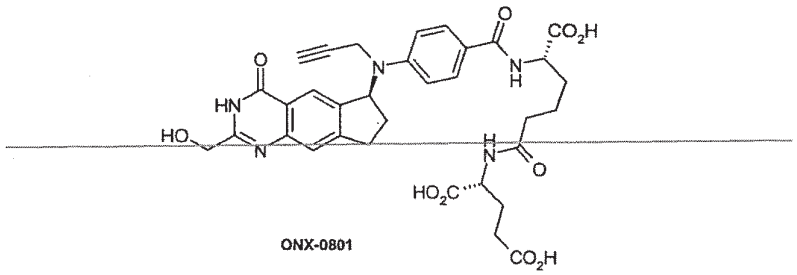
(IX)

wherein X is a halide.

63. A process according to any one of claims 1 to 45, wherein the cyclopentaquinazoline compound is (6*RS*)-4-(N-(2-(hydroxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclo-penta[g]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino]benzoic acid.

64. A process according to any one of claims 1 to 45, wherein the cyclopentaquinazoline compound is (6*S*)-4-(N-(2-(hydroxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclo-penta[g]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino]benzoic acid.

65. A process according to any one of claims 1 to 45, wherein the cyclopentaquinazoline compound is *N*-{*N*-{4-[*N*-((6*S*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclo-penta[g]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino]benzoyl}-L-γ-glutamyl}-D-glutamic acid (ONX-0801).



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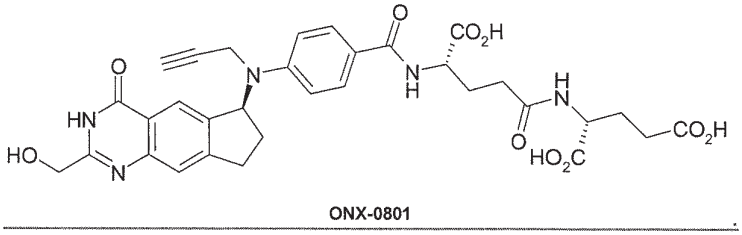

ONX-0801

6566. A compound, useful in the methods of claims 1 to 6465, selected from:

5-(*t*-butoxyacetamido)-6-bromoindan-1-one;

5-(benzyloxyacetamido)-6-cyanoindan-1-one;

5-(*t*-butoxyacetamido)-6-cyanoindan-1-one;

6-aminocarbonyl-5-(benzyloxyacetamido)indan-1-one;

6-aminocarbonyl-5-(t-butoxyacetamido)indan-1-one;

2-(benzylyoxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;

2-(hydroxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
2-(*t*-butoxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
2-(*t*-butyldimethylsiloxymethyl)-4,6-dioxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R,S)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(S)-2-(*t*-butyldimethylsiloxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R,S)-2-(*t*-butoxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(R)-2-(*t*-butoxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
(S)-2-(*t*-butoxymethyl)-6-hydroxy-4- oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazoline;
t-butyl (6R*S*)-4,*N*-((2-(*t*-butyldimethylsiloxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate;
t-butyl (6*S*)-4,*N*-((2-(*t*-butyldimethylsiloxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate;
t-butyl (6*R*)-4,*N*-((2-(*t*-butyldimethylsiloxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate;
t-butyl (6R*S*)-4,*N*-((2-(*t*-butoxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate;
t-butyl (6*S*)-4,*N*-((2-(*t*-butoxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate; and
t-butyl (6R)-4,*N*-((2-(*t*-butoxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoate.

~~66~~67. Use of a compound according to claim ~~65~~66, or a compound selected from
5-(benzyloxyacetamido)-6-bromoindan-1-one;
(6*S*)-4,*N*-((2-(hydroxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoic acid;
(6*R*)-4,*N*-((2-(hydroxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoic acid; and
(6R*S*)-4,*N*-((2-(hydroxymethyl)-4-oxo-3,4,7,8-tetrahydro-3*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino)benzoic acid