the efficacy of meropenem against drug resistant bacteria when co-administered with meropenem. The invention relates specifically to methods of forming these compounds.

[0008] It is contemplated that other approved carbapenems might also benefit from co-formulation with the compounds of the invention. Other currently approved carbapenems include: ertapenem, doripenem, panipenem, biapenem and tebipenem.

[0009] Until comparatively recently, bacterial infections were one of the most common causes of death, disfigurement and disablement. During the 19th century a series of antibiotic drug classes were developed, meaning that the successful treatment of bacterial infections has become routine. However, microbial resistance to antibiotics is becoming a significant problem and many consider that this will become one of the most significant challenges to human health. Indeed, in some bacterial pathogens, multidrug resistance has already become common.

[0010] The greatest unmet medical need is the dearth of effective treatments for multidrug resistant Gram-negative bacteria. Therefore discovery of novel antibiotics that are active against WHO listed pathogens of critical concern, or drugs that circumvent existing bacterial resistance mechanisms is essential.

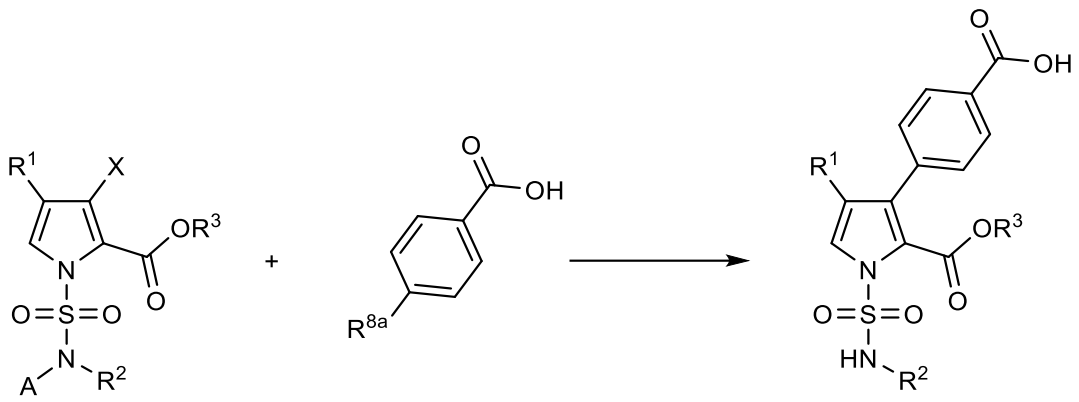
[0011] WO2019/220125 and GB1916915.0 (unpublished) disclose a series of compounds which are inhibitors of metallo-β-lactamases used in combination with antibacterial agents to treat bacterial infections.

[0012] It is an aim of certain embodiments of this invention to provide alternative methods of synthesising metallo-β-lactamase inhibitors. It is an aim to provide methods of synthesising metallo-β-lactamase inhibitors which are more scalable, provide purer product or are more resource efficient than those previously disclosed.

~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

[0012a] In a first aspect of the present disclosure, there is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising

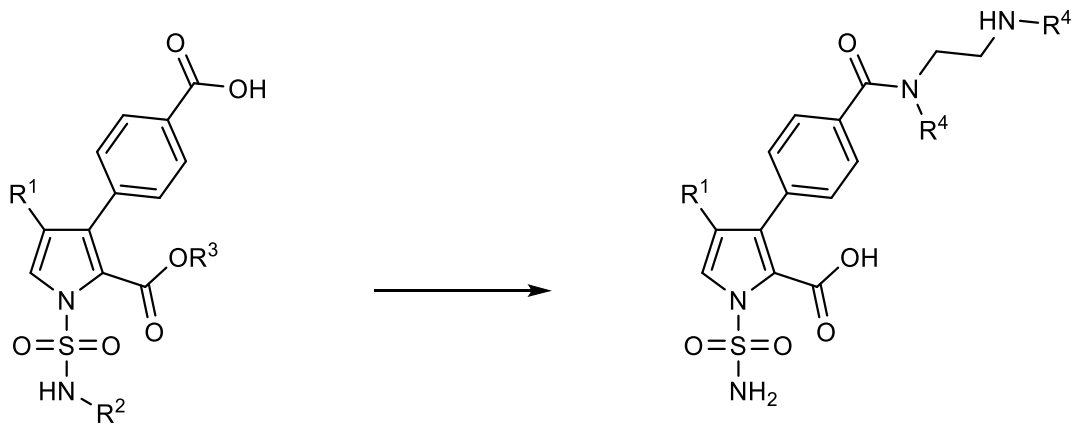
(a) reacting the compound of formula **(I)** with the compound of formula **(II)** in the presence of Pd/C to form the compound of formula **(III)**:



(I) (II) (III)

; and

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula (**III**):



(III) (IV)

wherein

X is independently selected from Cl, Br, I, N_2^+ or OSO_2CF_3;

R^1 is independently selected from H or C_{1-4} alkyl;

R^2 is a protecting group;

R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-4} alkyl;

R^{8a} is BF_3K or $B(OR^{9a})_2$; wherein either R^{9a} is at each occurrence H or C_{1-4} alkyl; or the two R^{9a} substituents together form $(CR^aR^b)_n$; or the two R^{9a} substituents together form -C(O)-(CR^aR^b)-N(R^c)-(CR^aR^b)-C(O)-;

R^a, R^b and R^c are independently selected at each occurrence from H and C_{1-4} alkyl;

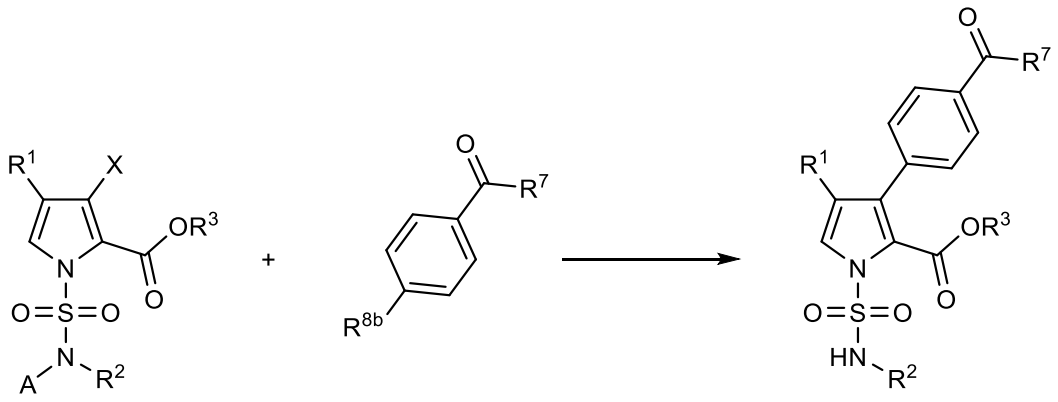
n is 2 or 3;

and

A is independently selected from H or a cation.

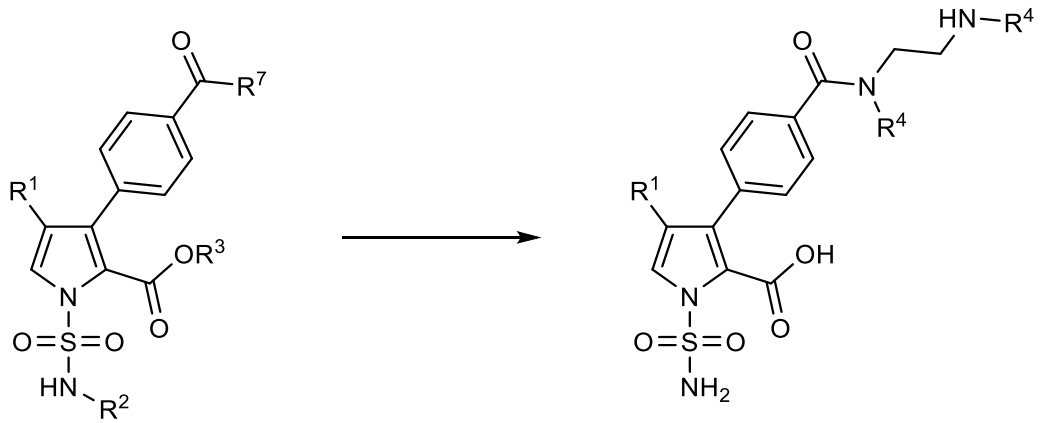
[0012b] In another aspect of the present disclosure, there is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising

(a) reacting the compound of formula **(I)** with a compound of formula **(IX)** to form a compound of formula **(X)**;



(I) **(IX)** **(X)**

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula **(X)**:



(X) **(IV)**

wherein

X is independently selected from Cl, Br, I, N_2^+ or $OS(O)_2CF_3$;

R^1 is independently selected from H or C_{1-4} alkyl;

R^2 is a protecting group;

R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-6} alkyl;

R^5 is a protecting group;

R^7 is independently selected from -OR^{7a} and -$N(R^4)CH_2CH_2NR^4R^5$;

R^{7a} is selected from -C_{1-6} alkyl and -CH_2-aryl;

R^{8b} is independently selected from BF_3K or $B(OR^{9b})_2$, wherein each R^{9b} is H; or the two R^{9b} substituents together are $(CR^aR^b)_n$ and form a ring comprising the oxygen and boron atoms; or the two R^{9a} substituents together are -C(O)-(CR^aR^b)-$N(R^c)$-(CR^aR^b)-C(O)-;

R^a, R^b and R^c are independently selected at each occurrence from H and C_{1-4} alkyl;

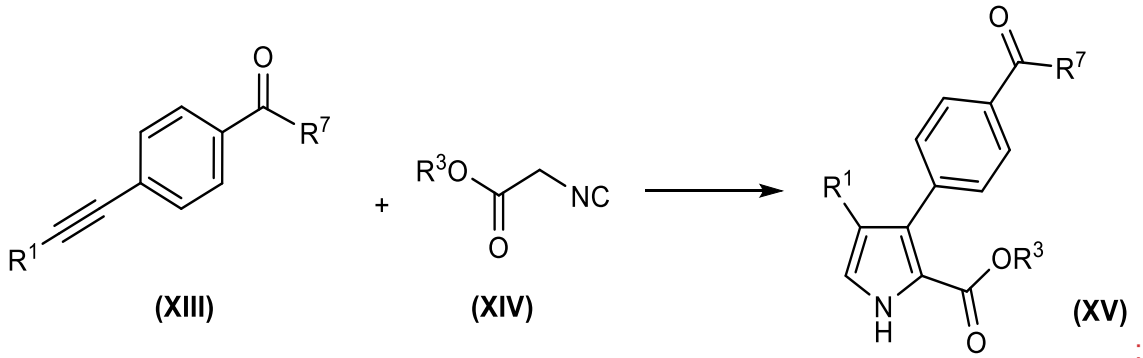
n is 2 or 3;

and

A is independently selected from H or a cation.

[0012c] In a further aspect of the present disclosure, there is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising

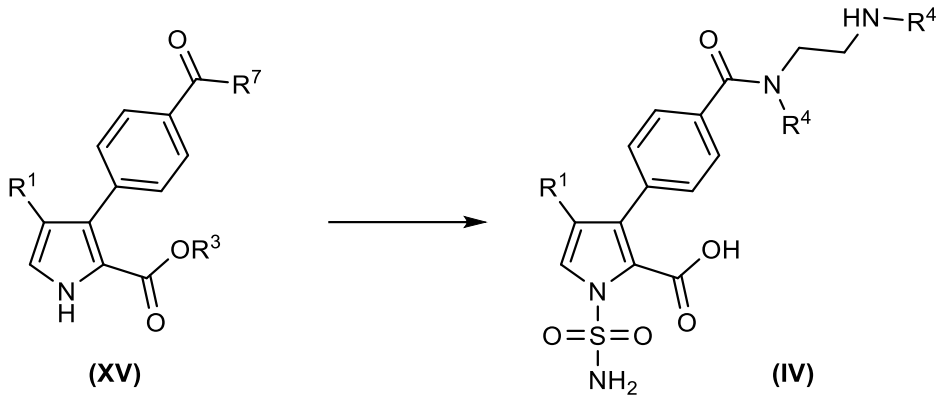
(a) reacting a compound of formula **(XIII)** with a compound of formula **(XIV)** to form a compound of formula **(XV):**



(XIII) **(XIV)** **(XV)**

; and

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula (**XV):**



wherein

R^1 is independently selected from H or C_{1-4} alkyl;

R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-6} alkyl;

R^7 is independently selected from -OR^{7a} and -$N(R^4)CH_2CH_2NR^4R^5$; and

R^{7a} is C_{1-6} alkyl or CH_2-aryl.

[0013] In each of the below ~~aspect~~examples of the present disclosure~~invention~~, the compounds of formulae **(I)** to **(XIX)** may be a free acid or free base as shown, or may be a pharmaceutically acceptable salt thereof.

[0014] In a first ~~aspect~~example of the present disclosure ~~invention~~ is provide a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising:

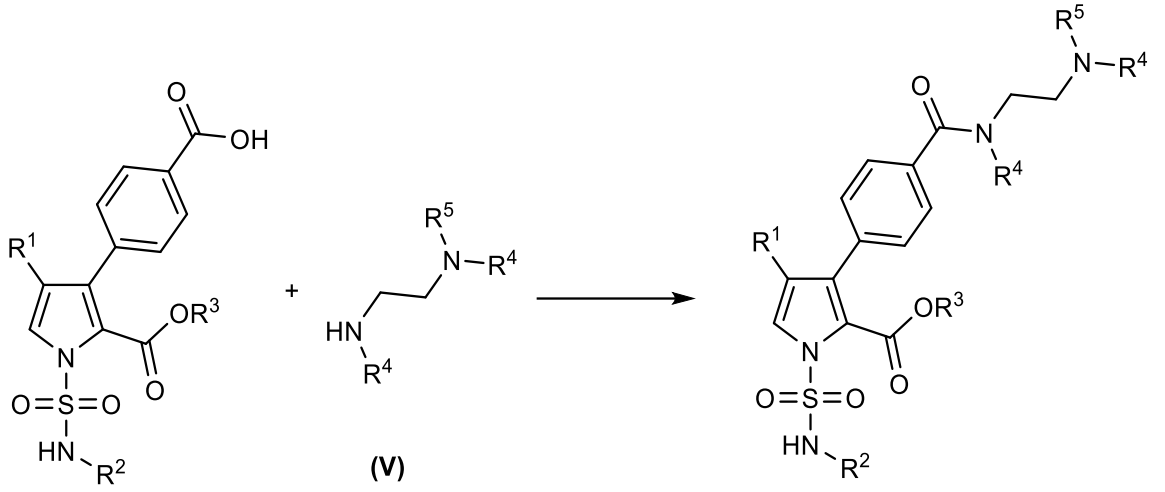
(a) reacting the compound of formula **(I)** with the compound of formula **(II)** in the presence of Pd/C to form the compound of formula **(III)**:

and

A is H or a cation.

[0015] In certain ~~embodiments~~examples, step (b) of the first ~~aspect~~example may comprise the steps of

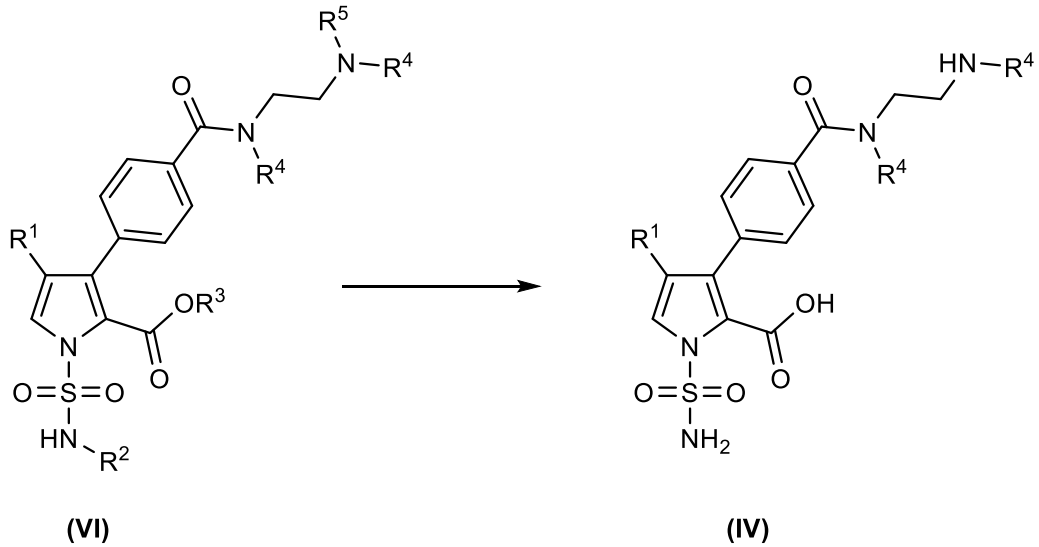
(i) reacting the compound of formula **(III)** with a compound of formula **(V)** to form the compound of formula **(VI)**:



(III) + **(V)** → **(VI)** ;

and

(ii) cleaving the R^2, R^3 and R^5 substituents from the compound of formula **(VI)** to form the compound of formula **(IV)** or a pharmaceutically acceptable salt thereof:

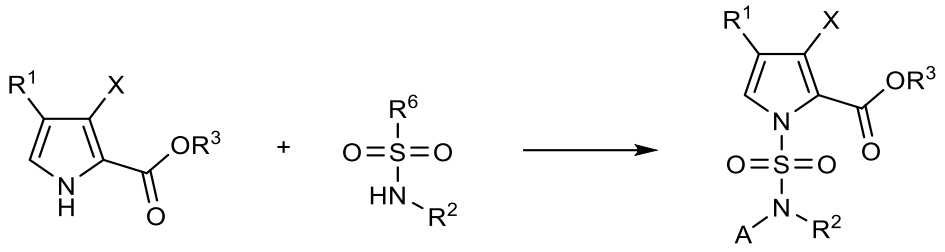


(VI) → **(IV)**

wherein

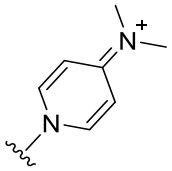
R^5 is a protecting group.

[0016] In certain ~~embodiments~~examples, the compound of formula **(I)** is formed by reacting a compound of formula **(VII)** with a compound of formula **(VIII)** to form the compound of formula **(I)**:



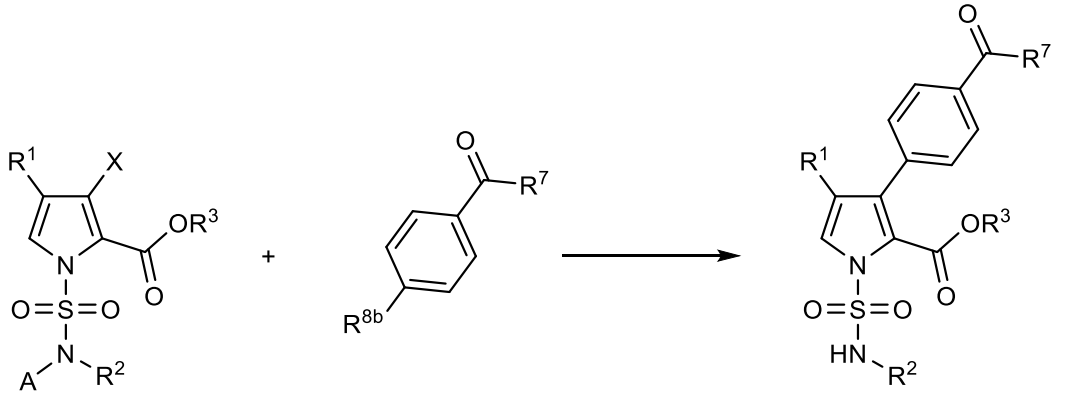
(VII) **(VIII)** **(I)**

,

wherein R^6 is independently selected from F, Cl, Br, I, or  .

[0017] In a second ~~aspect~~example of the present disclosure ~~invention~~ is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising:

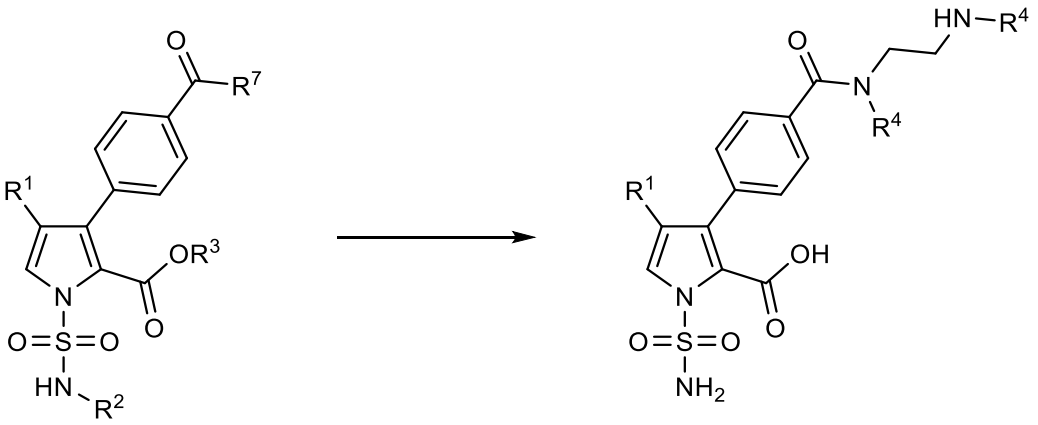
(a) reacting the compound of formula **(I)** with a compound of formula **(IX)** to form a compound of formula **(X)**;



(I) **(IX)** **(X)**

,

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula **(X)**:



(X) **(IV)** ,

wherein

X is independently selected from Cl, Br, I or $OS(O)_2CF_3$;

R^1 is independently selected from H or C_{1-4} alkyl;

R^2 is a protecting group;

R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-6} alkyl;

R^5 is a protecting group;

R^7 is independently selected from -OR^{7a} or -$N(R^4)CH_2CH_2NR^4R^5$;

R^{7a} is selected from -C_{1-6} alkyl and -CH_2-aryl;R^{8b} is independently selected from BF_3K or $B(OR^{9b})_2$, wherein each R^{9b} is H or C_{1-4} alkyl; or the two R^{9b} substituents together form $(CR^aR^b)_n$; or the two R^{9a} substituents together form -C(O)-(CR^aR^b)-$N(R^c)$-(CR^aR^b)-C(O)-;

R^a, R^b and R^c are independently selected at each occurrence from H and C_{1-4} alkyl;

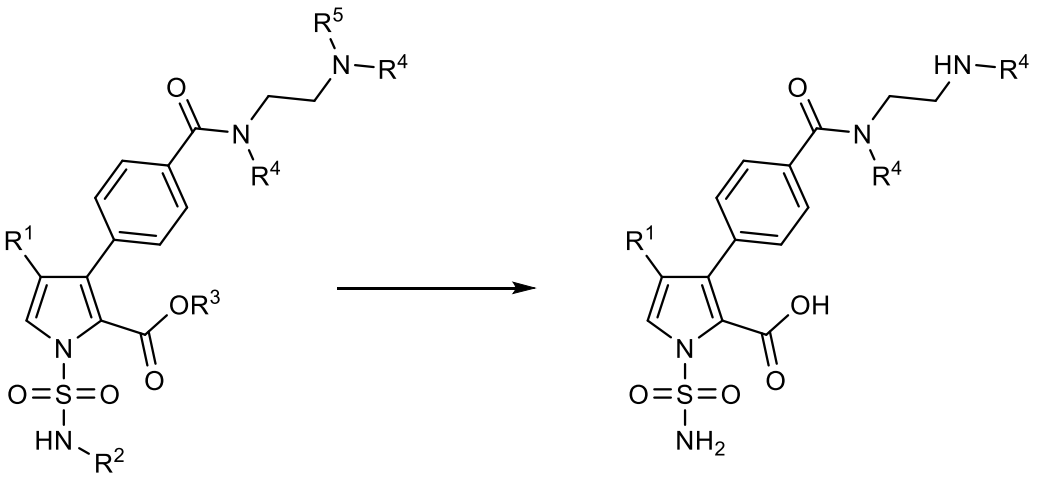
n is 2 or 3;

and

A is independently selected from H or a cation.

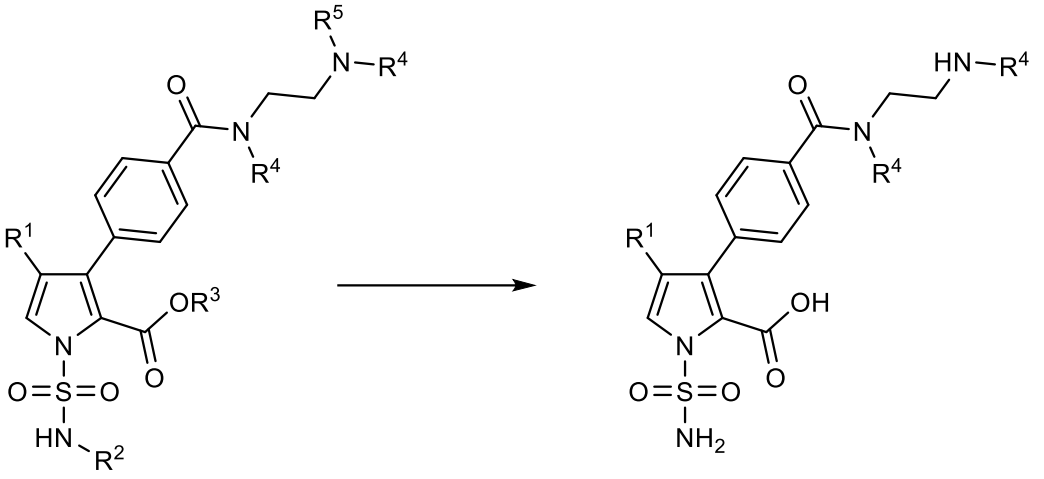
[0018] In ~~certain embodiments of~~ the second ~~aspect~~example, when R^7 is -OR^{7a}, step (b) may comprise

(i) cleaving the R^{7a} substituent from the compound of formula **(Xa)** to form a compound of formula **(III)**;



(VI) **(IV)**

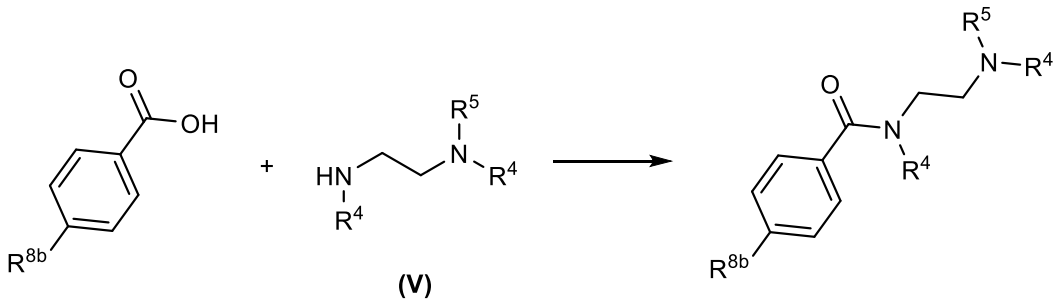
[0019] In ~~another embodiment of the~~ second ~~aspect~~example, when R^7 is -N(R-^{4})$CH_2CH_2NR^4R^5$ (i.e. the compound of formula **(X)** is a compound of formula **(VI)**) step (b) may comprise cleaving the R^2, R^3 and R^5 substituents from the compound of formula **(VI)** to form the compound of formula **(IV)** or a pharmaceutically acceptable salt thereof:



(VI) **(IV)**

[0020] This reaction may be as described above for the first ~~aspect~~example of the present disclosure~~invention~~. Thus, in certain ~~embodiments~~examples, the R^2, R^3 and R^5 substituents may be cleaved from the compound of formula **(VI)** via catalytic hydrogenation, e.g. as described for the first ~~aspect~~example of the present disclosure~~invention~~.

[0021] In further ~~embodiments~~examples, the process may comprise reacting a compound of formula **(XI)** with a compound of formula **(V)** to form the compound of formula **(XII)** (a specific example of a compound of formula **(IX)**):



(XI) **(V)** **(XII)**

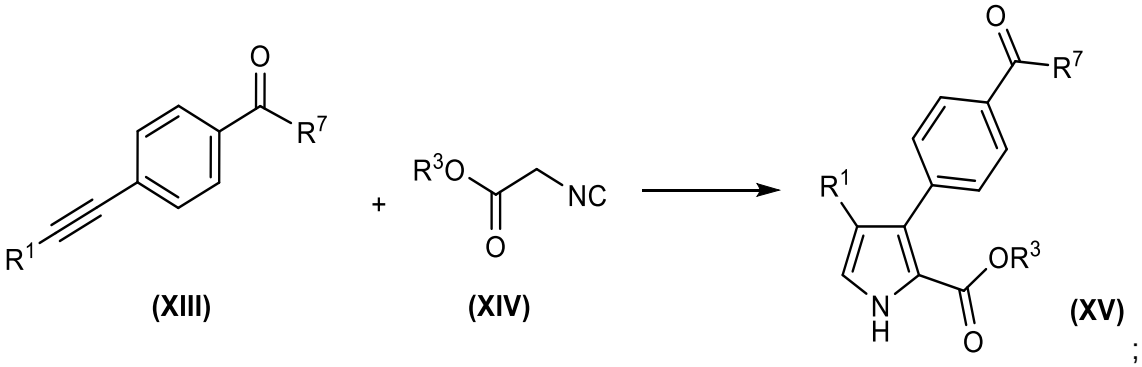
.

[0022] The compound of formula **(XII)** can then be reacted with the compound of formula **(I)**.

[0023] The compound of formula **(I)** may be produced as described above for the first ~~aspect~~example of the present disclosure~~invention~~.

[0024] In a third ~~aspect~~example of the present disclosure ~~invention~~ is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising

(a) reacting a compound of formula **(XIII)** with a compound of formula **(XIV)** to form a compound of formula **(XV):**

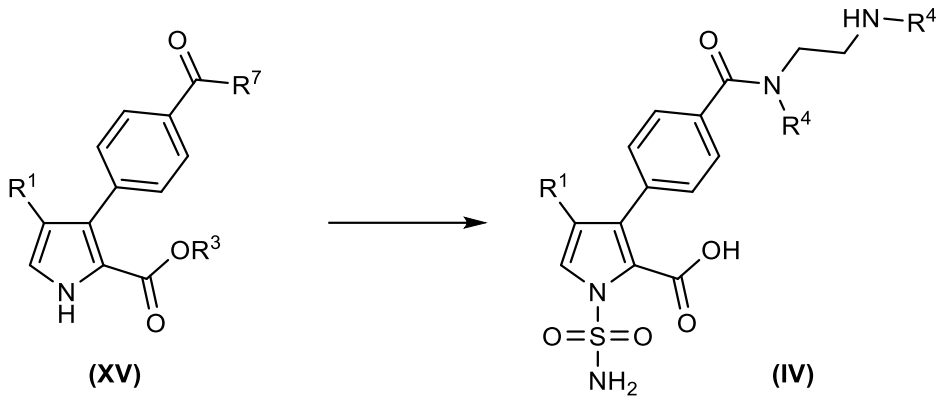


(XIII) **(XIV)** **(XV)**

;

and

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula (**XV):**



(XV) **(IV)**

wherein

R^1 is independently selected from H or C_{1-4} alkyl;

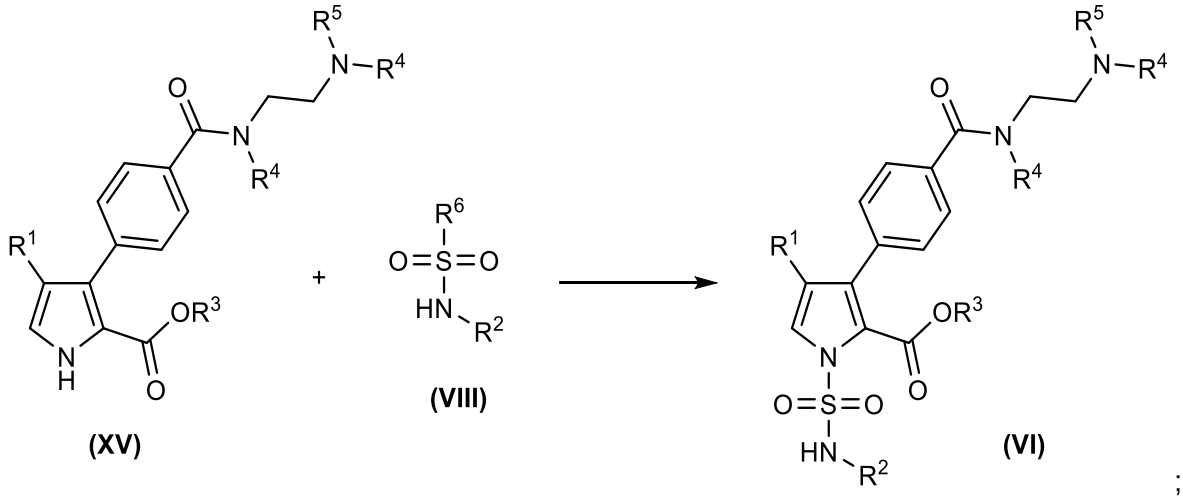
R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-6} alkyl;

R^7 is independently selected from -OR^{7a}, and -$N(R^4)CH_2CH_2NR^4R^5$; and

[0025] R^{7a} is C_{1-6} alkyl or CH_2-aryl. In ~~certain embodiments of~~ the third ~~aspect~~example, when R^7 is -$N(R^4)CH_2CH_2NR^4R^5$, step (b) may comprise

(i) reacting a compound of formula **(XV)** with a compound of formula **(VIII)** to form the compound of formula **(VI):**

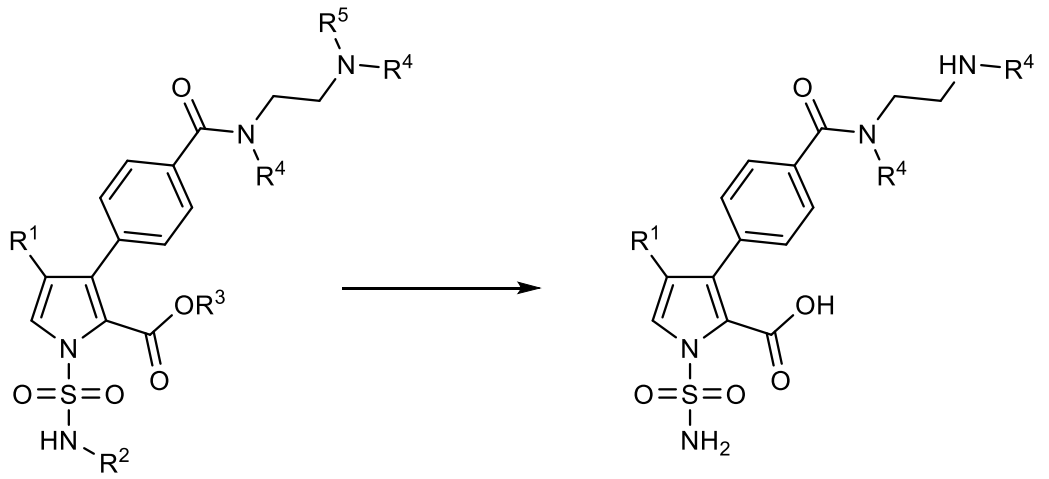


(XV) **(VIII)** **(VI)**

;

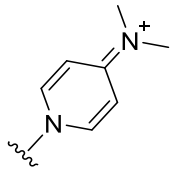
and

(ii) cleaving the R^2, R^3 and R^5 substituents from the compound of formula **(VI)** to form the compound of formula **(IV)** or a pharmaceutically acceptable salt thereof:



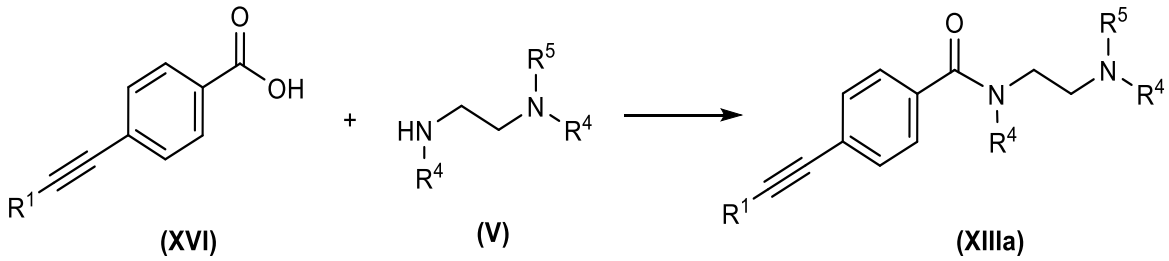
(VI) **(IV)** ,

wherein R^5 is a protecting group; and R^6 is independently selected from F, Cl, Br, I or



.

[0026] In ~~certain embodiments of~~ the third ~~aspect~~example, when R^7 is -N(R-4)$CH_2CH_2NR^4R^5$, the compound of formula **(XIIIa)** may be formed by reacting a compound of formula **(XVI)** with a compound of formula **(V)**:



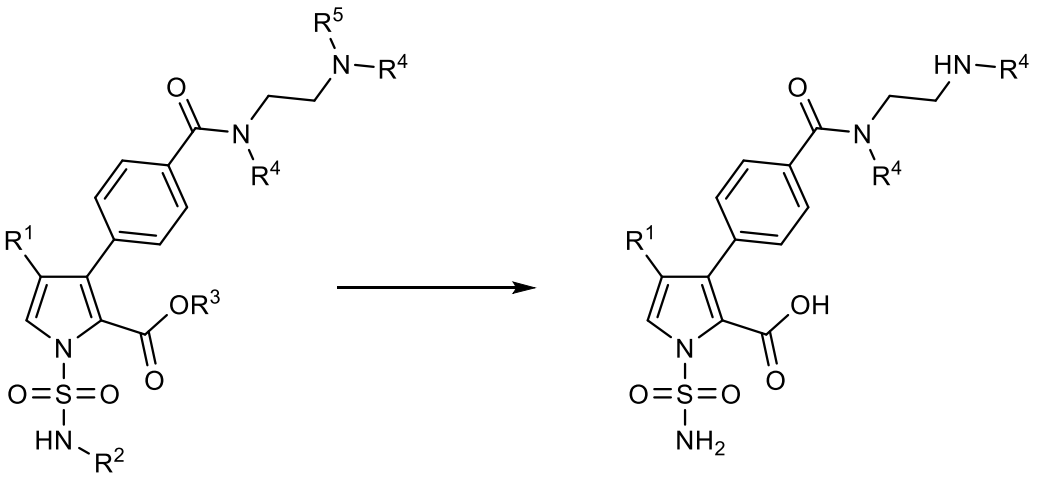
(XVI) **(V)** **(XIIIa)** ,

wherein R^5 is a protecting group.

[0027] In ~~certain embodiments of~~ the third ~~aspect~~example, when R^7 is -OR^{7a}, step (b) may comprise

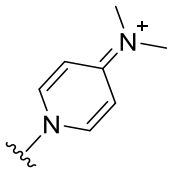
(i) cleaving the R^{7a} substituent from the compound of formula **(XVb)** to form a compound of formula **(XVII)**;

(iv) cleaving the R^2, R^3 and R^5 substituents from the compound of formula **(VI)** to form the compound of formula **(IV)** or a pharmaceutically acceptable salt thereof:



(VI) **(IV)** ,

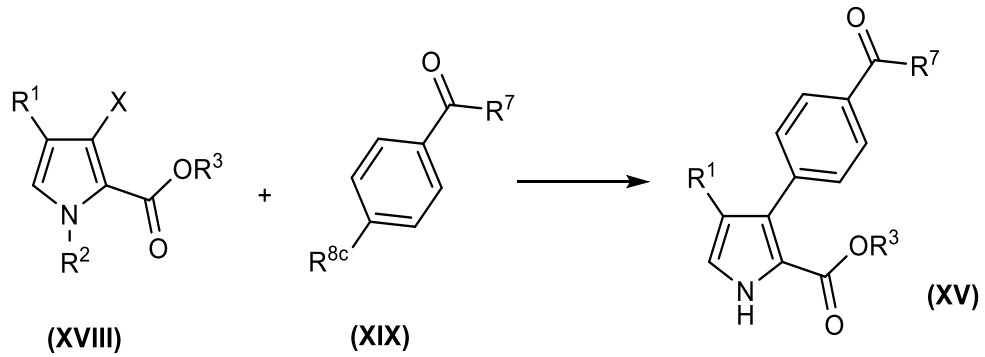
wherein R^5 is a protecting group; and R^6 is independently selected from F, Cl, Br, I or



.

[0028] In a fourth ~~aspect~~example of the present disclosure ~~invention~~ is provided a method of forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof, the method comprising:

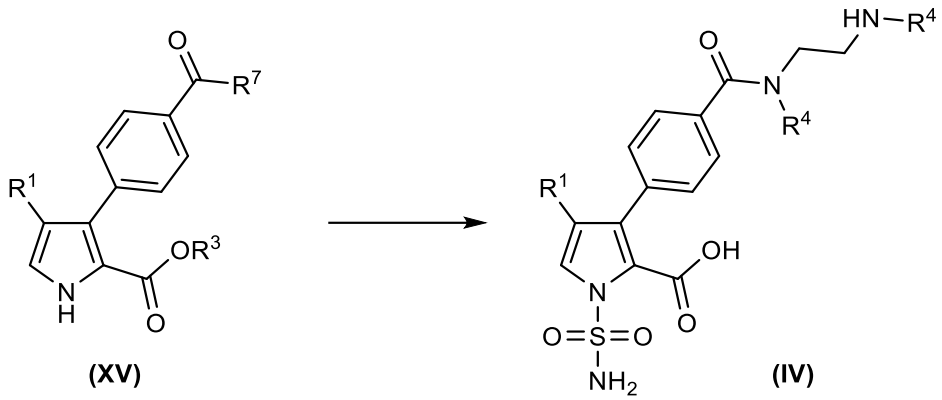
(a) reacting a compound of formula **(XVIII)** with a compound of formula **(XIX)** to form a compound of formula **(XV)**:



(XVIII) **(XIX)** **(XV)**

; and

(b) forming a compound of formula **(IV)** or a pharmaceutically acceptable salt thereof from the compound of formula (**XV):**



wherein

R^1 is independently selected from H or C_{1-4} alkyl;

R^2 is a protecting group;

R^3 is independently selected from -CH_2-aryl or *tert*-butyl;

each R^4 is independently at each occurrence a C_{1-6} alkyl;

R^7 is independently selected from -OR^{7a}, and -$N(R^4)CH_2CH_2NR^4R^5$;

R^{7a} is C_{1-6} alkyl or CH_2-aryl; and

R^{8c} is BF_3K or $B(OR^{9c})_2$; wherein either R^{9c} is at each occurrence H or C_{1-4} alkyl; or the two R^{9c} substituents together form $(CR^aR^b)_n$; or the two R^{9c} substituents together form -C(O)-(CR^aR^b)-$N(R^c)$-(CR^aR^b)-C(O)-.

[0029] In ~~certain embodiments of~~ the fourth ~~aspect~~example, step (b) may comprise converting the compound of formula **(XV)** to the compound of formula **(IV)** or pharmaceutically acceptable salt thereof according to any of the approaches described above for the third ~~aspect~~example.

[0030] R^1 may be H. R^1 may be C_{1-4} alkyl.

[0031] R^2 may be independently selected at each occurrence from: tert-butyloxycarbonyl group (Boc), benzyloxycarbonyl (Cbz), *tert*-butyl (^{t}Bu), *para*-methoxybenzyl (PMB) and phthalimide. R^2 may be independently selected from tert-butyloxycarbonyl group (Boc) or benzyloxycarbonyl (Cbz). R^2 may be tert-butyloxycarbonyl group (Boc). R^2 may be benzyloxycarbonyl (Cbz).

[0032] R^3 may be -CH_2-aryl, e.g. benzyl or para-methoxybenzyl. R^3 may be benzyl. R^3 may be *tert*-butyl.

[0033] R^4 may be independently selected at each occurrence from methyl, ethyl, n-propyl or iso-propyl. R^4 may be methyl. R^4 may be ethyl.

[0034] R^5 may be independently selected from: tert-butyloxycarbonyl group (Boc) or benzyloxycarbonyl (Cbz). R^5 may be tert-butyloxycarbonyl group (Boc). R^5 may be benzyloxycarbonyl (Cbz).

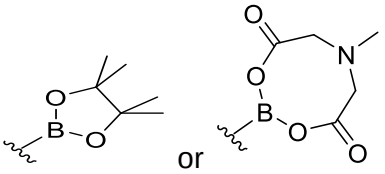
[0035] It may be that R^2 is Cbz, R^5 is Cbz and R^3 is benzyl. It may be that R^2 is Boc, R^5 is Boc and R^3 is tert-butyl.

[0036] R^2, R^3 and R^5 may be selected such that each of R^2, R^3 and R^5 are cleaved under the same conditions. For example, each of R^2, R^3 and R^5 may be cleaved via catalytic hydrogenation (e.g. where R^2, R^5 and R^3 are benzyl and Cbz groups). Alternatively, each of R^2, R^3 and R^5 may be cleaved using a Bronsted acid (e.g. where R^2, R^5 and R^3 are tert-butyl and Boc groups).

[0037] Alternatively, it may be that R^2, R^3 and R^5 are selected such that they are all cleaved under different conditions or such that any two of R^2, R^3 and R^5 are cleaved under different conditions to the remaining one of R^2, R^3 and R^5. Thus, it may be that R^2, R^3 and R^5 may be selected such that R^2 and R^5 are not cleaved under conditions which result in the cleavage of R^3.

[0038] R^7 may be $-OR^{7a}$ e.g. $-O-CH_3$, $-O-CH_2CH_3$, $-CH_2CH_2CH_3$, or $O-C(CH_3)_3$. R^7 may be $O-C(CH_3)_3$. R^7 may be O-benzyl. Alternatively, R^7 may be $N(R^4)CH_2CH_2NR^4R^5$, e.g. $N(R^4)CH_2CH_2NR^4Cbz$ or $N(R^4)CH_2CH_2NR^4Boc$.

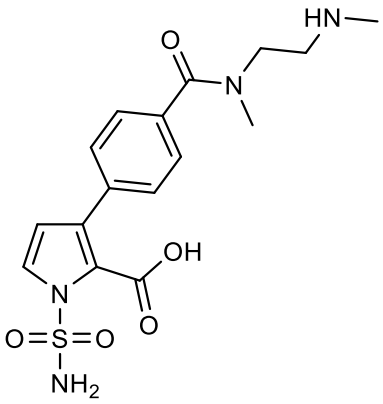
[0039] R^{8a}, R^{8b} or R^{8c} may each independently be selected from BF_3K, $-B(OH)_2$, $-B(OCH_3)_2$,



or

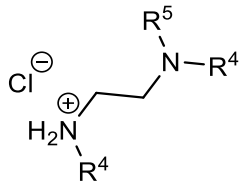
.

[0040] In ~~certain embodiments of~~ any of the first, second or third ~~aspect~~examples, the compound of formula **(IV)** is a compound of formula **(IVa):**



(**IVa)**.

[0041] In ~~certain embodiments of~~ any of the first, second or third ~~aspect~~examples, the compound of formula **(V)** is a compound of formula **(Va):**



(**Va**).

[0042] X may be independently selected from Cl, Br and I. X may be Cl. X may be Br.

[0043] It may be that R^{9a} at each occurrence H. Thus, R^{8a} may be $B(OH)_2$.

[0044] Reacting the compound of formula **(I)** with the compound of formula **(II)** may be conducted in the presence of an inorganic base, e.g. $NaHCO_3$. Reacting the compound of formula **(I)** with the compound of formula **(II)** may be conducted in a mixture of water and a C_1-C_4-alcohol, e.g. methanol. Reacting the compound of formula **(I)** with the compound of formula **(II)** may be conducted in a mixture of water and an aromatic hydrocarbon, e.g. toluene.

[0045] Reacting the compound of formula **(III)** with the compound of formula **(V)** may be conducted by first converting the compound of formula **(III)** to an acid chloride and subsequently reacting the acid chloride with the amine **(V)**. Conversion of formula **(III)** to an acid chloride may be achieved using oxalyl chloride, e.g. in the presence of DMAP or DMF. Alternatively, it may be achieved using thionyl chloride, e.g. in the presence of DMAP or DMF. Reaction of the acid chloride with the amine **(V)** may be conducted in the presence of a base, e.g. an inorganic base, e.g. $NaHCO_3$.

[0046] Reacting the compound of formula **(III)** with the compound of formula **(V)** may be achieved using a suitable amide coupling reagent, e.g. propanephosphonic acid anhydride. The reaction may be conducted in the presence of a suitable organic base, e.g. triethylamine. The reaction may be conducted in acetonitrile.

[0047] Converting the compound of formula **(VI)** to the compound of formula **(IV)** may be achieved using a palladium catalysed hydrogenation, e.g. using H_2 and Pd/C. The reaction may be conducted in the presence of NH_3 and methanol. The reaction may be conducted in 1,4-dioxane. The reaction may be conducted in a polyfluorinated C_1-C_4-alcohol, e.g. 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol.

[0048] Reacting a compound of formula **(VII)** with a compound of formula **(VIII)** is typically conducted in the presence of a base, e.g. NaH. The reaction may be performed in THF.

[0049] A may be Na.