Claims

1. A method of synthesising a small molecule compound, including:

a) providing a solid support in fluid communication with a computer-controlled flow system;

b) covalently bonding a first precursor to the solid support for forming an extension thereon;

c) performing at least one reaction, the reaction including:

i) purging the extension with air or gas;

ii) conditioning the extension with a first solvent;

iii) reacting a first reactant with the extension for synthesising the compound on the solid support; and

d) cleaving the compound from the solid support;

wherein the first precursor, the first solvent and the first reactant are deliverable to the solid support via the computer-controlled flow system.

2. The method according to claim 1, wherein the first reactant is provided in the first solvent.

3. The method according to claim 1 or 2, further including a step (ciii~~i~~civ) after step (ciii) of washing the compound with the first solvent.

4. The method according to any one of claims 1 to 3, further including a step of washing the extension with a pre-solvent~~purging with air or gas~~ before the conditioning step (cii).

5. The method according to ~~any one of~~ claim~~s 1 to 4~~ 3, further including a step of purging with air or gas after the washing step (civ~~ii~~).

~~6. The method according to any one of claims 1 to 5, wherein the solid support is a 2-chlorotrityl chloride resin.~~

~~7~~6. The method according to any one of claims 1 to ~~6~~5, further including a step of altering a temperature of the reaction.

~~8~~7. The method according to any one of claims 1 to ~~7~~6, wherein the first precursor comprises an amino moiety.

~~9~~8. The method according to any one of claims 1 to ~~8~~7, wherein the at least one reaction is selected from a SN_2 reaction, hydrazine condensation, Thorpe reaction, Claisen condensation, S_NAr reaction, amide coupling, N-triflation, reductive amination, phenyl-hydrazine cyclization, pyrazole cyclization, click chemistry, or Mitsunobu reaction.

~~10~~9. The method according to any one of claims 1 to ~~9~~8, wherein the first precursor further comprises a second moiety selected from the group consisting of halide (except fluoride), tosylate, amino, carboxyl, carbonyl, triflate, aryl, alkynyl, azidyl, alkenyl, tetrazinyl, tetrazolyl, hydroxyl, hydrazoic acid, imide, thiophenol, sulphonamide, arylsulfonylhyrazine, hydrazine, or cyanoalkylacyl.

~~11~~10. The method according to any one of claims 1 to ~~10~~9, wherein the compound is cleaved using trifluoroacetic acid.

~~12~~11. A method of synthesising prexasertib, derivatives, salts, solvates or stereoisomers thereof, comprising:

a) providing a 2-chlorotrityl chloride resin in communication with a computer-controlled flow system;

b) covalently bonding a compound of Formula (I) to the 2-chlorotrityl chloride resin for forming an extension thereon, the compound of Formula (I) is:

$$T-M-NHR_1 \quad (I)$$

wherein M is optionally substituted alkyl;

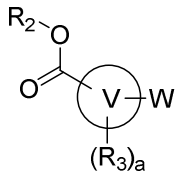
T is selected from halide (except fluoride), tosylate, hydroxyl, carboxyl, hydrazoic acid, imide, phenol, thiophenol, sulphonamide, arylsulfonylhyrazine, alkynyl, azidyl, alkenyl, tetrazinyl, or tetrazolyl;

R_1 is selected from H, optionally substituted alkyl, optionally substituted alkenyl;

c) performing a first reaction, the first reaction including:

i) conditioning the extension with a first solvent;

ii) reacting a compound of Formula (II) with the extension for synthesising a first intermediate on the solid support, the compound of Formula (II) is:



(II)

wherein V is selected from optionally substituted aryl or optionally substituted heteroaryl;

W is selected from halide (except fluoride), tosylate, hydroxyl, carboxyl, hydrazoic acid, imide, phenol, thiophenol, sulphonamide, arylsulfonylhyrazine, alkynyl, azidyl, alkenyl, tetrazinyl, or tetrazolyl;

R_2 is optionally substituted alkyl;

R_3 is independently selected from halide, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy;

a is an integer selected from 0, 1, 2 or 3;

d) performing a second reaction, the second reaction including:

i) conditioning the first intermediate with a second solvent;

ii) reacting CH_3CN and lithium diisopropylamide with the first intermediate for synthesising a second intermediate on the solid support;

e) performing a third reaction, the third reaction including:

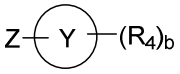
i) conditioning the second intermediate with a third solvent;

ii) reacting NH_2NH_2 or NH_2NHPh with the second intermediate for synthesising a third intermediate on the solid support;

f) performing a fourth reaction, the fourth reaction including:

i) conditioning the third intermediate with a fourth solvent;

ii) reacting a compound of Formula (III) with the third intermediate for synthesising a fourth intermediate on the solid support, the compound of Formula (III) is:


(III);

Wherein Y is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl;

Z is selected from carboxyl, carbonyl, alkenylacyl, triflate, aryl, alkyl (substituted with carboxyl, carbonyl or alkenylacyl), or alkoxy (substituted with carboxyl, carbonyl or alkenylacyl);

R_4 is selected from halo, cyano, optionally substituted alkoxy, optionally substituted alkyl, or optionally substituted alkenyl;

b is an integer selected from 0, 1, 2, or 3; and

g) cleaving the compound from the solid support;

wherein the compounds of Formula (I), (II), (II), CH_3CN, lithium diisopropylamide, NH_2NH_2 and solvents are deliverable to the 2-chlorotrityl chloride resin via the computer-controlled flow system.

~~13~~12. The method according to claim ~~12~~11, wherein when the synthesised compound is prexasertib, a yield is at least 60%.

~~14~~13. The method according to claim ~~12~~ 11 or ~~13~~12, wherein when the synthesised compound is prexasertib, a purity is at least 99%.

~~15~~14. A system for synthesising a small molecule compound, including:

a) a flow system;

b) a solid support in fluid communication with the flow system;

b) a first precursor covalently bonded to the solid support for forming an extension thereon;

c) at least a first solvent for conditioning the extension;

d) at least a first reactant for performing at least one reaction on the extension to synthesise the compound; and

d) a controller configured to regulate the flow system for flowing the first

precursor, the first solvent and the first reactant to the solid support.;

wherein the system is configured to performing at least one reaction, the reaction including:

i) purging the extension with air or gas;

ii) conditioning the extension with the first solvent;

iii) reacting the first reactant with the extension for synthesising the compound on the solid support; and

d) cleaving the compound from the solid support.

~~16~~15. The system according to claim ~~15~~14, wherein the solid support is contained in a reaction vessel; and wherein the flow system is connected to the reaction vessel for fluid communication with an interior thereof.

~~17~~16. The system according to claim ~~15~~ 14 or ~~16~~15, wherein the flow system includes at least one multi-port input valve in communication with the controller, and wherein the controller is configured to actuate the at least one multi-port input valve for selective flow of the first precursor, the first solvent or the first reactant into the reaction vessel.

~~18~~17. The system according to any one of claims ~~15~~ 14 to ~~17~~16, wherein the flow system includes a multi-port output valve, and wherein the controller is configured to actuate the multi-port output valve for selective flow of output fluid from the reaction vessel to one of a plurality of output vessels.

~~19~~18. The system according to any one of claims ~~15~~ 14 to ~~18~~17, wherein the flow system includes a pressure regulator for regulating pressure inside the reaction vessel.

~~20~~19. The system according to any one of claims ~~15~~ 14 to ~~19~~18, further including at least one heating element in thermal communication with the reaction vessel, wherein the controller is configured to alter the temperature of the reaction.

~~21~~20. The system according to any one of claims ~~15~~–14 to ~~20~~19, further including a circulative flow path for allowing the flow to return to a starting bottle and/or a one-way flow path for allowing the flow to elute to a waste bottle.