

Antibiotic compounds, methods of manufacturing the same, pharmaceutical compositions containing the same and uses thereof

5 Field of the Invention

[0001] The present invention provides novel compounds that are therapeutically active as antibiotic compounds. The present invention furthermore provides pharmaceutical compositions comprising the compounds of the invention. It also provides uses of these compounds and compositions for the treatment of bacterial infections caused by *N. gonorrhoeae*. Moreover, methods of making the compounds of the present invention are also provided.

Background of the Invention

[0002] *Neisseria gonorrhoeae* is a species of Gram-negative diplococci bacteria responsible for the sexually transmitted infection gonorrhea, that typically causes an uncomplicated (non-disseminated) disease.

[0003] The most common site of *N. gonorrhoeae* infection is the urogenital tract. Men with this infection may experience dysuria with penile discharge, and women may have mild vaginal mucopurulent discharge, severe pelvic pain. Other *N. gonorrhoeae* infections include anorectal, conjunctival, pharyngeal, and ovarian/uterine. In women, gonococci may cause endocervical infections, or upper genital tract disease. Gonococcal infections of women are closely associated with infertility. If untreated, local *N. gonorrhoeae* infections can progress to bacteremia with attendant septic arthritis. When infection involves the eyes, especially in newborns, blindness can result if treatment is not prompt. Rarely, bacteremia results in dissemination (complicated gonorrhea) to the joints, skin, endocardium or meninges.

[0004] Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobials. In 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted health authorities to cease recommending fluoroquinolones for treatment of gonorrhea in the United States. Recent treatment failures with cefixime or other oral cephalosporins have been reported in Asia, Europe, South Africa and Canada. Ceftriaxone treatment failures for pharyngeal infections have been reported in Australia, Japan, and Europe. Consequently, global organizations such as WHO recommend that local resistance data should determine the choice of therapy.

[0005] Recently there have been sporadic reports of *N. gonorrhoeae* strains resistant to both cephalosporins and macrolides, thereby leaving no treatment options for these patients. The fear is that, due to the ability of *Neisseria sp.*, to rapidly disseminate and integrate their genetic material (promiscuous transformation), these ultra-drug resistant
5 genotypes can spread rapidly.

[0006] FabI inhibition is a relatively new concept for developing antibiotic compounds. FabI is an enzyme involved in bacterial fatty acid synthesis. Administration of compounds inhibiting this enzyme may selectively affect bacteria relying on this enzyme without affecting the host (patient). Antibiotic agents relying on this working principle are
10 disclosed for instance in WO 03/088897 A2 and WO 2013/190384 A1, the content of which is incorporated in its entirety into the present application. These compounds are, however, primarily directed to the treatment of *S. aureus* infections. Further compounds with FabI inhibitory action, but focussing primarily on the treatment of infections other than *N. gonorrhoeae*, are disclosed in WO 2007/053131 A, WO 2007/067416 A, WO 01/27103 A, WO
15 2008/098374 A, Yao et al., J. Biol. Chem., 2016, 291, 171-181, WO 2008/009122 A, US 2015/210719 A and US 2017/174683 A.

Problems underlying the Invention

[0007] In view of the above situation, there is a need for providing further drugs and pharmaceutical compositions that show antibiotic activity against *N. gonorrhoeae*.

20 [0008] It is particularly desired to obtain such further drugs and pharmaceutical compositions, which may be used as fallback treatment of bacterial infections caused by *N. gonorrhoeae* if the standard treatment with ceftriaxone is not effective.

[0009] There is, furthermore, a need for further antibiotic drugs and medicaments for treating a variety of related bacterial infections.

25 [0010] It is further desired that such antibiotic drugs and pharmaceutical compositions exhibit an acceptable therapeutic index and no serious side effects.

Summary of the Invention

[0011] The present invention solves the above problems by providing compounds and pharmaceutical compositions that are effective in the treatment of infections by *N. gonorrhoeae* and related bacteria.
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[0012] The compounds of the present invention act as antibiotic agents by means of a working mechanism involving FabI inhibition. This mechanism differs from that of cephalosporins, which act by disruption of peptidoglycan layers of bacterial cell walls. Moreover, the compounds of the present invention have a chemical structure different from that of cephalosporins. It may therefore be expected that the compounds and pharmaceutical compositions of the present invention are effective also in strains that are resistant to ceftriaxone.

[0013] The compounds and pharmaceutical compositions of the present invention furthermore show a high therapeutic index and low side effects.

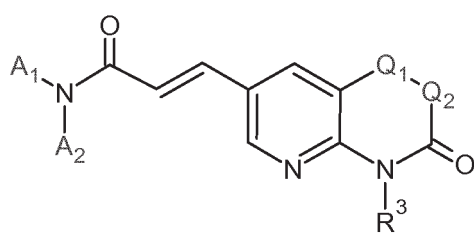
[0014] According to one embodiment, the compounds and pharmaceutical compositions of the present invention show chemical, physical and pharmacokinetic properties suitable for oral and/or intramuscular administration.

[0015] In one embodiment, the present invention also provides therapeutic uses of the compounds described herein and methods of treatment of bacterial infections involving the administration of the compounds of the present invention to patients in need thereof.

[0016] In other embodiments, the present invention further provides methods for preparing the compounds of the present invention.

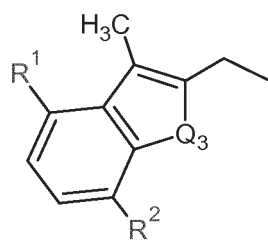
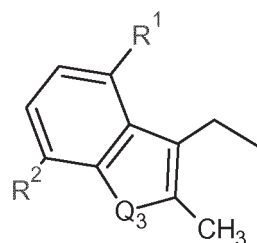
[0017] Thus the present invention provides in particular the following:

[0018] 1. Compound, which is selected from the group of compounds represented by general formula I



wherein

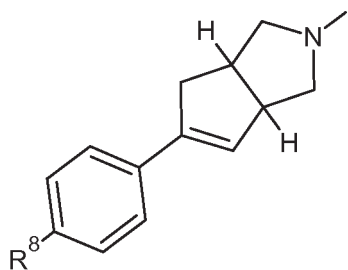
A₁ represents a moiety selected from the groups A₁₁ and A₁₂ having the following structures

A₁₁ andA₁₂;

wherein the line connected to the exocyclic methylene group represents a single covalent
5 bond formed with the nitrogen atom of formula I;

A₂ represents a methyl group;

or A₁ and A₂ together with the nitrogen atom to which they are bonded form the following
10 moiety A₃:

A₃;

wherein the exocyclic line connected to the nitrogen atom of the bicycle represents the
15 covalent bond between nitrogen and carbonyl group in the left-hand side of formula I;

Q₁ represents $-\text{CH}=\text{CR}^7-$, CH_2 or NH ;

Q₂ represents CR^4R^5 , or $\text{CR}^4\text{R}^5-\text{CR}^6\text{R}^7$, wherein the CR^4R^5 group binds to Q₁;

or Q₁-Q₂ represents $-\text{N}=\text{CR}^7-\text{CHR}^7-$ or its tautomer $-\text{NH}-\text{CR}^7=\text{CR}^7-$

Q₃ represents O or S;

R¹ represents a group selected from H, -NH₂;

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R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NR⁹R¹⁰, -O-Alk¹, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, -O-(CH₂)₁₋₄-NR⁹R¹⁰, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent
10 substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N and O, which Het¹ group may optionally
15 be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN, -(CH₂)₀₋₄-OH; wherein R⁹ is selected from H and -C₁₋₄-alkyl; wherein R¹⁰ is selected from H, -C₁₋₄-alkyl and -C(=O)-CH₃; wherein Alk¹ represents an alkyl group having 1 to 6 carbon atoms, which is linear, branched, cyclic or a combination thereof, which Alk¹ group may optionally be substituted by one or more groups selected from -OH, -O-alkyl

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R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-
25 C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

30

R⁴ represents a group selected from H, C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F;

R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

or R⁴ and R⁵ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom;

R⁶ represents a group selected from H, -OH, C₁₋₄-alkyl, -OPO₃R^{3a}₂;

R⁷ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, C₁₋₄-alkylene-F, -CN;

or R⁶ and R⁷ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom; the cyclic group may optionally carry a substituent selected from -OH, -O-alkyl;

R⁸ represents a group selected from -O-Ar² and -O-Het²;

wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N, S and O, wherein said heterocycle may optionally carry one or two substituents selected from oxo, halogen, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, and CN;

and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

2. Compound according to item 1, wherein

Q₂ represents CR⁴R⁵-CR⁶R⁷, wherein the CR⁴R⁵ group binds to Q₁; or Q₁-Q₂ represents –N=CR⁷-CHR⁷- or its tautomer –NH-CR⁷=CR⁷-;

R⁴ represents a group selected from C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F; and

R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

and the remaining variable groups are as defined in claim 1.

3. Compound according to item 1, wherein

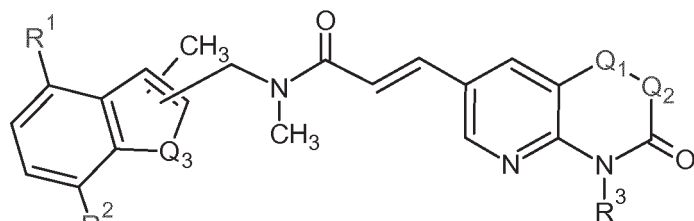
Q₂ represents CR⁴R⁵-CR⁶R⁷, wherein the CR⁴R⁵ group binds to Q₁; or Q₁-Q₂ represents –N=CR⁷-CHR⁷- or its tautomer –NH-CR⁷=CR⁷-;

R⁴ represents a group selected from H, C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F; and

R⁵ represents a group selected from C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

and the remaining variable groups are as defined in claim 1.

[0019] 4. Compound according to item 1, 2 or 3 wherein the compound is selected from the group of compounds represented by general formula II



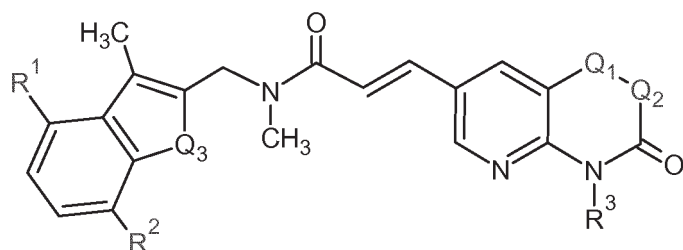
II

wherein

R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified in item 1 above;

and wherein the five-membered heterocycle comprising Q₃ is bonded to the methylene-amide moiety at the 2-position and to the methyl group at the 3-position or is bonded to the methylene-amide moiety at the 3-position and to the methyl group at the 2-position.

[0020] 5. Compound according to item 4, wherein the compound is selected from the group of compounds represented by general formula III



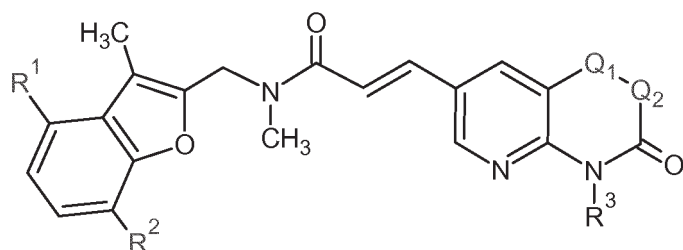
III

5

wherein

R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified in item 1, 2 or 3 above.

10 [0021] 6. Compound according to item 5, wherein the compound is selected from the group of compounds represented by general formula IV

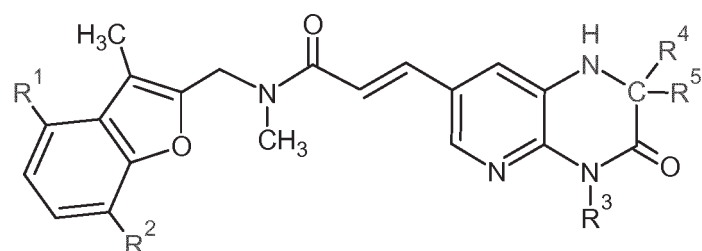


IV

15 wherein

R¹, R², R³, Q₁, Q₂ have the same meanings as specified in item 1, 2 or 3 above.

[0022] 7. Compound according to item 6, wherein the compound is selected from the group of compounds represented by general formula Va or general formula Vb

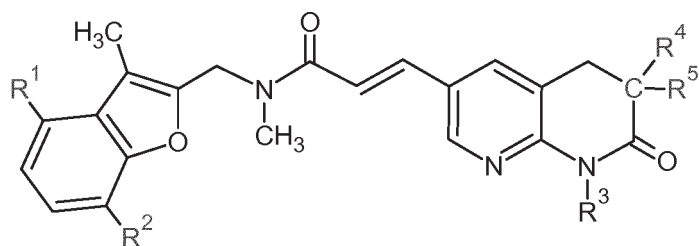


Va;

wherein R^1 , R^2 and R^3 have the same meanings as specified in item 1 above; R^4 represents a group selected from H, C_{1-4} -alkyl and C_{1-4} -alkylene-F and R^5 represents a group selected from H, C_{1-4} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-OR³;

5

or



Vb

10

wherein

R^1 , R^2 and R^3 have the same meanings as specified in item 1 above; R^4 represents a group selected from H, C_{1-4} -alkyl and C_{1-4} -alkylene-F; and R^5 represents a group selected from H, C_{1-4} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-OR³, -OH; and -OPO₃R^{3a}₂.

15

[0023] 8. Compound according to item 7, wherein

R^1 represents H, NH₂;

20

R^2 represents H;

R^3 represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

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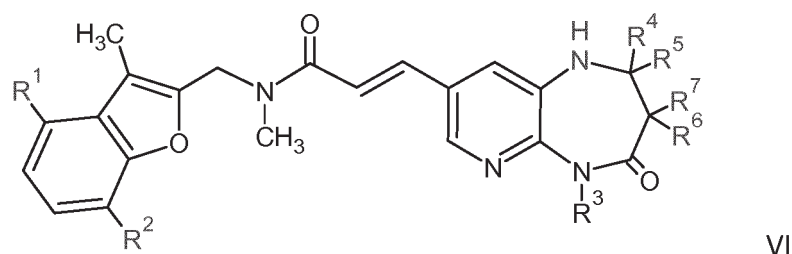
R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-OH$, and $-O-C_{1-6}$ -alkyl;

5 R^4 represents H, C_{1-4} -alkyl; and

R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene-OR³.

[0024] 9. Compound according to item 6, wherein the compound is selected from the group of compounds represented by general formula VI



wherein

15 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified in item 1, 2 or 3 above.

[0025] 10. Compound according to item 9, wherein

R^1 represents H, NH_2 ;

20

R^2 represents H;

R^3 represents a group selected from H, $-PO_3R^{3a}_2$, $-CH_2-OPO_3R^{3a}_2$ and $-CH_2-O-C(=O)-R^{3b}$;

25 R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-CH_2-O-C(=O)-R^{3b}$ or $-CHMe-O-C(=O)-R^{3b}$ or $-CMe_2-O-C(=O)-R^{3b}$ or $-CH_2-O-C(=O)-O-R^{3b}$ or $-CHMe-O-C(=O)-O-R^{3b}$ or $-CMe_2-O-C(=O)-O-R^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-OH$, and $-O-C_{1-6}$ -alkyl;

5

R^4 represents H, C_{1-4} -alkyl; and

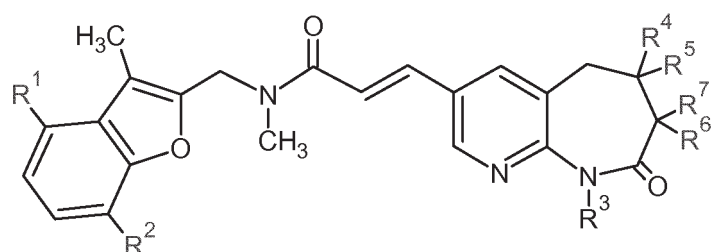
R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OR^3 ;

10 R^6 represents H, C_{1-4} -alkyl, OH , $-OPO_3R^{3a}_2$; and

R^7 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OH , C_{1-4} -alkylene- OR^3 , wherein R^3 is as specified above, C_{1-4} -alkylene- F .

15

[0026] 11. Compound according to item 6, wherein the compound is selected from the group of compounds represented by general formula VII



VII

20

wherein

R^1 , R^2 , R^3 , R^6 and R^7 have the same meanings as specified in item 1, 2 or 3 above.

25 **[0027]** 12. Compound according to item 11, wherein

R^1 represents H, NH_2 ;

R^2 represents H;

30

R^3 represents a group selected from H, $-\text{PO}_3\text{R}^{3a}_2$, $-\text{CH}_2-\text{OPO}_3\text{R}^{3a}_2$ and $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CH}_2-\text{O}-$
 5 $\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-\text{OH}$, and $-\text{O}-\text{C}_{1-6}\text{-alkyl}$;

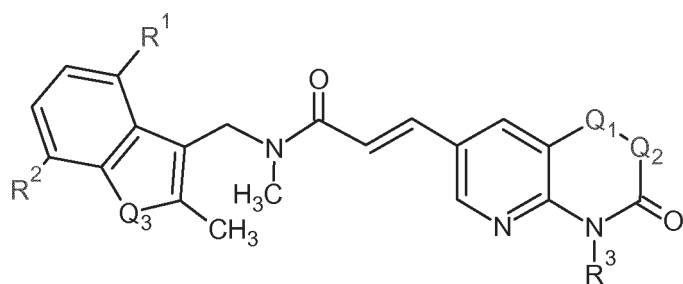
R^4 represents H, $\text{C}_{1-4}\text{-alkyl}$; and

R^5 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene}-\text{OR}^3$;

R^6 represents H, $\text{C}_{1-4}\text{-alkyl}$, OH , $-\text{OPO}_3\text{R}^{3a}_2$; and

R^7 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene}-\text{OH}$, $\text{C}_{1-4}\text{-alkylene}-\text{OR}^3$, wherein R^3 is as specified above, $\text{C}_{1-4}\text{-alkylene}-\text{F}$.

[0028] 13. Compound according to item 4, wherein the compound is selected from the group of compounds represented by general formula VIII



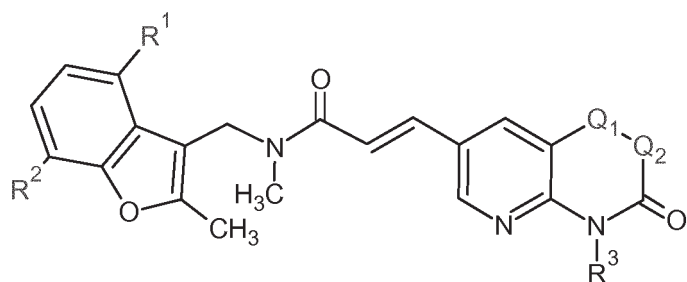
VIII

wherein

R^1 , R^2 , R^3 , Q_1 , Q_2 , Q_3 have the same meanings as specified in item 1, 2 or 3 above.

[0029] 14. Compound according to item 13, wherein the compound is selected from

5 the group of compounds represented by general formula IX



IX

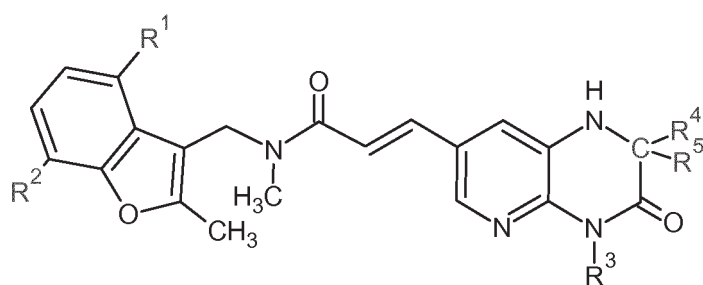
wherein

10

R^1 , R^2 , R^3 , Q_1 , Q_2 have the same meanings as specified in item 1, 2 or 3 above.

[0030] 15. Compound according to item 14, wherein the compound is selected from

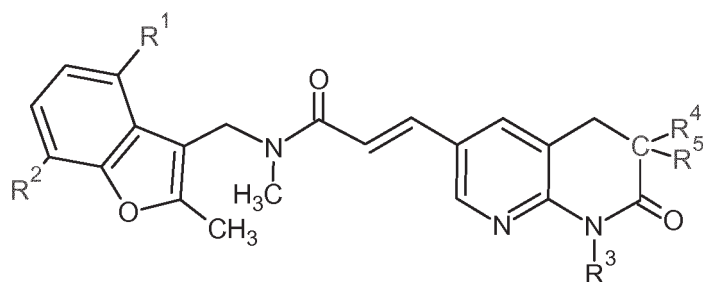
15 the group of compounds represented by general formula Xa and Xb



Xa

or

20



Xb

wherein

R¹, R², R³, R⁴ and R⁵ have the same meanings as specified in item 1 above.

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[0031] 16. Compound according to item 15, wherein

R¹ represents H;

10 R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from
15 N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

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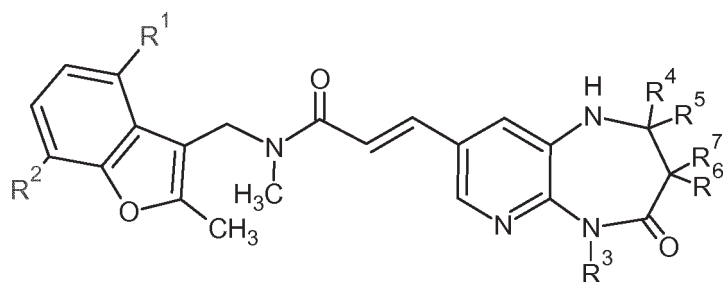
R³ represents H, -CH₂-OPO₃R^{3a}₂ wherein R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt;

R⁴ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-F; and

25

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH or C₁₋₄-alkylene-OR³, wherein R³ is as specified above .

30 **[0032]** 17. Compound according to item 14, wherein the compound is selected from the group of compounds represented by general formula XI



XI

wherein

- 5 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified in item 1, 2 or 3 above.

[0033] 18. Compound according to item 17, wherein

- 10 R^1 represents H;

R^2 represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

R^3 represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

- 25 R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

5 R⁴ represents H, C₁₋₄-alkyl; and

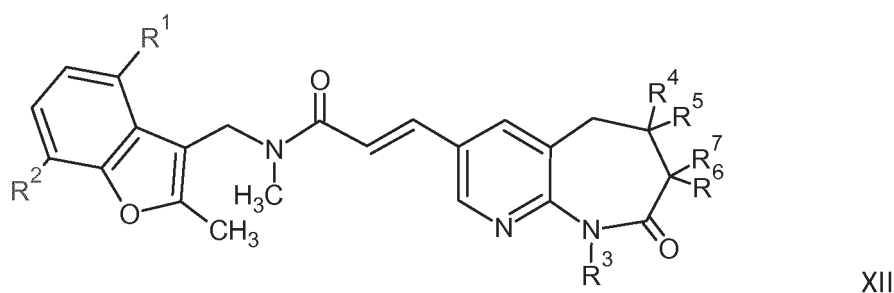
R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

10

R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F.

15 **[0034]** 19. Compound according to item 14, wherein the compound is selected from the group of compounds represented by general formula XII



20 wherein

R¹, R², R³, R⁶ and R⁷ have the same meanings as specified in item 1, 2 or 3 above.

25 **[0035]** 20. Compound according to item 19, wherein

R¹ represents H;

R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a

30 phenyl group that may optionally be substituted by one or more groups individually selected

from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

10 R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

15 R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

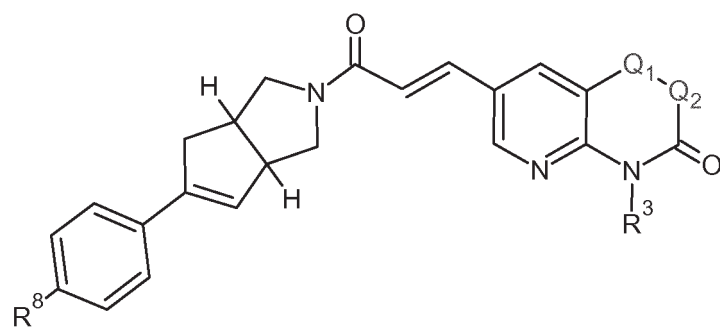
20 R⁴ represents H, C₁₋₄-alkyl; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

25 R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F.

30 [0036] 21. Compound according to item 1, wherein the compound is selected from the group of compounds represented by general formula XIII



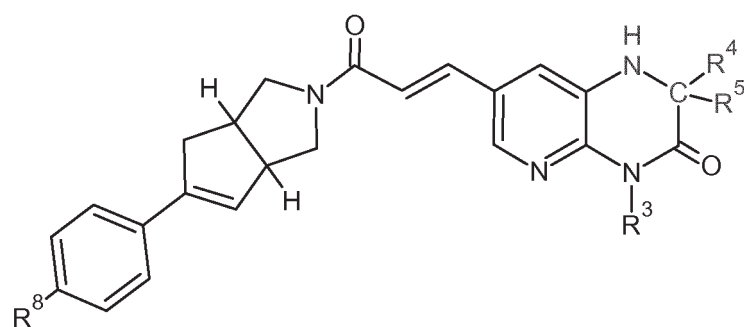
XIII

wherein

5

R^3 , R^8 , Q_1 , Q_2 have the same meanings as specified in item 1, 2 or 3 above.

[0037] 22. Compound according to item 21, wherein the compound is selected from
 10 the group of compounds represented by general formula XIVa or XIVb



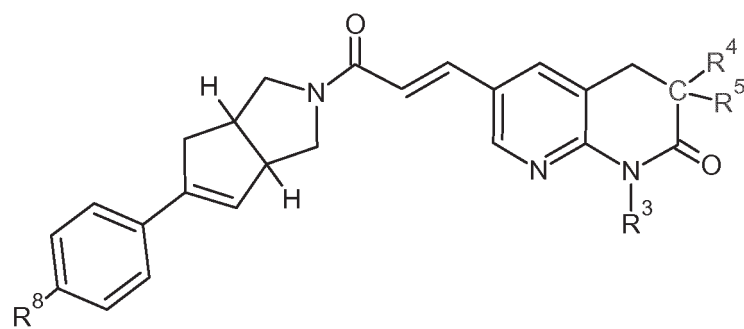
XIVa

15 wherein

R^3 , R^4 , R^5 , R^8 have the same meanings as specified in item 1 above;

or

20



XIVb

wherein

- 5 R^3 , R^4 , R^5 , R^8 have the same meanings as specified for general formula I above.

[0038] 23. Compound according to item 22, wherein

- 10 R^3 represents H, $-\text{CH}_2\text{-OPO}_3\text{R}^{3a}_2$ wherein R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt;

R^4 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene-F;

- 15 R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene-OH or C_{1-4} -alkylene-OR³, wherein R^3 is as specified above; and

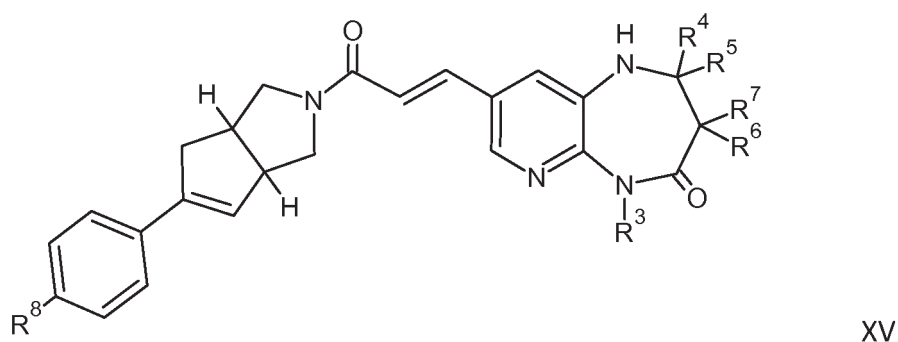
R^8 represents a group selected from $-\text{O-Ar}^2$ and $-\text{O-Het}^2$;

- 20 wherein Ar^2 represents a phenyl group that may optionally be substituted by one or more groups individually selected from $-\text{CN}$, $-\text{O-C}_{1-4}$ -alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N, S and O, wherein said heterocycle may optionally carry one or
- 25 two substituents selected from oxo, F, $-\text{O-C}_{1-4}$ -alkyl, C_{1-4} -alkyl, CN;

and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

- 5
[0039] 24. Compound according to item 21, wherein the compound is selected from the group of compounds represented by general formula XV



10 wherein

R³, R⁴, R⁵, R⁶, R⁷, R⁸ have the same meanings as specified in item 1, 2 or 3 above.

- 15
[0040] 25. Compound according to item 23, wherein

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

- 20 R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

- R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

R⁴ represents H, C₁₋₄-alkyl; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³;

R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

- 5 R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F
; and

R⁸ represents a group selected from -O-Ar² and -O-Het²,

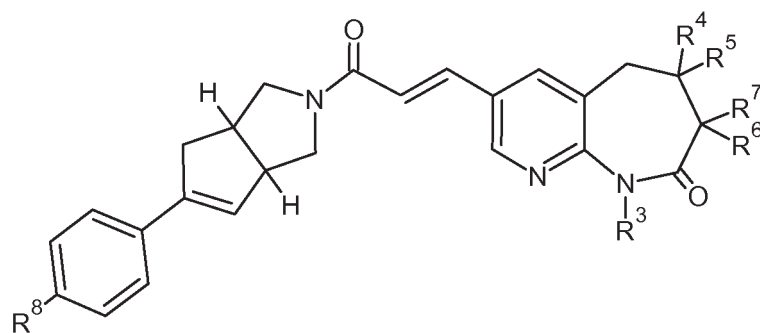
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wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms
15 individually selected from N, S and O, wherein said heterocycle may optionally carry one or two substituents selected from oxo, F, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, CN

and

- 20 wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl .

- 25 [0041] 26. Compound according to item 21, wherein the compound is selected from the group of compounds represented by general formula XVI



XVI

wherein

- 5 $R^3, R^4, R^5, R^6, R^7, R^8$ have the same meanings as specified in item 1, 2 or 3 above.

[0042] 27. Compound according to item 26, wherein

- 10 R^3 represents a group selected from H, $-PO_3R^{3a}_2$, $-CH_2-OPO_3R^{3a}_2$ and $-CH_2-O-C(=O)-R^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-CH_2-O-C(=O)-R^{3b}$ or $-CHMe-O-C(=O)-R^{3b}$ or $-CMe_2-O-C(=O)-R^{3b}$ or $-CH_2-O-C(=O)-O-R^{3b}$ or $-CHMe-O-C(=O)-O-R^{3b}$ or $-CMe_2-O-C(=O)-O-R^{3b}$;

15

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-OH$, and $-O-C_{1-6}$ -alkyl;

- 20 R^4 represents H, C_{1-4} -alkyl; and

R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OR^3 ;

R^6 represents H, C_{1-4} -alkyl, OH, $-OPO_3R^{3a}_2$; and

25

R^7 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene- OR^3 , wherein R^3 is as specified above, C_{1-4} -alkylene-F;

R⁸ represents a group selected from –O-Ar² and –O-Het²,

wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from –CN, –O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms selected N, S and O, wherein said heterocycle may optionally carry one or two substituents individually selected from oxo, F, –O-C₁₋₄-alkyl, C₁₋₄-alkyl, CN

and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from –O-C₁₋₄-alkyl, –CN, F, C₁₋₄-alkyl.

[0043] 28. Pharmaceutical composition comprising the compound of anyone of items 1 to 27.

[0044] 29. Compound according to anyone of items 1 to 27 or pharmaceutical composition according to item 26 for use in the treatment of a bacterial infection selected from infections by *N. gonorrhoeae*,

Bacillus Spp., in particular *Bacillus cereus*, *Bacillus coagulans*, *Bacillus megaterium*, *Bacillus subtilis*, *Bacillus anthracis*,

Bartonella Spp.,

Brucella Spp, in particular *Brucella abortus*, *Brucella melitensis*,

Campylobacter Spp., in particular *Campylobacter jejuni*,

Chlamydia trachomatis,

Enterococcus faecalis, *Enterococcus faecium*,

Legionella pneumophila,

Listeria Spp., in particular *Listeria monocytogenes*,

Proteus mirabilis,

Providencia stuartii

Rickettsia Spp., in particular Rickettsia rickettsii,

Bordetella pertussis, Bordetella parapertussis,

Burkholderia Spp., in particular Burkholderia pseudomallei, Burkholderia mallei,

5 Burkholderia cenocepacia,

Haemophilus influenza,

Kingella kingae,

Moraxella catarrhalis,

Streptomyces Spp.,

10 Nocardioiodes Spp.,

Frankia Spp.,

Propionibacterium acnes,

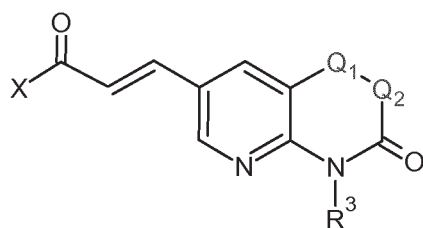
Mycobacterium Spp., in particular Mycobacterium smegmatis, Mycobacterium abscessus,

Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium avium and

15 combinations thereof, preferably infections by N. gonorrhoeae alone or in combination with Chlamydia trachomatis.

[0045] 31. Method of manufacturing a compound according to anyone of items 1 to 27, comprising the step of coupling a precursor compound of formula XVII

20



XVII

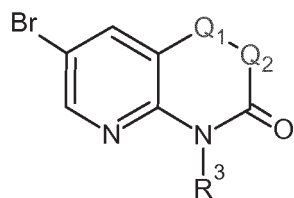
wherein Q₁, Q₂ and R³ have the same meanings as specified in item 1, 2 or 3 above, and

25 wherein X represents a leaving group,

with an amine compound of formula H-NA₁A₂, wherein A₁ and A₂ have the same meanings as specified in item 1 above.

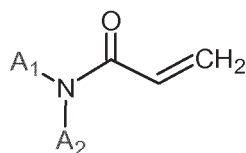
30

[0046] 32. Method of manufacturing a compound according to anyone of items 1 to 27, comprising the step of coupling a precursor compound of formula XVIII



XVIII

wherein R³, Q₁ and Q₂ have the same meanings as specified in item 1, 2 or 3 above,
with a precursor compound of formula XIX



XIX

wherein A₁ and A₂ have the same meanings as specified in item 1 above.

[0047] Definitions

[0048] The following definitions are provided to assist the reader. Unless otherwise defined, all terms of art, notations, and other scientific or medical terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the chemical and medical arts. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not be construed as representing a substantial difference over the definition of the term as generally understood in the art.

[0049] In some embodiments, the term “*about*” refers to a deviation of $\pm 10\%$ from the recited value. When the word “*about*” is used herein in reference to a number, it should be understood that still another embodiment of the invention includes that number not modified by the presence of the word “*about*”

[0050] “*Administering*” or “*administration of*” a drug to a patient (and grammatical equivalents of this phrase) refers to direct administration, which may be administration to a patient by a medical professional or may be self-administration, and/or indirect administration, which may be the act of prescribing a drug. E.g., a physician who instructs a

patient to self-administer a drug or provides a patient with a prescription for a drug is administering the drug to the patient.

[0051] **"Dose"** and **"dosage"** refer to a specific amount of active or therapeutic agents for administration. Such amounts are included in a **"dosage form,"** which refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active agent calculated to produce the desired onset, tolerability, and therapeutic effects, in association with one or more suitable pharmaceutical excipients such as carriers.

[0052] The terms **"treatment"** and **"therapy"**, as used in the present application, refer to a set of hygienic, pharmacological, surgical and/or physical means used with the intent to cure and/or alleviate a disease and/or symptoms with the goal of remediating the health problem. The terms **"treatment"** and **"therapy"** include preventive and curative methods, since both are directed to the maintenance and/or reestablishment of the health of an individual or animal. Regardless of the origin of the symptoms, disease and disability, the administration of a suitable medicament to alleviate and/or cure a health problem should be interpreted as a form of treatment or therapy within the context of this application.

[0053] **"Unit dosage form"** as used herein refers to a physically discrete unit of therapeutic formulation appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active agent employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active agent employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

[0054] The articles **"a"** and **"an"** are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, **"an element"** means one element or more than one element.

[0055] The term “**including**” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably. The term “**comprising**” is used to have the same meaning as “including”. The term “**consisting of**” is used to indicate that the listed element(s) is/are present but no other unmentioned elements. The term “**comprising**” is used to include the meaning of “**consisting of**” as a preferred embodiment.

[0056] The term “**FabI**” is art-recognized and refers to the bacterial enzyme believed to function as an enoyl-acyl carrier protein (ACP) reductase in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. This enzyme is believed to be widely distributed in bacteria and plants.

[0057] The term “**enzyme inhibitor**” refers to any compound that prevents an enzyme from effectively carrying out its respective biochemical roles. Therefore a “FabI inhibitor” is any compound that inhibits FabI from carrying out its biochemical role. The amount of inhibition of the enzyme by any such compound will vary and is described herein and elsewhere.

[0058] The term “**antibiotic agent**” or “**antibacterial agent**” shall mean any drug that is useful in treating, preventing, or otherwise reducing the severity of any bacterial disorder, or any complications thereof, including any of the conditions, disease, or complications arising therefrom and/or described herein. Antibiotic agents include, for example, cephalosporins, quinolones and fluoroquinolones, penicillins and beta lactamase inhibitors, carbapenems, monobactams, macrolides and lincosamides, glycopeptides, rifampin, oxazolidinones, tetracyclines, aminoglycosides, streptogramins, sulfonamides, and the like. Other antibiotic or antibacterial agents are disclosed herein, and are known to those of skill in the art. In certain embodiments, the term “antibiotic agent” does not include an agent that is a FabI inhibitor, so that the combinations of the present invention in certain instances will include one agent that is a FabI inhibitor and another agent that is not.

[0059] The term “**drug**” as used herein refers to any substance falling within at least one of the definitions given in Article 1, Items 2(a), 2(b) or 3a. of Directive 2001/83/EC of November 6, 2001 in the version of November 16, 2012 or in Article 1, Items 2(a) or 2(b) of Directive 2001/82/EC of November 6, 2001 in the version of August 7, 2009 and in Article 2 of Regulation (EC) No. 726/2004 of March 31, 2004.

[0060] The term “**illness**” as used herein refers to any illness caused by or related to infection by an organism.

[0061] The term “**bacterial illness**” as used herein refers to any illness caused by or related to infection by bacteria.

5 [0062] The term “**cis**” is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the same side of the double bond. Cis configurations are often labeled as (Z) configurations.

[0063] The term “**trans**” is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the opposite
10 sides of a double bond. Trans configurations are often labeled as (E) configurations.

[0064] The term “**therapeutic effect**” is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any measurable effect in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of
15 desirable physical or mental development and/or conditions in an animal or human. The phrase “**therapeutically-effective amount**” means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the
20 subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. For example, certain compositions of the present invention may be administered in a sufficient amount to produce a therapeutic effect at a reasonable benefit/risk ratio applicable to such treatment.

[0065] The term “**chiral**” is art-recognized and refers to molecules which have the
25 property of non-superimposability of the mirror image partner, while the term “**achiral**” refers to molecules which are superimposable on their mirror image partner. A “**prochiral molecule**” is a molecule which has the potential to be converted to a chiral molecule in a particular process.

[0066] The compounds of the disclosure may contain one or more chiral centers
30 and/or double bonds and, therefore, exist as geometric isomers, enantiomers or diastereomers. The enantiomer and diastereomers may be designated by the symbols “(+)”, “(-)”, “R” or “S,” depending on the configuration of substituents around the stereogenic

carbon atom, but the skilled artisan will recognize that a structure may denote one or more chiral centers implicitly. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocyclic ring, can also exist in the compounds of the present invention.

[0067] The symbol  denotes a bond that may be a single, double or triple bond as described herein.

[0068] Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as “cis” or “trans.” The term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans” or “Z/E.”

[0069] The term “**stereoisomers**” when used herein consist of all geometric isomers, enantiomers or diastereomers. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Conformational isomers and rotamers of disclosed compounds are also contemplated.

[0070] The term “**ED50**” is art-recognized. In certain embodiments, ED50 means the effective dose of a drug which produces 50% of its maximum response or effect, or alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations. The term “LD50” is art-recognized. In certain embodiments, LD50 means the dose of a drug which is lethal in 50% of test subjects. The term “therapeutic index” is an art-recognized term that refers to the therapeutic index of a drug, defined as ED50/LD50.

[0071] The term “**K_i**” is art-recognized and refers to the dissociation constant of the enzyme-inhibitor complex.

[0072] The term “**antimicrobial**” is art-recognized and refers to the ability of the compounds disclosed herein to prevent, inhibit or destroy the growth of microbes such as bacteria, fungi, protozoa and viruses.

[0073] The term “**antibacterial**” is art-recognized and refers to the ability of the compounds disclosed herein to prevent, inhibit or destroy the growth of microbes of bacteria.

[0074] The term “**microbe**” is art-recognized and refers to a microscopic organism. In certain embodiments the term microbe is applied to bacteria. In other embodiments the term refers to pathogenic forms of a microscopic organism.

[0075] The term “**alkyl**” as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-8 or 1-6 carbon atoms referred to herein as C₁-C₈alkyl, or C₁-C₆alkyl, respectively. The term “lower alkyl” as used herein specifically refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-4 or 1-3 carbon atoms, referred to herein as C₁-C₄alkyl, and C₁-C₃alkyl, respectively. Exemplary alkyl groups and lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl.

[0076] Moreover, the term “**alkyl**” (or “**lower alkyl**”) includes “substituted alkyls”, i.e. it should be understood as optionally carrying one or more substituents at one or more positions. That is, it refers also to alkyl moieties having one or more (e.g. two, three, four, five, six, etc.) substituents, each replacing a hydrogen on a carbon of the hydrocarbon backbone. Such substituents may include, for example, a hydroxyl, a carbonyl group (wherein the carbonyl group carries a hydrogen atom, an alkyl group or another group as defined in this paragraph, such as to yield a carboxyl, an alkoxycarbonyl, a formyl, or an acyl group), a thiocarbonyl-containing group (wherein the carbonyl group carries a hydrogen atom, an alkyl group or another group as defined in this paragraph, such as to yield a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, a phosphate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl,

a heterocyclyl, an aralkyl, a cycloalkyl, a heterocycle or an aromatic or heteroaromatic moiety. In all instances, wherein the above-mentioned groups have more than one valency, the further free valency can be saturated by a hydrogen atom, an alkyl group, a cycloalkyl group, a heterocyclic group, an aryl group or a heteroaryl group. It will further be

understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate, phosphinate and phosphate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), nitrile and isonitrile. For the avoidance of doubt, an alkyl group carrying another alkyl group should not be regarded as an alkyl group substituted with another alkyl group, but as a single branched alkyl group.

[0077] The term “**alkenyl**” is art-recognized and refers to a group corresponding to the alkyl group defined above, but carrying one or more carbon-carbon double bonds. Of course, the total number of double bonds is restricted by the number of carbon atoms in the alkenyl group and in order to allow for at least one double bond, the alkenyl group must have at least two carbon atoms. Except for this difference, the definitions and characterizations given for the alkyl group above apply equally to the alkenyl group.

[0078] The term “**alkynyl**” is art-recognized and refers to a group corresponding to the alkyl group defined above, but carrying one or more carbon-carbon triple bonds. Of course, the total number of double bonds is restricted by the number of carbon atoms in the alkenyl group and in order to allow for at least one triple bond, the alkynyl group must have at least two carbon atoms. Except for this difference, the definitions and characterizations given for the alkyl group above apply equally to the alkynyl group.

[0079] The term “**aryl**” is art-recognized and refers to 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as “heteroaryl” or “heteroaromatics.” The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, phosphate, carbonyl,

carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF₃, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

[0080] The term "**aralkyl**" or "**arylalkyl**" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[0081] The term "**carbocycle**" is art-recognized and refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

[0082] The term "**cycloalkyl**" as used herein refers to a monocyclic saturated or partially unsaturated alkyl or alkenyl group of for example 3-6, or 4-6 carbons, referred to herein, e.g., as "C₃₋₆cycloalkyl" or "C₄₋₆cycloalkyl," and derived from a cycloalkane.

Exemplary cycloalkyl groups include, but are not limited to, cyclohexane, cyclohexene, cyclopentane, cyclobutane, cyclopropane or cyclopentene. Said cycloalkyl group may be substituted at one or more positions with one or more substituents as described above.

[0083] The terms "**halo**" or "**halogen**" as used herein refer to F, Cl, Br, or I. "**Halide**" designates the corresponding anion of the halogens, and "**pseudohalide**" has the definition set forth on page 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson, Interscience Publishers, 1966.

[0084] The term "**amino**" as used herein refers to any group of the general structure -NR_aR_b, wherein, unless specified otherwise, R_a and R_b are independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic groups, as well as any other substituent group listed above with respect to the scope of substituted alkyl groups, with the exception of carbonyl groups, thiocarbonyl groups, imine groups, and substituent groups in which attachment to the remaining molecule is via a heteroatom selected from N, O, S and P. Alternatively, R_a and R_b may represent hydrocarbon groups that are linked to form a heterocycle together with the nitrogen atom to which they are attached.

[0085] The term "**heteroaryl**" as used herein refers to a monocyclic aromatic 4-6 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, which may be the same or different, such as nitrogen, oxygen, and sulfur.

Where possible, said heteroaryl ring may be linked to the adjacent radical through carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, benzofuran, thiophene, pyrrole, thiazole, oxazole, isothiazole, isoxazole, imidazole, pyrazole, triazole, pyridine, and pyrimidine. Said heteroaryl group may be substituted with one or more substituents as described for the aryl group above. The term "heteroaryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons or heteroatoms are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is a heteroaryl as defined above whereas the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aromatic rings and/or saturated, unsaturated or aromatic heterocycles.

[0086] The term "**heterocycle**" as used herein refers to a monocyclic ring containing one or more heteroatoms, for example one to three heteroatoms, which may be the same or different, such as nitrogen, oxygen, and sulfur. The remaining ring members are formed by carbon atoms. The heterocycle typically has 4 to 8 ring members and preferably 5 or 6 ring members. Unless specified otherwise, a heterocycle may be aromatic, partially or fully saturated. Unless specified otherwise, it may or may not contain permissible substituents as specified herein.

[0087] The terms "**hydroxy**" and "**hydroxyl**" as used herein refer to the radical -OH.

[0088] The term "**nitro**" is art-recognized and refers to -NO₂; the term "**sulphydryl**" is art-recognized and refers to -SH; and the term "**sulfonyl**" is art-recognized and refers to -SO₂-.

[0089] The definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0090] The terms "**triflyl**", "**tosyl**", "**mesyl**", and "**nonaflyl**" are art-recognized and refer to trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate, p-toluenesulfonate, methanesulfonate, and nonafluorobutanesulfonate functional groups and molecules that contain said groups, respectively.

[0091] The abbreviations **Me**, **Et**, **Ph**, **Tf**, **Nf**, **Ts**, and **Ms** represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by

organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations.

[0092] The term “**prodrug**” refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release the active drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug.

[0093] It will be understood that “**substitution**” or “**substituted with**” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[0094] The term “**substituted**” is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above, e.g. in connection with substituted alkyls. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. In this context, the term “permissible substituents” means any substituent that can be bonded to the core molecule without contravening general principles of chemical bond formation such as the maximum number of valence electrons for an atom of interest, and without making the compound so toxic for the patient that unacceptable toxicity is found even at the minimum dosage required for achieving a therapeutic effect.

[0095] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of the disclosure, the term “**hydrocarbon**” is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include

acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds that may be substituted or unsubstituted.

[0096] The term “**pharmaceutically-acceptable salts**” is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts, or inorganic or organic
5 base addition salts of compounds, including, for example, those contained in compositions of the present invention, and including those present in other approved drugs (wherein approval may be by any competent authority in the EU, USA, CA, JP, CN or KR).

Pharmaceutically acceptable salts are meant to be encompassed by the present invention.

Hence, all references to compounds of the invention are to be understood as references not

10 only to the compounds as such, but also to pharmaceutically acceptable salts of the respective compounds. According to one aspect, the pharmaceutically acceptable salts may be selected from the salts acknowledged as pharmaceutically acceptable in the literature at the filing date, and in particular as described in G.S. Paulekuhn et al. in J. Med. Chem. 2007, 50, 6665-6672 and references cited therein. If the compound of the invention is an acidic
15 compound, and in particular a prodrug containing a phosphate group, said compound of the invention may be provided in the form of pharmaceutically acceptable salts, wherein the compound forms the anion part and the counterion is selected from Na, K, Mg, Ca, or the protonated forms of the organic bases ethanolamine, meglumine, tromethamine (i.e. 2-amino-2-(hydroxymethyl)propane-1,3-diol), and deanol (i.e. 2-(dimethylamino)ethanol). The
20 stoichiometry of the salts is not particularly restricted. For instance, salts may be formed with the phosphate prodrugs of the invention (having 2 acidic protons) in any stoichiometric ratio of from 0 to 2 equivalents. Generally, pharmaceutically acceptable salts are formed such that the net charge of the salt is zero, i.e. that the total number of positive charges equals the total number of negative charges.

25 [0097] The term “**treating**” includes any significant effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0098] The term “**prophylactic**” or “**therapeutic**” treatment is art-recognized and refers to administration to the host of one or more of the subject compositions. If it is
30 administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if administered after

manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate or maintain the existing unwanted condition or side effects therefrom).

[0099] A “**patient**,” “**subject**” or “**host**” to be treated by the subject method may mean either a human or non-human animal. Non human animals include companion
5 animals (e.g. cats, dogs) and animals raised for consumption (i.e. food animals), such as cows, pigs, chickens. Non-human animals are preferably mammals.

[00100] The term “**mammal**” is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

[00101] The term “**bioavailable**” is art-recognized and refers to a form of the subject
10 disclosure that allows for it, or a portion of the amount administered, to be absorbed by, incorporated to, or otherwise physiologically available to a subject or patient to whom it is administered.

[00102] The term “**pharmaceutically acceptable carrier**” is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid
15 filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “**acceptable**” in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically
20 acceptable carriers include: (1) sugars, such as dextrose, lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch as well as starch derivatives such as cyclodextrins and modified cyclodextrins including preferably (2-hydroxypropyl)- β -cyclodextrin and sulfobutylether- β -cyclodextrin; (3) cellulose, and its derivatives, such as microcrystalline cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose,
25 hydroxypropylmethyl cellulose (HPMC), and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) matrix-forming polymeric excipients such as polyvinyl pyrrolidone (PVP), e.g. PVP K30, acrylic polymers and co-polymers such as the different grades of Eudragit and preferably Eudragit L100, hydroxypropylmethyl cellulose acetate succinate (HPMCAS), other copolymers such as polyethylene glycol-based copolymers like
30 Soluplus; (9) excipients, such as cocoa butter and suppository waxes; (10) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (11) glycols, such as propylene glycol; (12) polyols, such as glycerin, sorbitol, mannitol and

polyethylene glycol; (13) esters, such as ethyl oleate, glyceryl behenate and ethyl laurate; (14) agar; (15) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (16) alginic acid; (17) pyrogen-free water; (18) isotonic saline; (19) Ringer's solution; (20) ethyl alcohol; (21) phosphate buffer solutions; and (22) other non-toxic compatible substances employed in pharmaceutical formulations. The disclosed excipients may serve more than one function. For example, fillers or binders may also be disintegrants, glidants, anti-adherents, lubricants, sweeteners and the like.

[00103] The term "**solvent**" is used herein to mean a liquid chemical substance that is capable of dissolving a significant quantity of another substance of interest, the "solute", to thereby generate a clear homogeneous solution. The term "significant quantity" is determined by the intended use of the solution in such a manner that the intended use must be possible by the dissolved quantity of the solute. For instance, if it is intended to administer a compound of the present invention in the form of a solution by injection, the solvent must be capable of dissolving the compound in such amounts, to make administration of a therapeutic dose possible.

[00104] Unless specified otherwise, all reactions described herein are carried out at reaction temperatures that yield the desired target compound and that provide a reasonable compromise between reaction rate and selectivity. Typical reaction temperatures for Pd-based coupling reactions and Fe-based cyclization reactions are 80°C to 90°C while removal of protecting groups is typically accomplished at a temperature of from 0°C to room temperature (25°C).

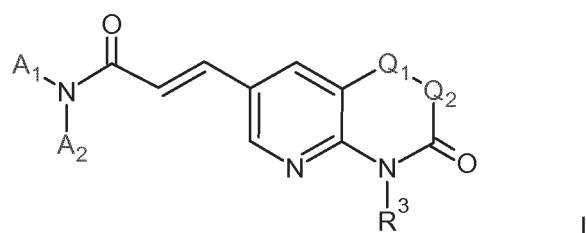
[00105] Unless specified otherwise, all characterizations of variable groups as being the same as specified for the compound of formula I, or the like, are to be understood such that the more specific meanings and combinations of meanings, as embodied by the formulae II to XVI, are also possible and even preferred.

[00106] Unless specified otherwise, the term "protective group" is used herein to characterize a group that is bonded to a functional group to prevent this functional group from participating in a contemplated chemical reaction. The protective group must be inert under the conditions of the contemplated chemical reaction, but it must be possible to remove the protective group from the compound such that no further transformations take place in other parts of the molecule. Suitable protective groups are described for each

functional group in "Greene's Protective Groups in Organic Synthesis", Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 20 Dec 2012.

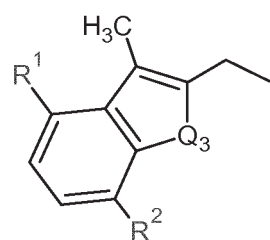
Compounds of the Invention

- 5 [00107] The present invention provides compounds, which exhibit favorable antibiotic activity via FabI inhibition. The compounds of the present invention are represented by the following general formula I

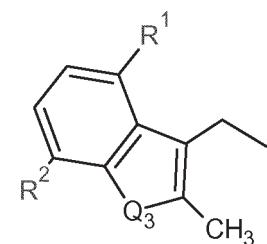


wherein

A₁ represents a moiety selected from the groups A₁₁ and A₁₂ having the following structures



A₁₁ and

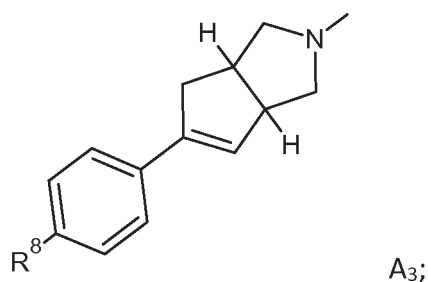


A₁₂;

wherein the line connected to the exocyclic methylene group represents a single covalent bond formed with the nitrogen atom of formula I;

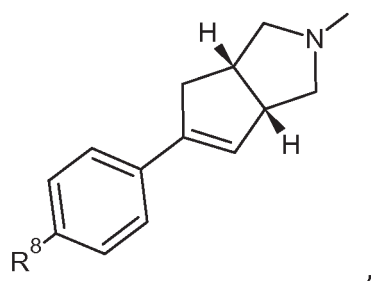
A₂ represents a methyl group;

or A₁ and A₂ together with the nitrogen atom to which they are bonded form the following moiety A₃:

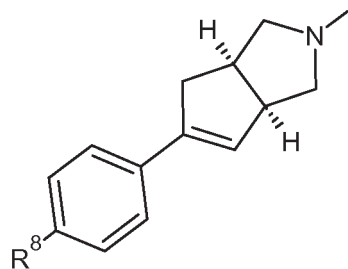


wherein moiety A₃ is not restricted in terms of its stereochemistry. It can be one

5 enantiomer:



10 or it can be the other enantiomer



or it can be any mixture thereof, including especially the racemic mixture of the above two

15 enantiomers. Any of these moieties is referred to as moiety A₃;

wherein in moiety A₃ the exocyclic line connected to the nitrogen atom of the bicycle represents the covalent bond between nitrogen and carbonyl group in the left-hand side of formula I;

20

Q₁ represents $-\text{CH}=\text{CR}^7-$, CH₂ or NH;

Q₂ represents CR⁴R⁵, or CR⁴R⁵-CR⁶R⁷, wherein the CR⁴R⁵ group binds to Q₁;

or Q_1 - Q_2 represents $-N=CR^7-CHR^7-$ or its tautomer $-NH-CR^7=CR^7-$

Q_3 represents O or S;

5

R^1 represents a group selected from H, $-NH_2$;

R^2 represents a group selected from H, $-O-Ar^1$, $-O-Het^1$, $-NR^9R^{10}$, $-O-Alk^1$, wherein Ar^1 represents a phenyl group that may optionally be substituted by one or more groups individually selected from $-CN$, $-O-C_{1-4}$ -alkyl, $-O-(CH_2)_{1-4}-NR^9R^{10}$, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups, which may for instance be selected from alkylene groups and alkylene groups carrying one or two heteroatoms individually selected from N and O within their backbone, which substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O wherein the N atom may carry a group selected from H and methyl, wherein Het^1 represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N and O, wherein said aromatic or non-aromatic heterocycle may optionally be substituted by one or more groups individually selected from $-C_{1-4}$ -alkyl, $-O-C_{1-4}$ -alkyl, $-CN$, $-(CH_2)_{0-4}-OH$, wherein R^9 is selected from H and $-C_{1-4}$ -alkyl; wherein R^{10} is selected from H, $-C_{1-4}$ -alkyl and $-C(=O)-CH_3$; wherein Alk^1 represents an alkyl group having 1 to 6 carbon atoms, which is linear, branched, cyclic or a combination thereof, which Alk^1 group may optionally be substituted by one or more groups selected from $-OH$, $-O$ -alkyl

R^3 represents a group selected from H, $-PO_3R^{3a}_2$, $-CH_2-OPO_3R^{3a}_2$ and $-CH_2-O-C(=O)-R^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-CH_2-O-C(=O)-R^{3b}$ or $-CHMe-O-C(=O)-R^{3b}$ or $-CMe_2-O-C(=O)-R^{3b}$ or $-CH_2-O-C(=O)-O-R^{3b}$ or $-CHMe-O-C(=O)-O-R^{3b}$ or $-CMe_2-O-C(=O)-O-R^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

5 R⁴ represents a group selected from H, C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F;

R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

10 or R⁴ and R⁵ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom;

R⁶ represents a group selected from H, -OH, C₁₋₄-alkyl, or -OPO₃R^{3a}₂;

15 R⁷ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, C₁₋₄-alkylene-F, -CN;

or R⁶ and R⁷ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom; the cyclic group may optionally carry a substituent
20 selected from -OH, -O-alkyl;

R⁸ represents a group selected from -O-Ar² and -O-Het²;

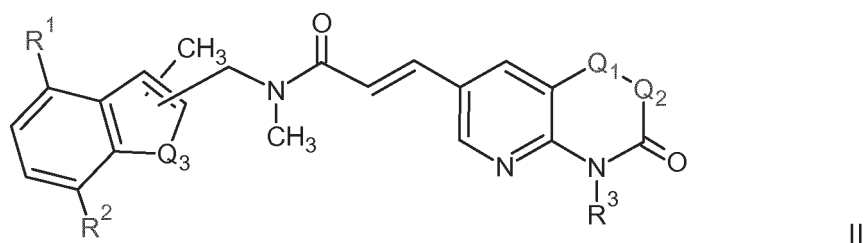
wherein Ar² represents a phenyl group that may optionally be substituted by one or more
25 groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N, S and O, wherein said heterocycle may optionally carry one or two substituents selected from oxo, halogen, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, and CN;

30

and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

- 5 [00108] In one embodiment, the compounds of the present invention are represented by general formula II



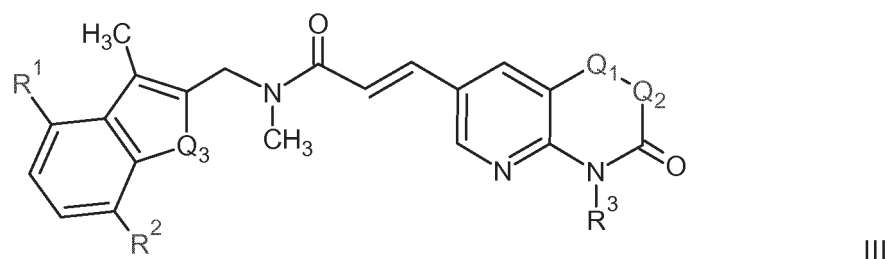
10 wherein

R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified for general formula I above;

and wherein the five-membered heterocycle comprising Q₃ is bonded to the methylene-
 15 amide moiety at the 2-position and to the methyl group at the 3-position or is bonded to the methylene-amide moiety at the 3-position and to the methyl group at the 2-position.

[00109] Preferably, the compounds of this embodiment are represented by general
 formula III

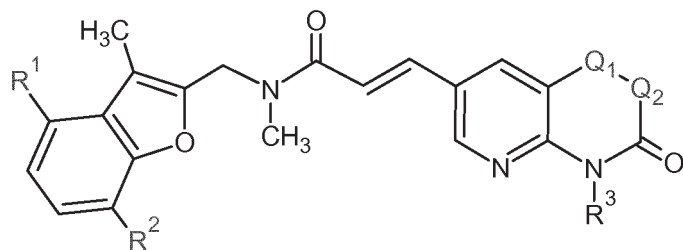
20



wherein

25 R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified for general formula I above.

[00110] In this embodiment, variable group Q₃ may especially represent an oxygen atom, such that the moiety at the left-hand side of the molecule is a benzofuran moiety. Such compounds are represented by general formula IV

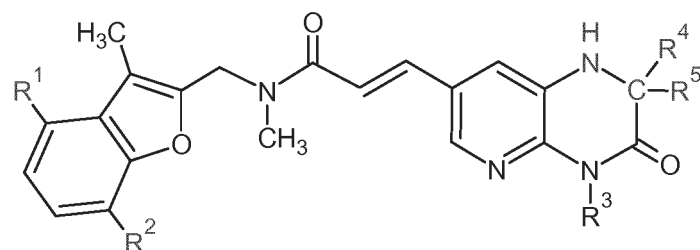


IV

wherein

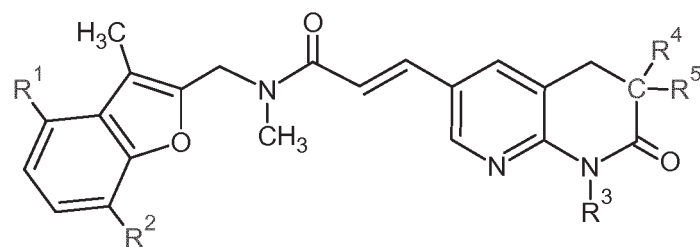
R¹, R², R³, Q₁, Q₂ have the same meanings as specified for general formula I above.

[00111] According to another preferred aspect of this embodiment, the variable groups Q₁ and Q₂ represent NH or CH₂ for Q₁ and CR⁴R⁵ for Q₂, respectively. The compounds of this aspect are represented by general formula Va or general formula Vb



Va;

or



Vb

wherein

R¹, R², R³, have the same meanings as specified for general formula I above. In formula Va, R⁴ represents a group selected from H, C₁₋₄-alkyl and C₁₋₄-alkylene-F and R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³. In formula Vb, R⁴ represents

a group selected from H, C₁₋₄-alkyl and C₁₋₄-alkylene-F and R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH; and -OPO₃R^{3a}₂.

- 5 **[00112]** The variable groups of general formula Va or Vb may preferably have the following meanings:

R¹ represents H, NH₂;

- 10 R² represents H;

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

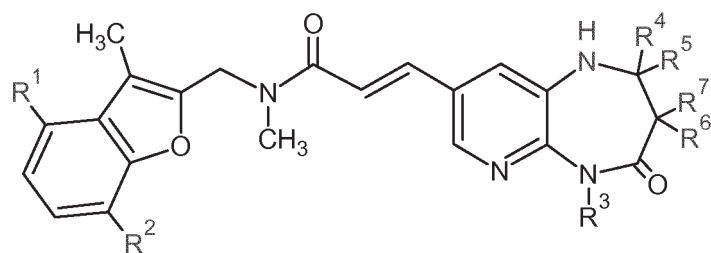
- R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

- R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

R⁴ represents H, C₁₋₄-alkyl; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

- 25 **[00113]** According to another aspect of this embodiment, the variable groups Q₁ and Q₂ represent NH and CR⁴R⁵-CR⁶R⁷, respectively. The compounds of this aspect are represented by general formula VI



VI

wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified for general formula I above.

5 [00114] In this aspect, the variable groups may preferably have the following meanings:

R^1 represents H, NH_2 ;

10 R^2 represents H;

R^3 represents a group selected from H, $-PO_3R^{3a}_2$, $-CH_2-OPO_3R^{3a}_2$ and $-CH_2-O-C(=O)-R^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically
15 acceptable salt or $-CH_2-O-C(=O)-R^{3b}$ or $-CHMe-O-C(=O)-R^{3b}$ or $-CMe_2-O-C(=O)-R^{3b}$ or $-CH_2-O-C(=O)-O-R^{3b}$ or $-CHMe-O-C(=O)-O-R^{3b}$ or $-CMe_2-O-C(=O)-O-R^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic
or a combination thereof, which R^{3b} group may optionally be substituted by one or more
20 groups independently selected from $-OH$, and $-O-C_{1-6}$ -alkyl;

R^4 represents H, C_{1-4} -alkyl; and

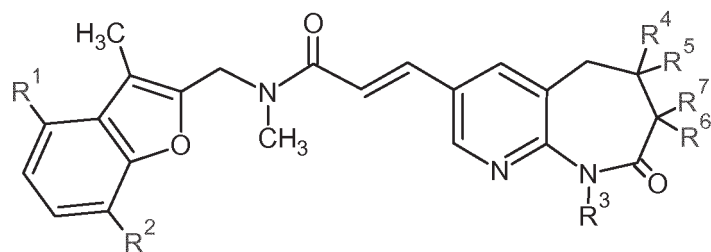
R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OR^3 .

25

R^6 represents H, C_{1-4} -alkyl, OH , $-OPO_3R^{3a}_2$; and

R^7 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OH , C_{1-4} -alkylene- OR^3 , wherein R^3 is as specified
30 above, C_{1-4} -alkylene-F.

[00115] According to yet another aspect of this embodiment, the variable group Q_1 represents a methylene group while Q_2 has the same meaning as in the preceding aspect, i.e. $-\text{CR}^4\text{R}^5-\text{CR}^6\text{R}^7$. The compounds of this aspect are represented by general formula VII



VII

wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified for general formula I above.

[00116] In the compounds of this aspect, the variable groups have preferably the following meanings:

R^1 represents H, NH_2 ;

R^2 represents H;

R^3 represents a group selected from H, $-\text{PO}_3\text{R}^{3a}_2$, $-\text{CH}_2-\text{OPO}_3\text{R}^{3a}_2$ and $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-\text{OH}$, and $-\text{O}-\text{C}_{1-6}\text{-alkyl}$;

R^4 represents H, $\text{C}_{1-4}\text{-alkyl}$; and

R^5 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene-OR}^3$;

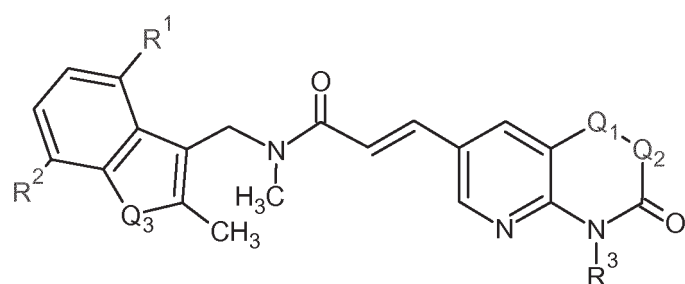
R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified

5 above, C₁₋₄-alkylene-F.

[00117] In another embodiment of the present invention, the bicyclic moiety on the left-hand side of the molecule is bonded via the 3-position of the five-membered

10 heterocycle. The compounds of this embodiment are represented by general formula VIII

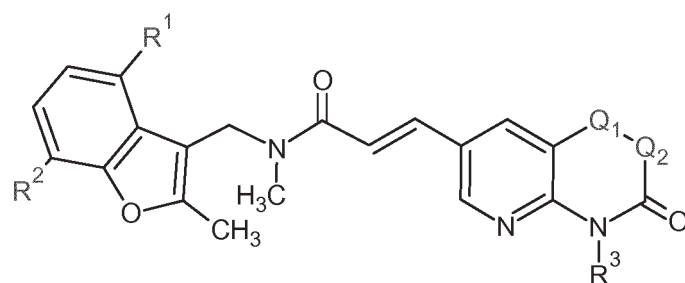


VIII

wherein

15 R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified for general formula I above.

[00118] In one specific aspect of this embodiment, the variable group Q₃ represents
 20 an oxygen atom, so that the bicyclic moiety on the left-hand side is a benzofurane moiety. The compounds of this aspect are represented by general formula IX

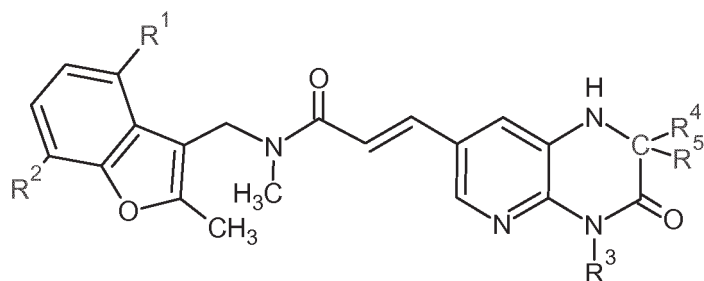


IX

25 wherein

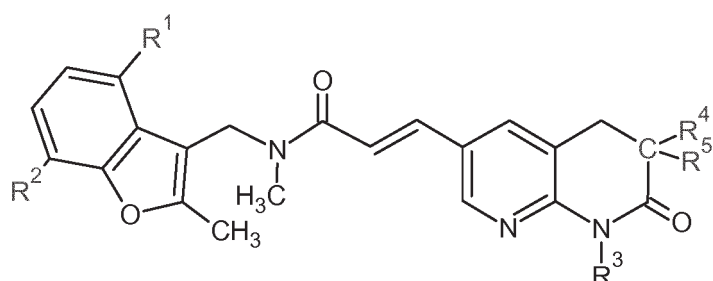
R¹, R², R³, Q₁, Q₂ have the same meanings as specified for general formula I above.

[00119] In this aspect, the variable groups Q_1 and Q_2 preferably represent NH or CH_2 for Q_1 and CR^4R^5 for Q_2 , respectively. Preferred compounds of this aspect are thus represented by general formula Xa and Xb



Xa;

or



Xb;

wherein

R^1 , R^2 , R^3 , R^4 and R^5 have the same meanings as specified for general formula I above.

[00120] The variable group meanings for the compounds of this aspect are preferably as follows:

R^1 represents H;

R^2 represents a group selected from H, $-O-Ar^1$, $-O-Het^1$, NH_2 , wherein Ar^1 represents a phenyl group that may optionally be substituted by one or more groups individually selected from $-CN$, $-O-C_{1-4}$ -alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het^1 represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully

saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

5 R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

10

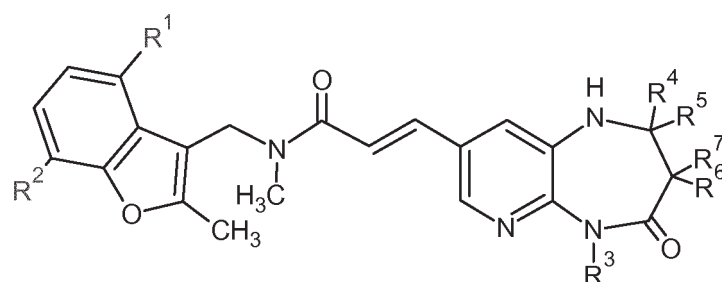
R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

15 R⁴ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-F; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH or C₁₋₄-alkylene-OR³, wherein R³ is as specified above.

20

[00121] Another preferred sub-genus of compounds of this aspect of the invention is represented by general formula XI



XI

25

wherein

R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the same meanings as specified for general formula I above.

30

[00122] For this sub-genus, the variable group meanings are preferably as follows:

R¹ represents H;

5 R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1
10 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

15 R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

20

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

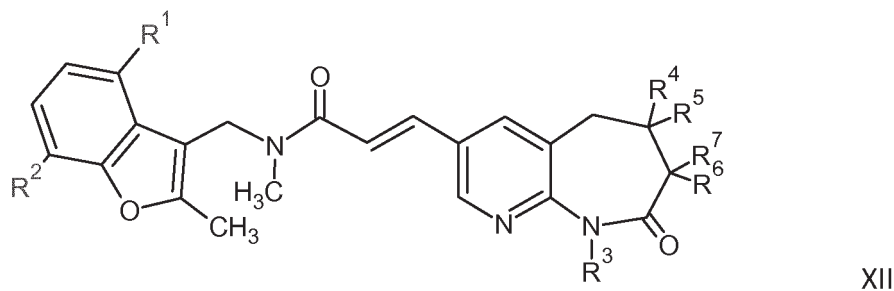
25 R⁴ represents H, C₁₋₄-alkyl; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

30 R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

R^7 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-OR³, wherein R³ is as specified above, C_{1-4} -alkylene-F.

- 5 **[00123]** Another preferred sub-genus of compounds of this aspect of the invention is represented by general formula XII



- 10 wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified for general formula I above.

- 15 **[00124]** The variable group meanings in this sub-genus of compounds are preferably as follows:

R^1 represents H;

- 20 R^2 represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O- C_{1-4} -alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from - C_{1-4} -alkyl, -O- C_{1-4} -alkyl, -CN;

30

R^3 represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$;

5

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-\text{OH}$, and $-\text{O}-\text{C}_{1-6}-\text{alkyl}$;

10 R^4 represents H, $\text{C}_{1-4}-\text{alkyl}$; and

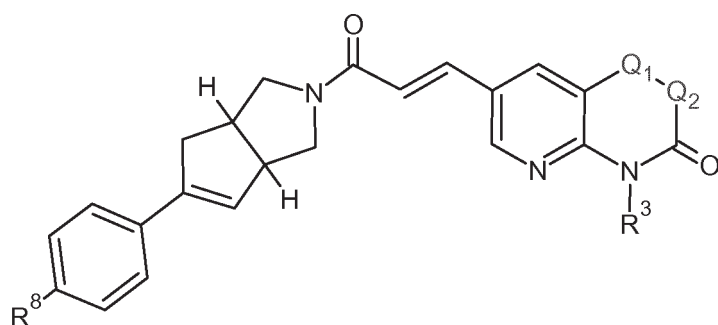
R^5 represents H, $\text{C}_{1-4}-\text{alkyl}$, $\text{C}_{1-4}-\text{alkylene}-\text{OR}^3$.

R^6 represents H, $\text{C}_{1-4}-\text{alkyl}$, OH , $-\text{OPO}_3\text{R}^{3a}_2$; and

15

R^7 represents H, $\text{C}_{1-4}-\text{alkyl}$, $\text{C}_{1-4}-\text{alkylene}-\text{OH}$, $\text{C}_{1-4}-\text{alkylene}-\text{OR}^3$, wherein R^3 is as specified above, $\text{C}_{1-4}-\text{alkylene}-\text{F}$.

20 **[00125]** Another embodiment of the present invention pertains to compounds represented by general formula XIII



XIII

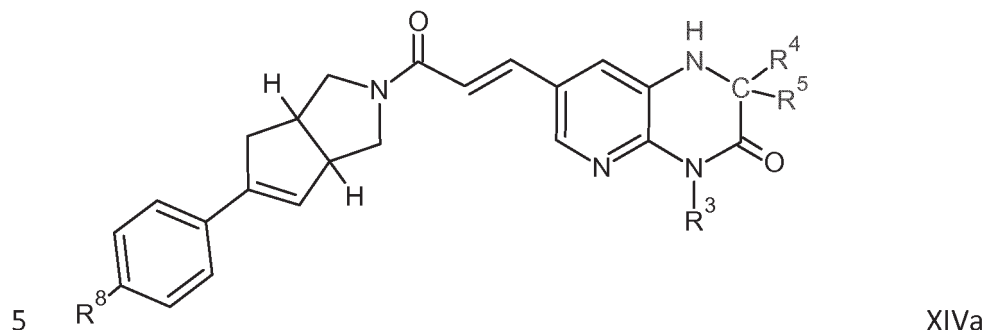
25

wherein

R^3 , R^8 , Q_1 , Q_2 have the same meanings as specified for general formula I above.

30

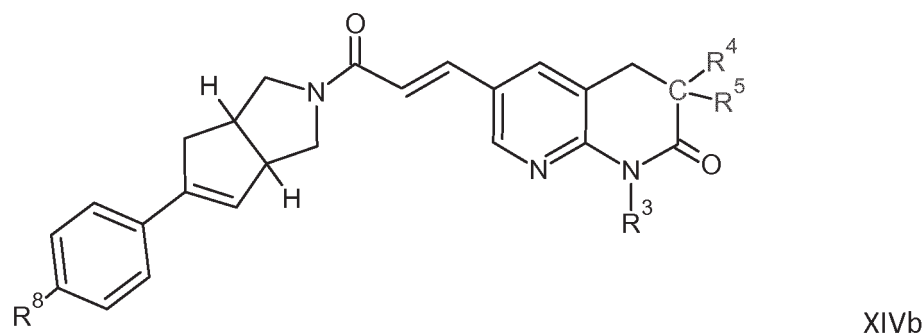
[00126] Among the compounds of this embodiment, a preferred aspect relates to compounds having an amino group NH or a methylene group CH₂ in the position of Q₁ and a group CR⁴R⁵ in the position of Q₂. These compounds are represented by general formula XIVa and XIVb



wherein

R³, R⁴, R⁵, R⁸ have the same meanings as specified for general formula I above;

or



wherein

R³, R⁴, R⁵, R⁸ have the same meanings as specified for general formula I above.

[00127] For this aspect of the invention, preferred variable group meanings are as follows:

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

5

R⁴ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-F; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH or C₁₋₄-alkylene-OR³, wherein R³ is as specified above;

10

R⁸ represents a group selected from -O-Ar² and -O-Het²;

wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N, S and O, wherein said heterocycle may optionally carry one or two substituents selected from oxo, F, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, CN;

15

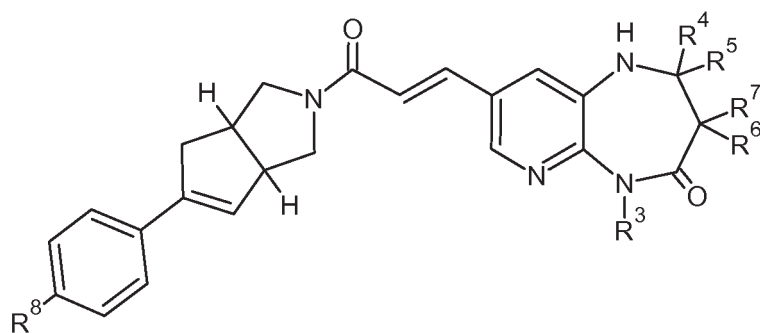
20 and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

25

[00128] In another preferred aspect of this embodiment, an amino group NH is present in the position of Q₁ and a group -CR⁴R⁵-CR⁶R⁷ is present in the position of Q₂. The compounds are thus represented by general formula XV

30



XV

wherein

- 5 R^3 , R^4 , R^5 , R^6 , R^7 , R^8 have the same meanings as specified for general formula I above.

[00129] Preferred substituent meanings for the compounds of this aspect are as follows:

- 10 R^3 represents a group selected from H, $-\text{PO}_3\text{R}^{3a}_2$, $-\text{CH}_2-\text{OPO}_3\text{R}^{3a}_2$ and $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$;

15

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-\text{OH}$, and $-\text{O}-\text{C}_{1-6}\text{-alkyl}$;

- 20 R^4 represents H, $\text{C}_{1-4}\text{-alkyl}$; and

R^5 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene-OR}^3$.

R^6 represents H, $\text{C}_{1-4}\text{-alkyl}$, OH, $-\text{OPO}_3\text{R}^{3a}_2$; and

25

R^7 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene-OH}$, $\text{C}_{1-4}\text{-alkylene-OR}^3$, wherein R^3 is as specified above, $\text{C}_{1-4}\text{-alkylene-F}$;

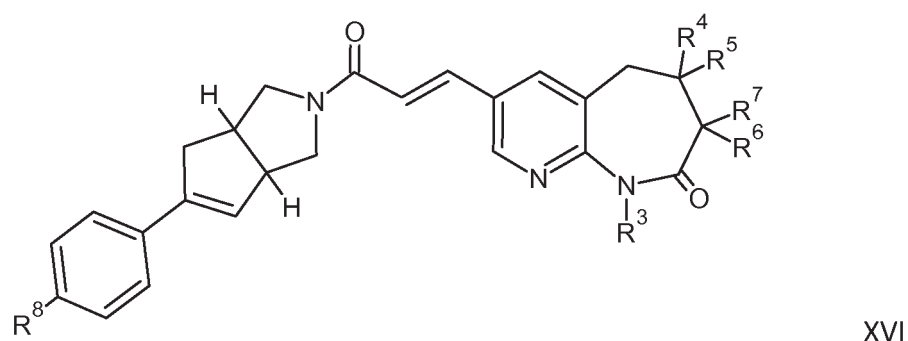
R⁸ represents a group selected from -O-Ar² and -O-Het²,

wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N, S and O, wherein said heterocycle may optionally carry one or two substituents selected from oxo, F, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, CN

and

wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

[00130] In a related aspect, variable group Q₁ represents a methylene group so that the compounds are represented by general formula XVI



wherein

R³, R⁴, R⁵, R⁶, R⁷, R⁸ have the same meanings as specified for general formula I above.

[00131] Preferred variable group meanings for this aspect are the following ones:

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

- 5 R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

R⁴ represents H, C₁₋₄-alkyl; and

10

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³;

R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

- 15 R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F;

R⁸ represents a group selected from -O-Ar² and -O-Het²,

- 20 wherein Ar² represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms selected N, S and O, wherein said heterocycle may optionally carry one or two substituents
- 25 individually selected from oxo, F, -O-C₁₋₄-alkyl, C₁₋₄-alkyl, CN

and

- wherein Het² represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2
- 30 heteroatoms individually selected from N, S and O, which may optionally be substituted by one or more groups individually selected from -O-C₁₋₄-alkyl, -CN, F, C₁₋₄-alkyl.

[00132] The present disclosure contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. However, the carbon-carbon double bond between the pyridine ring and the amide group in the center of the molecule must be in trans configuration, as shown in the above formulae. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[00133] If, for instance, a particular enantiomer of a compound disclosed herein is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[00134] Moreover, individual enantiomers and diastereomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses

encompass both enantio- and diastereoselective transformations. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00135] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. The compounds disclosed here may exist in single or multiple crystalline forms or polymorphs. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[00136] The invention also embraces isotopically labeled compounds of the invention which are as recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

[00137] Certain isotopically-labeled disclosed compounds (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the e.g., Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[00138] Prodrugs of the present invention contain at least one prodrug moiety, i.e. a moiety that is cleaved under physiologic conditions to thereby release the active species. Such prodrug moieties may be attached to the compounds of the present invention in all positions represented by variable group R^3 . A suitable prodrug moiety is the methylene phosphate moiety, as described in WO 2013/190384 A1. Further suitable prodrug moieties are phosphates or other solubilizing moieties as described in "Prodrugs: design and clinical

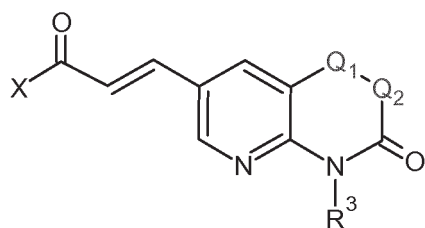
applications" (Rautio et al. Nature Reviews Drug Discovery, 2008, 7, 255). One specific prodrug modification is the conversion of an amine group to an N-oxide group. The above chemical formulae illustrate suitable positions for prodrug modifications by means of the methylene phosphate moiety and the phosphate moiety. It should be understood that these prodrug moieties may be replaced by other prodrug moieties. According to a preferred embodiment of the present invention, the prodrugs of the invention contain exactly one prodrug moiety.

Methods of Manufacture

[00139] The compounds of the present invention can be prepared using established organic chemistry synthetic methods and procedures and/or information described hereinbelow. Starting materials may either be purchased (if commercially available) or synthesized using established organic chemistry synthetic methods and procedures and/or information described hereinbelow.

Final Step Amide Coupling

[00140] Compounds disclosed herein may be prepared by means of the following method, which comprises the step of coupling a precursor compound of formula XVII



XVII

[00141] wherein Q₁, and Q₂ have the same meanings as specified hereinabove, wherein R₃ represents a hydrogen atom, and wherein X represents a leaving group,

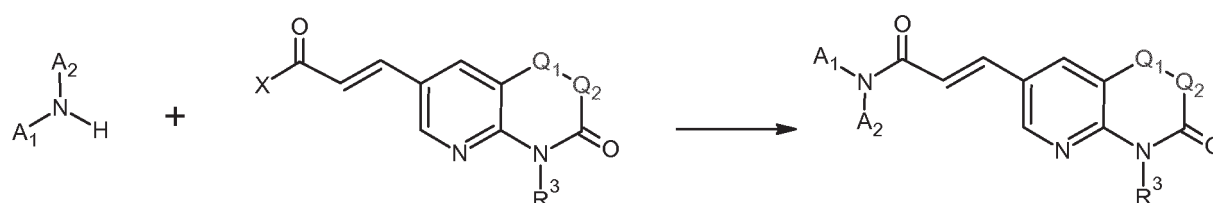
[00142] with an amine compound of formula H-NA₁A₂, herein sometimes referred to as formula XXIII, wherein A₁ and A₂ have the same meanings as specified hereinabove for the compound of formula I.

[00143] The leaving group may be selected from a hydroxyl group, tosylate group, triflate group, mesylate group, iodide, bromide and the like.

[00144] Especially if the leaving group is a hydroxyl group, the coupling reaction is preferably carried out in a solvent and in the presence of a coupling agent and more preferably in the presence of a solvent, a coupling group and a base. The solvent is preferably selected from DMF, THF, DCM. The coupling agent is preferably selected from HATU, HBTU, HCTU, TBTU, COMU, TOMBU, COMBU and most preferably HATU. The reaction is typically carried out in the presence of a base. The base is preferably selected from DIPEA.

[00145] This reaction sequence is illustrated by the following Scheme 1.

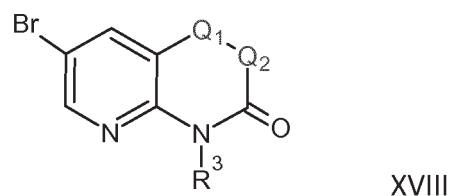
10 Scheme 1:



15 wherein A_1 and A_2 as well as Q_1 and Q_2 have the same meanings as specified for compound I hereinabove, and wherein R^3 represents a hydrogen atom.

Manufacture of Right-Hand Side Precursor

[00146] The precursor compound of formula XVII can be manufactured by reacting a compound of formula XVIII



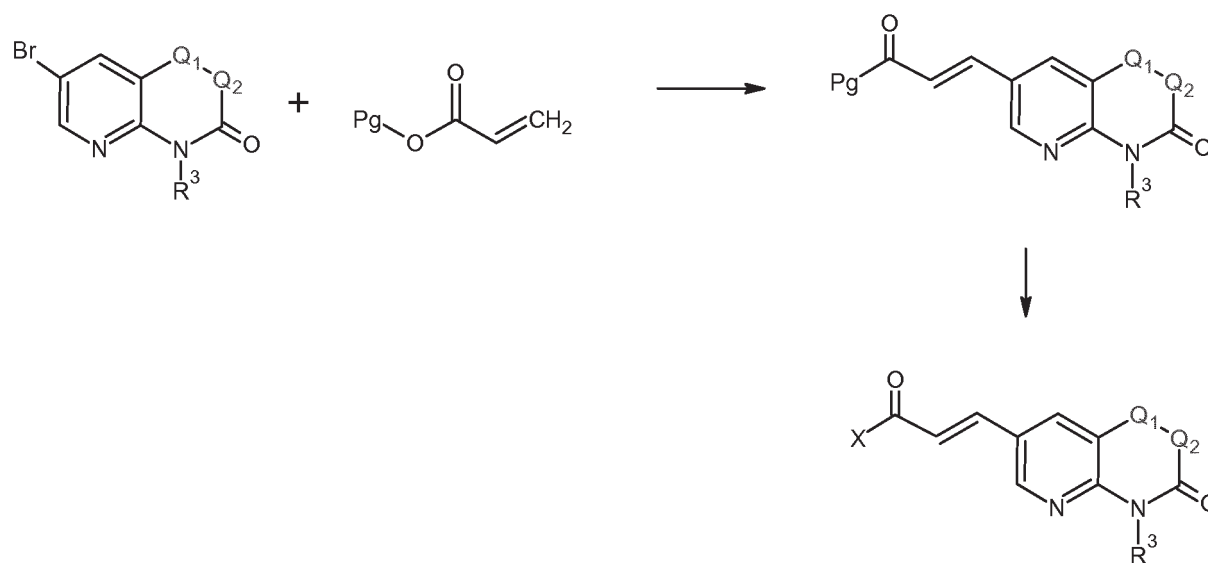
25 wherein Q_1 and Q_2 have the same meanings as specified for compound I hereinabove, and wherein R^3 represents a hydrogen atom,

with a carboxyl-protected acrylic acid, such as a C_{1-6} -alkyl ester (preferably tert-butyl ester) of acrylic acid. This coupling reaction is carried out under Heck coupling conditions and

preferably in the presence of a Pd(II)-salt such as Pd(OAc)₂ and a phosphine ligand such as Xantphos, tri-(*o*-tolyl)phosphine or 1,1-Bis(diphenylphosphino)ferrocene (dppf). The reaction is typically carried out in the presence of a solvent such as DMF, propionitrile or a combination thereof and also in the presence of a base such as DIPEA. The coupling reaction

5 is followed by deprotection and optionally introduction of a leaving group other than hydroxyl. This reaction sequence is illustrated by the following Scheme 2.

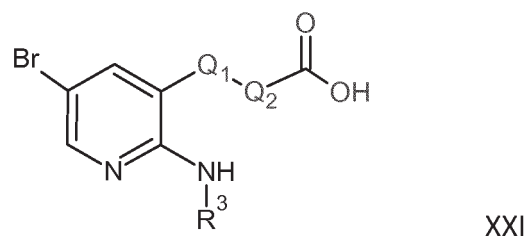
Scheme 2:



10 wherein Pg represents a protective group, Q₁ and Q₂ have the same meanings as specified for compound I hereinabove, and wherein R³ represents a hydrogen atom.

[00147] Precursor compound XX can be synthesized by means of a cyclization reaction

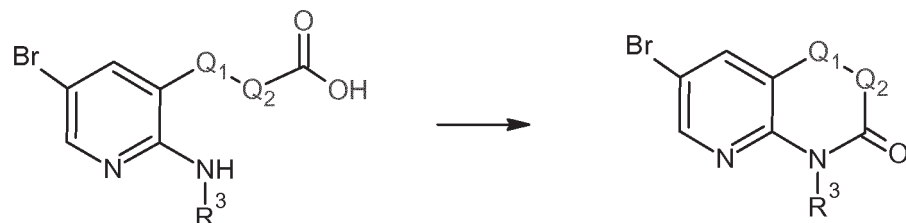
15 starting from a compound of formula XXI:



20 [00148] wherein Q₁ and Q₂ have the same meanings as specified for compound I hereinabove, and wherein R³ represents a hydrogen atom. The cyclization is typically

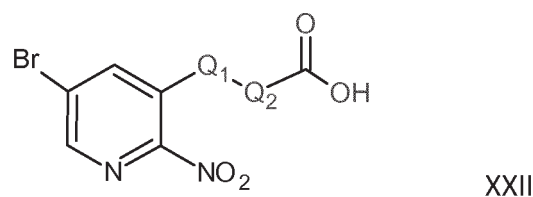
accomplished using coupling agents such as HATU in the presence of a base like DIPEA and in a solvent such as DMF. This reaction sequence is illustrated by the following Scheme 3.

Scheme 3:



wherein Q₁ and Q₂ have the same meanings as specified hereinabove, and wherein R³ represents a hydrogen atom.

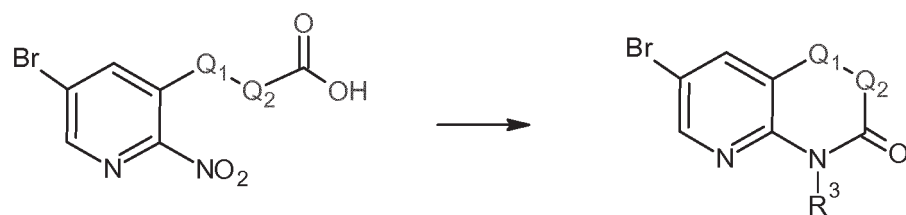
[00149] Alternatively, precursor compound XX can be synthesized by means of a cyclization reaction starting from a compound of formula XXII:



wherein Q₁ and Q₂ have the same meanings as specified for compound I hereinabove.

[00150] This variant of the cyclization reaction is typically carried out in the presence of a reducing agent such as Fe in acetic acid or a mixture of water, ethanol and ammonium chloride. This reaction step is illustrated by the following reaction scheme 4.

Scheme 4:

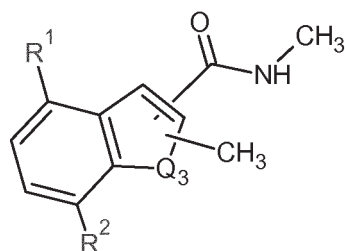


wherein Q₁ and Q₂ have the same meanings as specified for compound I hereinabove, and wherein R³ represents a hydrogen atom.

Manufacture of H-NA₁A₂ Precursor

[00151] If variable group A₁ is a group selected from groups A₁₁ and A₁₂ and A₂ is a methyl group, the precursor compound H-NA₁A₂ may be obtained by means of the following procedures.

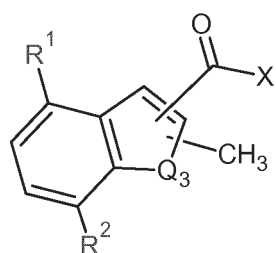
[00152] One option is to form an amide precursor XXIV that is subsequently reduced to the amine compound XXIII. The amide precursor XXIV has the following structure (wherein the structure XXIV permits the amide group to be bonded to the 2-position and the methyl group bonded to the 3-position or vice versa):



XXIV

wherein R¹, R² and Q₃ have the same meanings as indicated for compound I above or wherein R¹ and/or R² may represent a functional group that can be converted to the desired substituent at a later stage of the reaction sequence. Said functional group must of course be inert under the reaction conditions specified for the conversions described herein (i.e. from compound XXV to compound XXIII), but be susceptible to subsequent conversion under different reaction conditions. This can be, for instance, a Br substituent.

[00153] Compound XXIV can be synthesized by reacting an activated carboxylic acid derivative XXV



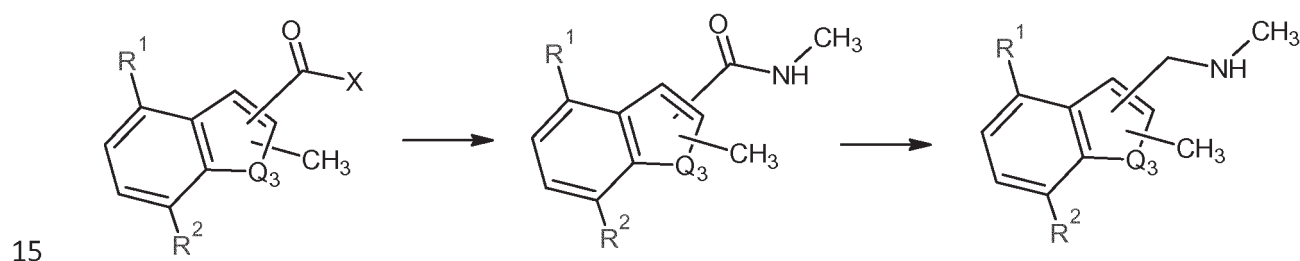
XXV

with methylamine. In formula XXV the variable group X represents a leaving group that can be, for instance, an alkoxy group, -OHet such as 1-hydroxybenzotriazole, carbamimidate, while R¹, R² and Q₃ have the same meanings as indicated for compound I above.

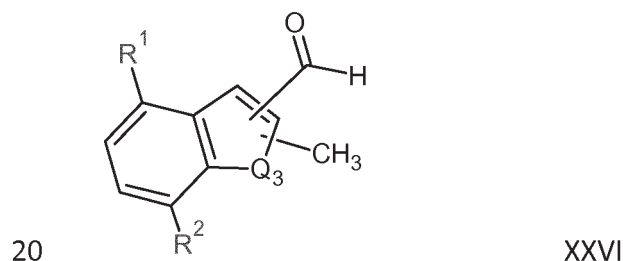
5 [00154] In a subsequent step, the amide group of compound XXIV is reduced to yield the amine XXIII. This can be done by means of a conventional reducing agent suitable for reducing carbonyl groups, such as BH₃. This reaction is typically performed in a solvent such as THF.

10 [00155] The sequence of reaction steps described above is illustrated by the following reaction scheme 5.

Scheme 5:



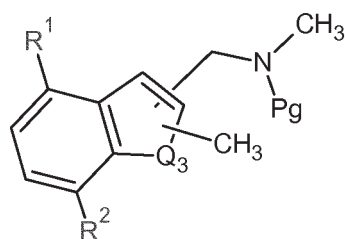
[00156] Alternatively, the amine compound XXIII can be prepared starting from the corresponding formyl derivative XXVI



wherein R¹, R² and Q₃ have the same meanings as indicated for compound I above or wherein R¹ and/or R² may represent a functional group that can be converted to the desired substituent at a later stage of the reaction sequence, as described above.

[00157] Formyl compound XXVI is reacted with protected N-methyl amine in the presence of a borohydride compound such as $\text{Na}(\text{OAc})_3\text{BH}$ in the presence of a solvent such as ethanol or 1,2-dichloroethane. Suitable protective groups are benzyl or p-methoxybenzyl. Intermediate compound XXVII is obtained.

5



XXVII

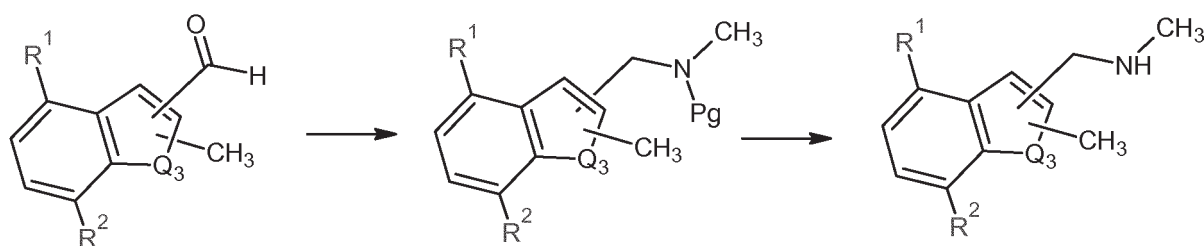
[00158] In formula XXVII Pg represents a protective group and R^1 , R^2 and Q_3 have the same meanings as indicated for compound I above or R^1 and/or R^2 may represent a functional group that can be converted to the desired substituent at a later stage of the reaction sequence, as described above.

10

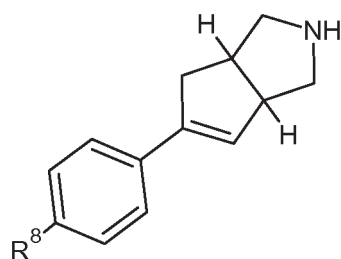
[00159] After the reaction, the protective group is removed, typically by hydrogenolysis, to yield amine compound XXIII. The reaction sequence is illustrated by the following Scheme 6.

15

Scheme 6:



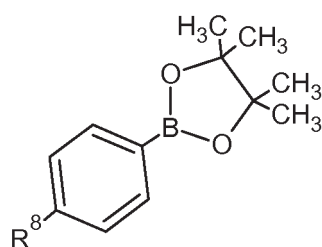
20 [00160] If variable groups A1 and A2 together form group A3, the precursor compound XXIII has the following structure XXIIIa:



XXIIIa

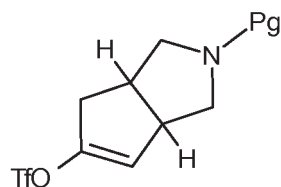
wherein R^8 has the same meaning as specified for compound I above.

- 5 **[00161]** Compound XXIIIa can be prepared by coupling precursor compound XXIV



XXIV

wherein R^8 has the same meaning as specified for compound I above,
with precursor compound XXV



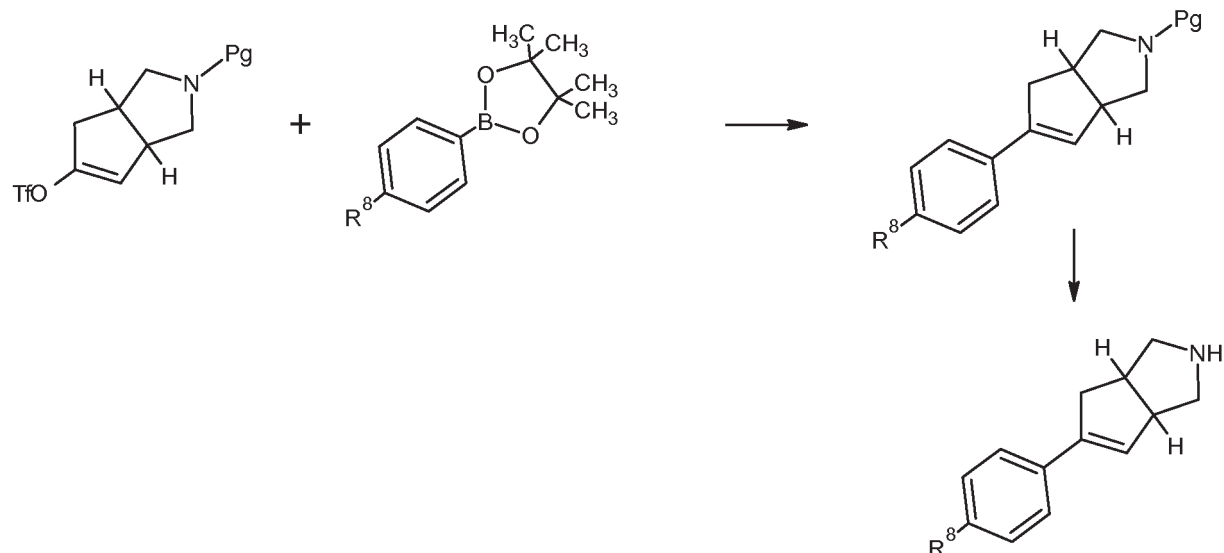
XXV

10

15

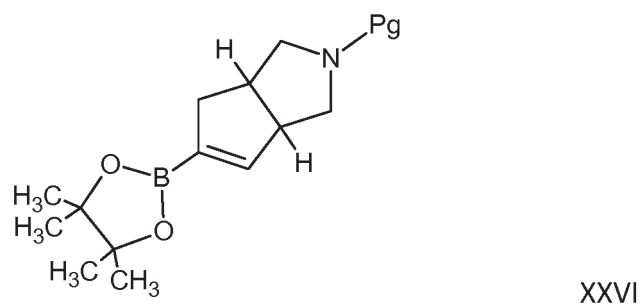
followed by deprotection, according to the following reaction scheme 7. The coupling reaction is typically carried out in the presence of a carbonate salt such as Na_2CO_3 or K_2CO_3 and a Pd-complex that is suitably selected from $\text{Pd}(\text{PPh}_3)_4$ and $\text{PdCl}_2(\text{dppf})$. A suitable reaction solvent is a mixture of water and 1,4-dioxane. The preferred protective group is a BOC group.

Scheme 7:



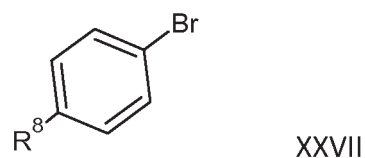
wherein Pg represents a protective group such as Boc, and R⁸ has the same meaning as specified for compound I above.

- 5 **[00162]** Alternatively, target compound XXIIIa can be obtained by coupling precursor compound XXVI



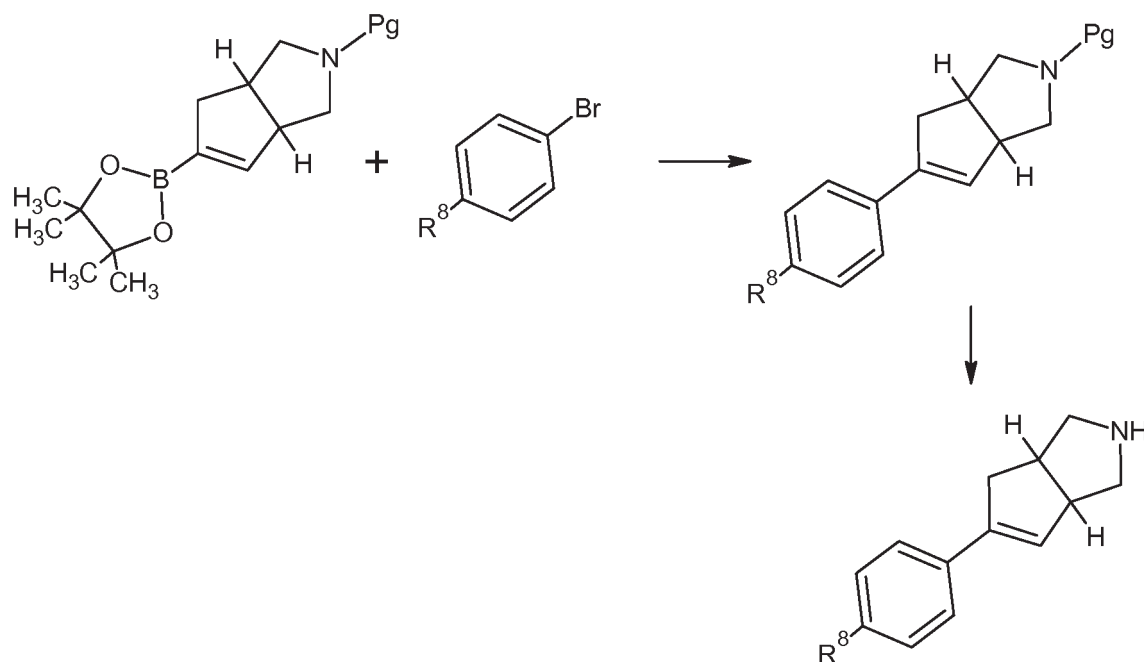
with precursor compound XXVII

10



- 15 followed by deprotection, according to the following reaction scheme 8. The coupling reaction is typically carried out in the presence of a carbonate salt such as K₂CO₃ and a Pd-complex such as PdCl₂(dppf). A suitable reaction solvent is 1,4-dioxane or a mixture of water and 1,4-dioxane. The preferred protecting group is a BOC group.

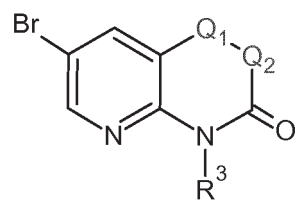
Scheme 8:



[00163] In the above reaction scheme, Pg represents a protective group and R₈ is as
 5 specified for compound I above.

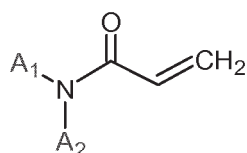
Final Step Heck Coupling

[00164] According to an alternative synthetic strategy, the compounds disclosed
 10 herein may be manufactured by means of the following method, which comprises the step
 of coupling a precursor compound of formula XVIII



XVIII

15 wherein Q₁ and Q₂ have the same meanings as specified for compound I hereinabove and
 wherein R³ represents a hydrogen atom, with a precursor compound of formula XIX



XIX

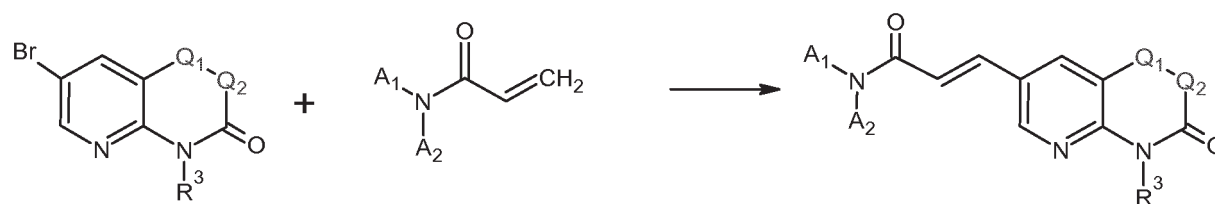
wherein A₁ and A₂ have the same meanings as specified hereinabove.

[00165] This coupling reaction is carried out under conditions of the Heck coupling.

- 5 Typically, it is carried out in the presence of a Pd(II) complex such as Pd-162 (i.e. [P(tBu)₃] Pd(crotyl) Cl), tetrabutylammonium chloride, N-cyclohexyl-N-methylcyclohexanamine and dioxane. It is also possible to use a combination of a Pd(II)-salt such as Pd(OAc)₂ with a phosphine ligand such as tri-o-tolylphosphan, a base like DIPEA and a solvent such as a mixture of DMF and ACN. The reaction is illustrated by the following reaction scheme 9.

10

Scheme 9:



[00166] In the above reaction scheme, Q₁, Q₂, A₁ and A₂ have the same meanings as specified for compound I above and R³ represents hydrogen.

15

[00167] The preparation of prodrugs of the compounds of the invention is typically accomplished by converting the respective compound of the invention with R³ being hydrogen to a compound of the same structure except that R³ represents a prodrug moiety that is cleavable under physiologic conditions for instance a phosphate-containing group as specified above. The prodrug moiety is preferably a methylene phosphate moiety. Such prodrug moieties and suitable reaction conditions for manufacturing methylene phosphate prodrugs are described in WO 2013/190384 A1.

20

[00168] Alternatively, the prodrug moiety may also be bonded to other parts of the molecule. In particular, it is contemplated to bind the prodrug moiety to the right-hand side of the molecule via variable groups R⁵ or R⁷, in which case these variable groups represent a group C₁₋₄-alkylene-OR³. The method of preparing such prodrugs is analogous to the method

25

described in WO 2013/190384 A1, but wherein the nitrogen atom carrying R³ must of course be suitably protected.

Pharmaceutical Compositions

5 **[00169]** Administration forms, pharmaceutical compositions and formulations

10 **[00170]** Pharmaceutical compositions of the disclosure may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the disclosure are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations disclosed herein may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, the compositions disclosed herein may be formulated as eye drops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, 15 a suspension aid, an emulsifying agent or a coating agent. The disclosed excipients may serve more than one function. For example, fillers or binders may also be disintegrants, glidants, anti-adherents, lubricants, sweeteners and the like.

20 **[00171]** In formulations of the disclosure, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

25 **[00172]** Subject compositions may be suitable for oral, nasal (e.g., by inhalation using a dry powder formulation or a nebulized formulation), topical (including buccal and sublingual), pulmonary (including aerosol administration), rectal, vaginal, aerosol and/or parenteral (e.g., by injection, for example, intravenous, intramuscular, or subcutaneous injection) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of a compound disclosed herein that may be combined with a carrier material to produce a single dose may vary depending upon the identity of the compound, the subject being 30 treated, and the particular mode of administration.

[00173] Methods of preparing these formulations include the step of bringing into association compositions of the disclosure with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00174] Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the disclosure may also be administered as a bolus, electuary, or paste.

[00175] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable excipients selected from: (1) fillers or extenders, such as starches, dextrose, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, celluloses (e.g., microcrystalline cellulose, methyl cellulose, hydroxypropylmethyl cellulose (HPMC) and carboxymethylcellulose), alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as croscarmellose sodium, sodium carboxymethyl starch (sodium starch glycolate), crosslinked polyvinylpyrrolidone (crospovidone), gellan gum, xanthan gum, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid and sodium alginate, certain silicates and especially calcium silicate, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) coloring agents; (11) complexing agents such as cyclodextrins and modified cyclodextrins including preferably (2-hydroxypropyl)- β -cyclodextrin and sulfobutylether- β -cyclodextrin; (12) matrix-forming polymeric excipients such as polyvinyl pyrrolidone (PVP), e.g. PVP K30, acrylic polymers and co-polymers such as the different

grades of Eudragit and preferably Eudragit L100, hydroxypropylmethyl cellulose acetate succinate (HPMCAS), other copolymers such as polyethylene glycol-based copolymers like Soluplus; and (13) carriers, such as sodium citrate or dicalcium phosphate. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like. The disclosed excipients may serve more than one function. For example, fillers or binders may also be disintegrants, glidants, anti-adherents, lubricants, sweeteners and the like. It is possible in accordance with the present invention to use two or more excipients, wherein said two or more excipients may belong to the same and/or different categories. There is no restriction in this respect.

Preferred Oral Formulations

Binders

[00176] A binder is advantageously used for increasing the particle size of active ingredient alone or with excipients and improve its handling properties. There is no particular limitation on the binder material that can be employed in the present invention..

[00177] Suitable binder materials include povidone (polyvinylpyrrolidone), copovidone (Poly(1-vinylpyrrolidone-co-vinyl acetate)), maltodextrin, poloxamer (a block copolymer with a first poly(ethylene oxide) block, a second and central poly(propylene oxide) block and a third poly(ethylene oxide) block), polyethylene glycol, polyethylene oxide, magnesium aluminosilicate, gelatin, acacia, alginic acid, carbomer (e.g. carbopol), dextrin, dextrans (a purified mixture of saccharides developed from the controlled enzymatic hydrolysis of starch), guar gum, hydrogenated vegetable oil, liquid glucose, wax, starch (pregelatinized and plain), sodium alginate and mixtures thereof.

[00178] The use of povidone and copovidone is preferred.

[00179] The binder may be present in a relative amount of from 0.5 wt% to 15 wt%, preferably from 1 wt% to 12 wt% and more preferably 4 wt% to 10 wt%.

Diluents

[00180] Diluents are advantageously used for increasing the bulk of the pharmaceutical composition and for facilitating handling of the composition. There is no particular limitation on the diluent material that can be employed in the present invention.

[00181] Suitable diluent materials include mannitol, isomalt, histidine, lactose (including anhydrous or monohydrate forms), calcium phosphate (including dibasic and tribasic calcium phosphate), calcium carbonate, calcium sulfate, sucrose, fructose, maltose, xylitol, sorbitol, maltitol, aluminium silicate, dextrose, starch (pregelatinized or plain),
5 glucose, dextrates (a purified mixture of saccharides developed from the controlled enzymatic hydrolysis of starch), magnesium carbonate, and mixtures thereof.

[00182] The use of mannitol, xylitol, sorbitol, isomalt and/or histidine is preferred. Mannitol is particularly preferred.

[00183] The diluent may be present in a relative amount that is not particularly
10 restricted. Suitable amounts may range from 2 wt% to 85 wt%, preferably from 8 wt% to 80 wt% and more preferably 10 wt% to 50 wt%.

Surfactant

[00184] A surfactant may advantageously be used for assisting wettability of the tablet and of the active ingredient. The surfactant is an optional but preferred component. There is
15 no particular limitation on the surfactant material that can be employed in the present invention

[00185] Suitable surfactant materials include sodium lauryl sulfate, poloxamer, sodium docusate, sorbitan esters, polyethylene oxide, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 (ethoxylated sorbitan esterified with fatty acids wherein the number
20 indicates the number of repeating units of polyethylene glycol), and mixtures thereof.

[00186] The use of sodium lauryl sulfate is preferred.

[00187] The surfactant may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0 wt% or more to 7 wt%, preferably from 0.1 wt% to 6.5 wt% and more preferably 1 wt% to 6 wt%.

Disintegrant

[00188] A disintegrant is used for accelerating disintegration of the pharmaceutical composition to thereby assist in dissolution and uptake of the active ingredient. There is no particular limitation on the disintegrant material that can be employed in the present
invention.

[00189] Suitable disintegrant materials include crosslinked polyvinylpyrrolidone (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), croscarmellose sodium, gellan gum, xanthan gum, magnesium aluminosilicate, sodium alginate,

pregelatinized starch, alginic acid, guar gum, homo- and copolymers of (meth)acrylic acid and salts thereof such as polacrillin potassium, and mixtures thereof.

[00190] The use of crospovidone is preferred

[00191] The disintegrant may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0 wt% or more to 20 wt%, preferably from 1 wt% to 15 wt% and more preferably 2 wt% to 10 wt%.

Glidant

[00192] A glidant is advantageously used for improving flowability of the pharmaceutical composition to thereby improve its handling properties. The glidant is an optional but preferred component. There is no particular limitation on the glidant material that can be employed in the present invention.

[00193] Suitable glidant materials include colloidal silica dioxide, magnesium oxide, magnesium silicate, tribasic calcium phosphate, and mixtures thereof.

[00194] The use of colloidal silica dioxide is preferred.

[00195] The glidant may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0 wt% or more to 5 wt%, preferably from 0.1 wt% to 4 wt% and more preferably 0.2 wt% to 1 wt%.

Lubricant

[00196] Lubricants are advantageously used to facilitate tableting, in particular by preventing sticking of the tablets to the tablet punch. The lubricant is an optional but preferred component. There is no particular limitation on the lubricant material that can be employed in the present invention.

[00197] Suitable lubricant materials include magnesium stearate, sodium stearyl fumarate, talc, stearic acid, leucine, poloxamer, polyethylene glycol, glyceryl behenate, glycerin monostearate, magnesium lauryl sulfate, sucrose esters of fatty acids, calcium stearate, aluminum stearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, sodium benzoate, zinc stearate, palmitic acid, carnauba wax, sodium lauryl sulfate, polyoxyethylene monostearates, calcium silicate, and mixtures thereof.

[00198] The use of a lubricant selected from magnesium stearate and sodium stearyl fumarate, and combinations thereof is preferred.

[00199] The lubricant may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0 wt% or more to 7 wt%, preferably from 0.1 wt% to 4 wt% and more preferably 0.5 wt% to 3.5 wt%.

Matrix forming polymers and copolymers

5 [00200] Suitable matrix-forming polymers and copolymers include polyvinyl pyrrolidine (PVP), acrylic polymers and co-polymers such as the different grades of Eudragit, hydroxypropylmethyl cellulose acetate succinate (HPMCAS), as well as other copolymers such as polyethylene glycol-based copolymers like Soluplus.

[00201] Preferred matrix-forming polymers and copolymers are HPMC AS and
10 Soluplus.

[00202] The matrix-forming polymers and copolymers may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0.1 g to 10 g, preferably from 0.2 g to 5 g and more preferably from 0.3 g to 4 g.

Complexing agents

15 [00203] Suitable complexing agents include cyclodextrins and modified cyclodextrins.

[00204] Preferred complexing agents include (2-hydroxypropyl)- β -cyclodextrin and sulfobutylether- β -cyclodextrin.

[00205] The complexing agents may be present in a relative amount that is not particularly restricted. Suitable amounts may range from 0.1 g to 24 g, preferably from 0.1 g
20 to 10 g and more preferably from 0.1 g to 5 g.

Other types of excipients

[00206] The composition of the present invention may contain further excipients that are commonly used in the art.

[00207] Such further excipients may include release rate modifiers, plasticizer, film
25 forming agent, colorant, anti-tacking agent and/or pigment for coating the compositions of the present invention. Further types of excipients, which may be present, include flavoring agents, sweeteners, antioxidants, absorption accelerators and/or bulking agents. Relative amounts of such excipients are not particularly limited. They may be determined by the skilled person based on common general knowledge and routine procedures.

30 [00208] Film forming agents are advantageously used for providing the tablets of the invention with a coherent coating. Suitable film forming agents include isomalt, polyvinyl alcohol, polyethylene glycol, maltodextrin, sucrose, xylitol, maltitol, enteric coating agents

such as materials selected from the group consisting of methyl acrylate-methacrylic acid copolymers, polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, shellac, sodium alginate and zein. It is preferred to use a combination of film forming agents comprising polyvinyl alcohol and one or more second agents selected from isomalt, maltodextrin, sucrose, xylitol, and maltitol. It is particularly preferred to use a combination of film forming agents comprising at least polyvinyl alcohol and isomalt.

[00209] Suitable plasticizers include sorbitol, triacetin, poloxamer, polyethylene glycol, glycerin, propylene glycol, polyethylene glycol monomethyl ether, acetyl tributyl citrate, acetyl triethyl citrate, castor oil, glyceryl monostearate, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, triethyl citrate, and tributyl citrate.

[00210] For each of the above-mentioned categories of excipients it is possible to use only a single substance or a combination of two or more substances belonging to the same category. Of course, it is not necessary that members of each and every category are present.

[00211] Formulations and compositions of the invention may include the compounds disclosed herein in the form of particles of amorphous substance or in any crystalline form. The particle size is not particularly limited. For instance, formulations and compositions may include micronized crystals of the disclosed compounds. Micronization may be performed on crystals of the compounds alone, or on a mixture of crystals and a part or whole of pharmaceutical excipients or carriers. Mean particle size of micronized crystals of a disclosed compound may be for example about 5 to about 200 microns, or about 10 to about 110 microns. The compounds of the invention may also be present in the form of a molecular dispersion within a polymeric matrix. In yet another embodiment, the compounds of the invention may be complexed with suitable complexing agents such as cyclodextrins.

[00212] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin, microcrystalline cellulose, or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric

coatings and other coatings well known in the pharmaceutical-formulating art. The disclosed excipients may serve more than one function. For example, fillers or binders may also be disintegrants, glidants, anti-adherents, lubricants, sweeteners and the like.

[00213] It will be appreciated that a disclosed composition may include lyophilized or freeze dried compounds disclosed herein. For example, disclosed herein are compositions that disclosed compounds crystalline and/or amorphous powder forms. Such forms may be reconstituted for use as e.g., an aqueous composition.

[00214] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00215] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00216] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[00217] Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, and patches. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

[00218] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

5 **[00219]** Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

10 **[00220]** Compositions and compounds of the disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in
15 the subject compositions.

[00221] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens,
20 pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00222] It should be noted that excipients given as examples may have more than one function. For example, fillers or binders can also be disintegrants, glidants, anti-adherents,
25 lubricants, sweeteners and the like.

[00223] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile
30 injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. For example, provided herein is an aqueous

composition that includes a disclosed compound, and may further include for example, dextrose (e.g., about 1 to about 10 weight percent dextrose, or about 5 weight percent dextrose in water (D5W)).

[00224] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00225] It will be appreciated that contemplated formulations, such as oral formulations (e.g. a pill or tablet), may be formulated as controlled release formulation, e.g., an immediate release formulation, a delayed release formulation, or a combination thereof.

[00226] In certain embodiments, the subject compounds may be formulated as a tablet, pill, capsule or other appropriate ingestible formulation (collectively hereinafter "tablet"). In certain embodiments, a therapeutic dose may be provided in 10 tablets or fewer. In another example, a therapeutic dose is provided in 50, 40, 30, 20, 15, 10, 5 or 3 tablets.

[00227] In a certain embodiment, a disclosed compound is formulated for oral administration as a tablet, capsule, or an aqueous solution or suspension. In another embodiment of a tablet form the tablets are formulated such that the resulting amount of antibacterial agent (or antibacterial agents) provided in 20 tablets, if taken together (e.g., over time) once administered, would provide a therapeutically effective dose and/or a dose of at least the median effective dose (ED50), e.g., the dose at which at least 50% of individuals exhibited the quantal effect of inhibition of bacterial cell growth or protection (e.g., a statistically significant reduction in infection). In a further embodiment, tablets may be formulated such that the total amount of antibacterial agent (or antibacterial agents) provided upon administration in 10, 5, 2 or 1 tablets would provide a therapeutically effective dose and/or at least an ED50 dose to a patient (human or non-human mammal). In other embodiments, the amount of antibacterial agent (or antibacterial agents) provided, upon administration, in 20, 10, 5 or 2 tablets taken in a 24 hour time period would provide a dosage regimen providing, on average, a mean plasma level of the antibacterial agent(s) of a

therapeutically effective dose and/or at least the ED50 concentration (the concentration for 50% of maximal effect of, e.g., inhibiting bacterial cell growth). In other embodiments less than 100 times, 10 times, or 5 times the ED50 is provided. In other embodiments, a single dose of tablets (1-20 tablets) provides about 40 mg to 3000 mg of compound(s). These
5 specified unit dose amounts apply also for other oral dosage forms.

[00228] Likewise, compounds disclosed herein can be formulated for parenteral administration, as for example, for subcutaneous, intramuscular or intravenous injection, e.g., the antibacterial agent can be provided in a sterile solution or suspension (collectively hereinafter "injectable solution"). The injectable solution may be, in some embodiments,
10 formulated such that the amount of antibacterial agent (or antibacterial agents) provided in, for example, in about 0.1 to about 200cc bolus injection, or a dose administered intravenously, would provide a dose of at least the median effective dose, or less than 100 times the ED50, or less than 10 or 5 times the ED50. The injectable solution may be formulated such that the total amount of antibacterial agent (or antibacterial agents)
15 provided (upon administration) in 100, 50, 25, 10, 5, 2.5, or 1 cc injections would provide a therapeutically effective amount and/or an ED50 dose to a patient, or less than 100 times the ED50, or less than 10 or 5 times the ED50. In other embodiments, the amount of antibacterial agent (or antibacterial agents) provided, upon administration, in a total volume of 100cc, 50, 25, 5 or 2cc to be injected at least twice in a 24 hour time period would provide
20 a dosage regimen providing, on average, a mean plasma level of the antibacterial agent(s) of a therapeutically effective amount and/or at least the ED50 concentration, or less than 100 times the ED50, or less than 10 or 5 times the ED50. In other embodiments, a single dose injection provides about 40 mg to 3000 mg, or about 100 mg to about 1000 mg of antibacterial agent. In case of i.m. administration, the same amount indications apply, in
25 principle, too. However, the upper end of the unit dose range may be lower depending on the solubility of the drug compound and the maximum tolerable amount for injection.

Unit Dosages

[00229] If treatment of the patient by the pharmaceutical compositions of the present invention is by means of oral administration, a single unit dose of the pharmaceutical
30 composition of the present invention is typically administered one, two or three times a day. The daily dosage is determined by the physician in accordance with the above guidance taking severity of the infection, gender, weight, age and general condition of the patient into

account. Preferred oral daily dosages range from 40 to 3000 mg, preferably 100 mg to 2000 mg. By consequence, typical unit dosages may range from 40 to 2000 mg, depending on the intended frequency of administration.

[00230] In case of parenteral administration (for instance in i.v. or i.m. administration),

5 the pharmaceutical compositions of the present invention are typically administered two, three or more times a day. Preferred daily dosages are in the range of from 40 to 3000 mg, so that typical unit dosages are from 40 to 3000 mg and preferably 100 to 1000 mg. The upper limits of the specified ranges are subject to their feasibility. For instance, in case of i.m. administration, it may happen that the maximum dose that can be administered in a
10 single shot is restricted due to low solubility and correspondingly increased volume of the drug solution. In such a case, the maximum unit dosages are limited by the maximum tolerated dose.

Drug combinations

[00231] Compositions are also contemplated herein that include one or more of the
15 disclosed compounds with a second component. Second components in such compositions of the present disclosure are usually an antibiotic agent other than a disclosed compound. Additional components may also be present, including FabI inhibitors or other antibiotic agents. The contemplated methods of treatment disclosed herein, in some embodiments, may further comprise administering another agent such as one described below. For
20 example, a method of treating a bacterial infection is provided that comprises administering a disclosed compound and further comprises administering an antibiotic agent or antibacterial agent described below. The compound disclosed herein and the second component may be part of the same dosage form or may be formulated in two separate dosage forms. If they are formulated in two separate dosage forms, the dosage form with
25 the second component may be administered at the same time, before or after the dosage form with the compound disclosed herein.

[00232] Non-limiting examples of antibiotic agents that may be used in the antibacterial compositions of the disclosure include cephalosporins, quinolones and fluoroquinolones, penicillins, penicillins and beta lactamase inhibitors, carbapenems,
30 monobactams, macrolides and lincosamines, glycopeptides, rifampin, oxazolidinones, tetracyclines, aminoglycosides, streptogramins, sulfonamides, and others. Each family comprises many members.

[00233] Cephalosporins can be further categorized by generation. Non-limiting examples of cephalosporins by generation include the following. Examples of cephalosporins: First generation compounds include Cefadroxil, Cefazolin, Cephalexin, Cephalothin, Cephapirin, and Cephadrine. Second generation compounds include Cefaclor, Cefamandol, Cefonicid, Cefotetan, Cefoxitin, Cefprozil, Ceftmetazole, Cefuroxime, Cefuroxime axetil, and Loracarbef. Third generation include Cefdinir, Ceftibuten, Cefditoren, Cefetamet, Cefpodoxime, Cefprozil, Cefuroxime (axetil), Cefuroxime (sodium), Cefoperazone, Cefixime, Cefotaxime, Cefpodoxime proxetil, Ceftazidime, Ceftizoxime, and Ceftriaxone. Fourth generation compounds include Cefepime.

[00234] Non-limiting examples of quinolones and fluoroquinolones include Cinoxacin, Ciprofloxacin, Enoxacin, Gatifloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, Oxolinic acid, Gemifloxacin, and Perfloxacin.

[00235] Non-limiting examples of penicillins include Amoxicillin, Ampicillin, Bacampicillin, Carbenicillin Indanyl, Mezlocillin, Piperacillin, and Ticarcillin.

[00236] Non-limiting examples of penicillins and beta lactamase inhibitors include Amoxicillin-Clavulanic Acid, Ampicillin-Sulbactam, Benzylpenicillin, Cloxacillin, Dicloxacillin, Methicillin, Oxacillin, Penicillin G (Benzathine, Potassium, Procaine), Penicillin V, Piperacillin+Tazobactam, Ticarcillin+Clavulanic Acid, and Nafcillin. Non-limiting examples of carbapenems include Imipenem-Cilastatin and Meropenem.

[00237] A non-limiting example of a monobactam includes Aztreonam. Non-limiting examples of macrolides and lincosamines include Azithromycin, Clarithromycin, Clindamycin, Dirithromycin, Erythromycin, Lincomycin, and Troleandomycin. Non-limiting examples of glycopeptides include Teicoplanin and Vancomycin. Non-limiting examples of rifampins include Rifabutin, Rifampin, and Rifapentine. A non-limiting example of oxazolidinones includes Linezolid. Non-limiting examples of tetracyclines include Demeclocycline, Doxycycline, Methacycline, Minocycline, Oxytetracycline, Tetracycline, and Chlortetracycline.

[00238] Non-limiting examples of aminoglycosides include Amikacin, Arbakacin, Gentamicin, Kanamycin, Sisomicin, Arbekacin, Neomycin, Netilmicin, Streptomycin, Tobramycin, and Paromomycin. A non-limiting example of streptogramins includes Quinopristin+Dalbapristin.

[00239] Non-limiting examples of sulfonamides include Mafenide, Silver Sulfadiazine, Sulfacetamide, Sulfadiazine, Sulfamethoxazole, Sulfasalazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole, and Sulfamethizole.

[00240] Non-limiting examples of other antibiotic agents include Bacitracin,
 5 Chloramphenicol, Colistimethate, Fosfomycin, Isoniazid, Methenamine, Metronidazole, Mupirocin, Nitrofurantoin, Nitrofurazone, Novobiocin, Polymyxin B, Spectinomycin, Tobramycin, Tigecycline, Trimethoprim, Colistin, Cycloserine, Capreomycin, Pyrazinamide, para-Aminosalicylic acid, and Erythromycin ethylsuccinate + sulfisoxazole.

10 Therapeutic Uses

Medical indications

[00241] The compounds of the present invention may be used for treating bacterial infections in a patient. They are in particular suitable for use in treating infections by *N. gonorrhoeae*. Other therapeutic indications for which the compounds of the present
 15 invention may be used are as follows:

Bacillus Spp, in particular *Bacillus cereus*, *Bacillus coagulans*, *Bacillus megaterium*,
Bacillus subtilis, *Bacillus anthracis*
Bartonella Spp.

Brucella Spp, in particular *Brucella abortus*, *Brucella melitensis*.

20 *Campylobacter Spp.*, in particular *Campylobacter jejuni*, *Campylobacter coli*
Enterococcus faecalis, *Enterococcus faecium*, *Legionella pneumophila*.

Listeria Spp. In particular *Listeria monocytogenes*.

Proteus mirabilis, *Providencia stuartii*.

Rickettsia Spp., in particular *Rickettsia rickettsii*.

25 *Burkholderia Spp.*, in particular *Burkholderia pseudomallei*, *Burkholderia mallei*,
Burkholderia cenocepacia.

Bordetella pertussis, *Bordetella parapertussis*. *Haemophilus influenza*, *Kingella kingae*, *Moraxella catarrhalis*.

Streptomyces Spp.

30 *Nocardioide Spp*.

Frankia Spp.

Propionibacterium acnes.

Mycobacterium Spp., in particular Mycobacterium smegmatis, Mycobacterium abscessus, Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium avium.

5 Patients

[00242] The compounds of the present invention may be used for treating bacterial infections in patients that are human patients or non-human animals, preferably humans and non-human mammals.

Daily dosages

10 [00243] The dosage of any disclosed compound or composition will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the compositions may be readily determined by techniques
15 known to those of skill in the art or as taught herein.

[00244] In certain embodiments, the dosage of the subject compounds will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg.

20 [00245] An effective dose or amount, and any possible effects on the timing of administration of the formulation, may need to be identified for any particular composition of the disclosure. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any subject composition and method of treatment
25 or prevention may be assessed by administering the composition and assessing the effect of the administration by measuring one or more applicable indices, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

[00246] The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon
30 the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of

administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

5 **[00247]** While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same
10 parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

[00248] Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

15 **[00249]** The use of the subject compositions may reduce the required dosage for any individual agent contained in the compositions because the onset and duration of effect of the different agents may be complimentary.

[00250] Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for
20 determining the LD50 and the ED50.

[00251] The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any subject composition lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity and/or that give rise to a statistically significant reduction in
25 infection in at least 50% e.g. 60%, 70%, 80%, 90%, 100%, of individuals with little or no toxicity, wherein little toxicity may for instance mean non serious and/or predictable and transient toxicity. For instance, the dosage of the subject composition may be chosen such that a reasonable benefit/risk ratio is accomplished by the treatment. The dosage may vary within this range depending upon the dosage form employed and the route of
30 administration utilized. For compositions of the disclosure, the therapeutically effective dose may be estimated initially from cell culture assays.

Administration frequency

[00252] The compounds and compositions disclosed herein may be administered once or multiple times a day, in particular once daily (qd), twice daily (bid), three times a day (tid) or four times a day (qid).

5

Duration of treatment

[00253] The compounds and compositions disclosed herein may be administered for an unlimited period of time. It is advantageous that they are administered for a period of time to eradicate the bacterial infection completely or at least to such an extent that the patient's immune system can cope with any remaining pathologic bacteria. Typical durations of administration are from 1 day to 2 weeks and especially from 1 to 5 days. In case of i.m. administration, typical durations of administration may range from 1 shot to 4 shots and preferably 1 shot. Multiple shots may be administered on the same day, on consecutive days or on in intervals with days of no administration in between.

15

Methods of treatment

[00254] In another aspect, disclosed herein are methods of treating a bacterial infection, comprising administering to a patient in need thereof the pharmaceutical composition comprising a disclosed compound.

20 [00255] In certain embodiments, disclosed herein are methods of treating a N. gonorrhoeae infection in a patient in need thereof, comprising administering a compound of the invention as disclosed herein. Other contemplated methods include treating infections by one or more of the bacteria or microbes listed above in a patient in need thereof.

[00256] For example, disclosed here is a method of treating an N. gonorrhoeae or
25 other bacterial infection in a patient in need thereof comprising administering a composition comprising a disclosed compound, which method further comprises administering, in the same or a separate dosage form, an additional antibacterial or antibiotic agent as disclosed herein.

Abbreviations

30 [00257] The following abbreviations are used in the present disclosure.

CC Column chromatography

DCM	Dichloromethane
N	Normal
g	Gram
pH	Potential of Hydrogen
mol	Mole
v/v	Volume/volume
vol	Volume
m/z	Mass to charge ratio
°C	degree Celsius
TEA	Triethylamine
Et ₂ O	Diethyl ether
HPLC	High performance liquid chromatography
Boc	<i>tert</i> -butoxycarbonyl
h	hour
mL	milliliter
eq.	Equivalent
M	Mass
Me	Methyl, CH ₃
MeOH	Methanol
AcOH	Acetic acid
THF	Tetrahydrofuran
DIPEA	<i>N,N</i> -Diisopropylethylamine
Pd(OAc) ₂	Palladium(II) acetate
EtOH	Ethanol
DCE	1,2-Dichloroethane
EtOAc	Ethyl acetate
Et ₃ N	Triethylamine
Aq.	Aqueous
RT, rt	Room temperature
R ^t , t _{ret}	Retention time
DMF	Dimethylformamide
ACN	Acetonitrile
NH ₄ OAc	Ammonium acetate
TFA	Trifluoroacetic acid
HOBT/HOBt	1-Hydroxybenzotriazole
TLC	Thin layer chromatography
H ₂ O	Water
sat.	Saturated
sol.	Solution

EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
NMR	Nuclear Magnetic Resonance
s	<i>singlet</i>
d	<i>doublet</i>
t	<i>triplet</i>
m	<i>multiplet</i>
dd	<i>double of doublet</i>
MHz	Megahertz
ppm	parts per million
H	Proton
J	Coupling constant
UPLC-MS	Ultra-performance liquid chromatography-tandem mass spectrometry
DMSO	Dimethyl sulfoxide
CDCl ₃	Deuterated chloroform
ML	Mother liquor
SCX	Strong Cation Exchange Chromatography
LCMS	Liquid Chromatography Mass Spectrometry
HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
HPLC	High-performance liquid chromatography
HBTU	(2-(1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, Hexafluorophosphate Benzotriazole Tetramethyl Uronium
HCTU	2-(6-Chlor-1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethylaminium-hexafluorophosphate
TBTU	O-(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
COMU	(1-Cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium-hexafluorophosphate
TOMBU	<i>N</i> -{[1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidine-5(6 <i>H</i>)-ylideneaminoxy](dimethylamino)methylene}- <i>N</i> -methylmethaneaminium hexafluorophosphate
COMBU	4-{[1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidine-5(6 <i>H</i>)-ylideneaminoxy](dimethylamino)methylene}morpholin-4-ium hexafluorophosphate
Cy ₂ NCH ₃	<i>N</i> -Cyclohexyl- <i>N</i> -methylcyclohexanamine
PMB	<i>p</i> -Methoxybenzyl
STAB	Sodium triacetoxymethylborohydride

IM or i.m. Intramuscular administration
IV or i.v. Intravenous administration

[00258] The following examples are in no way intended to limit the scope of the present invention, but are provided only to illustrate the inventive compounds and their preparation.

5 Examples

General Procedures

[00259] All starting materials and solvents were obtained either from commercial sources or prepared according to the literature citation. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate or
10 sodium sulfate

[00260] Column chromatography was performed on pre-packed silica (230-400 mesh, 40-63 μ m) cartridges using the eluent indicated. SCX was purchased from Silicycle and treated with 1M hydrochloric acid prior to use. Unless stated otherwise the reaction mixture to be purified was first diluted with MeOH and made acidic with a few drops of AcOH. This
15 solution was loaded directly onto the SCX and washed with MeOH. The desired material was then eluted by washing with 0.7 M NH₃ in MeOH.

Analytical Methods

Analytical LCMS

20 [00261] Analytical LCMS was carried out using either acidic or basic methods as follows:

Method 1a:

[00262] Waters X-Select CSH C18, 2.5 μ m, 4.6x30 mm column eluting with a gradient
25 of 0.1% Formic acid in MeCN in 0.1% Formic acid in water. The gradient from 5-95% 0.1% Formic acid in MeCN occurs between 0.00-3.00 minutes at 2.5mL/min with a flush from 3.01-3.5 minutes at 4.5mL/min. A column re-equilibration to 5% MeCN is from 3.60-4.00 minutes at 2.5mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity or Agilent 1200 VWD at 254nm. Mass spectra were measured using an Agilent 6120

or Agilent 1956 MSD running with positive/negative switching or an Agilent 6100 MSD running in either positive or negative mode.

Method 1b:

- 5 **[00263]** Waters X-Select BEH C18, 2.5 μ m, 4.6x30 mm column eluting with a gradient of MeCN in aqueous 10mM ammonium bicarbonate. The gradient from 5-95% MeCN occurs between 0.00-3.00 minutes at 2.5mL/min with a flush from 3.01-3.5 minutes at 4.5mL/min. A column re-equilibration to 5% MeCN is from 3.60-4.00 minutes at 2.5mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity or Agilent 1200 VWD at
- 10 254nm. Mass spectra were measured using an Agilent 6120 or Agilent 1956 MSD running with positive/negative switching or an Agilent 6100 MSD running in either positive or negative mode.

Method 1c:

- 15 **[00264]** The product was analysed by UPLC (Acquity and SQD Waters system, Water (HPLC grade) UPLC® BEH C18, 50 x 2.1 mm, 1.7 μ m, (0.1% HCOOH in water, 0.1% HCOOH in acetonitrile) 3 min method, 5-95% MeCN/water).
- [00265]** All UPLC-MS analyses were performed on a UPLC Acquity and SQD Waters system. Masslynx software was used to launch and analyse experiments using OALogin and
- 20 automatic or manual integrations. Details of the method used are listed below.

Chemicals:

Water (HPLC grade)

Acetonitrile ACN (HPLC grade)

Formic acid 98% (for LC-MS)

Mobile phase description:

<i>Solution A1:</i>	0.06% HCOOH in water
<i>Solution B1:</i>	0.06% HCOOH in acetonitrile
<i>Solution A2:</i>	Water
<i>Solution B2:</i>	Acetonitrile
<i>Weak Wash</i>	Water-ACN (7:3)
<i>Strong Wash</i>	Water-ACN (1:9)
<i>Seal Wash</i>	Water-ACN (1:1)

UPLC parameters:

<i>Column:</i>		UPLC® BEH C18, 50 x 2.1 mm, 1.7 µm		
<i>Mobile phase:</i>		A1: 0.06% HCOOH in water B1: 0.06% HCOOH in acetonitrile		
<i>Gradient:</i>	Time [min]	FlowRate [mL/min]	A1 [%]	B1 [%]
	0.00	0.9	95	5
	0.10	0.9	95	5
	3.00	0.9	0	100
	3.10	0.9	95	5
<i>Column Temperature:</i>		40°C		
<i>UV Detection:</i>		210-400nm		
<i>Injection volume:</i>		1 to 10 µL (on demand)		

[00266] MASS SPECTROSCOPY Method : Performed based on MS Tune parameters:

5 Routine.ipr as shown below.

AS+ Source	
Voltages	
Capillary (kV)	3.50
Cone (V)	30
Extractor (V)	3
RF Lens (V)	0.1
Temperatures	
Source Temp (°C)	150
Dessolvation Temp (°C)	350

AS+ Source	
Analyser	
LM resolution	15.0
HM resolution	15.0
Ion energy	0.6
Gain	1.00

[00267] The method is carried out based on the information “MS Method:

pos_neg_3mn_30v”. Points per peak: 3.846. Total run time: 3.0 min. MS scan, Time 0.00 to
 10 3.00, Mass 100.00 to 900.00 ES⁺.

[00268] UPLC-MS mass spectra were recorded on a SQ detector Acquity Waters
 (Waters Corporation, Waters Milford, 34 Maple St., Milford, USA) equipped with software

Empower 2 pro in a positive ionization mode. Ionization conditions: Capillary 2.25 KV, Cone 160 V, Source 100 °C, Desolvation 150 °C; Gas flow → Desolvation 500 L/h, Cone 50 L/h.

Analytical UPLC/MS

[00269] Alternatively analytical UPLC/MS was carried out using either acidic or basic methods as follows:

[00270] **Method 2a:** Waters Acquity CSH C18, 1.7 µm, 2.1x30 mm column eluting with a gradient of 0.1% Formic acid in MeCN in 0.1% Formic acid in water. The gradient is structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurs between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN is from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa detector with ESI pos/neg switching.

[00271] **Method 2b:** Waters Acquity BEH C18, 1.7 µm, 2.1x30 mm column eluting with a gradient of MeCN in aqueous 10 mM Ammonium Bicarbonate. The gradient is structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurs between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN is from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa detector with ESI pos/neg switching.

Preparative HPLC

[00272] Preparative HPLC was carried out using a Waters Xselect CSH C18, 5 µm, 19x50 mm column using either a gradient of either 0.1% Formic Acid in MeCN in 0.1% aqueous Formic Acid or a gradient of MeCN in aqueous 10 mM Ammonium Bicarbonate; or a Waters Xbridge BEH C18, 5 µm, 19x50 mm column using a gradient MeCN in aqueous 10 mM Ammonium Bicarbonate. Fractions were collected following detection by UV at a single wavelength measured by a variable wavelength detector on a Gilson 215 preparative HPLC or Varian PrepStar preparative HPLC; by mass and UV at a single wavelength measured by a ZQ single quadrupole mass spectrometer, with positive and negative ion electrospray, and a dual wavelength detector on a Waters FractionLynx LCMS.

Preparative Chiral High Performance Liquid Chromatography

[00273] **Method 3a:** Chiralpak® IA (Daicel Ltd.) column (2x 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of (% of ethanol) ethanol in a 4:1 mixture of heptane + 0.2%TFA and chloroform, UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping chloroform (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹.

[00274] **Method 3b:** Chiralpak® IC (Daicel Ltd.) column (2x 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of (% of ethanol) ethanol in heptane + 0.2% diethylamine , UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping chloroform (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹.

Analytical Chiral High Performance Liquid Chromatography

[00275] **Method 4a:** Chiralpak® IA (Daicel Ltd.) column (4.6 mm x 25 mm), flow rate 1 mL min⁻¹ eluting with a mixture of (% of ethanol) ethanol in a 4:1 mixture of isohexane + 0.2%TFA and chloroform, UV detection at 254 nm.

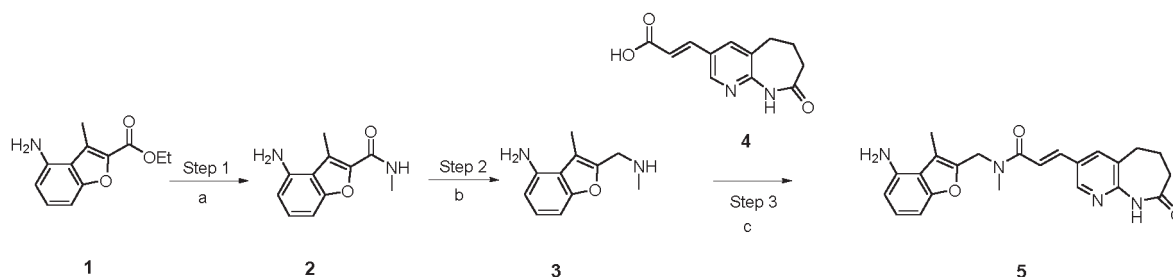
[00276] **Method 4b:** Chiralpak® IC (Daicel Ltd.) column (4.6 mm x 25 mm), flow rate 1 mL min⁻¹ eluting with a mixture of (% of ethanol) ethanol in isohexane + 0.2% diethylamine, UV detection at 254 nm.

¹H NMR Spectroscopy

[00277] ¹H NMR Spectra were acquired on a Bruker Avance III spectrometer at 400 MHz using residual undeuterated solvent as reference.

Example 1. Synthesis of (E)-N-((4-amino-3-methylbenzofuran-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound 5).

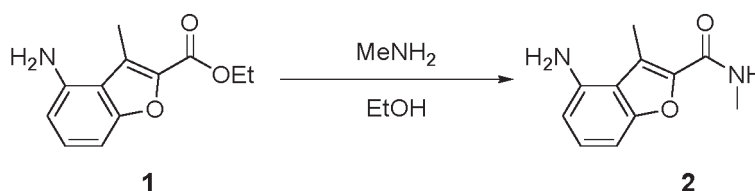
[00278] General Synthetic Scheme.



Reaction conditions: a) MeNH₂, EtOH; b) BH₃ THF, reflux; c) HATU, DIPEA, DMF

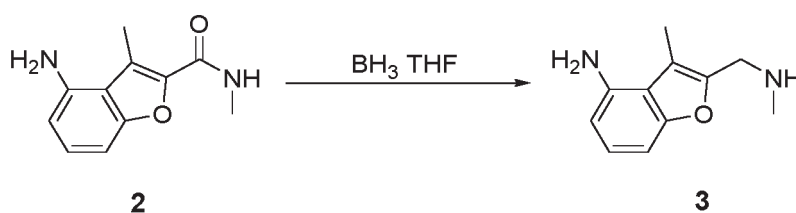
[00279] The synthesis of (E)-3-(8-oxo-6,7,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid (compound **4**) was previously reported by AFFINIUM PHARMECEUTICALS, INC:

5 WO2007/67416, 2007, A2.



[00280] **Step 1.** 4-Amino-N,3-dimethylbenzofuran-2-carboxamide (compound **2**). Ethyl

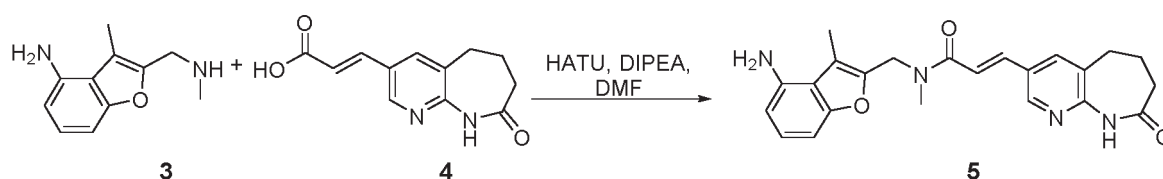
10 4-amino-3-methylbenzofuran-2-carboxylate **1** (0.1 g, 0.46 mmol) was dissolved in methanamine (10 mL, 80 mmol, 33% in EtOH) and the reaction was stirred at RT for ~ 36 h. The solvent was removed *in vacuo* to give the desired product **2** as a pale brown crystalline solid (0.097 g, quantitative). R^t 1.25 min (Method 1a); m/z 205 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 8.24 (q, J = 4.6 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.68 (dd, J = 8.2, 0.8 Hz, 1H), 6.43 (dd, J = 7.9, 0.8 Hz, 1H), 5.41 (s, 2H), 2.74 (d, J = 4.7 Hz, 3H), 2.72 (s, 3H).



[00281] **Step 2.** 3-Methyl-2-((methylamino)methyl)benzofuran-4-amine (compound **3**).

20 To a suspension of compound **2** (300 mg, 1.47 mmol) in dry THF (30 mL) at 0 °C was added borane tetrahydrofuran complex (7.34 mL, 7.34 mmol, 1 M in THF). After warming to RT the reaction mixture was heated under reflux for 3 h. The mixture was quenched with methanol (20 mL) whilst still at reflux, then 1 N hydrochloric acid (2 mL) was added and the mixture

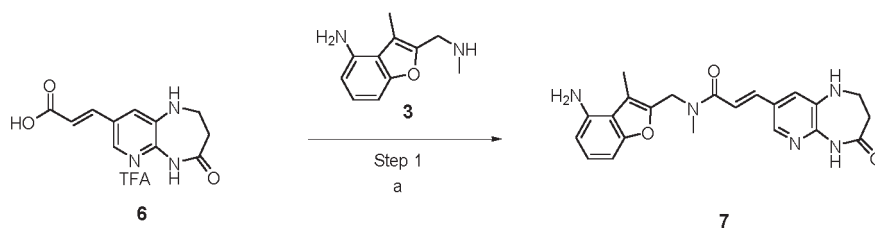
continued to heat at reflux for 30 mins. The mixture was cooled to RT then evaporated to dryness. The residue was taken up into methanol (50 mL) and applied to an SCX column. The column was washed with methanol (50 mL) and the product eluted with 10% methanolic ammonia. The solvent was removed *in vacuo* to afford the desired product **3** as a yellow oil (0.20 g, 68%). R^t 0.17 min (Method 1a); m/z 160 $[M - NHCH_3]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 6.88 (t, J = 7.9 Hz, 1H), 6.63 (dd, J = 8.1 Hz, 0.8 Hz, 1H), 6.36 (dd, J = 7.8 Hz, 0.8 Hz, 1H), 5.10 (s, 2H), 3.66 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H).



[00282] Step 3. (E)-N-((4-Amino-3-methylbenzofuran-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **5**). A solution of 3-methyl-2-((methylamino)methyl)benzofuran-4-amine **3** (0.07 g, 0.35 mmol), (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid **4** (0.07 g, 0.29 mmol) and DIPEA (0.26 mL, 1.47 mmol) in DMF (2 mL) was stirred for 10 mins. Then HATU (0.17 g, 0.44 mmol) was added in one portion and the reaction mixture stirred for 2 h. Water (20 mL) was added to the mixture and the resulting precipitate collected by filtration. The solid was washed with water (10 mL) and dried on the filter paper before being dissolved in the minimum amount of DMSO possible and precipitated by addition of water. The solid was collected then the crude material was further purified by chromatography (0-10% MeOH in DCM) to give the compound **5** as a tan solid (0.04 g, 29%). R^t 1.54 min (Method 1a); m/z 405 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6 , 363 K): δ , ppm 9.56 (s, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 15.4 Hz, 1H), 7.27 (d, J = 15.6 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 6.66 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 6.41 (dd, J = 7.8 Hz, 0.8 Hz, 1H), 4.93 (s, 2H), 4.77 (s, 2H), 3.07 (s, 3H), 2.77 (t, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.32 (t, J = 7.2 Hz, 2H), 2.15 (p, J = 7.7, 7.3 Hz, 2H).

Example 2. Synthesis of (E)-N-((4-amino-3-methylbenzofuran-2-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **7**).

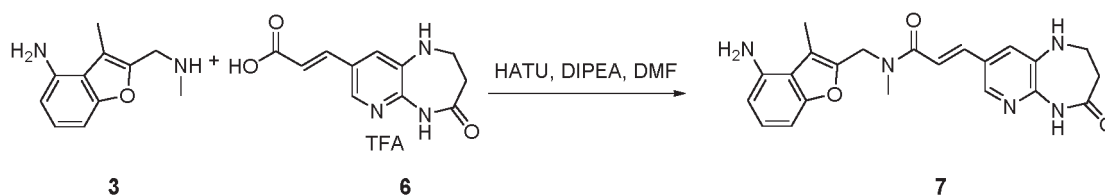
[00283] General Synthetic Scheme.



Reaction conditions: (a) HATU, DIPEA, DMF

5 The synthesis of (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid hydrochloride (compound **6**) was previously reported by AFFINIUM PHARMECEUTICALS, INC: WO2007/67416, 2007, A2; AURIGENE DISCOVERY TECHNOLOGIES LIMITED: WO2013/80222, 2013, A1; Ramnauth Jailall and co-workers, Bioorg. Med. Chem. Lett., 2009, 19, pp. 5359-5362.

10



[00284] **Step 1.** (E)-N-((4-Amino-3-methylbenzofuran-2-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **7**). A solution

15 of 3-methyl-2-((methylamino)methyl)benzofuran-4-amine **3** (0.05 g, 0.26 mmol), (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid TFA salt **6** (0.05 g, 0.22 mmol) and DIPEA (0.38 mL, 2.19 mmol) in DMF (2 mL) was stirred for 10 mins. Then 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (0.13 g, 0.33 mmol) was added in one portion and the reaction mixture stirred for 2 hours. Water

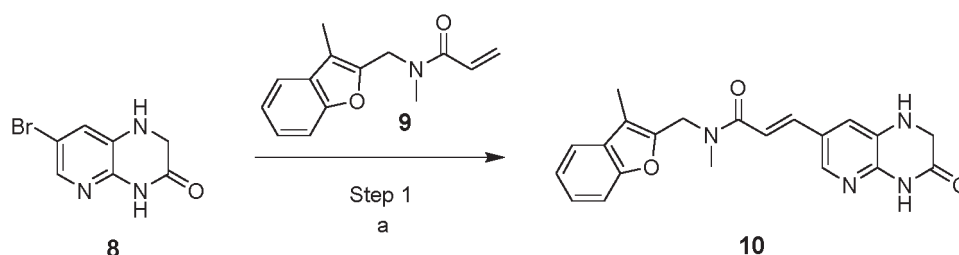
20 (20 mL) was added to the mixture and the resulting precipitate collected by filtration. The solid was washed with water (10 mL) and dried on the filter paper before being dissolved in the minimum amount of DMSO possible and precipitated by addition of water. The solid was collected then the crude material was further purified by chromatography (0-10 % MeOH in DCM) to give the desired product **7** as a yellow solid (0.05 g, 53%). R^t 1.43 min (Method 1a); m/z 406 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6 , 363 K): δ , ppm 9.14 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.45-7.34 (m, 2H), 7.09 (d, J = 15.7 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 6.66 (dd, J =

25

8.2 Hz, 0.8 Hz, 1H), 6.41 (dd, $J = 7.8$ Hz, 0.8 Hz, 1H), 5.82 (d, $J = 4.6$ Hz, 1H), 4.93 (s, 2H), 4.74 (s, 2H), 3.48-3.40 (m, 2H), 3.05 (s, 3H), 2.69-2.62 (m, 2H), 2.43 (s, 3H).

Example 3. Synthesis of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylamide (compound **10**).

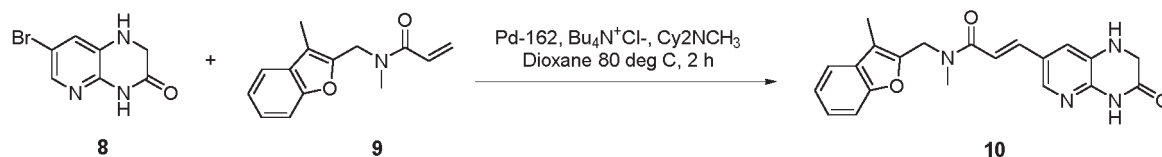
[00285] General Synthetic Scheme.



Reaction conditions: a) Pd-162, $\text{Bu}_4\text{N}^+\text{Cl}^-$, Cy_2NCH_3 Dioxane 80 deg C, 2 h

[00286] The synthesis of 7-bromo-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one (compound **8**) was previously reported by CEPHALON, INC - WO2007/130468, 2007, A2.

[00287] N-Methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **9**) was prepared as described in the patents of AFFINIUM PHARMACEUTICALS, INC. - WO2007/67416, 2007, A2 and VITAS PHARMA RESEARCH PRIVATE LIMITED, WO2013/42035, 2013, A1.

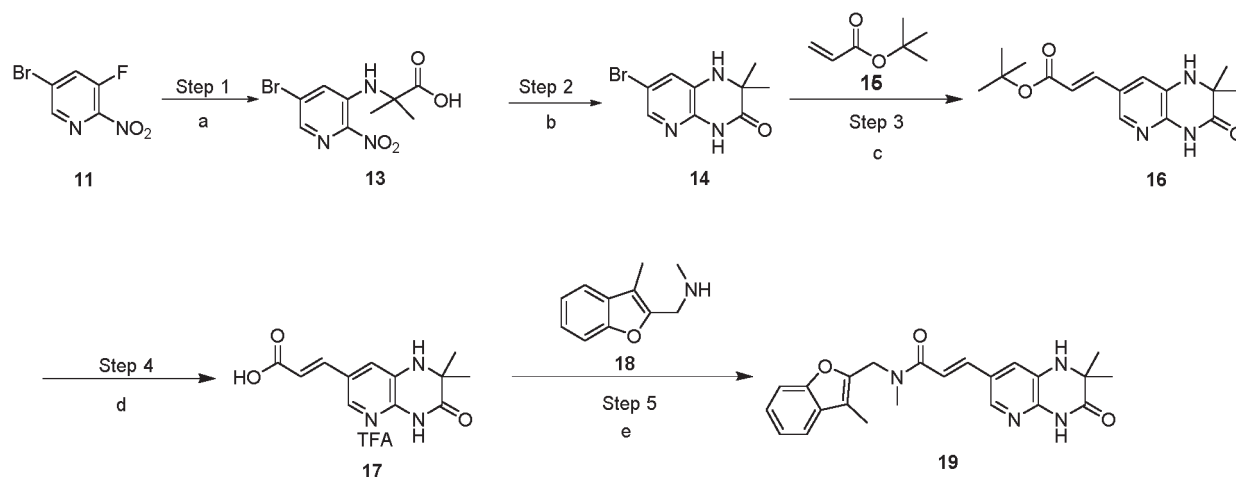


[00288] **Step 1.** (E)-N-Methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylamide (compound **10**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (23.12 mg, 0.101 mmol), 7-bromo-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one **8** (23 mg, 0.10 mmol), tetrabutylammonium chloride hydrate (2.98 mg, 10.09 μmol), $[\text{P}(\text{tBu})_3]\text{Pd}(\text{crotyl})\text{Cl}$ (Pd-162) (4.03 mg, 10.09 μmol). The vial was flushed with nitrogen (5 mins). 1,4-Dioxane (3 mL) and

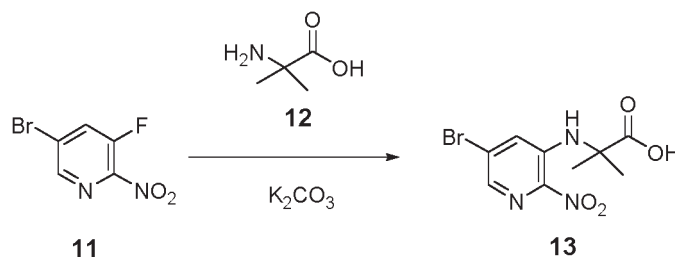
N-cyclohexyl-N-methylcyclohexanamine (43.2 μ L, 0.20 mmol) were added and the reaction mixture was purged with nitrogen (5 mins). The mixture was heated to 80 °C for 2 h and allowed to cool to room temperature. The solvent was evaporated to dryness. The residue was taken up in DCM (5 mL) and sat. NaHCO₃ (5 mL) was added. The aqueous phase was separated and extracted with DCM (2 $\times$ 5 mL). The combined organic phases were passed through a phase separator and concentrated *in vacuo*. The crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **10** as a yellow solid (6.2 mg, 0.016 mmol, 16% yield). *R*_t 1.20 min (Method 2a); 377.0 [M + H]⁺ (ES⁺). ¹H NMR Acquired at 360K (400 MHz, DMSO-d₆): δ , ppm 10.49 (s, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.58-7.54 (m, 1H), 7.47 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.42 (d, *J* = 15.4 Hz, 1H), 7.31-7.23 (m, 3H), 7.07 (d, *J* = 15.9 Hz, 1H), 5.99 (s, 1H), 4.84 (s, 2H), 3.85 (d, *J* = 1.9 Hz, 2H), 3.10 (s, 3H), 2.28 (s, 3H).

Example 4. Synthesis of (E)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **19**).

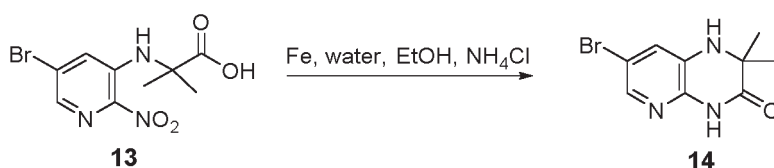
[00289] General Synthetic Scheme.



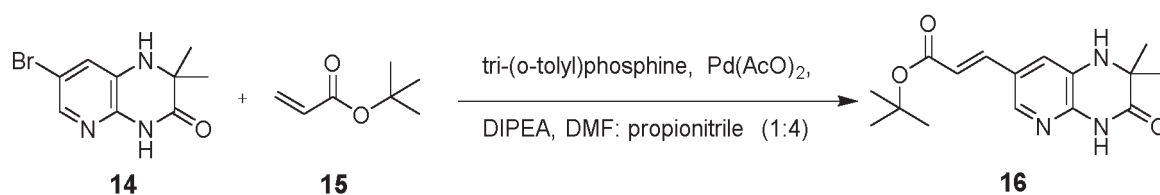
Reaction conditions: a) 2-Amino-2-methylpropanoic acid **12**, K₂CO₃/THF Reflux, overnight; b) Fe, water, EtOH, NH₄Cl; c) tri-(*o*-tolyl)phosphine, Pd(AcO)₂, DIPEA, DMF: propionitrile (1:4 *v/v*); d) TFA/DCM; e) T₃P, DIPEA, DMF



[00290] Step 1. 2-((5-Bromo-2-nitropyridin-3-yl)amino)-2-methylpropanoic acid (compound **13**). A mixture of 5-bromo-3-fluoro-2-nitropyridine **11** (30.0 g, 135.7 mmol), K₂CO₃ (38.96 g, 282.31 mmol) and 2-amino-2-methylpropanoic acid **12** (20.9 g, 203.6 mmol) in THF (500 mL) was heated at 90 °C for 16 hours. The progress of reaction was monitored by TLC. The reaction mixture was allowed to cool to RT and concentrated to dryness. The crude product was dissolved in water (500 mL) and washed with ethyl acetate (100 mL). The aqueous layer was acidified with 1N HCl solution to pH 2 and extracted with ethyl acetate (2 × 250 mL). The organic layer was dried over NaSO₄, filtered, and concentrated *in vacuo* to afford the crude compound. To the crude compound was added 50 mL diethyl ether and stirred for 30 min, filtered the solid mass and dried under vacuum to afford the title compound **13** as a yellow solid (26.0 g, 63 % yield). m/z 304/306 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 13.48 (s, 1H), 7.90 (s, 1H), 8.10 (s, 1H), 7.97 (s, 1H), 7.39 (s, 1H), 1.60 (s, 6H).



[00291] Step 2. 7-Bromo-2,2-dimethyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one (compound **14**). To a stirred solution of 2-((5-bromo-2-nitropyridin-3-yl)amino)-2-methylpropanoic acid **13** (26.0 g, 85.4 mmol) in EtOH:water (1:1, 520 mL) and was added NH₄Cl (10.42 g, 194 mmol) followed by iron powder (10.31 g, 184.6 mmol). The reaction mixture was stirred at 80 °C for 2 h. The progress of reaction was monitored by TLC. The reaction mixture was allowed to cool to RT and diluted with ethyl acetate (500 mL), filtered through Celite[®] and washed with THF (200 mL), MeOH (200 mL). The filtrate was concentrated *in vacuo* to afford the crude compound. To the crude compound was added 50 mL diethyl ether and stirred for 30 min, filtered the solid mass and dried under vacuum to afford the title compound **14** as an off white solid (12.5 g, 57% yield). m/z 256/258 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.83 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.54 (s, 1H), 1.25 (s, 6H).



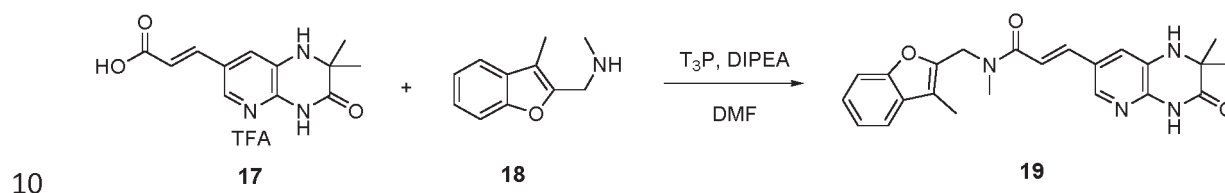
[00292] Step 3. tert-Butyl (E)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylate (compound **16**). In a seal tube, a stirred solution of 7-bromo-2,2-dimethyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one **14** (5.0 g, 19.5 mmol) and DIPEA (14.3 g, 78.12 mmol) in DMF:propionitrile (1:4, 75 mL) was purged with nitrogen gas for 10 min. Then added tert-butyl acrylate **15** (7.5 g, 58.5 mmol), tri-(o-tolyl)phosphine (1.18 g, 3.9 mmol) and palladium(II) acetate (4.37 g, 1.95 mmol) to the reaction mixture and again purged with nitrogen gas for 5 min. The reaction mixture was heated at 90 °C for 18 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was cooled to RT and diluted with 10% MeOH in DCM (50 mL), filtered through Celite®, washed 10% MeOH in DCM (50 mL) and filtrate was concentrated *in vacuo* to afford the crude material, which was triturated with diethyl ether (20 mL) and n-pentane (20 mL), filtered and dried under vacuum to give the title compound **16**. Note: Reaction was performed in one more batch (each of 5 g, total 10.0 g) to yield total 6.5 g, 55% as a yellow solid. m/z 304.41 $[M + H]^+$ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ , ppm 10.88 (s, 1H), 7.87 (s, 1H), 7.45-7.41 (d, J = 16.0 Hz, 1H), 7.18 (s, 1H), 6.32-6.27 (m, 2H), 1.47 (s, 9H), 1.26 (s, 6H).



[00293] Step 4. ((E)-3-(2,2-Dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylic acid trifluoroacetate (compound **17**). Trifluoroacetic acid (30.0 mL) was added to a cool suspension of tert-butyl (E)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylate **16** (6.0 g, 19.8 mmol) in DCM (60 mL) at 0 °C. The reaction mixture was stirred at RT for 3 h. The progress of reaction was monitored by TLC and LCMS, then concentrated *in vacuo*. The residue was triturated with diethyl ether (2 × 50 mL) and the solid collected by filtration to afford the title compound **17** as a yellow solid (4.5 g, 92%

yield). m/z 248.05 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 12.33 (s, 1H), 10.89 (s, 1H), 9.78 (s, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.50-7.46 (d, J = 16.0 Hz, 1H), 7.19 (d, J = 1.2 Hz, 1H), 6.36 (s, 1H), 6.32-6.28 (d, J = 16.0 Hz, 1H), 1.26 (s, 6H).

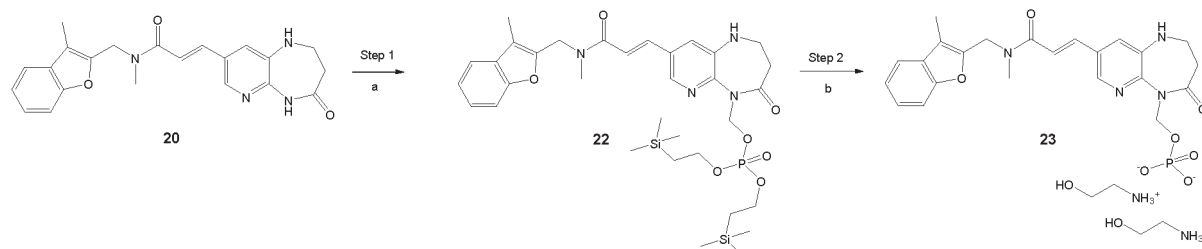
- 5 **[00294]** The synthesis of N-methyl-1-(3-methylbenzofuran-2-yl)methanamine (compound **18**) was described previously by AFFINIUM PHARMACEUTICALS, INC. - WO2008/98374, 2008, A1 and/or VITAS PHARMA RESEARCH PRIVATE LIMITED, WO2013/42035, 2013, A1.



- [00295]** **Step 5.** (E)-3-(2,2-Dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **19**). DIPEA (16.7.0 mL, 91.0 mmol) was added dropwise to a stirred solution of N-methyl-1-(3-methylbenzofuran-2-yl)methanamine **18** (3.8 g, 18.21 mmol) and (E)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)acrylic acid trifluoroacetate **17** (4.5 g, 13.04 mmol) in DMF (25 mL) and THF (25 mL). The reaction was stirred for 5 mins then T3P 50% in ethyl acetate (34.7 mL, 54.6 mmol) was added at 0 °C and the reaction was stirred for a further 4h at rt. The progress of reaction was monitored by TLC. The reaction mixture was diluted with water (500 mL) and the solid collected, washed with water (2 × 50 mL) and dried under vacuum. The crude compound was taken in diethyl ether (50 mL), and stirred for 15 min at rt. Filtered the solid mass and washed with diethyl ether (25 mL), dried under vacuum to give (E)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **19** as a light yellow solid (3.55 g, 67.5% yield).
- 25 The filtrate was concentrated to give 3.5 g mixture. m/z 405.21 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 10.84 (s, 1H), 7.90 (s, 1H), 7.57-7.55 (d, J = 7.2 Hz, 1H), 7.50-7.42 (m, 2H), 7.30-7.22 (m, 3H), 7.03-6.99 (d, J = 15.2 Hz, 1H), 6.35-6.33 (d, J = 9.6, Hz, 1H), 4.94-4.78 (d, J = 64.8 Hz, 2H), 3.16-2.94 (d, 3H), 2.26 (s, 3H), 1.25 (s, 6H).

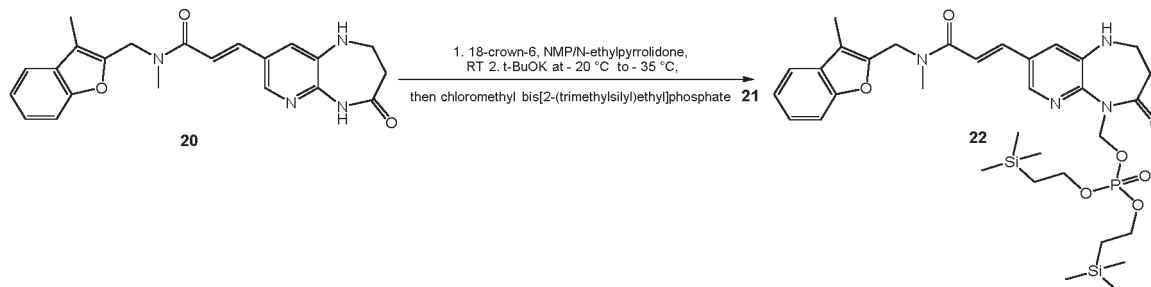
Example 5. Synthesis of 2-hydroxyethan-1-aminium (e)-(8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5h-pyrido[2,3-b][1,4]diazepin-5-yl)methyl phosphate (compound **23**).

5 **[00296]** General Synthetic Scheme.



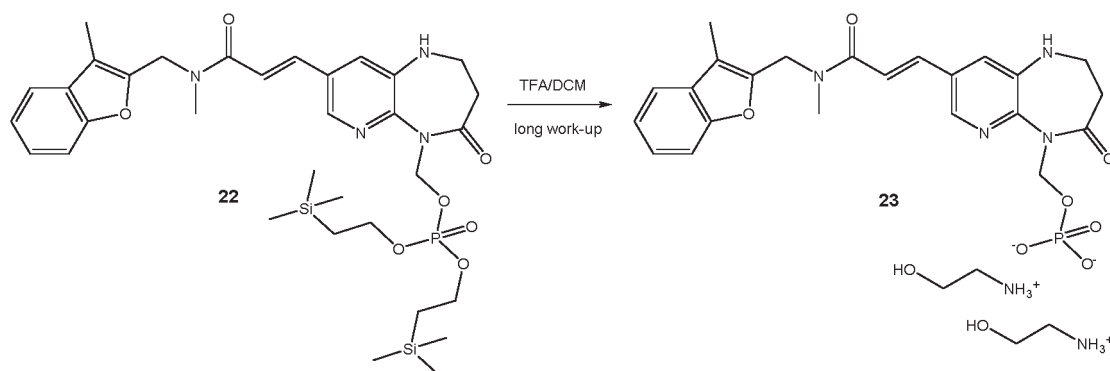
Reaction conditions: a) 1. 18-crown-6, NMP/N-ethylpyrrolidone, RT 2. t-BuOK at -20 °C to -35 °C, then chloromethyl bis[2-(trimethylsilyl)ethyl] phosphate **21**; b) TFA/DCM, long work-up

[00297] The full synthesis of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **20**) was described previously in Bioorganic & Medicinal Chemistry Letters (2009), 19(18), 5359-5362 and WO 2007067416.



15 **[00298]** **Step 1.** (E)-(8-(3-(Methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl bis(2-(trimethylsilyl)ethyl) phosphate (compound **22**). To a sealed 10 mL vial under nitrogen containing (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide **20** (250 mg; 1 eq; previously milled under dry stirring for 10 minutes) and 18-crown-6 (208 mg; 1.24 eq) was added N-methyl-2-pyrrolidone (1.0 mL; 4 vols) and N-ethylpyrrolidone (0.275 mL; 1.10 vols). Then mixture was stirred at 25 °C for 10 minutes, and submitted to degassing cycles (5 cycles; vacuum/nitrogen). Reaction mixture was then cooled down to -20 °C (not measured; bath temp at -30 °C) and potassium tert-butoxide (82 mg; 1.1 eq) was added portionwise over 2

minutes. Reaction mixture was again submitted to degassing cycles (3 cycles; vacuum/nitrogen) and was then stirred at $-20\text{ }^{\circ}\text{C}$ (temperature bath: $-30\text{ }^{\circ}\text{C}$) for 1 h 30 min until nearly complete solubilisation (dark green mixture). Reaction mixture was cooled down to $-35\text{ }^{\circ}\text{C}$ (not measured; bath temp at $-45\text{ }^{\circ}\text{C}$) and a degassed (5 cycles; vacuum/nitrogen) solution of chloromethyl bis[2-(trimethylsilyl)ethyl]phosphate **21** (Carbogen Amcis) (1.058 g; 1.4 eq; 29.1% w/w in heptane) was added over 4 minutes keeping temperature at $-35\text{ }^{\circ}\text{C}$ (not measured; bath temp at $-45\text{ }^{\circ}\text{C}$). Reaction mixture (biphasic) was stirred at $-35\text{ }^{\circ}\text{C}$ for 16 h until nearly completion as indicated by UPLC/MS: (Starting material: $R_t = 1.62\text{ min}$; 34.5% (AUC); ES^+ : 391.5. Product: $R_t = 2.50\text{ min}$; 34.25% (AUC); ES^+ : 701.79). N-Methyl-2-pyrrolidone (0.64 mL), methyl cyclohexane (1.25 mL), toluene (0.35 mL) and water (0.37 mL) were added to the reaction mixture keeping temperature at $-20\text{ }^{\circ}\text{C}$ (not measured; bath temp at $-30\text{ }^{\circ}\text{C}$). Then after stirring and phase separation, lower phase was extracted with MTBE ($3 \times 2\text{ mL}$) keeping temperature at $-20\text{ }^{\circ}\text{C}$. All upper phases were then combined and washed with half saturated sodium chloride solution ($2 \times 6\text{ mL}$). All washing were done keeping temperature at $-10\text{ }^{\circ}\text{C}$ (not measured; bath temp at $-20\text{ }^{\circ}\text{C}$). Organic phase was then dried over sodium sulfate, filtered and rinsed with MTBE ($2 \times 3\text{ mL}$) at 25°C . Concentration to dryness was done keeping bath temperature below $25\text{ }^{\circ}\text{C}$ to give crude compound as orange foam ($m = 150.73\text{ mg}$; purity: 88.36% (AUC)). Stored overnight under nitrogen at $-25\text{ }^{\circ}\text{C}$. The crude compound was purified by normal phase chromatography (SiO_2 ; $40\text{-}63\text{ }\mu\text{m}$). Conditioning was done with n-heptane, then crude compound was solubilised in a mixture of n-heptane/MTBE/DIPEA: 2/1/0.75% (3 mL) and MTBE (2 mL) and injected. Elution was done with cold eluents (stored few hours in ice maker). First eluent (n-heptane/MTBE/DIPEA: 2/1/0.75%), second eluent (MTBE/DIPEA: 100/0.2%), third eluent (methyl acetate/DIPEA: 100/0.2%). Product was finally eluted with the third eluent. Fractions were combined and concentrated to dryness (temperature bath: $25\text{ }^{\circ}\text{C}$) to give title compound **22** as yellow oil ($m = 122.5\text{ mg}$; purity: 96% (AUC); ES^+ : 701.7; yield: 26.5%). Stored at $-25\text{ }^{\circ}\text{C}$ until next step.



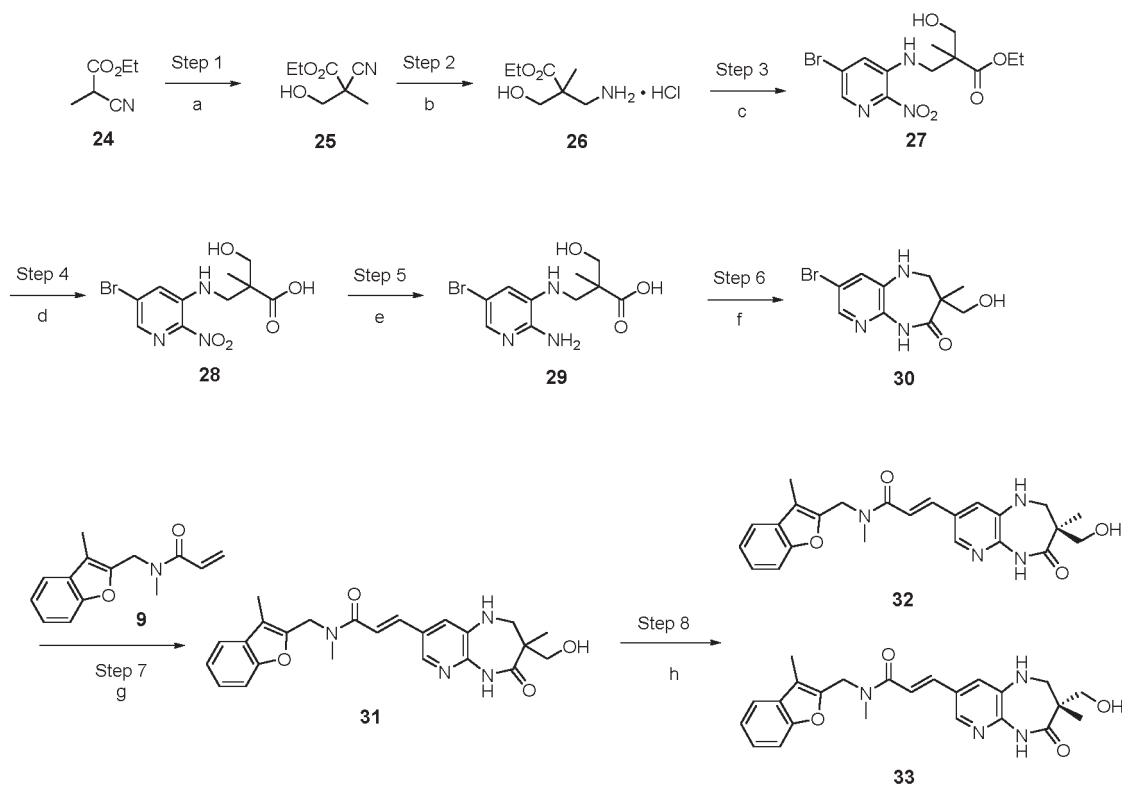
[00299] Step 2. 2-Hydroxyethan-1-aminium (E)-(8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-

- 5 b][1,4]diazepin-5-yl)methyl phosphate (compound **23**). In a sealed 2.5 mL vial under nitrogen was prepared a solution of TFA (0.369 mL; 19.3 eq) in anhydrous dichloromethane (0.32 mL; 2.6 vols) at -20°C , this solution was called solution N° 1. In a sealed 2.5 mL vial under nitrogen was prepared a solution of (E)-(8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-
- 10 b][1,4]diazepin-5-yl)methyl bis(2-(trimethylsilyl)ethyl) phosphate **22** (123 mg; 1eq) in anhydrous toluene (0.408 mL; 3.33 vols) at -10°C , this solution was called solution N° 2. Then solution N° 2 was added to solution N° 1 under stirring over 10 minutes keeping temperature at -20°C (not measured; bath temp at -30°C). Then vial containing solution N° 2 was rinsed with anhydrous dichloromethane (0.404 mL; 3.3 vols) which was then added to
- 15 solution N° 1. Reaction mixture was then stirred for 25 minutes under nitrogen keeping temperature at -20°C (not measured; temperature was adjusted keeping yellowish reaction mixture at the freezing limit (TFA): slight trouble). Completion of hydrolysis was confirmed by UPLC/MS (Product: $R_t = 1.34$ min; ES^- : 499.3. Starting material: $R_t = 2.49$ min; 0% (AUC)). In a sealed 20 mL vial under nitrogen was prepared a solution of ethanolamine (274 mg;
- 20 26.5eq) in a mixture of acetone (1.814 mL; 14.8 vols) and water (0.050 mL; 0.41 vols) at 0°C (not measured; bath temperature: -5°C), this solution was called solution N° 3. Then previous reaction mixture was cooled down to -20°C (not measured; just slightly above freezing point) and added through cannula to solution N° 3 under gentle stirring (100 rpm; can be increased to have an homogeneous solution (biphasic)) over 10 minutes keeping
- 25 temperature at 0°C (bath temp at -5°C). Then vial containing reaction mixture was rinsed with dichloromethane (0.208 mL; 1.7 vols) which was then added to solution N° 3. Then final reaction mixture was stirred at 200 rpm at 0°C (measured internally) for 30 minutes and

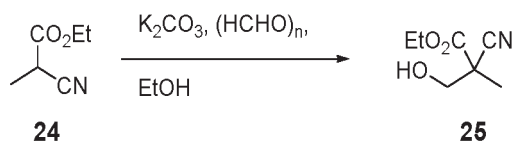
stored at 4 °C for 14 h in the fridge until precipitation was observed. Reaction mixture was allowed to warm up to 25 °C and was filtered through a glass filter. Resulting cake was washed with ethanol (2 × 2 mL) but complete dissolution was observed. Filtrate was concentrated to dryness (bath temperature at 25 °C) and resulting oil was dissolved in a mixture of acetone (1.5 mL), toluene (1.5 mL) and MTBE (3 mL). Resulting solution was stored at -25 °C for 1 h 30 min until complete precipitation. Suspension was filtered through a glass filter, and resulting solid was washed with a mixture of 1-butanol (2 mL) and MTBE (4 mL) then with MTBE (2 × 2 mL) and finally with 2-butanone (1 × 3 mL and 1 × 2 mL). However, after drying NMR analysis on isolated solid showed only TFA·ethanolamine salt. Filtrate was stored at -25 °C for 16 h until precipitation was observed. Suspension was filtered through a glass filter and resulting yellow solid was washed several time with 2-butanone (2 mL) until acceptable amount of TFA·ethanolamine salt was measured by NMR. Finally, after drying at 25 °C under vacuum, title compound **23** was obtained as yellow powder (m = 42.41 mg; purity: 100% (AUC); ES⁻: 499.3; 2 eq of ethanolamine by NMR; 2.4% w/w of TFA·ethanolamine salt; yield: 40.6%). ¹H NMR (400 MHz, D₂O): δ, ppm 8.13 (d, J = 1.7 Hz, 1H), 7.47 (dd, J = 1.8 Hz, 6.6 Hz, 1H), 7.43-7.08 (m, 5H), 6.87 (d, J = 15.8 Hz, 1H), 5.46 (d, J = 5.6 Hz, 2H), 4.68 (s, 1H), 4.60 (s, 1H), 3.72 (t, J = 5.2 Hz, 4H), 3.65-3.55 (m, 2H), 3.05 (t, J = 5.2 Hz, 4H), 3.05 (s, 1.8H), 2.92 (s, 1.2H), 2.53-2.42 (m, 2H, m), 2.09 (s, 1.8H), 2.08 (s, 1.2H) (rotamers).

Example 6. Synthesis of (E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **31**) as well as two enantiomers (S,E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **32**) and (R,E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **33**).

[00300] General Synthetic Scheme.

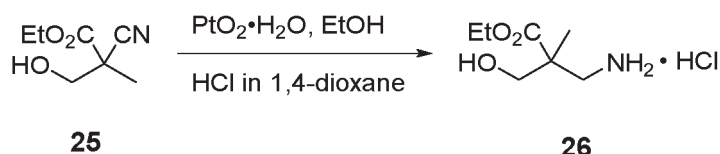


Reaction conditions : a) K_2CO_3 , $(HCHO)_n$, EtOH; b) HCl in 1,4-dioxane, $PtO_2 \cdot H_2O$, EtOH; c) 5-bromo-3-fluoro-2-nitropyridine **11**, TEA, EtOH, Δ ; d) LiOH, water/THF; e) Fe, NH_4Cl , EtOH, H_2O , 90 °C; f) HATU, DIPEA, DMF; g) Pd-162, Cy_2NMe , NBu_4Cl , 1,4-dioxane, 80 °C; h) chiral separation



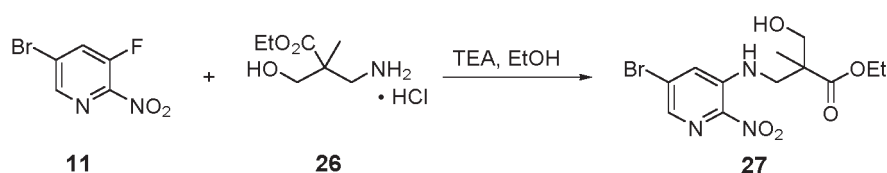
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[00301] Step 1. Ethyl 2-cyano-3-hydroxy-2-methylpropanoate (compound **25**). A mixture of paraformaldehyde (3.54 g, 118 mmol), ethyl 2-cyanopropanoate **24** (TCI – Tokyo Chemical Industry) (10 g, 79 mmol) and potassium carbonate (32.6 g, 236 mmol) in ethanol (500 mL) was stirred for 18 hours. The solid was removed by filtration through a plug of Celite® and the filtrate evaporated to dryness. The crude product was purified by silica chromatography (0-50% EtOAc/isohehexane) to afford the title compound **25** as a clear colourless oil (6.01 g, 48%). 1H NMR (400 MHz, $CDCl_3$): δ , ppm 4.30 (q, $J = 7.1$ Hz, 2H), 3.98-3.83 (m, 2H), 2.59 (s, 1H), 1.58 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H).

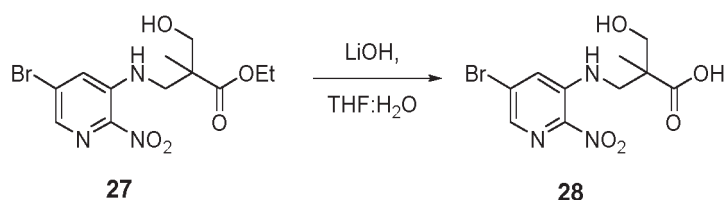


15

[00302] Step 2. Ethyl 3-amino-2-(hydroxymethyl)-2-methylpropanoate hydrochloride (compound **26**). A mixture of platinum(IV) oxide (0.14 g, 0.64 mmol), ethyl 2-cyano-3-hydroxy-2-methylpropanoate **25** (1.00 g, 6.36 mmol) and HCl (4M in 1,4-dioxane, 3.18 mL, 12.73 mmol) in a solvent of ethanol (12 mL) was stirred under an atmosphere of hydrogen at 5 bar for 18 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) and evaporated to dryness to give the title compound **26** as a colourless gum (1.38 g, quant. yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (s, 3H), 5.31 (s, 1H), 4.13 - 4.07 (m, 2H), 3.64 - 3.44 (m, 2H), 3.09 - 2.91 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.13 (s, 3H).



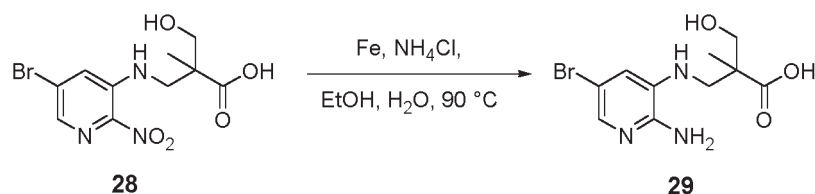
[00303] Step 3. Ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoate (compound **27**). A mixture of ethyl 3-amino-2-(hydroxymethyl)-2-methylpropanoate hydrochloride **26** (322 mg, 1.63 mmol), triethylamine (757 μL, 5.43 mmol) and 5-bromo-3-fluoro-2-nitropyridine **11** (300 mg, 1.36 mmol) in a solvent of ethanol (20 mL) was heated and stirred under reflux for 1 hours. The reaction mixture was evaporated to dryness. The crude product was purified by silica chromatography (0-100% EtOAc/isohexane) to afford the title compound **27** as a yellow gum (485 mg, 94%). R_t 1.17 min (Method 2b) m/z 362/364 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-d₆): δ, ppm 8.24 (t, J = 6.0 Hz, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 5.19 (t, J = 5.2 Hz, 1H), 4.08 (qd, J = 7.1 Hz, 2.2 Hz, 2H), 3.66-3.60 (m, 3H), 3.54 (dd, J = 10.6 Hz, 5.0 Hz, 1H), 1.19-1.16 (m, 3H).



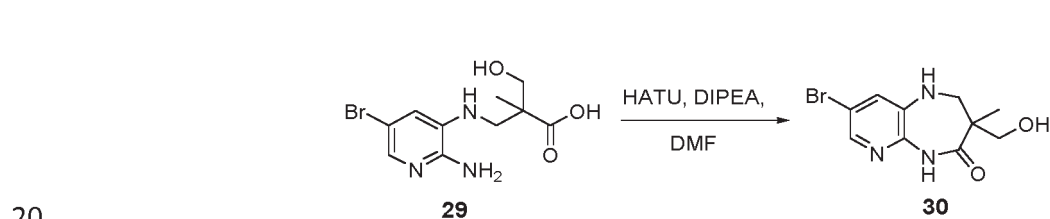
[00304] Step 4. 3-((5-Bromo-2-nitropyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoic acid (compound **28**). A mixture of ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoate **27** (480 mg, 1.38 mmol) and lithium hydroxide monohydrate (49.5 mg, 2.07 mmol) in a solvent mixture of THF (20 mL) and water

(5 mL) was stirred for 1 hour at RT. The mixture was acidified to pH ~3 by the addition of an aqueous solution of 1M HCl and the mixture evaporated to dryness to give the title compound **28** (501 mg, quant. yield) which was used in the next step without further purification. R^t 0.59 min (Method 2b) 332/334 $[M - H]^-$ (ES^-).

5



[00305] Step 5. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoic acid (compound **29**). A mixture of 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoic acid **28** (460 mg, 1.38 mmol), iron powder (615 mg, 11.01 mmol) and ammonium chloride (147 mg, 2.75 mmol) in a solvent mixture of ethanol (30 mL) and water (8 mL) was heated and stirred under reflux for 1 hour. The reaction mixture was filtered through a plug of Celite® and the filtrate evaporated to dryness. The residue was triturated with ice water (10 mL), the solid collected and dried in vacuo to give the title compound **29** as grey solid (180 mg, 41% yield). R^t 0.71 min (Method 1b) m/z 304/306 $[M + H]^+$ (ES^+); 302/304 $[M - H]^-$ (ES^-). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 7.32 (s, 1H), 7.17 (s, 2H), 6.79 (s, 1H), 5.78 (s, 2H), 4.79 (d, $J = 59.7$ Hz, 2H), 3.54 (q, $J = 10.6$ Hz, 2H), 3.25-3.12 (m, 2H), 1.13 (s, 3H).

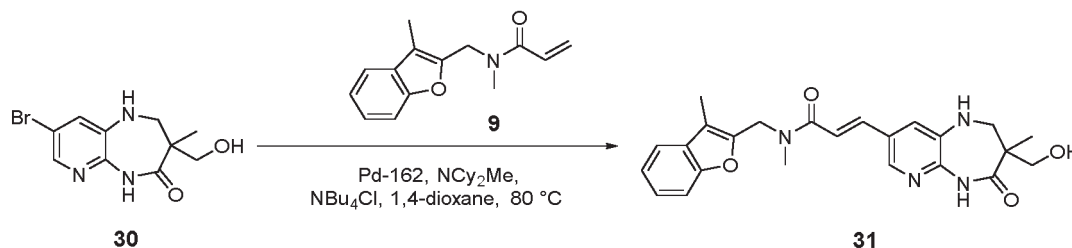


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[00306] Step 6. 8-Bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **30**). To a solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2-(hydroxymethyl)-2-methylpropanoic acid **29** (165 mg, 0.54 mmol) and DIPEA (284 μ L, 1.63 mmol) in DMF (5 mL) was added HATU (309 mg, 0.81 mmol) and the mixture stirred for 1 hour. The reaction mixture was evaporated to dryness and the crude product was purified by silica chromatography (0-100% EtOAc/isohehexane) to afford the title compound **30** as a tan solid (31 mg, 20% yield). R^t 1.33 min (Method 1b) m/z 286/288 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.51 (s, 1H), 7.67 (d, $J = 2.1$ Hz, 1H), 7.25 (d, J

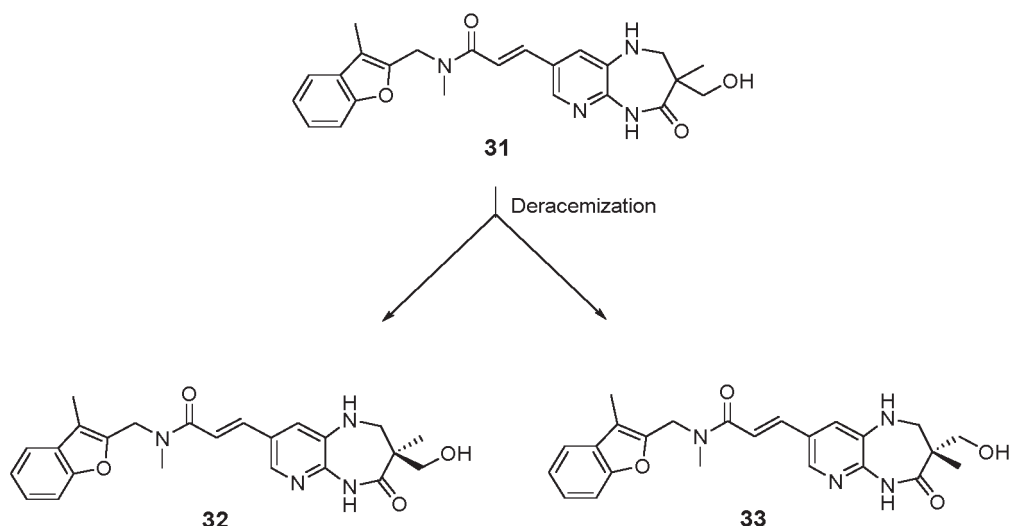
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= 2.1 Hz, 1H), 6.38 (t, J = 4.5 Hz, 1H), 4.79 (t, J = 5.5 Hz, 1H), 3.60 (dd, J = 10.5 Hz, 5.7 Hz, 1H), 3.44 (dd, J = 10.6 Hz, 5.3 Hz, 1H), 3.20 (dd, J = 13.8 Hz, 3.7 Hz, 1H), 3.07 (dd, J = 13.8 Hz, 5.3 Hz, 1H), 1.08 (s, 3H).



[00307] Step 7. (E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **31**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (61.7 mg, 0.27 mmol), 8-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **30** (70 mg, 0.25 mmol), tetrabutylammonium chloride hydrate (7.24 mg, 0.02 mmol), [P(tBu)₃]Pd(crotyl)Cl (Pd-162) (Johnson Matthey) (9.77 mg, 0.02 mmol). The reaction vial was flushed with nitrogen for 5 mins. 1,4-Dioxane (10 mL) and N-cyclohexyl-N-methylcyclohexanamine (0.11 mL, 0.49 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 °C for 30 mins. The reaction mixture was evaporated to dryness and the crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **31** as a yellow solid (71.2 mg, 66% yield). R_t 1.85 min (Method 1b) m/z 435 [M + H]⁺ (ES)⁺. ¹H NMR (400 MHz, DMSO-d₆, 363 K): δ, ppm 8.88 (s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.58-7.54 (m, 1H), 7.49-7.36 (m, 3H), 7.32-7.22 (m, 2H), 7.17-7.04 (m, 1H), 5.90 (s, 1H), 4.84 (s, 2H), 3.67 (d, J = 10.5 Hz, 1H), 3.51 (d, J = 10.6 Hz, 1H), 3.27 (d, J = 13.9 Hz, 1H), 3.15-3.07 (m, 4H), 2.28 (s, 3H), 1.15 (s, 3H).

[00308] Step 8. Chiral separation of compound **31**.



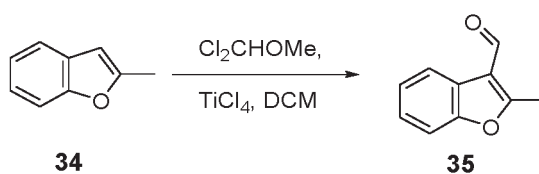
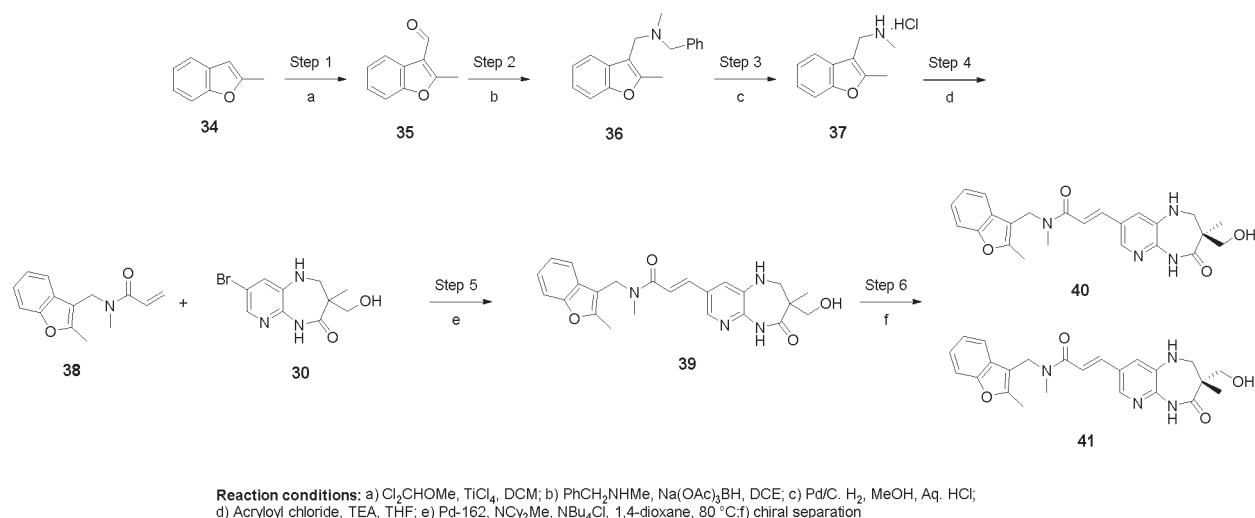
[00309] Chiral method separation: Apparatus: Isolera (Biotage). Chiralpak® IA (Daicel Ltd.) glass column (20 μ m; 250 mm $\times$ 25 mm), flow rate 40 mL min⁻¹ eluting with a mixture of Acetonitrile/Ethanol (8/2 v/v). UV detection at 254 nm. Temperature: 30 °C. Run time: 25 min. Samples were loaded after filtration through 0.2 μ m PTFE filter directly onto the column. Amount injected: 46.4 mg of **31** in 10 mL of eluent (polishing filtration through a 0.2 μ m PTFE filter).

[00310] (S,E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **32**). Pure fractions of first enantiomer were collected and concentrated. The first enantiomer was obtained as a yellow solid (m = 12.95 mg; chiral purity: 99.66%). R^t 1.53 min (Method 1c) m/z 435.5 (M + H)⁺ (ES⁺). The stereochemistry of obtained enantiomer was randomly assigned.

[00311] (R,E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **33**). Pure fractions of second enantiomer were collected and concentrated. The second enantiomer was obtained as yellow solid (m = 8.97 mg; chiral purity: 98.20%). R^t 1.53 min (Method 1c) m/z 435.5 [M + H]⁺ (ES⁺). The stereochemistry of obtained enantiomers was randomly assigned.

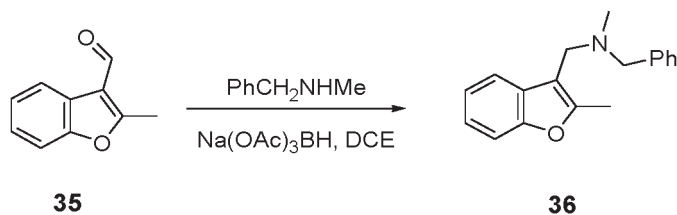
Example 7. Synthesis of (E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **39**) as well as two enantiomers (S,E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **40**) and (R,E)-3-(3-(hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **41**).

[00312] General Synthetic Scheme.

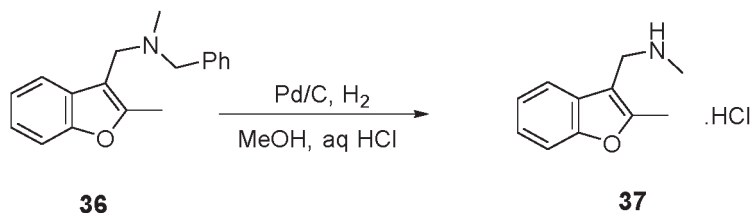


[00313] **Step 1.** 2-Methylbenzofuran-3-carbaldehyde (compound **35**). To a solution of dichloro(methoxy)methane (5.1 mL, 56.7 mmol) and 2-methylbenzofuran **34** (5.0 g, 37.8 mmol) in DCM (100 mL) stirred at 0°C was added dropwise tin(IV) chloride (1M in DCM) (60.5 mL, 60.5 mmol) over 30 mins. Upon completion of addition the mixture was allowed to warm to RT over 30 mins, then poured onto ice cold saturated sodium hydrogen carbonate solution (500 mL). The mixture was extracted into DCM (2×100 mL) and the organics separated and dried. Filtration and evaporation gave the crude product which was purified by silica chromatography (0-50% EtOAc/isohexane) to afford the title compound **35** as a

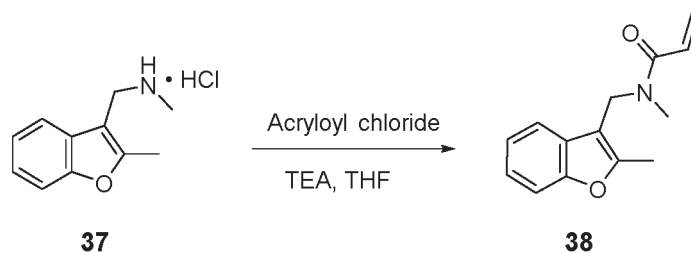
yellow solid (5.30 g, 86%). ^1H NMR (400 MHz, CDCl_3): δ , ppm 10.16 (s, 1H), 8.06-8.01 (m, 1H), 7.41-7.35 (m, 1H), 7.34-7.23 (m, 2H), 2.70 (s, 3H).



[00314] Step 2. N-Benzyl-N-methyl-1-(2-methylbenzofuran-3-yl)methanamine (compound **36**). To a solution of 2-methylbenzofuran-3-carbaldehyde **35** (1.00 g, 6.24 mmol) and N-methyl-1-phenylmethanamine (0.98 mL, 7.49 mmol) in DCE (20 mL) was added sodium triacetoxyborohydride (1.99 g, 9.37 mmol) and the mixture stirred for 72 hours. The reaction mixture was washed with saturated sodium bicarbonate solution (20 mL) and dried over sodium sulfate. Filtration and evaporation gave the title compound **36** as a pale yellow oil (1.60 g, 94% yield) which was used without further purification. ^1H NMR (400 MHz, DMSO-d_6): δ , ppm 7.63-7.58 (m, 1H), 7.48-7.43 (m, 1H), 7.33 (d, $J = 4.8$ Hz, 4H), 7.28-7.20 (m, 3H), 3.56 (s, 2H), 3.52 (s, 2H), 2.42 (s, 3H), 2.08 (s, 3H).

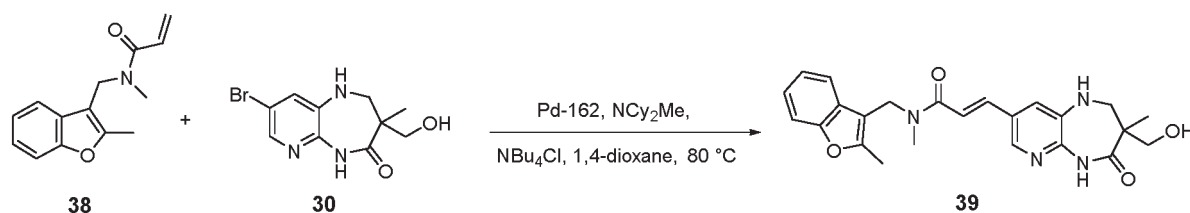


[00315] Step 3. N-Methyl-1-(2-methylbenzofuran-3-yl)methanamine hydrochloride (compound **37**). A mixture of N-benzyl-N-methyl-1-(2-methylbenzofuran-3-yl)methanamine **36** (1.60 g, 6.03 mmol) and Pd-C 87L 5% on carbon (0.64 g, 6.03 mmol) in methanol (20 mL) acidified to pH 1 with 1M hydrochloric acid was hydrogenated at 5 bar and left to stir at RT for 18 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness to give the title compound **37** as a white solid (737 mg, 56%). ^1H NMR (400 MHz, DMSO-d_6): δ , ppm 9.24 (s, 2H), 7.89-7.80 (m, 1H), 7.59-7.49 (m, 1H), 7.34-7.23 (m, 2H), 4.24 (s, 2H), 2.57 (s, 3H), 2.55 (s, 3H).



[00316] Step 4. N-Methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **38**). To a suspension of N-methyl-1-(2-methylbenzofuran-3-yl)methanamine hydrochloride

37 (300 mg, 1.42 mmol) and triethylamine (600 μ L, 4.25 mmol) in dry THF (10 mL) was added acryloyl chloride (154 mg, 1.70 mmol) dropwise at RT over 15 mins. The mixture was allowed to stir for 1 hour and then poured onto water (30 mL). The organic solvent was removed by rotary evaporation to give a solid. This solid was collected by filtration, washed with water (10 mL) and dried to give the title compound **38** (316 mg, 95%) as a colourless solid. R^t 1.94 min (Method 1b) m/z 230 $[M + H]^+$ (ES^+).

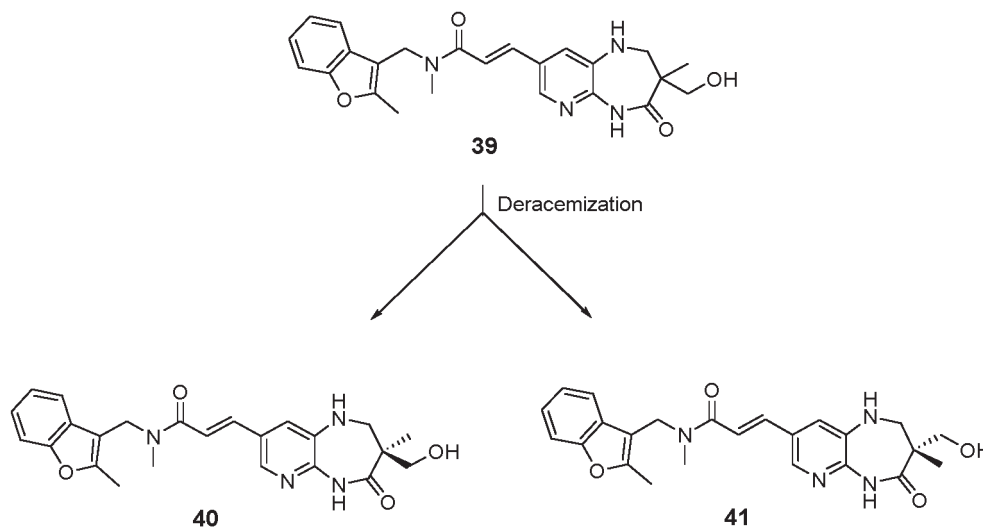


[00317] Step 5. (E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-

pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **39**). A reaction vial was charged with N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide **38** (72.0 mg, 0.32 mmol), 8-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **30** (90.0 mg, 0.32 mmol), tetrabutylammonium chloride hydrate (9.3 mg, 0.031 mmol), $[P(tBu)_3]Pd(crotyl)Cl$ (Pd-162) (12.6 mg, 0.03 mmol). The reaction vial was flushed with nitrogen for 5 mins. 1,4-Dioxane (10 mL) and N-cyclohexyl-N-methylcyclohexanamine (0.14 mL, 0.63 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 $^{\circ}C$ for 30 mins. The reaction mixture was evaporated to dryness and the crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **39** as a yellow solid (94.3 mg, 68% yield). R^t 1.21 min (Method 2a) m/z 435 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6 , 363 K): δ , ppm 8.88 (s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.58-7.36 (m, 4H), 7.28-7.04 (m, 3H), 5.88 (t, J = 4.7 Hz, 1H), 4.77 (s, 2H), 4.45 (t, J = 5.5 Hz, 1H), 3.67 (dd, J

= 10.6 Hz, 5.7 Hz, 1H), 3.54-3.48 (m, 1H), 3.26 (dd, $J = 13.9$ Hz, 3.9 Hz, 1H), 3.11 (dd, $J = 13.9$ Hz, 5.3 Hz, 1H), 3.01 (bs, 3H), 1.14 (s, 3H). Note: Methyl group at the benzofuran underneath solvent peak.

5 [00318] **Step 6. Chiral separation of compound 39.**



[00319] **Chiral method separation:** Apparatus: Isolera (Biotage). Chiralpak® IA (Daicel Ltd.) glass column (20 μ m; 250 mm $\times$ 25 mm), flow rate 40 mL min⁻¹ eluting with a mixture of Acetonitrile/Ethanol (8/2 v/v). UV detection at 254 nm. Temperature: 30 °C. Run time: 25 min. Samples were loaded after filtration through 0.2 μ m PTFE filter directly onto the column. Amount injected: 56.1 mg of **39** in 10 mL of eluent (polishing filtration through a 0.2 μ m PTFE filter).

15 [00320] (S,E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **40**). Pure fractions of first enantiomer were collected and concentrated. The first enantiomer was obtained as a yellow solid ($m = 21.11$ mg; chiral purity: 98.82%). R^t 1.50 min (Standard) m/z 435.5 $[M + H]^+$ (ES⁺). The stereochemistry of obtained enantiomer was

20 randomly assigned

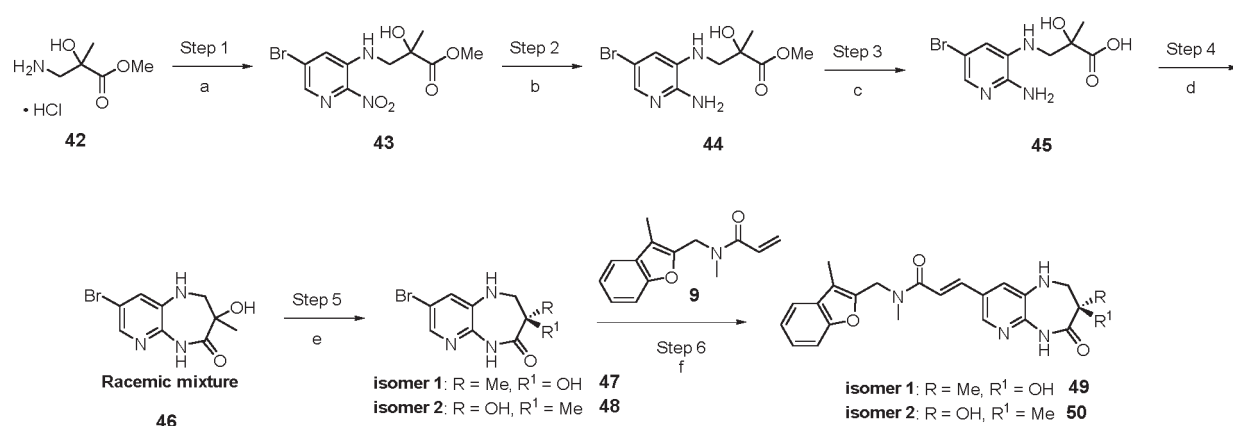
[00321] (R,E)-3-(3-(Hydroxymethyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **41**). Pure fractions of second enantiomer were collected and concentrated. The second enantiomer was obtained as a yellow solid ($m = 18.22$ mg; chiral purity: 99.49%). R^t 1.50 min

25

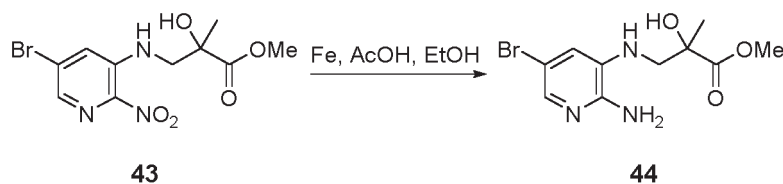
(Standard) m/z 435.5 $[M + H]^+$ (ES^+). The stereochemistry of obtained enantiomer was randomly assigned.

Example 8. Synthesis of (R,E)-3-(3-Hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **49**) and (S,E)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **50**).

[00322] General Synthetic Scheme.



[00323] **Step 1.** Methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxy-2-methylpropanoate (compound **43**). To a stirred solution of 5-bromo-3-fluoro-2-nitropyridine **11** (0.33 g, 1.47 mmol) in THF (5 mL) was added methyl 3-amino-2-hydroxy-2-methylpropanoate hydrochloride **42** (Enamine) (0.25 g, 1.47 mmol) followed by potassium carbonate (0.41 g, 2.95 mmol). The reaction mass was stirred at reflux for 2 h. The reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo to afford the title compound **43** as a yellow oil (0.48 g, 94% yield). R^t 1.03 min (Method 2a) m/z 334/336 $[M + H]^+$ (ES^+).

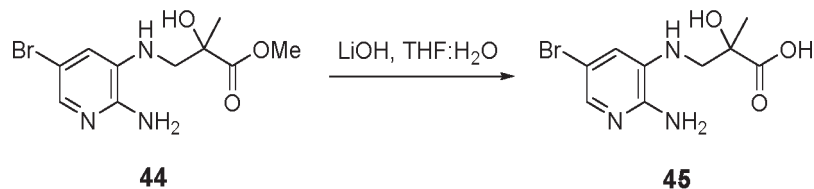


[00324] Step 2. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-

5 methylpropanoate (compound **44**). To a stirred solution of methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxy-2-methylpropanoate **43** (0.48 g, 1.44 mmol) in EtOH (6 mL) was added acetic acid (1.64 mL, 28.7 mmol) followed by iron powder (0.80 g, 14.4 mmol). The reaction mixture was stirred at 90 °C for 30 min. The reaction mixture was allowed to cool to room temperature and neutralised to pH 8 with solid NaHCO₃. The

10 resulting reaction mixture was diluted with H₂O (10 mL) and EtOAc (10 mL). The aqueous phase was separated and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with H₂O (10 mL), passed through a hydrophobic frit, and concentrated in vacuo to afford the title compound **44** (0.43 g, 50%). R_t 0.58 min (Method 2a) m/z 304/306 [M + H]⁺ (ES⁺).

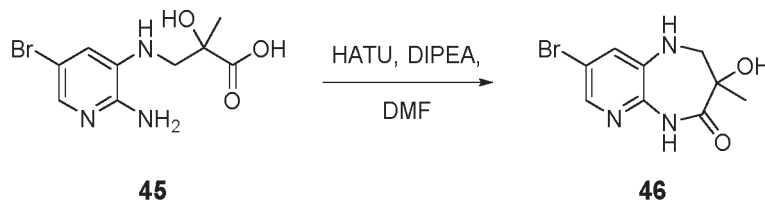
15



[00325] Step 3. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-

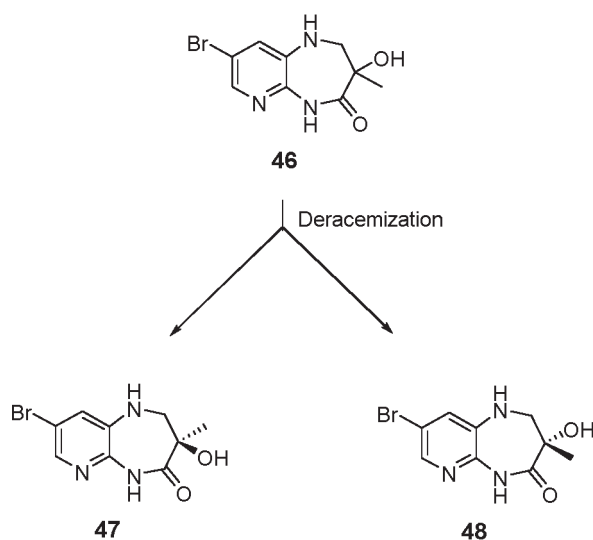
20 methylpropanoic acid (compound **45**). To a stirred solution of methyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylpropanoate **44** (0.35 g, 1.15 mmol) in THF (1.5 mL) was added a solution of LiOH (0.14 g, 5.8 mmol) in H₂O (1.5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated to dryness to give the title compound **45** as a colourless solid (320 mg, 34% yield) which was used in the next step without further purification. R_t 0.73 min (Method 2a) m/z 290/292 [M + H]⁺ (ES⁺).

25



[00326] Step 4. 8-Bromo-3-hydroxy-3-methyl-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **46**). To a stirred solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylpropanoic acid **45** (0.32 g, 1.1 mmol) in DMF (4 mL) was added DIPEA (0.58 mL, 3.3 mmol) followed by HATU (0.63 g, 1.65 mmol). The reaction mixture was stirred at room temperature for 1 h. Water (4 mL) was added. The aqueous phase was separated and extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with H₂O (3 × 5 mL), passed through a hydrophobic frit, and concentrated *in vacuo* to afford the title compound **46** as a colourless solid (41 mg, 14% yield). *R*_t 0.83 min (Method 2a) *m/z* 272/274 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ, ppm 9.92 (s, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 6.50 (t, *J* = 4.6 Hz, 1H), 5.34 (s, 1H), 3.28-3.05 (m, 2H), 1.22 (s, 3H).

[00327] Step 5. Chiral separation of racemate **46**.

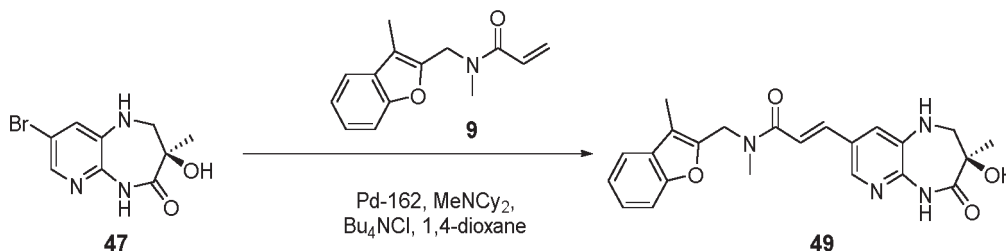


The enantiomers were separated by chiral prep HPLC using Method 3a. Chirality was arbitrarily assigned.

[00328] (R)-8-Bromo-3-hydroxy-3-methyl-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **47**). First eluting isomer: *R*_t 6.4 min (Method 4a); *R*_t 0.83 min (Method 2a) *m/z* 272/274 [M + H]⁺ (ES⁺).

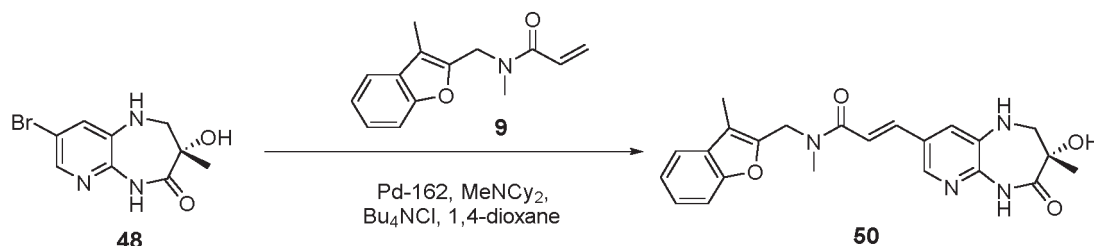
[00329] (S)-8-Bromo-3-hydroxy-3-methyl-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **48**). Second eluting enantiomer: R^t 11.7 min (Method 4a); R^t 0.83 min (Method 2a) m/z 272/274 $[M + H]^+$ (ES^+).

5



[00330] **Step 6a.** (R,E)-3-(3-Hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound

49). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (22 mg, 0.1 mmol), (R)-8-bromo-3-hydroxy-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **47** (27 mg, 0.1 mmol), tetrabutylammonium chloride hydrate (3 mg, 0.01 mmol), $[P(tBu)_3]Pd(crotyl)Cl$ (Pd-162) (4 mg, 0.01 mmol). The vial was flushed with nitrogen for 5 mins. 1,4-Dioxane (2 mL) and N-cyclohexyl-N-methylcyclohexanamine (42 μ L, 0.20 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 $^{\circ}C$ for 3 h and allowed to cool to room temperature. The solvent was evaporated to dryness. The crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **49** as a yellow solid (20 mg, 48%). R^t 19 min (Method 4a). R^t 1.23 min (Method 2a) m/z 421 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $DMSO-d_6$): δ , ppm 9.37 (s, 1H), 7.95 (d, $J = 1.9$ Hz, 1H), 7.60-7.53 (m, 1H), 7.49-7.45 (m, 1H), 7.42 (d, $J = 15.4$ Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.30-7.24 (m, 2H), 7.18-7.07 (m, 1H), 6.06 (s, 1H), 4.92 (s, 1H), 4.84 (s, 2H), 3.20 (dd, $J = 6.7$ Hz, 4.7 Hz, 2H), 3.10 (s, 3H), 2.28 (s, 3H), 1.29 (s, 3H).

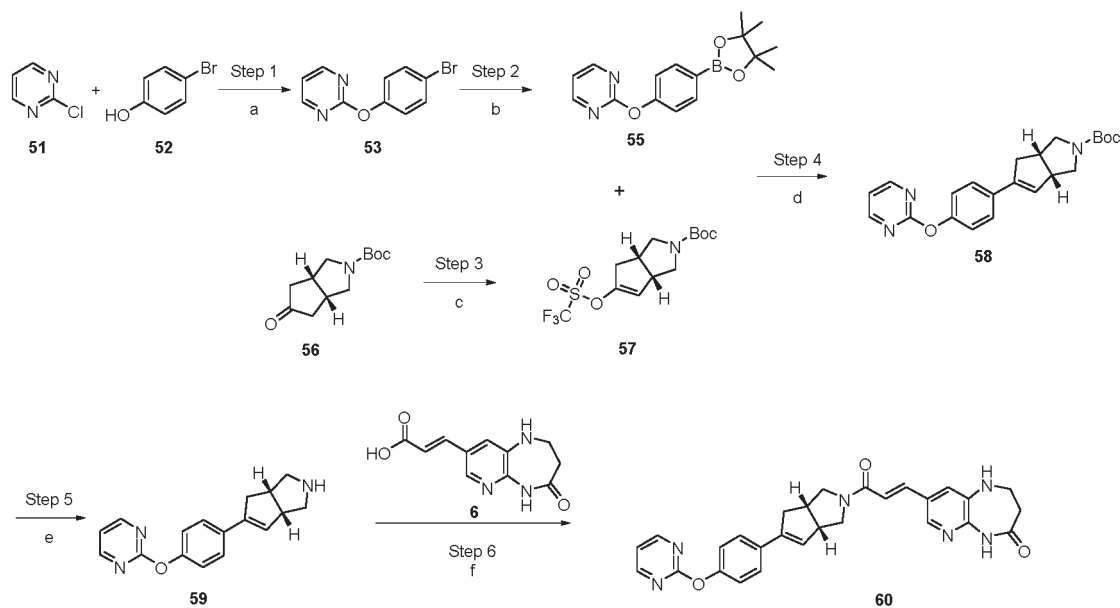


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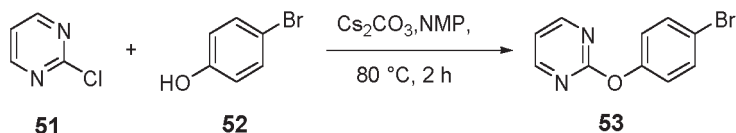
[00331] Step 6b. (S,E)-3-(3-Hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **50**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (23 mg, 0.1 mmol), (S)-8-bromo-3-hydroxy-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **48** (27 mg, 0.1 mmol), tetrabutylammonium chloride hydrate (3 mg, 0.01 mmol), [P(tBu)₃]Pd(crotyl)Cl (Pd-162) (4 mg, 0.01 mmol). The vial was flushed with nitrogen for 5 mins. 1,4-Dioxane (2 mL) and N-cyclohexyl-N-methylcyclohexanamine (43 µL, 0.20 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 °C for 3 h and allowed to cool to room temperature. The solvent was evaporated to dryness. The crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **50** as a yellow solid (34 mg, 80% yield). R_t 33 min (Method 4a). R_t 1.23 min (Method 2a) m/z 421 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.37 (s, 1H), 7.95 (d, J = 1.9 Hz, 1H), 7.60-7.53 (m, 1H), 7.49-7.45 (m, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.30-7.24 (m, 2H), 7.18-7.07 (m, 1H), 6.06 (s, 1H), 4.92 (s, 1H), 4.84 (s, 2H), 3.20 (dd, J = 6.7, 4.7 Hz, 2H), 3.10 (s, 3H), 2.28 (s, 3H), 1.29 (s, 3H).

Example 9. Synthesis of 8-((E)-3-oxo-3-((3aS,6aR)-5-(4-(pyrimidin-2-yloxy)phenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **60**).

[00332] General Synthetic Scheme.



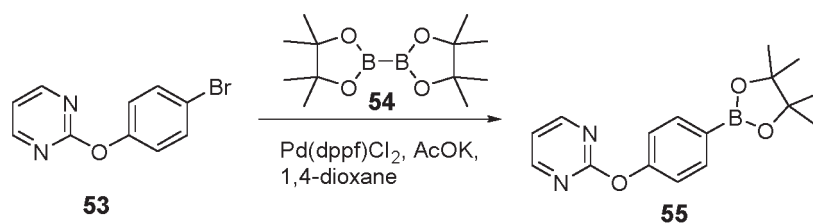
Reaction conditions: a) Cs_2CO_3 , NMP, 80 °C, 2 h; b) Bis(pinacolato)diboron **54**, $\text{Pd}(\text{dppf})\text{Cl}_2$, AcOK, 1,4-dioxane; c) LHMDS, Comins' reagent, THF, -78 °C to rt; d) Na_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, H_2O , 1,4-dioxane, 90 °C; e) TFA, DCM; f) DIPEA, HATU, DMF



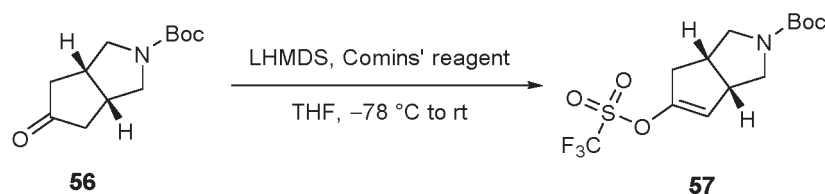
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[00333] Step 1. 2-(4-Bromophenoxy)pyrimidine (compound 53). A mixture of 2-chloropyrimidine **51** (Alfa Aesar) (2 g, 17 mmol), 4-bromophenol **52** (Sigma-Aldrich) (3.6 g, 21 mmol) and Cs_2CO_3 (17 g, 52 mmol) in N-methyl-2-pyrrolidone (50 mL) was heated at 80 °C for 2 hours. The reaction mixture was allowed to cool to room temperature, and poured into water (200 mL). The mixture was extracted with EtOAc (2 × 100 mL). The organics were combined and washed with brine (2 × 100 mL), passed through an hydrophobic frit, and concentrated in vacuo. The crude product was purified by chromatography (0-50% EtOAc/isohexane) to afford the title compound **53** as a colourless crystalline solid (3.95 g, 90% yield). R^t 1.86 min (Method 1a) m/z 251/253 $[\text{M} + \text{H}]^+$ (ES⁺). ^1H NMR (400 MHz, CDCl_3): δ , ppm 8.59 (d, J = 4.7 Hz, 2H), 7.59-7.53 (m, 2H), 7.15-7.10 (m, 2H), 7.08 (t, J = 4.8 Hz, 1H).

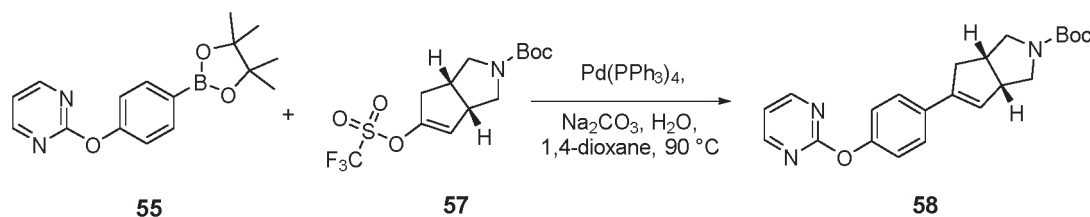
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Step 2 (compound **55**). A mixture of 2-(4-bromophenoxy)pyrimidine **53** (0.5 g, 2.0 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) **54** (Fluorochem) (0.7 g, 2.8 mmol), potassium acetate (0.6 g, 6.0 mmol) and PdCl₂(dppf) (0.07 g, 0.1 mmol) in 1,4-dioxane (20 mL) was stirred at 85 °C for 16 h. The reaction mixture was allowed to cool to room temperature, filtered through Celite®, and concentrated in vacuo. The crude residue was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were passed through a phase separator and evaporated to dryness to give the crude product **55** as a dark brown solid (0.6 g, 2.0 mmol, quant. yield). R^t 2.23 min (Method 1a) m/z 299 [M + H]⁺ (ES⁺).



3,3a,4,6a-tetrahydrocyclopenta [c]pyrrole-2(1H)-carboxylate (compound **57**). To a stirred solution of tert-butyl 5-oxohexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **56** (Ark Pharm) (3 g, 13.3 mmol) in THF (60 mL) was slowly added a solution of LHMDs (1M in THF) (17 mL, 17.3 mmol) at -78°C . The reaction mixture was stirred at -78°C for 30 min, then a solution of N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (7.3 g, 18.6 mmol) in THF (20 mL) was slowly added. The mixture was stirred for an additional 1 h at -78°C , allowed to warm up to room temperature and stirred for 2 h. The reaction mixture was concentrated in vacuo. The crude residue was purified by chromatography (0-50% EtOAc/isohexane) to afford the title compound **57** as a pale yellow oil (4.4 g, 91% yield). R^t 1.29 min (Method 1a) m/z 302 $[\text{M} + \text{H}^t\text{Bu}]^+$ (ES^+). ^1H NMR (400 MHz, CDCl_3): δ , ppm 5.58 (d, $J = 1.9$ Hz, 1H), 3.72 (dd, $J = 11.4$ Hz, 8.5 Hz, 1H), 3.53 (dd, $J = 11.8$ Hz, 8.3 Hz, 1H), 3.40 (ddt, $J = 8.6$ Hz, 6.0 Hz, 2.7 Hz, 2H), 3.16 (dd, $J = 11.4$, 6.5 Hz, 1H), 3.04-2.80 (m, 2H), 2.51-2.33 (m, 1H), 1.46 (s, 9H).



[00336] Step 4. tert-Butyl (3aS,6aR)-5-(4-(pyrimidin-2-yloxy)phenyl)-3,3a,4,6a-

5 tetrahydrocyclopenta[c] pyrrole-2(1H)-carboxylate (compound **58**). To a stirred suspension of (3aS,6aS)-tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **57** (0.28 g, 0.77 mmol), 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyrimidine **55** (0.30 g, 1.00 mmol), Pd(PPh₃)₄ (0.09 g, 0.08 mmol) in 1,4-dioxane (20 mL) was added a solution of Na₂CO₃ (0.5 g, 5.0 mmol) in H₂O (2.5 mL). The reaction mixture was stirred at 85 °C for 16 h. The reaction mass was allowed to cool to room temperature, filtered through Celite®, and concentrated *in vacuo*. The crude residue was diluted with water (50 mL), extracted with EtOAc (2 × 50 mL). The combined organic layers were passed through a phase separator and evaporated to dryness. The crude product was purified by chromatography (0-100% EtOAc/isohexane) to afford the

15 title compound **58** as a clear colourless oil (0.18 g, 60% yield). R_t 2.44 min (Method 1a) m/z 324 [M + H-^tBu]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.59 (d, J = 4.8 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.21-7.15 (m, 2H), 7.06 (t, J = 4.8 Hz, 1H), 6.03 (s, 1H), 3.72 (dd, J = 10.7 Hz, 8.4 Hz, 1H), 3.61-3.47 (m, 3H), 3.14-2.93 (m, 3H), 2.62 (d, J = 15.5 Hz, 1H), 1.47 (s, 9H).

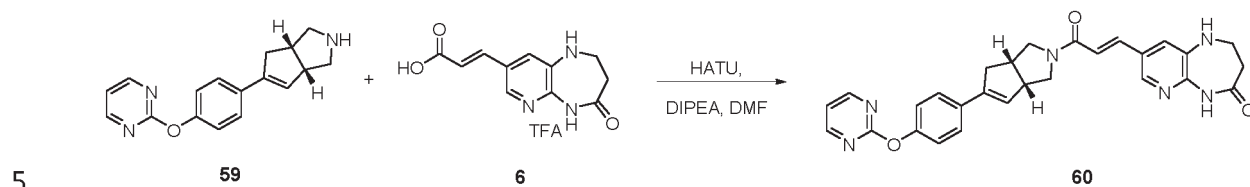
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[00337] Step 5. (3aR,6aS)-5-(4-(Pyrimidin-2-yloxy)phenyl)-1,2,3,3a,4,6a-

25 hexahydrocyclopenta[c]pyrrole (compound **59**). To a stirred solution of (3aR,6aS)-tert-butyl 5-(4-(pyrimidin-2-yloxy)phenyl)-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **58** (0.18 g, 0.47 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo. The resulting oil was taken up in MeOH (5 mL) and applied to an SCX column. The column was washed with

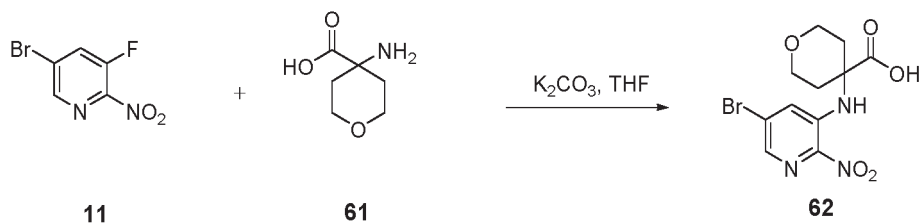
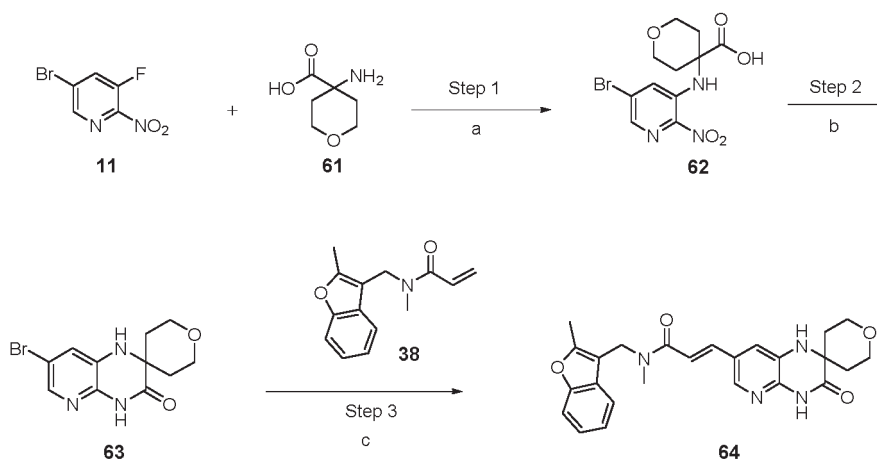
methanol (5 mL) and the product eluted with 10% methanolic ammonia (5 mL) to afford the title compound **59** as a colourless crystalline solid (0.09 g, 69%). R^t 0.92 min (Method 1a) m/z 280 $[M + H]^+$ (ES^+).



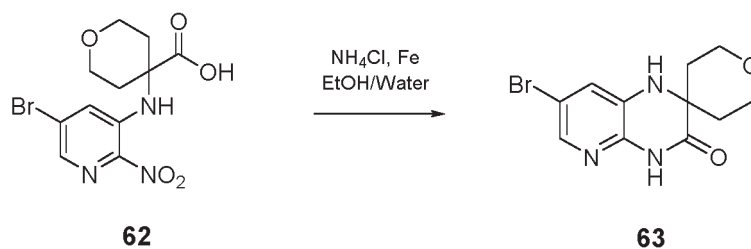
[00338] Step 6. 8-((E)-3-Oxo-3-((3aS,6aR)-5-(4-(pyrimidin-2-yloxy)phenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **60**). To a stirred solution of (3aS,6aR)-5-(4-(pyrimidin-2-yloxy)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole **59** (0.09 g, 0.31 mmol) in DMF (2 mL) was added (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (79 mg, 0.34 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.27 mL, 1.54 mmol). The reaction mixture was stirred at rt for 5 min and HATU (0.14 g, 0.37 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. H_2O (1 mL) was added and the reaction mixture sonicated. The solid was filtered and washed with H_2O (2 $\times$ 2 mL). The filtrate was discarded. The crude solid was purified by chromatography (0-10% MeOH/DCM) to afford the title compound **60** as a yellow solid (0.13 g, 79% yield). R^t 1.65 min (Method 1a) m/z 495 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.74 (d, J = 7.3 Hz, 1H), 8.64 (dd, J = 4.8 Hz, 1.5 Hz, 2H), 7.98 (dd, J = 9.3 Hz, 1.9 Hz, 1H), 7.58-7.51 (m, 2H), 7.38-7.30 (m, 2H), 7.27 (td, J = 4.8 Hz, 0.8 Hz, 1H), 7.21-7.14 (m, 2H), 6.87 (dd, J = 15.5 Hz, 9.4 Hz, 1H), 6.22-6.15 (m, 1H), 6.03 (d, J = 14.4 Hz, 1H), 4.06-3.77 (m, 2H), 3.72-3.50 (m, 2H), 3.45-3.39 (m, 2H), 3.24-2.84 (m, 3H), 2.69-2.55 (m, 3H).

Example 10. Preparation of (E)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)-3-(3'-oxo-2,3,3',4',5,6-hexahydro-1'H-spiro[pyran-4,2'-pyrido[2,3-b]pyrazin]-7'-yl)acrylamide (compound **64**).

[00339] General Synthetic Scheme.

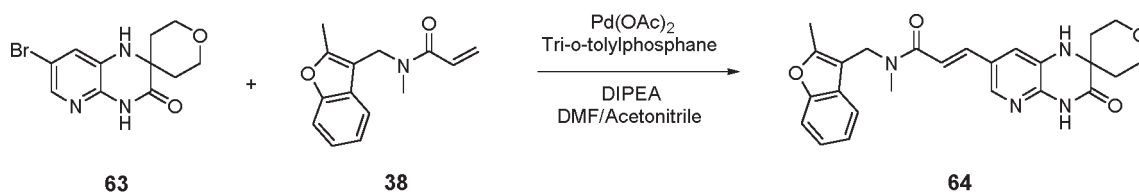


- 5 **[00340] Step 1.** 4-((5-Bromo-2-nitropyridin-3-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (compound **62**). 5-Bromo-3-fluoro-2-nitropyridine **11** (800 mg, 3.62 mmol, 1.0 eq) and 4-aminotetrahydro-2H-pyran-4-carboxylic acid **61** (Combi-Blocks) (735 mg, 5.06 mmol, 1.4 eq) were dissolved in THF (10 mL), then K_2CO_3 (1 g) was added. The resulting reaction mixture was heated to 90 °C overnight in a sealed tube. The UPLC analysis showed almost complete conversion of the SM with the formation of the expected product ($R_t = 1.11$ min; $ES^+ = 348.1$). The solvent was removed under vacuum and the residue was dissolved in a mixture of water/EtOAc. An aqueous phase was acidified with aq. 1M HCl to pH 1 and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to dryness. The resulting yellow solid was diluted with EtOAc. The precipitate, thus formed, was filtered off to afford the product **62** as a yellow solid with a purity of 99% (535 mg, 42% yield). The filtrate was concentrated to dryness to yield less pure product **62** as a brown solid with a purity of 93% (550 mg, 43.8% yield). Both batches were used in the next step without further purification. R_t 1.09 min (Method 1c) m/z 346.1/348.1 $[M + H]^+$ (ES^+) (isotop effect)



[00341] Step 2. 7'-Bromo-1',2,3,4',5,6-hexahydro-3'H-spiro[pyran-4,2'-pyrido[2,3-b]pyrazin]-3'-one (compound **63**).

To a stirred solution of 4-((5-bromo-2-nitropyridin-3-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **62** (535 mg, 1.5 mmol, 1.0 eq), NH₄Cl (165 mg, 3.1 mmol, 2.0 eq) and iron (170 mg, 3.1 mmol, 2.0 eq) was suspended in a mixture of EtOH/Water (1:1 v/v, 10 mL). The resulting suspension was heated to 80 °C for 1.5 h. The UPLC analysis showed formation of the product (Rt = 1.09 min; ES⁺ = 300.1) with complete conversion of the starting material. The reaction mass was diluted with EtOAc (and small amount of MeOH), filtered through 0.22 μm filter and washed with acetonitrile. The solution was concentrated to dryness and diluted with AcOEt and washed with water. The organic phase was dried (MgSO₄), filtered and concentrated to dryness. The residue was purified on silica gel using SNAP Ultra cartridge 25 g and DCM/MeOH 99:1 to 95:5 v/v as an eluent. Fractions containing the product were combined to afford the 7'-bromo-1',2,3,4',5,6-hexahydro-3'H-spiro[pyran-4,2'-pyrido[2,3-b]pyrazin]-3'-one **63** as a grey-green powder with a purity of 99% (220 mg, 48% yield). UPLC-MS m/z: 300.1 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.94 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 6.77 (s, 1H), 3.75-3.70 (m, 4H), 2.00-1.90 (m, 2H), 1.46 (d, J = 13.6 Hz, 2H).



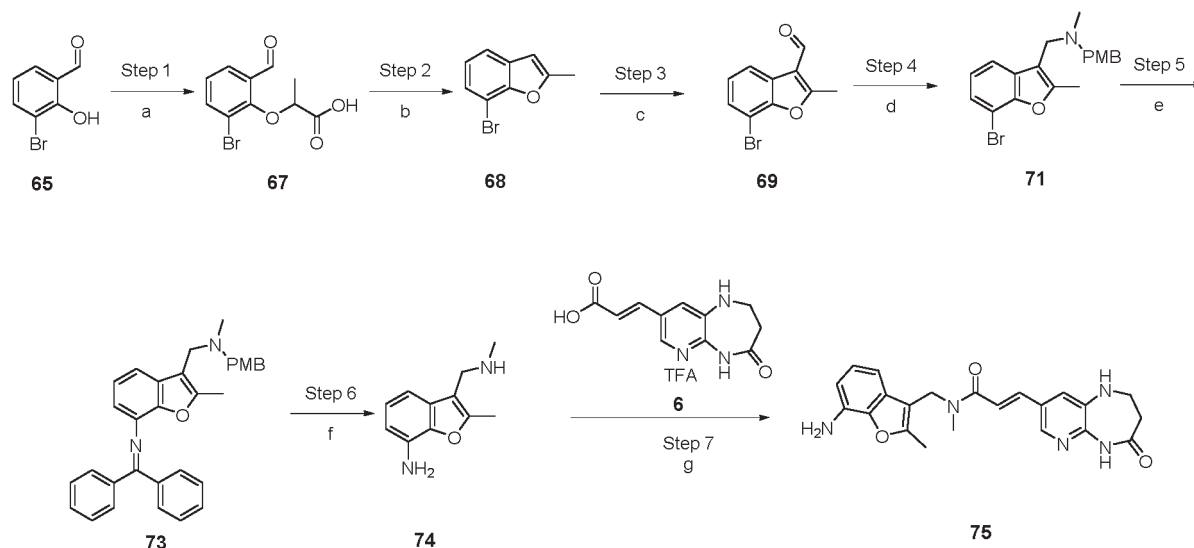
[00342] Step 3. (E)-N-Methyl-N-((2-methylbenzofuran-3-yl)methyl)-3-(3'-oxo-2,3,3',4',5,6-hexahydro-1'H-spiro[pyran-4,2'-pyrido[2,3-b]pyrazin]-7'-yl)acrylamide

(compound **64**). An oven dried vial was charged with 7'-bromo-1',2,3,4',5,6-hexahydro-3'H-spiro[pyran-4,2'-pyrido[2,3-b]pyrazin]-3'-one **63** (50 mg, 0.16 mmol), anhydrous DMF (0.9 mL) and acetonitrile (0.1 mL) were added. The reaction mixture was degassed with nitrogen for 5 min. Then, N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide **38** (58 mg, 0.25

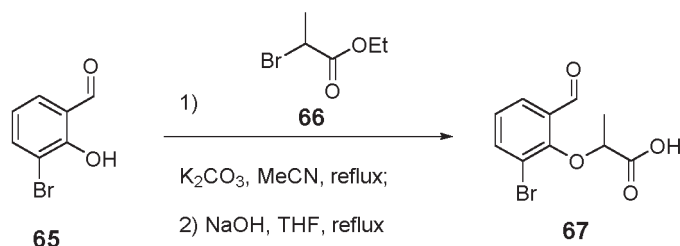
mmol) and DIPEA (109 μ L) were added and the mixture was degassed for the second time for 10 min. Finally, Pd(OAc)₂ (0.4 mg) and tri-*o*-tolylphosphane (1.0 mg) were added in one portion and the nitrogen was bubbled through the mixture for 1 min and the solution and heated at 100 °C overnight. The reaction was cooled to RT and filtered on a Celite[®] bed. The cake was rinsed with MeOH/AcOEt mixture and the filtrate concentrated under high vacuum to give the crude brown solid (250 mg) which was purified by Isolera (DCM 100% to DCM/AcOEt 0/100%). All fractions containing the product were evaporated to give the title molecule **64** as a white solid with a purity of 97% (46 mg, 0.10 mmol, 64% yield). R_t 1.55 min (Method 1c). UPLC-MS m/z: 447.1 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ , ppm 10.97 (s, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.52 (d, J = 15.4 Hz, 1H), 7.49-7.44 (m, 2H), 7.27-7.15 (m, 2H), 6.99 (d, J = 15.3 Hz, 1H), 6.63-6.56 (m, 1H), 4.89 (s, 2H), 4.75 (s, 2H), 3.79-3.66 (m, 4H), 3.05 (s, 2H), 2.83 (s, 1H), 1.99-1.89 (m, 2H), 1.46 (d, J = 14.3 Hz, 2H), 1.24 (s, 3H) (rotamers).

Example 11. Synthesis of (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **75**).

[00343] General Synthetic Scheme.



Reaction conditions: a) Ethyl 2-bromopropionate **66**, K₂CO₃, MeCN, reflux, then aq. NaOH, THF, reflux; b) NaOAc, Ac₂O, reflux; c) dichloro(methoxy)methane, SnCl₄ 1M in DCM, DCM, 0 °C to RT; d) 1-(4-methoxyphenyl)-N-methylmethanamine **70**, Na(OAc)₃BH, DCE; e) Pd₂(dba)₃, Xantphos, Benzophenone imine **72**, Cs₂CO₃, PhCH₃, 100 °C; f) 1-chloroethyl chloroformate, DCM, 0 °C - rt; g) HATU, DIPEA, DMF, rt.

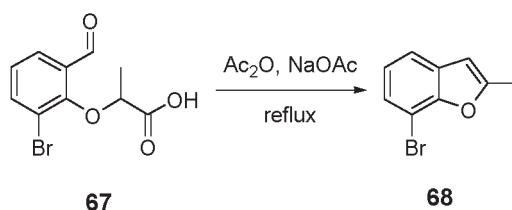


[00344] **Step 1.** 2-(2-Bromo-6-formylphenoxy)propanoic acid (compound **67**). K_2CO_3 (13.8 g, 99 mmol) was added in one portion to a stirred solution of 3-bromo-2-

hydroxybenzaldehyde **65** (10 g, 49.7 mmol) and ethyl 2-bromopropanoate **66** (5.9 mL, 45.2 mmol) in MeCN (80 mL) and the reaction was heated to reflux for 3 h. The reaction mixture was allowed to cool to RT, was filtered to remove K_2CO_3 and then concentrated *in vacuo*.

The resulting residue was dissolved in THF (50 mL) and a solution of NaOH (2M in H_2O , 57 mL, 113 mmol) was added. The mixture was heated to reflux for 2 h, then cooled to RT and concentrated in *vacuo*. The remaining aqueous material was acidified to pH 1 by dropwise addition of concentrated HCl and the product precipitated. The product was collected by filtration and dried by azeotroping with MeCN (2×50 mL) to give the desired product **67** as an orange oil which crystallised on standing to give an off-white solid (13.5 g, 99% yield). R^t 1.19 min (Method 2a) m/z 273/275 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $DMSO-d_6$): δ , ppm

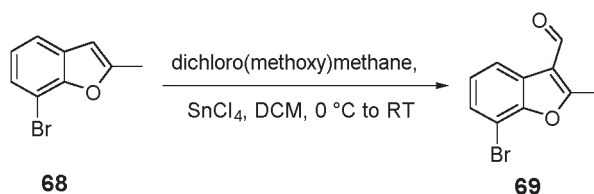
13.23 (s, 1H), 10.41 (d, $J = 0.8$ Hz, 1H), 7.97 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.74 (dd, $J = 7.7$ Hz, 1.7 Hz, 1H), 7.25 (td, $J = 7.8$ Hz, 0.9 Hz, 1H), 4.93 (q, $J = 6.8$ Hz, 1H), 1.60 (d, $J = 6.8$ Hz, 3H).



[00345] **Step 2.** 7-Bromo-2-methylbenzofuran (compound **68**). A mixture of 2-(2-bromo-6-formylphenoxy)propanoic acid **67** (13 g, 48 mmol) and sodium acetate (39 g, 48 mmol) in acetic anhydride (70 mL) was heated to reflux for 2 h. The mixture was allowed to cool to RT, then poured onto ice water (800 mL). The mixture was then extracted with DCM (3×300 mL) and the combined organic layers were washed with NaOH (2M aq, 2×200 mL) then brine (200 mL). The organic layer was dried by passing through a phase separator then concentrated in *vacuo*. The crude product was purified by column chromatography (5-10% EtOAc/isohexane) to give the desired product **68** as a colourless oil (6.72 g, 66% yield). R^t

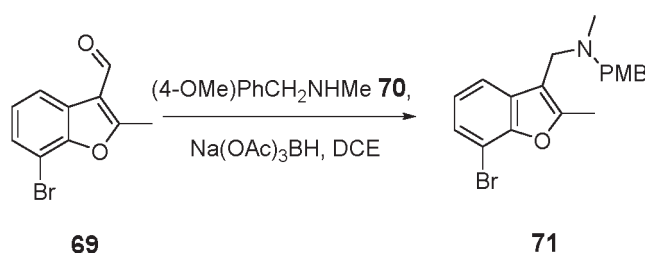
1.67 min (Method 2a) no m/z observed. ^1H NMR (400 MHz, DMSO- d_6): δ , ppm 7.53 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.43 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.71 (q, J = 1.1 Hz, 1H), 2.48 (d, J = 1.1 Hz, 3H).

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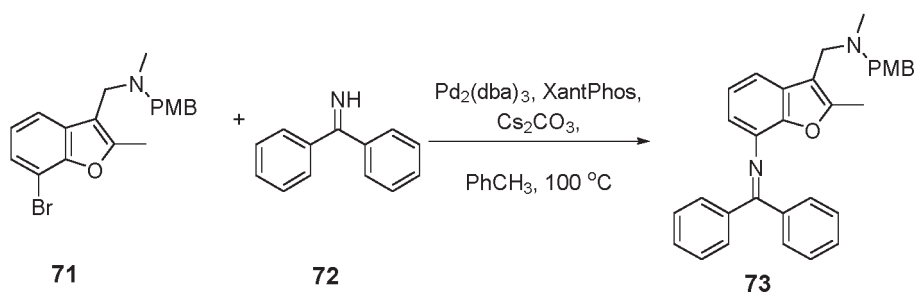
[00346] Step 3. 7-Bromo-2-methylbenzofuran-3-carbaldehyde (compound **69**). Tin (IV) chloride (38 mL, 38 mmol, 1M in DCM) was added dropwise over ~30 min to a stirred solution of dichloro(methoxy)methane (3.2 mL, 35 mmol) and 7-bromo-2-methylbenzofuran **68** (6.7 g, 32 mmol) in DCM (120 mL) at 0 °C. The reaction was allowed to return to RT over ~90 mins then poured into ice cold saturated sodium hydrogen carbonate solution (500 mL). The organic material was separated and the aqueous phase was extracted again with DCM (3 $\times$ 150 mL). The combined organic layers were washed with brine (200 mL) then dried by passing through a phase separation cartridge and concentrated in vacuo. The crude material was purified by recrystallisation from EtOAc/Hexane (1:1) to yield the desired product **69** as a pale yellow solid (4.5 g, 59% yield). R_t 1.48 min (Method 2a) m/z 239/241 [$M + H$] $^+$ (ES^+). ^1H NMR (400 MHz, DMSO- d_6): δ , ppm 10.20 (s, 1H), 7.98 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.59 (dd, J = 7.9 Hz, 1.1 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 2.84 (s, 3H).

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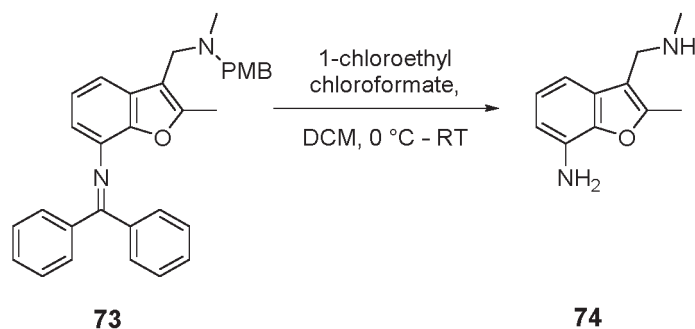


[00347] Step 4. 1-(7-Bromo-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine (compound **71**). Sodium triacetoxymethylborohydride (4.4 g, 21 mmol) was added in one portion to a stirred solution of 7-bromo-2-methylbenzofuran-3-carbaldehyde **69** (2 g, 8.37 mmol) and 1-(4-methoxyphenyl)-N-methylmethanamine **70** (1.3 mL, 8.37 mmol) in DCE (40 mL) at RT. The reaction mixture was stirred for ~ 16h then the solvent was concentrated in vacuo and the resulting residue was taken up in NaHCO₃ (100 mL, sat aq).

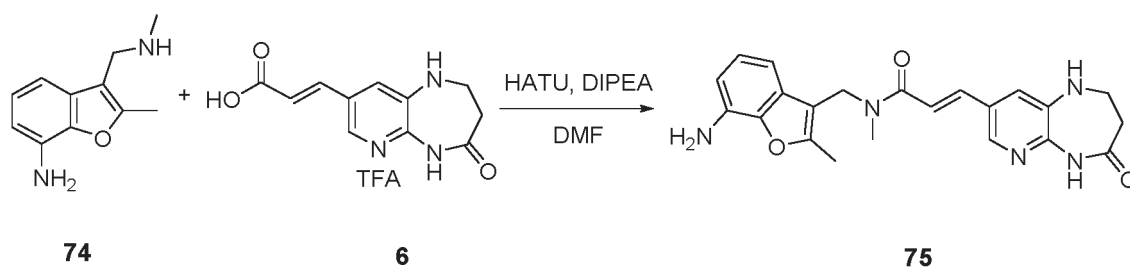
The aqueous material was extracted with DCM (3 × 100 mL) and the combined organic layers were washed with brine (100 mL) before being dried by passing through a phase separation cartridge. The crude material was purified by column chromatography (0-5% MeOH/DCM) to give the desired product **71** as a colourless oil (3.11 g, 92%). R^t 0.98 min (Method 2a) m/z 374/376 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 7.59 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.44 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 7.25-7.19 (m, 2H), 7.16 (t, J = 7.8 Hz, 1H), 6.92-6.84 (m, 2H), 3.73 (s, 3H), 3.52 (s, 2H), 3.44 (s, 2H), 2.45 (s, 3H), 2.04 (s, 3H).



[00348] Step 5. N-(Diphenylmethylene)-3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-amine (compound **73**). A 20 mL vial was evacuated and back filled with N_2 three times, then 1-(7-bromo-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **71** (0.3 g, 0.80 mmol), tris(dibenzylideneacetone)dipalladium(0) (75 mg, 0.08 mmol), cesium carbonate (0.52 g, 1.60 mmol) and Xantphos (70 mg, 0.12 mmol) were added and the vial was again evacuated and back filled with N_2 three times. Toluene (5 mL) and benzophenone imine **72** (0.14 mL, 0.80 mmol) were then added and the reaction mixture was heated to 100 °C and stirred for ~16 h. The reaction mixture was allowed to cool to rt, was filtered through Celite® and the cake was washed with DCM (100 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography (0-50% EtOAc/isohexane) to give the desired product **73** as a yellow oil (0.36 g, 70% yield). R^t 1.97 min (Method 1a); m/z 475 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6): δ , ppm 7.74-7.69 (m, 2H), 7.60-7.53 (m, 1H), 7.53-7.48 (m, 2H), 7.25-7.21 (m, 3H), 7.21-7.17 (m, 2H), 7.14-7.07 (m, 3H), 6.94 (t, J = 7.7 Hz, 1H), 6.91-6.85 (m, 2H), 6.48 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 3.73 (s, 3H), 3.43 (s, 2H), 3.38 (s, 2H), 2.32 (s, 3H), 1.99 (s, 3H).



[00349] Step 6. 2-Methyl-3-((methylamino)methyl)benzofuran-7-amine (compound **74**). 1-Chloroethyl chloroformate (0.12 ml, 1.14 mmol) was added dropwise to a stirred solution of *N*-(diphenylmethylene)-3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-amine **73** (0.36 g, 0.76 mmol) in DCM (5 mL) at 0 °C under N₂. The reaction was allowed to warm to room temperature and was stirred for ~16 h. The reaction mixture was concentrated *in vacuo* then taken up in MeOH (15 mL) and heated to reflux for 1h. The reaction mixture was allowed to cool to RT then was concentrated *in vacuo* and purified by column chromatography (0-10% MeOH (0.7M NH₃)/DCM) to give the desired product **74** as a yellow oil (78 mg, 46% yield). R_t 0.77 min (Method 1b); m/z 191 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 6.86-6.83 (m, 1H), 6.78 (dd, J = 7.7 Hz, 1.2 Hz, 1H), 6.46 (dd, J = 7.6, 1.2 Hz, 1H), 5.09 (s, 2H), 3.65 (s, 2H), 2.39 (s, 3H), 2.25 (s, 3H). Amine proton not assigned.

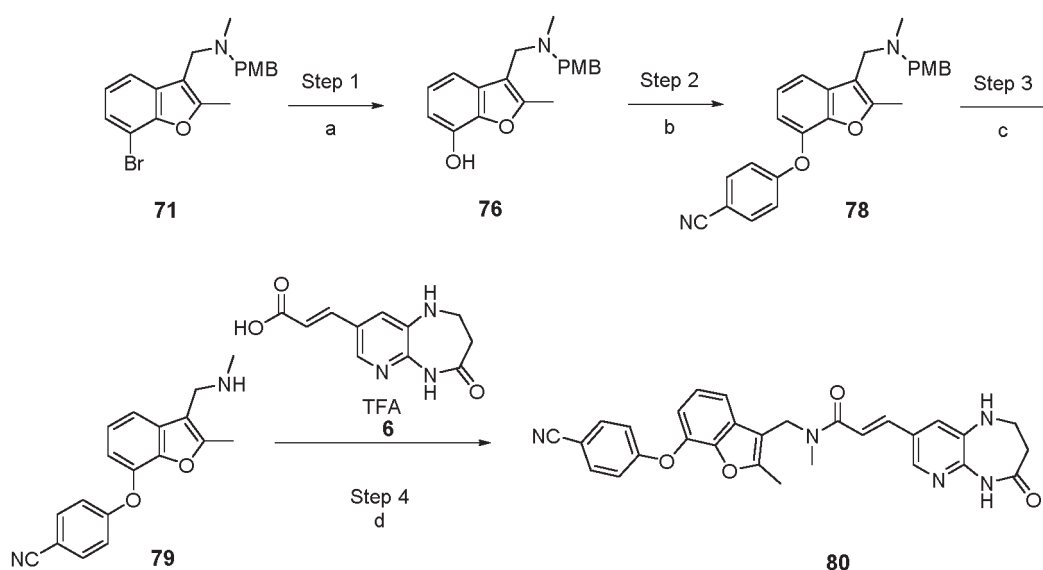


[00350] Step 7. (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **75**). DIPEA (0.2 mL, 1.15 mmol) was added dropwise to a stirred solution of 2-methyl-3-((methylamino)methyl)benzofuran-7-amine **74** (78 mg, 0.41 mmol) and (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (50 mg, 0.14 mmol) in DMF (2 mL) at rt. The reaction was stirred for 10 mins then HATU (70 mg, 0.18 mmol) was added and the reaction was stirred for 2h. The reaction mixture was diluted with

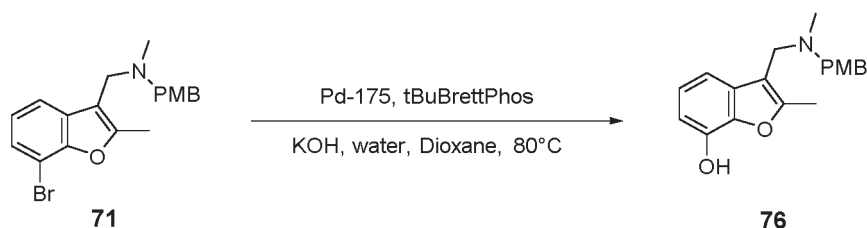
water (10 ml) and the precipitate collected by filtration. The crude material was purified by column chromatography (0-4% MeOH/DCM) to give the desired product **75** as a pale yellow solid (18 mg, 31% yield). R^t 1.30 min (Method 1a); m/z 406 $[M + H]^+$ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363K): δ , ppm 9.13 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 15.4 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 15.4 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 6.53 (dd, J = 7.7, 1.1 Hz, 1H), 5.79 (s, 1H), 4.86 (s, 2H), 4.71 (s, 2H), 3.46-3.40 (m, 2H), 2.98 (s, 3H), 2.68-2.61 (m, 2H), 2.46 (s, 3H).

Example 12. Synthesis of (E)-N-((7-(4-cyanophenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **80**).

[00351] General Synthetic Scheme

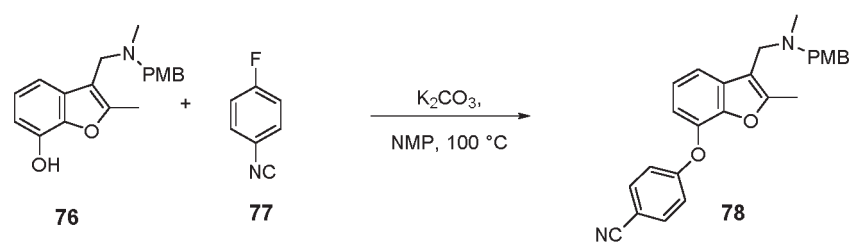


Reaction conditions: a) Pd-175, tBuBrettPhos, KOH, H₂O, dioxane, 80 °C; b) 4-Fluorobenzonitrile **77**, K₂CO₃, NMP, 100 °C; c) 1-chloroethyl chloroformate, DCM, 0 °C to RT; d) HATU, DIPEA, DMF

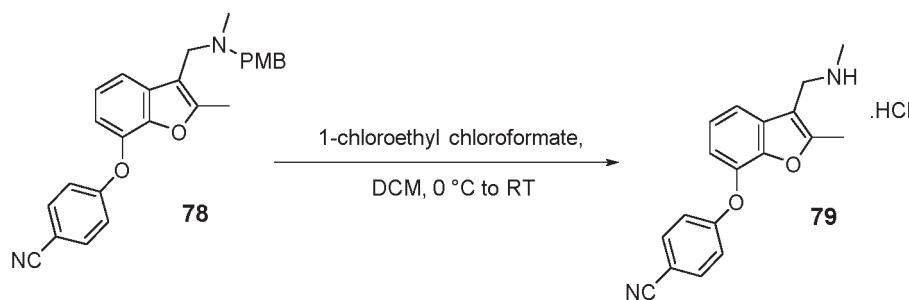


[00352] **Step 1.** 3-(((4-Methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-ol (compound **76**). A 100 mL round bottom flask was charged with 1-(7-bromo-2-

methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **71** (2.7 g, 7.21 mmol), Pd-175 (Johnson Matthey) (0.11 g, 0.14 mmol), tBuBrettPhos (0.07 g, 0.14 mmol) and potassium hydroxide (1.21 g, 21.6 mmol). It was then evacuated and backfilled with nitrogen three times and subsequently were added degassed 1,4-dioxane (15 mL) and degassed water (2.6 mL). The resulting mixture was heated to 80 °C and stirred for 2h. The mixture was cooled to rt and diluted with EtOAc (20 mL), then acidified with 1M HCl (20 mL) and stirred for 5 min until all the solid dissolved. The reaction mixture was neutralized with NaHCO₃ (25 mL, sat. aq.) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organic phases were washed with brine (25 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (0-5% MeOH/DCM) to afford the title compound **76** as a beige solid (1.80 g, 80%). R^t 1.12 min (Method 1a) m/z 312 [M + H]⁺ (ES⁺).

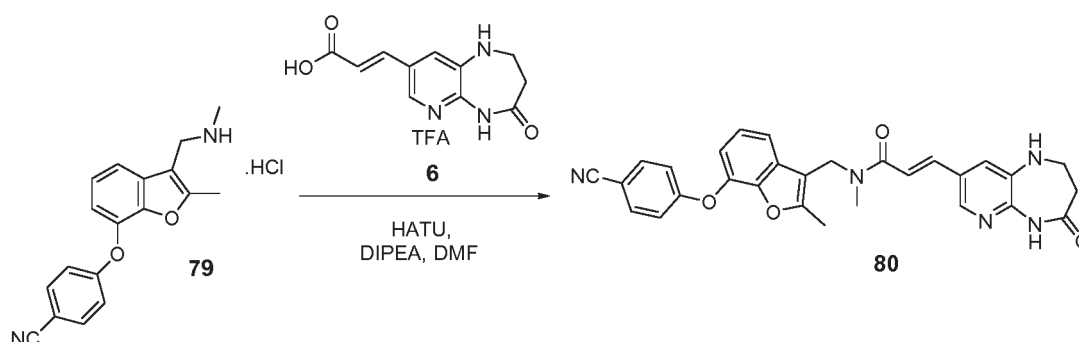


[00353] Step 2. 4-((3-((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-yl)oxy)benzonitrile (compound **78**). A mixture of 3-((4-methoxybenzyl)(methyl)amino)methyl-2-methylbenzofuran-7-ol **76** (150 mg, 0.48 mmol), 4-fluorobenzonitrile **77** (70 mg, 0.58 mmol) and potassium carbonate (133 mg, 0.96 mmol) in a solvent of N-methyl-2-pyrrolidone (6 mL) was heated at 100 °C for 12 h. The reaction mixture was cooled to RT and the mixture poured onto water (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by chromatography (1% MeOH/DCM) to afford the title compound **78** as a colourless oil (170 mg, 86%). R^t 1.65 min (Method 1a) m/z 413 [M + H]⁺ (ES⁺).



[00354] Step 3. 4-((2-Methyl-3-((methylamino)methyl)benzofuran-7-

5 yl)oxy)benzonitrile hydrochloride (compound **79**). To an ice cooled solution of 4-((3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-yl)oxy)benzonitrile **78** (185 mg, 0.45 mmol) in DCM (2 mL) was added 1-chloroethyl carbonochloridate (0.10 mL, 0.90 mmol) at 0°C. The reaction mixture was warmed to RT and stirred for 1h, and then concentrated *in vacuo*. The residue was dissolved in methanol (5 mL) and heated under
10 reflux for 1 h. The reaction mixture was evaporated to dryness and triturated with TBME (10 mL) to afford the title compound **79** as a yellow solid (185 mg, 47%). R^t 1.31 min (Method 1a) m/z 293 $[M + H]^+$ (ES^+).



[00355] Step 4. (E)-N-((7-(4-Cyanophenoxy)-2-methylbenzofuran-3-yl)methyl)-N-

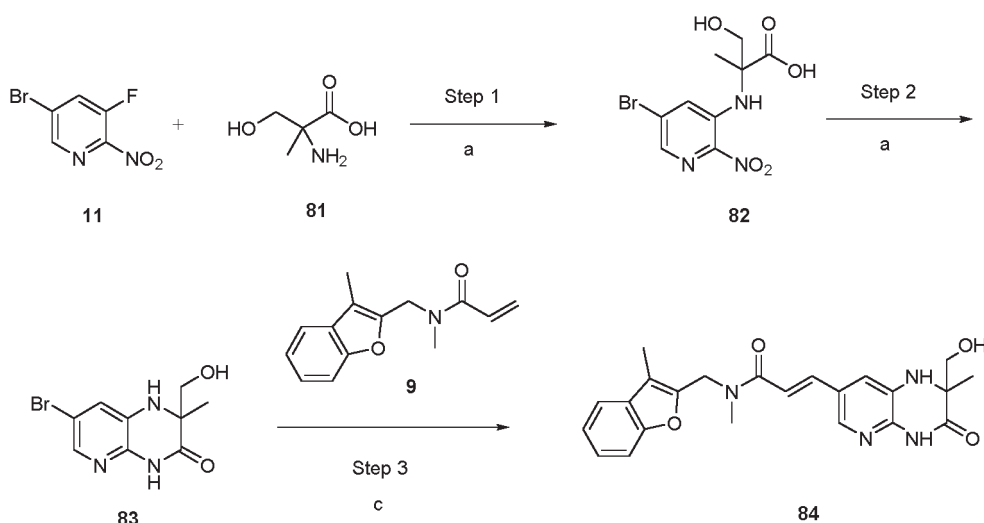
methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **80**). A solution of 4-((2-methyl-3-((methylamino)methyl)benzofuran-7-yl)oxy)benzonitrile hydrochloride **79** (69 mg, 0.20 mmol) in DMF (4 mL) was treated with (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (80 mg, 0.23 mmol), Hunig's Base (180 μ L, 1.05 mmol) and HATU (96 mg, 0.25 mmol) and then stirred at rt for 1 h. The reaction mixture was quenched with water (10 mL) and the solid was collected by filtration and dried. The crude product was purified by column chromatography (0-10% MeOH/DCM) to afford the title compound **80** as a pale yellow solid
20 (23mg, 21% yield). R^t 2.01 min (Method 1a) m/z 508 $[M + H]^+$ (ES^+). 1H NMR (500 MHz,
25

DMSO-d₆, 363 K): δ , ppm 9.15 (s, 1H), 7.99 (d, J = 1.9 Hz, 1H), 7.83-7.77 (m, 2H), 7.50-7.44 (m, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.15-7.06 (m, 3H), 7.06-7.01 (m, 1H), 5.81 (s, 1H), 4.79 (s, 2H), 3.47-3.40 (m, 2H), 3.04 (s, 3H), 2.69-2.62 (m, 2H), 2.46 (s, 3H).

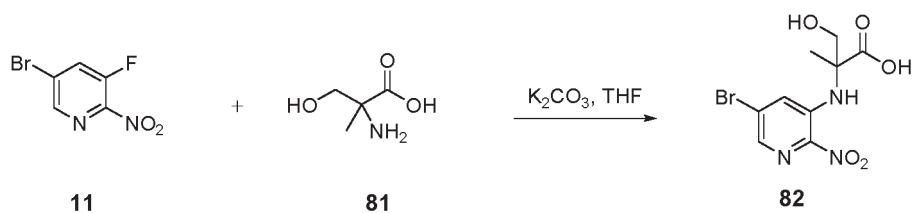
- 5 **Example 13.** Synthesis of (E)-3-(2-(hydroxymethyl)-2-methyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **84**).

[00356] General Synthetic Scheme.

10



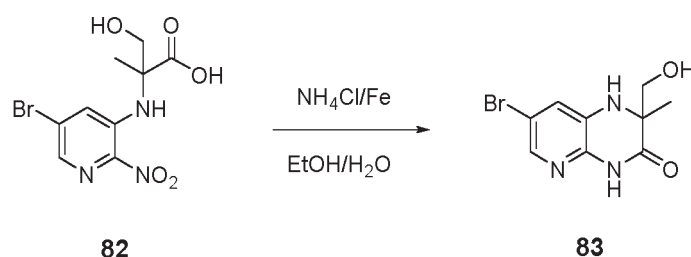
Reaction conditions: a) K₂CO₃, THF; b) NH₄Cl, Fe, EtOH/Water; c) Pd(OAc)₂, Tri-o-tolylphosphane, DIPEA in DMF/ACN



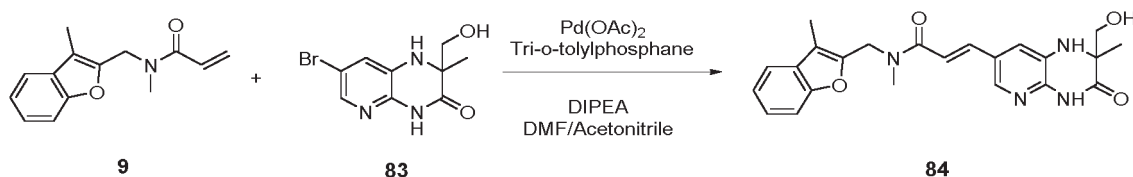
15

[00357] **Step 1.** 2-((5-Bromo-2-nitropyridin-3-yl)amino)-3-hydroxy-2-methylpropanoic acid (compound **82**). 5-Bromo-3-fluoro-2-nitropyridine **11** (800 mg, 3.62 mmol, 1.0 eq) and 2-amino-3-hydroxy-2-methylpropanoic acid **81** (Sigma-Aldrich) (736 mg, 5.07 mmol, 1.4 eq) were dissolved in THF (16.0 mL), then K₂CO₃ (999 mg) was added. The resulting reaction mixture was heated to 90 °C overnight in a sealed tube. The UPLC-MS analysis showed almost full conversion of the SM with formation of a good product (R_t = 0.94 min; ES⁺ = 322.0). The solvent was removed under vacuum. The residue was dissolved in a mixture of

water and EtOAc. An aq. layer was acidified with 1M HCl to pH 1-2. The phases were separated and the aq. phase was re-extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated to dryness. The crude product (800 mg) was purified by Isolera system using AcOEt/MeOH (100% to 80/20 v/v) to afford the title compound **82** as an orange solid with a purity of 60% (320 mg, 17% yield). The second batch with a purity of 80% was also isolated (40 mg, 3.45% yield). R^t 0.94 min (Method 1c). UPLC-MS m/z: 322.0 [M + H]⁺ (ES⁺).



[00358] Step 2. 7-Bromo-2-(hydroxymethyl)-2-methyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one (compound **83**). To a stirred solution of 2-((5-bromo-2-nitropyridin-3-yl)amino)-3-hydroxy-2-methylpropanoic acid **82** (40 mg, 0.124 mmol, 1.0 eq), NH₄Cl (13.4 mg, 0.25 mmol, 2.0 eq) and iron (14 mg, 0.25 mmol, 2.0 eq) was suspended in a mixture of EtOH/Water (1:1 v/v, 2 mL). The resulting suspension was heated to 80 °C for 1.5 h. The UPLC analysis showed the formation of the product (R_t = 0.89 min; ES⁺ = 272.1) with complete conversion of the starting material. The reaction was diluted with EtOAc/MeOH, filtered through 0.22 μm filter and the filter was rinsed with acetonitrile. The resulting solution was evaporated to dryness, then diluted with AcOEt, washed with water, dried (MgSO₄) and concentrated. The crude product **83** (37 mg, 0.136 mmol) as a red solid with a purity of 60% was isolated. The resulting material was used in the next step without further purification. R^t 0.89 min (Method 1c). LCMS: m/z: 272.1 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.80 (s, 1H), 7.52 (s, 1H), 7.07 (s, 1H), 6.47 (s, 1H), 5.12 (t, J = 5.6 Hz, 1H), 3.58 (dd, J = 6.1 Hz, 10.4 Hz, 1H), 3.29 (s, 1H), 1.25 (s, 3H).



[00359] **Step 3.** (E)-3-(2-(Hydroxymethyl)-2-methyl-3-oxo-1,2,3,4-

tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-

yl)methyl)acrylamide (compound **84**). An oven dried vial was charged with 7-bromo-2-

(hydroxymethyl)-2-methyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one **83** (37 mg, 0.13

5 mmol), anhydrous DMF (0.9 mL) and ACN (0.1 mL) were added and the reaction mixture was

degassed with nitrogen for 5 min. Then, N-methyl-N-((2-methylbenzofuran-3-

yl)methyl)acrylamide **9** (47 mg, 0.204 mmol) and DIPEA (93 μ L) were added and the mixture

was degassed for the second time for 10 min. Finally, Pd(OAc)₂ (0.3 mg) and tri-o-

tolylphosphane (0.83 mg) were added in one portion and the nitrogen was bubbled through

10 the mixture for 1 min and the solution was heated at 100 °C overnight. The reaction mass

was cooled to RT, filtered on a 0.22 μ M filter, washed with MeOH/AcOEt mixture and

concentrated under high vacuum. The crude brownish oil was purified by Isolera (n-

Heptane/AcOEt 7/3 $\text{v/v} \rightarrow 100\% \text{ AcOEt} \rightarrow \text{AcOEt/MeOH } 8/2 \text{ v/v}$) and then re-purified 2 more

times with DCM/MeOH (100% to 95/5 v/v). The targeted molecule **84** as a beige solid with a

15 purity of 94% was isolated (4.9 mg, 8.6% yield). R^t 1.47 min (Method 1c). LCMS: m/z : 421.3

[M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ , ppm 10.85 (s, 1H), 7.80 (s, 1H), 7.58 (d, J = 7.4

Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 16.1 Hz, 1H), 7.32-7.22 (m, 4H), 6.99 (d, J = 14.4

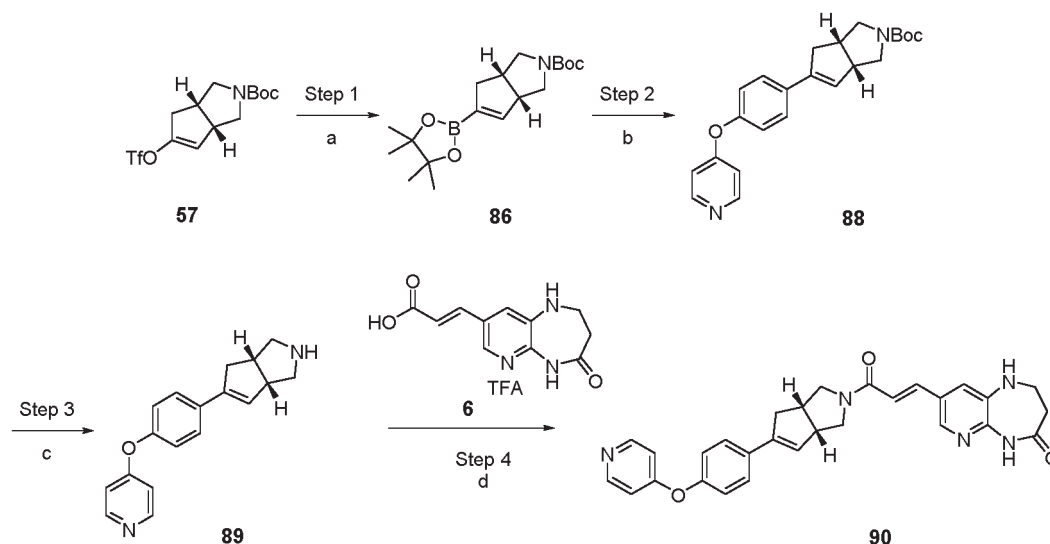
Hz, 1H), 6.20 (d, J = 13.1 Hz, 1H), 5.06 (t, J = 5.5 Hz, 1H), 4.95 (s, 2H), 4.80 (s, 2H), 3.62-3.53

(m, 1H), 2.96 (s, 1H), 2.28 (s, 3H), 1.25 (s, 6H) (rotamers).

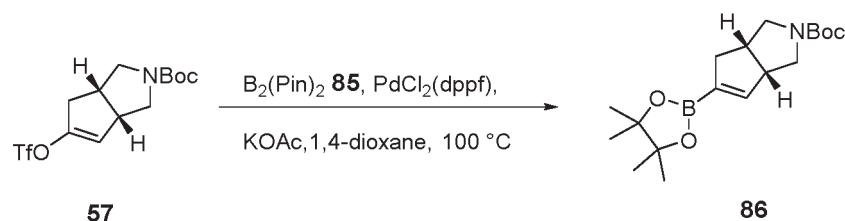
20

Example 14. Synthesis of 8-((E)-3-oxo-3-((3rS,6rR)-5-(4-(pyridin-4-yloxy)phenyl)-3,3r,4,6r-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **90**).

25 [00360] General Synthetic Scheme.



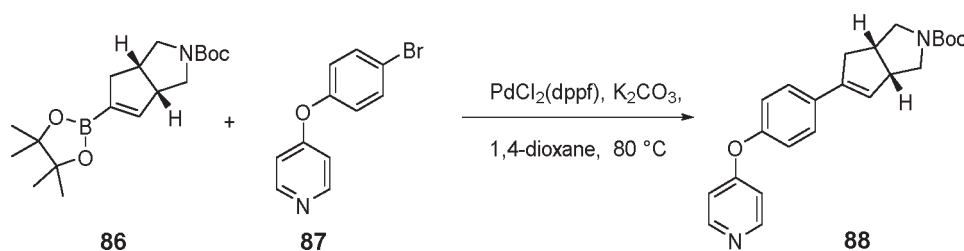
Reaction conditions: a) $B_2(\text{pin})_2$ **85**, KOAc, $\text{PdCl}_2(\text{dppf})$, 1,4-dioxane, 100 °C; b) 4-(4-bromophenoxy)pyridine **87**, K_2CO_3 , H_2O , $\text{PdCl}_2(\text{dppf})$, 1,4-dioxane, 80 °C; c) TFA, DCM; d) HATU, DIPEA, DMF



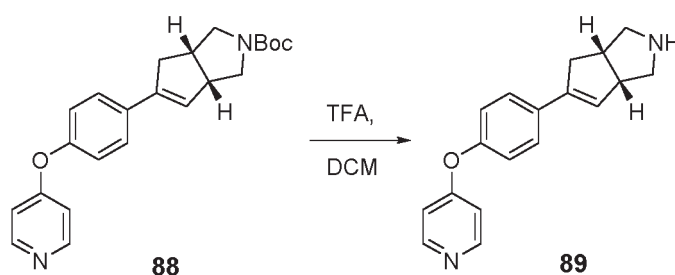
5

[00361] Step 1. *tert*-Butyl(3*r*,6*r*S)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3*r*,4,6*r*-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (compound **86**). A mixture of *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,3*r*,6,6*r*-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate **57** (2 g, 5.6 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) **85** (2.42 g, 9.5 mmol), potassium acetate (1.65 g, 16.8 mmol) and $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (0.46 g, 0.6 mmol) in 1,4-dioxane (20 mL) was degassed with nitrogen and then heated at 100 °C overnight. The mixture was diluted with water (30 mL), extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO_4 , filtered and evaporated to dryness. The crude product was purified by column chromatography (0-50% EtOAc/isoohexane) to afford the title compound **86** as a colourless oil (1.97 g, 94%). ^1H NMR (400 MHz, CDCl_3): δ , ppm 6.35 (q, J = 2.0 Hz, 1H), 3.66-3.61 (m, 1H), 3.54-3.44 (m, 2H), 3.39 (ddt, J = 8.0 Hz, 5.7 Hz, 2.5 Hz, 1H), 2.97 (dd, J = 10.9 Hz, 7.2 Hz, 1H), 2.89 (ddd, J = 9.0 Hz, 7.3 Hz, 1.6 Hz, 1H), 2.65 (ddt, J = 16.5 Hz, 7.2 Hz, 2.6 Hz, 1H), 2.38 (dq, J = 16.5 Hz, 1.8 Hz, 1H), 1.46 (s, 9H), 1.29 (s, 12H), 1.28 (s, 3H).

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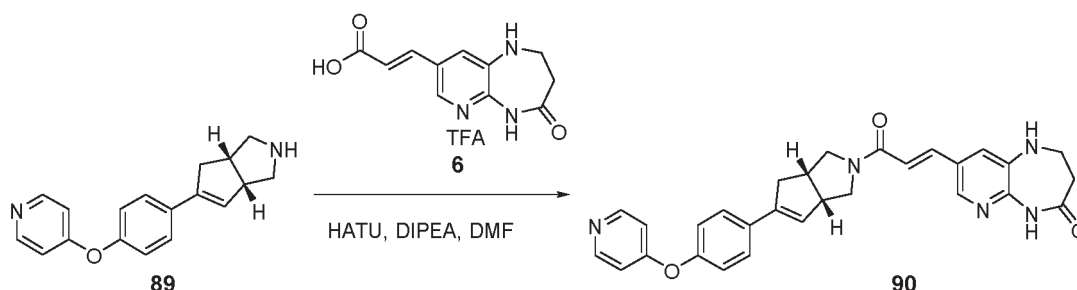
[00362] Step 2. tert-Butyl (3rR,6rS)-5-(4-(pyridin-4-yloxy)phenyl)-3,3r,4,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (compound **88**). A mixture of 4-(4-bromophenoxy)pyridine **87** (Enamine) (149 mg, 0.60 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **86** (200 mg, 0.6 mmol), K₂CO₃ (247 mg, 1.8 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (49 mg, 0.06 mmol) in 1,4-dioxane (3 mL) was degassed with nitrogen and then heated at 80 °C for 5 h. The mixture was diluted with water (30 mL), extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by chromatography (0-5% MeOH/DCM) to afford the title compound **88** as a brown oil (193 mg, 77%). R_t 2.49 min (Method 1b); m/z 379 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.47 (d, J = 5.6 Hz, 2H), 7.53-7.46 (m, 2H), 7.09-7.04 (m, 2H), 6.90-6.81 (m, 2H), 6.03 (s, 1H), 3.71-3.45 (m, 4H), 3.14-2.93 (m, 3H), 2.60 (s, 2H), 1.46 (s, 9H).



[00363] Step 3. (3rR,6rS)-5-(4-(Pyridin-4-yloxy)phenyl)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrole (compound **89**). Trifluoroacetic acid (1.5 mL) was added dropwise to a stirred solution of tert-butyl 5-(4-(pyridin-4-yloxy)phenyl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **88** (193 mg, 0.5 mmol) in DCM (1.5 mL) at RT. The reaction mixture was stirred for 2 h then the solvent was concentrated *in vacuo* and the resulting residue was taken up in methanol (30 mL) and applied to an SCX column. The column was washed with methanol (50 mL) and the product eluted with 10% methanolic ammonia. The mixture was then evaporated affording the title compound **89** as a yellow oil

(115 mg, 73%). R^t 1.36 min (Method 1b); m/z 279 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $CDCl_3$): δ , ppm 8.48-8.41 (m, 2H), 7.44 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.3$ Hz, 2H), 6.87-6.76 (m, 2H), 5.95-5.94 (m, 1H), 3.78 (s, 2H), 3.51 (d, $J = 7.4$ Hz, 1H), 3.10-2.80 (m, 5H), 2.51 (dd, $J = 15.6$, 2.6 Hz, 1H).

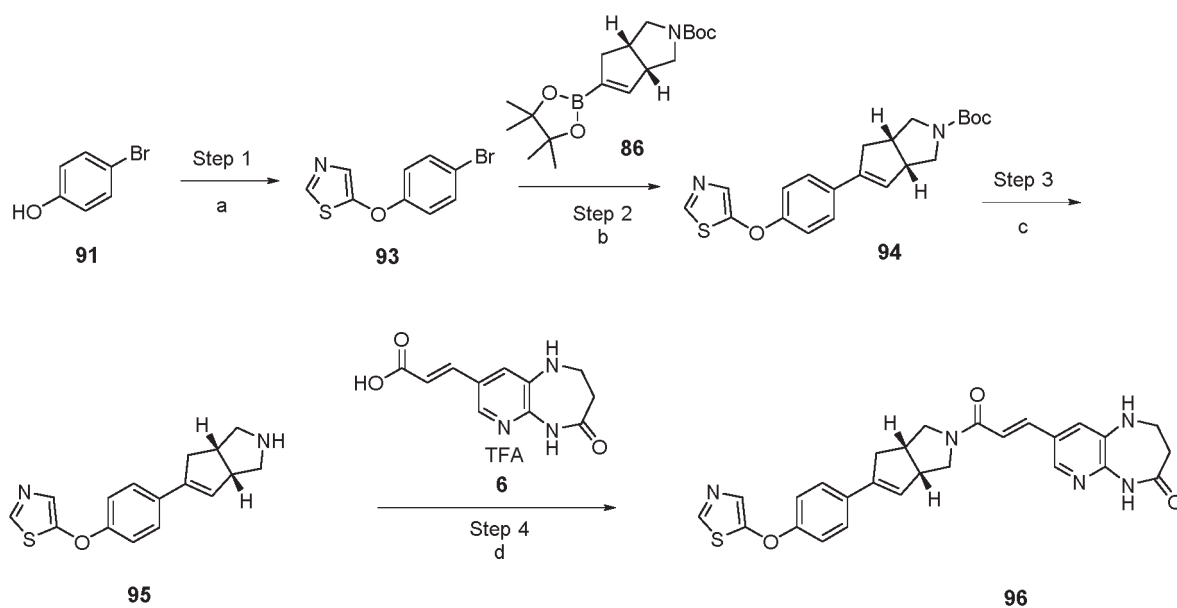
5



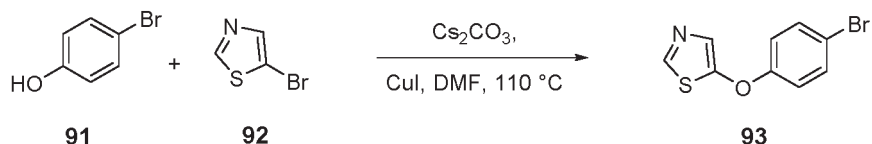
[00364] Step 4. 8-((*E*)-3-Oxo-3-((3*rS*,6*rR*)-5-(4-(pyridin-4-yloxy)phenyl)-3,3*r*,4,6*r*-tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4*H*-pyrido[2,3-
 10 b][1,4]diazepin-4-one (compound **90**). A suspension of (3*rS*,6*rR*)-5-(4-(pyridin-4-yloxy)phenyl)-1,2,3,3*r*,4,6*r*-hexahydrocyclopenta[*c*]pyrrole **89** (115 mg, 0.4 mmol), (*E*)-3-(4-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (136 mg, 0.4 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (0.28 mL, 1.6 mmol) in DMF (2 mL) was stirred for 10 min. HATU (157 mg, 0.4 mmol) was added in one portion and the reaction
 15 mixture was left to stir at RT for 1 h. The mixture was diluted with water (10 mL) and the precipitate was collected by filtration. The crude product was purified by column chromatography (0-5% MeOH/DCM) to afford the title compound **90** as a yellow solid (92 mg, 45% yield). R^t 1.74min (Method 1b); m/z 494 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $DMSO-d_6$): δ , ppm 9.73 (d, $J = 6.6$ Hz, 1H), 8.47-8.43 (m, 2H), 7.98 (dd, $J = 8.2$ Hz, 2.0 Hz, 1H), 7.61-7.56 (m, 2H), 7.38-7.30 (m, 2H), 7.18-7.13 (m, 2H), 6.93-6.83 (m, 3H), 6.22 (d, $J = 3.6$ Hz, 1H),
 20 6.05-5.98 (m, 1H), 4.00 (t, $J = 9.9$ Hz, 1H), 3.88-3.78 (m, 1H), 3.70 (m, 1H), 3.65-3.52 (m, 1H), 3.45-3.39 (m, 2H), 3.21-3.13 (m, 1H), 3.04-2.88 (m, 2H), 2.68-2.57 (m, 3H).

Example 15. Synthesis of 8-((*E*)-3-oxo-3-((3*rS*,6*rR*)-5-(4-(thiazol-5-yloxy)phenyl)-3,3*r*,4,6*r*-tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4*H*-pyrido[2,3-
 25 b][1,4]diazepin-4-one (compound **96**).

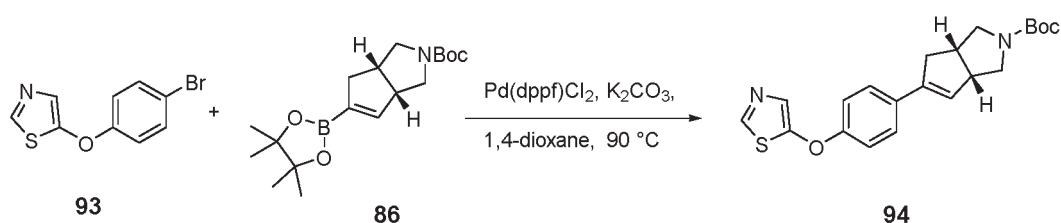
[00365] General Synthetic Scheme.



Reaction conditions: a) 5-Bromothiazole **92**, Cs₂CO₃, CuI, DMF, 110 °C; b) Pd(dppf)Cl₂, K₂CO₃, 1,4-dioxane, 90 °C; c) TFA, DCM; d) HATU, DIPEA, DMF

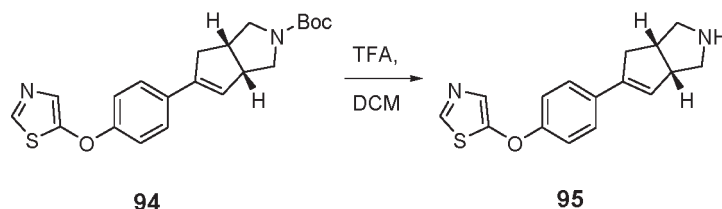


- 5 **[00366]** **Step 1.** 5-(4-Bromophenoxy)thiazole (compound **93**). To a stirred solution of 5-bromothiazole **92** (Fluorochem) (0.2 g, 1.2 mmol) in DMF (6 mL) was added 4-bromophenol **91** (0.25 g, 1.5 mmol), copper(I) iodide (0.23 g, 1.2 mmol), followed by cesium carbonate (1.19 g, 3.7 mmol). The reaction mixture was stirred at 110 °C for 5 h and allowed to cool to room temperature. The reaction mixture was partitioned between water (5 mL)
- 10 and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound **93** as a white solid (0.26 g, 84%). R_t 2.19 min (Method 1a) m/z 256/258 [M + H]⁺ (ES⁺).

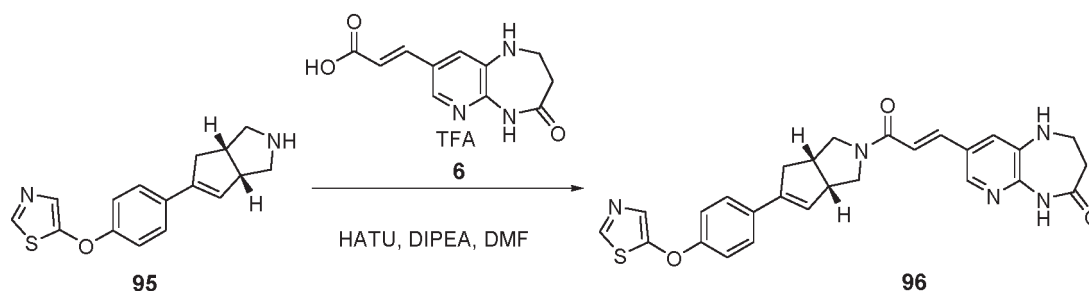


- [00367]** **Step 2.** tert-Butyl (3R,6R)-5-(4-(thiazol-5-yloxy)phenyl)-3,3,4,6-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (compound **94**). A mixture of 5-(4-bromophenoxy)thiazole **93** (0.17 g, 0.7 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **86** (0.22 g, 0.7 mmol), K₂CO₃ (0.28 g, 2.0 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (0.05 g, 0.07 mmol) in 1,4-dioxane (4 mL) was degassed with nitrogen and then stirred at 90 °C overnight. The reaction mixture was allowed to cool to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (0-50% EtOAc/isohehexane) to afford the title compound **94** as a thick colourless oil (0.06 g, 23% yield). R^t 2.68 min (Method 1a) m/z 329 [M + H-tBu]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 8.77 (s, 1H), 7.63 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.13 (s, 1H), 3.62-3.53 (m, 1H), 3.49-3.35 (m, 3H), 3.11-2.81 (m, 4H), 1.37 (s, 9H).



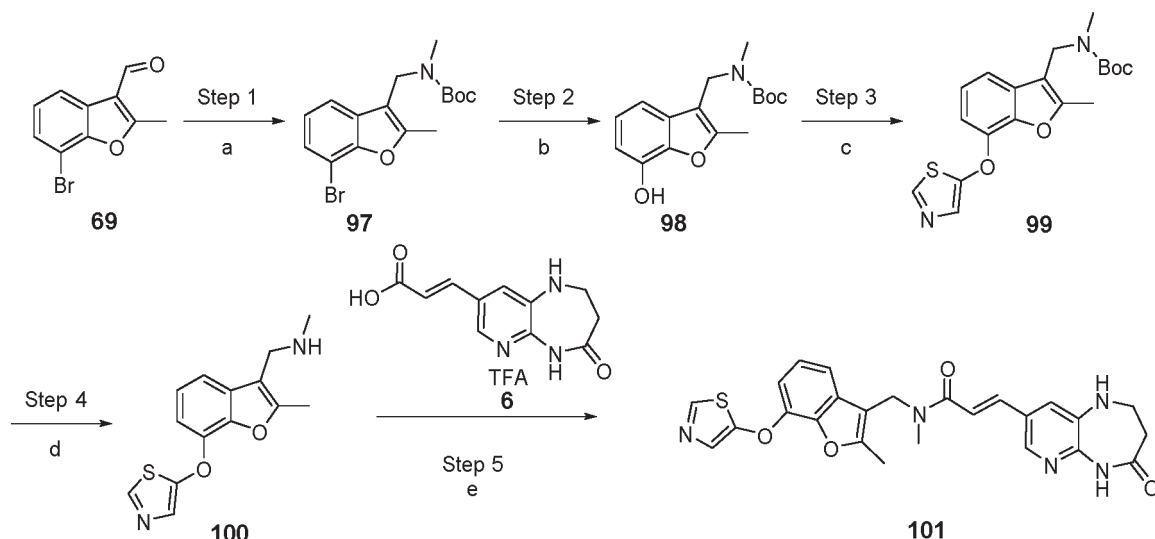
[00368] Step 3. 5-(4-((3rS,6rR)-1,2,3,3r,4,6r-Hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)thiazole (compound **95**). To a stirred solution of (3rS,6rR)-tert-butyl 5-(4-(thiazol-5-yloxy)phenyl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **94** (0.06 g, 0.2 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*. The resulting oil was taken up in MeOH (5 mL) and applied to an SCX column. The column was washed with methanol (5 mL) and the product eluted with 10% methanolic ammonia (5 mL) to afford the title compound **95** as a colourless crystalline solid (34 mg, 74 %). The crude product was used in the next step without further purification. R^t 1.17 min (Method 1a) m/z 285 [M + H]⁺ (ES⁺).



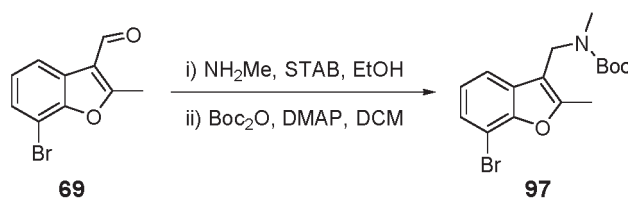
[00369] Step 4. 8-((E)-3-Oxo-3-((3aS,6aR)-5-(4-(thiazol-5-yloxy)phenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **96**). To a stirred solution of 5-(4-((3rS,6rR)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)thiazole **95** (34 mg, 0.1 mmol) in DMF (2 mL) was added (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (31 mg, 0.13 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.1 mL, 0.6 mmol). The reaction mixture was stirred at RT for 5 min and HATU (55 mg, 0.1 mmol) was added. The resulting mixture was stirred for 3 h. Water (1 mL) was added and the reaction mixture sonicated. The solid was filtered and washed with H₂O (2 × 2 mL). The filtrate was discarded. The crude solid was purified by column chromatography (0-10% MeOH/DCM) to afford the title compound **96** as a yellow solid (25 mg, 40%). R^t 1.85 min (Method 1a) m/z 500 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.74 (d, J = 7.3 Hz, 1H), 8.76 (d, J = 1.3 Hz, 1H), 7.98 (dd, J = 9.1 Hz, 1.9 Hz, 1H), 7.63 (t, J = 1.2 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.39-7.28 (m, 2H), 7.20-7.09 (m, 2H), 6.86 (dd, J = 15.5 Hz, 9.6 Hz, 1H), 6.17 (s, 1H), 6.02 (d, J = 14.0 Hz, 1H), 4.02-3.78 (m, 2H), 3.68 (d, J = 12.1 Hz, 1H), 3.64-3.49 (m, 2H), 3.45-3.35 (m, 2H), 3.19-3.08 (m, 1H), 3.03-2.87 (m, 2H), 2.64-2.58 (m, 2H).

Example 16. Synthesis of (E)-N-methyl-N-((2-methyl-7-(thiazol-5-yloxy)benzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **101**).

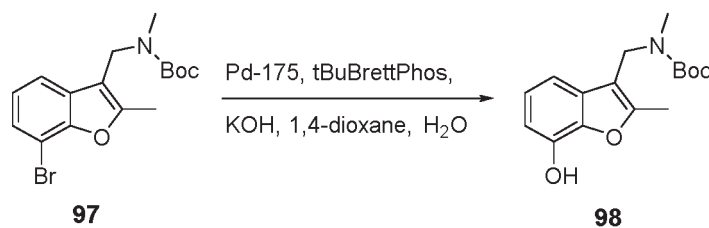
[00370] General Synthetic Scheme.



Reaction conditions: a) i) NH₂Me, STAB, EtOH; ii) Boc₂O, DMAP, DCM; b) Pd-175, tBuBrettPhos, KOH, 1,4-dioxane, H₂O; c) 5-Bromothiazole **92**, CuI, N,N-dimethyl glycine, Cs₂CO₃, DMF; d) TFA, DCM; e) HATU, DIPEA, DMF



- 5 **[00371] Step 1.** tert-Butyl ((7-bromo-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate (compound **97**). Methanamine (33% in EtOH, 0.5 mL, 4.4 mmol) was added dropwise to a stirred solution of 7-bromo-2-methylbenzofuran-3-carbaldehyde **69** (2.8 g, 3.7 mmol) and sodium triacetoxyborohydride (STAB) (1.9 g, 9.2 mmol) in EtOH (100 mL) at 0 °C. The reaction mixture was allowed to return to RT and stirred
- 10 for 5 h. The reaction mixture was then concentrated in vacuo and the resulting residue was taken up in EtOAc (100 mL) and NaHCO₃ (aq. sat. 100 mL). The organic material was separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried using MgSO₄ and concentrated in vacuo. The resulting residue was dissolved in DCM (80 mL), followed by addition of DMAP
- 15 (0.6 g, 4.6 mmol) and di-tert-butyl dicarbonate (1.6 g, 7.3 mmol) and the reaction mixture was stirred at RT for 16 h. The crude reaction mixture was concentrated in vacuo and purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound **97** as a yellow oil which crystallised on standing (1.0 g, 69% yield). R_t 1.86 min (Method 1a) m/z 376/378 [M + Na]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 7.55 (br s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.17 (br s, 1H), 4.48 (s, 2H), 2.67 (s, 3H), 2.51 (s, 3H), 1.44 (s, 9H).
- 20



[00372] Step 2. tert-Butyl ((7-hydroxy-2-methylbenzofuran-3-

yl)methyl)(methyl)carbamate (compound **98**). 1,4-Dioxane (5 mL) and degassed H₂O (1.5 mL)

were added to a mixture of tert-butyl ((7-bromo-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate **97** (1.0 g, 2.9 mmol), Pd-175 (0.06 g, 0.07 mmol), tBuBrettPhos (0.03 g, 0.07 mmol) and KOH (0.5 g, 8.8 mmol) under an atmosphere of nitrogen and the

reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was allowed to cool to RT then was poured into water (50 mL). The aqueous mixture was adjusted to pH 6 using 1 M

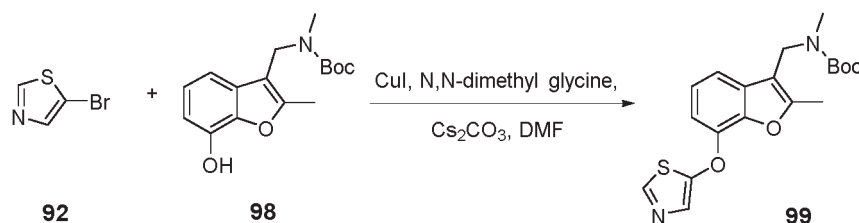
HCl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried using MgSO₄ and concentrated in vacuo. The crude material was

purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound

98 as a pale brown solid (0.58 g, 67% yield). R_t 2.18 min (Method 1a) m/z 314 [M + Na]⁺ (ES⁺).

¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.85 (s, 1H), 6.96 (br s, 2H), 6.76-6.56 (m, 1H), 4.44 (s,

2H), 2.65 (s, 3H), 2.44 (s, 3H), 1.44 (s, 9H).



[00373] Step 3. tert-Butyl methyl((2-methyl-7-(thiazol-5-yloxy)benzofuran-3-

yl)methyl)(methyl)carbamate (compound **99**). DMF (5 mL) was added to a mixture of Cs₂CO₃ (0.9 g,

2.8 mmol), 5-bromothiazole **92** (0.17 g, 1.03 mmol), tert-butyl ((7-hydroxy-2-

methylbenzofuran-3-yl)methyl)(methyl)carbamate **98** (0.2 g, 0.686 mmol), 2-

(dimethylamino)acetic acid (0.07 g, 0.69 mmol) and CuI (0.13 g, 0.69 mmol) under an

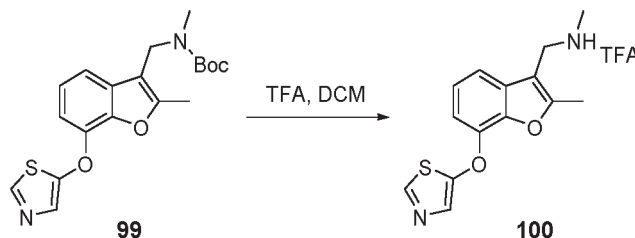
atmosphere of N₂ and the reaction mixture was heated to 110 °C. The reaction was stirred at

this temperature for 24 h then a further equivalent of 5-bromothiazole (0.17 g, 1.03 mmol)

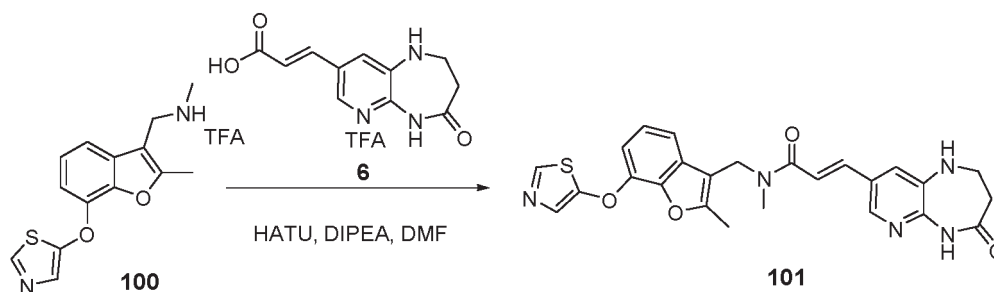
was added and the reaction was stirred for a further 16 h at the same temperature. The

reaction mixture was allowed to cool to RT then was stirred over the weekend. The crude

mixture was dry loaded onto Celite® and purified by column chromatography (0-100% EtOAc/isohexane) to afford the title compound **99** as a yellow oil (54 mg, 20% yield). R^t 2.51 min (Method 1a) m/z 375 $[M + H]^+$ (ES^+).



[00374] Step 4. N-Methyl-1-(2-methyl-7-(thiazol-5-yloxy)benzofuran-3-yl)methanamine trifluoroacetate (compound **100**). Trifluoroacetic acid (2.5 mL) was added dropwise to a stirred solution of tert-butyl methyl((2-methyl-7-(thiazol-5-yloxy)benzofuran-3-yl)methyl)carbamate **99** (0.05 g, 0.13 mmol) in DCM (2.5 mL) at RT. The reaction was stirred for 30 min then was concentrated *in vacuo* to give **100** as an yellow oil which was used in the next step without further purification. R^t 1.39 min (Method 1a) m/z 275 $[M + H]^+$ (ES^+).



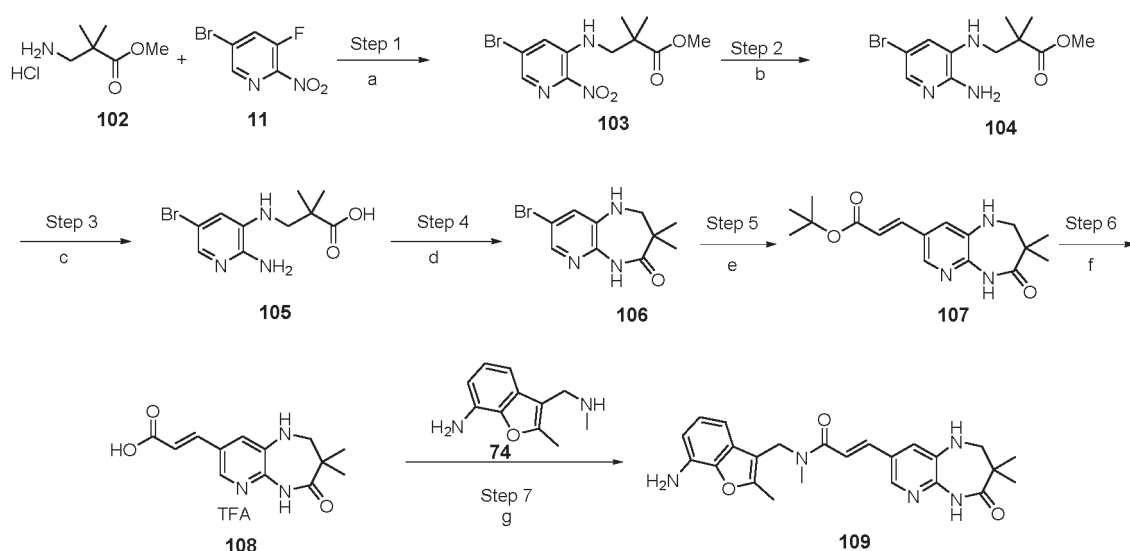
[00375] Step 5. (E)-N-Methyl-N-((2-methyl-7-(thiazol-5-yloxy)benzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **101**). DIPEA (0.5 mL, 2.86 mmol) was added dropwise to a stirred solution of N-methyl-1-(2-methyl-7-(thiazol-5-yloxy)benzofuran-3-yl)methanamine trifluoroacetate **100** (0.05 g, 0.13 mmol) and (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (0.06 g, 0.16 mmol) in DMF (2 mL) at RT. The reaction was stirred for 10 mins then HATU (0.08 g, 0.20 mmol) was added and the reaction was stirred for 16 h. The reaction mixture was diluted with water (10 mL) and the precipitate collected by filtration. The crude material was purified by column chromatography (0-5% MeOH/DCM) to give the title compound **101** as a pale yellow solid (57 mg, 73% yield). R^t 1.78 min (Method 1a) m/z

490 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.14 (s, 1H), 8.66 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.58 (s, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.43-7.35 (m, 2H), 7.19 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 15.5 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 5.79 (t, J = 4.2 Hz, 1H), 4.78 (s, 2H), 3.48-3.39 (m, 2H), 3.02 (s, 3H), 2.67-2.62 (m, 2H), 2.51 (s, 3H).

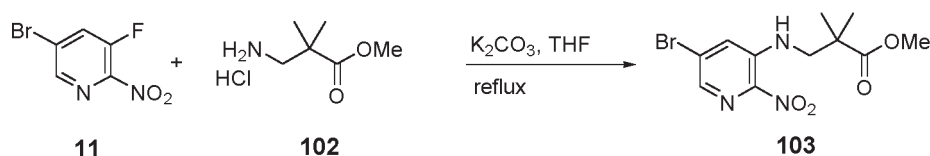
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Example 17. Synthesis of (E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **109**).

10 **[00376]** General Synthetic Scheme.



Reaction conditions: (a) K_2CO_3 , THF, reflux; (b) Fe, AcOH, EtOH, 90 °C; (c) LiOH, THF : H₂O, RT; (d) HATU, DIPEA, DMF, RT; (e) tert-butyl acrylate, Pd-116, DIPEA, NBu₄Cl, 1,4-dioxane, 90 °C; (f) TFA, DCM; (g) HATU, DIPEA, DMF

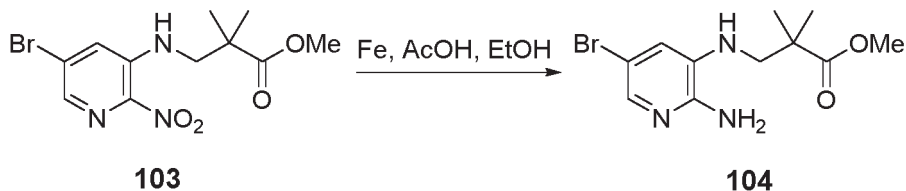


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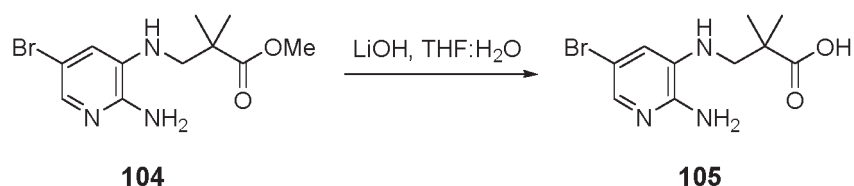
[00377] **Step 1.** Methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2,2-dimethylpropanoate (compound **103**). To a solution of 5-bromo-3-fluoro-2-nitropyridine **11** (0.34 g, 1.55 mmol) in THF (5 mL) was added methyl 3-amino-2,2-dimethylpropanoate hydrochloride **102** (0.20 g, 1.55 mmol) and K_2CO_3 (0.43 g, 3.10 mmol). The reaction mass was stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature, diluted with water (15 mL), and extracted with EtOAc (3 × 15 mL). The organic layers were

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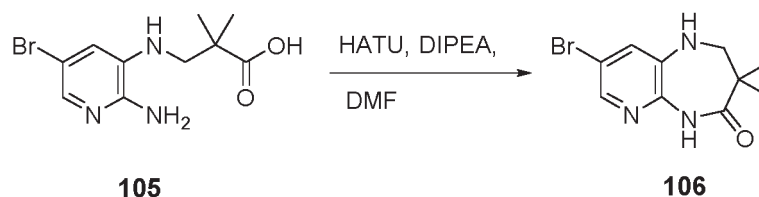
combined, dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford the title compound **103** (0.51 g, 82% yield) as a yellow oil. The crude product was used in the next step without further purification. R^t 2.15 min (Method 1a); m/z 332/334 $[\text{M} + \text{H}]^+$ (ES^+).



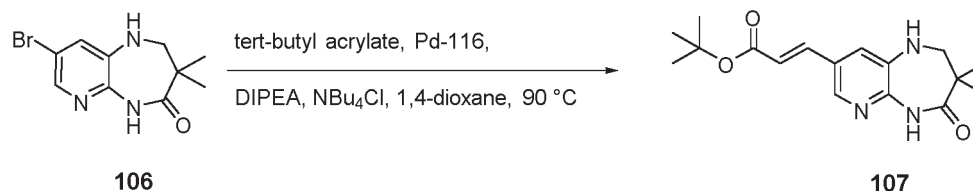
[00378] Step 2. Methyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2,2-dimethylpropanoate (compound **104**). To a stirred solution of methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2,2-dimethylpropanoate **103** (0.51 g, 1.55 mmol) in EtOH (8 mL) was added acetic acid (1.80 mL, 30.9 mmol) followed by iron (0.86 g, 15.5 mmol). The reaction mixture was stirred at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature and neutralised to pH 8 with solid NaHCO_3 . The stirring was continued until the effervescence ceased. The reaction mixture was diluted with H_2O (5 mL) and EtOAc (5 mL). The aqueous phase was extracted with EtOAc (2×5 mL). The combined organic phases were washed with H_2O (10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford the title compound **104** (424 mg, 84% yield) as a brown solid. The crude product was used in the next step without further purification. R^t 1.25 min (Method 1a); m/z 302/304 $[\text{M} + \text{H}]^+$ (ES^+).



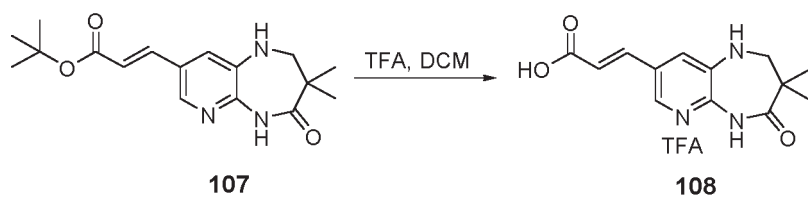
[00379] Step 3. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2,2-dimethylpropanoic acid (compound **105**). To a stirred solution of methyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2,2-dimethylpropanoate **104** (424 mg, 1.40 mmol) in THF (1 mL) was added a solution of lithium hydroxide (170 mg, 7.01 mmol) in H_2O (1 mL). The reaction mixture was stirred at room temperature for 3 h. Solvent was removed *in vacuo* to afford the title compound **105** (404 mg, 1.40 mmol, quant. yield) as a brown solid. The crude product was used in the next step without further purification. R^t 1.10 min (Method 1a); m/z 288/290 $[\text{M} + \text{H}]^+$ (ES^+).



[00380] Step 4. 8-Bromo-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **106**). To a stirred solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2,2-dimethylpropanoic acid **105** (404 mg, 1.40 mmol) in DMF (3 mL) was added DIPEA (730 μ L, 4.21 mmol) followed by HATU (800 mg, 2.10 mmol). The reaction mixture was stirred at room temperature for 1 h and then aq. 1M HCl (3 mL) was added. The aqueous phase was extracted with DCM (2 $\times$ 5 mL). The combined organic extracts were washed with H₂O (3 $\times$ 5 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica chromatography (0-5% MeOH in DCM) to afford 8-bromo-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **106** (317 mg, 84% yield) as a white solid. *R*^t 1.68 min (Method 1a); *m/z* 270/272 [*M* + *H*]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ , ppm 7.97 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 3.09 (s, 2H), 1.23 (s, 6H).

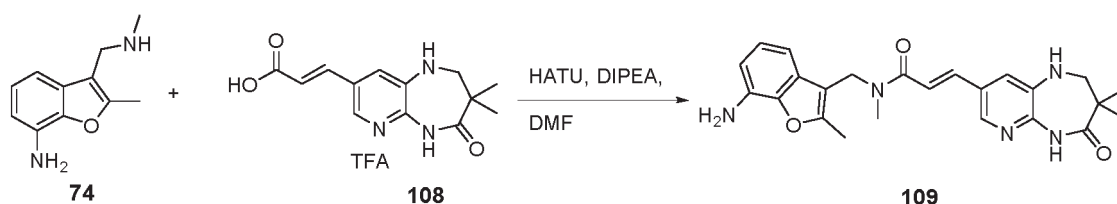


[00381] Step 5. tert-Butyl (E)-3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate (compound **107**). DIPEA (1.3 mL, 7.4 mmol) and tert-butyl acrylate (1.1 mL, 7.5 mmol) were added dropwise to a stirred solution of 8-bromo-3,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **106** (1 g, 3.7 mmol), Bu₄NCl (0.1 g, 0.4 mmol) and [P(*t*Bu)₃]₂Pd (Pd-116, Johnson Matthey) (0.1 g, 0.2 mmol) in 1,4-dioxane (20 mL) under N₂. The reaction mixture was heated to 90 °C and stirred for 2 h. The reaction mixture was cooled to RT and concentrated *in vacuo*. The crude material was purified by column chromatography (0-100% EtOAc/isohexane) to afford the title compound **107** as a yellow oil (0.97 g, 80% yield). *R*^t 2.07 min (Method 1a); *m/z* 318 [*M* + *H*]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ , ppm 9.51 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 16.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.21 (s, 1H), 3.05 (d, *J* = 4.4 Hz, 2H), 1.48 (s, 9H), 1.15 (s, 6H).



[00382] Step 6. (E)-3-(3,3-Dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-

5 b][1,4]diazepin-8-yl)acrylic acid TFA salt (compound **108**). Trifluoroacetic acid (5 mL) was added dropwise to a stirred solution of (E)-tert-butyl 3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate **107** (0.97 g, 3.1 mmol) in CH₂Cl₂ (10 mL) at RT and the reaction was stirred for 2 h. The reaction mixture was concentrated in vacuo and the resulting solid was triturated with MTBE (50 mL) then collected by filtration to
 10 give the desired product **108** as a yellow solid (0.81 g, 70%). R_t 1.25 min (Method 1a); m/z 262 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 12.38 (br s, 1H), 9.51 (s, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 6.25 (s, 1H), 3.08 - 3.00 (m, 2H), 1.15 (s, 6H).



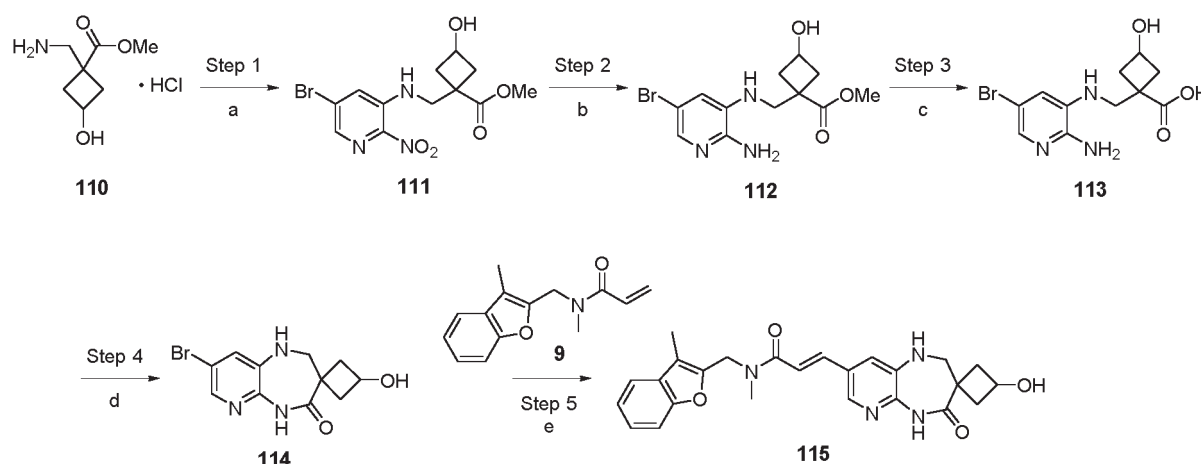
[00383] Step 7. (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **109**). DIPEA (0.5 mL, 2.9 mmol) was added dropwise to a stirred solution of 2-methyl-3-

20 ((methylamino)methyl)benzofuran-7-amine **74** (0.04 g, 0.2 mmol) and (E)-3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **108** (0.07 g, 0.2 mmol) in DMF (2 mL) at RT. The reaction was stirred for 10 min then HATU (0.09 g, 0.2 mmol) was added and the reaction was stirred for 16 h. The reaction mixture was diluted with water (10 mL) and the precipitate collected by filtration. The crude material was
 25 purified by column chromatography (0-5% MeOH/DCM) to afford the title compound **109** as a yellow solid (19 mg, 24% yield). R_t 1.57 min (Method 1a); m/z 434 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆, 363 K): δ, ppm 8.77 (s, 1H), 7.92 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 15.4 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 15.6 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.74 (d, J = 7.3

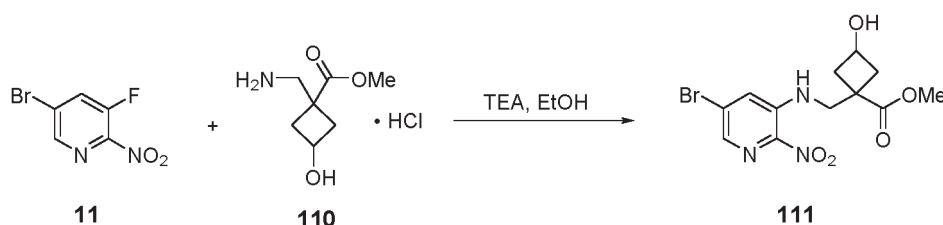
Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 6.03-5.91 (m, 1H), 4.86 (s, 2H), 4.71 (s, 2H), 3.07 (d, J = 4.6 Hz, 2H), 2.97 (s, 3H), 2.47 (s, 3H), 1.18 (s, 6H).

Example 18. Synthesis of (E)-3-(3-hydroxy-4'-oxo-1',2',4',5'-tetrahydrospiro[cyclobutane-1,3'-pyrido[2,3-b][1,4]diazepin]-8'-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **115**).

[00384] General Synthetic Scheme.



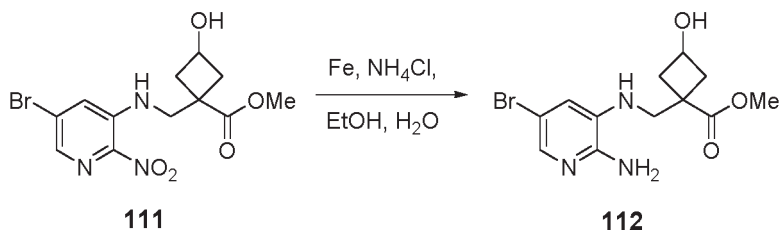
Reaction conditions : a) 5-Bromo-3-fluoro-2-nitropyridine **11**, TEA, EtOH, reflux; b) Fe, NH₄Cl, EtOH, H₂O, reflux; c) LiOH, H₂O, THF; d) HATU, DIPEA, DMF; e) Pd-162, MeNCy₂, NBu₄Cl, 1,4-dioxane, 80 °C.



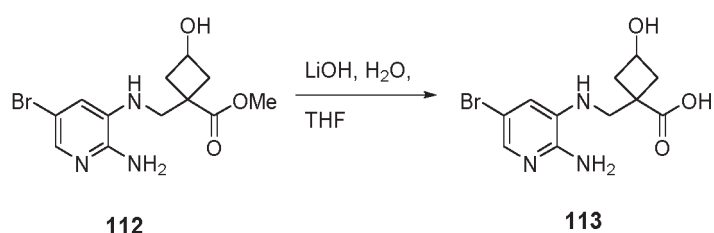
[00385] **Step 1.** Methyl 1-(((5-bromo-2-nitropyridin-3-yl)amino)methyl)-3-

hydroxycyclobutanecarboxylate (compound **111**). To a solution of 5-bromo-3-fluoro-2-nitropyridine **11** (230 mg, 1.0 mmol) in ethanol (10 mL) was added methyl 1-(aminomethyl)-3-hydroxycyclobutanecarboxylate hydrochloride **110** (Enamine) (200 mg, 1.0 mmol) and TEA (0.6 mL, 4.1 mmol). The reaction mixture was heated under reflux overnight. The solvent was removed *in vacuo* and the reaction was partitioned between water (2 mL) and ethyl acetate (2 mL). The organic extract was separated, dried with MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (0-100% EtOAc/isohexane) to give the title compound **111** as a yellow oil (250 mg, 61% yield). R_f 1.58

min (Method 1a); m/z 360/362 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.10 (s, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 4.58 (tt, J = 7.2 Hz, 5.8 Hz, 1H), 3.81 (s, 3H), 3.72 (d, J = 5.6 Hz, 2H), 2.93-2.88 (m, 2H), 2.10-2.06 (m, 2H) (missing OH).

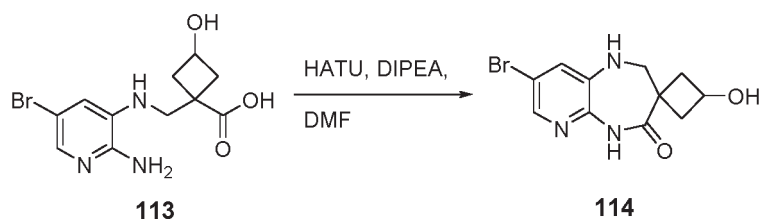


[00386] Step 2. Methyl 1-(((2-amino-5-bromopyridin-3-yl)amino)methyl)-3-hydroxycyclobutane carboxylate (compound **112**). A mixture of methyl 1-(((5-bromo-2-nitropyridin-3-yl)amino)methyl)-3-hydroxycyclobutanecarboxylate **111** (245 mg, 0.7 mmol), iron powder (152 mg, 2.7 mmol) and ammonium chloride (364 mg, 6.8 mmol) in a solvent mixture of ethanol (12 mL) and water (3 mL) was heated under reflux for 1 hour. The mixture was filtered hot through a pad of Celite[®] before being concentrated *in vacuo*. The residue was partitioned between water (20 mL) and DCM (20 mL) and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to give the title compound **112** as a yellow oil (180 mg, 76%). R_t 0.91 min (Method 1a); m/z 330/332 [M + H]⁺ (ES⁺).



[00387] Step 3. 1-(((2-Amino-5-bromopyridin-3-yl)amino)methyl)-3-hydroxycyclobutanecarboxylic acid (compound **113**). A mixture of methyl 1-(((2-amino-5-bromopyridin-3-yl)amino)methyl)-3-hydroxycyclobutanecarboxylate **112** (175 mg, 0.5 mmol) and lithium hydroxide (66 mg, 2.7 mmol) in a solvent mixture of THF (4.5 mL) and water (1.5 mL) was stirred at RT for 3 h. The reaction was then acidified to pH 3 by the addition of acetic acid (~0.4 mL). The solvent was removed in vacuo to give the title compound **113** as a

yellow solid (190 mg, 98% yield) which was used in the next step without further purification. R^t 0.53 min (Method 1a); m/z 316/318 $[M + H]^+$ (ES^+).



5

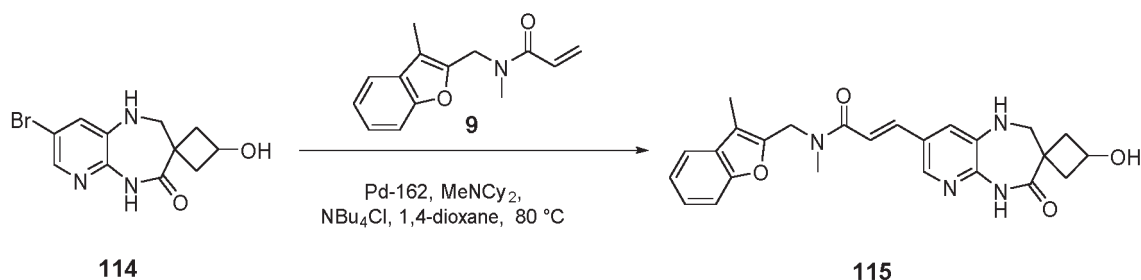
[00388] Step 4. 8'-Bromo-3-hydroxy-1',2'-dihydrospiro[cyclobutane-1,3'-pyrido[2,3-b][1,4]diazepin]-4'(5'H)-one (compound **114**). To a stirred solution of 1-(((2-amino-5-

bromopyridin-3-yl)amino)methyl)-3-hydroxycyclobutanecarboxylic acid **113** (172 mg, 0.5 mmol) in DMF (2.5 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.5 mL, 2.7 mmol)

10 followed by HATU (250 mg, 0.7 mmol). The reaction mixture was stirred at RT for 1 h. Water (4 mL) was then added and the resulting mixture extracted with DCM (3×5 mL). The combined organic phases were washed with brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (0-10%

MeOH/DCM) to give the title compound **114** as a colourless solid (30 mg, 17% yield). R^t 1.20 min (Method 1a); m/z 298/300 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, CD_3OD): δ , ppm 7.72 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 4.28 (p, J = 7.2 Hz, 1H), 3.46 (s, 2H), 2.85-2.66 (m, 2H), 1.94-1.79 (m, 2H).

15



20 **[00389] Step 5.** (E)-3-(3-Hydroxy-4'-oxo-1',2',4',5'-tetrahydrospiro[cyclobutane-1,3'-pyrido[2,3-b][1,4]diazepin]-8'-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **115**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (25 mg, 0.1 mmol), 8'-bromo-3-hydroxy-1',2'-

dihydrospiro[cyclobutane-1,3'-pyrido[2,3-b][1,4]diazepin]-4'(5'H)-one **114** (28 mg, 0.1

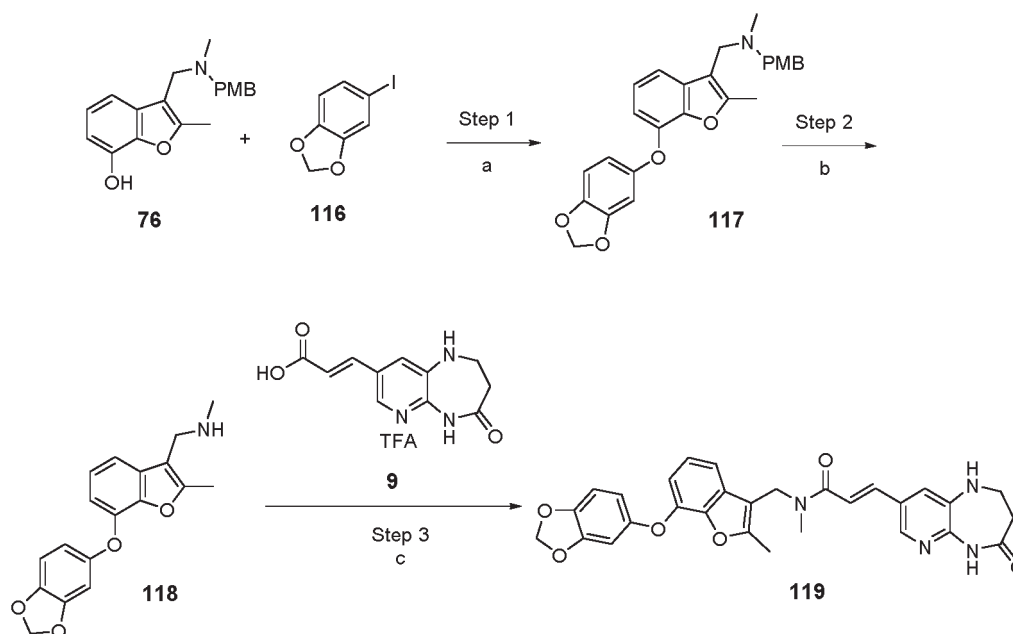
25 mmol), Bu_4NCl (3 mg, 9.4 μmol), $[P(tBu)_3]Pd(crotyl)Cl$ (Pd-162) (4 mg, 9.4 μmol). The vial was flushed with nitrogen for 5 min. 1,4-Dioxane (2.5 mL) and N-cyclohexyl-N-

methylcyclohexanamine (41 μ L, 0.2 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 $^{\circ}$ C for 1 h and allowed to cool to room temperature. Ethyl acetate (5 mL) was added and the resulting solution was washed with H₂O (5 mL), brine (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo*.

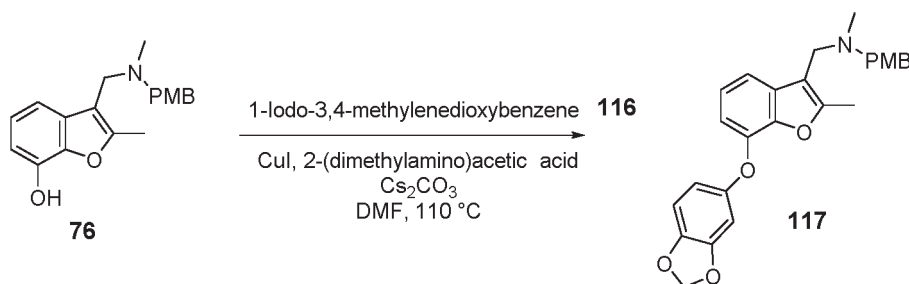
- 5 The crude product was purified by column chromatography (0-10% MeOH/DCM) to give the title compound **115** as a pale yellow solid (22 mg, 49%). R^t 1.79 min (Method 1a); m/z 447 $[M + H]^+$ (ES⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ , ppm 9.05 (s, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 7.6, 1.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.45-7.34 (m, 2H), 7.33-7.19 (m, 2H), 7.10 (d, J = 15.6 Hz, 1H), 5.97 (d, J = 4.7 Hz, 1H), 4.84 (s, 3H), 4.21-4.03 (m, 1H), 3.41 (d, J = 3.9 Hz, 2H), 3.10 (s, 3H), 2.64-2.54 (m, 2H), 2.28 (s, 3H), 1.83-1.74 (m, 2H).

Example 19. Synthesis of (E)-N-((7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **119**).

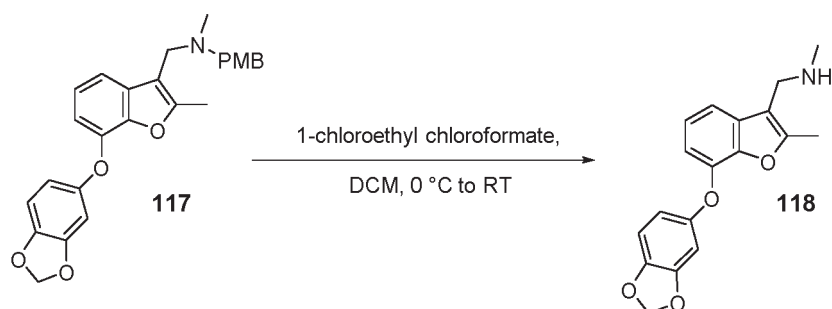
[00390] General Synthetic Scheme.



Reaction conditions: a) CuI, 2-(dimethylamino)acetic acid, Cs₂CO₃ DMF, 110 $^{\circ}$ C; b) 1-chloroethyl chloroformate, DCM, 0 $^{\circ}$ C to RT; c) HATU, DIPEA, DMF

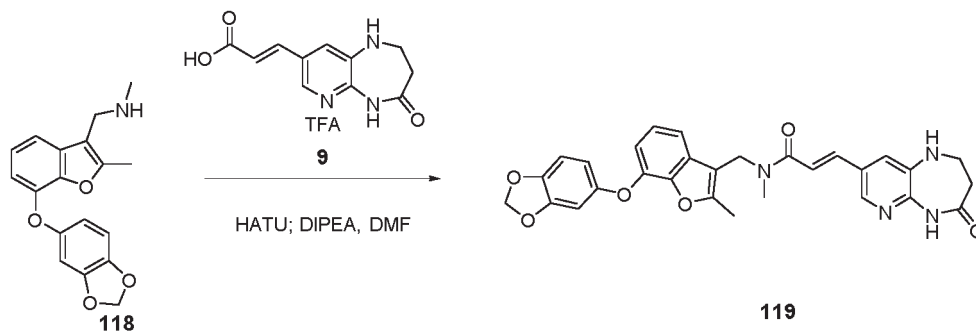


[00391] Step 1. 1-(7-(Benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine (compound **117**). A mixture of 3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-ol **76** (150 mg, 0.48 mmol), 1-iodo-3,4-methylenedioxybenzene **116** (Fluorochem) (358 mg, 1.45 mmol), 2-(dimethylamino)acetic acid (50 mg, 0.48 mmol), copper(I) iodide (92 mg, 0.48 mmol) and cesium carbonate (942 mg, 2.89 mmol) was evacuated and backfilled with nitrogen (3 times). DMF (3 mL) was added and the mixture was heated to 110 °C overnight. The reaction mixture was allowed to cool to RT, poured onto water (30 mL) and the crude product extracted into ethyl acetate (2 × 30 mL). The organic extracts were combined and dried over Na₂SO₄. The crude product was purified by chromatography [0-10% (0.7M Ammonia/MeOH)/DCM] to afford the title compound **117** as a clear yellow gum (85 mg, 38% yield). R_t 1.69 min (Method 1a) m/z 432 [M + H]⁺ (ES⁺).



[00392] Step 2. 1-(7-(Benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine (compound **118**). To a solution of 1-(7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **117** (85 mg, 0.20 mmol) in DCM (2 mL) was added 1-chloroethyl carbonochloridate (0.031 mL, 0.29 mmol) at 0 °C and the mixture allowed to attain RT then stirred for 1 hour. The mixture was evaporated to dryness and the residue was taken up into methanol (5 mL) and the mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to RT and the solution applied directly to an SCX column (1 g). The column was washed with methanol (10 mL) and

the crude product was eluted with 10% methanolic ammonia solution (10 mL) to give the title compound **118** as a yellow oil (60 mg, 90% yield). R^t 1.38 min (Method 1a) m/z 281[M + H]⁺ (ES⁺).



[00393] Step 3. (E)-N-((7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-

yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-

yl)acrylamide (compound **119**). A solution of 1-(7-(benzo[d][1,3]dioxol-5-yloxy)-2-

methylbenzofuran-3-yl)-N-methylmethanamine **118** (60 mg, 0.19 mmol), (E)-3-(4-oxo-

2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **9** (67 mg,

0.19 mmol) and DIPEA (135 μ L, 0.77 mmol) in DMF (3 mL) was added HATU (73 mg, 0.19

mmol) and the mixture was stirred at RT for 1 hour. The reaction mixture was quenched by the addition of water (10 mL). The solid was collected by filtration and dried. The crude

product was initially purified by chromatography (0-10% MeOH/DCM) to afford the title compound **119** as a pale yellow solid (LCMS purity 93%). This solid was further purified by

trituration with acetonitrile (10 mL) followed by further trituration with DMF (2 mL) and

washing the collected solid with TBME (10 mL) to afford the title compound **119** as a pale

yellow solid (14 mg, 13% yield). R^t 2.12 min (Method 1a) m/z 527[M + H]⁺ (ES⁺). ¹H NMR (500

MHz, DMSO- d_6 , 363 K): δ , ppm 9.14 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H),

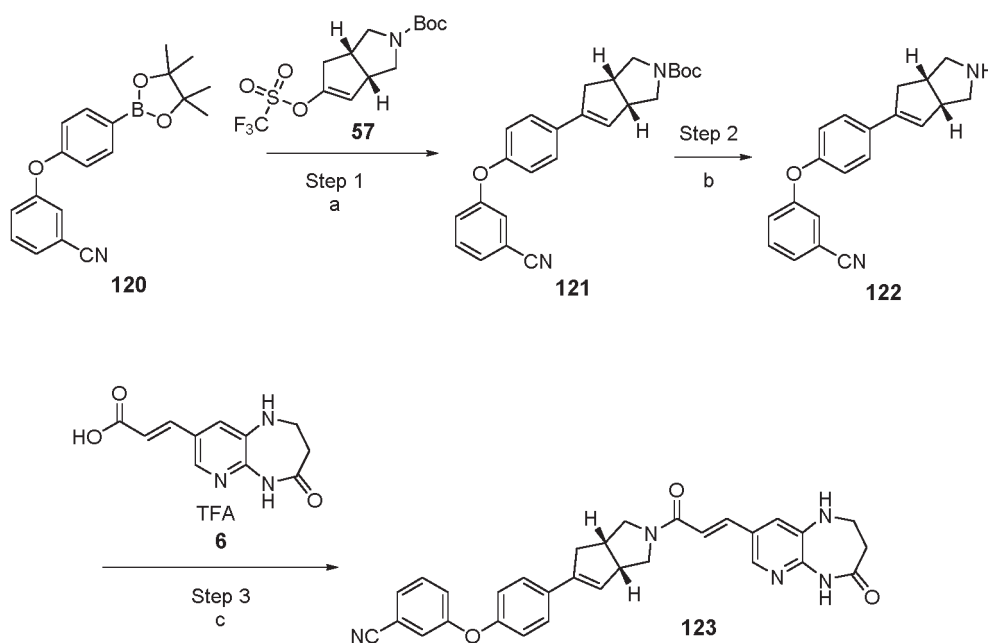
7.38 (d, J = 1.9 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.15-7.06 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.78

(dd, J = 8.0, 1.0 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.50 (dd, J = 8.4, 2.5 Hz, 1H), 6.01 (s, 2H), 5.80

(s, 1H), 4.77 (s, 2H), 3.44 (dd, J = 6.9, 3.5 Hz, 2H), 2.67-2.62 (m, 2H), 1.20 (s, 1H). Both CH₃

protons obscured by solvent and water

Example 20. Synthesis of 3-(4-((3*r*S,6*r*R)-2-((E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3*r*,4,6*r*-hexahydrocyclopenta[*c*]pyrrol-5-yl)phenoxy)benzonitrile (compound **123**).

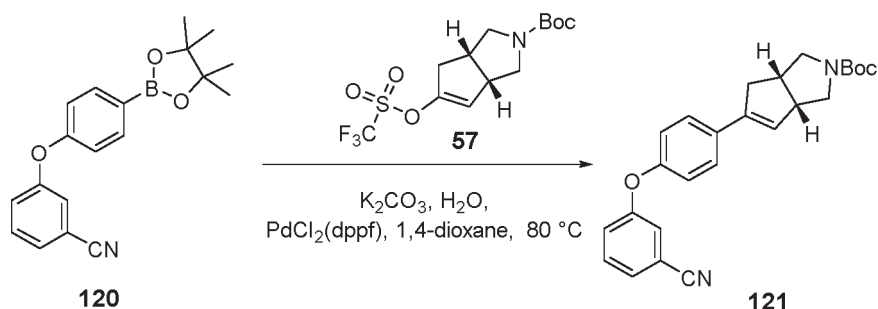
[00394] General Synthetic Scheme.

Reaction conditions: a) K_2CO_3 , H_2O , $PdCl_2(dppf)$, 1,4-dioxane, 80 °C; b) TFA, DCM; c) HATU, DIPEA, DMF

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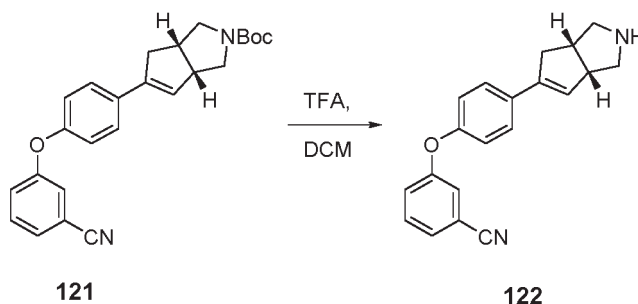
[00395] The synthesis of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzonitrile (compound **120**) was previously reported by Abbott Laboratories - US2002/156081, 2002, A1. This compound is also commercially available from Fluorochem (CAS: 330792-98-8).

10

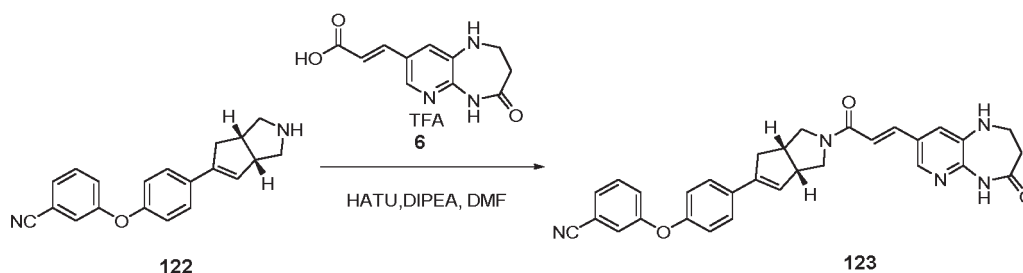


[00396] **Step 1.** tert-Butyl (3rS,6rR)-5-(4-(3-cyanophenoxy)phenyl)-3,3r,4,6r-tetrahydro-cyclopenta[c] pyrrole-2(1H)-carboxylate (compound **121**). A mixture of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzonitrile **120** (250 mg, 0.78 mmol), tert-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-

carboxylate) **57** (278 mg, 0.8 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (64 mg, 0.08 mmol), potassium carbonate (323 mg, 2.3 mmol) and water (1.5 mL) in 1,4-dioxane (4 mL) was stirred at 80 °C overnight. The reaction was cooled to RT, filtered through Celite®, and washed with EtOAc (50 mL). The mixture was then evaporated under vacuum to afford the title compound **121** as a brown oil (396 mg, quant. yield) which was used in the following step without further purification. R^t 2.86 min (Method 1b); m/z 347 [M + H-tBu]⁺ (ES⁺).



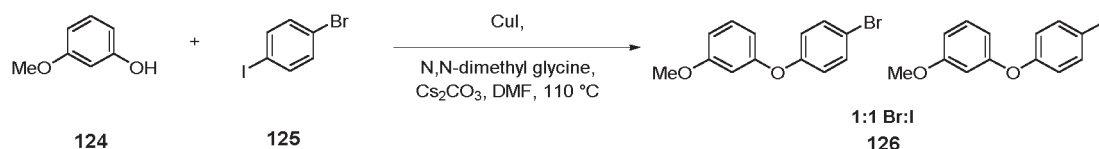
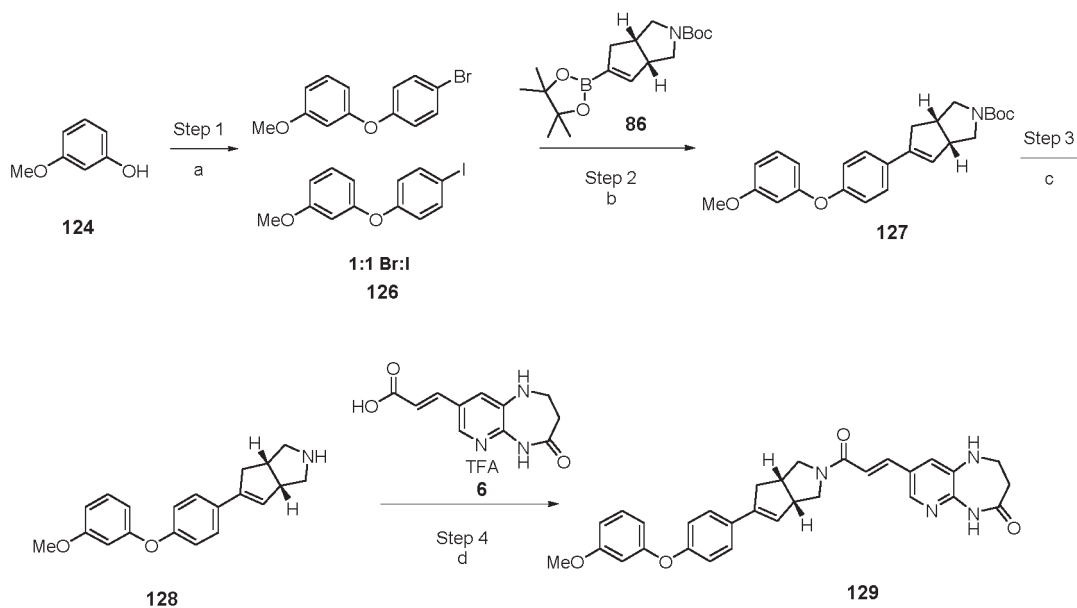
[00397] Step 2. 3-(4-((3*r*S,6*r*R)-1,2,3,3*r*,4,6*r*-Hexahydrocyclopenta[*c*]pyrrol-5-yl)phenoxy)benzonitrile (compound **122**). Trifluoroacetic acid (2.5 mL) was added dropwise to a stirred solution of tert-butyl 5-(4-(3-cyanophenoxy)phenyl)-3,3*r*,6,6*r*-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate **121** (313 mg, 0.8 mmol) in DCM (2.5 mL) at RT. The reaction mixture was stirred for 2 h then the solvent was concentrated *in vacuo* and the resulting residue was taken up in methanol (30 mL) and applied to an SCX column. The column was washed with methanol (50 mL) and the product eluted with a solution of 10% methanolic ammonia. The mixture was then evaporated affording the title compound **122** as a yellow oil (154 mg, 64% yield). R^t 1.75 min (Method 1b); m/z 303 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.44-7.39 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.24-7.18 (m, 2H), 6.97 (d, J = 8.5 Hz, 2H), 5.93 (d, J = 2.6 Hz, 1H), 3.50-3.45 (m, 1H), 3.06-2.98 (m, 2H), 2.97-2.90 (m, 2H), 2.90-2.84 (m, 1H), 2.82-2.75 (m, 1H), 2.49 (m, 1H), 2.41 (br s, 1H).



[00398] Step 3. 3-(4-((3*r*S,6*r*R)-2-((*E*)-3-(4-Oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-
b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3*r*,4,6*r*-hexahydrocyclopenta[*c*]pyrrol-5-
yl)phenoxy)benzonitrile (compound **123**). A suspension of 3-(4-((3*r*S,6*r*R)-1,2,3,3*r*,4,6*r*-
hexahydrocyclopenta[*c*]pyrrol-5-yl)phenoxy)benzonitrile **122** (70 mg, 0.2 mmol), (*E*)-3-(4-
5 oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (76
mg, 0.2 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (0.20 mL, 1.2 mmol) in DMF (1 mL) was
stirred for 10 min. HATU (88 mg, 0.2 mmol) was added in one portion and the reaction
mixture was left to stir at room temperature for 1 h. The mixture was diluted with water (10
mL) and the precipitate was collected by filtration. The crude product was purified by
10 column chromatography (0-5% MeOH/DCM) to afford the title compound **123** as a yellow
solid (87 mg, 72% yield). *R*_t 2.08 min (Method 1*b*); *m/z* 518 [*M* + *H*]⁺ (*ES*⁺). ¹*H* NMR (400 MHz,
DMSO-*d*₆): δ, ppm 9.74 (d, *J* = 6.9 Hz, 1*H*), 7.98 (dd, *J* = 8.4 Hz, 1.9 Hz, 1*H*), 7.60-7.53 (m, 4*H*),
7.50-7.47 (m, 1*H*), 7.37-7.31 (m, 3*H*), 7.09-7.04 (m, 2*H*), 6.87 (dd, *J* = 15.5 Hz, 9.0 Hz, 1*H*),
6.18 (d, *J* = 4.7 Hz, 1*H*), 6.05-6.00 (m, 1*H*), 4.00 (t, *J* = 9.9 Hz, 1*H*), 3.87-3.79 (m, 2*H*), 3.69-3.51
15 (m, 2*H*), 3.43-3.37 (m, 2*H*), 3.19-3.12 (m, 1*H*), 3.03-2.90 (m, 2*H*), 2.66-2.59 (m, 3*H*).

Example 21. Synthesis of 8-((*E*)-3-((3*r*S,6*r*R)-5-(4-(3-methoxyphenoxy)phenyl)-3,3*r*,4,6*r*-
tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-oxoprop-1-en-1-yl)-1,2,3,5-tetrahydro-4*H*-
20 pyrido[2,3-*b*][1,4]diazepin-4-one (compound **129**).

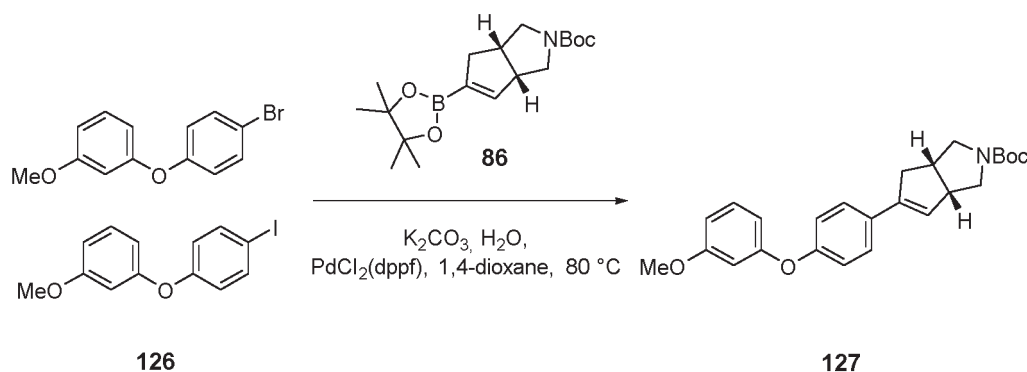
[00399] General Synthetic Scheme.



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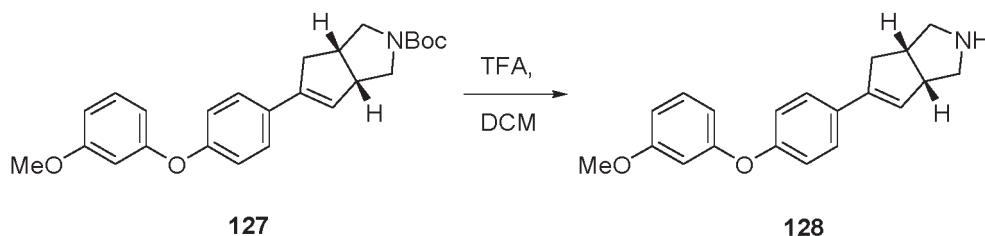
[00400] Step 1. 1-(4-Bromophenoxy)-3-methoxybenzene and 1-(4-Iodophenoxy)-3-methoxybenzene (compound **126**). A mixture of 1-bromo-4-iodobenzene **125** (Sigma Aldrich) (500 mg, 1.8 mmol), copper(I)iodide (337 mg, 1.8 mmol), N,N-dimethylglycine (182 mg, 1.8 mmol), cesium carbonate (2.30 g, 7.1 mmol) and 3-methoxyphenol **124** (Sigma Aldrich) (0.19 mL, 1.8 mmol) was evacuated and backfilled with nitrogen (3 times). DMF (10 mL) was added and the mixture was heated to 110 °C overnight. The mixture was filtered through a pad of Celite® washing with EtOAc (50 mL) and then evaporated to dryness. The crude product was purified by column chromatography (0-10% EtOAc/isohexane) to afford a mixture of the title compounds **126** as a dark oil (338 mg, 53% yield) which was used in the following step without further purification. ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.66-7.62 (m, 1H), 7.51-7.43 (m, 3H), 7.28-7.24 (m, 2H), 6.96-6.89 (m, 3H), 6.82-6.79 (m, 1H), 6.71 (ddt, J = 8.3 Hz, 2.2 Hz, 1.3 Hz, 2H), 6.60 (dq, J = 9.4 Hz, 1.3 Hz, 4H), 3.81 (s, 6H).

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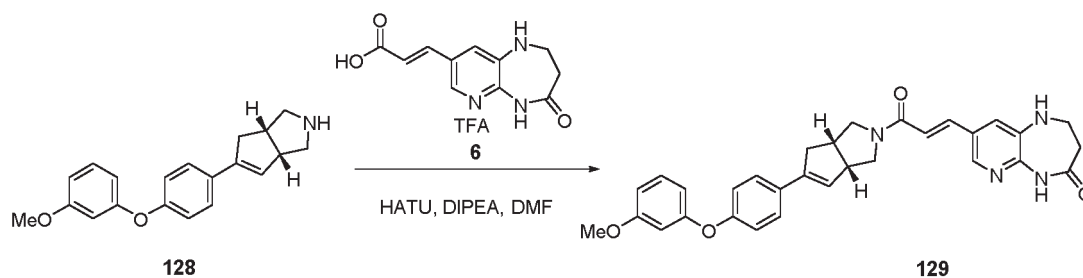
[00401] Step 2. tert-Butyl(3rS,6rR)-5-(4-(3-methoxyphenoxy)phenyl)-3,3r,4,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (compound **127**). A mixture of 1-(4-

iodophenoxy)-3-methoxybenzene **126** (169 mg, 0.51 mmol), 1-(4-bromophenoxy)-3-methoxybenzene **126** (169 mg, 0.6 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **86** (375 mg, 1.1 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (91 mg, 0.1 mmol), potassium carbonate (464 mg, 3.4 mmol) and water (2 mL) in 1,4-dioxane (6 mL) was stirred at 80 °C for 4 h. The reaction was cooled to RT, filtered through Celite®, and washed with EtOAc (50 mL). The mixture was then evaporated under vacuum. The crude product was purified by column chromatography (0-50%EtOAc/isohexane) to afford the title compound **127** as a white solid (209 mg, 45% yield). R^t 3.00 min (Method 1b); m/z 352 [M + H-tBu]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.44-7.38 (m, 2H), 7.23 (td, J = 8.2 Hz, 7.4 Hz, 1.2 Hz, 1H), 7.03-6.96 (m, 2H), 6.69-6.66 (m, 1H), 6.63-6.57 (m, 2H), 5.97 (br s, 1H), 3.79 (d, J = 2.1 Hz, 3H), 3.75-3.69 (m, 1H), 3.59-3.48 (m, 3H), 3.11 (dd, J = 11.0 Hz, 6.9 Hz, 1H), 3.06-2.99 (m, 1H), 2.97-2.90 (m, 1H), 2.59 (d, J = 15.7 Hz, 1H), 1.47 (s, 9H).



[00402] Step 3. (3rS,6rR)-5-(4-(3-Methoxyphenoxy)phenyl)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrole (compound **128**). Trifluoroacetic acid (1 mL) was added dropwise to a stirred solution of tert-butyl 5-(4-(3-methoxyphenoxy)phenyl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **127** (209 mg, 0.5 mmol) in DCM (1 mL) at

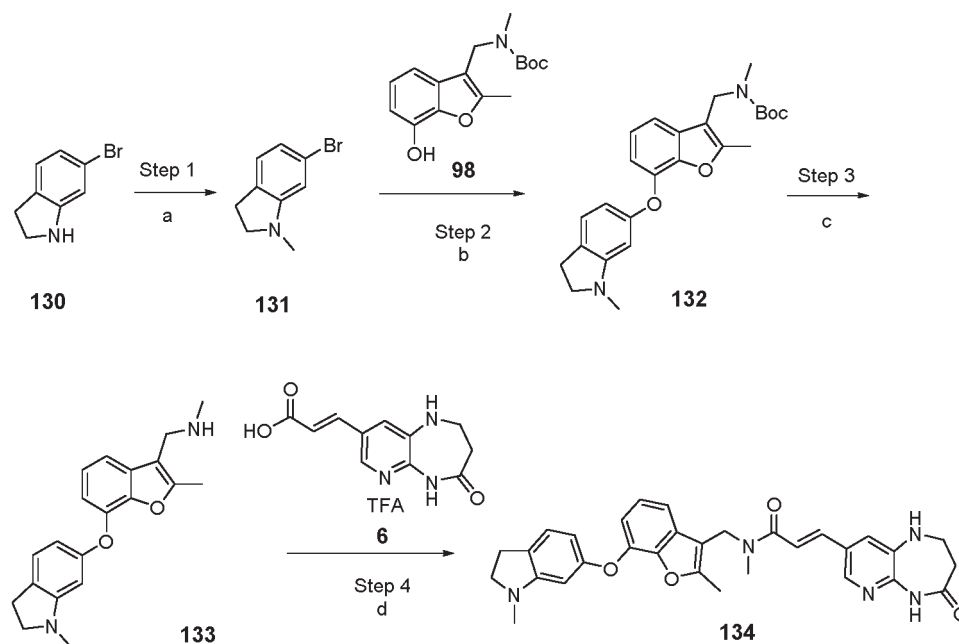
RT. The reaction mixture was stirred for 1 h then the solvent was concentrated *in vacuo*. The resulting residue was taken up in methanol (30 mL) and applied to an SCX column. The column was washed with methanol (50 mL) and the product eluted with a solution of 10% methanolic ammonia. The mixture was then evaporated to afford the title compound **128** as a yellow oil (157 mg, 96% yield). R^t 1.91 min (Method 1b); m/z 308 $[M + H]^+$ (ES^+). 1H NMR ($CDCl_3$): δ , ppm 7.37 (d, J = 8.5 Hz, 2H), 7.23-7.17 (m, 1H), 6.99-6.93 (m, 2H), 6.67-6.62 (m, 1H), 6.59-6.55 (m, 2H), 5.89-5.87 (m, 1H), 3.75 (s, 3H), 3.47-3.42 (m, 3H), 3.05-2.78 (m, 5H), 2.50-2.46 (m, 1H), 1.36 (d, J = 8.3 Hz, 1H).



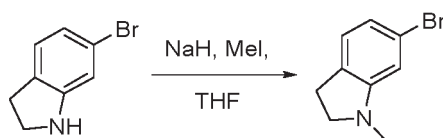
[00403] Step 4. (3R,6R)-5-(4-(3-Methoxyphenoxy)phenyl)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrole (compound **129**). A suspension of (3R,6R)-5-(4-(3-methoxyphenoxy)phenyl)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrole **128** (70 mg, 0.3 mmol), (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (75 mg, 0.3 mmol), N-ethyl-N-isopropylpropan-2-amine (0.2 mL, 1.2 mmol) in DMF (1.5 mL) was stirred for 10 min. HATU (87 mg, 0.3 mmol) was added in one portion and the reaction mixture was left to stir at room temperature for 1 h. The mixture was diluted with water (10 mL) and the precipitate was collected by filtration. The crude product was purified by column chromatography (0-5% MeOH/DCM) to afford the title compound **129** as a yellow solid (86 mg, 70% yield). R^t 2.19 min (Method 1b); m/z 523 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $DMSO-d_6$): δ , ppm 9.74 (d, J = 6.8 Hz, 1H), 7.98 (dd, J = 8.4 Hz, 1.9 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.38-7.26 (m, 3H), 7.01-6.97 (m, 2H), 6.89-6.84 (m, 1H), 6.72 (dd, J = 8.3 Hz, 2.4 Hz, 1H), 6.59-6.58 (m, 1H), 6.56-6.53 (m, 1H), 6.14-6.13 (m, 1H), 6.05-5.98 (m, 1H), 3.99 (t, J = 9.8 Hz, 1H), 3.87-3.78 (m, 1H), 3.73 (d, J = 0.8 Hz, 3H), 3.68-3.51 (m, 2H), 3.42 (td, J = 6.1 Hz, 3.4 Hz, 2H), 3.20-3.11 (m, 1H), 3.02-2.87 (m, 2H), 2.61 (dt, J = 10.9 Hz, 6.0 Hz, 3H).

Example 22. Synthesis of (E)-N-methyl-N-((2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **134**).

5 **[00404]** General Synthetic Scheme.



Reaction conditions: a) NaH, MeI, THF, 0 °C; b) CuI, N,N-dimethyl glycine, Cs₂CO₃, DMF, 110 °C; c) TFA, DCM; d) HATU, DIPEA, DMF



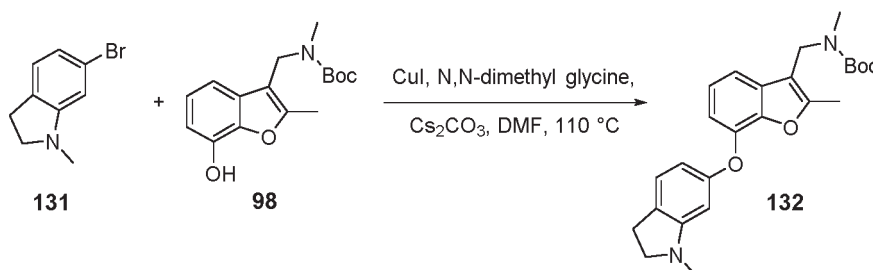
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[00405] **Step 1.** 6-Bromo-1-methylindoline (compound **131**). Sodium hydride (60% in mineral oil, 0.15 g, 3.8 mmol) was added in small portions to a stirred solution of 6-bromoindoline **130** (0.5 g, 2.5 mmol) in THF (20 mL) at 0 °C under N₂. The reaction mixture was stirred for 30 min then iodomethane (0.2 mL, 2.5 mmol) was added and the reaction mixture was allowed to warm to RT. The reaction mixture was stirred at RT over the weekend then chilled to 0 °C and quenched by addition of sat. NH₄Cl (50 mL). The aqueous mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried with MgSO₄, and concentrated in vacuo. The crude material was purified by column chromatography (0-20% EtOAc/isohexane) to afford the title compound **131** as a brown oil (0.44 g, 76%). R_t 2.39 min (Method 1a) m/z 212/214 [M +

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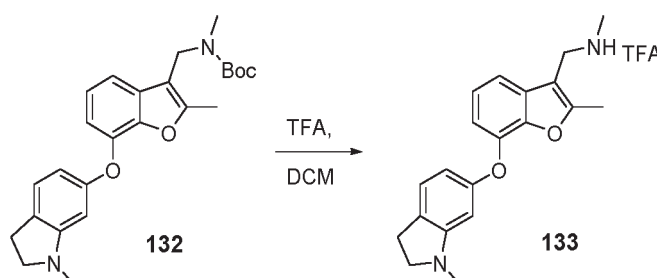
$\text{H}]^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6): δ , ppm 6.97-6.91 (m, 1H), 6.69 (dd, $J = 7.6$ Hz, 1.8 Hz, 1H), 6.62 (d, $J = 1.7$ Hz, 1H), 3.28 (t, $J = 8.3$ Hz, 2H), 2.82 (t, $J = 8.5$ Hz, 2H), 2.69 (s, 3H).



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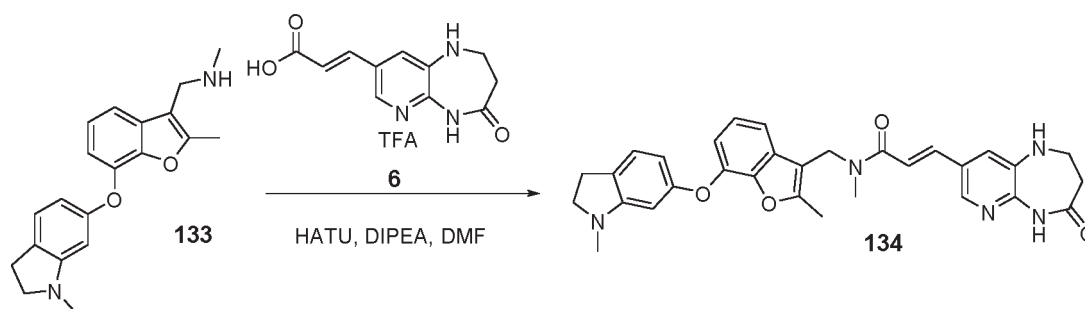
[00406] Step 2. tert-Butyl methyl((2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methyl)carbamate (compound **132**). DMF (5 mL) was added to a mixture of Cs_2CO_3 (0.67 g, 2.1 mmol), 6-bromo-1-methylindoline **131** (Fluorochem) (0.4 g, 1.9 mmol), tert-butyl ((7-hydroxy-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate **98** (0.15 g, 0.5 mmol), 2-(dimethylamino)acetic acid (0.05 g, 0.5 mmol) and CuI (0.1 g, 0.5 mmol) under an atmosphere of N_2 and the reaction mixture was heated to 110°C . The reaction mixture was stirred at this temperature for 16 h then the reaction mixture was allowed to cool to RT. The crude mixture was dry loaded onto Celite[®] and purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound **132** as a colourless oil (41 mg, 19% yield). R^t 3.02 min (Method 1a) m/z 423 $[\text{M} + \text{H}]^+$ (ES^+).

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[00407] Step 3. N-Methyl-1-(2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methanamine trifluoroacetate (compound **133**). Trifluoroacetic acid (2 mL) was added dropwise to a stirred solution of tert-butyl methyl((2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methyl)carbamate **132** (0.04 g, 0.1 mmol) in DCM (2 mL) at RT. The reaction was stirred for 30 min then was concentrated *in vacuo* to afford the title compound **133** as a brown oil which was used in the next step without further purification. R^t 2.02 min (Method 1a) m/z 323 $[\text{M} + \text{H}]^+$ (ES^+).

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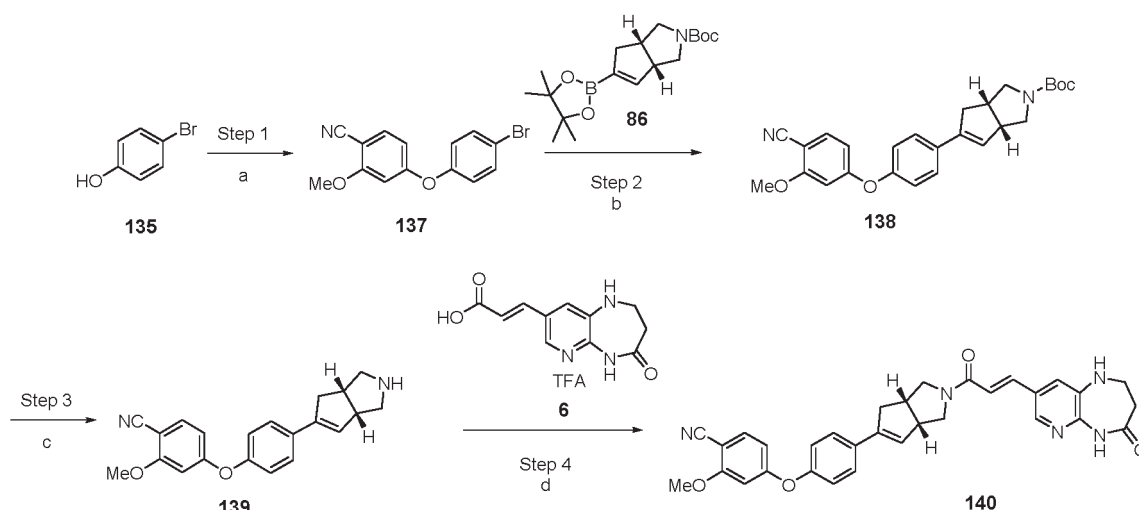


[00408] Step 4. (E)-N-Methyl-N-((2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide

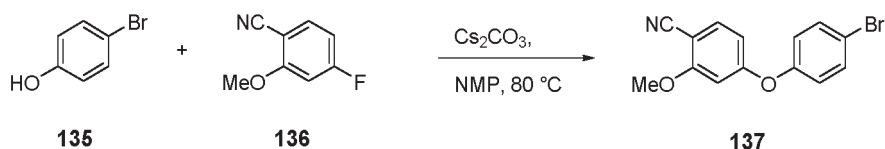
5 (compound **134**). DIPEA (0.5 mL, 2.9 mmol) was added dropwise to a stirred solution of N-methyl-1-(2-methyl-7-((1-methylindolin-6-yl)oxy)benzofuran-3-yl)methanamine trifluoroacetate **133** (0.07 g, 0.2 mmol) and (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (0.06 g, 0.2 mmol) in DMF (2 mL) at RT. The reaction was stirred for 10 min then HATU (0.08 g, 0.2 mmol) was added and the
 10 reaction was stirred for 2 h. The reaction mass was diluted with H₂O (10 mL) and the precipitate collected by filtration. The crude material was purified by column chromatography (0-3% MeOH/DCM) to afford the title compound **134** as a pale yellow solid (20 mg, 23% yield). R_t 2.13 min (Method 1a) m/z 538 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, 363 K, DMSO-d₆): δ, ppm 9.14 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.16-7.04 (m, 2H), 6.95 (dt, J = 7.8, 1.1 Hz, 1H), 6.78 (dd, J = 8.0, 1.1 Hz, 1H), 6.21-6.13 (m, 2H), 5.79 (s, 1H), 4.77 (s, 2H), 3.46-3.41 (m, 2H), 3.33 (t, J = 8.2 Hz, 2H), 3.02 (s, 3H), 2.87 (t, J = 8.2 Hz, 2H), 2.67 (s, 3H), 2.66-2.62 (m, 2H), 2.49 (s, 3H).

Example 23. Synthesis of 2-methoxy-4-(4-((3*r*S,6*r*R)-2-((E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3*r*,4,6*r*-hexahydrocyclopenta[*c*]pyrrol-5-yl)phenoxy)benzonitrile (compound **140**).

[00409] General Synthetic Scheme.

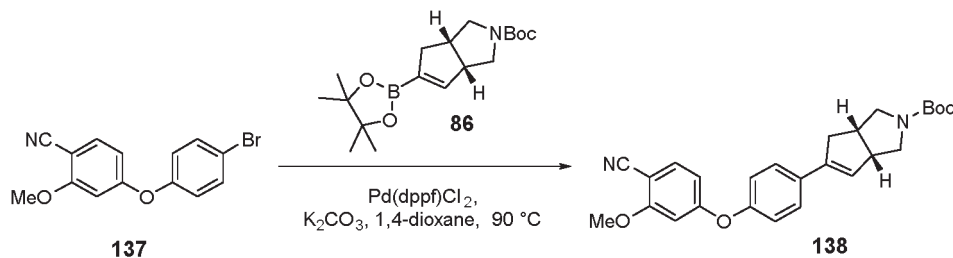


Reaction conditions: a) 4-Fluoro-2-methoxybenzonitrile **136**, Cs_2CO_3 , NMP, 80 °C; b) $\text{Pd}(\text{dppf})\text{Cl}_2$, K_2CO_3 , 1,4-dioxane, 90 °C; c) TFA, DCM; d) HATU, DIPEA, DMF



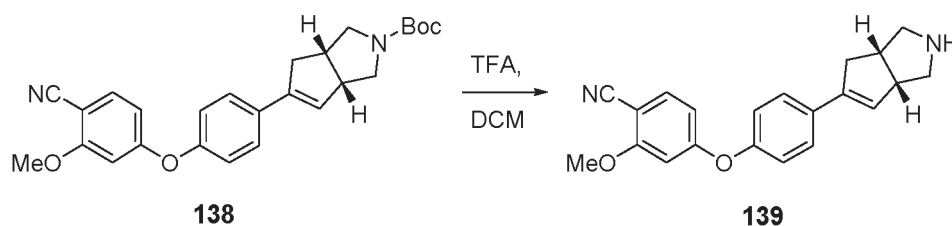
- 5 [00410] **Step 1.** 4-(4-Bromophenoxy)-2-methoxybenzonitrile (compound **137**). A mixture of 4-fluoro-2-methoxybenzonitrile **136** (Fluorochem) (1 g, 6.6 mmol), 4-bromophenol **135** (1.37 g, 7.94 mmol) and Cs_2CO_3 (6.47 g, 19.9 mmol) in N-methyl-2-pyrrolidone (20 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature, and was poured into water (50 mL). The mixture was extracted with ethyl acetate (2 × 50 mL). The organics were combined and washed with brine (2 × 50 mL), passed through a hydrophobic frit, and concentrated *in vacuo*. The crude product was purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound **137** as a clear colourless oil which crystallised upon standing (2.02 g, 70% yield). R^t 2.56 min (Method 1a) m/z 304/306 $[\text{M} + \text{H}]^+$ (ES^+).

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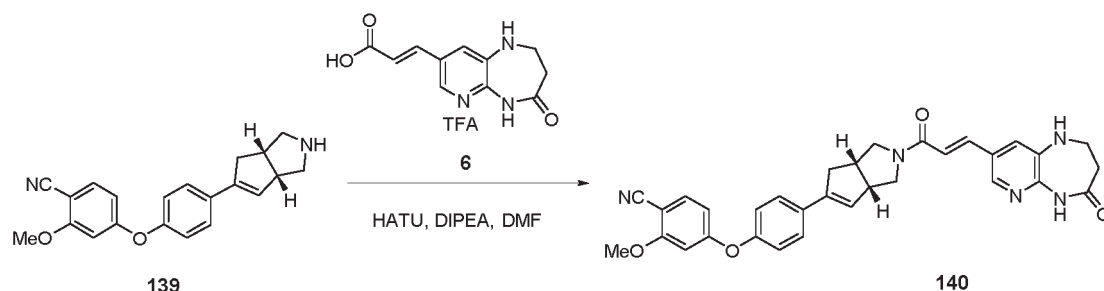
[00411] Step 2. tert-Butyl (3rS,6rR)-5-(4-(4-cyano-3-methoxyphenoxy)phenyl)-3,3r,4,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (compound **138**). A mixture of 4-(4-bromophenoxy)-2-methoxybenzonitrile **137** (0.18 g, 0.6 mmol), (3rR,6rS)-tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-

5 2(1H)-carboxylate **86** (0.2 g, 0.6 mmol), K₂CO₃ (0.25 g, 1.8 mmol) in water (1 mL) and PdCl₂(dppf)-CH₂Cl₂ adduct (0.05 g, 0.06 mmol) in 1,4-dioxane (4 mL) was degassed with nitrogen and then stirred at 80 °C overnight. The reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), filtered and
10 concentrated *in vacuo*. The crude product was purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound **138** as a thick colourless oil (0.23 g, 73% yield). R_t 2.93 min (Method 1a) m/z 377 [M + H-tBu]⁺ (ES⁺). ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.51-7.44 (m, 3H), 7.07-7.02 (m, 2H), 6.59 (d, J = 2.2 Hz, 1H), 6.53 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 6.06-6.01 (m, 1H), 3.88 (s, 3H), 3.77-3.68 (m, 1H), 3.59-3.48 (m, 3H), 3.12 (dd, J = 11.0 Hz, 6.9
15 Hz, 1H), 3.10-2.93 (m, 2H), 2.62 (d, J = 15.7 Hz, 1H), 1.47 (s, 9H).



[00412] Step 3. 4-(4-((3rS,6rR)-1,2,3,3r,4,6r-Hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)-2-methoxybenzonitrile (compound **139**). To a stirred solution of (3rR,6rS)-tert-butyl 5-(4-(4-cyano-3-methoxyphenoxy)phenyl)-3,3r,6,6r-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **138** (0.23 g, 0.5 mmol) in DCM (2 mL) was added TFA (1.6 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo. The resulting oil was taken up in MeOH (5 mL) and applied to an SCX column. The
20 column was washed with methanol (5 mL) and the product eluted with 10% methanolic ammonia (5 mL) to afford the title compound **139** as a colourless crystalline solid (0.1 g, 56%). R_t 1.50 min (Method 1a) m/z 333 [M + H]⁺ (ES⁺).

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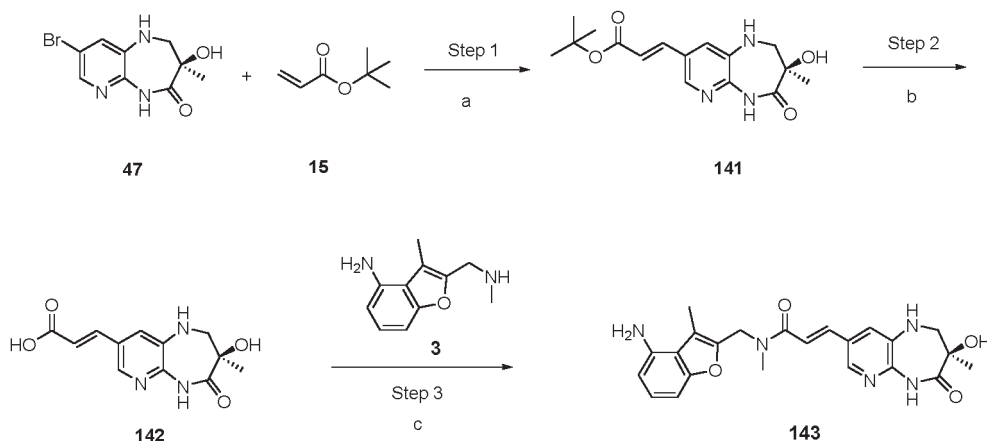


[00413] Step 4. 2-Methoxy-4-(4-((3R,6R)-2-((E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrol-5-

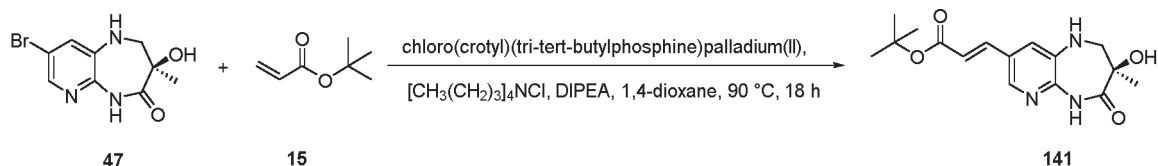
5 yl)phenoxy)benzonitrile (compound **140**). To a stirred solution of 4-(4-((3R,6R)-1,2,3,3r,4,6r-hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)-2-methoxybenzonitrile (0.1 g, 0.29 mmol) in DMF (2 mL) was added (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate (75 mg, 0.32 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.26 mL, 1.46 mmol). The reaction mixture was stirred at RT for 5
10 min and HATU (0.1 g, 0.35 mmol) was added. The reaction mixture was stirred for 1 h. Water (2 mL) was added and the aqueous phase extracted with DCM (3 × 5 mL). The combined organic phases were washed with H₂O (2 × 5 mL), brine (5 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The crude solid was purified by column chromatography (0-10% MeOH/DCM) to afford the title compound **140** as a yellow solid (0.1 g, 62% yield). R^t 2.11
15 min (Method 1a) m/z 548 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.74 (d, J = 6.7 Hz, 1H), 7.98 (dd, J = 8.3, 1.9 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.60-7.55 (m, 2H), 7.39-7.29 (m, 2H), 7.15-7.11 (m, 2H), 6.91-6.83 (m, 2H), 6.53 (ddd, J = 8.5 Hz, 6.1 Hz, 2.2 Hz, 1H), 6.20 (t, J = 3.2 Hz, 1H), 6.02 (d, J = 13.2 Hz, 1H), 4.05-3.96 (m, 0.5H), 3.90-3.76 (m, 4H), 3.70 (d, J = 12.0 Hz, 0.5H), 3.67-3.48 (m, 2H), 3.45-3.39 (m, 2H), 3.20-2.92 (m, 3H), 2.70-2.57 (m, 3H)
20 (rotamers).

[00414] Example 24. Synthesis of (R,E)-N-((4-amino-3-methylbenzofuran-2-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **143**).

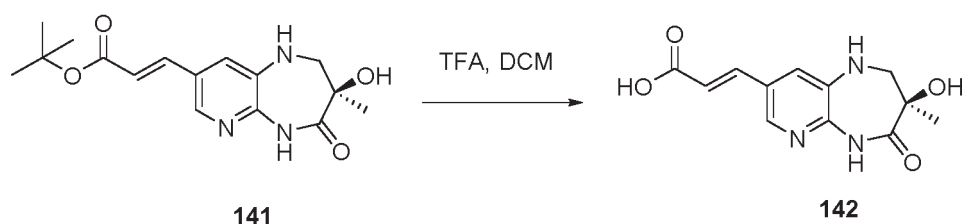
25 **[00415] General Synthetic Scheme**



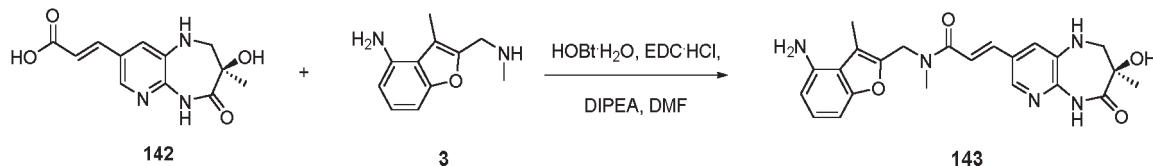
Reaction conditions: a) Chloro(crotyl)(tri-tert-butylphosphine)palladium(II), $[\text{CH}_3(\text{CH}_2)_3]_4\text{NCl}$, DIPEA, 1,4-dioxane, 90 °C, 18 h; b) TFA, DCM, 0 °C to RT; c) HOBt·H₂O, EDC·HCl, DIPEA, DMF



[00416] Step 1. tert-Butyl (R,E)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate (compound **141**). A 100 mL flask vial was charged with (R)-8-bromo-3-hydroxy-3-methyl-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one **47** (ChiralTek; chirality arbitrarily assigned; 2.0 g, 7.2 mmol), $n\text{-Bu}_4\text{NCl}$ (0.240 mg, 0.86 mmol), chloro(crotyl)(tri-tert-butylphosphine)palladium(II) (0.144 g, 0.36 mmol) and the mixture was purged with nitrogen for 10 mins. Then, tert-butyl acrylate **15** (1.57 mL, 10.8 mmol), 1,4-dioxane (52 mL) and DIPEA (2.45 mL, 14.4 mmol) were added and the nitrogen bubbled through the mixture for an additional 5 mins. The reaction mixture was heated at 90 °C for 18 h and cooled to RT. The reaction mass was filtered using 0.22uM filters, washed with MeCN and concentrated to dryness in vacuo. Acetonitrile was added to the crude material, sonicated and the yellow precipitate was filtered off to afford **141** (2.1 g, 6.5 mmol, 91.3% yield) as a yellow solid. R^t 1.45 min; LCMS: m/z : 321.3 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.97 (s, 1H), 7.93 (d, J = 1.7 Hz, 1H), 7.42 (d, J = 16.1 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 6.34 (d, J = 16.1 Hz, 1H), 6.26 (s, 1H), 5.31 (s, 1H), 3.15 (d, J = 53.8 Hz, 2H), 1.47 (s, 9H), 1.23 (s, 3H).



[00417] Step 2. (R,E)-3-(3-Hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid (compound **142**). To a solution of tert-butyl (R,E)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate **141** (0.364 g, 1.03 mmol) in DCM (9.1 mL) 2,2,2-trifluoroacetic acid (0.117 g, 1.03 mmol) was added at 0 °C. After completion of reaction (UPLC-MS control) all solvents were removed under vacuum. Then, DCM was added and the resulting mixture was added into a cold Et₂O. The yellow precipitate was filtered off and washed with Et₂O to afford the title compound **142** (0.287 g, 1.09 mmol, 106% yield) as a yellow solid. R^t 0.68 min; LCMS: m/z: 264.2 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 12.39 (s, 1H), 9.98 (s, 1H), 7.92 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 15.6 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 6.35 (d, J = 16.3 Hz, 1H), 3.23-3.09 (m, 3H), 1.23 (s, 3H).

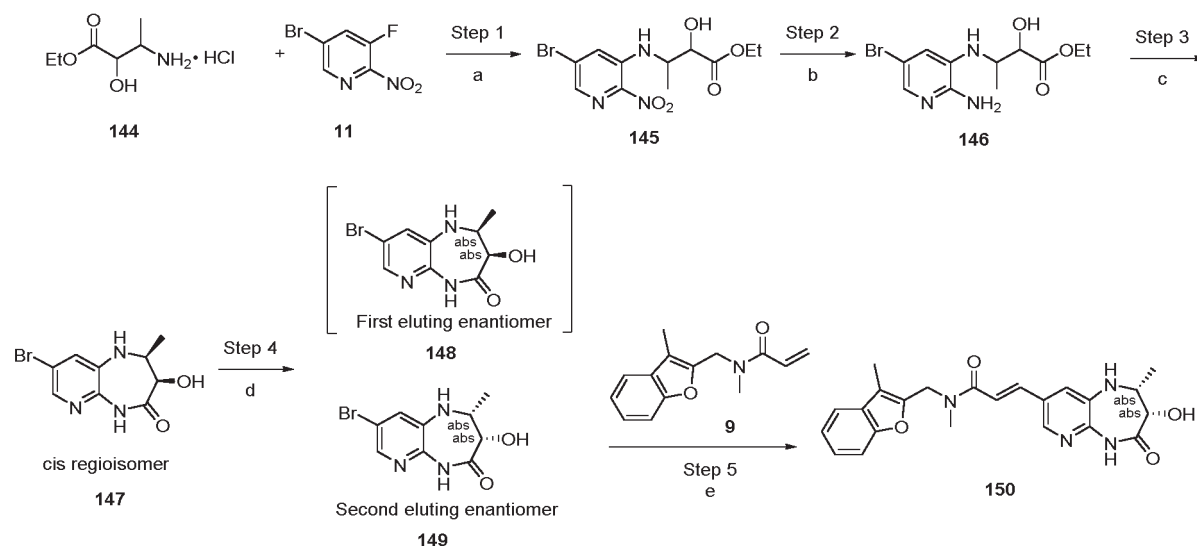


[00418] Step 3. (E)-N-[(4-Amino-3-methyl-benzofuran-2-yl)methyl]-3-[(3R)-3-hydroxy-3-methyl-4-oxo-2,5-dihydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl]-N-methyl-prop-2-enamide (compound **143**). In a microwave vial covered with aluminium foil, a mixture of (E)-3-[(3R)-3-hydroxy-3-methyl-4-oxo-2,5-dihydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl]prop-2-enoic acid **142** (35 mg, 0.13 mmol) and 3-methyl-2-(methylaminomethyl)benzofuran-4-amine **3** (42.93 mg, 0.16 mmol) was dissolved in DMF (0.22 mL). HOBt·H₂O (31.83 mg, 0.20 mmol) and EDC·HCl (39.84 mg, 0.20 mmol) were added to the reaction mixture and after 2 mins of stirring at room temperature, DIPEA (0.08 mL, 0.46 mmol) was added. The resulting mixture was stirred in the dark overnight at room temperature. The reaction mass was diluted with acetonitrile, no precipitation was observed but after few additional minutes very thin solid was present. The mixture was diluted with DMF and purified by preparative HPLC and lyophilized to afford **143** (25.7 mg, 0.0575 mmol, 43.72 % yield) as a yellow solid. R^t 1.11

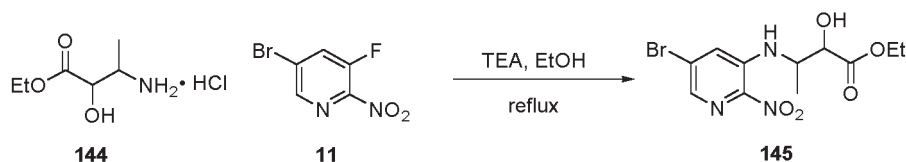
min; LCMS: m/z : 436.4 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.93 (s, 1H), 7.98 (d, $J = 11.6$ Hz, 1H), 7.46-7.31 (m, 2.5H), 7.10-7.00 (m, 0.5H), 6.91 (t, $J = 7.9$ Hz, 1H), 6.67-6.61 (m, 1H), 6.38 (d, $J = 7.9$ Hz, 1H), 6.27-6.22 (m, 1H), 5.28 (s, 1H), 5.17 (br s, 2H), 4.83 (s, 0.8H, rotamer), 4.69 (s, 1.2H, rotamer), 3.23-3.07 (m, 4H), 2.92 (s, 1H), 2.46-2.38 (m, 3H), 1.23 (s, 3H).

[00419] Example 25. Synthesis of (E)-3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **150**).

[00420] General Synthetic Scheme.



Reaction conditions: a) TEA, EtOH, reflux; b) Fe, NH₄Cl, EtOH, H₂O, reflux; c) NaH, THF, 0 °C to RT; d) Chiral Sep; e) Pd-162, MeNCy₂, NBu₄Cl, 1,4-dioxane, 80 °C.

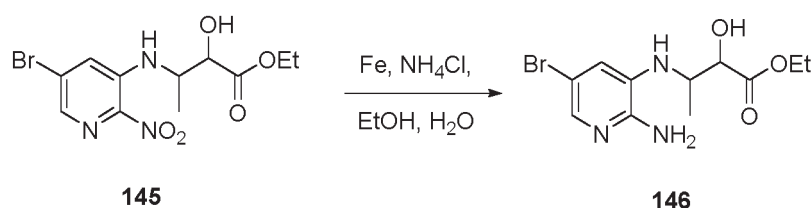


[00421] Step 1. Ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxybutanoate (compound **145**). TEA (2.8 mL, 20.1 mmol) was added to a stirred solution of 5-bromo-3-fluoro-2-nitropyridine **11** (1.1 g, 5.0 mmol) and ethyl 3-amino-2-hydroxybutanoate hydrochloride **144** (0.9 g, 4.9 mmol) in EtOH (20 mL) and the reaction mixture was heated to reflux for 4 h. The reaction mixture was allowed to cool to RT then was concentrated in

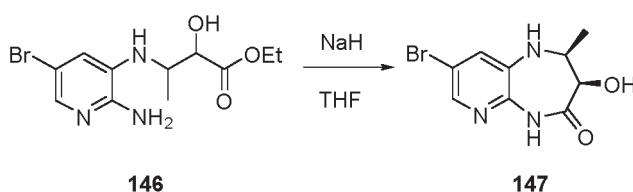
vacuo and the crude material was purified by column chromatography (DCM, then 0-10% MeOH/DCM) to give diastereomer 1 as a yellow solid (0.55 g, 32%) and diastereomer 2 as a yellow oil (0.50 g, 26%) along with a further portion which contained both diastereomers in the form of a yellow oil (0.22 g, 13%).

5 **[00422]** Diastereomer 1: R^t 1.76 min (Method 1a) m/z 348/350 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 8.04 (d, J = 1.9 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 6.12 (d, J = 4.8 Hz, 1H), 4.39-4.30 (m, 1H), 4.24 (dd, J = 4.8 Hz, 2.8 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 1.24 (d, J = 6.5 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H).

[00423] Diastereomer 2: R^t 1.80 min (Method 1a) m/z 348/350 $[M + H]^+$ (ES^+).
10 1H NMR (400 MHz, DMSO- d_6): δ , ppm 8.01 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H), 6.09 (d, J = 5.8 Hz, 1H), 4.28 (dd, J = 5.9 Hz, 4.2 Hz, 1H), 4.26-4.19 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H).

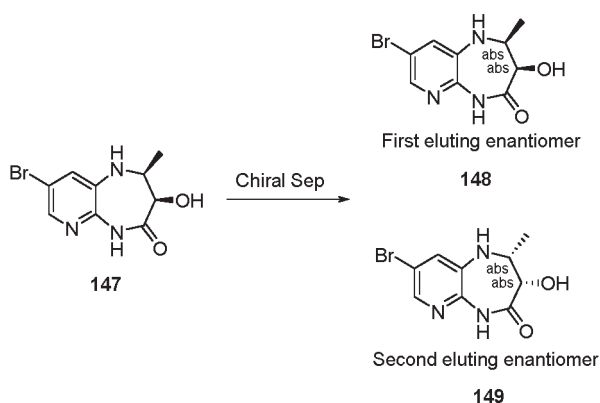


15 **[00424]** **Step 2.** Ethyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxybutanoate (compound **146**). A mixture of ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxybutanoate **145** (Diastereomer 1) (0.55 g, 1.6 mmol), iron powder (0.71 g, 12.6 mmol) and ammonium chloride (0.34 g, 6.3 mmol) in a solvent mixture of EtOH (50 mL) and H₂O (10
20 mL) was stirred at reflux for 1 hour. The reaction mixture was dry loaded on Celite® and purified by column chromatography (0-100% EtOAc/iso-hexane) to give the desired product **146** as a brown solid (0.28 g, 56%). R^t 0.99 min (Method 1a) m/z 318/320 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 7.28 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 5.72 (s, 2H), 5.46 (d, J = 6.7 Hz, 1H), 4.64 (d, J = 9.2 Hz, 1H), 4.11 (dd, J = 6.7 Hz, 3.4 Hz, 1H), 4.08-3.95
25 (m, 2H), 3.88-3.76 (m, 1H), 1.21-1.05 (m, 6H).



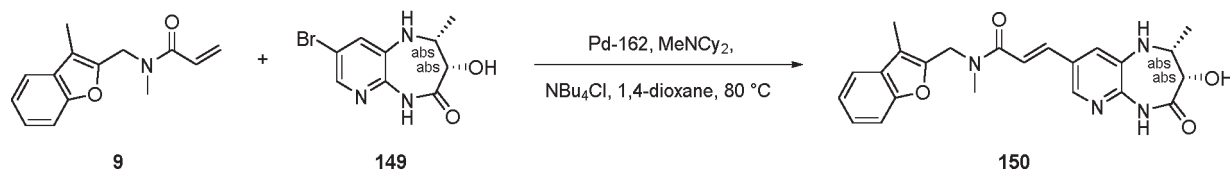
[00425] Step 3. 8-Bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **147**). Sodium hydride (60% in mineral oil, 0.2 g, 5.00 mmol) was added in small portions to a stirred solution of ethyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxybutanoate **146** (1.0 g, 3.14 mmol) in THF (5.0 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4 h. The reaction was quenched by careful addition of NH₄Cl (50 mL) and the aqueous mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried with MgSO₄, concentrated in vacuo and purified by column chromatography (0-50% EtOAc/iso-hexane) to give the desired product **147** as a brown solid (0.34 g, 37%). R_t 1.18 min (Method 1a) m/z 272/274 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 10.23 (s, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 6.36 (d, J = 5.6 Hz, 1H), 5.18 (d, J = 4.9 Hz, 1H), 4.18 (dd, J = 4.8 Hz, 3.2 Hz, 1H), 3.79-3.65 (m, 1H), 1.08 (d, J = 6.5 Hz, 3H).

[00426] Chiral separation of compound **147**.



[00427] Step 4. (2S,3R)-8-Bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **148**) and (2R,3S)-8-bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **149**). Enantiomers were separated by chiral prep HPLC using a Chiralpak® IC (Daicel Ltd.) column (2 x 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of 10% ethanol in heptane + 0.2% diethylamine, UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping ethanol (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹. Chirality was arbitrarily assigned.

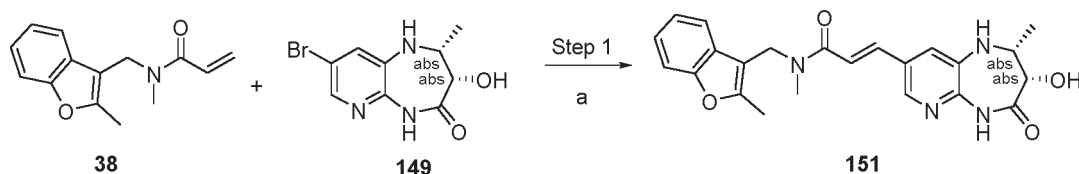
First eluting enantiomer (compound **148**). R^t 9.6 min (Method 4b). Second eluting enantiomer (compound **149**). R^t 13.5 min (Method 4b).



[00428] Step 5. (E)-3-((2R,3S)-3-Hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **150**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (42 mg, 0.18 mmol), (2R,3S)-8-bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **149** (50 mg, 0.18 mmol), NBu₄Cl (5.0 mg, 0.02 mmol) and [P(tBu)₃]Pd(crotyl)Cl (Pd-162) (7.0 mg, 0.02 mmol) and the vial was evacuated and backfilled with N₂ three times. 1,4-Dioxane (5.0 mL) and N-cyclohexyl-N-methylcyclohexanamine (79 μ L, 0.37 mmol) were added and the reaction mixture was heated to 80 °C and stirred for ~16 h. The reaction was allowed to cool to RT, the solvent was removed in vacuo and the solid was washed with isohexane. The crude material was then purified by column chromatography (0-3% MeOH/DCM) to give the desired product as a pale yellow solid. The solid was partially dissolved in MeCN and water was added until the product precipitated. The precipitate was collected by filtration and dried by azeotroping with MeCN (2 $\times$ 2 mL) to give the desired product **150** as a pale yellow solid (35 mg, 45%). R^t 1.83 min (Method 1a) m/z 421 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ , ppm 9.80 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.59-7.52 (m, 1H), 7.49-7.37 (m, 3H), 7.31-7.22 (m, 2H), 7.12 (d, J = 15.7 Hz, 1H), 5.91 (d, J = 5.7 Hz, 1H), 4.84 (s, 2H), 4.76 (d, J = 4.7 Hz, 1H), 4.22 (dd, J = 4.7 Hz, 3.4 Hz, 1H), 3.82-3.71 (m, 1H), 3.10 (s, 3H), 2.27 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H).

[00429] Example 26. Synthesis of (E)-3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide (compound **151**).

[00430] General Synthetic Scheme.



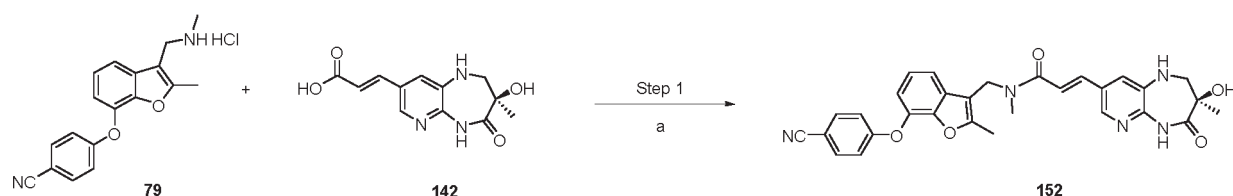
Reaction conditions: a) Pd-162, MeNCy₂, NBu₄Cl, 1,4-dioxane, 80 °C.

[00431] Step 1. (E)-3-((2R,3S)-3-Hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide

(compound **151**). A reaction vial was charged with N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide **38** (42 mg, 0.18 mmol), (2R,3S)-8-bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **149** (50 mg, 0.18 mmol), NBu₄Cl (5.0 mg, 0.02 mmol) and [P(tBu)₃]Pd(crotyl)Cl (Pd-162) (7.0 mg, 0.02 mmol) and the vial was evacuated and backfilled with N₂ three times. 1,4-Dioxane (5.0 mL) and N-cyclohexyl-N-methylcyclohexanamine (79 µL, 0.37 mmol) were added and the reaction mixture was heated to 80 °C and stirred for 3 h. The reaction was allowed to cool to RT, the solvent was removed in vacuo and the solid was washed with isohexane. The crude material was then purified by column chromatography (0-3% MeOH/DCM) to give the desired product as a pale yellow solid. The solid was partially dissolved in MeCN and water was added until the product precipitated. The precipitate was collected by filtration and dried by azeotroping with MeCN (2 × 2 mL) to give the desired product **151** as a pale yellow solid (14 mg, 17%). R^t 1.80 min (Method 1a) m/z 421 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ, ppm 9.80 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.49-7.42 (m, 2H), 7.39 (d, J = 2.0 Hz, 1H), 7.26-7.15 (m, 2H), 7.10 (d, J = 15.9 Hz, 1H), 5.89 (d, J = 5.8 Hz, 1H), 4.80-4.73 (m, 3H), 4.21 (dd, J = 4.7 Hz, 3.4 Hz, 1H), 3.81-3.71 (m, 1H), 3.00 (s, 3H - obscured by solvent peak), 2.50 (s, 3H, - obscured by solvent peak), 1.11 (d, J = 6.5 Hz, 3H).

[00432] Example 27. Synthesis of (R,E)-N-((7-(4-cyanophenoxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **152**).

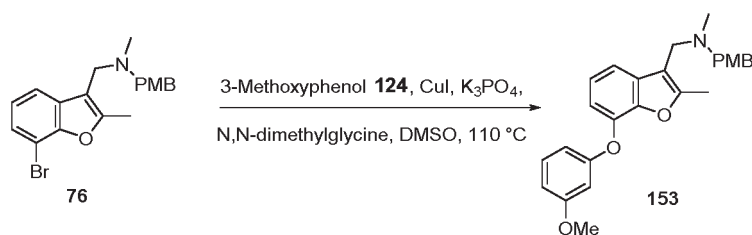
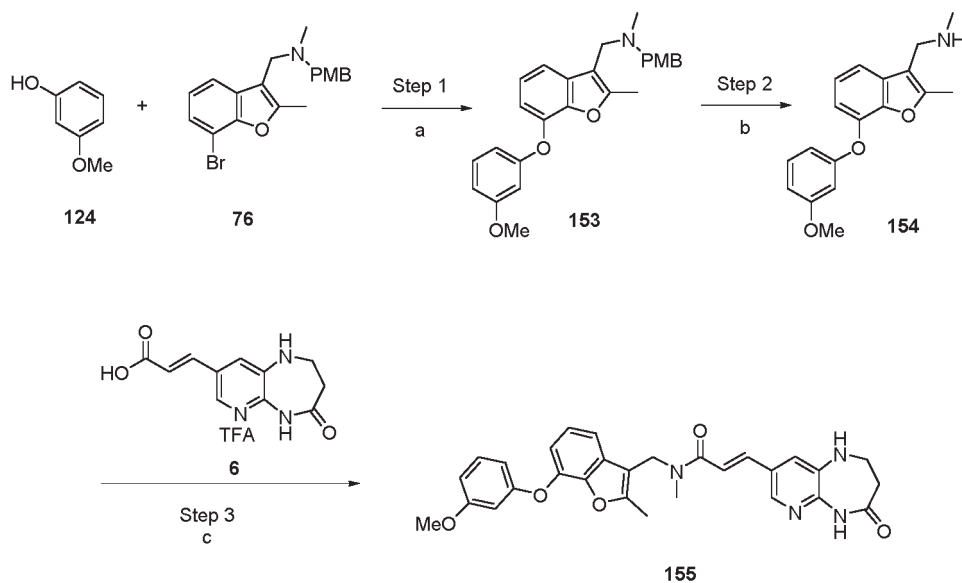
[00433] General Synthetic Scheme.



[00434] Step 1. (R,E)-N-((7-(4-Cyanophenoxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **152**) was obtained from the amine **79** and the acid **142** as a yellow solid in standard amine to amide coupling reaction described e.g. for compound **143** (Purity = 95%; Yield = 38%). R^t 1.72 min; LCMS: m/z : 538.5 $[M + H]^+$. 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.93 (s, 1H), 7.98 (s, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.57-7.19 (m, 4H), 7.15-6.99 (m, 4H), 6.24 (br s, 1H), 5.28 (br s, 1H), 4.91 (s, 0.3H, rotamer), 4.76 (s, 1.7H, rotamer), 3.22-3.09 (m, 2H), 3.07 (s, 2.3H, rotamer), 2.87 (s, 0.7H, rotamer), 2.48 (s, 3H, partially under DMSO peak), 1.23 (s, 3H).

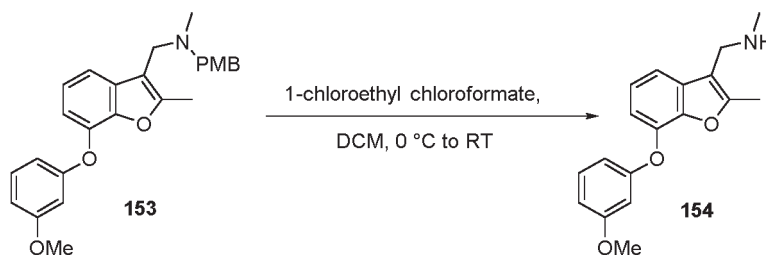
[00435] Example 28. Synthesis of (E)-N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **155**).

[00436] General Synthetic Scheme.

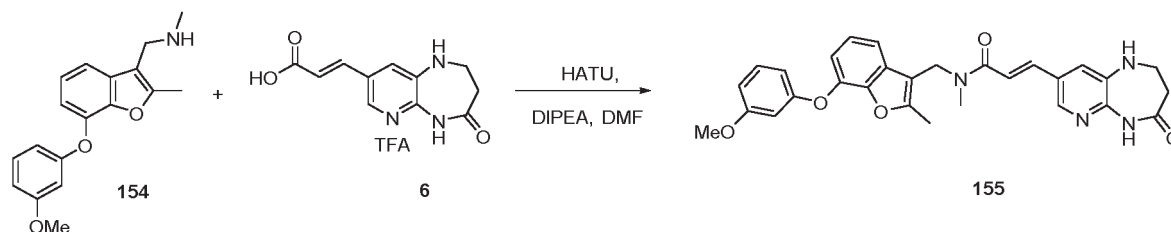


[00437] Step 1. N-(4-Methoxybenzyl)-1-(7-(3-methoxyphenoxy)-2-methylbenzofuran-

3-yl)-N-methylmethanamine (compound **153**). A mixture of 1-(7-bromo-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **76** (200 mg, 0.53 mmol), 3-methoxyphenol **124** (Sigma-Aldrich) (80 mg, 0.64 mmol), 2-(dimethylamino)acetic acid (11 mg, 0.11 mmol), copper(I) iodide (10 mg, 0.05 mmol) and potassium phosphate tribasic (230 mg, 1.1 mmol) was evacuated and backfilled with nitrogen (3 x). DMSO (2 mL) was added and the mixture was heated to 110 °C overnight. Further aliquots of copper(I) iodide (10 mg, 0.05 mmol) and 3-methoxyphenol **124** (80 mg, 0.64 mmol) were added and heating continued for a further 3 hours. The reaction mixture was allowed to cool to RT, was filtered through Celite® and the filtrate was diluted with brine (20 mL). The crude mixture was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by chromatography (0-100% EtOAc/iso-hexane) to afford the title compound **153** as a light orange oil (103 mg, 43%). R_t 1.76 min (Method 1a) m/z 418 [M + H]⁺ (ES⁺).



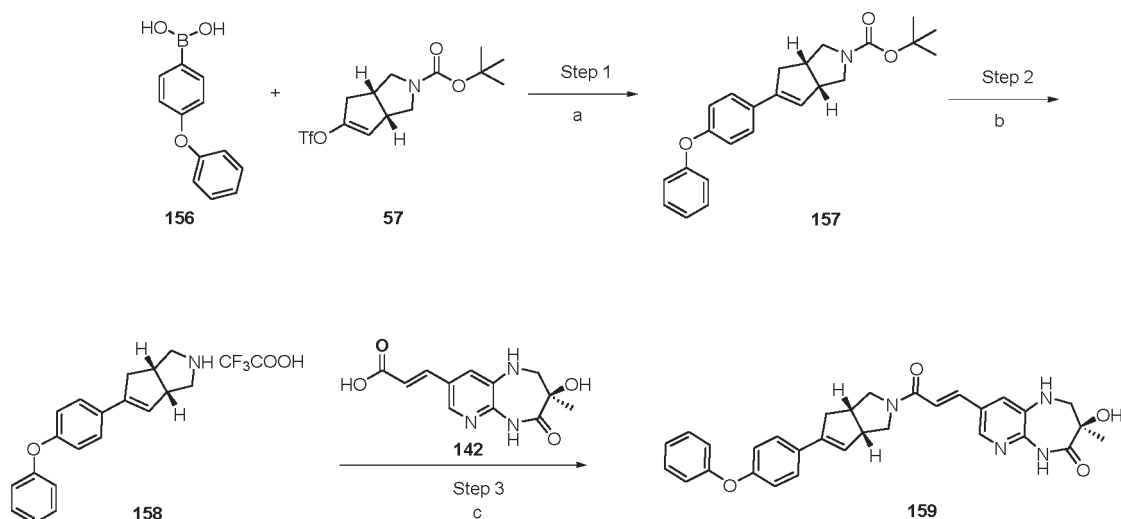
[00438] Step 2. 1-(7-(3-Methoxyphenoxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine (compound **154**). To an ice cooled solution of N-(4-methoxybenzyl)-1-(7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **153** (100 mg, 0.24 mmol) in DCM (2 mL) was added 1-chloroethyl chloroformate (0.031 mL, 0.29 mmol). The mixture was allowed to attain RT and stirred for a further 20 mins, then was evaporated to dryness. The residue was taken up into methanol (5 mL) and heated under reflux for 1 hour. The mixture was evaporated to dryness and the residue was dissolved in methanol (4 mL) and applied to an SCX column (2 g). The column was washed with methanol (20 mL) and the product eluted with a solution of 10% methanolic ammonia (10 mL) to give the title compound **154** as a colourless gum (42 mg, 47%), which was used in the next step without further purification. R^t 1.40 min (Method 1b) m/z 267 $[M - NHCH_3]^+$ (ES^+).



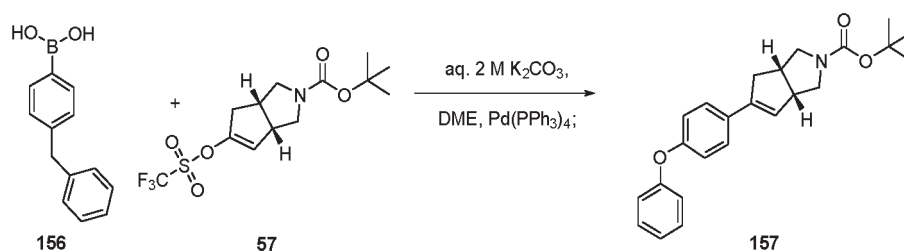
[00439] Step 3. (E)-N-((7-(3-Methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **155**). To a solution of 1-(7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **154** (40 mg, 0.11 mmol), (E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid trifluoroacetate **6** (31 mg, 0.09 mmol) and DIPEA (78 μ L, 0.45 mmol) in DMF (2 mL) was added HATU (41 mg, 0.11 mmol) and the mixture was stirred at RT for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) and the solid was collected and dried. The crude product was purified by chromatography (0-10% MeOH/DCM) to afford the title compound **155** as a pale yellow solid (25 mg, 54%). R^t 2.17

min (Method 1a) m/z 513 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6 , 363 K): δ , ppm 9.13 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 15.5 Hz, 1H), 7.41-7.34 (m, 2H), 7.26 (t, J = 8.2 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 15.6 Hz, 1H), 6.88 (dd, J = 7.9 Hz, 1.0 Hz, 1H), 6.72 (ddd, J = 8.3 Hz, 2.4 Hz, 0.8 Hz, 1H), 6.61 (t, J = 2.4 Hz, 1H), 6.57 (ddd, J = 8.1 Hz, 2.3 Hz, 0.8 Hz, 1H), 5.80 (s, 1H), 4.78 (s, 2H), 3.76 (s, 3H), 3.47-3.42 (m, 2H), 3.03 (s, 3H), 2.70 - 2.63 (m, 2H), 2.48 (s, 3H).

[00440] Example 29. Synthesis of (R)-3-hydroxy-3-methyl-8-((E)-3-oxo-3-((3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **159**).

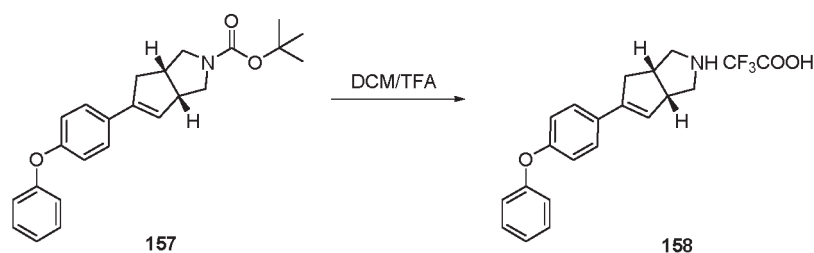


Reaction conditions: a) aq. 2 M K_2CO_3 , DME, $Pd(PPh_3)_4$; b) TFA/DCM, 0 °C to RT; c) HOBT, EDC, DIPEA, DMF

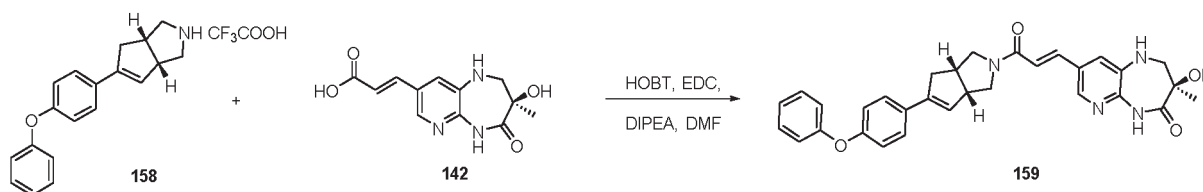


[00441] Step 1. tert-Butyl (3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (compound **157**) was synthesized following the procedure described in US2017/0174683 A1. In a microwave vial was added, tert-butyl (3aR,6aR)-5-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,6a-

tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **57** (104 mg, 0.276 mmol), (4-phenoxyphenyl)boronic acid **156** (96 mg, 0.448 mmol) and a solution of 2 M K₂CO₃ (276 μ L, 0.552 mmol) in ethylene glycol dimethyl ether (1 mL) was purged with nitrogen for 10 mins in ultrasound bath. Then tetrakisphenyl-phosphinepalladium (30 mg, 0.025 mmol) was added. The resulting suspension was stirred at 100 °C for 30 min under microwave irradiation. The resulting solution was cooled down to RT. Water and EtOAc were added, the organic layer was separated, washed with water then brine and dried (MgSO₄) and evaporated till dryness to afford a brown oil which was purified on silica gel using SNAP ultra column (10 g) and n-Hept/AcOEt 95/5 to 50/50 as an eluent. Good fractions were collected and concentrated to dryness to afford tert-butyl (3aR,6aS)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrole-2(1H)-carboxylate **157** as a colourless oil which crystallised as a white solid upon standing (85 mg, Purity = 99%, Yield = 85%). R_t 2.65 min; LCMS: m/z: 322.2 [M + H]⁺.

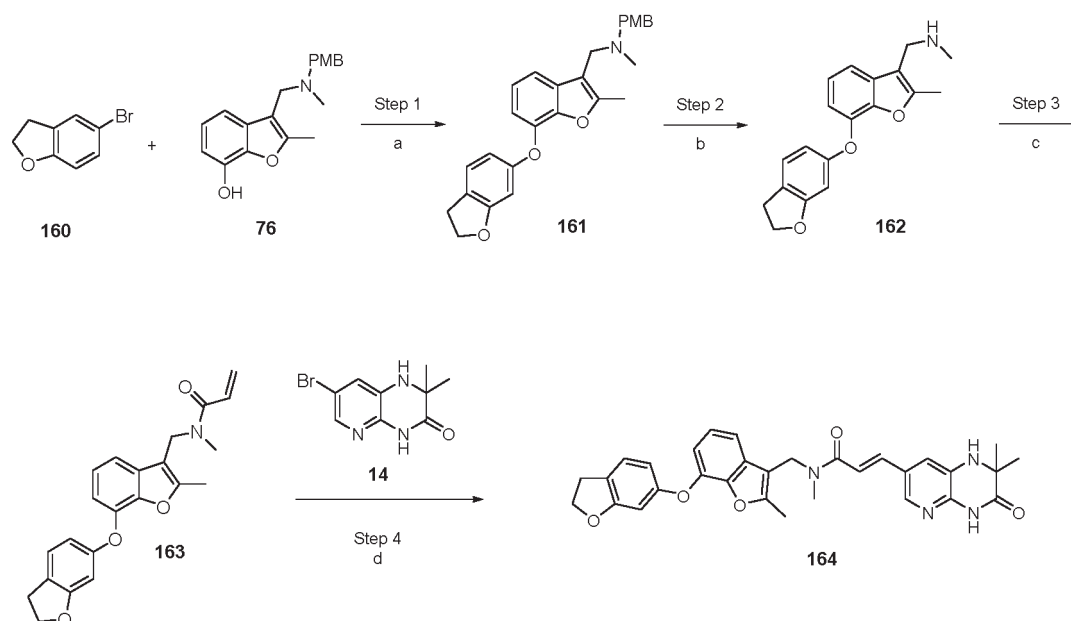


[00442] Step 2. (3aS,6aR)-5-(4-Phenoxyphenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate (compound **158**). To a solution of tert-butyl (3aR,6aS)-5-(4-phenoxyphenyl)-3,3a,6,6a-tetrahydro-1H-cyclopenta[c]pyrrole-2-carboxylate **157** (85 mg, 0.23 mmol) in DCM (1.0 mL) was added dropwise 2,2,2-trifluoroacetic acid (25.67 mg, 0.23 mmol). The reaction was stirred at room temperature until complete conversion of the starting material was detected. After completion of reaction solvents were removed by vacuum to afford the title compound **158** (88 mg) as a yellow oil. R_t 1.29 min (Method 1b); m/z 278.6 [M + H]⁺ (ES⁺).

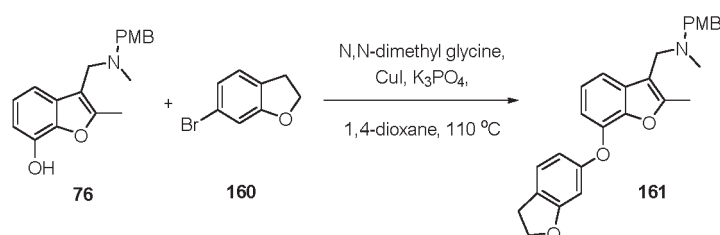


[00443] **Step** **3.** (R)-3-Hydroxy-3-methyl-8-((E)-3-oxo-3-((3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **159**). To a microwave vial covered with aluminium foil, (3aR,6aS)-5-(4-phenoxyphenyl)-1,2,3,3a,6,6a-hexahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate **158** (44.6 mg, 0.11mmol), HOBT·H₂O (26.18 mg, 0.17 mmol, 1.5 eq.), EDC·HCl (32.77 mg, 0.17 mmol) and (E)-3-[(3R)-3-hydroxy-3-methyl-4-oxo-2,5-dihydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl]prop-2-enoic acid **142** (30 mg, 0.11 mmol) were added and the solid was dissolved in DMF (0.2 mL). After 2 mins of stirring at RT, DIPEA (0.07 mL, 0.40 mmol) was added. The reaction mixture was stirred in the dark overnight at the same temperature. After completion of the reaction, water and acetonitrile were added to the mixture, the suspension was sonicated, the precipitate was filtered off and washed with MTBE. The crude material (18 mg) was further purified by autoprep. The title compound **159** (6.6 mg) as a yellow foam was isolated. R^t 1.91 min (Method 1b); m/z 523.5 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.95 (d, J = 5.3 Hz, 1H), 7.92 (m, 1H), 9.50 (d, J = 8.3 Hz, 2H), 7.42-7.28 (m, 4H), 7.14 (t, J = 6.2 Hz, 1H), 7.03-6.95 (m, 4H), (dd, J = 6.8 Hz, 15.5 Hz, 1H), 6.28-6.21 (m, 1H), 6.13 (br s, 1H), 5.30 (d, J = 4.4 Hz, 1H), 4.05-3.75 (m, 2H), 3.73-3.49 (m, 2H), 3.22-3.10 (m, 2H), 3.10-2.91 (m, 2H), 2.69-2.55 (m, 2H), 1.23 (d, J = 4.1 Hz, 3H). Note: Aliphatic signals partially obscured by water and solvent peaks.

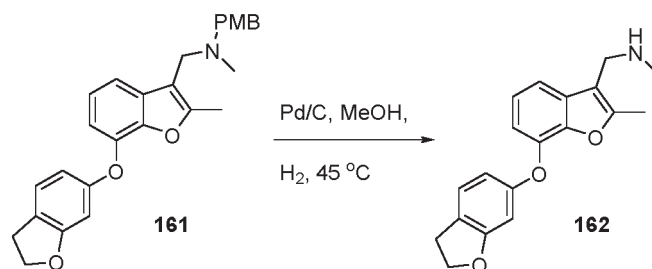
[00444] **Example 30.** Synthesis of (E)-N-((7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methylacrylamide (compound **164**).



Reaction conditions: a) CuI, N,N-dimethyl glycine, K₃PO₄, 1,4-dioxane, 110 °C; b) Pd/C, MeOH, H₂, 45 °C; c) acryloyl chloride, TEA, DCM, 0 °C to RT; d) Pd-116, DIPEA, Bu₄NCl, 1,4-dioxane, 80 °C.

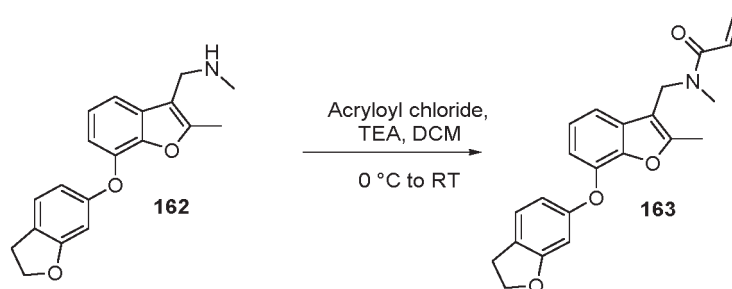


[00445] Step 1. 1-(7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine (compound **161**). A mixture of 3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-ol **76** (200 mg, 0.64 mmol), 6-bromo-2,3-dihydrobenzofuran **160** (153 mg, 0.77 mmol), N,N-dimethyl glycine (66 mg, 0.64 mmol), CuI (122 mg, 0.64 mmol) and K₃PO₄ (273 mg, 1.3 mmol) was evacuated and backfilled with nitrogen three times. DMSO (3 mL) was added and the mixture was heated to 110 °C and stirred for 16 h. The reaction mixture was cooled to RT. Ethyl acetate (10 mL) was added and the mixture was filtered through Celite®. The resulting solution was washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography (0-10% MeOH/DCM) to give the title compound **161** as a colourless oil (80 mg, 27%). R_t 1.77 min (Method 1a) m/z 430 [M + H]⁺ (ES⁺).



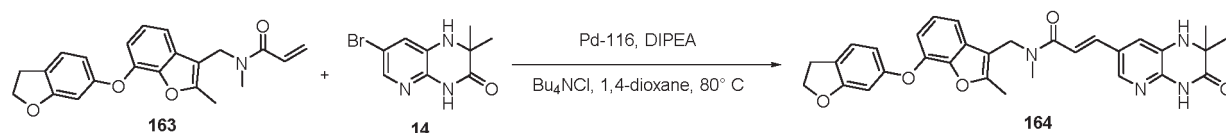
[00446] **Step 2.** 1-(7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine (compound **162**). A solution of 1-(7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **161** (80 mg, 0.19 mmol) in methanol (5 mL) was passed through a H-cube with a 10% Pd/C catalytic cartridge and using 'Full H₂' mode at 45 °C. The solvent was concentrated in vacuo to give the title compound **162** as a colourless oil (43 mg, 70%). R^t 1.45 min (Method 1a) m/z 279 [M - MeNH]⁺ (ES⁺).

10

**[00447]**

[00448] **Step 3.** N-((7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **163**). To an ice cooled solution of 1-(7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **160** (160 mg, 0.52 mmol) and TEA (300 μL, 2.07 mmol) in DCM (10 mL) was added dropwise a solution of acryloyl chloride (42 μL, 0.52 mmol) in DCM (1.0 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h. The reaction was quenched with water (5.0 mL) and the two phases separated. The organic phase was dried with MgSO₄, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-100% EtOAc/iso-hexane) to give the title compound **163** as a colourless oil (120 mg, 60%). R^t 2.36 min (Method 1a); m/z 364 [M + H]⁺ (ES⁺).

20

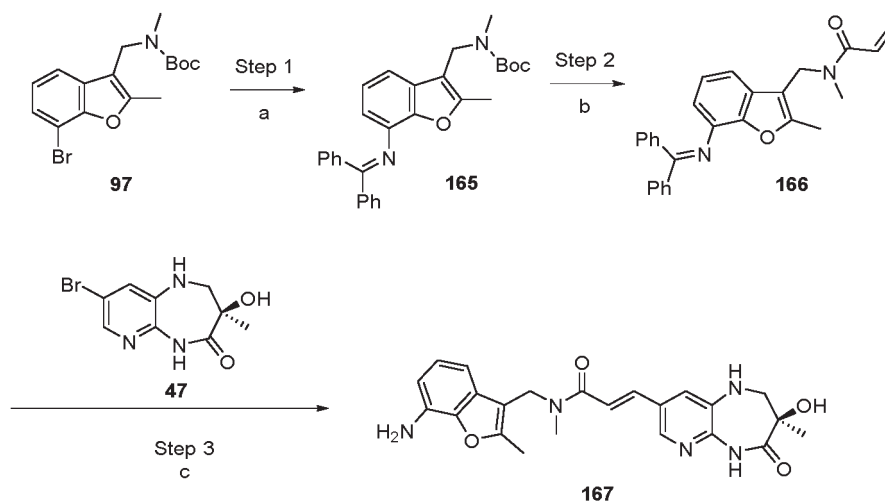


[00449] Step 4. (E)-N-((7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-

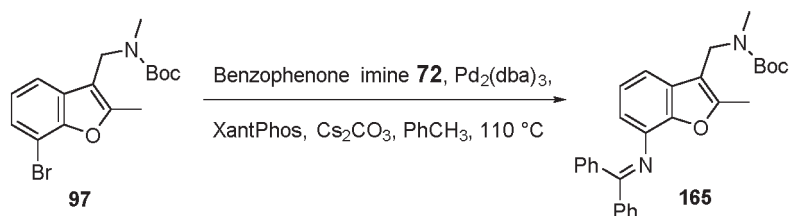
methylacrylamide (compound **164**). A reaction vial was charged with N-((7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **163** (60 mg, 0.16 mmol), 7-bromo-2,2-dimethyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one **14** (42 mg, 0.16 mmol), tetrabutylammonium chloride hydrate (5.0 mg, 0.02 mmol) and Pd[P(tBu)₃]₂ (Pd-116) (9.0 mg, 0.02 mmol) and the vial was evacuated and backfilled with N₂ three times. 1,4-Dioxane (4.0 mL) and DIPEA (58 µL, 0.33 mmol) were added and the reaction mixture was heated to 80 °C and stirred overnight. The reaction was allowed to cool to RT, the solvent was removed in vacuo. The crude material was then purified by column chromatography (0-3% MeOH/DCM) to give the desired product **164** as a pale yellow solid (66 mg, 74%). R_t 2.72 min (Method 1b); m/z 539 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, VT NMR): δ, ppm 10.42 (s, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.48 (d, J = 15.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 1.9 Hz, 1H), 7.18-7.13 (m, 2H), 7.04 (d, J = 15.4 Hz, 1H), 6.83 (dd, J = 7.9 Hz, 1.0 Hz, 1H), 6.47 (dd, J = 8.1 Hz, 2.3 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 6.04 (s, 1H), 4.78 (s, 2H), 4.57 (t, J = 8.6 Hz, 2H), 3.15 (t, J = 8.6 Hz, 2H), 3.03 (s, 3H), 2.49 (s, 3H), 1.31 (s, 6H).

[00450] Example 31. Synthesis of (R,E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **167**).

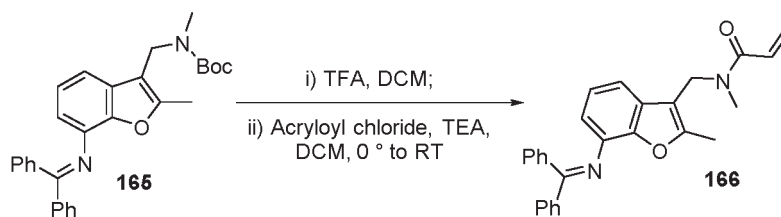
[00451] General Synthetic Scheme.



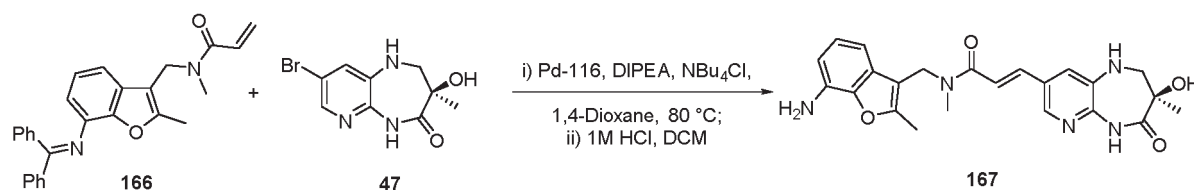
Reaction conditions: a) $\text{Pd}_2(\text{dba})_3$, Xantphos, benzophenone imine **72**, Cs_2CO_3 , PhCH_3 , 110°C ; b) i) TFA, DCM; ii) Acryloyl chloride, TEA, DCM, 0°C to RT; b) i) Pd-116, NBu_4Cl , DIPEA, 1,4-Dioxane, 80°C ; ii) 1M HCl, DCM.



- 5 **[00452] Step 1.** tert-Butyl ((7-((diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate (compound **165**). tert-Butyl ((7-bromo-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate **97** (2.0 g, 5.65 mmol), tris(dibenzylideneacetone)dipalladium (0.52 g, 0.57 mmol), Cs_2CO_3 (3.68 g, 11.3 mmol) and Xantphos (0.49 g, 0.85 mmol) were added to a flask and the flask was evacuated and back filled with N_2 three times. Toluene (40
- 10 mL) was added and N_2 was bubbled through the reaction mixture for 10 mins. Benzophenone imine **72** (1.1 mL, 6.78 mmol) was then added and the reaction mixture was heated to reflux for ~24 h. The reaction mixture was allowed to cool to RT, was stirred over the weekend and then was concentrated in vacuo. The crude material was purified by column chromatography (DCM) to give the desired product **165** as a yellow oil which
- 15 crystallised on standing (1.67 g, 65%). R_t 3.09 min (Method 1b); m/z 455 $[\text{M} + \text{H}]^+$ (ES^+). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ , ppm 7.76-7.65 (m, 2H), 7.63-7.55 (m, 1H), 7.55-7.46 (m, 2H), 7.33-7.21 (m, 3H), 7.16-7.04 (m, 3H), 7.01-6.88 (m, 1H), 6.49 (d, $J = 7.6$ Hz, 1H), 4.40 (s, 2H), 2.61 (s, 3H), 2.37 (s, 3H), 1.43 (s, 9H).



[00453] Step 2. N-((7-((Diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **166**). TFA (15 mL, 195 mmol) was added dropwise to a stirred solution of tert-butyl ((7-((diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate **165** (0.8 g, 1.76 mmol) in DCM (30 mL) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated in vacuo and the resulting residue was taken up in DCM (30 mL), cooled to 0 °C and TEA (5.0 mL, 35.9 mmol) followed by acryloyl chloride (0.17 mL, 2.11 mmol) were added. The reaction was allowed to return to RT and was stirred for ~16 h. The reaction mixture was quenched with water (50 mL), then the organic phase was separated and the aqueous phase was extracted again with DCM (2 × 50 mL). The combined organic layers were dried by passing through a phase separation cartridge and concentrated in vacuo. The crude material was purified by column chromatography (0-3% MeOH/DCM) to give impure material which was purified again by column chromatography (0-30% EtOAc/iso-hexane) to give the desired product **166** as a yellow oil (0.16 g, 21% over 2 steps).

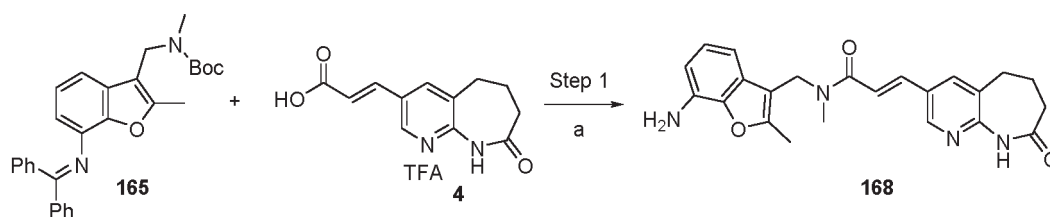


[00454] Step 3. (R,E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **167**). A reaction vial was charged with N-((7-((diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **166** (0.12 g, 0.29 mmol), (R)-8-bromo-3-hydroxy-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **47** (80 mg, 0.29 mmol), NBu₄Cl (9 mg, 0.03 mmol) and Pd-116 (15 mg, 0.03 mmol) and the vial was evacuated and backfilled with N₂ three times. 1,4-Dioxane (5 mL) and DIPEA (0.10 mL, 0.59

mmol) were added and the reaction mixture was heated to 80 °C and stirred for 3 h. The reaction mass was allowed to cool to RT, then was diluted with HCl (10 mL, 1M Aq) and the aqueous mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with aq. 1 M HCl (2 × 20 mL), then the combined aqueous layers were neutralised with sat. aq. NaHCO₃. The resulting precipitate was collected by filtration and purified by column chromatography (0-5% MeOH/DCM) to give the desired product **167** as a pale yellow solid (42 mg, 33% over 2 steps). R_t 1.32 min (Method 1a); m/z 436 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ, ppm 9.36 (s, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 15.4 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 15.3 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 6.03 (t, J = 4.6 Hz, 1H), 4.91 (s, 1H), 4.87 (s, 2H), 4.71 (s, 2H), 3.21 (dd, J = 13.4, 3.7 Hz, 1H), 3.16 (dd, J = 13.4, 5.6 Hz, 1H), 2.98 (s, 3H), 2.47 (s, 3H), 1.28 (s, 3H).

[00455] Example 32. Synthesis of (E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **168**).

[00456] General Synthetic Scheme.



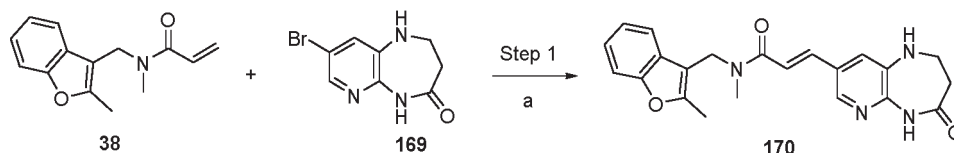
Reaction conditions: a) i) TFA, DCM; ii) HATU, DIPEA, DMF; iii) 1M HCl, DCM.

[00457] Step 1. (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **168**). TFA (2.5 mL, 32.4 mmol) was added dropwise to a stirred solution of tert-butyl ((7-((diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)(methyl)carbamate **165** (0.15 g, 0.21 mmol) in DCM (5.0 mL) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated in vacuo and the resulting residue was taken up in DMF (2.0 mL) and (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid

trifluoroacetate **4** (75 mg, 0.21 mmol) followed by DIPEA (1.0 mL, 5.73 mmol) were added. The reaction was stirred for 10 mins then HATU (0.12 g, 0.32 mmol) was added and the reaction was stirred for a further ~16 h at RT. The reaction mixture was diluted with aq. 1 M HCl (10 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with HCl (2 × 20 mL, 1 M aq.) and the combined aqueous layers were neutralised with sat. aq. NaHCO₃. The resulting precipitate was collected by filtration and purified by column chromatography (0-5% MeOH/DCM) to give the desired product **168** as an off-white solid (40 mg, 43% over 3 steps). R_t 1.41 min (Method 1a); m/z 405 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ, ppm 9.55 (s, 1H), 8.47 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 15.4 Hz, 1H), 7.34-7.20 (m, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.53 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 4.86 (s, 2H), 4.73 (s, 2H), 2.97 (s, 3H), 2.76 (t, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 2.14 (p, J = 7.2 Hz, 2H).

[00458] Example 33. Synthesis of (E)-N-methyl-N-((2-methylbenzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **169**).

[00459] General Synthetic Scheme.



Reaction conditions: a) Pd-162, NCy₂NMe, NBu₄Cl, 1,4-dioxane, 80 °C

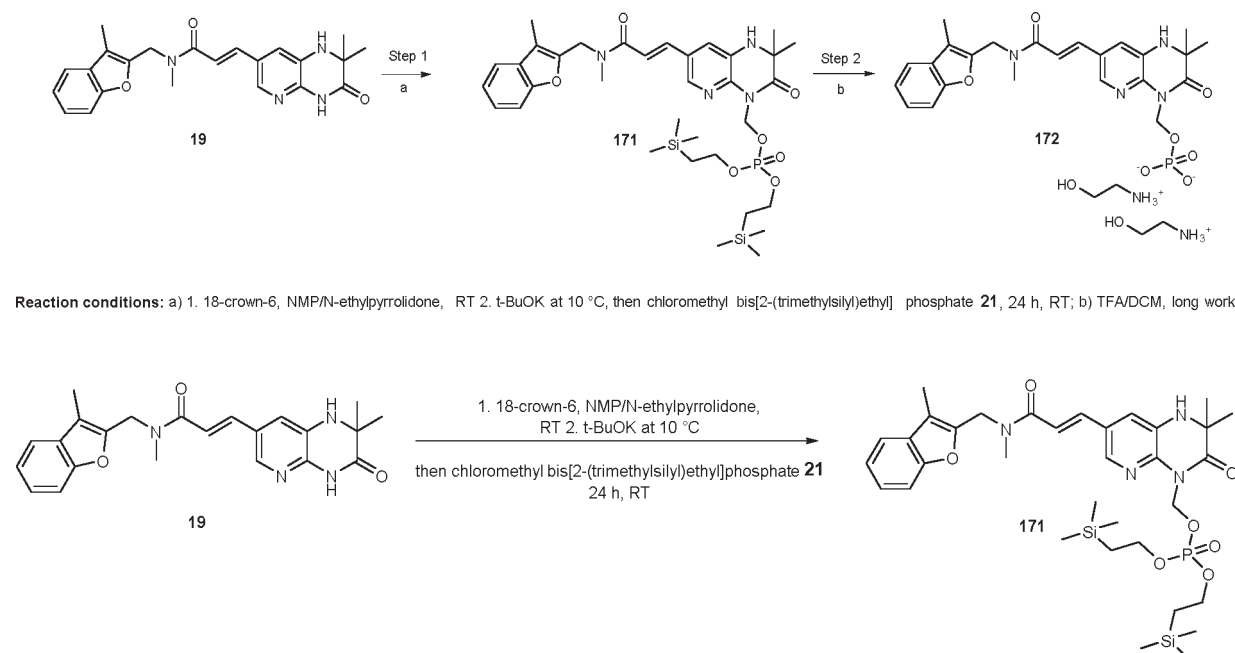
[00460] The 8-bromo-1,2,3,5-tetrahydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (compound **169**) was synthesized according to the literature procedures described by AFFINIUM PHARMECEUTICALS, INC: WO2007/67416, 2007, A2 and AURIGENE DISCOVERY TECHNOLOGIES LIMITED; WO2013/80222, 2013, A1.

[00461] Step 1. (E)-N-Methyl-N-((2-methylbenzofuran-3-yl)methyl)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide (compound **170**). A reaction vial was charged with N-methyl-N-((2-methylbenzofuran-3-yl)methyl)acrylamide **38** (150 mg, 0.65 mmol), 8-bromo-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **169** (158 mg, 0.65 mmol), tetrabutylammonium chloride hydrate (19.36 mg, 0.07 mmol), [P(tBu)₃]Pd(crotlyl)Cl (Pd-162) (26.1 mg, 0.07 mmol). The reaction vial was flushed with

nitrogen for 5 mins. 1,4-Dioxane (10 mL) and N-cyclohexyl-N-methylcyclohexanamine (280 μ L, 1.31 mmol) were added and the reaction mixture was purged with nitrogen for a further 5 mins. The mixture was heated to 80 °C for 1 h. The reaction mixture was allowed to cool to RT and the solid collected by filtration, washed with 1,4-dioxane (10 mL), followed by acetonitrile (10 mL) and the solid dried in vacuo to give the title compound **170** as a pale yellow solid (192 mg, 74%). R^t 1.83 min (Method 1b) m/z 391 $[M + H]^+$ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆, 363 K): δ , ppm 9.17 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.50-7.43 (m, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.26-7.16 (m, 2H), 7.10 (d, J = 15.5 Hz, 1H), 5.81 (d, J = 4.8 Hz, 1H), 4.77 (s, 2H), 3.47-3.41 (m, 2H), 2.69-2.62 (m, 2H). Note: Both CH₃ signals obscured by water and solvent peaks.

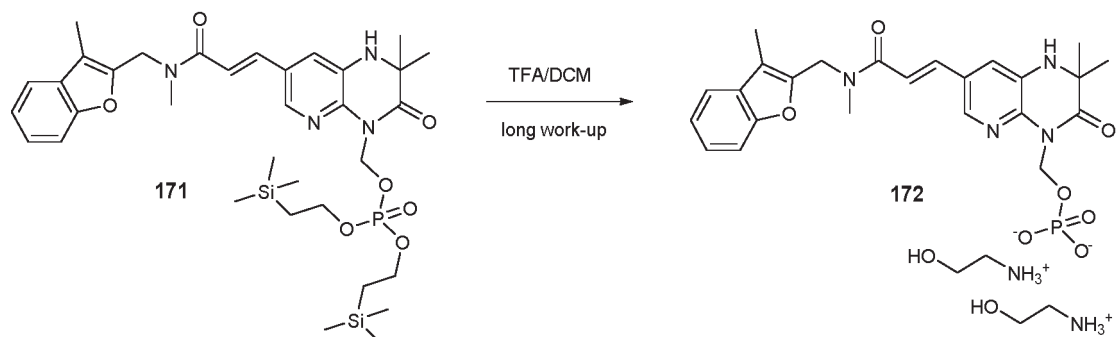
[00462] Example 34. Synthesis of 2-hydroxyethan-1-aminium (E)-(2,2-dimethyl-7-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-3-oxo-2,3-dihydropyrido[2,3-b]pyrazin-4(1H)-yl)methyl phosphate (compound **172**).

[00463] General Synthetic Scheme.



[00464] Step 1. (E)-(3,3-Dimethyl-6-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl bis(2-(trimethylsilyl)ethyl) phosphate (compound **171**). In a sealed 6 mL microwave vial under

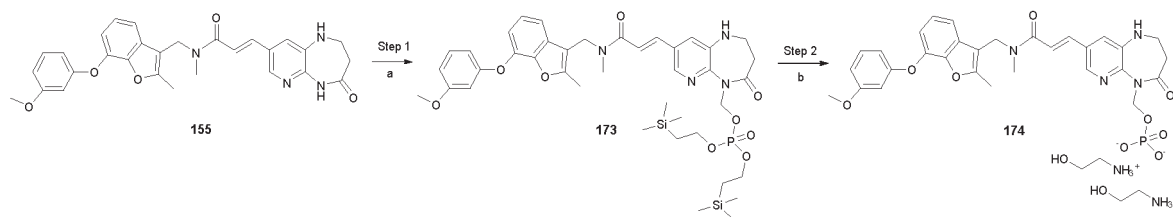
N₂, (E)-3-(2,2-dimethyl-3-oxo-1,4-dihydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-[(3-methylbenzofuran-2-yl)methyl]prop-2-enamide **19** (500 mg, 1.23 mmol, 1.00 eq.) and 1,4,7,10,13,16-hexaoxacyclooctadecane (408.37 mg, 1.53 mmol, 1.24 eq.) were put in suspension in N-ethylpyrrolidone (3.0 mL) at RT. Then resulting yellow suspension was stirred at RT for 5 minutes, and submitted to degassing cycles (5 cycles; vacuum/nitrogen). Then reaction mixture was cooled down to 10 °C and potassium 2-methylpropan-2-olate (1.3 mL, 1.3 mmol, 1.05 eq, 1 M in THF) was added dropwise over 5 minutes. Resulting yellow solution was again submitted to degassing cycles (3 cycles; vacuum/nitrogen) and was then stirred at RT for 20 minutes. Then, chloromethyl bis(2-(trimethylsilyl)ethyl)phosphate **21** (1997.1 mg, 1.73 mmol, 1.4 eq., 30% w/w in Heptane) was added dropwise to the reaction mixture at RT over 5 minutes. Reaction mixture was then stirred at RT for 22 hrs (UPLC/MS: Starting material: Rt = 1.64 min; 41% (AUC); ES+: 405.4. Product: Rt = 2.68 min; 44% (AUC); ES+: 715.6). A mixture of saturated solution of ammonium acetate (7 mL; pH = 9) and THF (5 mL) was added to the reaction mixture. After shaking, phase were separated and second washing was done with a mixture of brine (7 mL) and THF (5 mL). The third washing was done with brine (7 mL) and methyl cyclohexane (7 mL) was then added to the organic phase. Resulting suspension was filtered through a glass filter and solid was then washed with methyl cyclohexane (7 mL). Filtrate was concentrated to dryness at 25 °C under vacuum to give yellow oil which was purified by flash chromatography (SiO₂) eluting first with MTBE 99.8%-DIEA 0.2% then with MTBE 89.8%-Acetonitrile 10%-DIEA 0.2%. Fractions of interest were combined and concentrated to dryness at RT under vacuum to give the title compound **171** as an yellow oil (m = 440.6 mg; UPLC purity: 98% (AUC); ES+: 715.6; 48.9% yield).



[00465] Step 2. 2-Hydroxyethan-1-aminium (E)-(3,3-dimethyl-6-(3-(methyl((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl phosphate (compound **172**). In the 50 mL flask containing [2,2-dimethyl-7-

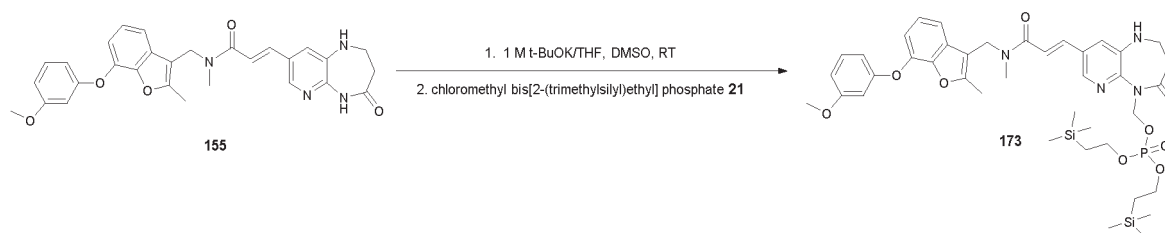
[(E)-3-[methyl-[(3-methylbenzofuran-2-yl)methyl]amino]-3-oxo-prop-1-enyl]-3-oxo-1H-pyrido[2,3-b]pyrazin-4-yl)methyl bis(2-trimethylsilylethyl)phosphate (440.6 mg, 0.60 mmol, 1 eq.) under N₂ was added anhydrous toluene (4 mL). The reaction mixture was stirred at 0 °C until complete solubilisation and a solution of TFA (0.93 mL, 12.08 mmol, 20 eq.) in anhydrous DCM (2 mL) at 0 °C was added dropwise over 1 minute under stirring. The reaction mixture was then stirred at 0 °C for 1 minute maximum and it was then immediately concentrated under deep vacuum in a rotavapor (bath temperature: 1°C) until 2 mL was left. Then, anhydrous toluene (4 mL) was added and reaction mixture was concentrated until 2 mL was left. This co-evaporation was repeated 4 times. Then, a second co-evaporation cycle to dryness was done twice using each time anhydrous toluene (4 mL). Final residue was obtained as thick yellow oil. Completion of hydrolysis was confirmed by UPLC/MS (Product: R^t 1.40 min; ES⁻: 513.5. Starting material: R^t 2.68 min; 0% (AUC)). Stored in dry ice during preparation for the next step. In a 50 mL flask under N₂ was prepared a solution of ethanolamine (186.31 mg, 3.02 mmol, 5 eq.) in acetone (10 mL) at 0 °C which was then added in one shot to a solution of previous intermediate in dichloromethane (5 mL) at 0 °C. Immediate precipitation was observed and resulting milky clear yellow suspension was stirred at 0°C for 10 minutes. After filtration through a glass filter, sticky solid was washed with acetone (1 × 5 mL; 2 × 10 mL) then with diethyl ether (2 × 10 mL). Suspension must be not filtered completely and each time a layer of solvent should be present before proceeding to the next washing, excepted for the last one. Then, the resulting nice cream solid was sucked dry for only 2-3 seconds and final drying was done under vacuum at RT to give the title compound **172** as yellow powder (m = 253.7 mg; UPLC purity : 99% (AUC); ES⁻: 513.5; 2 eq of ethanolamine by NMR; 1.3% w/w of TFA:ethanolamine salt; 65.3% yield). ¹H NMR (400 MHz, D₂O): δ, ppm 7.72 (d, J = 3.8 Hz, 1H), 7.27-6.92 (m, 7H), 6.65 (d, J = 15.6 Hz, 1H), 5.58 (dd, J = 3.3 Hz, 11.2 Hz, 2H), 4.55 (s, 1H, rotamer), 4.49 (s, 1H, rotamer), 3.74-3.70 (m, 4H), 3.06-3.02 (m, 4H), 2.90 (s, 2H, rotamer), 2.84 (s, 1H, rotamer), 1.98 (s, 2H, rotamer), 1.96 (s, 1H, rotamer), 1.26-1.20 (m, 6H).

[00466] Example 35. Synthesis of 2-hydroxyethan-1-aminium (E)-(8-(3-(((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)(methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl phosphate (compound **174**).

[00467] General Synthetic Scheme.

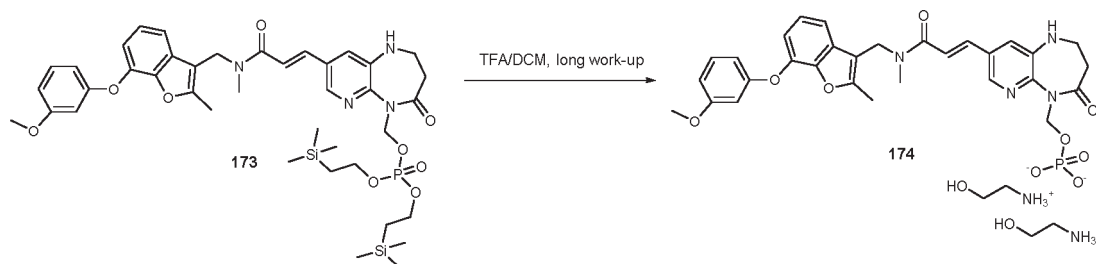
Reaction conditions: a) 1. 1 M t-BuOK/THF, DMSO, RT, 2. chloromethyl bis[2-(trimethylsilyl)ethyl] phosphate **21**; b) TFA/DCM, long work-up

5



[00468] **Step 1.** (E)-(8-(3-(((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)(methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl bis(2-(trimethylsilyl)ethyl) phosphate (compound **173**). In a sealed 6 mL microwaves vial under nitrogen, containing (E)-N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylamide **155** (400 mg, 0.76 mmol, 1.00 eq.) in suspension in anhydrous DMSO (3.2 mL) at RT was added dropwise potassium 2-methylpropan-2-olate (0.83 mL, 0.83 mmol, 1.10 eq.; 1 M in THF) over 2 minutes. Then the resulting dark yellow solution was submitted to degassing cycles (5 cycles ; vacuum/nitrogen) and was then stirred at RT for 20 minutes. Then reaction mixture was added dropwise over 13 minutes to a solution of chloromethyl bis(2-(trimethylsilyl)ethyl) phosphate **21** (1.47 mL, 1.06 mmol, 1.4eq. ; 30% in hexane) under vigorous stirring, then reaction mixture (orange biphasic solution) was stirred vigorously for 45 minutes to show good conversion by UPLC/MS (starting material: R^t 1.82 min; 14% (AUC at 254 nm); ES+: 513.6). Product: R^t 2.66 min; 65% (AUC at 254 nm); ES+: 823.8). The reaction mixture was quenched with a sat. solution of AcONH₄ (6 mL) and extracted four times with MTBE (4 × 6 mL). Combined organic phases were washed with brine and dried over Na₂SO₄ to give after concentration under vacuum at 20°C a thick orange oil (m = 643 mg; UPLC/MS : 72% (AUC at 254 nm)).

[00469] Purification was done by flash chromatography (SiO₂; eluting first with MTBE 99.5%-DIEA 0.5% then MTBE 93%-Acetonitrile 6.5%-DIEA 0.5% and finally MTBE 85%-Acetonitrile 14.5%-DIEA 0.5%). Fractions of interest were combined and concentrated to dryness at RT under vacuum to give the title compound as yellow foam (m = 219.5 mg; UPLC purity: 96% (AUC at 254 nm); 33.82% yield). Medium yield was explained by some degradation during flash chromatography (confirmed by TLC 2D experiments).



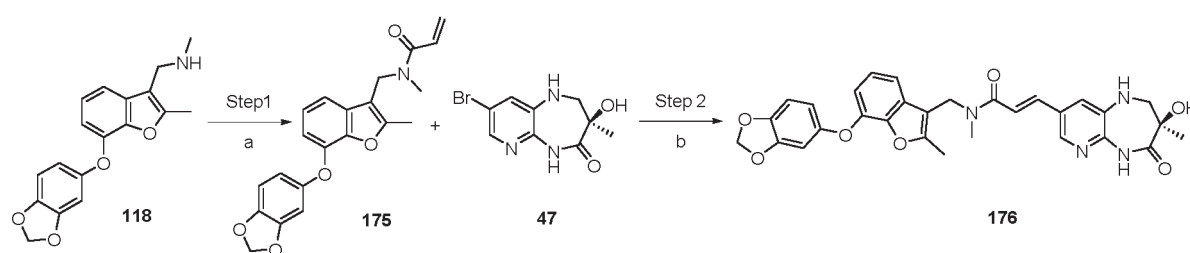
[00470] Step 2. 2-Hydroxyethan-1-aminium (E)-(8-(3-(((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)(methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl phosphate (compound **174**). In a 100 mL flask containing [8-[(E)-3-[[7-(3-methoxyphenoxy)-2-methyl-benzofuran-3-yl]methyl-methyl-amino]-3-oxo-prop-1-enyl]-4-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-5-yl]methyl bis(2-trimethylsilylethyl) phosphate **173** (219.5 mg, 0.26 mmol, 1.0 eq.) under N₂ was added anhydrous toluene (4 mL). The resulting mixture was then stirred at 0 °C until full dissolution and a solution of 2,2,2-trifluoroacetic acid (0.93 mL, 12.08 mmol, 20 eq.) in anhydrous DCM (2.0 mL) at 0 °C was added dropwise over 30 seconds. The reaction mixture was stirred at 0 °C for 3 minutes and reaction mass was then immediately concentrated under deep vacuum with a rotavapor (bath temperature: 1 °C) until 2 mL was left. Then anhydrous toluene (4 mL) was added and reaction mixture was concentrated until 2 mL was left. This co-evaporation was repeated four times to remove all residual TFA (yellow foam). UPLC/MS (expected product: R^t 1.58 min; ES⁻: 621.6; 92% (AUC at 254 nm). API: R^t 1.81 min; 2% (AUC at 254 nm)). No starting material left.

[00471] In a 50 mL flask under N₂ was prepared a solution of ethanolamine (186.31 mg, 3.02 mmol, 5.0 eq.) in THF (10 mL) at 0 °C which was then added in one shot to a solution of previous intermediate in THF (5 mL) at 0 °C. Precipitation was observed after few minutes under stirring at 0-5°C and suspension was then filtered through a glass filter (solid

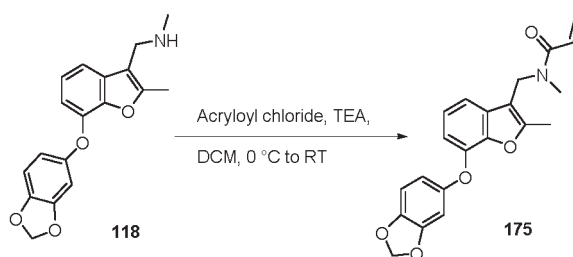
was apparently hydroscopic and filtration was stopped before cake went dry). Thick suspension was washed with THF (2×10 mL; filtration was stopped each time just before completion). UPLC/MS of the filtrate showed the API as major product and only traces of the expected prodrug). Finally thick suspension was washed with diethyl ether (2×4 mL), and solid was sucked dry for few secondes only. Then resulting yellow solid was dried under vacuum at RT overnight to give the title compound (135.37 mg; 69.2% yield). UPLC/MS; method: 3 min acid_standard; 254 nm; purity 97.50% (max plot AUC), ES-: 621.58. ^1H NMR (400 MHz, D_2O , 333K): δ , ppm 78.62 (s, 1H), 7.92 (bs, 1H), 7.85 (d, $J=15.7$ Hz, 1H), 7.55 (m, 1H), 7.31 (m, 3H), 6.94 (m, 1H), 6.84 (m, 1H), 6.75 (s, 1H), 6.66 (d, $J=7.6$ Hz, 1H), 5.97 (s, 1H, rotamer), 5.96 (s, 1H, rotamer), 5.10 (s, 1H, rotamer), 5.01 (s, 1H, rotamer), 4.22 (t, $J=5.3$ Hz, 4H), 4.03 (m, 2H), 3.91 (s, 1H, rotamer), 3.89 (s, 2H, rotamer), 3.54 (t, $J=5.2$ Hz, 4H), 3.31 (s, 3H), 2.88 (m, 1H), 2.78 (m, 1H), 2.64 (s, 3H). TFA-ethanolamine salt content: 7.6% w/w.

[00472] Example 36. Synthesis of (R,E)-N-((7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **176**).

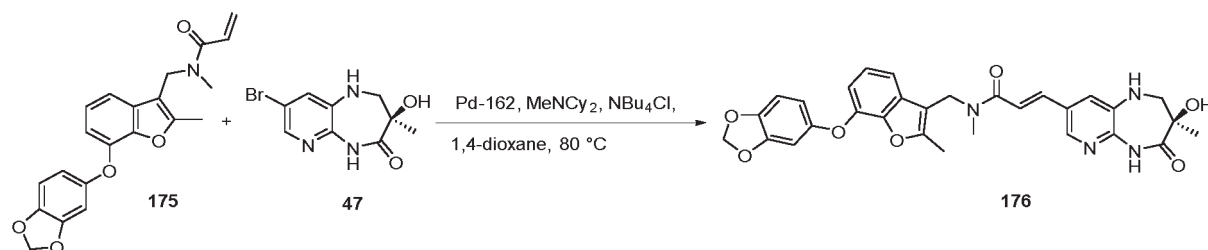
[00473] General Synthetic Scheme.



Reaction conditions: a) Acryloyl chloride, TEA, 0 °C to RT; b) Pd-162, MeNCy₂, NBu₄Cl, 1,4-dioxane, 80 °C



[00474] Step 1. N-((7-(Benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **175**). To an ice cooled solution of 1-(7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **118** (196 mg, 0.63 mmol) and TEA (350 μ L, 2.52 mmol) in DCM (10 mL) was added dropwise a solution of acryloyl chloride (51 μ L, 0.63 mmol) in DCM (1.0 mL). Upon completion of addition the mixture was allowed to warm to RT. The mixture was washed with water (5.0 mL) and the organics separated through a phase separation cartridge and evaporated to dryness. The crude product was purified by column chromatography (0-50% EtOAc/isohexane) to afford the title compound **175** as a clear colourless oil (120 mg, 51%). R_t 2.29 min (Method 1a) m/z 366 $[M + H]^+$ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ , ppm 7.27 (d, J = 7.7 Hz, 1H), 7.13 (td, J = 7.9, 0.9 Hz, 1H), 6.90-6.76 (m, 3H), 6.70 (dd, J = 2.6 Hz, 0.9 Hz, 1H), 6.51 (ddd, J = 8.4 Hz, 2.4 Hz, 0.9 Hz, 1H), 6.18 (ddd, J = 16.7 Hz, 2.4 Hz, 0.9 Hz, 1H), 6.02 (d, J = 0.9 Hz, 2H), 5.71 (dd, J = 10.5 Hz, 2.4 Hz, 1H), 4.71 (s, 2H), 2.94 (s, 3H), 2.47 (s, 3H).

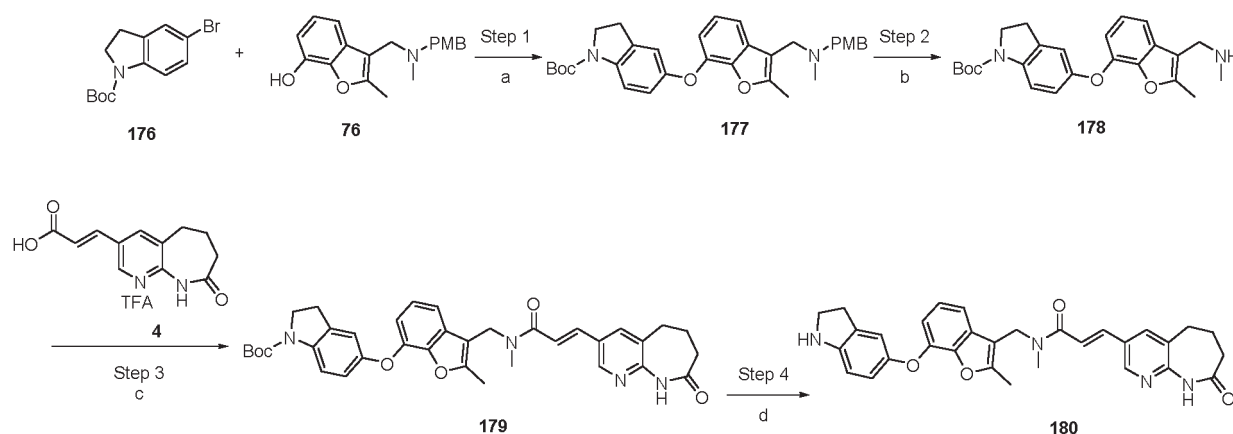


[00475] Step 2. (R,E)-N-((7-(Benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **176**). A reaction vial was charged with N-((7-(benzo[d][1,3]dioxol-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **175** (50 mg, 0.14 mmol), (R)-8-bromo-3-hydroxy-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **47** (37 mg, 0.14 mmol), NBu₄Cl (4.0 mg, 0.01 mmol) and [P(tBu)₃]Pd(crotyl)Cl (Pd-162) (6.0 mg, 0.01 mmol) and the vial was flushed with N₂ (5 mins). 1,4-Dioxane (2.0 mL) and N-cyclohexyl-N-methylcyclohexanamine (59 μ L, 0.27 mmol) were added and the reaction mixture was purged again with N₂ (5 mins). The reaction mixture was heated to 80 °C for 1 h, then was allowed to cool to RT and evaporated to dryness. The residue was triturated with iso-hexane (10 mL) and the crude solid was purified by chromatography (0-5% MeOH/DCM) to afford the title compound **176** as a pale yellow solid (41 mg, 53%). R_t 2.15 min (Method 1a); m/z 557 $[M + H]^+$ (ES⁺). ¹H NMR (500 MHz, DMSO-

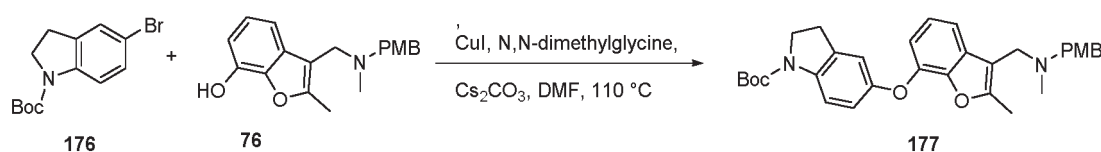
d₆, 363 K): δ , ppm 9.37 (s, 1H), 7.96 (d, J = 1.9 Hz, 1H), 7.47 (d, J = 15.4 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.9 Hz, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.4 Hz, 2.5 Hz, 1H), 6.06-6.02 (m, 1H), 6.02 (s, 2H), 4.92 (d, J = 1.1 Hz, 1H), 4.78 (s, 2H), 3.25-3.13 (m, 2H), 3.00 (d, J = 1.1 Hz, 3H), 2.49 (s, 3H), 1.29 (s, 3H).

[00476] **Example 37.** Synthesis of (E)-N-((7-(indolin-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **180**)

[00477] General Synthetic Scheme.

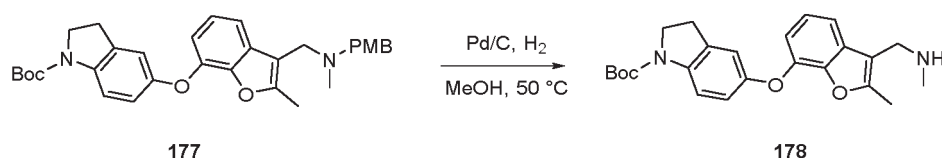


Reaction conditions: a) CuI, N,N-dimethylglycine, Cs₂CO₃, DMF, 110 °C; b) Pd/C, MeOH, H₂, 50 °C; c) HATU, DIPEA, DMF; d) TFA, DCM.

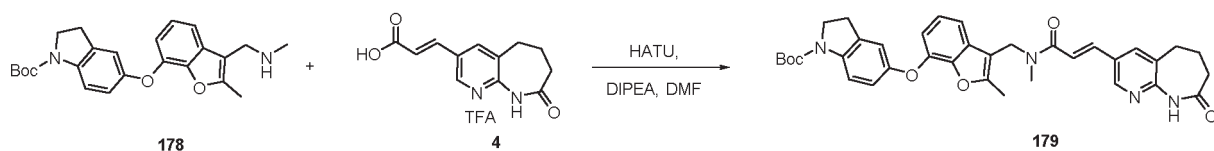


[00478] **Step 1.** tert-Butyl 5-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-yl)oxyindoline-1-carboxylate (compound **177**). A mixture of 3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzofuran-7-ol **76** (150 mg, 0.48 mmol), copper(I) iodide (92 mg, 0.48 mmol), N,N-dimethylglycine (50 mg, 0.48 mmol), Cs₂CO₃ (628 mg, 1.9 mmol) and tert-butyl 5-bromoindoline-1-carboxylate **176** (144 mg, 0.48 mmol) was evacuated and backfilled with nitrogen (3 ×). DMF (3 mL) was added and the mixture was

heated to 110 °C overnight. The mixture was diluted with water (5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over MgSO₄, filtered and concentrated under vacuum. The crude product was purified by chromatography (0-100% EtOAc/iso-hexane) to afford the title compound **177** as a dark yellow oil (129 mg, 49%). R^t 3.21 min (Method 1b); m/z 529 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, CDCl₃): δ, ppm 7.47-7.24 (m, 4H), 7.09 (t, J = 7.8 Hz, 1H), 6.97-6.87 (m, 4H), 6.71 (d, J = 7.9 Hz, 1H), 4.02 (br s, 2H), 3.83 (s, 3H), 3.56 (s, 2H), 3.52 (s, 2H), 3.08 (t, J = 8.6 Hz, 2H), 2.46 (s, 3H), 2.21 (s, 3H), 1.59 (s, 9H).

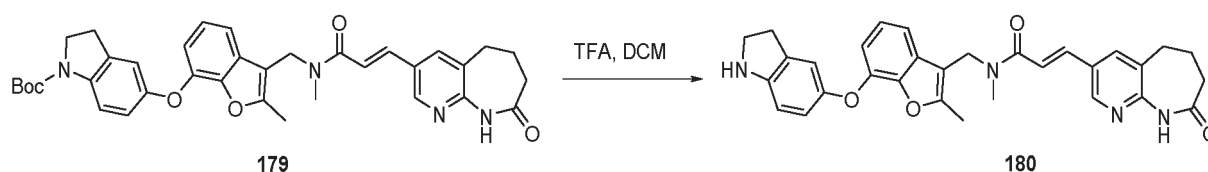


[00479] Step 2. tert-Butyl 5-((2-methyl-3-((methylamino)methyl)benzofuran-7-yl)oxy)indoline-1-carboxylate (compound **178**). A solution of tert-butyl 5-((3-((4-methoxybenzyl)(methylamino)methyl)-2-methylbenzofuran-7-yl)oxy)indoline-1-carboxylate **177** (129 mg, 0.24 mmol) in MeOH (5 mL) was hydrogenated in the H-Cube (10% Pd/C, 30x4 mm, Full hydrogen, 50 °C, 1 mL/min). The solvent was removed in vacuo, then the residue was redissolved in MeOH and was loaded onto a SCX column (1 g). The column was washed with MeOH (50 mL) and then the product was eluted with 0.7 M methanolic ammonia and concentrated in vacuo. The crude product was purified by chromatography (0-10% (0.7 M NH₃/MeOH)/DCM) to afford the title compound **178** as a colourless oil (54 mg, 52 %). R^t 2.41 min (Method 1b); m/z 322 (M - tBu-NHCH₃)⁺ (ES⁺).



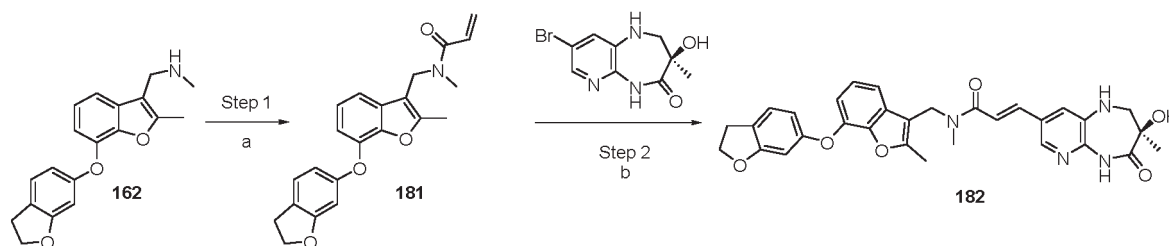
[00480] Step 3. (E)-tert-Butyl 5-((2-methyl-3-((N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamido)methyl)benzofuran-7-yl)oxy)indoline-1-carboxylate (compound **179**). To a suspension of tert-butyl 5-((2-methyl-3-

((methylamino)methyl)benzofuran-7-yl)oxy)indoline-1-carboxylate **178** (100 mg, 0.24 mmol), (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid trifluoroacetate **4** (109 mg, 0.24 mmol) and DIPEA (0.21 mL, 1.22 mmol) in DMF (2.0 mL) was added HATU (102 mg, 0.27 mmol) and the reaction mixture was stirred for 2 h. Water (3.0 mL) was then added and the solid was collected by filtration. The crude solid was purified by chromatography (0-10% MeOH/DCM) to give the title compound **179** as a yellow solid (100 mg, 62%). R^t 2.63 min (Method 1a); m/z 623 $[M + H]^+$ (ES^+).

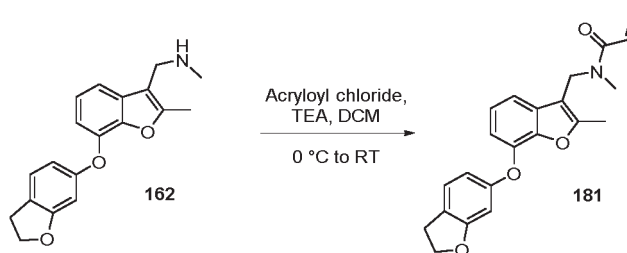


[00481] Step 4. (E)-N-((7-(Indolin-5-yloxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **180**). TFA (2 mL, 25 mmol) was added dropwise to a stirred solution of (E)-tert-butyl 5-((2-methyl-3-((N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamido)methyl)benzofuran-7-yl)oxy)indoline-1-carboxylate **179** (100 mg, 0.16 mmol) in DCM (4.0 mL). The reaction was stirred for 30 min before being concentrated in vacuo. The resulting yellow oil was suspended in $NaHCO_3$ (10 mL) and stirred for 30 mins. The aqueous mixture was extracted with DCM (3×10 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo to give the title compound **180** as a beige solid (50 mg, 56%). R^t 1.36 min (Method 1a); m/z 523 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, $DMSO-d_6$): δ , ppm 9.57 (s, 1H), 8.49 (d, $J = 2.2$ Hz, 1H), 8.03 (d, $J = 2.2$ Hz, 1H), 7.57 (d, $J = 15.4$ Hz, 1H), 7.36-7.18 (m, 2H), 7.07 (t, $J = 7.9$ Hz, 1H), 6.87-6.79 (m, 1H), 6.67 (dd, $J = 8.4$ Hz, 2.5 Hz, 2H), 6.50 (d, $J = 8.3$ Hz, 1H), 5.12 (s, 1H), 4.79 (s, 2H), 3.46 (t, $J = 8.5$ Hz, 2H), 3.01 (s, 3H), 2.93 (t, $J = 8.5$ Hz, 2H), 2.77 (t, $J = 7.2$ Hz, 2H), 2.50 (s, 3H), 2.32 (t, $J = 7.2$ Hz, 2H), 2.15 (p, $J = 7.2$ Hz, 2H).

[00482] Example 38. Synthesis of (R,E)-N-((7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **182**).

[00483] General Synthetic Scheme.

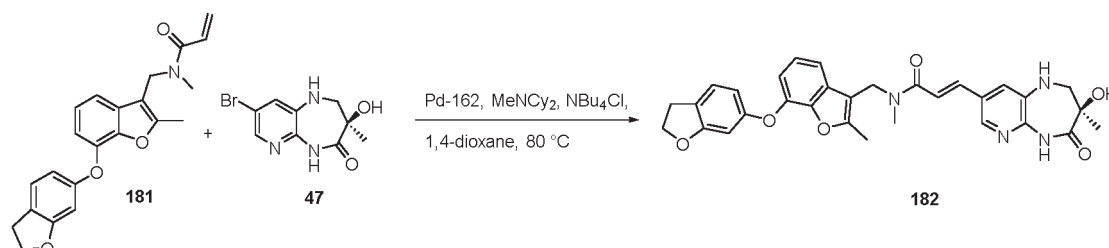
Reagents and conditions: a) Acryloyl chloride, TEA, DCM, 0 °C to RT; b) Pd-162, MeNCy₂, NBu₄Cl, 1,4-dioxane, 80 °C



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[00484] **Step 1.** N-((7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **181**). To an ice cooled solution of 1-(7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **162** (160 mg, 0.52 mmol) and TEA (300 μ L, 2.07 mmol) in DCM (10 mL) was added dropwise a solution of acryloyl chloride (42 μ L, 0.52 mmol) in DCM (1.0 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h. The reaction was quenched with water (5.0 mL) and the two phases separated. The organic phase was dried with MgSO₄, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-100% EtOAc/iso-hexane) to give the title compound **181** as a colourless oil (120 mg, 60%). R^t 2.36 min (Method 1a); m/z 364 $[M + H]^+$ (ES^+).

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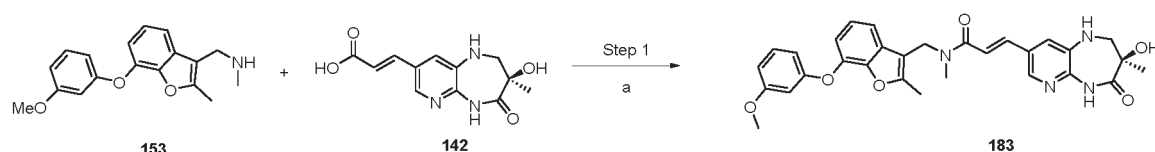
[00485] **Step 2.** (R,E)-N-((7-((2,3-Dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-

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yl)-N-methylacrylamide (compound **182**). A reaction vial was charged with N-((7-((2,3-dihydrobenzofuran-6-yl)oxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **181** (60 mg, 0.17 mmol), (R)-8-bromo-3-hydroxy-3-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **47** (45 mg, 0.17 mmol), NBu₄Cl (5 mg, 0.02 mmol),
 5 [P(tBu)₃]Pd(crotlyl)Cl (Pd-162) (7 mg, 0.02 mmol) and the vial was flushed with N₂ for 5 mins. 1,4-Dioxane (3.0 mL) and N-cyclohexyl-N-methylcyclohexanamine (75 µL, 0.35 mmol) were added and the reaction mixture was purged with N₂ for a further 5 mins. The mixture was heated to 80 °C for 1 h and then allowed to cool to RT. Ethyl acetate (5.0 mL) was added and the resulting solution was washed with water (5.0 mL) and brine (5.0 mL), dried over MgSO₄,
 10 filtered and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to give the title compound **182** as a pale yellow solid (29 mg, 36%). R^t 2.12 min (Method 1a); m/z 555 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆, 363 K): δ, ppm 9.38 (s, 1H), 7.96 (d, J = 1.9 Hz, 1H), 7.47 (d, J = 15.4 Hz, 1H), 7.41-7.25 (m, 2H), 7.25-7.03 (m, 3H), 6.83 (dd, J = 7.9 Hz, 1.1 Hz, 1H), 6.47 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 6.05
 15 (s, 1H), 4.93 (s, 1H), 4.78 (s, 2H), 4.57 (t, J = 8.6 Hz, 2H), 3.25-3.11 (m, 4H), 3.03 (s, 3H), 2.48 (s, 3H), 1.29 (s, 3H).

[00486] **Example 39.** Synthesis of (R,E)-3-(3-hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **183**).
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[00487] General Synthetic Scheme.



Reagents and conditions: a) HOBt·H₂O, EDC·HCl, DIPEA, DMF

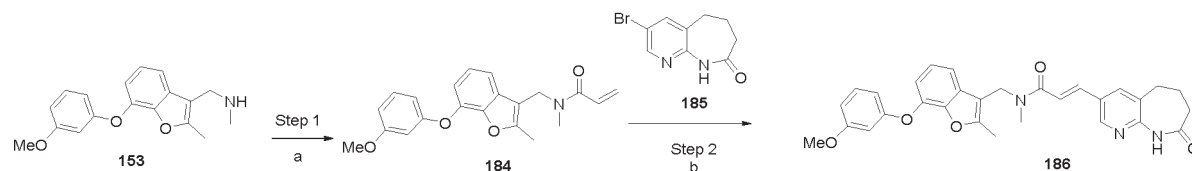
[00488] **Step 1.** (R,E)-3-(3-Hydroxy-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **183**). A microwave vial covered by a aluminium foil was charged with HOBt·H₂O (8.04 mg, 0.05 mmol) and (E)-3-[(3R)-3-hydroxy-3-methyl-4-oxo-2,5-dihydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl]prop-2-enoic acid **142** (9.21 mg, 0.04 mmol) and
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DMF (0.3 mL). 1-[7-(3-methoxyphenoxy)-2-methyl-benzofuran-3-yl]-N-methyl-methanamine **153** (10.41 mg, 0.04 mmol) and EDCl·HCl (10.06 mg, 0.05 mmol) were added and after 2 mins of stirring at RT DIPEA (0.02 mL, 0.12 mmol) was added. The reaction mixture was stirred in the dark overnight at RT. Then, water and acetonitrile were added, the mixture was

sonicated and the precipitate was filtered off. The crude product (24 mg) was purified by preparative HPLC using a gradient water/ACN 100% to 100% to afford the title compound **183** as a yellow oil (3.7 mg, 19.4% yield). R^t 1.83 min (Method 1b); m/z 543.5 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.93 (s, 1H), 7.98 (s, 1H), 7.52-7.17 (m, 5H), 7.06 (d, J = 15.5 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 1.7 Hz, 7.9 Hz, 1H), 6.61-6.56 (m, 1H), 6.51 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 6.28-6.19 (m, 1H), 5.28 (s, 1H), 4.90, 4.75 (2 s, 2H), 3.73 (s, 3H), 3.21-3.08 (m, 2H), 3.06, 2.96 (2 s, 3H), 2.45 (s, 3H), 1.23 (s, 3H) (rotamers).

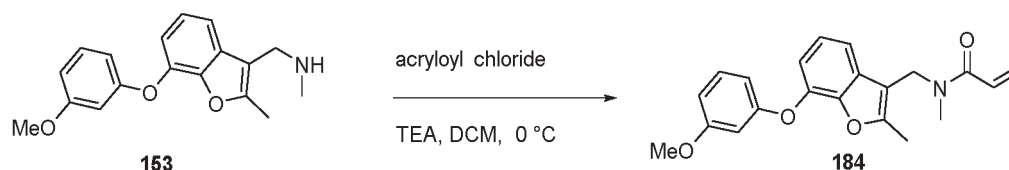
Example 40. Synthesis of (E)-N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **186**).

General Synthetic Scheme.

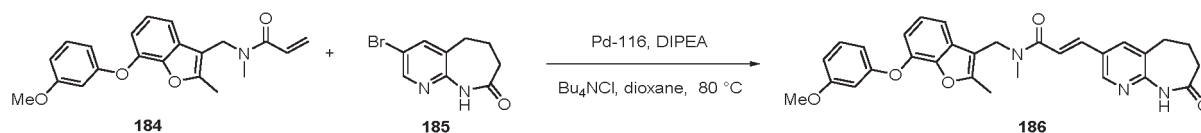


Reaction conditions: a) Acryloyl chloride, TEA, DCM, 0 °C; b) Pd-116, DIPEA, NBu₄Cl, dioxane, 80 °C

The synthesis of 3-bromo-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one (compound **185**) was previously reported by AFFINIUM PHARMECEUTICALS, INC: WO2007/67416, 2007, A2.



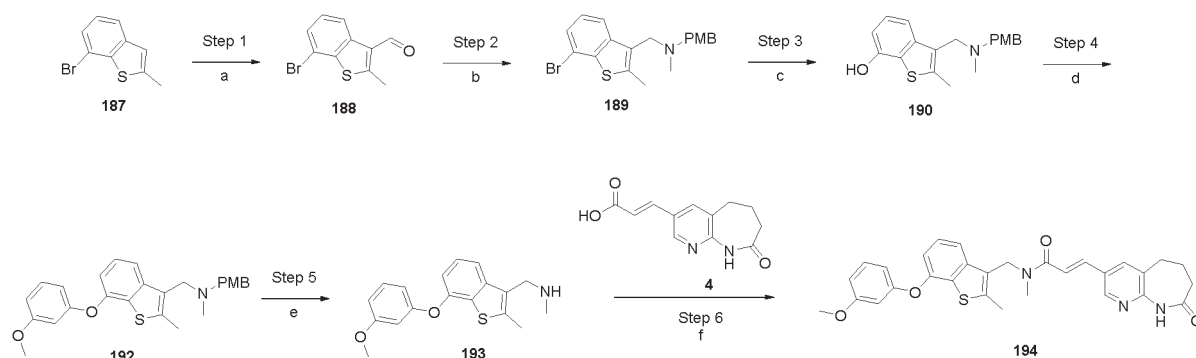
[00492] Step 1. N-((7-(3-Methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide (compound **184**). To a stirred solution of 1-(7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)-N-methylmethanamine **153** (155 mg, 0.52 mmol) in DCM (1.5 mL) was added TEA (0.22 mL, 1.58 mmol) and acryloyl chloride (0.051 mL, 0.63 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then allowed to warm at RT. The reaction mixture was quenched with water (5.0 mL) followed by extraction into DCM (20 mL). The organics separated and dried by passing through an hydrophobic frit, and then concentrated in vacuo. The crude product was purified by silica chromatography (0-100% EtOAc/isohexane) to afford the title compound **184** as a yellow oil (122 mg, 67%). R^t 2.32 min (Method 1b); m/z 352 $[M + H]^+$ (ES^+).



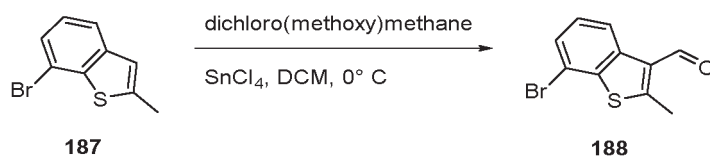
[00493] Step 2. (E)-N-((7-(3-Methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **186**). A reaction vial was charged with N-((7-(3-methoxyphenoxy)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **184** (55 mg, 0.16 mmol), 3-bromo-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one **185** (38 mg, 0.16 mmol), $n\text{-Bu}_4\text{NCl}\cdot\text{H}_2\text{O}$ (5.0 mg, 0.02 mmol) and $\text{Pd}[\text{P}(\text{tBu})_3]_2$ (Pd-116) (8.00 mg, 0.02 mmol) and the vial was evacuated and backfilled with N_2 (3 $\times$). 1,4-Dioxane (4.0 mL) and DIPEA (55 μL , 0.30 mmol) were added and the reaction mixture was heated to 80 °C for 30 mins. The reaction mixture was evaporated to dryness and the crude product was purified by chromatography (0-10% MeOH/DCM) to afford the title compound **186** as a pale yellow solid (42 mg, 52%). R^t 2.26 min (Method 1a); m/z 512 $[M + H]^+$ (ES^+). ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 363K): δ , ppm 9.57 (s, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.57 (d, J = 15.5 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 8.2 Hz, 2H), 7.17 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.72 (dd, J = 8.3 Hz, 2.3 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.56 (dd, J = 8.3 Hz, 2.2 Hz, 1H), 4.80 (s, 2H), 3.76 (s, 3H), 3.00 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 2.32 (t, J = 7.2 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H).

[00494] Example 41. Synthesis of (E)-N-((7-(3-methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide (compound **194**).

5 **[00495] General Synthetic Scheme.**



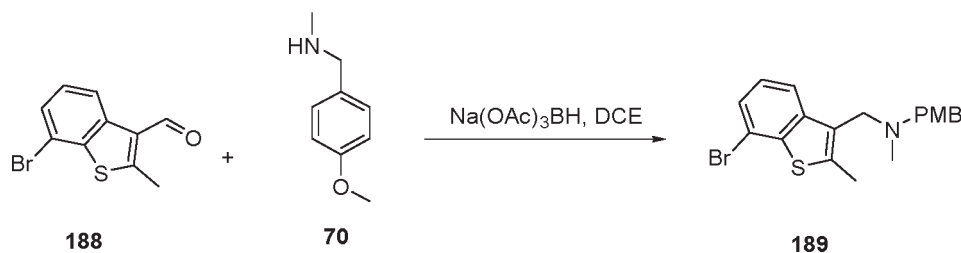
Reaction conditions: a) Dichloro(methoxy)methane, tin(IV) chloride, DCM, 0° C; b) 1-(4-methoxyphenyl)-N-methylmethanamine, Na(OAc)₃BH, DCE; c) Pd-175, tBuBrettPhos, KOH, 1,4-dioxane, H₂O, 80° C; d) 3-bromoanisole **191**, CuI, N,N-dimethyl glycine, Cs₂CO₃, DMF, 110° C; e) ACE-Cl, MeOH, 0° C to RT; f) HATU, DIPEA, DMF



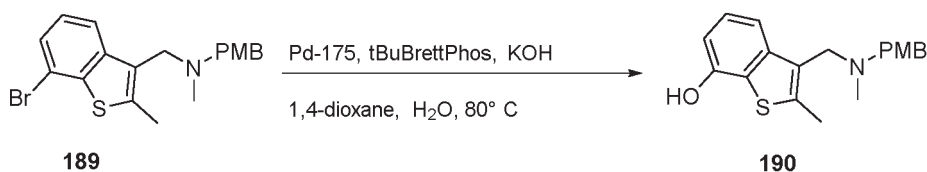
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[00496] Step 1. 7-Bromo-2-methylbenzo[b]thiophene-3-carbaldehyde (compound **188**). To a solution of 7-bromo-2-methylbenzo[b]thiophene **187** (950 mg, 4.18 mmol) and dichloro(methoxy)methane (0.42 mL, 4.64 mmol) in DCM (20 mL) at 0 °C was added dropwise a solution of tin(IV) chloride (1M in DCM, 5 mL, 5.00 mmol) over 15 mins. Upon completion of addition the mixture was allowed to warm to RT over 1 hour, then poured onto ice cold sat. NaHCO₃ solution (50 mL). The mixture was extracted into DCM (2 × 100 mL), the organic extracts were combined, dried over Na₂SO₄, filtered and concentrated under vacuum. The crude product was purified by chromatography (0-10% EtOAc/isohexane) to afford the title compound **188** as a white solid (780 mg, 69 %). ¹H NMR (500 MHz, CDCl₃): δ, ppm 10.37 (s, 1H), 8.58 (dd, J = 8.2 Hz, 1.1 Hz, 1H), 7.55 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 7.39-7.35 (m, 1H), 2.97 (s, 3H).

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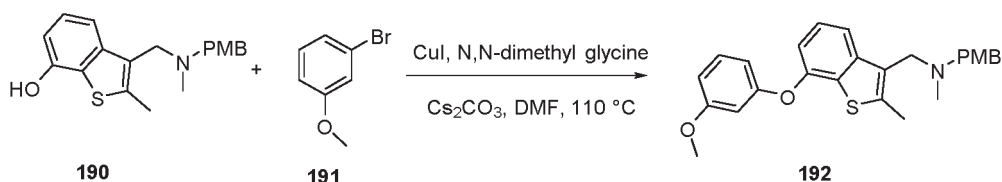
[00497] Step 2. 1-(7-Bromo-2-methylbenzo[b]thiophen-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine (compound **189**). Sodium triacetoxyborohydride (1.61 g, 7.74 mmol) was added in one portion to a stirred solution of 7-bromo-2-methylbenzo[b]thiophene-3-carbaldehyde **188** (790 mg, 3.10 mmol) and 1-(4-methoxyphenyl)-N-methylmethanamine **70** (0.46 mL, 3.07 mmol) in DCE (12 mL) at RT. The reaction mixture was stirred for ~ 16 h then the solvent was concentrated in vacuo and the resulting residue was taken up in NaHCO_3 (25 mL, sat aq.). The aqueous material was extracted with DCM (3×30 mL) and the combined organic layers were washed with brine (30 mL) before being dried by passing through a phase separation cartridge. The crude material was purified by chromatography (0-50% EtOAc/iso-hexane) to give the title compound **189** as a brown oil (1.05 g, 86%). R^t 3.18 min (Method 1b); m/z 390/392 $[\text{M} + \text{H}]^+$ (ES^+).



[00498] Step 3. 3-(((4-Methoxybenzyl)(methyl)amino)methyl)-2-methylbenzo[b]thiophen-7-ol (compound **190**). A flask was charged with 1-(7-bromo-2-methylbenzo[b]thiophen-3-yl)-N-(4-methoxybenzyl)-N-methylmethanamine **189** (1.05 g, 2.69 mmol), Pd-175 (0.04 g, 0.05 mmol), tBuBrettPhos (0.03 g, 0.05 mmol) and KOH (0.45 g, 8.08 mmol). It was evacuated/backfilled with nitrogen (3 times) and subsequently were added 1,4-dioxane (5.0 mL) and degassed water (0.8 mL). The resulting mixture was heated to 80°C and stirred for 3 hours. The mixture was cooled to RT and diluted with EtOAc (20 mL), then acidified with 1M HCl (20 mL). The mixture was stirred for 5 min until all solid was dissolved. The mixture was treated with sat. aq. NaHCO_3 (50 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2×50 mL). The combined organic

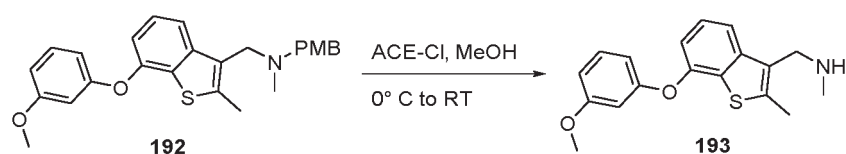
extracts were dried over MgSO_4 , filtered and concentrated. The crude product was purified by chromatography (0-50% EtOAc/iso-hexane) to afford the title compound **190** as a brown oil (879 mg, 99%). R^t 2.51 min (Method 1b); m/z 328 $[\text{M} + \text{H}]^+$ (ES^+).

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[00499] Step 4. N-(4-Methoxybenzyl)-1-(7-(3-methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)-N-methylmethanamine (compound **192**). A mixture of 3-(((4-methoxybenzyl)(methyl)amino)methyl)-2-methylbenzo[b]thiophen-7-ol **190** (250 mg, 0.76 mmol), copper(I) iodide (150 mg, 0.76 mmol), 2-(dimethylamino)acetic acid (80 mg, 0.76 mmol) and Cs_2CO_3 (1.0 g, 3.05 mmol) was evacuated and backfilled with nitrogen (3 times). DMF (5.0 mL) and 1-bromo-3-methoxybenzene **191** (0.12 mL, 0.92 mmol) were added and the mixture was heated to 110 °C overnight. The mixture was filtered through a pad of Celite® washing with EtOAc (40 mL). The filtrate was evaporated to dryness. The crude product was purified by chromatography (0-30% EtOAc/iso-hexane) to afford the title compound **192** as a colourless oil (287 mg, 86%). R^t 3.15 min (Method 1b); m/z 434 $[\text{M} + \text{H}]^+$ (ES^+).

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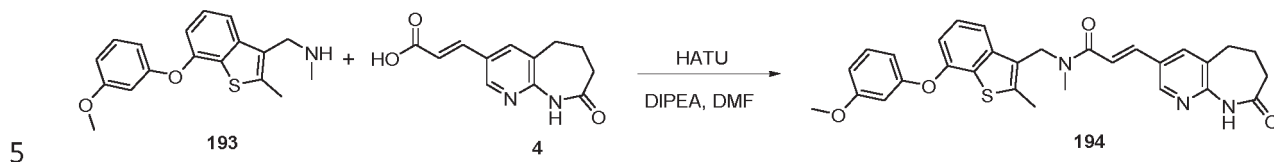


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[00500] Step 5. 1-(7-(3-Methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)-N-methylmethanamine (compound **193**). 1-Chloroethyl chloroformate (0.15 mL, 1.37 mmol) was added dropwise to a stirred solution of N-(4-methoxybenzyl)-1-(7-(3-methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)-N-methylmethanamine **192** (290 mg, 0.66 mmol) in DCM (9.0 mL) at 0 °C under N_2 . The reaction was allowed to warm to RT and stirred overnight. The solvent was then concentrated in vacuo and the residue was redissolved in MeOH (15 mL) and heated to reflux for 1 h. The mixture was cooled to RT and applied onto a SCX column.

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The column was washed with methanol (50 mL), the product eluted with 10% methanolic ammonia and evaporated affording the title compound **193** as a dark oil (122 mg, 51%). R^t 2.11 min (Method 1b); m/z 283 $[M - NHCH_3]^+$ (ES^+).



[00501] Step 6. (E)-N-((7-(3-Methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide

(compound **194**). A suspension of 1-(7-(3-methoxyphenoxy)-2-methylbenzo[b]thiophen-3-yl)-N-methylmethanamine **193** (64 mg, 0.20 mmol), (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid **4** (91 mg, 0.20 mmol), DIPEA (0.18 mL, 1.03 mmol) in DMF (1.0 mL) was stirred for 10 mins. HATU (78 mg, 0.20 mmol) was added in one portion and the reaction mixture stirred for 1 hour. The mixture was diluted with water (10 mL), extracted with DCM (3×20 mL), washed with brine, passed through a phase separator and evaporated. The crude product was purified by chromatography (0-3% MeOH/DCM). The fractions collected were then evaporated and the solid was triturated with MeCN to afford the title compound **194** as a white solid (21 mg, 19%). R^t 2.36 min (Method 1b); m/z 528 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6): δ , ppm 9.57 (s, 1H), 8.49 (d, $J = 2.1$ Hz, 1H), 8.03 (d, $J = 2.2$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 15.4$ Hz, 1H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.30-7.27 (m, 2H), 6.90 (d, $J = 7.8$ Hz, 1H), 6.76 (dd, $J = 8.3$ Hz, 2.3 Hz, 1H), 6.64-6.63 (m, 1H), 6.60 (dd, $J = 8.2$ Hz, 2.3 Hz, 1H), 4.94 (s, 2H), 3.76 (s, 3H), 2.96 (s, 3H), 2.77 (t, $J = 7.2$ Hz, 2H), 2.59 (s, 3H), 2.32 (t, $J = 7.2$ Hz, 2H), 2.18-2.12 (m, 2H).

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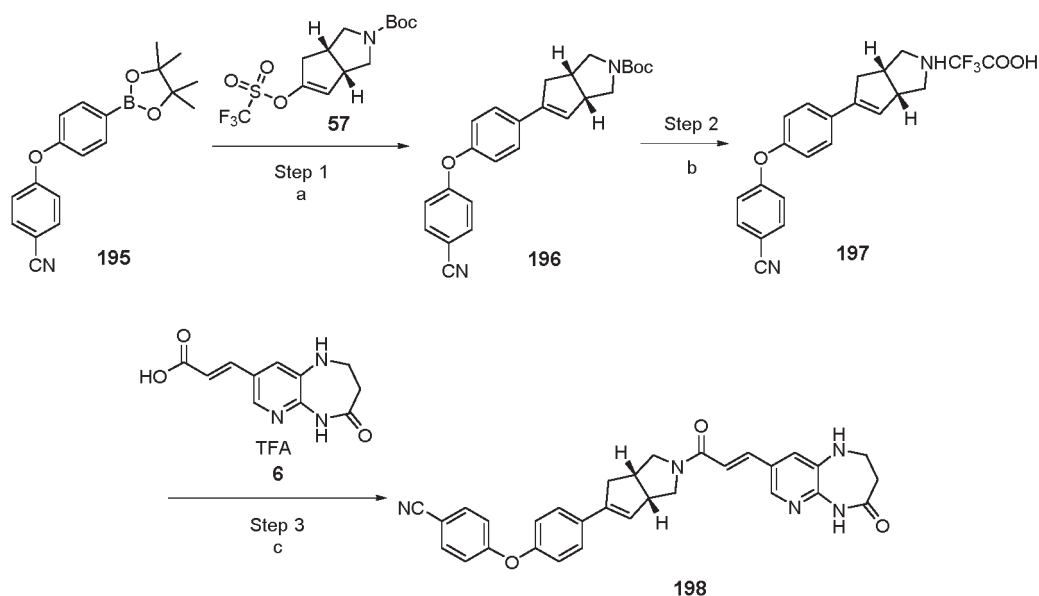
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[00502] Example 42. Synthesis of 4-(4-((3aR,6aS)-2-((E)-3-(4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)benzonitrile (compound **198**).

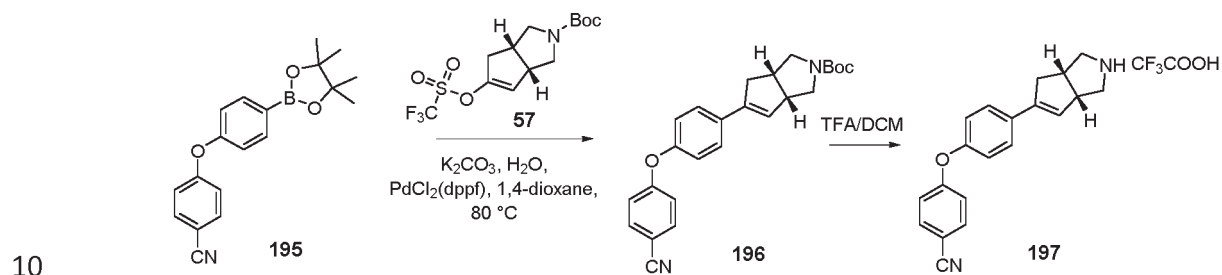
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[00503] General Synthetic Scheme.

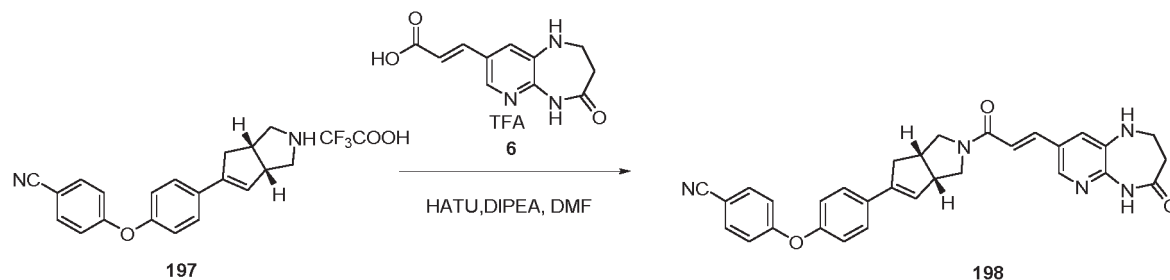


Reaction conditions: a) K_2CO_3 , H_2O , $PdCl_2(dppf)$, 1,4-dioxane, 80 °C; b) TFA, DCM; c) HATU, DIPEA, DMF

[00504] The synthesis of 4-(4-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzonitrile (compound **195**) was previously reported by Abbott Laboratories; US2002/156081, 2002, A1 and X-RX DISCOVERY, INC.; WO2015/48662, 2015, A2. The pinacol ester **195** was prepared in 90% yield with a purity of 93% (R^t = 2.40 min (standard); m/z 321.1 [$M + H$]⁺ (ES^+)).



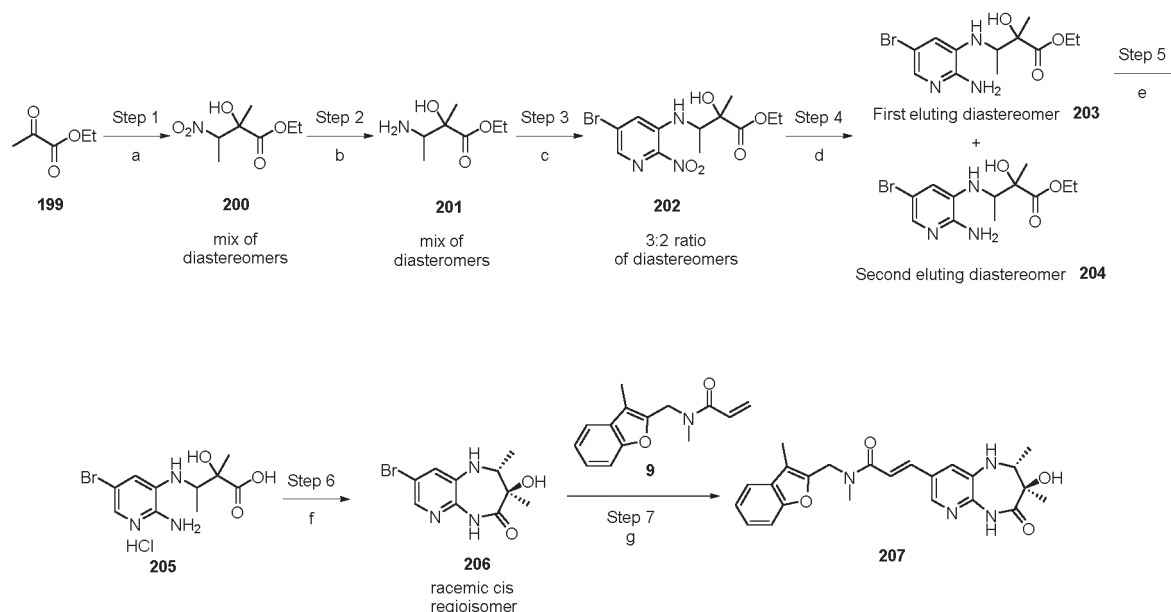
[00505] **Steps 1 and 2.** 4-(4-((3aS,6aR)-1,2,3,3a,4,6a-Hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)benzonitrile 2,2,2-trifluoroacetate (compound **197**) was synthesized from compounds **57** and **195** via the intermediate **196** in 2 steps following the procedure described in Example 20 and US2017/0174683 A1. The crude product (TFA salt) **197** was used in the next step without further purification (R^t = 1.26 min (standard); m/z 303.6 [$M + H$]⁺ (ES^+)).



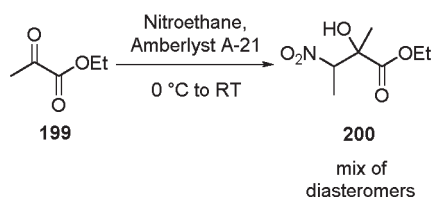
[00506] Step 3. 4-(4-((3aR,6aS)-2-((E)-3-(4-Oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acryloyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrol-5-yl)phenoxy)benzonitrile (compound **198**) was obtained from the acid **6** and the amine **197** as a yellow solid with a purity of 99% (19% yield) in standard amine to amide coupling reaction described in Example 20. $R^t = 1.78$ min (standard); m/z 518.3 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, DMSO- d_6): δ , ppm 9.73 (d, $J = 4.9$ Hz, 1H), 7.98 (d, $J = 6.2$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.58 (d, $J = 8.3$ Hz, 2H), 7.39-7.28 (m, 2H), 7.16-7.05 (4H, m), 6.86 (dd, $J = 6.7$ Hz, 15.5 Hz, 1H), 6.20 (s, 1H), 6.05-6.00 (m, 1H), 4.05-3.75 (m, 2H), 3.73-3.49 (m, 2H), 3.47-3.36 (m, 3H), 3.22-3.10 (m, 1H), 3.10-2.91 (m, 1H), 2.69-2.55 (m, 3H).

[00507] Example 43. Synthesis of (E)-3-(3-hydroxy-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **207**).

[00508] General Synthetic Scheme.



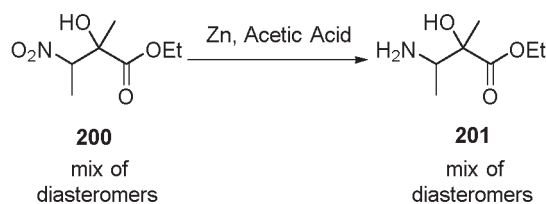
Reaction conditions: a) Nitroethane, Amberlyst A-21, 0 °C to RT; b) Zn, Acetic Acid; c) 5-Bromo-3-fluoro-2-nitropyridine **11**, TEA, EtOH, reflux; d) Fe, NH₄Cl, EtOH, H₂O, reflux, separation of diastereomers; e) LiOH, H₂O, THF, MeOH; f) HATU, DIPEA, DMF; g) Pd-116, DIPEA, NBu₄Cl, 1,4-dioxane, 80 °C.



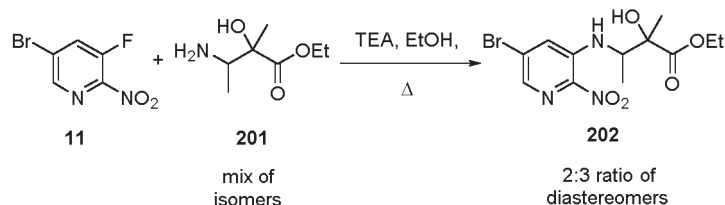
- 5 **[00509]** **Step 1.** Ethyl 2-hydroxy-2-methyl-3-nitrobutanoate (compound **200**). Ethyl 2-oxopropanoate **199** (15.6 mL, 140 mmol) was added dropwise to a stirred suspension of Amberlyst A-21 (14 g, 140 mmol) in nitroethane (10.0 mL, 140 mmol) at 0 °C. The reaction mixture was allowed to warm to RT and was stirred for ~16 h. The resin was removed by filtration and washed with DCM (3 × 100 mL). The filtrate was concentrated in vacuo to give the desired product **200** as a yellow oil (20.6 g, 73%) in an approximately 2:1 ratio of diastereomers.

[00510] Major Diastereomer: ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 5.94 (s, 1H), 5.04 (q, J = 6.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.46 (d, J = 6.8 Hz, 3H), 1.31 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H).

- 15 **[00511]** Minor Diastereomer: ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 6.08 (s, 1H), 4.88 (q, J = 6.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.36 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H).



[00512] Step 2. Ethyl 3-amino-2-hydroxy-2-methylbutanoate (compound **201**). To a solution of ethyl 2-hydroxy-2-methyl-3-nitrobutanoate **200** (5 g, 26.2 mmol) in acetic acid (300 mL), Zinc powder was added by portion (68.4 g, 1046 mmol). The mixture was stirred at RT for 4 h, then was filtered over a Celite® pad. The filtrate was neutralized by addition of sat. aq. Na₂CO₃ (~700 mL) and extracted with EtOAc (2 × 700 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure affording the title compound **201** as a yellow oil. The aqueous layer was then evaporated and the residue was divided into two portions and each of these were solubilised again in water (300 mL). The aqueous material was filtered to remove the salts formed, extracted with EtOAc (2 × 400 mL) and DCM (2 × 400 mL), and the combined organic layers were dried over MgSO₄, filtered and evaporated to dryness. ¹H NMR analysis of the three fractions were consistent with product structure at 100% purity and they were combined affording the title compound **201** as a yellow oil (1.12 g, 27%). ¹H NMR (DMSO-d₆): δ, ppm δ 4.12-4.07 (m, 2H), 2.94-2.84 (m, 1H), 1.24-1.15 (m, 6H), 0.94-0.91 (m, 3H). NH₂ and OH not observed (mix of isomers).

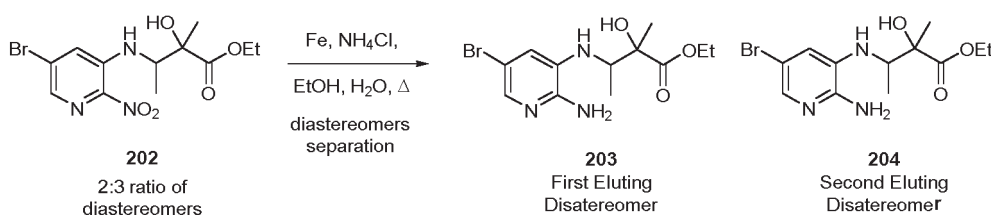


[00513] Step 3. Ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxy-2-methylbutanoate (compound **202**). Triethylamine (1.8 mL, 12.8 mmol) was added to a stirred solution of 5-bromo-3-fluoro-2-nitropyridine **11** (1.3 g, 5.88 mmol) and ethyl 3-amino-2-hydroxy-2-methylbutanoate **201** (1.06 g, 4.27 mmol) in EtOH (20 mL) and the reaction mixture was heated to reflux for ~16 h. The reaction mixture was allowed to cool to RT, then was concentrated in vacuo and the crude material was purified by column

chromatography (0-10% MeOH/DCM) to give the desired product **202** as a yellow oil (1.24 g, 79%) in an approximately 3:2 ratio of diastereomers.

[00514] Diastereomer 1: R^t 1.90 min (Method 1a) m/z 362/364 [M + H]⁺ (ES⁺).
¹H NMR (400 MHz, DMSO-d₆): δ, ppm 8.11-8.02 (m, 2H), 7.91-7.84 (m, 1H), 5.96 (s, 1H), 4.31-4.23 (m, 1H), 4.00 (q, J = 7.1 Hz, 2H), 1.34 (s, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H).

[00515] Diastereomer 2: R^t 1.96 min (Method 1a) m/z 362/364 [M + H]⁺ (ES⁺).
¹H NMR (400 MHz, DMSO-d₆) δ 8.13-8.00 (m, 2H), 7.89-7.85 (m, 1H), 5.98 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.15-4.08 (m, 1H), 1.34 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H).

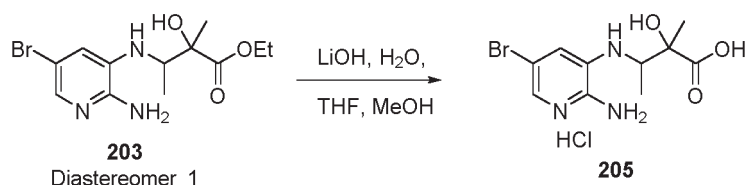


[00516] **Step** **4.** Ethyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylbutanoate (compounds **203** and **204**). A mixture of ethyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-hydroxy-2-methylbutanoate **202** (1.2 g, 3.31 mmol), iron (1.48 g, 26.5 mmol) and NH₄Cl (0.71 g, 13.3 mmol) in a mixture of EtOH (20 mL) and H₂O (5 mL) was heated and stirred under reflux for ~16 h. The reaction mass was allowed to cool to RT, then was dry loaded on Celite® and purified by column chromatography (0-50% EtOAc/iso-hexane) to give the desired product as a brown solid: Diastereomer 1 **203** (154 mg, 14%) and Diastereomer 2 **204** (280 mg, 25%).

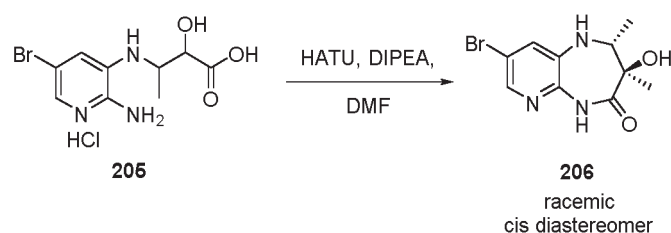
[00517] Diastereomer 1 **203**: R^t 1.14 min (Method 1a) m/z 332/334 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 7.28 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 5.63 (s, 2H), 5.11 (s, 1H), 4.39 (d, J = 10.1 Hz, 1H), 3.96 (q, J = 7.0 Hz, 2H), 3.86-3.78 (m, 1H), 1.28 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H).

[00518] Diastereomer 2 **204**: R^t 1.13 min (Method 1a) m/z 332/334 $[M + H]^+$ (ES⁺). ¹H NMR (400 MHz, DMSO- d_6): δ , ppm 7.27 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 5.77 (s, 2H), 5.44 (s, 1H), 4.48 (d, J = 9.7 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.76-3.67 (m, 1H), 1.29 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H).

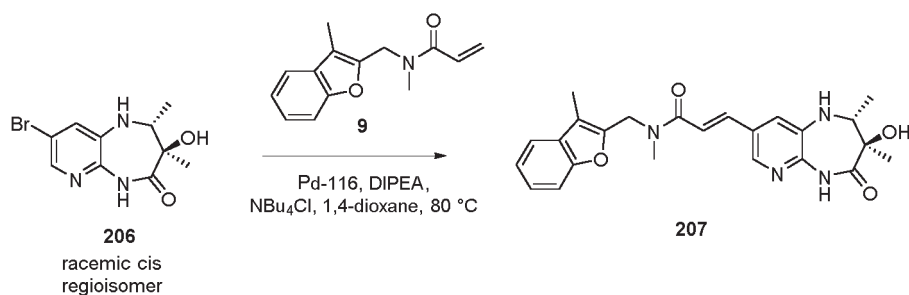
[00519]



[00520] Step 5. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylbutanoic acid hydrochloride (compound **205**). Lithium hydroxide (1 M aq., 0.6 mL, 0.6 mmol) was added dropwise to a stirred solution of ethyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylbutanoate **203** (65 mg, 0.20 mmol) in THF (5 mL) and MeOH (1 mL) at RT and the reaction mixture was stirred for 4 h. The mixture was acidified to ~pH 5 by the addition of 1 M HCl (aq.) and the reaction mixture was concentrated in vacuo. The residue was azeotroped with MeCN (5 mL) to give the desired product **205** as a brown solid (68 mg, quant). R^t 0.84 min (Method 1a) m/z 304/306 $[M + H]^+$ (ES^+).



[00521] Step 6. 8-Bromo-3-hydroxy-2,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **206**). DIPEA (0.13 mL, 0.76 mmol) was added to a stirred solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2-hydroxy-2-methylbutanoic acid hydrochloride **205** (65 mg, 0.19 mmol) in DMF (2 mL) at RT. After 10 mins, HATU (75 mg, 0.20 mmol) was added and the reaction mixture was stirred for ~16 h. The reaction mixture was quenched with MeOH (5 mL) and H₂O (30 mL). The aqueous mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (2 × 50 mL), dried with MgSO₄, and concentrated in vacuo. The crude material was purified by column chromatography (0-50% EtOAc/isohexane) to give the desired product **206** as a white solid (21 mg, 38%). R^t 1.21 min (Method 2a) m/z 286/288 $[M + H]^+$ (ES^+). ¹H NMR (DMSO-d₆): δ , ppm 10.25 (s, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 6.4 Hz, 1H), 5.12 (s, 1H), 3.31-3.24 (m, 1H), 1.16 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H). The cis stereochemistry of obtained diastereomer was assigned by the NMR studies including NOE and ROESY experiments.

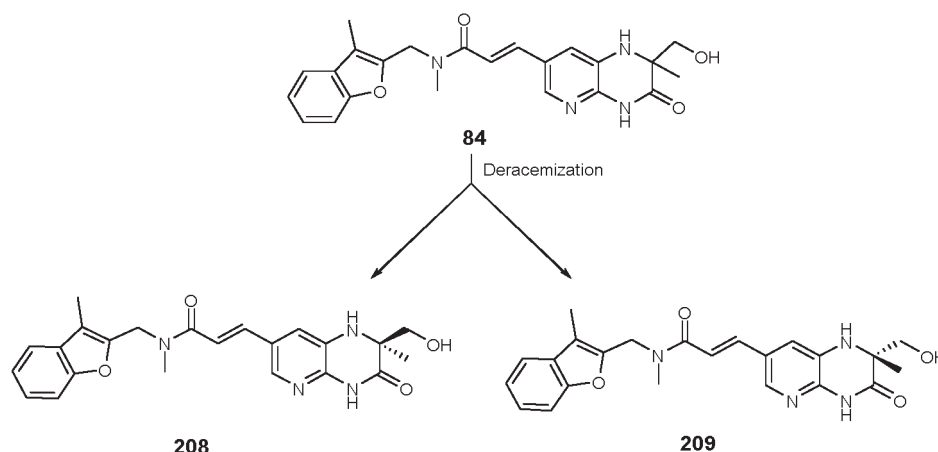


[00522] Step 7. (E)-3-(3-Hydroxy-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound

207). A flask was charged with 8-bromo-3-hydroxy-2,3-dimethyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **206** (40 mg, 0.14 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (32 mg, 0.140 mmol), NBu₄Cl (4 mg, 0.01 mmol) and Pd-116 (7 mg, 0.01 mmol) and the flask was evacuated and backfilled with N₂ three times. 1,4-Dioxane (2.5 mL) and DIPEA (0.05 mL, 0.28 mmol) were added and the reaction mixture was heated to 80 °C and stirred for 3 h. The solvent was removed in vacuo and the crude material was purified by column chromatography (0-5% MeOH/DCM) to give the desired product **207** as a yellow solid (36 mg, 59%). R_t 1.93 min (Method 1a) m/z 435 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-d₆, 363 K): δ, ppm 9.72 (s, 1H), 7.95 (d, J = 1.9 Hz, 1H), 7.59-7.53 (m, 1H), 7.49-7.35 (m, 3H), 7.32-7.21 (m, 2H), 7.12 (d, J = 15.4 Hz, 1H), 6.32 (d, J = 6.4 Hz, 1H), 4.84 (s, 2H), 4.79 (d, J = 1.1 Hz, 1H), 3.39-3.30 (m, 1H), 3.09 (s, 3H), 2.27 (s, 3H), 1.24 (s, 3H), 1.08 (d, J = 6.7 Hz, 3H).

[00523] Example 44. Synthesis of (S,E)-3-(2-(hydroxymethyl)-2-methyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **208**) and (R,E)-3-(2-(hydroxymethyl)-2-methyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **209**).

[00524] Chiral separation of compound **84**



[00525] **Chiral method separation:** Apparatus: Isolera (Biotage). Column: Chiralpak IA (20 μ m; glass column; 250mm $\times$ 25mm). Eluent: Acetonitrile/Ethanol (8/2 v/v). Flow 40 mL/min. Temperature: 25 $^{\circ}$ C. Run time: 25 min.

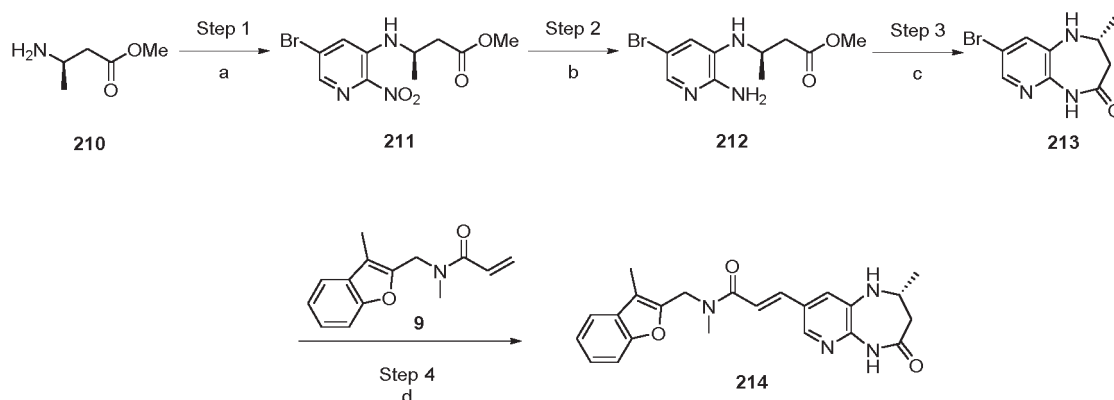
[00526] Amount injected: 30 mg of compound **84** in 20 mL of eluent (dissolution under reflux, followed by cooling and quick injection). Some degradation of the product during hot dissolution was observed, but by-products were not present in fractions of interest.

[00527] (S,E)-3-(2-(Hydroxymethyl))-2-methyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **208**). Pure fractions of first enantiomer were collected and concentrated until precipitation was observed. Then evaporation to dryness was done under nitrogen flux at RT. The first enantiomer was obtained as a cream powder (m = 8.6 mg; chiral purity: 99.84%). The stereochemistry of obtained enantiomer was randomly assigned.

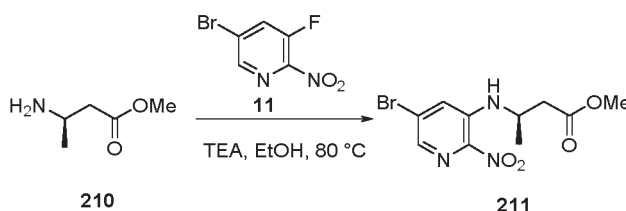
[00528] (R,E)-3-(2-(Hydroxymethyl))-2-methyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **209**). Pure fractions of second enantiomer were collected and concentrated until precipitation was observed. Then evaporation to dryness was done under nitrogen flux at RT. The second enantiomer was obtained as cream powder (m = 6.9 mg; chiral purity: 99.59%). The stereochemistry of obtained enantiomer was randomly assigned.

[00529] Example 45. Synthesis of (R,E)-N-methyl-3-(2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **214**).

5 **[00530] General Synthetic Scheme.**



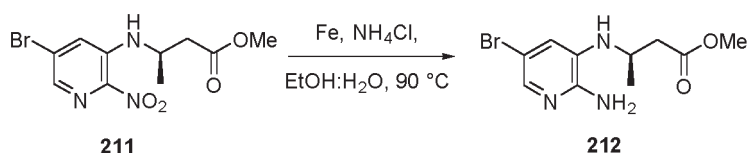
Reaction conditions: a) 5-Bromo-3-fluoro-2-nitropyridine **11**, TEA, EtOH, 80 °C; b) Fe, NH₄Cl, EtOH, Water, 90 °C; c) NaH, THF, 0 °C to RT; d) Pd-116, Bu₄NCl, DIPEA, 1,4-Dioxane, 80 °C.



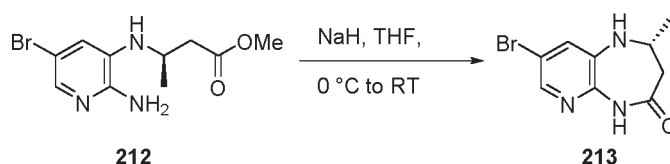
10

[00531] Step 1. (R)-Methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)butanoate (compound **211**). To a stirred solution of 5-bromo-3-fluoro-2-nitropyridine **11** (430 mg, 1.95 mmol) in MeCN (10 mL) was added (R)-methyl 3-aminobutanoate hydrochloride **210** (300 mg, 1.95 mmol) followed by TEA (700 μ L, 4.88 mmol). The reaction mixture was stirred at reflux for 2 h and then was allowed to cool to RT. The reaction mixture was concentrated in vacuo, then the crude material was dissolved in ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried with MgSO₄, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-100% EtOAc/isohexane) to afford the title compound **211** as a yellow solid (590 mg, 90%). R_t 1.89 min (Method 1a) m/z 318/320 [M + H]⁺ (ES⁺).

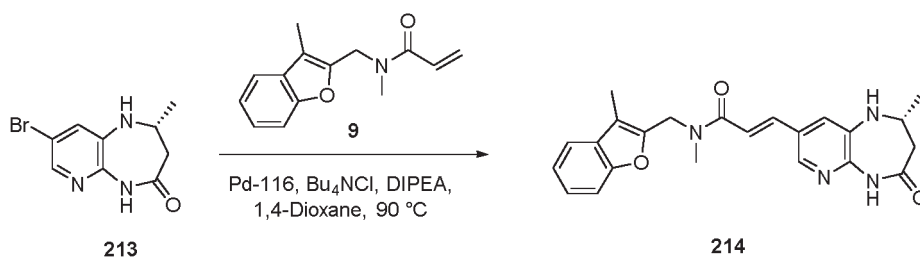
20



[00532] Step 2. (R)-Methyl 3-((2-amino-5-bromopyridin-3-yl)amino)butanoate (compound **212**). To a mixture of methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)butanoate **211** (570 mg, 1.85 mmol) in EtOH (35 mL) and water (8.75 mL) was added iron (415 mg, 7.42 mmol) and ammonia hydrochloride (400 mg, 7.42 mmol). The resulting reaction was heated and stirred at 90 °C for 1 h, before being filtered through a plug of Celite® while still hot. The filtrate was evaporated to dryness and the crude product was purified by chromatography (0-10% MeOH/DCM) to give the title compound **212** as a colourless solid (430 mg, 76%). R^t 1.00 min (Method 1a) m/z 288/290 $[M + H]^+$ (ES^+).



[00533] Step 3. (R)-8-Bromo-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **213**). Sodium hydride (60% in mineral oil, 83 mg, 2.08 mmol) was added in small portions to a stirred solution of methyl 3-((2-amino-5-bromopyridin-3-yl)amino)butanoate **212** (400 mg, 1.39 mmol) in THF (20 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2 h. The reaction was quenched by careful addition of sat. aq. NH_4Cl (20 mL) and the aqueous mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with MgSO_4 and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to give the title compound **213** as a colourless solid (170 mg, 45%). R^t 1.30 min (Method 1a) m/z 256/258 $[M + H]^+$ (ES^+).



[00534] Step 4. (R,E)-N-Methyl-3-(2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **214**). A

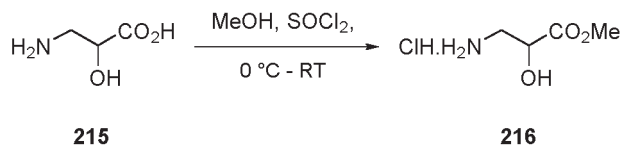
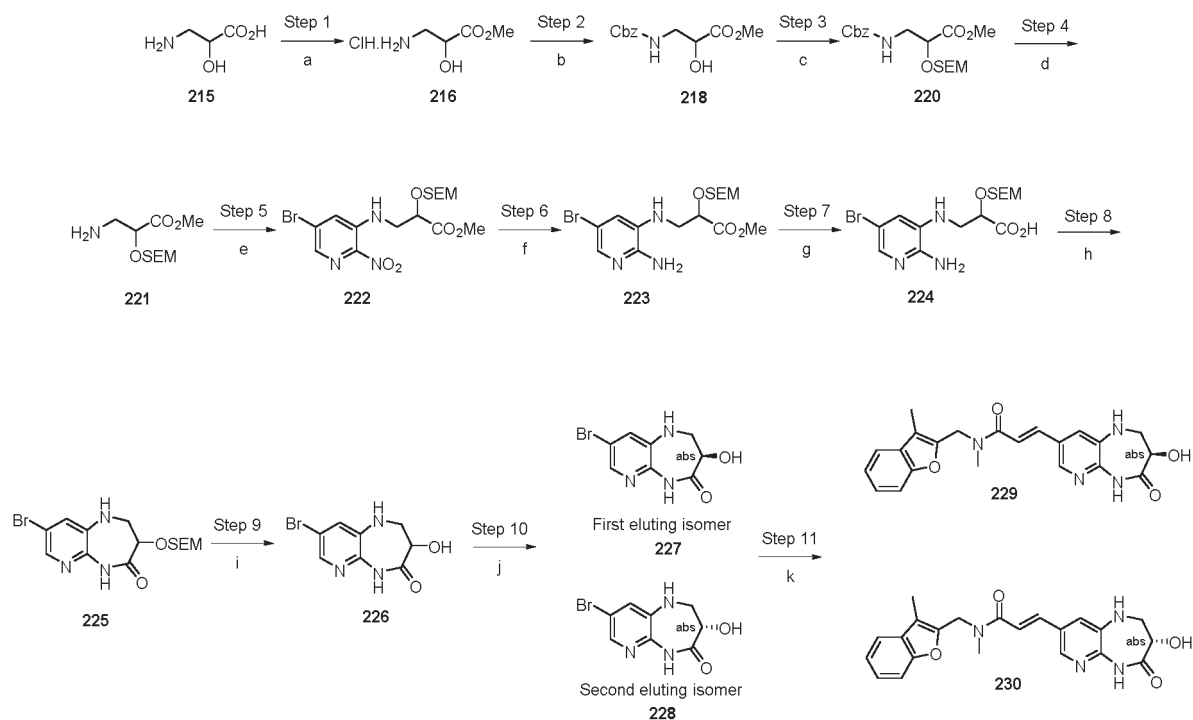
5 flask was charged with (R)-8-bromo-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **213** (80 mg, 0.31 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (**9**) (70 mg, 0.31 mmol), tetrabutylammonium chloride hydrate (9.2 mg, 0.03 mmol) and Pd-116 (16 mg, 0.03 mmol) and the flask was evacuated and backfilled with N₂ three times. 1,4-Dioxane (2.5 mL) and DIPEA (0.11 mL) were added and the reaction

10 mixture was heated to 90 °C for 2 h. Water (10 mL) was then added and the aqueous mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried by passing through a phase separation cartridge and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to give the title compound **214** as a yellow solid (68 mg, 52%). R_t 1.89 min (Method 1a) m/z 405 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-

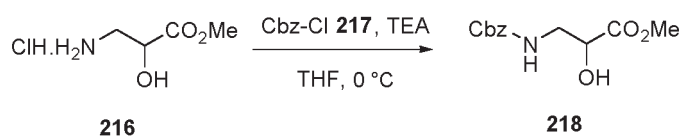
15 d₆, 363K): δ, ppm 9.42-9.22 (m, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 7.4 Hz, 1.5 Hz, 1H), 7.53-7.38 (m, 3H), 7.27 (dtd, J = 20.7 Hz, 7.3 Hz, 1.3 Hz, 2H), 7.12 (d, J = 15.4 Hz, 1H), 5.57-5.38 (m, 1H), 4.85 (s, 2H), 3.81 (ddt, J = 7.7 Hz, 6.3 Hz, 3.2 Hz, 1H), 3.10 (s, 3H), 2.61 (dd, J = 14.3 Hz, 3.1 Hz, 1H), 2.45 (dd, J = 14.4 Hz, 7.7 Hz, 1H), 2.28 (s, 3H), 1.25 (d, J = 6.4 Hz, 3H).

20 **[00535] Example 46.** Synthesis of (R,E)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **229**) and (S,E)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **230**).

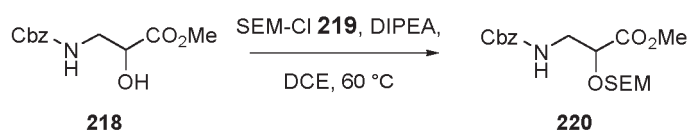
25 **[00536] General Synthetic Scheme.**



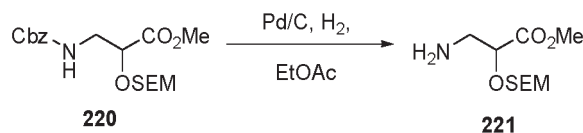
- 5 **[00537] Step 1.** Methyl 3-amino-2-hydroxypropanoate hydrochloride (compound **216**). To a suspension of 3-amino-2-hydroxypropanoic acid **215** (4.0 g, 38 mmol) in methanol (154 mL) stirred in ice water was added dropwise thionyl chloride (8.3 mL, 114 mmol). Upon completion of addition, the mixture was stirred at RT overnight. The reaction mixture was evaporated to dryness to give the title compound **216** as a colourless gum, (6.1 g, quant.). ¹H NMR (DMSO-d₆): δ, ppm 8.25 (br s, 3H), 6.07 (br s, 1H), 4.41 (dd, J = 8.7 Hz, 3.8 Hz, 1H), 3.68 (s, 3H), 3.12-3.06 (m, 1H), 2.96-2.86 (m, 1H).
- 10



[00538] Step 2. Methyl 3-(((benzyloxy)carbonyl)amino)-2-hydroxypropanoate (compound **218**). To an ice cooled mixture of methyl 3-amino-2-hydroxypropanoate hydrochloride **216** (5.92 g, 38 mmol) and triethylamine (22 mL, 152 mmol) in THF (100 mL) was added dropwise benzyl chloroformate **217** (5.4 mL, 38 mmol). The mixture was allowed to warm to RT and stirred for a further 2 h. The mixture was evaporated to dryness and the residue was redissolved in ethyl acetate (100 mL), washed with water (2 × 100 mL) and the organic phase was dried over sodium sulfate. The crude product was purified by silica chromatography (0-50% EtOAc/isohexane) to afford the title compound **218** as a clear colourless oil (5.50 g, 56%). ¹H NMR (CDCl₃): δ, ppm 7.40-7.28 (m, 5H), 5.15-5.10 (m, 3H), 4.28 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H), 3.66-3.49 (m, 2H), 3.19 (s, 1H).

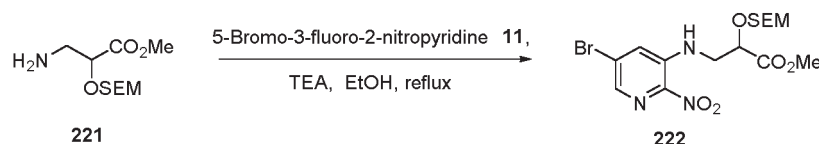


[00539] Step 3. Methyl 3-(((benzyloxy)carbonyl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate (compound **220**). A mixture of 2-(trimethylsilyl)ethoxymethyl chloride **219** (2.3 mL, 13.2 mmol), DIPEA (3.4 mL, 19.7 mmol) and methyl 3-(((benzyloxy)carbonyl)amino)-2-hydroxypropanoate **218** (3.30 g, 13.2 mmol) in DCE (100 mL) was stirred at 60 °C for 24 h. The mixture was allowed to cool to RT, the solvent was removed in vacuo, and the crude product was purified by silica chromatography (0-50% EtOAc/isohexane) to afford the title compound **220** as a clear colourless oil (4.40 g, 83%). ¹H NMR (CDCl₃): δ, ppm 7.41-7.32 (m, 5H), 5.19 (br s, 1H), 5.18-5.09 (m, 2H), 4.78 (s, 2H), 4.29 (dd, J = 6.3 Hz, 4.3 Hz, 1H), 3.76 (s, 3H), 3.66 (m, 3H), 3.54 (m, 1H), 0.92 (m, 2H), 0.03 (s, 9H).

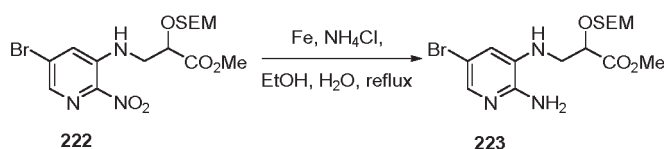


[00540] Step 4. Methyl 3-amino-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate (compound **221**). A mixture of methyl 3-(((benzyloxy)carbonyl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate **220** (4.40 g, 11.5 mmol) and 10% Pd/C (1.2 g,

Type 87L) in a solvent of ethyl acetate (100 mL) was stirred under H₂ at 5 bar pressure for 1 h. The catalyst was removed by filtration and the filtrate evaporated to dryness to afford the title compound **221** as a yellow oil (2.6 g, 89%). ¹H NMR (DMSO-d₆): δ, ppm 4.66 (dd, J = 13.2 Hz, 4.7 Hz, 2H), 4.01 (dd, J = 6.5 Hz, 4.7 Hz, 1H), 3.64 (s, 3H), 3.63-3.50 (m, 2H), 2.82 (m, 1H), 2.75 (m, 1H), 1.45 (s, 2H), 0.91-0.77 (m, 2H), 0.01 (s, 9H).

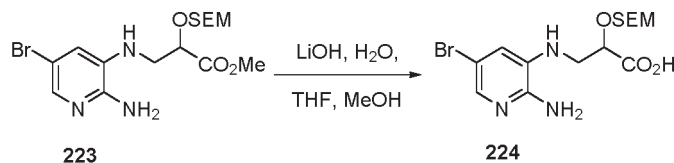


[00541] Step 5. Methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate (compound **222**). A mixture of methyl 3-amino-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate **221** (2.60 g, 10.4 mmol), TEA (7.3 mL, 52.1 mmol) and 5-bromo-3-fluoro-2-nitropyridine **11** (2.30 g, 10.4 mmol) in a solvent of EtOH (80 mL) was heated under reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was purified by silica chromatography (0-50% EtOAc/isohexane) to afford the title compound **222** as a yellow oil (4.30 g, 90%). R_t 2.67 min (Method 1a); m/z 448/450 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-d₆): δ, ppm 8.08 (t, J = 6.1 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 1.8 Hz, 1H), 4.76-4.62 (m, 2H), 4.44 (dd, J = 7.2 Hz, 4.6 Hz, 1H), 3.77 (q, J = 7.3 Hz, 6.2 Hz, 2H), 3.69 (s, 3H), 3.55-3.43 (m, 2H), 0.81-0.70 (m, 2H), -0.06 (s, 9H).



[00542] Step 6. Methyl 3-((2-amino-5-bromopyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate (compound **223**). A mixture of methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate **222** (4.30 g, 9.5 mmol), iron powder (2.67 g, 47.7 mmol) and ammonium chloride (5.1 g, 95.0 mmol) in a solvent of ethanol (100 mL) and water (30 mL) was heated and stirred under reflux for 1 h. The mixture was allowed to cool to RT and was filtered through a plug of Celite®. The filtrate was evaporated to dryness and the residue taken up into DCM (130 mL).

The organics were washed with water (200 mL) and dried over sodium sulfate. Filtration and evaporation gave the title compound **223** as a yellow oil (3.01 g, 74%). R^t 1.76 min (Method 1a); m/z 420/422 $[M + H]^+$ (ES^+).



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[00543] Step 7. 3-((2-Amino-5-bromopyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoic acid (compound **224**). To a stirred solution of methyl

3-((2-amino-5-bromopyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate **223** (3.30 g, 7.85 mmol) in THF (200 mL) and MeOH (50 mL) was added a solution of LiOH monohydrate (0.23 g, 9.42 mmol) in water (30 mL) and the reaction mixture was stirred at RT for 1 h. The mixture was evaporated to dryness and the residue taken up into water (30 mL) and the pH was adjusted to ~pH 5 by the addition of acetic acid (~1 mL). The solid was collected by filtration, washed with water (4 mL) and dried to give the title compound **224** as a beige solid (2.75 g, 84%). R^t 1.58 min (Method 1a); m/z 406/408 $[M + H]^+$ (ES^+). 1H NMR (DMSO- d_6): δ , ppm 7.31 (d, J = 2.1 Hz, 1H), 6.75 (d, J = 2.1 Hz, 1H), 5.75 (d, J = 6.1 Hz, 2H), 5.37 (s, 1H), 4.67-4.64 (m, 2H), 4.22 (m, 1H), 3.55-3.31 (m, 4H), 0.78-0.74 (m, 2H), -0.06 (s, 9H). Acidic proton not observed.

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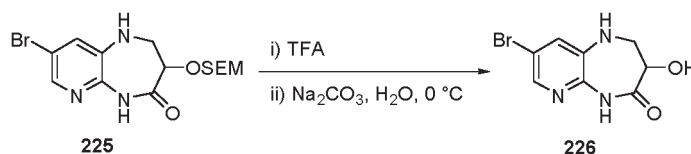


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[00544] Step 8. 8-Bromo-3-((2-(trimethylsilyl)ethoxy)methoxy)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **225**). To a solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methoxy)propanoic acid **224** (2.75 g, 6.77 mmol) and DIPEA (6.0 mL, 33.8 mmol) in DMF (3 mL) was added HATU (3.0 g, 8.12 mmol) and the mixture was stirred at RT for 30 mins. The mixture was poured onto ice water (30 mL) and the solid collected and dried to give the title compound **225** as a beige solid (2.50 g, 93%). R^t 2.27 min (Method 1b); m/z 388/390 $[M + H]^+$ (ES^+). 1H NMR (DMSO- d_6): δ ,

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ppm 10.05 (s, 1H), 7.71 (s, 1H), 7.28 (s, 1H), 6.21 (d, J = 4.5 Hz, 1H), 4.65 (q, J = 6.9 Hz, 2H), 4.23 (d, J = 5.4 Hz, 1H), 3.56-3.45 (m, 4H), 0.88-0.82 (m, 2H), -0.02 (s, 9H).



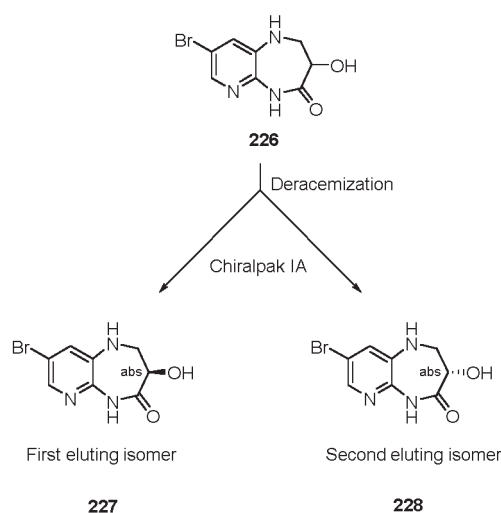
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[00545] Step 9. 8-Bromo-3-hydroxy-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **226**). TFA (10 mL) was added in one portion to 8-bromo-3-((2-(trimethylsilyl)ethoxy)methoxy)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **225** (800 mg, 2.1 mmol) and the solution was allowed to stand at RT for 5 mins before being carefully poured onto crushed ice (100 g). The resultant mixture was carefully neutralised by the addition of solid sodium carbonate and extracted with ethyl acetate (2 x 100 mL). The organics were combined and dried over sodium sulfate. Filtration and evaporation gave a gum which was triturated with acetonitrile (10 mL) to give the title compound **226** as an off white solid (310 mg, 57%). R^t 1.04 min (Method 1a); m/z 258/260 $[M + H]^+$ (ES^+). 1H NMR (DMSO- d_6): δ , ppm 10.12 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 6.37 (dd, J = 6.2 Hz, 2.8 Hz, 1H), 5.24 (d, J = 4.7 Hz, 1H), 4.16 (ddd, J = 8.4 Hz, 4.8 Hz, 3.1 Hz, 1H), 3.45 (ddd, J = 12.3 Hz, 6.1 Hz, 3.1 Hz, 1H), 3.29 (td, J = 9.1 Hz, 4.5 Hz, 1H).

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[00546] Step 10. Chiral separation of racemate **226**.

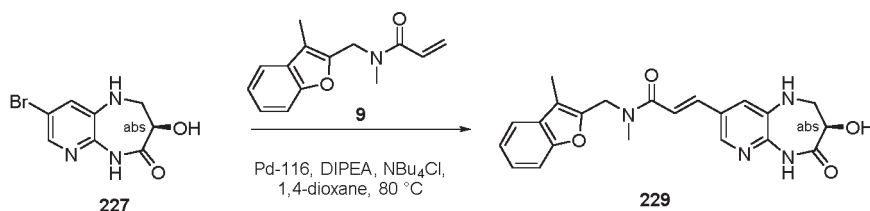
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[00547] The enantiomers were separated by chiral prep HPLC using Chiralpak® IA (Daicel Ltd.) column (2 x 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of 25% Acetonitrile:75% water, UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping acetonitrile (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹. Chirality was arbitrarily assigned.

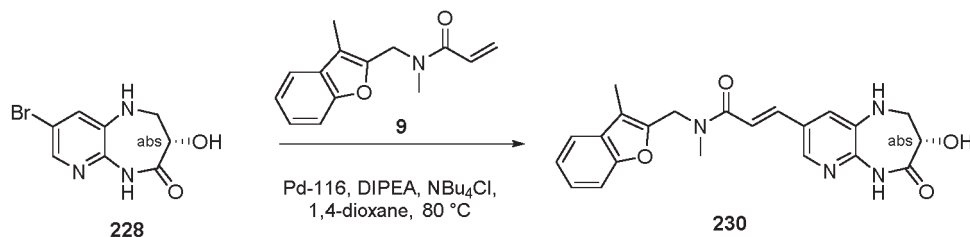
[00548] (R)-8-Bromo-3-hydroxy-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **227**). First eluting isomer: R^t 7.98 min (Analytical Method: Chiralpak® IA, column (4.6 mm x 25 mm), flow rate 1 mL min⁻¹, eluent: 30% acetonitrile : 70% 10 mmol aqueous ammonium bicarbonate solution).

[00549] (S)-8-Bromo-3-hydroxy-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **228**). Second eluting isomer: R^t 13.09 min (Analytical Method: Chiralpak® IA, column (4.6 mm x 25 mm), flow rate 1 mL min⁻¹, eluent: 30% acetonitrile : 70% 10mmol aqueous ammonium bicarbonate solution).



[00550] **Step 11a.** (R,E)-3-(3-Hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **229**). A reaction vial was charged with (R)-8-bromo-3-hydroxy-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **227** (50 mg, 0.19 mmol), DIPEA (70 μ L, 0.39 mmol), tetrabutylammonium chloride hydrate (6 mg, 0.02 mmol), and Pd[P(^tBu)₃]₂ (Pd-116) (10 mg, 0.02 mmol) and the vial was flushed with nitrogen (5 mins). 1,4-Dioxane (5 mL) and N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (49 mg, 0.21 mmol) were added, the reaction mixture was purged with nitrogen again (5 mins), and then the reaction mixture was heated and stirred at 80 °C for 30 mins. The reaction mixture was allowed to cool to RT, then was evaporated to dryness and the crude product was purified by column chromatography (0-10% MeOH/DCM) to afford the title compound **229** as a pale yellow solid (61 mg, 77%). R^t 1.77 min (Method 1b); m/z 407 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-d₆, 363K): δ ,

ppm 9.65 (s, 1H), 7.99 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.49-7.37 (m, 3H), 7.33-7.21 (m, 2H), 7.13 (d, J = 14.6 Hz, 1H), 5.89 (d, J = 5.5 Hz, 1H), 4.91-4.77 (m, 3H), 4.22-4.16 (m, 1H), 3.52 (ddd, J = 12.4 Hz, 6.0 Hz, 3.3 Hz, 1H), 3.27 (ddd, J = 12.1 Hz, 8.8 Hz, 2.8 Hz, 1H), 3.10 (s, 3H), 2.28 (s, 3H).



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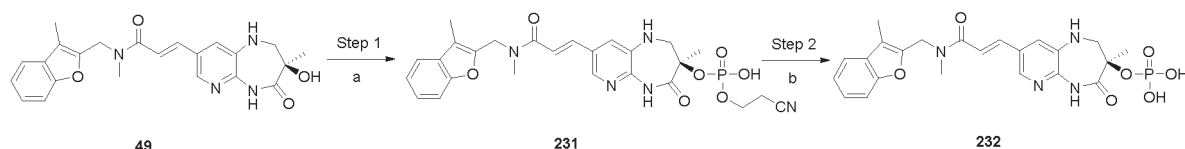
[00551] Step 11b. (S,E)-3-(3-Hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **230**). A reaction vial was charged with (S)-8-bromo-3-hydroxy-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **228** (50 mg, 0.19 mmol), DIPEA (70 μ L, 0.39 mmol), tetrabutylammonium chloride hydrate (6 mg, 0.02 mmol) and Pd[P(^tBu)₃]₂ (Pd-116) (10 mg, 0.02 mmol) and the vial was flushed with nitrogen (5 mins). 1,4-Dioxane (5 mL) and N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (50 mg, 0.21 mmol) were added, the reaction mixture was purged with nitrogen again (5 mins), and then the reaction mixture was heated and stirred at 80 °C for 30 mins. The reaction mixture was allowed to cool to RT, then was evaporated to dryness and the crude product was purified by silica chromatography (0-10% MeOH/DCM) to afford the title compound **230** as a pale yellow solid (58 mg, 73%). *R*^t 1.76 min (Method 1b); *m/z* 407 [M + H]⁺ (ES⁺). ¹H NMR (DMSO-d₆, 363K): δ , ppm 9.65 (s, 1H), 7.99 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.49-7.36 (m, 3H), 7.27 (dt, J = 21.1 Hz, 7.4 Hz, 2H), 7.13 (d, J = 15.7 Hz, 1H), 5.93-5.84 (m, 1H), 4.90-4.80 (m, 3H), 4.18 (dt, J = 8.5 Hz, 3.8 Hz, 1H), 3.52 (ddd, J = 12.3 Hz, 6.1 Hz, 3.4 Hz, 1H), 3.27 (ddd, J = 12.2 Hz, 8.9 Hz, 2.8 Hz, 1H), 3.10 (s, 3H), 2.28 (s, 3H).

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[00552] Example 47. Synthesis of (R,E)-3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate (compound **232**).

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[00553] General Synthetic Scheme.



Reaction conditions: a) i. bis(2-cyanoethyl) diisopropylphosphoramidite, 1H-tetrazole, 1 day, RT; ii. 0.1 M iodine solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C, 20% w/w Na₂S₂O₃; b) BSTFA, ACN, Barton's base, 35 min at 0 °C then HCOOH.

[00554] Step 1. 2-Cyanoethyl ((R)-3-methyl-8-((E)-3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-

b][1,4]diazepin-3-yl) hydrogen phosphate (compound **231**). To a solution of the substrate **49**

(250 mg, 0.59 mmol, 1 equiv.) in dry DCM (5.95 mL) were added bis(2-cyanoethyl) diisopropylphosphoramidite (645 mg, 2.38 mmol, 4 equiv.) and 1H-tetrazole (5.29 mL, 2.38 mmol, 4 equiv., 0.45 M in MeCN) under N₂ at rt. The mixture was stirred at rt for 1 day, then evaporated partially. The resulting phosphite was oxydized by treatment with a 0.1 M iodine

solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C until persistence of iodine coloration. The mixture was allowed to return at rt, then after 1 h, the mixture was quenched using sodium thiosulfate 20% w/w under stirring until disappearance of iodine coloration. The aqueous

phase was removed and the organic phase was dried over Na₂SO₄, diluted with MeOH and DCM and filtered. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford, after lyophilisation, the desired product **231** (165

mg, 0.30 mmol, 50%) as a yellow solid. The product was directly engaged in the next step.

[00555] Step 2. (R,E)-3-Methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl

dihydrogen phosphate (compound **232**). To a solution of **231** (2.65 g, 4.79 mmol, 1 eq.) in

MeCN (28.5 mL) were added N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) (6.36 mL, 23.9 mmol, 5 eq.), then 2-tert-butyl-1,1,3,3-tetramethylguanidine (Barton's base) (4.14 mL, 19.9 mmol, 4.1 eq.). The mixture was at 0 °C for 35 min, then formic acid was added to quench the reaction. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1%

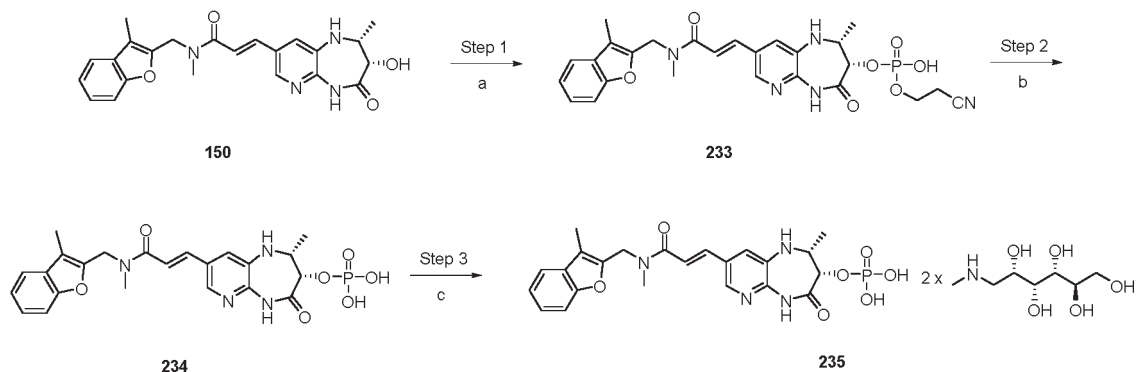
HCO₂H) in water (0.1% HCO₂H) and lyophilized to obtain the desired compound **232** (1.26 g,

250 mmol, 52%). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.89 (s, 1H), 8.05-7.96 (m, 1H), 7.61-7.53 (m, 1H), 7.52-7.02 (m, 6H), 6.20 (m, 1H), 4.95 (s, 0.8H), 4.79 (s, 1.2H), 3.62-3.41 (m, 2H), 3.17 (s, 2H), 2.95 (s, 1H), 2.31-2.21 (s, 3H). ³¹P NMR (162 MHz, DMSO-d₆) δ -4.8. MS (Method 1c): m/z = 501.1 [M + H]⁺.

[00556] Example 48. Synthesis of [(2R,3S)-2-methyl-8-[(E)-3-[methyl-[(3-methylbenzofuran-2-yl)methyl]amino]-3-oxo-prop-1-enyl]-4-oxo-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-3-yl] dihydrogen phosphate - (2R,3R,4R,5S)-6-(methylamino)hexane-1,2,3,4,5-pentol salt (compound **235**).

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[00557] General Synthetic Scheme.



Reaction conditions: a) i. bis(2-cyanoethyl) diisopropylphosphoramidite, 1H-tetrazole, 1 day, RT; ii. 0.1 M iodine solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C, 20% w/w Na₂S₂O₃; b) BSTFA, ACN, 2-tert-butyl-1,1,3,3-tetramethylguanidine, 35 min at 0 °C then HCOOH; c) H₂O and MeCN (60 mL, 1/1), meglumine, 2 eq

[00558] Step 1. 2-Cyanoethyl ((2R,3S)-2-methyl-8-((E)-3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl) hydrogen phosphate (compound **233**). To a mixture of **150** (129 mg, 0.31 mmol, 1 eq.) in dry CH₂Cl₂ (2.80 mL) were added bis(2-cyanoethyl)diisopropylphosphoramidite (0.24 mL, 0.92 mmol, 3 equiv.) and 1H-tetrazole (1.36 mL, 0.61 mmol, 2 equiv., 0.45 M in MeCN). The mixture was stirred at rt for 16 h. After completion of the reaction, a solution of 0.2 M iodine solution (I₂ in water/pyridine/THF, 1/19/80) was added at 0 °C until persistence of iodine coloration. The mixture was allowed to return at rt, then after 2 h, the mixture was quenched using sodium thiosulfate (20% w/w) under stirring until disappearance of iodine coloration. The aqueous phase was removed and the organic phase was dried over Na₂SO₄, diluted with MeOH and CH₂Cl₂ and filtered. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford, after lyophilization, the desired compound **233** (159 mg) as a yellow solid. The product was directly engaged in the next step.

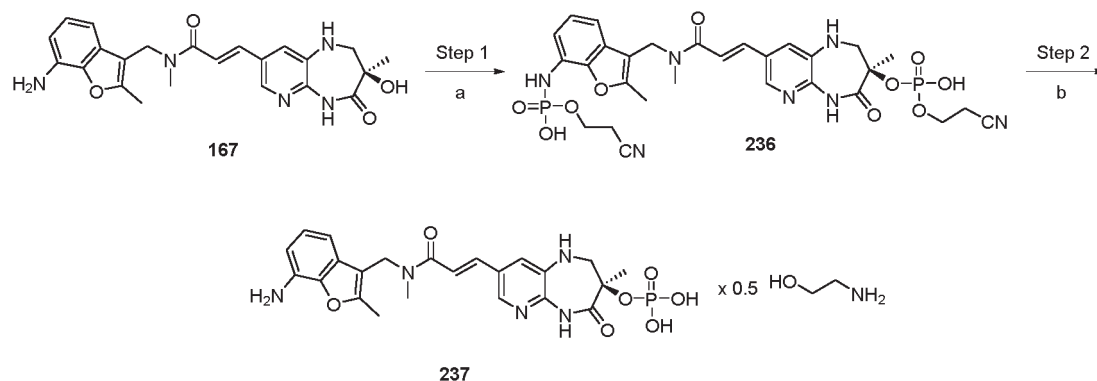
[00559] Step 2. (2R,3S)-2-Methyl-8-((E)-3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-

b)[1,4]diazepin-3-yl dihydrogen phosphate (compound **234**). To a mixture of **233** (159 mg, 0.29 mmol, 1 equiv.) in dry MeCN (14.4 mL) were added N,O-bis(trimethylsilyl)trifluoroacetamide (0.31 mL, 1.15 mmol, 4 equiv.), then 2-tert-butyl-1,1,3,3-tetramethylguanidine (0.20 mL, 0.96 mmol, 3.3 equiv.). The mixture was stirred at 0 °C for 10 min, then formic acid (0.11 mL, 2.87 mmol, 10 eq.) was added to quench the reaction. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford, after lyophilization, the desired compound **234** (33 mg, 0.06 mmol, 22%) as a yellow solid. The desired compound was used to make meglumine salt.

[00560] Step 3. [(2R,3S)-2-Methyl-8-[(E)-3-[methyl-[(3-methylbenzofuran-2-yl)methyl]amino]-3-oxo-prop-1-enyl]-4-oxo-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-3-yl] dihydrogen phosphate - (2R,3R,4R,5S)-6-(methylamino)hexane-1,2,3,4,5-pentol salt (compound **235**). To a solution of the substrate **234** (1 equiv.) in water and MeCN (60 mL, 1/1) at rt was added the corresponding base (meglumine, 2 eq.). The mixture was stirred, sonicated and lyophilized to afford the desired product **235**. ¹H NMR (400 MHz, D₂O): δ, ppm 7.80-7.65 (m, 1H), 7.25-7.46 (m, 7H), 4.52-4.25 (m, 2H), 4.18-4.02 (m, 3H), 3.83-3.69 (m, 6H), 3.67-3.56 (m, 4H), 3.26-3.04 (m, 4H), 2.89-2.75 (m, 6H), 2.72 (s, 6H), 1.84 (s, 3H), 1.25-1.16 (m, 6H). ³¹P NMR (162 MHz, D₂O) δ 3.1. MS (Method 1c): m/z = 501.1 [M + H]⁺.

[00561] Example 49. Synthesis of 2-aminoethanol; (R,E)-8-(3-(((7-amino-2-methylbenzofuran-3-yl)methyl)(methyl)amino)-3-oxoprop-1-en-1-yl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate (compound **237**).

[00562] General Synthetic Scheme.



Reaction conditions: a) i. bis(2-cyanoethyl) diisopropylphosphoramidite, 1H-tetrazole, 1 day, RT; ii. 0.1 M iodine solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C, 20% w/w Na₂S₂O₃; b) i. BSTFA, ACN, Barton's base, 35 min at 0 °C then HCOOH; ii. water, HOCH₂CH₂NH₂ (5.0 eq.)

[00563] Step 1. 2-Cyanoethyl hydrogen (3-(((E)-3-((3R)-3-(((2-cyanoethoxy)(hydroxy)phosphoryl)oxy)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-

b][1,4]diazepin-8-yl)-N-methylacrylamido)methyl)-2-methylbenzofuran-7-yl)phosphoramidate (compound **236**). To a mixture of **167** (200 mg, 0.46 mmol, 1 eq.) in dry CH₂Cl₂ (4.59 mL) were added bis(2-cyanoethyl)diisopropylphosphoramidite (0.48 mL, 1.84 mmol, 4 eq.) and 1H-tetrazole (4.08 mL, 1.84 mmol, 4 eq., 0.45 M in MeCN). The mixture was stirred at rt for 16 h, then partially evaporated and a solution of 0.2 M iodine solution (water/pyridine/THF, 1/19/80) was added at 0 °C until persistence of iodine coloration. The mixture was allowed to return at rt. After 2 h, the mixture was quenched using sodium thiosulfate 20% w/w under stirring until disappearance of iodine coloration. The aqueous phase was removed and the organic phase was dried over Na₂SO₄, diluted with MeOH and CH₂Cl₂ and filtered. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford, after lyophilization, the desired compound **236** (245 mg) as a yellow solid.

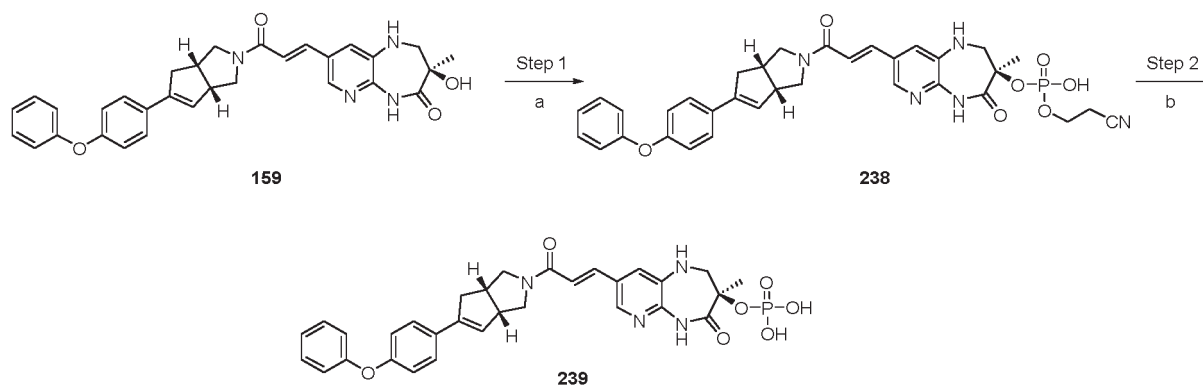
[00564] Step 2. 2-Aminoethanol; (R,E)-8-(3-(((7-amino-2-methylbenzofuran-3-yl)methyl)(methyl)amino)-3-oxoprop-1-en-1-yl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate (compound **237**). To a mixture of **236** (240 mg, 0.34 mmol, 1 eq.) in dry MeCN (18.9 mL) were added BSTFA (0.91 mL, 3.42 mmol, 10 eq.), then 2-tert-butyl-1,1,3,3-tetramethylguanidine (Barton's base) (0.59 mL, 2.85 mmol, 8.3 eq.). The mixture was stirred at 0 °C for 5/10 min, then HCOOH was added to quench the reaction and water (1 mL). After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford a powder containing the desired dihydrogen phosphate. The residue was dissolved in water + ethanolamine in excess (> 5 equiv.). The mixture was purified eluting with 5-100% MeCN in water to afford, after lyophilization, the

desired compound **237** (89 mg, 0.15 mmol, 45%) as a yellow solid. ^1H NMR (400 MHz, D_2O): δ , ppm 7.88-7.78 (m, 1H), 7.44-7.26 (m, 2H), 7.21-6.61 (m, 4H), 4.76-4.59 (m, 2H), 3.59 (t, J = 5.5 Hz, 1H), 3.55-3.46 (m, 2H), 3.00-2.81 (m, 3H), 2.77 (t, J = 5.5 Hz, 1H), 2.46-2.28 (m, 3H), 1.59-1.46 (m, 3H). ^{31}P NMR (162 MHz, D_2O) δ 0.0. MS (Method 1c): m/z = 516.1 $[\text{M} + \text{H}]^+$.

5

[00565] Example 50. Synthesis of (R)-3-methyl-4-oxo-8-((E)-3-oxo-3-((3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate (compound **239**).

[00566] General Synthetic Scheme.



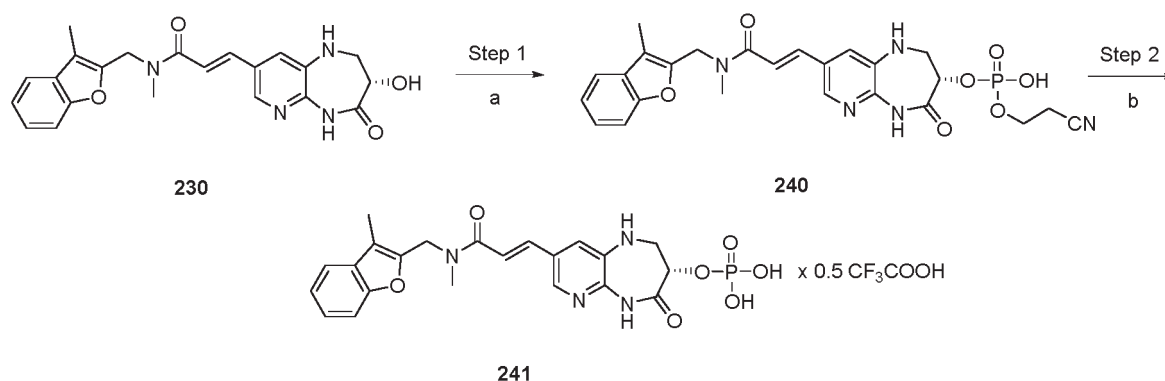
Reaction conditions: a) i. bis(2-cyanoethyl) diisopropylphosphoramidite, 1H-tetrazole, 1 day, RT; ii. 0.1 M iodine solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C, 20% w/w $\text{Na}_2\text{S}_2\text{O}_3$; b) BSTFA, ACN, Barton's base, 35 min at 0 °C then HCOOH.

[00567] Step 1. 2-Cyanoethyl ((R)-3-methyl-4-oxo-8-((E)-3-oxo-3-((3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-2,3,4,5-

tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl) hydrogen phosphate (compound **238**). To a mixture of **159** (400 mg, 0.77 mmol, 1 eq.) in dry CH_2Cl_2 (7.65 mL) were added bis(2-cyanoethyl)diisopropylphosphoramidite (831 mg, 3.06 mmol, 4 eq.) and 1H-tetrazole (6.80 mL, 3.07 mmol, 4 eq., 0.45 M in MeCN). The mixture was stirred at rt for 16 h, then evaporated and a solution of 0.2 M iodine solution (water/pyridine/THF, 1/19/80) was added at 0 °C until persistence of iodine coloration. The mixture was allowed to return at rt, then after 2 h, the mixture was quenched using aqueous sodium thiosulfate 20% w/w until disappearance of iodine coloration. The aqueous phase was removed and the organic phase was dried over Na_2SO_4 , diluted with MeOH and CH_2Cl_2 and filtered. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford the desired compound **238** (421 mg) as a yellow solid. The product was directly used in the next step.

[00568] Step 2. (R)-3-Methyl-4-oxo-8-((E)-3-oxo-3-((3aS,6aR)-5-(4-phenoxyphenyl)-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)prop-1-en-1-yl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate (compound **239**). To a mixture of **238** (421 mg, 0.64 mmol, 1 eq.) in dry MeCN (35.54 mL) were added BSTFA (1.71 mL, 6.42 mmol, 10 eq.), then Barton's base (1.11 mL, 5.35 mmol, 8.3 eq.). The mixture was stirred at rt for 5/10 min, then formic acid was added to quench the reaction. After evaporation, the residue was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA). The precipitate was recovered and lyophilized to afford the desired compound **239** (123 mg, 0.20 mmol, 32%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 9.89 (d, J = 5.6 Hz, 1H), 8.11-7.90 (m, 1H), 7.59-7.27 (m, 7H), 7.15 (t, J = 7.4 Hz, 1H), 7.09-6.93 (m, 5H), 6.86 (dd, J = 15.5, 6.4 Hz, 1H), 6.13 (s, 1H), 4.15-2.78 (m, 9H), 2.62 (d, J = 15.9 Hz, 1H), 1.61-1.49 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ -73.6 (residual traces of TFA). ³¹P NMR (162 MHz, DMSO-d₆) δ -4.8. MS (Method 1c): m/z = 603.2 [M + H]⁺.

[00569] Example 51. Synthesis of (S,E)-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate 2,2,2-trifluoroacetate (compound **241**).



Reaction conditions: a) i. bis(2-cyanoethyl) diisopropylphosphoramidite, 1H-tetrazole, 1 day, RT; ii. 0.1 M iodine solution (water/2,6-lutidine/THF, 1/19/80) at 0 °C, 20% w/w Na₂S₂O₃; b) BSTFA, ACN, Barton's base, 35 min at 0 °C then HCOOH.

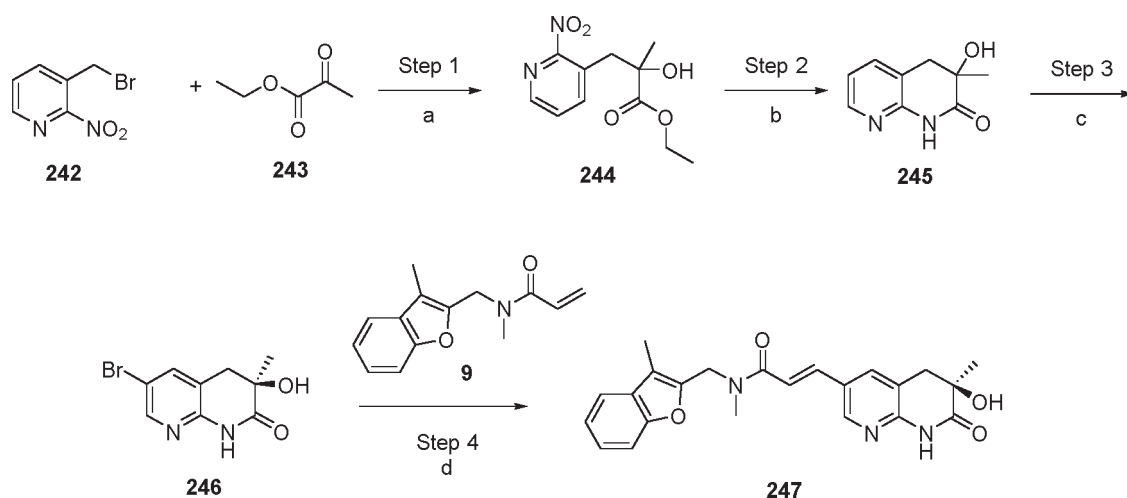
[00571] Step 1. 2-Cyanoethyl ((S)-8-((E)-3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-

b)[1,4]diazepin-3-yl) hydrogen phosphate (compound 240). To a mixture of **230** (200 mg, 0.49 mmol, 1 equiv.) in dry DMF (4.92 mL) were added bis(2-cyanoethyl)diisopropylphosphoramidite (0.51 mL, 1.97 mmol, 4 equiv.) and 1H-tetrazole (4.37 mL, 1.97 mmol, 4 equiv., 0.45 M in MeCN). The mixture was stirred at 60 °C for 4 hours, then MeCN was evaporated and a solution of 0.2 M iodine solution (I₂ in water/pyridine/THF, 1/19/80) was added at 0 °C until persistence of iodine coloration. The mixture was allowed to return at rt, then after 2 h, the mixture was quenched using sodium thiosulfate 20% w/w under stirring until disappearance of iodine coloration. The aqueous phase was removed and the organic phase was dried over Na₂SO₄, diluted with MeOH and CH₂Cl₂ and filtered. After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford the desired compound **240** (199 mg) after lyophilization. The product was directly engaged in the next step.

[00572] Step 2. (S,E)-8-(3-(Methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-3-yl dihydrogen phosphate 2,2,2-trifluoroacetate (compound **241**). To a mixture of **240** (120 mg, 0.22 mmol, 1 eq.) in dry MeCN (12.3 mL) were added BSTFA (0.59 mL, 1.85 mmol, 8.3 eq.), then Barton's base (0.39 mL, 2.22 mmol, 10 eq.). The mixture was stirred at rt for 10 min, then formic acid (0.08 mL, 2.22 mmol, 10 eq.) was added to quench the reaction and MeOH (1 mL). After evaporation, the crude was purified eluting with 5-100% MeCN (0.1% TFA) in water (0.1% TFA) to afford, after lyophilization, the desired compound (42 mg, 0.07 mmol, 31%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.23 (s, 1H), 8.18-8.04 (m, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.54-7.35 (m, 4H), 7.31-7.07 (m, 3H), 6.10 (s, 1H), 4.96 (s, 0.8H), 4.80 (s, 1.2H), 4.74-4.57 (m, 1H), 3.69 (dd, J = 12.3, 3.3 Hz, 1H), 3.51 (dd, J = 12.3, 8.5 Hz, 1H), 3.18 (s, 1.7H), 2.95 (s, 1.3H), 2.28 (d, J = 4.4 Hz, 3H). ³¹P NMR (162 MHz, DMSO-d₆) δ -1.9. ¹⁹F NMR (376 MHz, DMSO-d₆) δ -74.1 (traces of TFA)

[00573] MS (Method 1c): m/z = 487.0 [M + H]⁺.

[00574] Example 52. Synthesis of (R,E)-3-(6-hydroxy-6-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **247**).

[00575] General Synthetic Scheme.

Reaction Conditions: a) N1,N1,N'1,N'1,N2,N2,N'2,N'2-octamethylethene-1,1,2,2-tetraamine, DMF, -20 °C to RT; b) Fe, NH₄Cl, EtOH, water, 90 °C; c) NBS, K₂CO₃, MeCN, followed by chiral separation; d) Pd-116, DIPEA, NBu₄Cl, 1,4-dioxane, 80 °C.

5 **[00576]** **Step 1.** Ethyl 2-hydroxy-2-methyl-3-(2-nitropyridin-3-yl)propanoate (compound **244**). To a stirring solution of 3-(bromomethyl)-2-nitropyridine **242** (850 mg, 3.92 mmol) in anhydrous DMF (15 mL), was added ethyl pyruvate **243** (1.3 mL, 11.8 mmol) at -20 °C. The resulting solution was stirred and maintained at this temperature for 30 min. N1,N1,N'1,N'1,N2,N2,N'2,N'2-octamethylethene-1,1,2,2-tetraamine (1.0 mL, 4.31 mmol) was then added. A red colour immediately developed with the formation of a fine white precipitate. The solution was vigorously stirred at -20 °C for 1 h and then warmed up to RT for 2 h. The orange-red turbid solution was filtered and water (80 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organic extracts were washed with water (3 x 40 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to give title compound **244** as a colourless solid (630 mg, 57%). R_t 1.48 min (Method 1a) m/z 255 [M + H]⁺ (ES⁺).

20 **[00577]** **Step 2.** 3-Hydroxy-3-methyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one (compound **245**). To a solution of ethyl 2-hydroxy-2-methyl-3-(2-nitropyridin-3-yl)propanoate **244** (630 mg, 2.48 mmol) in ethanol (35 mL) and water (8.8 mL) were added

iron (554 mg, 9.9 mmol) and ammonium chloride (530 mg, 9.91 mmol). The resulting mixture was heated under reflux for 1 h. The reaction mixture was filtered through a plug of Celite® when still hot. The filtrate was then evaporated to dryness. The crude product was purified by chromatography (0-10% MeOH/DCM) to give title compound **245** as a colourless solid (350 mg, 75%). R^t 0.56 min (Method 1a) m/z 179 $[M + H]^+$ (ES^+).

[00578] Step 3. (R)-6-Bromo-3-hydroxy-3-methyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one (compound **246**). N-Bromosuccinimide (619 mg, 3.48 mmol) and K_2CO_3 (962 mg, 6.96 mmol) were added in one portion to a stirred solution of 3-hydroxy-3-methyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one **245** (310 mg, 1.74 mmol) in acetonitrile (20 mL) at 0 °C. The reaction was allowed to warm up to RT and then stirred overnight. After this time more N-bromosuccinimide (619 mg, 3.48 mmol) and K_2CO_3 (962 mg, 6.96 mmol) were added and the resulting mixture was stirred for 3 h. The reaction was quenched by addition of H_2O (10 mL) then extracted with DCM (3 x 10 mL). The combined organic layers were dried by passing through a phase separation cartridge and concentrated in vacuo. The crude product was purified by chromatography (0-100% EtOAc/isohexane) to afford the racemate as a white solid (200 mg, 42%). The racemate was submitted for a chiral separation giving first peak (R)-6-bromo-3-hydroxy-3-methyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one **246** (60 mg). R^t 1.19 min (Method 1a) m/z 257/259 $[M + H]^+$ (ES^+). The *absolute configuration arbitrarily assigned*.

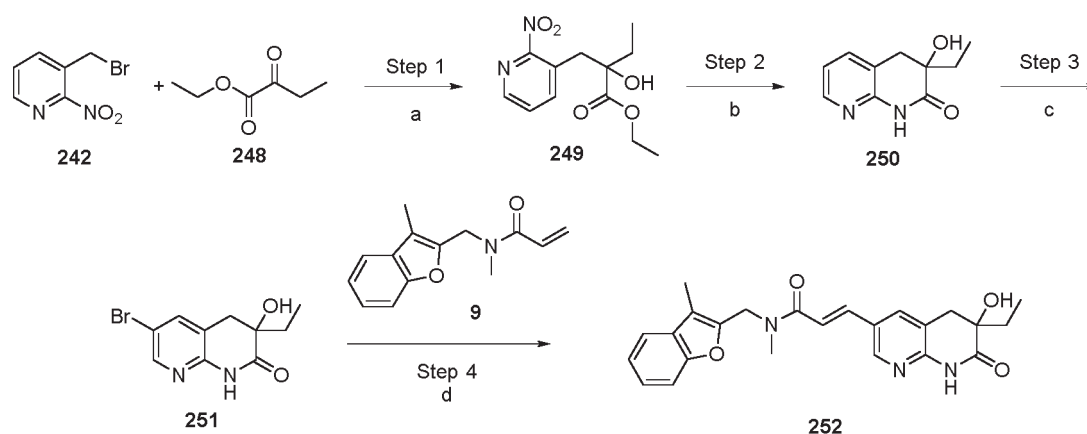
[00579] Step 4. (R,E)-3-(6-Hydroxy-6-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **247**). A flask was charged with (R)-6-bromo-3-hydroxy-3-methyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one **246** (60 mg, 0.23 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (54 mg, 0.23 mmol), NBu_4Cl (7 mg, 0.03 mmol) and Pd-116 (12 mg, 0.03 mmol) and the flask was evacuated and backfilled with N_2 three times. 1,4-Dioxane (2 mL) and DIPEA (85 μ L, 0.46 mmol) were added and the reaction mixture was heated to 80 °C for 2 h. Water (2 mL) was then added and the aqueous mixture was extracted with DCM (3 x 5 mL). The combined organic extracts were dried by passing through a phase separation cartridge and concentrated in vacuo. The crude material was purified by column chromatography (0-5% MeOH/DCM). The resulting product was triturated with MeCN (2 mL). The precipitate was collected by filtration and dried to give the title compound **247** as a

pale yellow solid (30 mg, 32%). R^t 1.83 min (Method 1a) m/z 406 $[M + H]^+$ (ES^+). 1H NMR (DMSO- d_6): δ , ppm 10.29 (s, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.61-7.43 (m, 3H), 7.34-7.14 (m, 3H), 5.19 (d, J = 1.5 Hz, 1H), 4.86 (s, 2H), 3.11 (s, 3H), 2.94 (s, 2H), 2.28 (s, 3H), 1.29 (s, 3H).

5

[00580] Example 53. Synthesis of (E)-3-(6-ethyl-6-hydroxy-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **252**).

10 **[00581] General Synthetic Scheme.**



Reaction Conditions: a) N1,N1,N'1,N'1,N2,N2,N'2,N'2-octamethylethene-1,1,2,2-tetraamine, DMF, -20 °C; b) Fe, NH_4Cl , EtOH, water, 90 °C; c) NBS, K_2CO_3 , ACN, 0 °C-RT; d) Pd-116, DIPEA, NBu_4Cl , 1,4-dioxane, 80 °C.

[00582] Step 1. Ethyl 2-hydroxy-2-ethyl-3-(2-nitropyridin-3-yl)propanoate (compound

15 **249**). To a stirring solution of 3-(bromomethyl)-2-nitropyridine **242** (425 mg, 1.96 mmol) in anhydrous DMF (7.5 mL) was added ethyl 2-oxobutanoate **248** (765 mg, 5.88 mmol) at -20 °C. The resulting solution was stirred for 30 min. After this time N1,N1,N'1,N'1,N2,N2,N'2,N'2-octamethylethene-1,1,2,2-tetraamine (0.5 mL, 2.15 mmol) was added. The solution was vigorously stirred at -20 °C for 1 h and then warmed up to RT and stirred for 2 h. The orange-red turbid solution was filtered and hydrolyzed with water (40 mL). The aqueous solution was extracted with ethyl acetate (3 x 20 mL), the combined organic layers were washed with water (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography (0-10%

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MeOH/DCM) to afford the title compound **249** as a colourless solid (380 mg, 66%). R^t 1.75 min (Method 1a) m/z 269 $[M + H]^+$ (ES^+).

[00583] Step 2. 3-Hydroxy-3-ethyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one (compound **250**). To a stirred solution of ethyl 2-hydroxy-2-((2-nitropyridin-3-yl)methyl)butanoate **249** (370 mg, 1.38 mmol) in ethanol (18 mL) and water (5 mL) was added iron (308 mg, 5.52 mmol) and ammonia hydrochloride (295 mg, 5.52 mmol). The reaction mixture was heated at 90 °C for 1 hour. The reaction mixture was allowed to cool to room temperature and was filtered through a plug of Celite®. The filtrate was evaporated to dryness and the crude product was purified by chromatography (0-10% MeOH/DCM) to afford the title compound **250** as a colourless solid (200 mg, 72%). R^t 0.89 min (Method 1a) m/z 193 $[M + H]^+$ (ES^+).

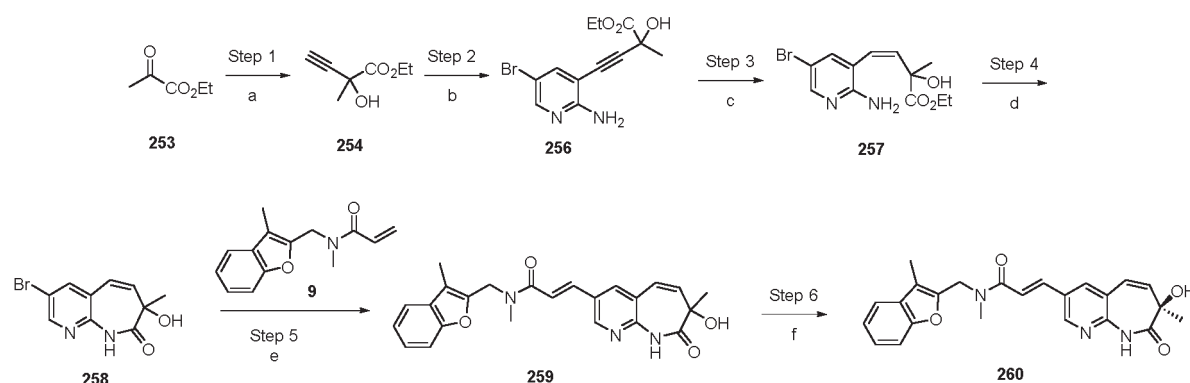
[00584] Step 3. 6-Bromo-3-hydroxy-3-ethyl-3,4-dihydro-1,8-naphthyridin-2(1H)-one (compound **251**). N-Bromosuccinimide (361 mg, 2.03 mmol) and K_2CO_3 (561 mg, 4.06 mmol) were added in one portion to a stirred solution of 3-ethyl-3-hydroxy-3,4-dihydro-1,8-naphthyridin-2(1H)-one **250** (195 mg, 1.01 mmol) in acetonitrile (15 mL) at 0 °C. The reaction was allowed to return to RT and was stirred overnight. The reaction was filtered over a celite pad, and the solids rinsed with acetonitrile (20 mL). The filtrate was evaporated in vacuo and the crude product was purified by chromatography (0-100% EtOAc/isohehexane) to afford the title compound **251** as a white solid (142 mg, 51%). R^t 1.20 min (Method 2a) m/z 271/273 $[M + H]^+$ (ES^+). 1H NMR (400 MHz, $CDCl_3$): δ , ppm 9.21 (s, 1H), 8.32 (dd, J = 2.3 Hz, 1.1 Hz, 1H), 7.69 (t, J = 1.7 Hz, 1H), 3.72 (s, 1H), 3.14 (d, J = 16.1 Hz, 1H), 3.07 (d, J = 16.1 Hz, 1H), 1.68-1.50 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

[00585] Step 4. (E)-3-(6-Ethyl-6-hydroxy-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **252**). A reaction vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (118 mg, 0.52 mmol), 6-bromo-3-ethyl-3-hydroxy-3,4-dihydro-1,8-naphthyridin-2(1H)-one **251** (140 mg, 0.52 mmol), tetrabutylammonium chloride hydrate (15 mg, 0.05 mmol) and Pd-116 (26 mg, 0.05 mmol) and the vial was flushed with nitrogen (5 mins). 1,4-Dioxane (8 mL) and DIPEA (180 μ L, 1.03 mmol) were added to the vial, and the reaction mixture was heated to 80 °C for 50 minutes. The crude material was evaporated in vacuo and purified by

chromatography (0-10% MeOH/DCM). The product was re-crystallized in DCM/hexanes (5 mL), then triturated with acetonitrile (2 mL) to give the title compound **252** as a white solid (144 mg, 66%). R^t 1.59 min (Method 2a) m/z 420 $[M + H]^+$ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆, 363K): δ , ppm 10.33 (s, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.01-7.97 (m, 1H), 7.61-7.53 (m, 1H), 7.53-7.44 (m, 2H), 7.32-7.20 (m, 3H), 4.95 (s, 1H), 4.86 (s, 2H), 3.11 (s, 3H), 2.97 (s, 2H), 2.28 (s, 3H), 1.66-1.48 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

[00586] **Example 54.** Synthesis of (R,E)-3-(7-hydroxy-7-methyl-8-oxo-8,9-dihydro-7H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **260**).

[00587] General Synthetic Scheme.



Reaction conditions: a) ethynyl magnesium bromide, -78 °C to RT; b) bis(triphenylphosphine)palladium(II)chloride, 5-bromo-3-iodo-pyridyl-2-amine **255**, CuI, TEA, THF, 80 °C; c) H₂, Pd/C, EtOAc; d) NaH, THF, 0 °C - RT; e) Pd-116, DIPEA, NBu₄Cl, 1,4-Dioxane, 80 °C; f) chiral separation.

[00588] **Step 1.** Ethyl 2-hydroxy-2-methylbut-3-ynoate (compound **254**). A solution of ethynylmagnesium bromide (0.5 M in THF, 99 mL, 49.6 mmol) was added dropwise, over ~1 h, to a solution of ethyl 2-oxopropanoate **253** (4.6 mL, 41.3 mmol) in THF (60 mL) at -78 °C. The mixture was stirred at this temperature for an additional 15 mins then allowed to warm to RT. The reaction mixture was then poured onto saturated ammonium chloride solution (50 mL) and the mixture was extracted with TBME (2 × 30 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo and the crude product was purified by silica chromatography (0-40% MTBE/isohexane) to give the title compound **254** as a pale yellow oil (0.85 g, 14%). ¹H NMR (400 MHz, DMSO-d₆): δ , ppm 6.28 (s, 1H), 4.15 (qd, J = 7.1 Hz, 1.5 Hz, 2H), 3.46 (s, 1H), 1.51 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H).

[00589] Step 2. Ethyl 4-(2-amino-5-bromopyridin-3-yl)-2-hydroxy-2-methylbut-3-ynoate (compound **256**). A vial was charged with copper iodide (31 mg, 0.16 mmol), bis(triphenylphosphine)palladium chloride (94 mg, 0.13 mmol) and 5-bromo-3-iodopyridin-2-amine **255** (0.80 g, 2.7 mmol) and the vial was evacuated and backfilled with N₂ three times. Ethyl 2-hydroxy-2-methylbut-3-ynoate **254** (0.42 g, 2.95 mmol), TEA (1.1 mL, 8.1 mmol) and THF (10 mL) were added and the mixture was degassed with N₂ for 10 mins before being heated to reflux for 2 h. The reaction mixture was allowed to cool to RT, filtered through a plug of Celite® and which was washed with EtOAc (20 mL). The filtrate was concentrated in vacuo and the crude product was purified by silica chromatography (0-100% EtOAc/isohexane) to afford the title compound **256** as a clear yellow oil (810 mg, 91%). R^t 1.66 min (Method 1a); m/z 313/315 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 8.03 (d, J = 2.4 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 6.57 (s, 1H), 6.45 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.61 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H).

[00590] Step 3. (Z)-Ethyl 4-(2-amino-5-bromopyridin-3-yl)-2-hydroxy-2-methylbut-3-enoate (compound **257**). A mixture of ethyl 4-(2-amino-5-bromopyridin-3-yl)-2-hydroxy-2-methylbut-3-ynoate **256** (0.45 g, 1.44 mmol) and 5% Pd/C (0.15 g, 1.44 mmol) in EtOAc (50 mL) was stirred under H₂ at 1 bar for 30 min. The catalyst was removed by filtration, then the filtrate was concentrated in vacuo and purified by column chromatography (0-100% EtOAc/isohexane) to give the desired product **257** as a colourless oil (0.17 g, 27%). R^t 0.98 min (Method 1a); m/z 315/317 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 7.87 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 2.5 Hz, 1H), 6.21 (d, J = 12.1 Hz, 1H), 5.97 (s, 2H), 5.81 (d, J = 12.1 Hz, 1H), 5.74 (s, 1H), 3.83-3.68 (m, 2H), 1.41 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H).

[00591] Step 4. 3-Bromo-7-hydroxy-7-methyl-7H-pyrido[2,3-b]azepin-8(9H)-one (compound **258**). Sodium hydride (60% in mineral oil, 0.03 g, 0.79 mmol) was added in small portions to a stirred solution of (Z)-ethyl 4-(2-amino-5-bromopyridin-3-yl)-2-hydroxy-2-methylbut-3-enoate **257** (0.17 g, 0.52 mmol) in THF (15 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2 h. The reaction was quenched by careful addition of sat. aq. NH₄Cl (50 mL) and the aqueous mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried with

MgSO₄ and concentrated in vacuo to give the desired product **258** as an off white solid (0.17 g, quant) which was used in the next step without further purification. R^t 1.38 min (Method 1a); m/z 269/271 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.93 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 10.9 Hz, 1H), 6.04 (d, J = 10.9 Hz, 1H), 5.39 (s, 1H), 1.23 (s, 3H).

[00592] Step 5. (E)-3-(7-Hydroxy-7-methyl-8-oxo-8,9-dihydro-7H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **259**). A flask was charged with 3-bromo-7-hydroxy-7-methyl-7H-pyrido[2,3-b]azepin-8(9H)-one **258** (0.08 g, 0.30 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (0.07 g, 0.31 mmol), Bu₄NCl (9 mg, 0.03 mmol) and Pd-116 (15 mg, 0.03 mmol) and the flask was evacuated and backfilled with N₂ three times. 1,4-Dioxane (2.5 mL) and DIPEA (0.2 mL, 1.15 mmol) were added and the reaction mixture was heated to 80 °C and stirred for 2 h. The reaction was allowed to cool to RT, was concentrated in vacuo and purified by column chromatography (0-3% MeOH/DCM) to give the desired product **259** as a white solid (71 mg, 56%). R^t 1.96 min (Method 1a); m/z 418 [M + H]⁺ (ES⁺). ¹H NMR (400 MHz, DMSO-d₆, 363 K): δ, ppm 10.52 (s, 1H), 8.60 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.58-7.50 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.39-7.17 (m, 3H), 6.72 (d, J = 10.9 Hz, 1H), 6.04 (d, J = 11.1 Hz, 1H), 5.08 (s, 1H), 4.87 (s, 2H), 3.11 (s, 3H), 2.27 (s, 3H), 1.22 (s, 3H).

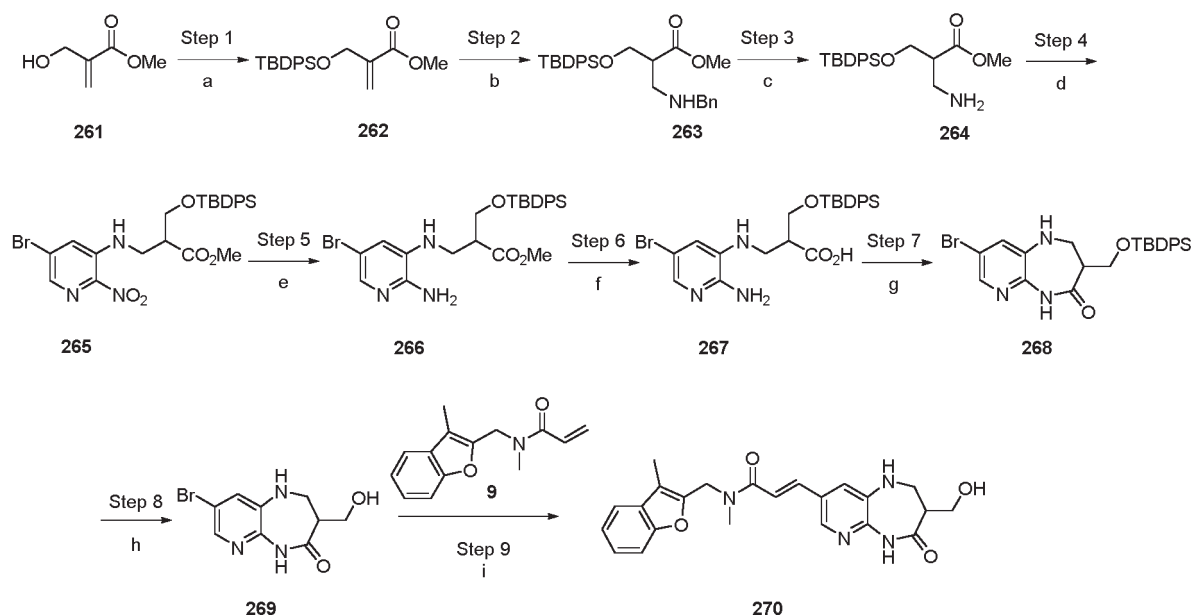
[00593] Step 6. Chiral separation of compound **259**. Chiral method separation: Apparatus: Isolera (Biotage). Column: Chiralpak IA (20μm; glass column; 250mm x 25mm). Eluent: CH₃CN 90 - Ethyl Acetate 10. Flow: 50mL/min. Temperature: 25 °C. Amount injected: 38.4 mg of **259** in 10 mL of CH₃CN 90 - Ethyl Acetate 10 and 2 mL of MeOH (dissolution at 50°C in ultrasonic bath), followed by cooling and quick injection).

[00594] (R,E)-3-(7-Hydroxy-7-methyl-8-oxo-8,9-dihydro-7H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **260**). Pure fractions of the first enantiomer were collected and concentrated to dryness. Solid was then slurried in diethyl ether, transferred in a registration vial and concentrated first under nitrogen flux then under vacuum at RT. First enantiomer was obtained as white solid (m = 13.04 mg; chiral purity: 100%). The *absolute configuration arbitrarily assigned*.

[00595] Example 55. Synthesis of (E)-3-(3-(hydroxymethyl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **270**).

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[00596] General Synthetic Scheme.



Reaction conditions: a) TBDPSCl, imidazole, DMF, 0 °C-RT; b) Benzylamine, MeOH, 0 °C-RT; c) H₂, Pd/C, MeOH, 50 °C; d) 5-Bromo-3-fluoro-2-nitropyridine 11, TEA, EtOH, reflux; e) Fe, NH₄Cl, EtOH, H₂O, reflux; f) LiOH, H₂O, THF, MeOH; g) HATU, DIPEA, DMF; h) TBAF, THF; i) Pd-116, DIPEA, NBu₄Cl, 1,4-dioxane, 80 °C.

[00597] Step 1. Methyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)acrylate (compound **262**). Imidazole (1.29 g, 19.0 mmol) and tert-butyldichlorodiphenylsilane (4.95 mL, 19.0 mmol) were added to a stirred solution of methyl 2-(hydroxymethyl)acrylate **261** (1.77 mL, 17.2 mmol) in DMF (20 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for ~16 h. The reaction mixture was diluted with EtOAc (30 mL) and NaHCO₃ (30 mL, Sat Aq) was added. The organic phase was separated and the aqueous phase was extracted again with EtOAc (3 × 30 mL). The combined organic fractions were washed with water (3 × 50 mL) and brine (2 × 50 mL), dried using MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (0-50% EtOAc/isohexane) to give the desired product **262** as colourless oil (5.34 g, 87%). R_t 3.16 min (Method 1a) m/z 377 [M + Na]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 7.66-7.59 (m, 4H), 7.52-7.41 (m, 6H), 6.25 (q, J = 1.8 Hz, 1H), 6.03 (q, J = 2.0 Hz, 1H), 4.36 (s, 2H), 3.64 (s, 3H), 1.01 (s, 9H).

5 butyldiphenylsilyl)oxy)methyl)acrylate **262** (2.4 g, 6.77 mmol) in MeOH (30 mL) at 0 °C and the reaction was allowed to return to RT. The reaction was stirred for ~16 h, then was concentrated in vacuo and the crude material was purified by column chromatography (0-20% EtOAc/isohexane) to give the desired compound **263** as a colourless oil (0.99 g, 31%). R_t 2.11 min (Method 1a) m/z 462 [M + H]⁺ (ES⁺). ¹H NMR (500 MHz, DMSO-d₆): δ, ppm 7.62-7.56 (m, 4H), 7.50-7.38 (m, 6H), 7.31-7.17 (m, 5H), 3.88-3.79 (m, 2H), 3.63 (s, 2H), 3.62 (s, 3H), 2.83 (p, J = 6.6 Hz, 1H), 2.72 (dd, J = 11.7 Hz, 7.0 Hz, 1H), 2.64 (dd, J = 11.7 Hz, 6.8 Hz, 1H), 2.17 (s, 1H), 0.94 (s, 9H).

15 (compound **264**). A solution of methyl 3-(benzylamino)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)propanoate **263** (1.5 g, 3.25 mmol) and palladium on carbon (0.35 g, 3.25 mmol) in MeOH (65 mL) was hydrogenated at 5 bar and 50 °C for 24 h. The palladium was removed by filtration through Celite® and the filtrate was concentrated in vacuo to give the desired product **264** as a mixture pale yellow oil (1.05 g, 87%) which was
20 used in the next step without further purification.

Methyl-3-((5-bromo-2-nitropyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoate (compound **265**). To a stirred solution of 5-bromo-3-fluoro-2-nitropyridine **11** (630 mg, 2.83 mmol) in EtOH (15 mL) was added methyl 3-amino-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoate **264** (1.0 g, 2.83 mmol) followed by TEA (1.0 mL, 7.07 mmol). The reaction mixture was stirred at reflux for 2 h, before being concentrated in vacuo. The crude material was purified by column chromatography (0-100% ethyl acetate/isohexane) to give the title compound **265** as a brown oil (490 mg, 29%). R^t 3.15 min (Method 1a) m/z 572/574 [M + H]⁺ (ES⁺).

[00601] Step**5.**

Methyl-3-((2-amino-5-bromopyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoate (compound **266**). To a mixture of methyl 3-((5-bromo-2-nitropyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoate **265** (500 mg, 0.85 mmol) were added iron (190 mg, 3.42 mmol) and ammonium chloride (185 mg, 3.42 mmol) in ethanol (35 mL) and water (8.8 mL). The resulting reaction mixture was heated at 90 °C for 1 hour, before being filtered through a plug of Celite® when still hot. The filtrate was then evaporated to dryness. The crude product was purified by (0-10% MeOH/DCM) to give the title compound **266** as a colourless solid (300 mg, 64%). R^t 2.59 min (Method 1a) m/z 542/544 $[M + H]^+$ (ES^+).

[00602] Step 6.

3-((2-Amino-5-bromopyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoic acid (compound **267**). Lithium hydroxide (1 M aq., 618 μ L, 0.618 mmol) was added dropwise to a stirred solution of methyl-3-((2-amino-5-bromopyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoate **266** (305 mg, 0.56 mmol) in THF (8.0 mL) and MeOH (1.5 mL). The reaction was stirred at the same temperature for 80 minutes then stored at -20 °C overnight. The mixture was quenched with AcOH (0.5 mL) and solvents evaporated in vacuum. The resulting crude material was purified by chromatography (0-10% MeOH/DCM) to give the title compound **267** as a white solid (76 mg, 25%). R^t 1.77 min (Method 2a) m/z 528/530 $[M + H]^+$ (ES^+).

[00603] Step 7.

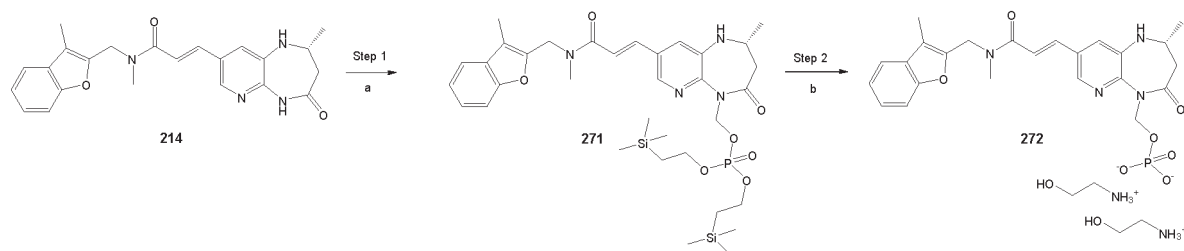
8-Bromo-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **268**). DIPEA (0.13 mL, 0.72 mmol) was added to a stirred solution of 3-((2-amino-5-bromopyridin-3-yl)amino)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propanoic acid **267** (76 mg, 0.14 mmol) in DMF (2.0 mL). HATU (66 mg, 0.17 mmol) was added to the mixture and the reaction mixture was stirred for 1 hour. The mixture was quenched with MeOH (4.0 mL) and partitioned between water (65 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 $\times$ 50 mL) and the combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$ and evaporated in vacuo to give the title compound **268** as an amber oil (101 mg, 85%) which was used in the following step without further purification. R^t 2.33 min (Method 2a) m/z 510/512 $[M + H]^+$ (ES^+).

[00604] **Step 8.** 8-Bromo-3-(hydroxymethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (compound **269**). A solution of 8-bromo-3-(((tert-butyl)diphenylsilyl)oxy)methyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **268** (101 mg, 0.12 mmol) in THF (4.0 mL) was treated TBAF (1 M in THF, 0.2 mL, 0.2 mmol). After 20 minutes the solvent was evaporated in vacuo and the crude product was purified by chromatography on silica gel (0-100% EtOAc/isohehexane) to afford the title compound **269** as a white solid (26 mg, 78%). R^t 0.93 min (Method 2a) m/z 272/274 $[M + H]^+$ (ES^+).

[00605] **Step 9.** (E)-3-(3-(Hydroxymethyl)-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **270**). A vial was charged with N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **9** (22 mg, 0.096 mmol), 8-bromo-3-(hydroxymethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **269** (26 mg, 0.096 mmol), tetrabutylammonium chloride hydrate (2.8 mg, 9.56 μ mol), Pd-116 (4.9 mg, 9.56 μ mol). The vial was flushed with nitrogen for 5 min. 1,4-Dioxane (2.0 mL) and DIPEA (33 μ L, 0.19 mmol) were added and the reaction mixture was heated to 80 °C for 1 hour then allowed to cool to RT. The solvent was evaporated in vacuo, and the crude material was purified by chromatography (0-10% MeOH/DCM). The resulting material was further triturated from MeCN (2.0 mL) to afford the title compound **270** as a pale yellow solid (20 mg, 49%). R^t 1.45 min (Method 2a) m/z 421 $[M + H]^+$ (ES^+). 1H NMR (DMSO- d_6 , 363K): δ , ppm 9.18 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 7.4 Hz, 1.6 Hz, 1H), 7.50-7.39 (m, 2H), 7.38 (d, J = 1.9 Hz, 1H), 7.32-7.20 (m, 2H), 7.12 (d, J = 15.4 Hz, 1H), 5.84 (s, 1H), 4.84 (s, 2H), 4.35 (s, 1H), 3.82-3.74 (m, 1H), 3.60-3.52 (m, 2H), 3.35-3.26 (m, 1H), 3.10 (s, 3H), 2.78-2.69 (m, 1H), 2.28 (s, 3H).

[00606] **Example 56.** Synthesis of 2-hydroxyethan-1-aminium (R,E)-(2-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl phosphate (compound **272**).

[00607] General Synthetic Scheme.



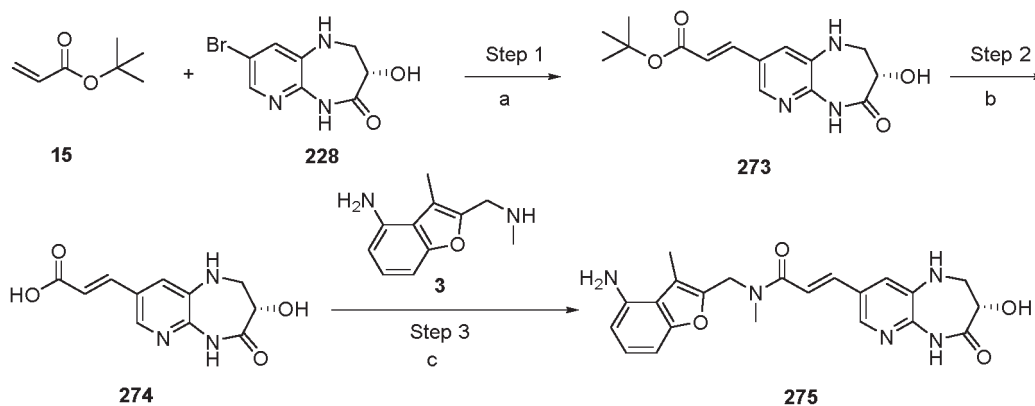
Reaction conditions: a) 1. 18-crown-6, NMP/N-ethylpyrrolidone, RT 2. t-BuOK at -20 °C to -35 °C, then chloromethyl bis[2-(trimethylsilyl)ethyl] phosphate **21**; b) TFA/DCM, long work-up

[00608] Step 1. [(2R)-2-Methyl-8-[(E)-3-[methyl-[(3-methylbenzofuran-2-yl)methyl]amino]-3-oxo-prop-1-enyl]-4-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl bis(2-trimethylsilyl)ethyl) phosphate (compound **271**). To a 25 mL flask vial under nitrogen, containing (E)-N-methyl-N-[(3-methylbenzofuran-2-yl)methyl]-3-[(2R)-2-methyl-4-oxo-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-8-yl]prop-2-enamide **214** (1.0 g, 2.47 mmol, 1 eq.) in suspension in anhydrous DMSO (10 mL) at 25°C was added a solution of potassium 2-methylpropan-2-olate (2.6 mL, 2.6 mmol, 1.05 eq., 1M in THF) over 5 minutes under stirring. Then, the resulting orange solution was stirred at 25 °C for 15 minutes and added dropwise at 25°C over 30 minutes to a solution of chloromethyl bis(2-(trimethylsilyl)ethyl) phosphate (4.8 mL, 3.46 mmol, 1.4 eq., 30% in hexane) under vigorous stirring. The reaction mixture was then stirred at 25 °C for 10 minutes until nearly completion as indicated by UPLC/MS (method: 3min_acid_standard; 254 nm; R_t = 1.56 min (starting material; 7%); R_t = 1.62 min (not determined; 4%); R_t = 1.79 min (not determined; 4%); R_t = 2.27min (other regioisomer; 15%); R_t = 2.57 min (expected product; 70%). Reaction mixture was washed with n-heptane (2 × 40 mL) then DMSO phase was quenched with a saturated solution of ammonium acetate (50 mL) and aqueous phase was then extracted with MTBE (4 × 50 mL). Combined organic phases were then washed with brine (100 mL), dried over Na₂SO₄, filtered and *concentrated* in a vacuum rotary evaporator (bath temperature : 20 °C) to give the crude title compound **271** as a yellow foam (1.686 g, 1.768 mmol, 71.5% yield). UPLC-MS (Method 1c): 3min_acid_standard; 254 nm; 75%.

[00609] Step 2. 2-Hydroxyethan-1-aminium (R,E)-(2-methyl-8-(3-(methyl[(3-methylbenzofuran-2-yl)methyl]amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl phosphate (compound **272**). To a 100 mL three-necked flask under nitrogen, containing a solution of [(2R)-2-methyl-8-[(E)-3-[methyl-[(3-

methylbenzofuran-2-yl)methyl]amino]-3-oxo-prop-1-enyl]-4-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl bis(2-trimethylsilylethyl) phosphate **271** (1686 mg, 1.77 mmol, 1 eq.) in anhydrous dichloromethane (27.0 mL) at -20 °C under stirring was added dropwise a solution of 2,2,2-trifluoroacetic acid (2.6 mL, 33.6 mmol, 19 eq.) in anhydrous DCM (27 mL) keeping temperature below -15 °C. Then, the reaction mixture was stirred at -12 °C over 1 h 30 min until completion as indicated by UPLC/MS (sample was prepared in acetonitrile with one drop of ethanolamine; 3 min_acid_standard; 254 nm; R_t = 1.35 min (expected product; ES- : 513.2; 74%); R_t = 1.56 min (API; 12%); R_t = 1.81 min (hemi hydrolyzed phosphate)). Temperature was brought to -20 °C and a solution of ethanolamine (2.7 mL, 44.22 mmol, 25 eq.) in anhydrous DCM (27 mL) was added over 5 minutes. Subsequently, the reaction mixture was stirred at -15 °C for 1 h and was then concentrated (rotavapor) under deep vacuum keeping bath temp at 5°C. Then residue was slurried in 100 mL of cyclopentyl methyl ether and resulting suspension was filtered to give TFA·ethanolamine salt as a yellowish solid. The filtrate was concentrated (rotavapor) under deep vacuum keeping bath temp at 5°C to give the crude title product as a yellow oil m = 3.76 g (UPLC/MS; 3min_acid_standard; 254nm; purity : 87%). Stored at -20 °C overnight. The product was purified by chromatoflash on Isolera equipment (Biotage). Cartridge: C18 (25um); 120 g. Injection: crude product (3.76 g) was solubilised in 25 mL of (water 0.2% ethanolamine - CH₃CN 0.2%ethanolamine (95-5)) before injection. Fractions of interest were combined and lyophilised to give the title product **272** as a yellow solid (m = 738 mg) which showed an excess of ethanolamine by NMR. Product was slurried in methanol (5 mL), sonicated and suspension was filtered. Resulting pale yellow powder was washed with methanol (2 x 5 mL) and dried under vacuum to give the title compound **272** as a pale yellow powder (m = 300.3 mg; 26.7% yield). UPLC-MS (Method 1c): 3min_acid_standard; 254nm; purity 100% (AUC), ES-: 513.2. ¹H NMR (400 MHz, D₂O): δ , ppm 8.26 (1H, dd, J = 1.8, 15.0 Hz), 7.63 (1H, dd, J = 2.0, 16.2 Hz), 7.54-7.32 (3H, m), 7.29-7.16 (2.5H, m), 7.04 (0.5H, d, J = 15.6 Hz), 5.48-5.37 (2H, m), 4.81 (0.8H, s), 4.73 (1.2H, s), 3.99 (1H, qd, J = 6.1, 18.2 Hz), 3.72 (4H, t, J = 5.4 Hz), 3.15 (1.6H, s), 3.04 (4H, t, J = 5.0 Hz), 3.00 (1.4H, s), 2.64-2.55 (1H, m), 2.31-2.22 (1H, m), 2.19 (1.6H, s), 2.18 (1.4H, s), 1.20 (3H, dd, J = 2.8, 6.1 Hz). TFA·ethanolamine salt content: 0.07% w/w.

[00610] Example 57. Synthesis of (E)-N-[(4-amino-3-methyl-benzofuran-2-yl)methyl]-3-[(3S)-3-hydroxy-4-oxo-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-8-yl]-N-methyl-prop-2-enamide (compound **274**).



Reaction conditions: a) Pd-162, DIPEA, n-Bu₄NCl, dioxane-1,4, 90 °C, 5 h; TFA/DCM; c) DIPEA, HATU, DMF, rt.

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[00611] Step 1. tert-Butyl (S,E)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate (compound **273**). A mixture of (3S)-8-bromo-3-hydroxy-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-4-one **228** (182.76 mg, 0.70 mmol, 1 eq.), tetrabutylammonium chloride (23.39 mg, 0.08 mmol, 0.12 eq.), chloro(crotyl)(tri-tert-butylphosphine)palladium(II) (14.72 mg, 0.04 mmol, 0.05 eq.) were added in a flask under nitrogen atmosphere. The flask was purged and backfilled with nitrogen. 1,4-Dioxane (4.95 mL), tert-butyl acrylate **15** (0.24 mL, 1.68 mmol, 2.4 eq.), and DIPEA (0.24 mL, 1.4 mmol, 2.0 eq.) were added and nitrogen bubbled through the mixture for 5 mins. The reaction mixture was heated at 90 °C for 5 h. After cooling, the mixture was filtered using 0.22μm PTFE filters. Filters were then washed with DCM/MeOH 50/50. The combined filtrate were concentrated under reduced pressure until dryness. ACN was added and the resulting yellow suspension was put in ultrasound bath for a few minutes and then filtered over porosity 3 frit. The resulting yellow solid was washed with a cold ether to afford **273** (110 mg, 0.35 mmol, 51.07% yield) as a yellow solid. UPLC-MS (Method 1c): m/z 306.1 [M + H]⁺ (ES⁺).

20

[00612] Step 2. (S,E)-3-(3-Hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid (compound **274**). tert-Butyl (S,E)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate **273** (110 mg, 0.36 mmol, 1.0 eq.) was diluted with DCM (0.23 mL) and cooled to 0 °C. Trifluoroacetic acid (0.23 mL) was

added dropwise. The resulting yellow solution was stirred for 3 hours. UPLC analysis showed the complete conversion. Volatiles were removed under reduced pressure and the resulting residue was treated with a cold ether. The resulting suspension was put in ultrasound bath and filtered. The resulting yellow solid was dried overnight under high vacuum to afford the title compound **274** (90 mg, 0.35 mmol, 98.23% yield) as a yellow solid. UPLC-MS (Method 1c): m/z 250.1 $[M + H]^+$ (ES^+).

[00613] Step 3. (E)-N-[(4-Amino-3-methyl-benzofuran-2-yl)methyl]-3-[(3S)-3-hydroxy-4-oxo-1,2,3,5-tetrahydropyrido[2,3-b][1,4]diazepin-8-yl]-N-methyl-prop-2-enamide

(compound **275**). 3-Methyl-2-(methylaminomethyl)benzofuran-4-amine **3** (32.1 mg, 0.169

mmol, 1.2 eq.) and ((S,E)-3-(3-Hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid **274** (35.1 mg, 0.141 mmol, 1.0 eq.) were dissolved in DMF (0.7 mL). Subsequently, HATU (83.76 mg, 0.21 mmol, 1.5 equiv.) was added in one portion.

To this, DIPEA (0.098 mL, 0.564 mmol, 4.0 eq.) was added dropwise at RT and the resulting mixture was stirred at RT for 1 h. The resulting brown reaction mass was concentrated under

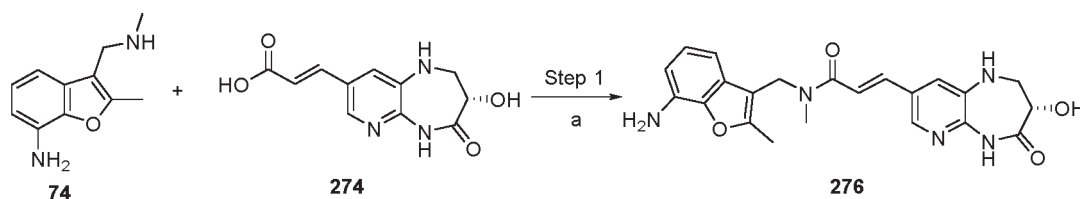
high vacuum (without work-up), the crude brown material was dissolved in a mixture of MeCN/H₂O (5 mL, 4:1 v/v , 2 injections) and purified by semi-preparative HPLC (98-100-30 min; 90% solvent A, 10% solvent B, 30 min) and lyophilized overnight to afford the title compound **275** as a yellow powder with a purity of 89.19% (49 mg, 82% yield). The solid,

thus obtained, was dried and solubilized in DMSO (0.5 -1 mL) and added slowly into a water

(6 mL). Quickly precipitating product with a purity of 93.14% was recovered by centrifugation and lyophilized overnight. The beige powder was obtained (10.5 mg). UPLC-

MS (Method 1c): m/z 422.1 $[M + H]^+$ (ES^+); t_{ret} = 1.02 min. ¹H NMR (400 MHz, DMSO- d_6): δ , ppm 10.07 (s, 1H), 7.97-7.94 (m, 1H), 7.37-7.28 (m, 2.4H), 7.06 (d, J = 15.4 Hz, 0.6H), 6.84 (t, J = 8.0 Hz, 1H), 6.58-6.56 (d, 1H), 6.30 (d, J = 7.8 Hz, 1H), 6.02 (br m, 1H), 5.13-5.11 (m, 3H), 4.77, 4.62 (rotamers, 2s, 2H), 4.08-4.06 (m, 1H), 3.41-3.38 (m, 1H), 3.21-3.16 (m, 1H), 3.01, 2.84 (rotomers, 2s, 3H), 2.34 (s, 3H).

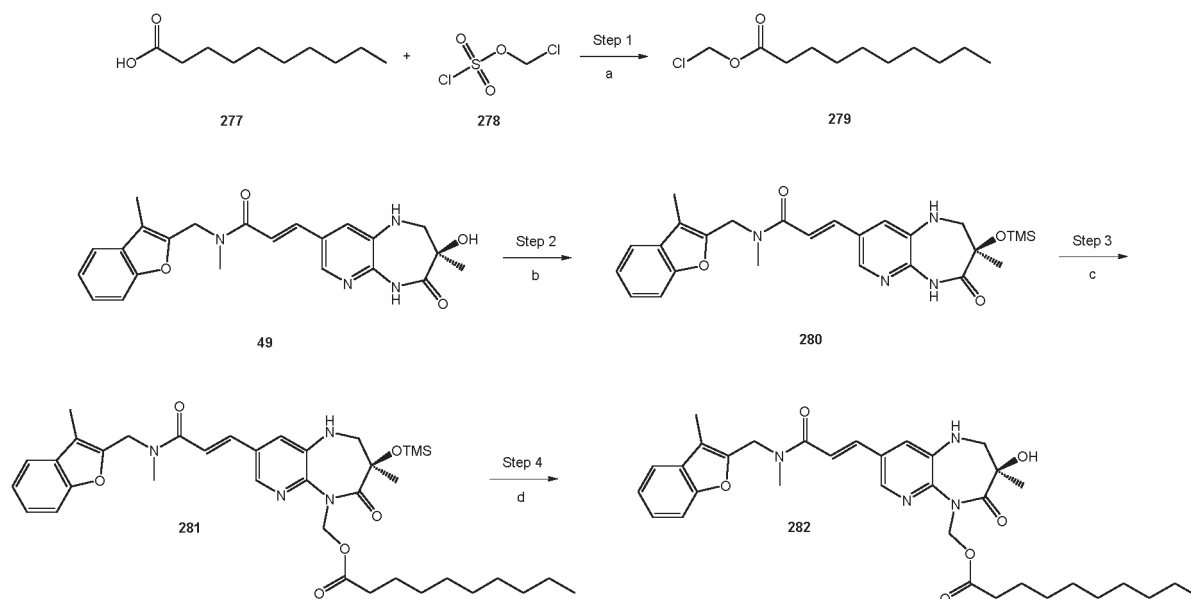
[00614] Example 58. Synthesis of (S,E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **276**).



Reaction conditions: a) DIPEA, HATU, DMF, rt.

[00615] Step 1. (S,E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-3-(3-hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **276**). 2-Methyl-3-((methylamino)methyl)benzofuran-7-amine **74** (31 mg, 0.164 mmol, 1.2 eq.) and (S,E)-3-(3-Hydroxy-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid **274** (34.14 mg, 0.137 mmol, 1.0 eq.) were dissolved in DMF (0.7 mL). Subsequently, HATU (81.37 mg, 1.5 mmol, 1.5 equiv.) was added in one portion. To this, DIPEA (0.096 mL, 0.54 mmol, 4.0 eq.) was added dropwise at RT and the resulting mixture was stirred at RT for 2 hrs. The resulting brown reaction mass was treated with water (5 mL). Quickly precipitating product was collected by centrifugation. The yellow solid with a purity of 66.53% was isolated (48 mg). The resulting impure material was re-purified by preparative HPLC. The yellow product, was suspended in a mixture of 4 mL of MeOH/DCM (sonication 1-2 min) and transferred into a 4 mL barcoded vial. After solvent evaporation and drying under high vacuum overnight at RT, the yellow solid with a purity of 100% (9.6 mg, 16.6% yield) was obtained. ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 10.14 (s, 1H), 8.05-8.01 (m, 1H), 7.49-7.38 (m, 2.3H), 7.06 (d, J = 15.4 Hz, 0.7H), 6.84 (t, J = 7.7 Hz, 1H), 6.74, 6.57 (2 d, 1H), 6.48 (d, J = 7.5 Hz, 1H), 6.08 (br m, 1H), 5.20 (d, J = 4.6 Hz, 2H), 5.16 (s, 1H), 4.82, 4.67 (rotamers, 2s, 2H), 4.15-4.12 (m, 1H), 3.47 (ddd, J = 3.3, 6.1 and 12.2 Hz, 1H), 3.28-3.22 (m, 1H), 3.01, 2.82 (rotomers, 2s, 3H), 2.50, 2.45 (rotamers, 2s, 3H). UPLC-MS (Method 1c): m/z 422.1 [M + H]⁺ (ES⁺); t_{ret} = 1.00 min.

[00616] Example 59. Synthesis of (R,E)-(3-hydroxy-3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl decanoate (compound **282**).



Reaction conditions: a) $n\text{-Bu}_4\text{NHSO}_4$, NaHCO_3 , $\text{DCM}/\text{H}_2\text{O}$ (1:1 V/V), 0°C to RT, overnight; b) 1-methyl-1H-imidazole, DMSO, RT; c) tBuOK , DMSO, RT, 30 min; d) 1M aq. HCl

[00617] Step 1. Chloromethyl decanoate (compound **279**). Decanoic acid **277** (1.0 g, 5.69 mmol, 1.0 eq.), tetrabutylammonium hydrogensulfate (99.57 mg, 0.28 mmol, 0.05 eq.) and sodium bicarbonate (1.92 g, 22.76 mmol, 4.0 eq.) were mixed in the flask. DCM (20 mL) and water (20 mL) were added. The resulting biphasic solution was cooled to 0°C and then treated with a solution of chloromethyl sulfurochloridate **278** (1.03 g, 6.26 mmol, 1.1 eq.) in DCM (0.5 mL). The mixture was stirred at 0°C for 40 mins and then at RT overnight. The reaction mixture was diluted with water and was extracted twice with DCM. The combined organic layers were dried over MgSO_4 to afford chloromethyl decanoate **279** (0.89 g, 4.06 mmol, 71.35 % yield) as a colourless oil.

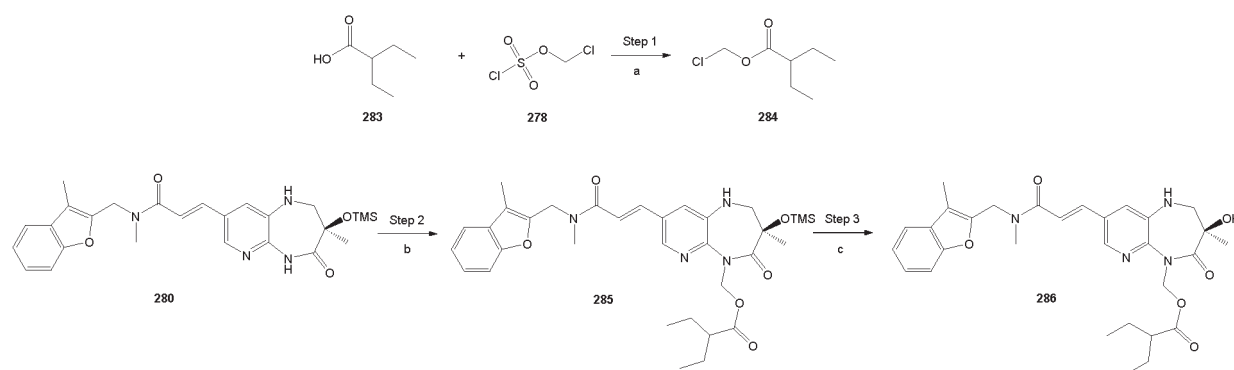
[00618] Step 2. (R,E)-N-Methyl-3-(3-methyl-4-oxo-3-((trimethylsilyl)oxy)-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (compound **280**). To 1-methyl-1H-imidazole (1.33 mL, 16.65 mmol, 7.0 eq.) in solution in anhydrous DMSO (10 mL) was added (E)-3-[(3R)-3-hydroxy-3-methyl-4-oxo-2,5-dihydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl]-N-methyl-N-[(3-methylbenzofuran-2-yl)methyl]prop-2-enamide **49** (1.0 g, 2.38 mmol, 1.0 eq.) in one portion at RT. The yellow solution was stirred at RT for 5 mins, TMSCl (1.54 mL, 11.89 mmol, 5.0 eq.) was then added in one portion. The reaction mixture was stirred at RT for 1 h, diluted with water and brine (1:1 v/v) and extracted with AcOEt (3 $\times$). The combined organic phases were washed with brine, dried over MgSO_4 , filtered and concentrated to dryness to give the title compound **280** (1.12 g, 2.27 mmol, 95.59% yield) as an yellow solid. UPLC-MS (Method 1c): R_t = 2.04 min. ES^+ = 493.3.

[00619] **Step** **3.** (R,E)-(3-Methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-3-((trimethylsilyl)oxy)-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl decanoate (compound **281**). (R,E)-N-Methyl-3-(3-methyl-4-oxo-3-((trimethylsilyl)oxy)-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide **280** (0.569 g, 1.16 mmol, 1.0 eq.) was diluted with DMSO (5 mL). To the resulting yellow solution potassium 2-methylpropan-2-olate (150.07 mg, 1.27 mmol, 1.1 eq.) was added. This reaction mixture was added dropwise over 7 mins to a vial containing chloromethyl decanoate **279** (1.02 g, 4.62 mmol, 4.0 eq). The reaction mass was stirred at RT for 30 mins, diluted with water and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and was concentrated to dryness. The residue was purified on silicagel using SNAP Ultra column (50g) and DCM/EtOAc 90/10 to 0/100 as eluent. Good fractions were collected and concentrated to dryness to afford product **281** as a beige foam (67 mg, 24% yield). UPLC-MS (Method 1c): Rt = 2.91 min. ES+ = 677.5.

[00620] **Step** **4.** (R,E)-(3-Hydroxy-3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl decanoate (compound **282**). (R,E)-(3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-3-((trimethylsilyl)oxy)-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl decanoate **281** was dissolved in MeOH (2 mL). 1M HCl in water (0.58 mL, 0.57 mmol, 2.0 eq) was added at RT. After 10 mins of stirring at room temperature, the UPLC analysis showed complete conversion. The reaction mixture was concentrated to dryness to afford an yellow oil which was diluted with EtOAc and washed twice with a sat. aq. solution of NaHCO₃. The combined organic layers was dried over MgSO₄ and concentrated to dryness. This crude product was purified by flash chromatography using SNAP Ultra column (25 g) and DCM/AcOEt 50/50 to 0/100 as an eluent. Good fractions were collected and concentrated to dryness to afford lipophilic prodrug **282** as a beige solid (103 mg, 0.16 mmol, 56.17% yield). UPLC-MS (Method 1c): Rt = 2.46 min ES+ = 605.4. ¹H NMR (400 MHz, DMSO-d₆): δ, ppm 7.88-7.85 (m, 1H), 7.65-7.63 (m, 1H), 7.60 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.28-7.20 (m, 2H), 7.20-7.06 (m, 1H), 6.79 (d, J = 15.4 Hz, 1H), 5.26-5.17 (m, 2H), 4.86, 4.69 (2s, 2H, rotamers), 4.08 (br s, 1H), 3.72 (d, J = 11.9 Hz, 1H), 3.25 (d, J = 12.4 Hz, 1H), 3.21, 3.07 (2s, 3H, rotamers), 2.30 (s, 3H), 2.23-2.19 (m, 2H), 1.61 (s, 3H), 1.55-1.51 (m, 2H), 1.15-1.35 (m, 12 H), 0.86 (t, J = 6.6 Hz, 3H).

[00621] Example 60. Synthesis of (R,E)-(3-hydroxy-3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl 2-ethylbutanoate (compound **286**).

5 **[00622] General Synthetic Scheme.**



Reaction conditions: a) $n\text{-Bu}_3\text{N HSO}_4$, NaHCO_3 , $\text{DCM/H}_2\text{O}$ (1:1 V/V), 0°C to RT, overnight; b) $t\text{BuOK}$, DMSO, RT, 30 min; c) 1M aq. HCl

10 **[00623] Step 1.** Chloromethyl 2-ethylbutanoate (compound **284**) was synthesized from 2-ethylbutanoic acid (**283**) and chloromethyl sulfurochloridate **278** as described for compound **279** (77.5% yield).

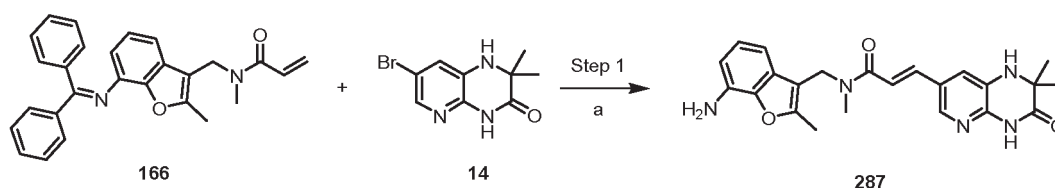
[00624] Step 2. (R,E)-(3-Methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-3-((trimethylsilyl)oxy)-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl 2-ethylbutanoate (compound **285**) was obtained according to the procedure described for compound **281** (49% yield). UPLC-MS (Method 1c): $R_t = 2.54$ min $\text{ES}^+ = 621.4$.

20 **[00625] Step 3.** (R,E)-(3-Hydroxy-3-methyl-8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-4-oxo-1,2,3,4-tetrahydro-5H-pyrido[2,3-b][1,4]diazepin-5-yl)methyl 2-ethylbutanoate (compound **286**) was obtained as described for compound **282** (79% yield). UPLC-MS (Method 1c): $R_t = 1.96$ min. $\text{ES}^+ = 549.3$. ^1H NMR (400 MHz, DMSO-d_6): δ , ppm 7.87-7.84 (m, 1H), 7.67 (t, $J = 6.9$ Hz, 1H), 7.59 (d, $J = 15.4$ Hz, 1H), 7.48 (d, $J = 7.2$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.28-7.20 (m, 2H), 7.06-7.04 (m, 1.3H), 6.79 (d, $J = 15.4$ Hz, 0.7H), 5.27-5.19 (m, 2H), 4.82, 4.69 (2s, 2H, rotamers), 4.08 (br s, 1H), 3.76 (d,

J = 11.9 Hz, 1H), 3.21-3.18 (m, 1H), 3.20, 3.08 (2s, 3H, rotamers), 2.30 (s, 3H), 2.15-2.09 (m, 1H), 1.59 (s, 3H), 1.56-1.37 (m, 4H), 0.81-0.72 (m, 6H).

[00626] **Example 61.** Synthesis of (E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methylacrylamide (compound **287**).

[00627] General Synthetic Scheme.

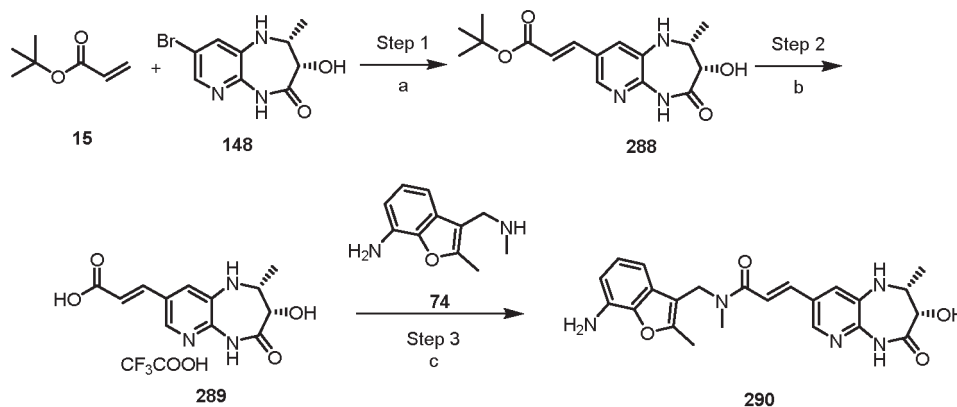


Reaction conditions: a) i) Pd-116, DIPEA, 1,4-dioxane, 80 °C; ii) HCl, MeOH

[00628] **Step 1.** (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-3-(2,2-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-7-yl)-N-methylacrylamide (compound **287**). To a mixture of N-((7-((diphenylmethylene)amino)-2-methylbenzofuran-3-yl)methyl)-N-methylacrylamide **166** (72 mg, 0.18 mmol), 7-bromo-2,2-dimethyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one **14** (45 mg, 0.18 mmol) and Pd-116 (9 mg, 0.02 mmol) was added 1,4-dioxane (2 mL) and DIPEA (0.06 mL, 0.35 mmol). The reaction mixture was purged with N₂, heated to 80 °C and stirred for 1 h. The reaction mixture was allowed to cool to RT, then was diluted with MeOH (2 mL) and HCl was added (5 mL, 1M Aq). The resulting mixture was stirred for 10 min then was diluted with HCl (5 mL, 1M Aq). The aqueous layer was extracted with DCM (3 x 10 mL), neutralised with solid NaHCO₃ until ~pH 8 and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), passed through a phase separator and concentrated in vacuo. The crude product was purified by chromatography (0-10% MeOH/DCM) to afford the title compound **287** as a pale yellow solid (26 mg, 34%). R_t 1.51 min (Method 1a) m/z 420 (M+H)⁺ (ES⁺). ¹H NMR (DMSO-d₆, 363 K): δ, ppm 10.41 (s, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.03 (d, J = 15.4 Hz, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.54 (dd, J = 7.8, 1.2 Hz, 1H), 6.04 (s, 1H), 4.88 (s, 2H), 4.72 (s, 2H), 2.98 (s, 3H), 2.47 (s, 3H), 1.30 (s, 6H).

[00629] Example 62. Synthesis of (E)-N-((7-amino-2-methylbenzofuran-3-yl)methyl)-3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **290**).

5 **[00630] General Synthetic Scheme.**



Reaction conditions: a) Pd-116, DIPEA, 1,4-dioxane, 90 °C; b) TFA, DCM; c) HATU, DIPEA, DMF

[00631] Step 1. (E)-tert-Butyl 3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate (compound **288**). (2R,3S)-8-Bromo-3-hydroxy-2-methyl-2,3-dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one **148** (350 mg, 1.29 mmol) and Pd-116 (33 mg, 0.064 mmol) were added to a vial and the vial was evacuated and re-filled with nitrogen (3 times). 1,4-Dioxane (7 mL), DIPEA (0.45 mL, 2.57 mmol), and tert-butyl acrylate **15** (0.37 mL, 2.57 mmol) were added and the reaction was stirred at 90 °C for 1 h. The reaction was allowed to cool to RT and then was concentrated in vacuo. The crude product was purified by chromatography (0-50% EtOAc/isoohexane) to give the title compound **288** as a yellow solid (414 mg, 96%). UPLC-MS (Method 1c): R^t = 1.74 min. m/z 320 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6): δ , ppm 10.30 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 16.0 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.11 (d, J = 5.7 Hz, 1H), 5.15 (d, J = 4.8 Hz, 1H), 4.18 (dd, J = 4.8, 3.3 Hz, 1H), 3.77 – 3.69 (m, 1H), 1.48 (s, 9H), 1.08 (d, J = 6.5 Hz, 3H).

[00632] Step 2. (E)-3-((2R,3S)-3-Hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid 2,2,2-trifluoroacetate (compound **289**). A mixture of (E)-tert-butyl 3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylate **288** (411 mg, 1.29 mmol) in DCM (5 mL) and TFA (5 mL) was stirred at RT for 1.5 h. The mixture was concentrated under reduced pressure to

give a pale orange gum. The gum was triturated with TBME (10 mL) to provide yellow solids which were filtered and washed with further TBME (10 mL) and then MeCN (2 x 10 mL) to give the title compound **289** as a bright yellow solid (260 mg, 53%). UPLC-MS (Method 1c): R^t = 0.90 min. m/z 264 $[M + H]^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6): δ , ppm 12.41 (s, 1H), 10.30 (s, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 16.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 6.15 (d, J = 5.7 Hz, 1H), 5.15 (br. s, 1H), 4.19 (d, J = 3.3 Hz, 1H), 3.78-3.69 (m, 1H), 1.08 (d, J = 6.5 Hz, 3H).

[00633] Step 3. (E)-N-((7-Amino-2-methylbenzofuran-3-yl)methyl)-3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)-N-methylacrylamide (compound **290**). DIPEA (110 μ L, 0.63 mmol) was added to a suspension of (E)-3-((2R,3S)-3-hydroxy-2-methyl-4-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepin-8-yl)acrylic acid 2,2,2-trifluoroacetate **289** (60 mg, 0.16 mmol) and HATU (72 mg, 0.19 mmol) in DMF (1 mL) and the mixture was stirred at RT for 2 mins. 2-Methyl-3-((methylamino)methyl)benzofuran-7-amine **74** (30 mg, 0.16 mmol) in DMF (1 mL) was added in a single portion and the reaction mixture was stirred at RT for 1.5 h. H_2O (10 mL) was added and the resultant yellow solids were filtered and washed with H_2O (5 mL). The crude product was purified by chromatography (2.5-5% MeOH/DCM) to afford the title compound **290** as a yellow solid (16 mg, 23%).

[00634] R^t 1.36 min (Method 1a) m/z 436 $(M+H)^+$ (ES^+). 1H NMR (500 MHz, DMSO- d_6 , 363K): δ , ppm 9.80 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 15.4 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H), 7.15 - 7.03 (m, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 5.89 (d, J = 5.7 Hz, 1H), 4.87 (s, 2H), 4.76 (d, J = 4.8 Hz, 1H), 4.71 (s, 2H), 4.21 (t, J = 3.9 Hz, 1H), 3.80 - 3.72 (m, 1H), 2.98 (s, 3H), 2.47 (s, 3H), 1.11 (d, J = 6.5 Hz, 3H).

[00635] Example 63 Formulation examples:

The compound of the present invention is formulated as a solution at a concentration of 10 mg/ml in a 40% Captisol aqueous vehicle or 30% Kleptose vehicle (30 minutes magnetic stirring at room temperature). This formulation is suitable for IV route.

[00636] The compound of the present invention is formulated as a solid dispersion at a drug load of 20 % in HPMC AS: The compound and the polymer are solubilized in a mix of methylene chloride: methanol (ratio 3:1 w/w), the polymer concentration being 1.4 % w/w

in the organic phase (batch scale 85 mg). This solution is then spray dried on a Procept 4M8-Trix spray dryer (process parameters: cyclone S, air speed 0.35 m³/min, inlet temperature 50°C, solution feed rate: 6 g/min, nozzle pressure 10 L/min, air cooling 80 L/min). The recovery is 64%. DSC and XRPD analyses confirm that a solid solution is obtained (amorphous physical form, single T_g at 95°C). The formulation is then formulated as tablets or granules for the PO route.

[00637] The compound of the present invention is formulated (at a concentration of 1mg/ml to 300mg/ml) as a nanosuspension or microsuspension in water or oil and stabilized by a polymer such as cellulose, 2-hydroxypropyl ether or Cellulose ethyl ether in a concentration between 0.01 and 10 %. Said formulation further comprises a surfactant such as Polyoxyethylene 20 sorbitan monooleate in a concentration of between 0.01 and 10 %. This formulation is suitable for administration via the oral route.

[00638] The compound of the present invention is formulated (at a concentration of 1mg/ml to 300mg/ml) as a nanosuspension or microsuspension in water or oil. The formulation further comprises a polymer such as Polyethylene Glycol 4000 or α-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) in a concentration of between 0.01 and 10 %, and a surfactant such as Polyoxyethylene 20 sorbitan monooleate in a concentration of between 0.01 and 10 %. The formulation is a sustained release formulation (sustained release between 12 and 72h). This formulation is suitable for administration via the intramuscular route.

[00639] The compound of the present invention is formulated as a nanosuspension or microsuspension in water at a concentration of 10 mg/ml. The formulation further comprises Polyethylene Glycol 4000 in a concentration of 10 %, and Polyoxyethylene 20 sorbitan monooleate in a concentration of 10%. This formulation is suitable for administration via the intramuscular route.

[00640] The compound of the present invention is formulated (at a concentration of 1mg/ml to 300mg/ml) as a nanosuspension or microsuspension in water in combination with an hydrophilic prodrug of the invention in a ratio (compound:hydrophilic prodrug compound) of from 1:99 to 99:1. The composition further comprises a polymer such as copovidone or acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidinone in a concentration of between 0.01 and 10 %, and a surfactant e.g. Polyoxyethylene 20 sorbitan monooleate in a concentration of between 0.01 and 10 %. The formulation is a sustained

release formulation (sustained release between 12 and 72h). This formulation is suitable for administration via the intramuscular route.

[00641] The compound of the present invention is formulated (at a concentration of 1mg/ml to 300mg/ml) as a solid dispersion, made of microgranules, microspheres or of an implant, at a drug load of 10 – 95 % within a PLGA (or other suitable matrix as PLA) in an aqueous or oily media such as sesame oil. The formulation is stabilized by a polymer, such as copovidone or acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidinone, in a concentration of between 0.01 and 10 %. Said formulation further comprises a surfactant Polyoxyethylene 20 sorbitan monooleate in a concentration of between 0.01 and 10 %. The formulation is a sustained release formulation (sustained release between 12 and 72h, e.g. 24 and 72h), this formulation is suitable for administration via the intramuscular route.

[00642] The compound of the present invention is formulated (at a concentration of 1mg/ml to 300mg/ml) as a hydrogel or an oleogel comprising a polymer such as PEG-PLA Polyethylene glycol-poly(lactic acid) or polysaccharides in a concentration of between 0.01 and 50 %. The formulation is a sustained release formulation (sustained release between 12 and 72h, e.g. 24 and 72h). This formulation is suitable for administration via the intramuscular route.

[00643] The compound of the present invention is formulated as a lipophilic solid or oily prodrug (at a concentration of 1mg/ml to 300mg/ml) with oil such as sesame oil and a cosolvent e.g. benzyl alcohol and/or ethanol. The formulation is a sustained release formulation (sustained release between 12 and 72h). This formulation is suitable for administration via the intramuscular route.

[00644] **Example 64 Antibacterial activity**

[00645] The exemplified compounds were tested for activity, relying on the following test procedures:

[00646] *Neisseria gonorrhoeae* FabI Inhibition Assay:

[00647] Inhibition of *Neisseria gonorrhoeae* FabI enzyme activity was tested by measuring the rate of NADH consumption (Δ absorbance at 340nm/ min) at 30 °C in 96-well plate format using an automated plate reader in the presence or absence of the test compounds. The assay mixture contained 100 mM Tris-HCl, pH 7.2, 100 mM ammonium acetate, 0.05% pluronic F-68, 25 μ M crotonyl ACP, 50 μ M NADH, 50 pM recombinant *N.*

gonorrhoeae FabI protein, 7.5% DMSO and test compounds at concentrations ranging from 0.17 to 10,000 nM in a final well volume of 100 µl. This dose-response inhibitory assay was performed using an 11-point, serial dilution series for each test compound. IC₅₀ values for each test compound were assigned from logistical sigmoid curve-fitting of the inhibition dose response curves.

[00648] MIC₅₀: MICs were determined in accordance with the appropriate Clinical and Laboratory Standards Institute (CLSI) methodology by the agar dilution susceptibility testing method in GC agar base. The screening panel of isolates used for evaluation of the activity against diverse *Neisseria gonorrhoeae* strains and to determine MIC₅₀ contained a minimum of 15 clinical isolates of *N. gonorrhoea* including several strains from the ATCC reference collection and Ciprofloxacin resistant strain. The MIC₅₀ represents the MIC value at which ≥ 50% of the isolates in a test population are inhibited; it is equivalent to the median MIC value.

[00649] **Caco-2 assay:** Compounds were incubated in a Caco-2 24-transwell system (Solvo Biotechnologies, Hungary) for 120 min, after which samples were taken from the donor and acceptor compartments of the transwell system. The integrity of each cell monolayer was controlled by measuring transepithelial electrical resistance (TEER) before the experiment. Lucifer yellow permeability (B to A) was also tested as a control on the same plate (all wells) after the actual experiment. The samples were analyzed using UPLC/MS/MS. The permeation of the compounds was monitored using relative LC/MS/MS peak areas (initial donor solution sample = 100%). The data were used to calculate apparent permeability (P_{app} in cm/s * 10⁻⁶) and recovery during the experiment.

[00650] **Prediction of hepatic extraction ratio (ER):** *In vitro* metabolic stability was assessed by determining the intrinsic metabolic clearance after incubation of the test compounds with mouse and human liver microsomes. In short, the study compounds were incubated with liver microsomes supplemented with cofactors (1 mM NADPH, 1 mM UDPGA + 15 mM alamethicin). At selected time points, the assays were quenched using an equal volume of cold acetonitrile and samples were analyzed by UPLC/HR-MS to monitor disappearance rate of the compounds. Substrate depletion was estimated based on peak areas (0 min = 100%), and is used to calculate half-lives and then *in vitro* clearances (CL_{int}, in µL/min/mg protein). With the use of species-specific physiologically-based scaling factors

(PBSF) and the Well-Stirred model of hepatic clearance as modified by Poulin *et al*, Journal of Pharmaceutical Sciences, vol. 101, no. 2, February 2012 and Poulin *et al*, Journal of Pharmaceutical Sciences, vol. 101, no. 11, November 2012, the *in vitro* CL_{int} was further transformed into *in vivo* CL_{int} and to hepatic extraction ratio (ER) for both mouse and human.

[00651] *Mouse Cassette PK and oral bioavailability determination:* Female BALB/c mice (n = 24 per group) received single intravenous (iv, 1 mg/kg) or oral (po, 2 mg/kg) doses of the compounds. Dose volumes were 5 ml/kg and 10 ml/kg for IV and oral administration, respectively. Compounds were co-formulated in a 10% DMSO (v/v) and 40% Captisol (w/v) in saline solution formulation (up to 3 compounds in a cassette). Blood samples (3 mice per time point) were taken at 0.0833, 0.25, 0.5, 1, 2, 4, 6 & 8 hrs after administration and the compound concentrations were measured in plasma using standard HPLC /MS analytical methods. T_{max}, C_{max}, AUC, clearance, volume of distribution and oral bioavailability were estimated from the plasma concentrations using non-compartmental pharmacokinetic models. In particular, oral bioavailability (F%) was defined as $F = \frac{(\text{Dose}_{iv} * \text{AUC}_{po})}{(\text{Dose}_{po} * \text{AUC}_{iv})} * 100$

[00652] *Cytotoxicity HepG2*

[00653] Day-1 : Preparation of plates C

- Cytotoxicity assays were performed in 96-well microtiter plates (Biofil, TCP 011096), the inner wells (60 inner wells surrounded by sterile water) received 190µL of culture medium with a predefined number of cells (7'500 viable cells/well). One plate C containing cells was be prepared for 2 compounds (8 concentrations, n=3/concentration). One background plate without cells was prepared for 6 compounds (8 concentrations, n=1/concentration)
- Plates were left on the bench for 30min to allow homogenous adhesion of cells within wells
- The plates were then Incubated overnight at 37°C with 5% CO₂

[00654] Day 0: Preparation of plate A

- Stock solutions were serially diluted (half-log dilution, 3.16x) in corresponding 100% DMSO in a 96-well PP plate (Greiner Bio-One, 7.651.261): 79 µl of a stock solution at 10'000 µM in 100% DMSO was added in column 3, 54 µl of 100% DMSO was added in columns 4 to 11. 25 µl of compound stock solution was transferred from column 3 to

column 4 (pipeted up and down 3X, tips changed after each transfer). This was continued up to column 10. For the positive control Doxorubicin, a stock solution at 1'000 μ M was used as a starting point.

[00655] Plate A:

		Compound 1 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 2 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 3 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 4 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 5 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 6 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Compound 7 10000 μ M	3164,5 6	1001, 44	316,91	100,29	31,74	10,04	3,18	100% DMSO	
		Doxorubicin 1000 μ M	316,46	100,1 4	31,69	10,03	3,17	1,00	0,32	100% DMSO	

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[00656] Preparation of plate B

- Compounds prepared in Plate A were diluted 5X in 200 μ l in complete medium in a 96-well PP plate (Greiner Bio-One, 7.651.261): In column 2, 200 μ l of medium containing 16% Triton X-100 was added. In columns 3 to 11, 160 μ l of medium was added. 40 μ l of the pre-diluted compounds from plate A were transferred to column 3 to 11 (Pipeted up and down 3X, tips changed after each transfer).

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[00657] Plate B:

	16% Triton X	Compound 1 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 2 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 3 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 4 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 5 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 6 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Compound 7 2000000 nM	632911,39	200288,42	63382,41	20057,72	6347,38	2008,66	635,65	20% DMSO	
	16% Triton X	Doxorubicin 200000 nM	63291,14	20028,84	6338,24	2005,77	634,74	200,87	63,57	20% DMSO	

- 20X solutions of plate B were diluted in plates C (with and without (background plate) cells): In columns 2 to 11, 10 μ l of plate B compound solutions were added(pipet up

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and down 3X, tips changed after each transfer). 2 compounds were distributed per plate C in triplicates (simplicate for background plate)

[00658] Example of Plate C:

	0.8% Triton X	Compound 7 100000 nM	31645,57	10014,42	3169,12	1002,89	317,37	100,43	31,78	1% DMSO	
	0.8% Triton X	Compound 7 100000 nM	31645,57	10014,42	3169,12	1002,89	317,37	100,43	31,78	1% DMSO	
	0.8% Triton X	Compound 7 100000 nM	31645,57	10014,42	3169,12	1002,89	317,37	100,43	31,78	1% DMSO	
	0.8% Triton X	Doxorubicin 10000 nM	3164,56	1001,44	316,91	100,29	31,74	10,04	3,18	1% DMSO	
	0.8% Triton X	Doxorubicin 10000 nM	3164,56	1001,44	316,91	100,29	31,74	10,04	3,18	1% DMSO	
	0.8% Triton X	Doxorubicin 10000 nM	3164,56	1001,44	316,91	100,29	31,74	10,04	3,18	1% DMSO	

- 5 • Plates C were incubated for 72 hours at 37°C with 5% CO₂

[00659] Day 3:

- 20 µl of Alamar blue was added and incubated for 6h at 37°C with or without CO₂
- fluorescence was read at exc 570 nm and emi 585 nm
- Background corrected fluorescence measurements were transformed in % scale by considering vehicle value (1% DMSO) as 100% activity (relative measurements), or they were normalized by considering Triton X-100 values as 0% viability and vehicle values as 100% viability (normalized measurements). Next, relative measurements and absolute measurements were analyzed using GraphPad Prism software to derive relative IC₅₀ and absolute IC₅₀ values respectively

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[00660] The results of these activity tests are summarized in Table 1 below.

Table 1

Compound number (patent example)	ngFabI IC ₅₀ (nM)	MIC ₅₀ (µg/mL)	Caco-2 Papp A2B (10 ⁻⁶ cm/s)	Predict Human hep ER	Mouse F (%)	Cytotoxicity % viability at 10 µM
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5(1)	< 10	< 1	22.6	0.17	100	NA
7(2)	< 10	< 1	7.6	0.12	68	NA
10(3)	< 10	< 1	22.6	0.22	73	NA
19(4)	< 10	< 1	16	0.26	62	100
31(6)	<10	<1	10.9	0.18	NA	NA
32(6)	< 10	< 1	10.8	0.08	42	NA
33(6)	<10	<1	11.5	0.09	NA	NA
39(7)	<10	<1	11.3	0.17	NA	NA
40(7)	< 10	< 1	10.3	0.21	57	NA
41(7)	<10	<1	12.2	0.09	NA	NA
49(8)	< 10	< 1	26	0.13	70	100
50(8)	<10	<1	19.1	0.09	NA	NA

60(9)	< 10	< 1	3	0.07	52	NA
64(10)	< 10	< 1	16.3	0.21	32	NA
75(11)	< 10	< 1	5.9	0.13	30	NA
80(12)	< 10	< 1	NA	0.25	35	NA
84(13)	< 10	< 1	3.29	0.40	24	NA
90(14)	< 10	< 1	10.7	0.03	7	NA
96(15)	< 10	< 1	NA	0.2	16	NA
101(16)	< 10	< 1	2.69	0.43	2	NA
109(17)	< 10	< 1	19.8	0.28	47	NA
115(18)	< 10	< 1	3.4	0.28	18	NA
119(19)	< 10	< 1	NA	0.08	NA	NA
123(20)	< 10	< 1	2.5	0.13	26	NA

129(21)	< 10	< 1	NA	0.02	26	NA
134(22)	< 10	< 1	NA	0.43	9	NA
140(23)	< 10	< 1	NA	0.13	13	NA
143(24)	< 10	< 1	2.3	0.06	59	NA
150(25)	< 10	< 1	25.1	0.08	20	100
151(26)	< 10	< 1	21.7	0.07	39	NA
152(27)	< 10	< 1	2.6	0.08	38	NA
155(28)	< 10	< 1	NA	0.32	28	NA
159(29)	< 10	< 1	0.7	0.32	35	100
164(30)	< 10	< 1	0.1	NA	10	NA
167(31)	< 10	< 1	5.3	0.12	35	100
168(32)	< 10	< 1	19.6	0.15	51	NA

170(33)	< 10	< 1	22.9	0.15	98	NA
176(36)	< 10	< 1	0	0.07	44	NA
180(37)	< 10	< 1	1.8	0.32	14	
182(38)	< 10	< 1	0.08	0.25	12	NA
183(39)	< 10	< 1	NA	NA	16	NA
186(40)	< 10	< 1	0.4	NA	23	NA
194(41)	< 10	< 1	0	NA	12	NA
198(42)	< 10	< 1	3.2	0.18	54	NA
207(43)	< 10	< 1	NA	NA	NA	NA
208(44)	< 10	< 1	0	0.21	NA	NA
209(44)	< 10	< 1	3.3	0.41	25	NA
214(45)	< 10	< 1	17.9	NA	88	NA

229(46)	< 10	< 1	20.7	NA	76	NA
230(46)	< 10	< 1	NA	NA	NA	NA
247(52)	<10	<1	NA	NA	NA	NA
252(53)	<10	<1	NA	NA	NA	NA
260(54)	<10	<1	35	0.03	56	NA
270(55)	<10	<1	5.5	0.05	NA	NA
275(57)	<10	<1	NA	NA	51	NA
276(58)	<10	<1	NA	NA	43	NA
287(61)	<10	<1	NA	0.34	NA	NA
290(62)	<10	<1	NA	0.1	NA	NA

NA: not available

[00661] **Example 65** *Chlamydia trachomatis* FabI Inhibition Assay

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[00662] Inhibition of *Chlamydia trachomatis* FabI enzyme activity was tested by measuring the rate of NADH consumption (Δ absorbance at 340nm/ min) at 30 °C in 96-well plate format using an automated plate reader in the presence or absence of the test

compounds. The assay mixture contained 100 mM MES, pH 7.0, 200 mM ammonium acetate, 4.0% glycerol, 0.02% pluronic F-68, 25 μ M crotonyl ACP, 50 μ M NADH, 0.5 nM recombinant *C. trachomatis* FabI protein, 7.5% DMSO and test compounds at concentrations ranging from 0.17 to 100,000 nM in a final well volume of 100 μ l. This dose-response inhibitory assay was performed using an 11-point, serial dilution series for each test compound. IC₅₀ values for each test compound were assigned from logistical sigmoid curve-fitting of the inhibition dose response curves.

[00663] Results are shown in Table 2.

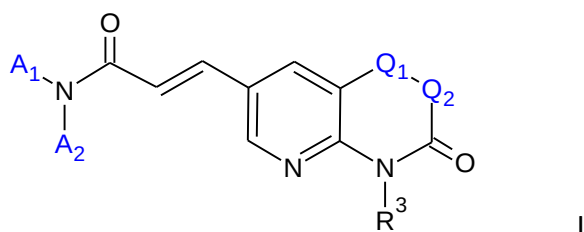
[00664] **Table 2**

COMPOUND NUMBER (PATENT EXAMPLE)	CT FABI IC ₅₀ (μ M)
229 (46)	<1
49 (8)	<1
152 (27)	<1
150 (25)	<1
32 (6)	<1
155 (28)	<1
40 (7)	<5
151 (26)	<5
260 (54)	<5
109 (17)	<5
214 (45)	<5
60 (9)	<5
275 (57)	<5

[00665] With respect to the designation of the United States of America, the following is stated: "This invention was made with government support under FAIN: IDSEP160030 awarded by HHS/ASPR. The government has certain rights in the invention."

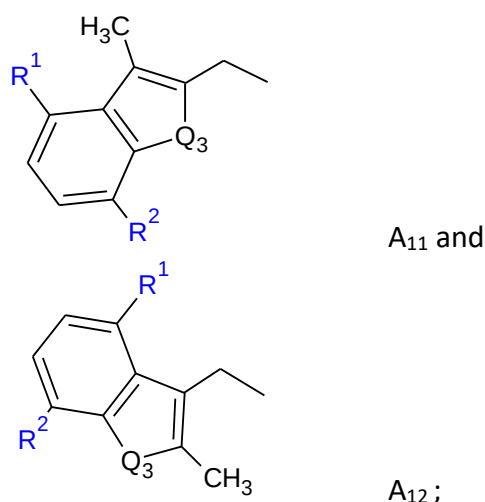
Claims

1. Compound, which is selected from the group of compounds represented by general formula I



wherein

10 A₁ represents a moiety selected from the groups A₁₁ and A₁₂ having the following structures



15 wherein the line connected to the exocyclic methylene group represents a single covalent bond formed with the nitrogen atom of formula I;

A₂ represents a methyl group;

20 Q₁ represents CH₂ or NH;

Q₂ represents CR⁴R⁵-CR⁶R⁷, wherein the CR⁴R⁵ group binds to Q₁;

Q₃ represents O or S;

25 R¹ represents a group selected from H, -NH₂;

R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NR⁹R¹⁰, -O-Alk¹, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, -O-(CH₂)₁₋₄-NR⁹R¹⁰, or wherein the phenyl group

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may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN, -(CH₂)₀₋₄-OH; wherein R⁹ is selected from H and -C₁₋₄-alkyl; wherein R¹⁰ is selected from H, -C₁₋₄-alkyl and -C(=O)-CH₃; wherein Alk¹ represents an alkyl group having 1 to 6 carbon atoms, which is linear, branched, cyclic or a combination thereof, which Alk¹ group may optionally be substituted by one or more groups selected from -OH, -O-alkyl;

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

R⁴ represents a group selected from H, C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F;

R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

or R⁴ and R⁵ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom;

R⁶ represents a group selected from H, -OH, C₁₋₄-alkyl, -OPO₃R^{3a}₂;

R⁷ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, C₁₋₄-alkylene-F, -CN;

with the proviso that at least one of R⁶ and R⁷ is not H;

or R⁶ and R⁷ together form a cyclic group having 4 to 6 ring members formed by methylene groups and optionally an oxygen atom; the cyclic group may optionally carry a substituent selected from -OH, -O-alkyl.

2. Compound according to claim 1, wherein

R⁴ represents a group selected from C₁₋₄-alkyl, CN and C₁₋₄-alkylene-F; and

R⁵ represents a group selected from H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, -OH, -OPO₃R^{3a}₂;

and the remaining variable groups are as defined in claim 1.

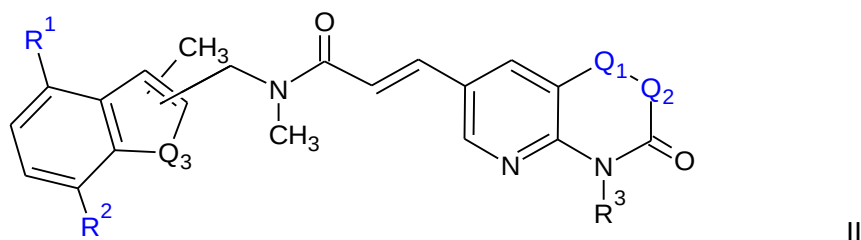
3. Compound according to claim 1, wherein

R^4 represents a group selected from H, C_{1-4} -alkyl, CN and C_{1-4} -alkylene-F; and

R^5 represents a group selected from C_{1-4} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-OR³, -OH, -OPO₃R^{3a}₂;

and the remaining variable groups are as defined in claim 1.

4. Compound according to claim 1, 2 or 3 wherein the compound is selected from the group of compounds represented by general formula II

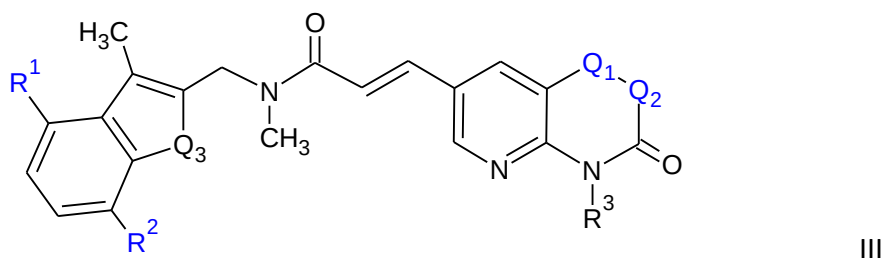


wherein

R^1 , R^2 , R^3 , Q_1 , Q_2 , Q_3 have the same meanings as specified in claim 1, 2 or 3 above;

and wherein the five-membered heterocycle comprising Q_3 is bonded to the methylene-amide moiety at the 2-position and to the methyl group at the 3-position or is bonded to the methylene-amide moiety at the 3-position and to the methyl group at the 2-position.

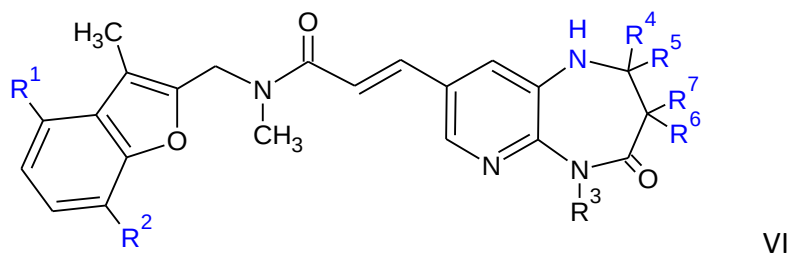
5. Compound according to claim 4, wherein the compound is selected from the group of compounds represented by general formula III



wherein

R^1 , R^2 , R^3 , Q_1 , Q_2 , Q_3 have the same meanings as specified in claim 1, 2 or 3 above.

6. Compound according to claim 5, wherein the compound is selected from the group of compounds represented by general formula VI



5 wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 have the same meanings as specified in claim 1, 2 or 3 above.

10 7. Compound according to claim 6, wherein

R^1 represents H, NH_2 ;

R^2 represents H;

15

R^3 represents a group selected from H, $-\text{PO}_3\text{R}^{3a}_2$, $-\text{CH}_2-\text{OPO}_3\text{R}^{3a}_2$ and $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{R}^{3b}$ or $-\text{CH}_2-\text{O}-$
20 $\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CHMe}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$ or $-\text{CMe}_2-\text{O}-\text{C}(=\text{O})-\text{O}-\text{R}^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-\text{OH}$, and $-\text{O}-\text{C}_{1-6}\text{-alkyl}$;

25

R^4 represents H, $\text{C}_{1-4}\text{-alkyl}$; and

R^5 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene-OR}^3$;

R^6 represents H, $\text{C}_{1-4}\text{-alkyl}$, OH , $-\text{OPO}_3\text{R}^{3a}_2$; and

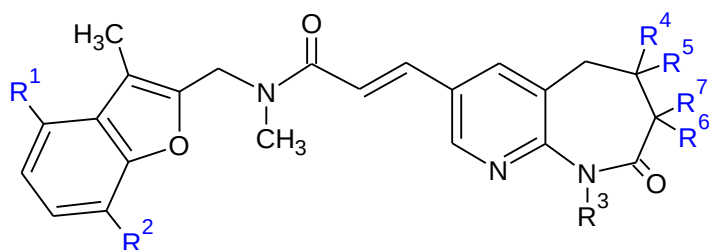
30

R^7 represents H, $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkylene-OH}$, $\text{C}_{1-4}\text{-alkylene-OR}^3$, wherein R^3 is as specified above, $\text{C}_{1-4}\text{-alkylene-F}$;

with the proviso that at least one of R^6 and R^7 is not H.

35

8. Compound according to claim 5, wherein the compound is selected from the group of compounds represented by general formula VII



VII

wherein

R^1 , R^2 , R^3 , R^6 and R^7 have the same meanings as specified in claim 1, 2 or 3 above.

9. Compound according to claim 8, wherein

R^1 represents H, NH_2 ;

R^2 represents H;

R^3 represents a group selected from H, $-PO_3R^{3a}_2$, $-CH_2-OPO_3R^{3a}_2$ and $-CH_2-O-C(=O)-R^{3b}$;

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or $-CH_2-O-C(=O)-R^{3b}$ or $-CHMe-O-C(=O)-R^{3b}$ or $-CMe_2-O-C(=O)-R^{3b}$ or $-CH_2-O-C(=O)-O-R^{3b}$ or $-CHMe-O-C(=O)-O-R^{3b}$ or $-CMe_2-O-C(=O)-O-R^{3b}$;

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from $-OH$, and $-O-C_{1-6}$ -alkyl;

R^4 represents H, C_{1-4} -alkyl; and

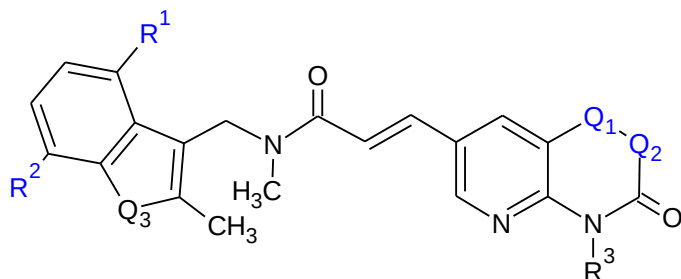
R^5 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OR^3 ;

R^6 represents H, C_{1-4} -alkyl, OH , $-OPO_3R^{3a}_2$; and

R^7 represents H, C_{1-4} -alkyl, C_{1-4} -alkylene- OH , C_{1-4} -alkylene- OR^3 , wherein R^3 is as specified above, C_{1-4} -alkylene- F ;

with the proviso that at least one of R6 and R7 is not H.

10. Compound according to claim 4, wherein the compound is selected from the group of compounds represented by general formula VIII

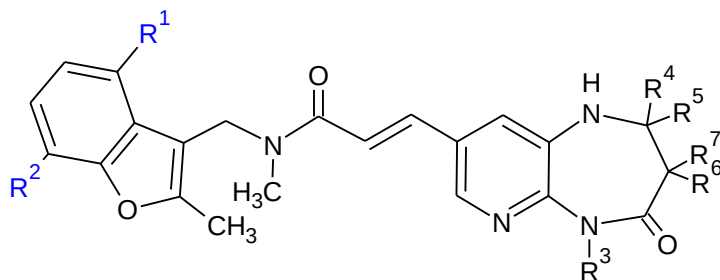


VIII

wherein

R¹, R², R³, Q₁, Q₂, Q₃ have the same meanings as specified in claim 1, 2 or 3 above.

11. Compound according to claim 9, wherein the compound is selected from the group of compounds represented by general formula XI



XI

wherein

R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the same meanings as specified in claim 1, 2 or 3 above.

12. Compound according to claim 11, wherein

R¹ represents H;

R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O,

which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

5

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

10 R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

R⁴ represents H, C₁₋₄-alkyl; and

15

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

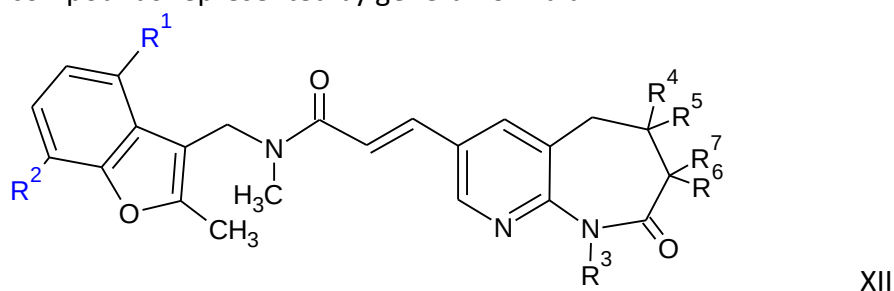
R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

20 R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F;

with the proviso that at least one of R⁶ and R⁷ is not H.

25

13. Compound according to claim 10, wherein the compound is selected from the group of compounds represented by general formula XII



30

wherein

R¹, R², R³, R⁶ and R⁷ have the same meanings as specified in claim 1, 2 or 3 above.

35

14. Compound according to claim 13, wherein

R¹ represents H;

5 R² represents a group selected from H, -O-Ar¹, -O-Het¹, -NH₂, wherein Ar¹ represents a phenyl group that may optionally be substituted by one or more groups individually selected from -CN, -O-C₁₋₄-alkyl, or wherein the phenyl group may carry two substituent groups at adjacent ring atoms such that these adjacent substituent groups may be bonded together to form a 5-membered heterocycle having one or two heteroatoms individually selected from
10 N and O, wherein Het¹ represents an aromatic heterocycle with 5 or 6 ring atoms including 1 or 2 heteroatoms individually selected from N, S and O, or a non-aromatic partially or fully saturated heterocycle with 6 ring atoms including 1 heteroatom selected from N, S and O, which Het¹ group may optionally be substituted by one or more groups individually selected from -C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -CN;

15 R³ represents a group selected from H, -PO₃R^{3a}₂, -CH₂-OPO₃R^{3a}₂ and -CH₂-O-C(=O)-R^{3b};

R^{3a} represents a hydrogen atom or a cation suitable for forming a pharmaceutically acceptable salt or -CH₂-O-C(=O)-R^{3b} or -CHMe-O-C(=O)-R^{3b} or -CMe₂-O-C(=O)-R^{3b} or -CH₂-O-
20 C(=O)-O-R^{3b} or -CHMe-O-C(=O)-O-R^{3b} or -CMe₂-O-C(=O)-O-R^{3b};

R^{3b} represents an alkyl group having 1 to 11 carbon atoms, which is linear, branched, cyclic or a combination thereof, which R^{3b} group may optionally be substituted by one or more groups independently selected from -OH, and -O-C₁₋₆-alkyl;

25 R⁴ represents H, C₁₋₄-alkyl; and

R⁵ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OR³.

30 R⁶ represents H, C₁₋₄-alkyl, OH, -OPO₃R^{3a}₂; and

R⁷ represents H, C₁₋₄-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-OR³, wherein R³ is as specified above, C₁₋₄-alkylene-F;

35 with the proviso that at least one of R⁶ and R⁷ is not H.

15. Pharmaceutical composition comprising the compound of any one of claims 1 to 14.

16. Use of a compound according to any one of claims 1 to 14 or pharmaceutical composition according to claim 15 in the manufacture of a medicament for the treatment of a bacterial infection selected from infections by *N. gonorrhoeae* and *Chlamydia trachomatis*.

- 5 17. Use of a compound or a pharmaceutical composition according to claim 16, wherein the infection is by *N. gonorrhoeae* alone or in combination with *Chlamydia trachomatis*.