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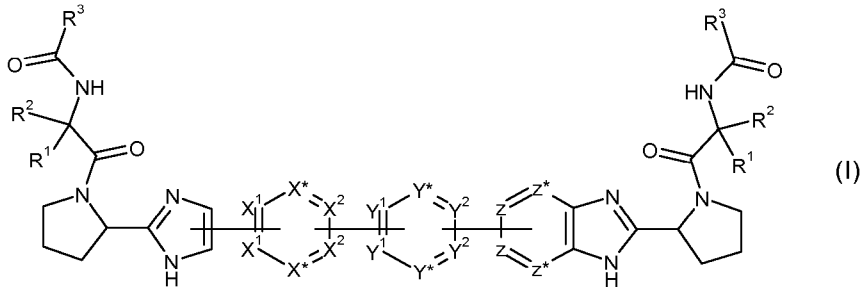

(I)

(57) Abstract: The present invention relates to compounds of the formula (I) and pharmaceutically acceptable salts thereof; to compositions containing such compounds; and to the of such compounds as inhibitors of HCV replication.

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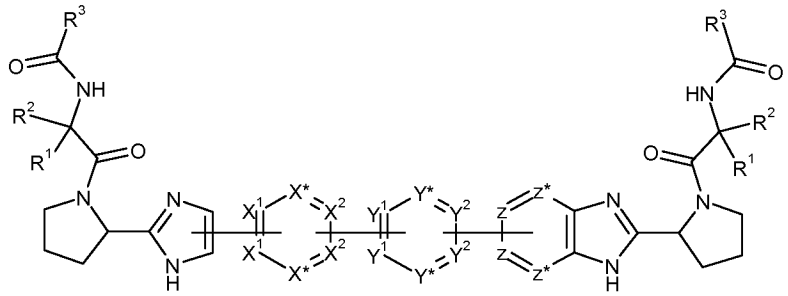
HEPATITIS C VIRUS INHIBITORS

The present invention is directed to certain compounds and pharmaceutically acceptable salts thereof, and their use as inhibitors of the replication of hepatitis C virus (HCV). The compounds of the present invention are useful for directly or indirectly inhibiting the activity of one or more HCV proteins and for treating diseases or conditions mediated by HCV such as, for example, hepatitis C. Whilst not wishing to be bound by any specific theory, it is believed that the compounds of the present invention inhibit HCV replication by direct or indirect inhibition of the non-structural 5A (NS5A) protein. For a discussion of the NS5A protein as a target for HCV therapy and a review of the patent literature on inhibitors of NS5A, see Schmitz and Tan, Recent Patents on Anti-Infective Drug Discovery, 3, 77-92 (2008).

Despite the large amount of research already performed in this area, there remains a need for inhibitors of HCV replication to treat hepatitis C. In particular, there is a need for HCV inhibitors which show activity against multiple HCV genotypes. Balanced activity against both genotype 1a and 1b is particularly desirable. Furthermore, there is a need for HCV inhibitors which retain activity against viral strains which, as a result of mutation, have developed resistance to known HCV inhibitors. A broad range of mutants have been described that result in reduced susceptibility to HCV inhibitors. With regard to compounds believed to act on the NS5A protein, mutations at Y93 and L31 in particular have been found to give rise to resistance. Resistance mutations associated with HCV inhibitor therapy (other than by NS3 protease or polymerase inhibition) are reviewed in more detail in Holler et al. Expert Opin. Drug Discov. 4(3), 293-314 (2009). Furthermore, preferred compounds should exhibit potent inhibition of the NS5A protein, whilst showing little affinity for other receptors, and show functional activity as inhibitors of HCV replication. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects. In particular, good cardiovascular, liver and cell based safety profiles are important features of preferred compounds. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

In a first aspect, the present invention provides compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

at each occurrence X* independently represents CR or N, at each occurrence X^1 independently represents C (in which case it is bonded to the imidazole ring), CR or N, and at each occurrence X^2 independently represents C (in which case it is bonded to the Y^1 containing ring), CR or N, provided that the total number of

N atoms in the 6-membered ring may not exceed 2 and provided that the total number of R substituents, other than H, on the 6-membered ring may not exceed 2;

at each occurrence Y* independently represents CR or N, at each occurrence Y^1 independently represents C (in which case it is bonded to the X^2 containing ring), CR or N, and at each occurrence Y^2 independently represents C (in which case it is bonded to the 9-membered bicyclic ring), CR or N, provided that the total number of N atoms in the 6-membered ring may not exceed 2 and provided that the total number of R substituents, other than H, on the 6-membered ring may not exceed 2;

at each occurrence Z* independently represents CH or N, and at each occurrence Z independently represents C (in which case it is bonded to the 6-membered Y^2 containing ring), CH or N, provided that the total number of N atoms in this 9-membered bicyclic ring does not exceed 3;

at each occurrence R independently represents H, OH, C_{1-4} alkoxy, CN, NH_2 or C_{1-4} alkylsulfonyl;

each R^1 is independently selected from H, C_{1-4} alkyl, halogen, C_{1-4} alkoxyalkyl, C_{3-6} cycloalkyl, phenyl, a 5- or 6-membered monocyclic heteroaryl, and a 4-, 5- or 6-membered monocyclic saturated heterocyclyl;

said phenyl being optionally substituted with up to 2 halogen atoms;

said C_{1-4} alkyl being optionally substituted with a group selected from OH, C_{1-4} alkoxy, C_{1-4} alkoxybenzyl, C_{3-6} cycloalkyl, C_{1-4} alkylsulfonyl, $-NR^aR^b$, $-CONR^aR^b$, phenyl, pyridinyl and indolyl;

said R^a and R^b being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl;

each R^2 is independently selected from H, C_{1-4} alkyl, halogen, and C_{1-4} alkoxyalkyl;

said C_{1-4} alkyl being optionally substituted by OH or NR^cR^d;

said R^c and R^d being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl; or

R^1 and R^2, together with the C atom to which they are attached, form a 4-, 5- or 6-membered saturated ring optionally containing 1 or 2 heteroatoms selected from O, S and NR^e;

said R^e being selected from H, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl and C_{1-4} alkylsulfonyl;

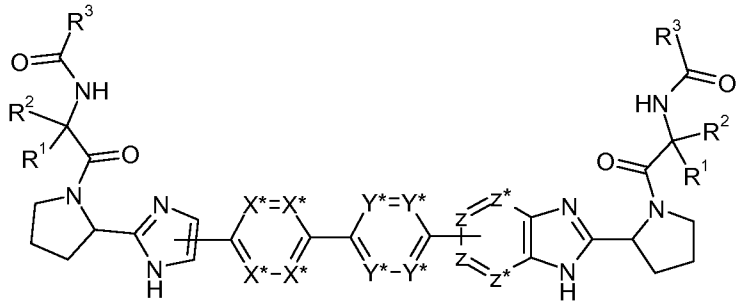
each R^3 is independently selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxyalkyl, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ and Ar;

said C_{1-4} alkyl being optionally substituted with Ar or NR^fR^g;

said R^f and R^g being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl; and

each Ar being independently selected from isoxazolyl, pyrazinyl, dihydrobenzimidazolyl, indazolyl, and tetrahydroquinolinyl, optionally substituted with C_{1-4} alkyl or a carbonyl group.

In a further embodiment of the first aspect, the present invention provides a compound of formula (Ia)

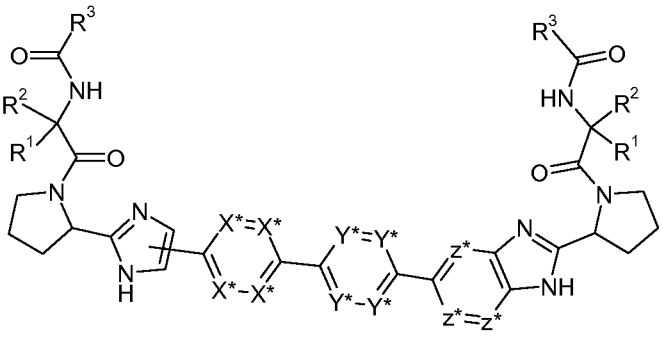


(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

X*, Y*, Z, Z*, R^1, R^2 and R^3 are as defined above.

In a further embodiment of the first aspect, the present invention provides a compound of formula (Ib)

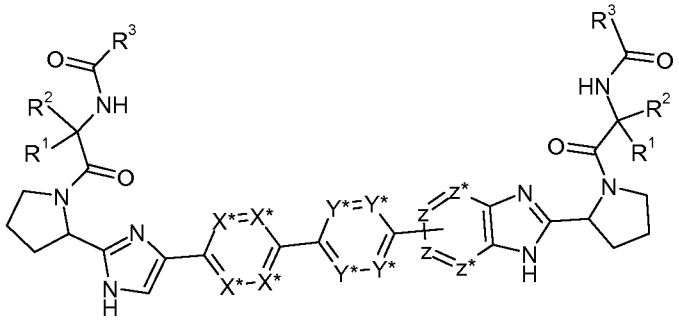


(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

X*, Y*, Z*, R^1, R^2 and R^3 are as defined above.

In a further embodiment of the first aspect, the present invention provides a compound of formula (Ic)

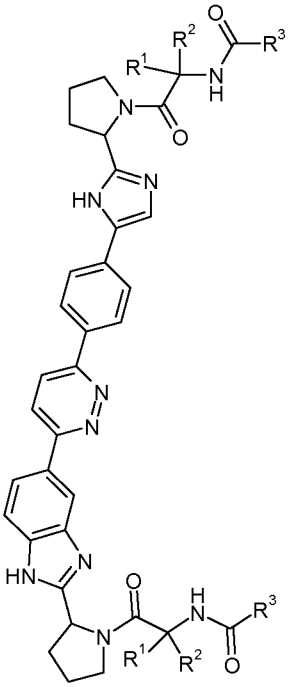


(Ic)

or a pharmaceutically acceptable salt thereof, wherein:

X*, Y*, Z, Z*, R^1, R^2 and R^3 are as defined above.

In a further embodiment of the first aspect, the present invention provides a compound of formula (I) selected from: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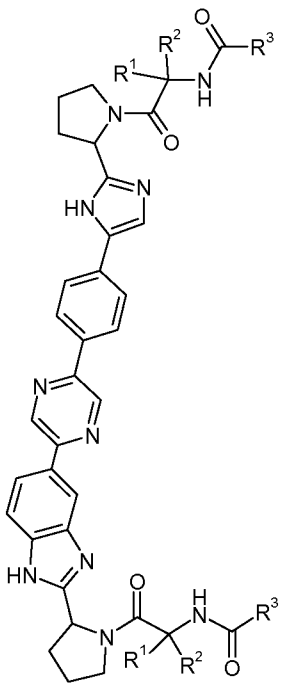
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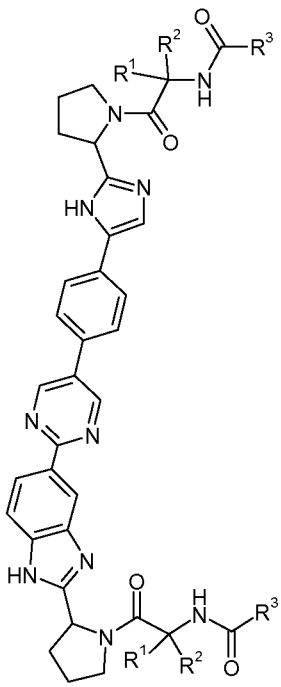
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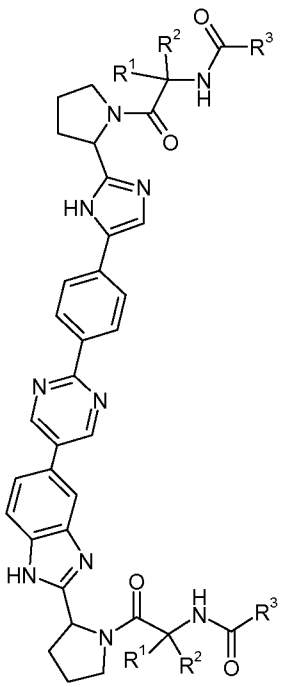
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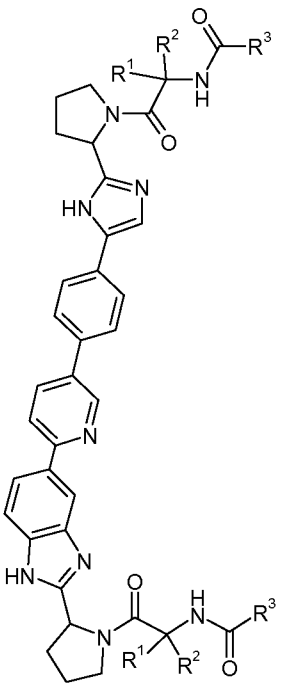
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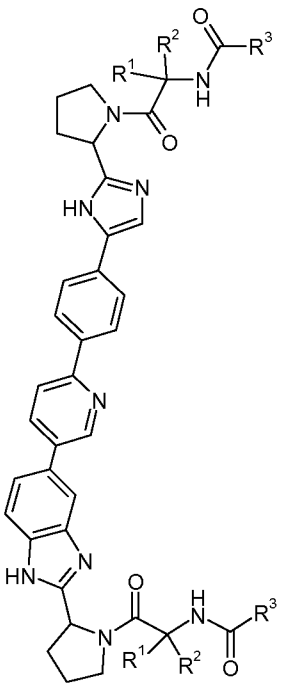
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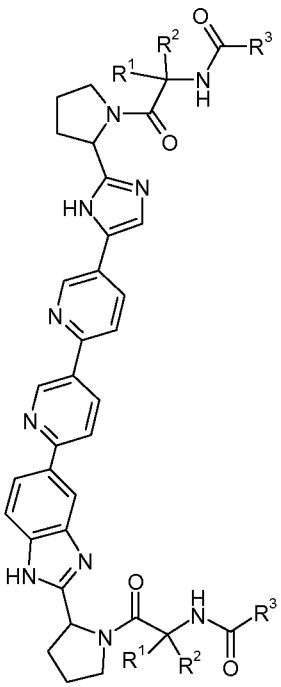
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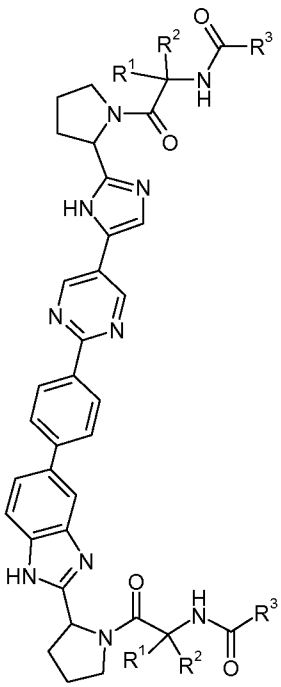
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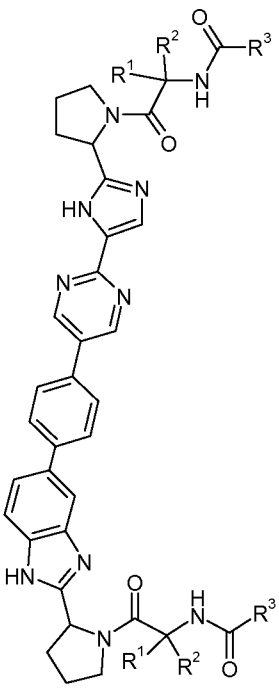
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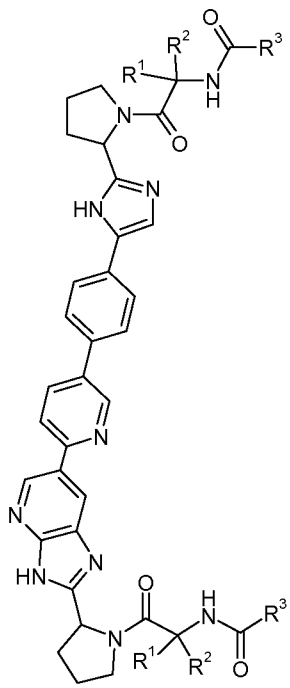
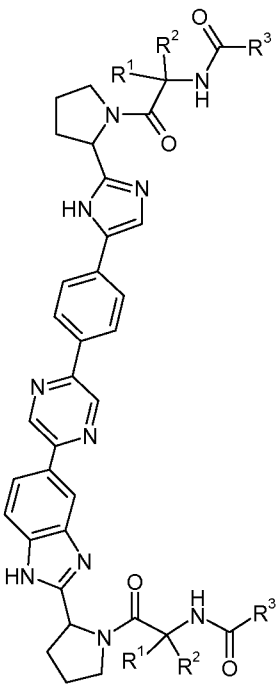

, or a pharmaceutically a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3 are as defined above.

In a preferred embodiment, the present invention provides a compound of formula (I) selected from: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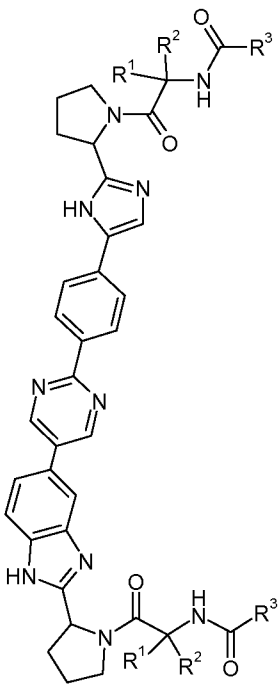

, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3 are as defined above. More particularly preferred is the embodiment wherein:

R^1 is H;

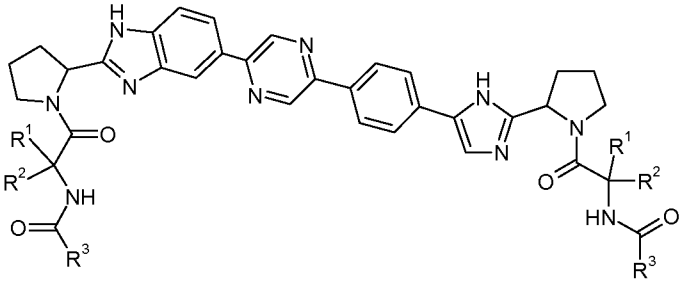
each R^2 is independently selected from H, C_{1-4} alkyl, halogen, and C_{1-4} alkoxyalkyl;

said C_{1-4} alkyl being optionally substituted by NR^cR^d;

said R^c and R^d being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl; and

each R^3 is independently C_{1-4} alkoxy.

In a further preferred embodiment, the present invention provides a compound of formula (I) selected from:



, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3 are as defined above. More particularly preferred is the embodiment wherein:

R^1 is H;

each R^2 is independently selected from H, C_{1-4} alkyl, halogen, and C_{1-4} alkoxyalkyl;

said C_{1-4} alkyl being optionally substituted by NR^cR^d;

said R^c and R^d being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl; and

each R^3 is independently C_{1-4} alkoxy.

Hereinafter, all references to a compound of formula (I) include compounds of formulae (I), (Ia), and (Ib) as described above.

In further embodiments of the first aspect, the present invention provides:

(i) at each occurrence X* independently represents CH or N, at each occurrence X^1 independently represents C (in which case it is bonded to the imidazole ring), CH or N, and at each occurrence X^2 independently represents C (in which case it is bonded to the Y^1 containing ring), CH or N, provided that the total number of N atoms in the 6-membered ring may not exceed 2;

(ii) at each occurrence Y* independently represents CH or N, at each occurrence Y^1 independently represents C (in which case it is bonded to the X^2 containing ring), CH or N, and at each occurrence Y^2 independently represents C (in which case it is bonded to the 9-membered bicyclic ring), CH or N, provided that the total number of N atoms in the 6-membered ring may not exceed 2;

(iii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) or (ii) above wherein Z* represents CH;

(iv) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (iii) above wherein each R^1 is independently selected from H, or C_{1-4} alkyl;

(v) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (iv) above wherein each R^1 is H;

(vi) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (iv) above wherein each R^1 is the same;

(vii) a compound of formula(I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (iv) above wherein each R^1 is different.

(viii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (viii) wherein at least one R^1 is C_{1-4} alkyl;

(ix) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (viii) wherein at least one R^1 is substituted C_{1-4} alkyl;

(x) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (ix) wherein at least one R^1 is C_{1-4} alkyl substituted by C_{1-4} alkyloxy;

(xi) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (ix) wherein at least one R^1 is C_{1-4} alkyl substituted by OH;

(xii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xi) above wherein each R^2 is independently selected from H, or C_{1-4} alkyl;

(xiii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xi) above wherein each R^2 is independently selected from C_{1-4} alkyl and C_{1-4} alkoxyalkyl;

(xiv) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xiii) above wherein each R^2 is independently C_{1-4} alkyl;

(xv) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xiv) above wherein each R^2 is the same;

(xvi) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xiv) above wherein each R^2 is different;

(xvii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xvi) above wherein at least one R^2 is C_{1-4} alkyl;

(xviii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (xvii) wherein at least one R^2 is isopropyl;

(xix) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) to (xvii) above wherein at least one R^2 is substituted C_{1-4} alkyl;

(xx) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (xix) above wherein R^2 is C_{1-4} alkyl substituted by C_{1-4} alkyloxy;

(xxi) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (xx) above wherein at least one R^2 is 1-methoxyethyl;

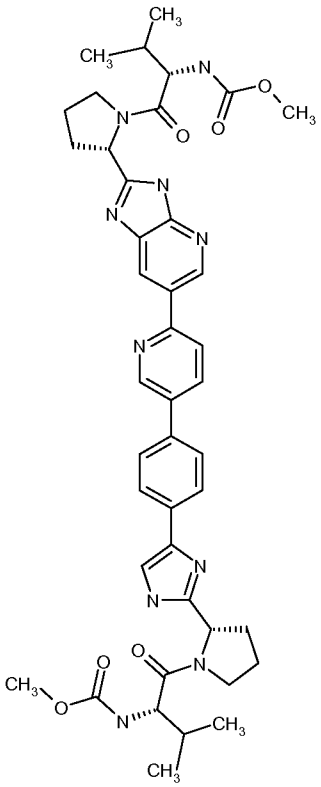
(xxii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (xix) above wherein R^2 is C_{1-4} alkyl substituted by OH;

(xxiii) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiments (i) or (xxii) above wherein each R^3 is independently C_{1-4} alkoxy;

(xxiv) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or in embodiment (xxiii) above, wherein each R^3 is methoxy.

For all of the formulae and embodiments depicted above, it is preferred that when R^1 is H, R^2 is isopropyl, and R^3 is methoxy.

In a further embodiment of the first aspect, the present invention provides a compound of formula (I) selected from: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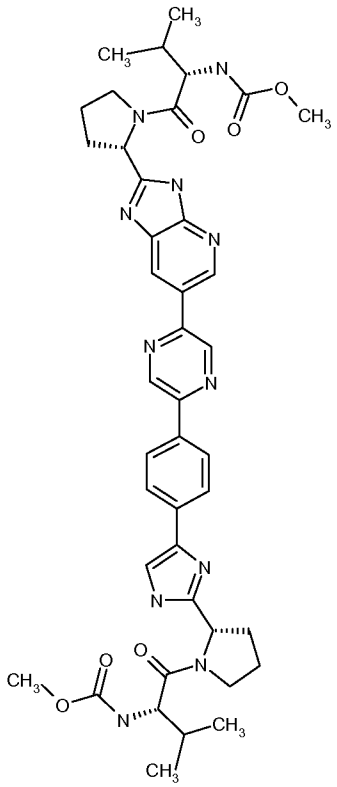
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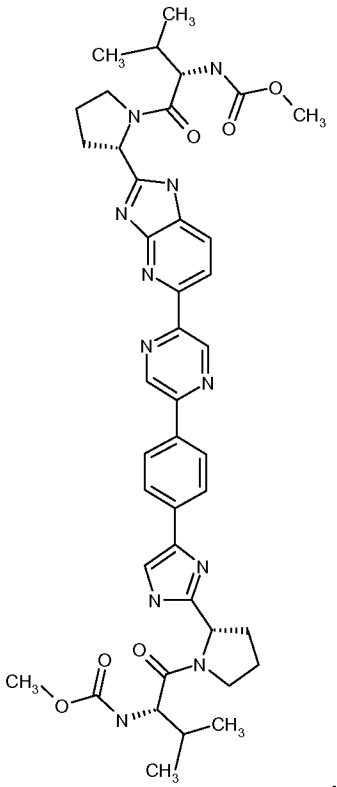
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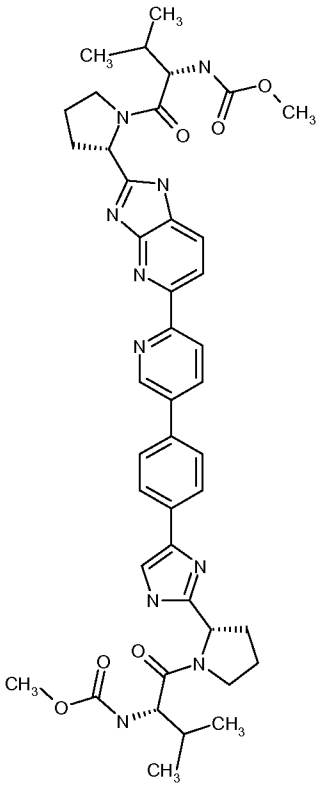
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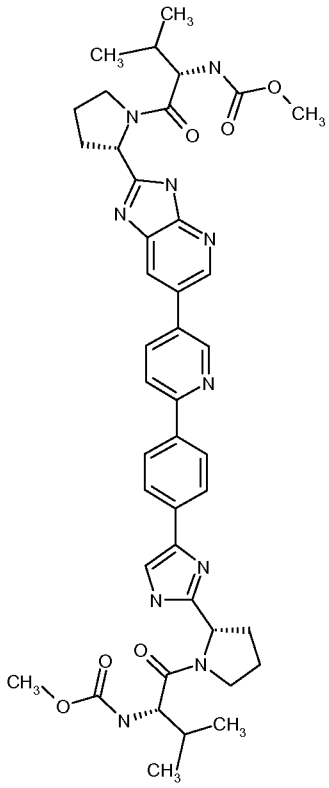
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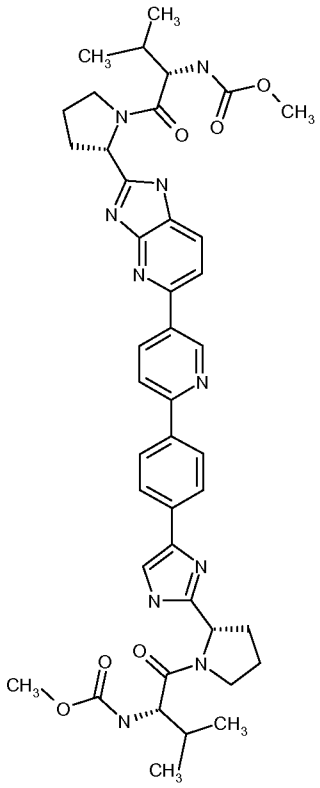
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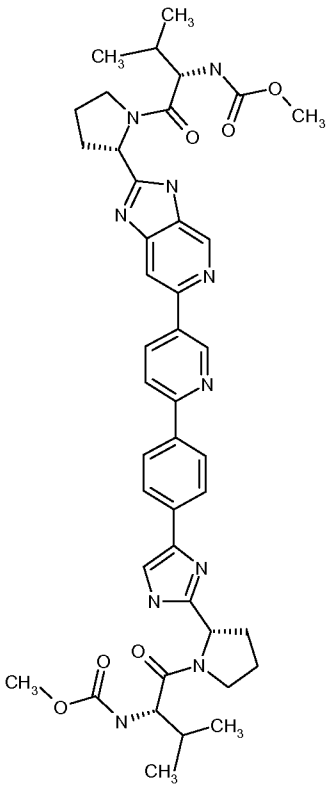
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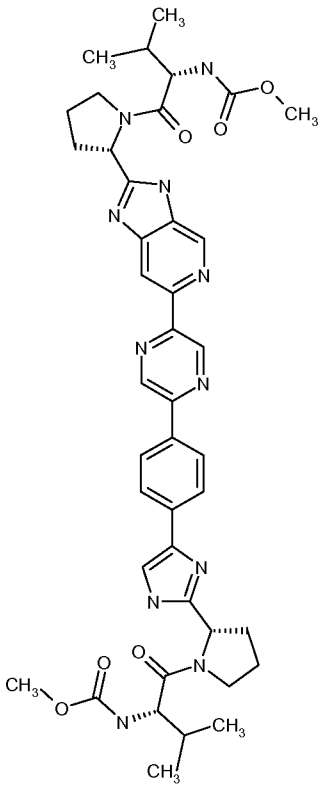
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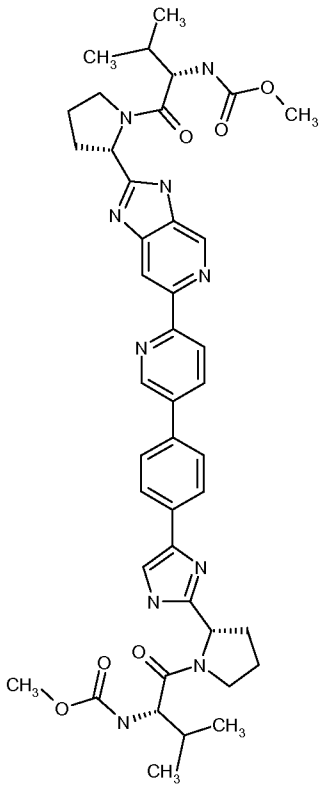
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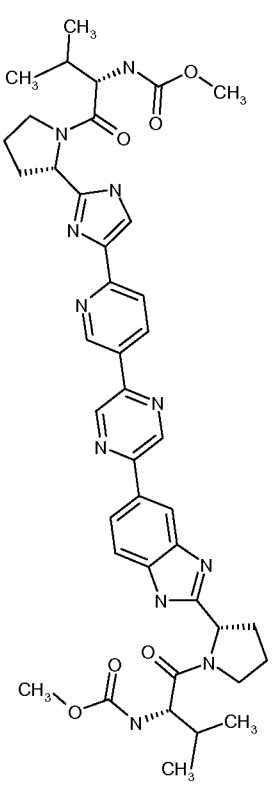
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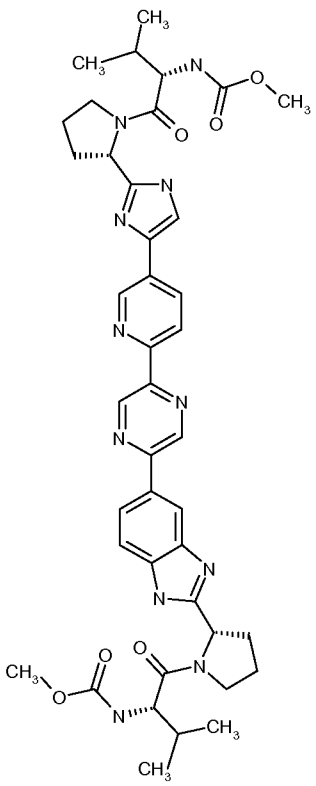
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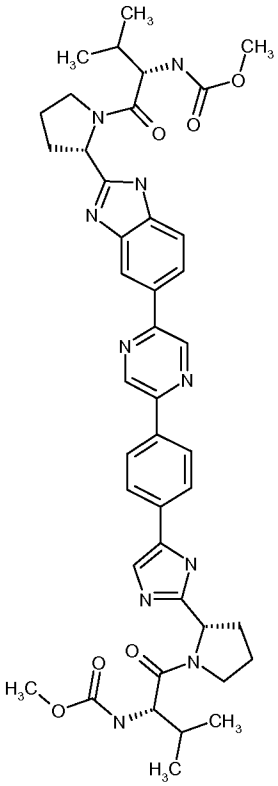
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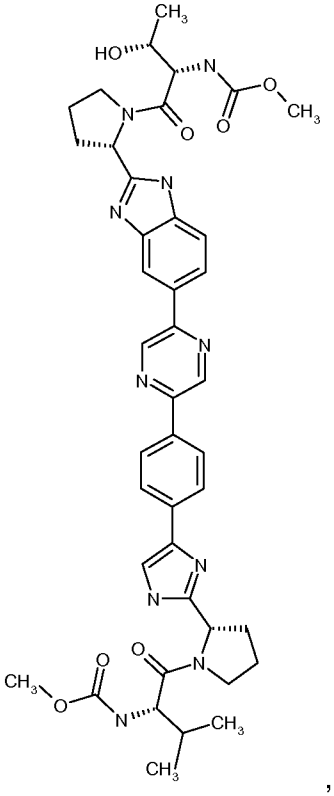
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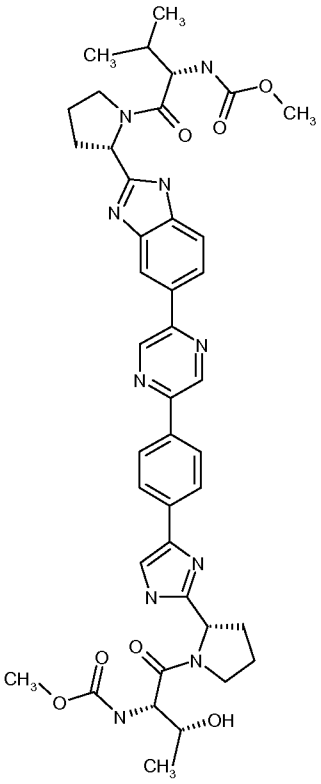
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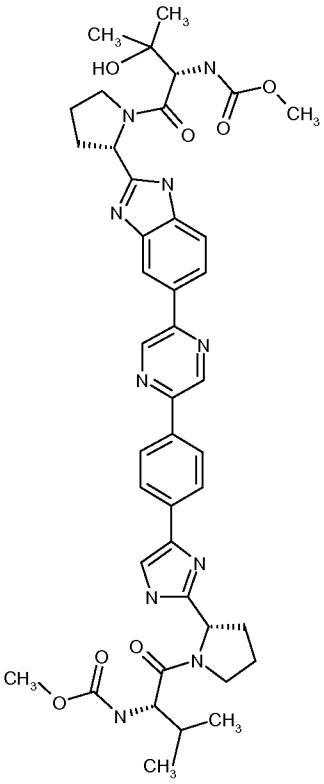
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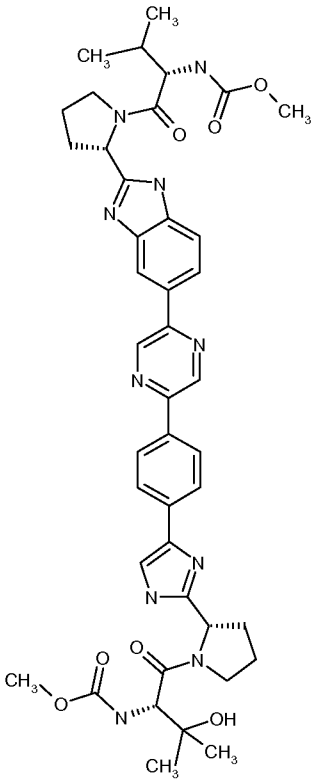
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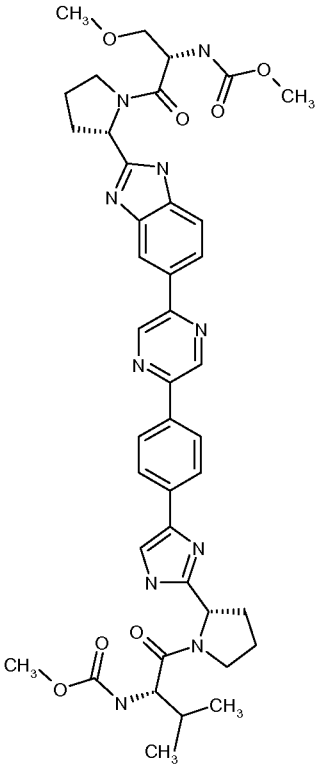
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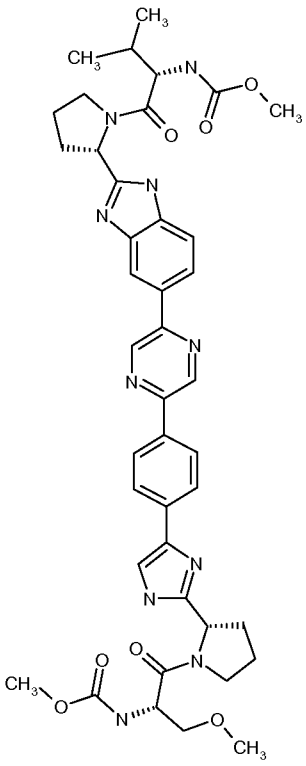
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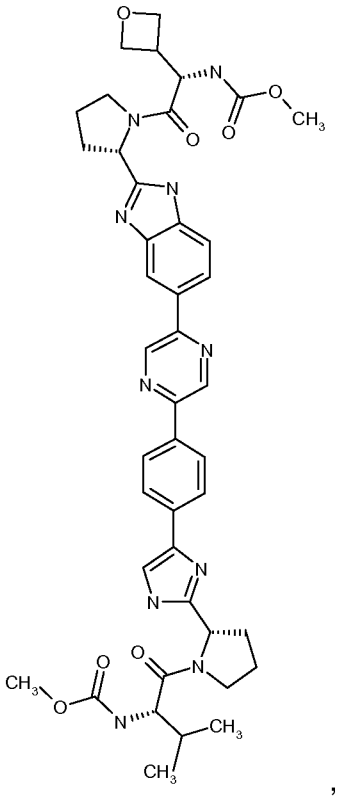
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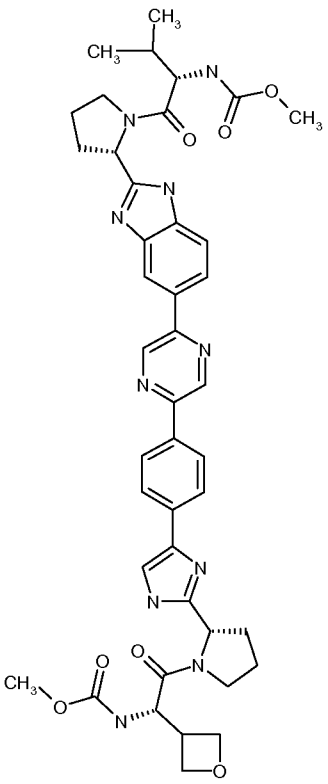
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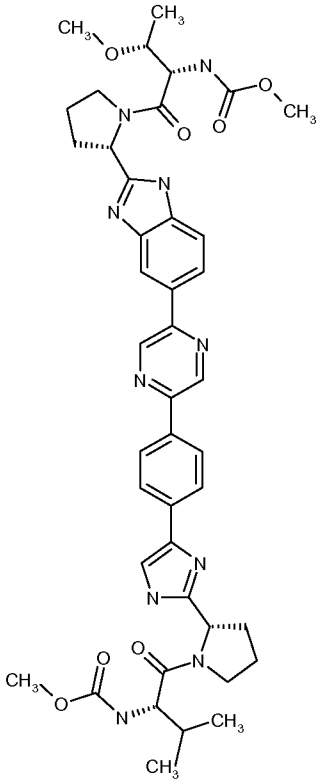
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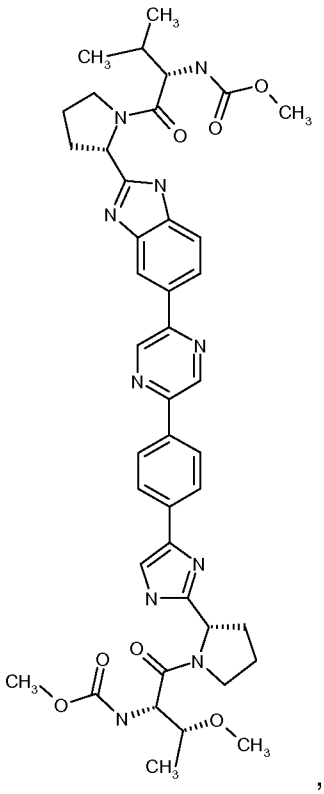
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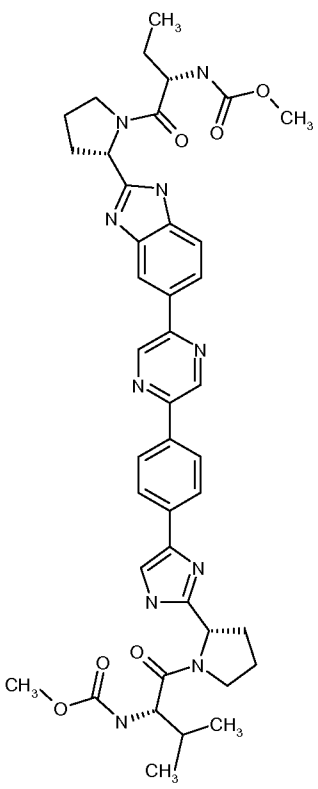
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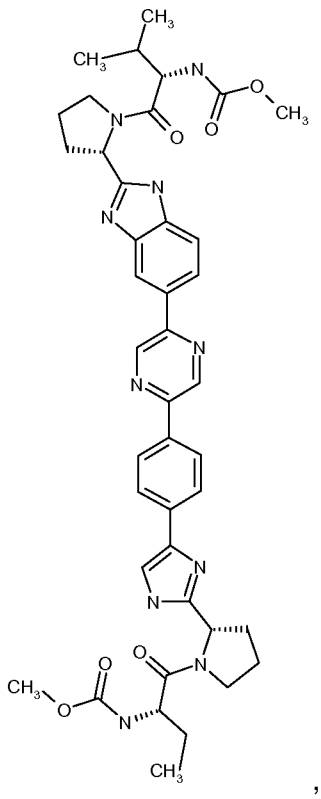

, or a pharmaceutically acceptable salt thereof.

In a further embodiment of the first aspect, the present invention provides the following compounds:

methyl {(2*S*)-1-[(2*S*)-2-{5-[6-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridazin-3-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[6-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-3-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-2,3'-bipyridin-6'-yl)-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl [(2*S*)-1-(2-{6-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyridin-2-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamate;

methyl (2*S*,3*R*)-3-methoxy-2-{[(2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidin-1-yl]carbonyl}butanoate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*,3*R*)-3-hydroxy-2-[(methoxycarbonyl)amino]butanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*,3*R*)-3-hydroxy-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-3-methoxy-2-[(methoxycarbonyl)amino]propanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-3-methoxy-1-[(2*S*)-2-(5-{4-[5-(2-{(2*S*)-1-[N-(methoxycarbonyl)-*O*-methyl-L-seryl] pyrrolidin-2-yl}-1*H*-benzimidazol-6-yl)pyrazin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-1-oxopropan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]propanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{[(methoxycarbonyl)amino]acetyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl} pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]propanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

or pharmaceutically acceptable salts thereof.

Particularly preferred embodiments of the present invention are:

methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl (2*S*,3*R*)-3-methoxy-2-{[(2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidin-1-yl]carbonyl}butanoate;

or pharmaceutically acceptable salts thereof.

'C_{1-4} alkyl' means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms. 'C_{1-2} alkyl' and 'C_{1-3} alkyl' have analogous meanings.

'C_{3-6}cycloalkyl' means an unsubstituted saturated monocyclic hydrocarbon radical having from 3 to 6 carbon atoms.

'C_{1-4} alkoxy' means -O-C_{1-4} alkyl (C_{1-4} alkyl being as defined above).

'C_{1-4} alkylsulfonyl' means -(SO_2)-C_{1-4} alkyl (C_{1-4} alkyl being as defined above).

'C_{1-4} alkoxyalkyl' means C_{1-3} alkyl-O-C_{1-3} alkyl (C_{1-3} alkyl being as defined above), provided that the total number of C atoms does not exceed 4.

'C_{1-4} alkylcarbonyl' means -(C=O)-C_{1-3} alkyl (C_{1-3} alkyl being as defined above).

'C_{1-4} alkoxycarbonyl' means -(C=O)-O-C_{1-3} alkyl (C_{1-3} alkyl being as defined above).

'C_{1-4} alkoxybenzyl' means $PhCH_2O$-C_{1-4} alkyl.

'Halogen' means a fluorine, chlorine, bromine or iodine atom.

'5- or 6-membered monocyclic heteroaryl' means a monocyclic aromatic group with a total of 5 atoms in the ring wherein from 1 to 4 of those atoms are each independently selected from N, O and S; or a monocyclic aromatic group with a total of 6 atoms in the ring wherein from 1 to 3 of those atoms are N. Preferred 5-membered monocyclic heteroaromatic groups have from 1 to 3 atoms in the ring which are each independently selected from N, O and S. 5-membered monocyclic heteroaromatic groups include pyrrolyl (also called azolyl), furanyl, thienyl (also called thiophenyl), pyrazolyl (also called 1H-pyrazolyl and 1,2-diazolyl), imidazolyl, oxazolyl (also called 1,3-oxazolyl), isoxazolyl (also called 1,2-oxazolyl), thiazolyl (also called 1,3-thiazolyl), isothiazolyl (also called 1,2-thiazolyl), triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl and thiatriazolyl. 6-membered monocyclic heteroaromatic groups include pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl.

'4-, 5- or 6-membered monocyclic saturated heterocyclyl' means a saturated monocyclic group with a total of 4 atoms in the ring wherein from 1 to 2 of those atoms are each independently selected from N, O and S, a saturated monocyclic group with a total of 5 atoms in the ring wherein from 1 to 2 of those atoms are each independently selected from N, O and S, or a saturated monocyclic group with a total of 6 atoms in the ring wherein from 1 to 2 of those atoms are each independently selected from N, O and S. 5-membered saturated heterocyclyl groups include tetrahydrofuranyl, pyrrolidinyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, dioxolanyl, thiazolidinyl, and isoxazolidinyl. 6-membered saturated heterocyclyl groups include tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, dioxanyl, thiomorpholinyl, and thioxanyl.

'Pharmaceutically acceptable salts' of the compounds of formula (I) include the acid addition and base salts thereof.

Suitable acid addition salts may be formed from acids which form non-toxic salts. Examples may include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts may be formed from bases which form non-toxic salts. Examples may include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of the compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may exist in both unsolvated and solvated forms and the definition of said compounds is intended to encompass solvates thereof. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see "Polymorphism in Pharmaceutical Solids" by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically

grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^-N^+(CH_3)_3$) polar head group. For more information, see "Crystals and the Polarizing Microscope" by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Hereinafter all references to a compound of formula (I) include references to salts, solvates, polymorphs, crystal habits, multi-component complexes and liquid crystals thereof.

Compounds of formula (I) contain at least two asymmetric carbon atoms (on the pyrrolidine rings) and can therefore exist as two or more stereoisomers. Compounds of formula (I) also contain aromatic moieties, such as the imidazole rings, wherein tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism (for example in the imidazole rings) as well as valence tautomerism (for example in the other aromatic moieties). It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the claimed compounds of the present invention are all stereoisomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counter ion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on a resin with an asymmetric stationary phase and with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluant affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art. See, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

Due to their structure, compounds of the present invention may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about a single bond may permit separation of different conformers. Certain conformers which are preferred for biological activity may also be selected for through intramolecular hydrogen bonding. Included within the scope of the claimed compounds of the present invention are all conformers of the compounds of formula (I), including compounds exhibiting more than one type of conformation, and mixtures of one or more thereof.

The compounds of the invention also includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H; carbon, such as ^{11}C, ^{13}C and ^{14}C; chlorine, such as ^{36}Cl; fluorine, such as ^{18}F; iodine, such as ^{123}I and ^{125}I; nitrogen, such as ^{13}N and ^{15}N; oxygen, such as ^{15}O, ^{17}O and ^{18}O; and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

In one embodiment, the compounds of formula (I) are comprised of atoms such that the average atomic mass or mass number for each atom of each element present corresponds to the average atomic mass or mass number for that element as it occurs in nature. In other words, such compounds are not isotopically enriched at any atomic position.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, and d_6-DMSO.

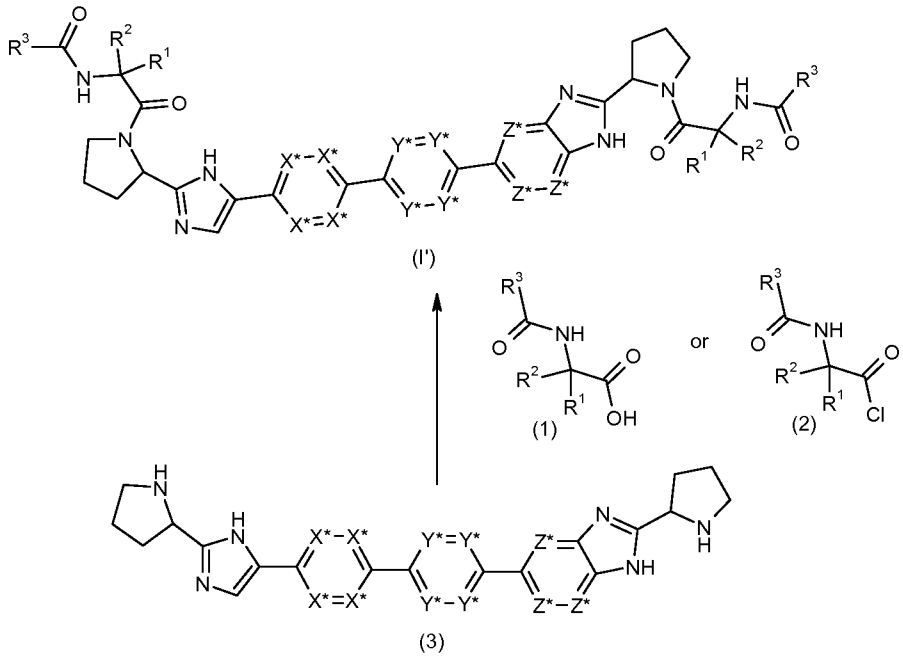
The routes below, including those mentioned in the Examples and Preparations, illustrate methods of synthesising the compounds of formula (I) and certain derivatives thereof. The skilled person will appreciate that the compounds of formula (I) or derivatives thereof, and intermediates thereto, as herein defined by the

invention, could be made by methods other than those specifically described herein, for example by adaptation of the methods described herein, for example by methods known in the art. Suitable guides to synthesis, functional group interconversions, use of protecting groups, etc., are for example: "Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989); Advanced Organic Chemistry" by J. March, Wiley Interscience (1985); "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978); "Organic Synthesis – The Disconnection Approach" by S Warren, Wiley Interscience (1982); "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982); "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons, Inc. (1999); and "Protecting Groups" by PJ, Kocienski, Georg Thieme Verlag (1994); and any updated versions of said standard works.

The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I) or derivatives as herein defined, in addition to any novel intermediates used therein.

In the following schemes, which depict general methods for obtaining compounds of general formula (I), the substituents are as previously defined for a compound of formula (I') or derivatives thereof, unless otherwise stated:

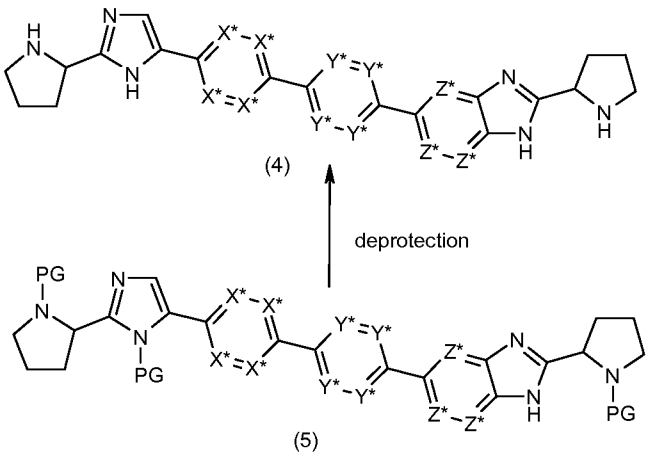
Scheme 1



Amide coupling is carried out using standard literature conditions. The acid (1) can be converted to the acid chloride (2) using a suitable chlorinating agent, such as oxalyl chloride or thionyl chloride, in a suitable solvent, such as dichloromethane or toluene, optionally in the presence of catalytic DMF, at a suitable temperature, typically of between 0 °C and room temperature. The acid chloride (2) can then be reacted with the amine of generic formula (3) in the presence of a base, such as triethylamine or diisopropylethylamine, in a suitable solvent, such as dichloromethane or toluene, at a temperature of between 0 °C and room temperature. Alternatively, the acid (1) can be converted to a suitable activated species with a coupling agent, such as EDCI.HCl, EDCI.MeI, HBTU, HATU, PyBop, DCC, or CDI, in a suitable solvent, such

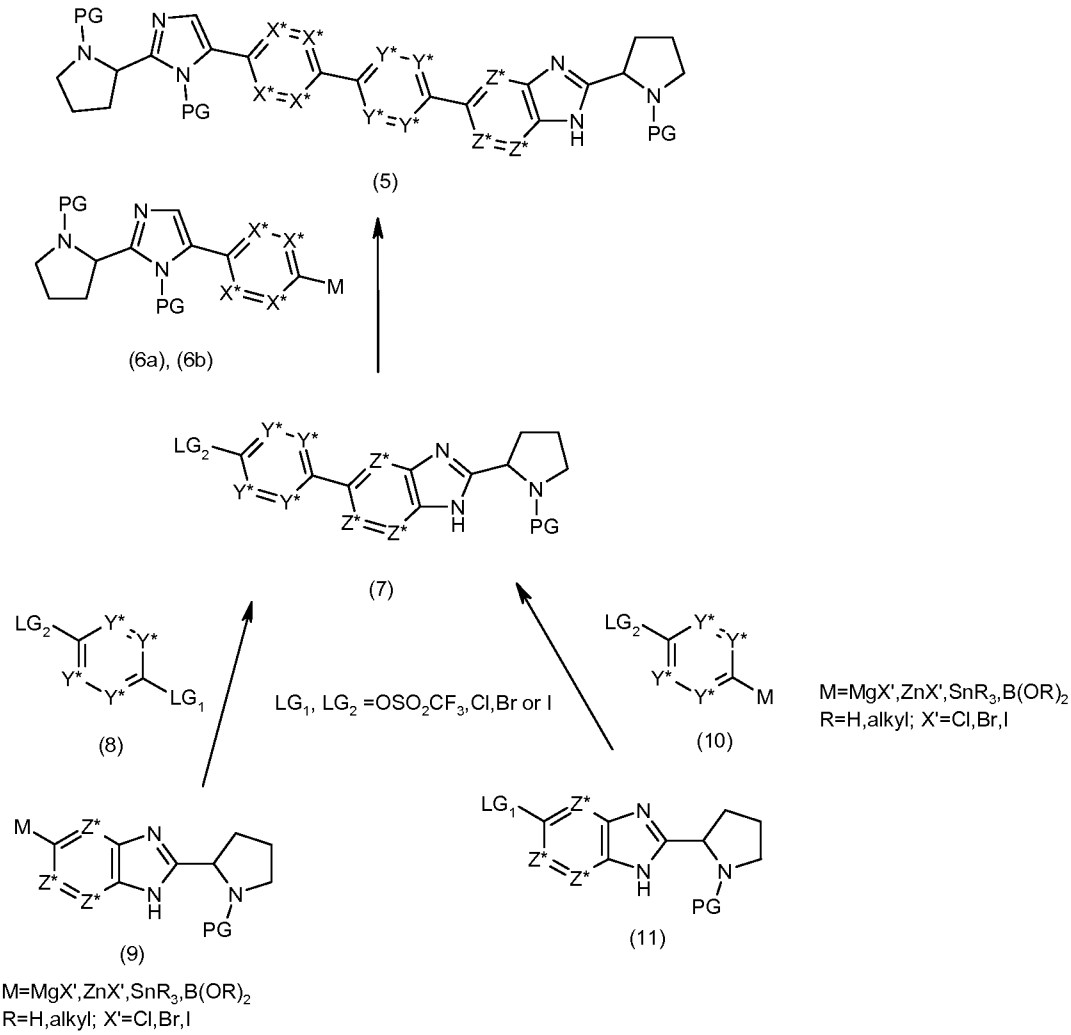
as dichloromethane, acetonitrile or DMF. In the presence of EDCI.HCl or EDCI.MeI, HOBT is optionally added. A suitable base, such as triethylamine or diisopropylethylamine, is also used and the reaction is typically carried out at room temperature.

Scheme 2



Amine (4) may be formed from protected amine (5), wherein one or more of the N moieties are protected by a suitable protecting group (PG). Note that, depending on the chemistry used to produce amine (5), protection of the imidazole N moiety may not be necessary. Suitable protecting groups for the pyrrolidine N moiety include, for example, t-butyloxycarbonyl (t-BOC). Suitable protecting groups for the imidazole N moiety include, for example, (trimethylsilyl)ethoxymethyl (SEM). Deprotection is carried out using known literature methods such as reaction with an acid (*e.g.* hydrochloric acid or trifluoracetic acid), in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux.

Scheme 3



Protected amine (5) may be formed by a palladium catalysed coupling between a metallated imidazole (6a) or (6b) (in which case without imidazole protecting groups i.e. PG=H on imidazole) and derivative (7).

Preferably, the reaction is carried out between the boronate ester (6b) ($M=B(OR)_2$) and a halide derivative (7) (LG_2= OSO_2CF_3, Cl, Br or I) using a suitable palladium catalyst, a suitable phosphine base and a suitable base in the presence of a suitable solvent at a temperature of typically around reflux (or at temperatures above the boiling point of the solvent e.g. 120 °C using microwave conditions).

A suitable palladium catalyst is tris(dibenzylideneacetone)dipalladium, bis (dibenzylideneacetone) palladium, palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium. A suitable phosphine base is tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxylbiphenyl. A suitable base is potassium carbonate, potassium phosphate or sodium hydrogen carbonate and solvents are DME, 1,4-dioxane or THF/water.

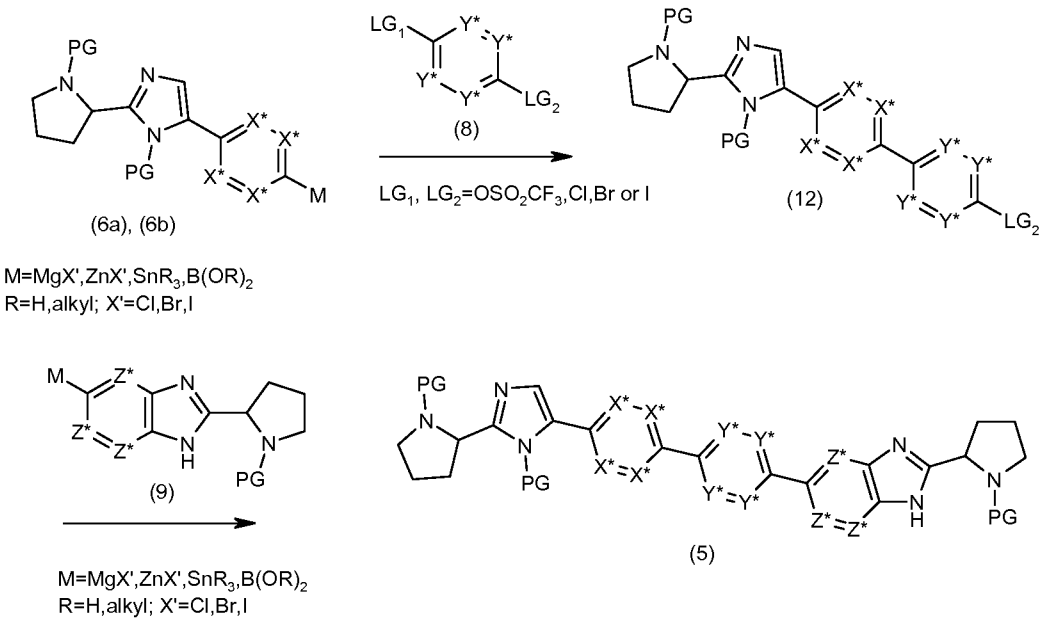
Alternatively, the cross coupling may be carried out between the trimethyl stannane (6a) or (6b) (M=$SnMe_3$) and derivative (7) using a suitable catalyst, such as tetrakis(triphenylphosphine)palladium, an optional copper (I) source, such as copper (I) chloride, a suitable base, such as cesium fluoride, and a suitable solvent, such as N,N-dimethylformamide, at a temperature of typically around 80 °C to 120 °C.

Derivative (7) (LG_2=OSO_2CF_3, Cl, Br, I) may be formed by the reaction of metallated derivative (9) (M=$B(OH)_2$ or $B(OR)_2$ or MgX′ or ZnX′) with derivative (8) using a suitable palladium catalyst, a suitable phosphine base, an optional copper (I) source, and a suitable base in the presence of a suitable solvent at a temperature of typically around reflux.

Suitable palladium catalysts are tris(dibenzylideneacetone)dipalladium, bis(dibenzylidene acetone)palladium, palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium. Suitable phosphine bases are tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxylbiphenyl. A suitable copper (I) source is copper (I) chloride. Suitable bases are potassium carbonate or sodium hydrogen carbonate. Suitable solvents are DME, 1,4-dioxane or THF/water.

Alternatively, compound (7) may be prepared by palladium catalysed coupling between a metallated aryl (10) (M=$B(OH)_2$ or MgX′ or ZnX′ or SnR_3) and derivative (11) (i.e. LG_1 = OSO_2CF_3 or Cl/Br/I).

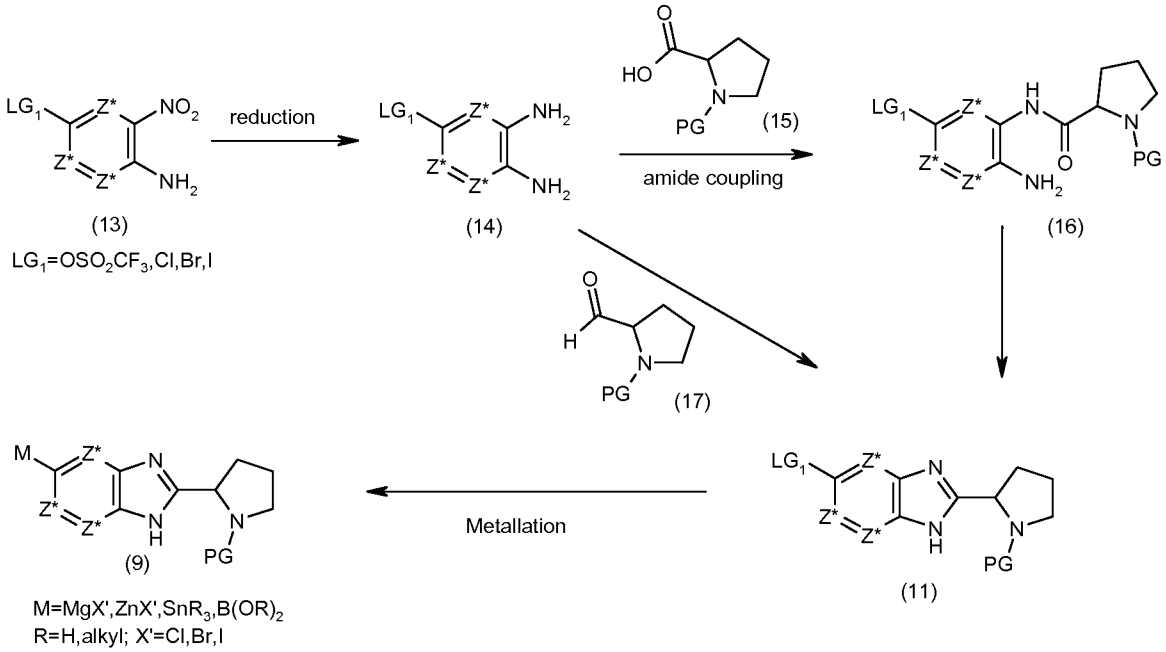
Scheme 4



Alternatively, protected amine (5) may be formed by a palladium catalysed coupling between a metallated derivative of general formula (9) and derivative (12) (i.e. LG_2= OSO_2CF_3 or Cl/Br/I). Preferably, the reaction is carried out between derivative (9) (M=$B(OR)_2$) and a halide imidazole derivative (12) (LG_2=OSO_2CF_3, Cl, Br or I) using a suitable palladium catalyst, such as (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, a suitable base, such as potassium phosphate or potassium carbonate, in the presence of a suitable solvent, such as 1,4-dioxane, THF/water or toluene/ethanol/water, at a temperature of typically around 60 °C to 120 °C.

Halide imidazole derivative (12) may be prepared by a palladium catalysed coupling between a metallated aryl imidazole (6a) or (6b), and aryl of general formula (8) (where Aryl-LG_1 (i.e. LG_1= OSO_2CF_3 or Cl/Br/I) is assumed to be a more reactive bond than aryl-LG_2 (i.e. LG_2= OSO_2CF_3 or Cl/Br/I)) using conditions such as those above described for Scheme 3.

Scheme 5



Organometallated derivative (9) may be formed from derivative (11) (when LG_1=OSO_2CF_3,Cl,Br,I) using a suitable organometallic reagent, such as butyllithium or isopropylmagnesium chloride (optionally used as the lithium chloride complex), in a suitable solvent, such as THF or diethylether at a temperature of between -78 °C and room temperature. The resulting species can be further converted into an organoboronate by reaction with a trialkylborate (such as trimethylborate) followed by hydrolysis with water or dilute base/acid. It may also be made by palladium coupling with a suitable boron source, such as bis(pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, using a suitable palladium catalyst, such as palladium acetate or (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, and a suitable base, such as sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate, in a suitable solvent, such as 1,4-dioxane or DME, at a temperature of typically around 80 °C to 120 °C. Alternatively, it may also be made by palladium cross coupling of a suitable organo stannane source, such as hexamethylditin, using a suitable palladium catalyst, such as tetrakis(triphenylphosphine)palladium, in a suitable solvent, such as 1,4-dioxane or toluene, at a temperature of typically around 80 °C to 120 °C.

Derivative (11) (LG_1=OSO_2CF_3,Cl,Br,I) can be prepared from amide derivative (16) under acidic conditions, preferably using acetic acid, at a temperature of typically around 70 °C to 110 °C. Alternatively, conversion of amide derivative (16) to derivative (11) can be carried out using phosphorus oxychloride at a temperature of typically around 120 °C.

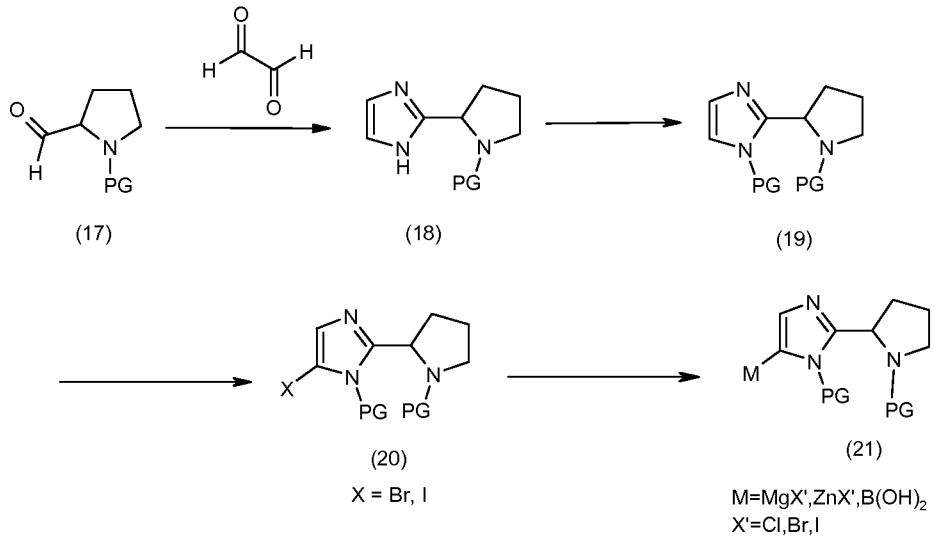
Amide derivative (16) is prepared from aniline (14) and carboxylic acid (15) using suitable coupling conditions as detailed above in Scheme 1.

Alternatively, derivative of general formula (11) can be synthesised directly from aniline (14) and aldehyde (17) in a suitable acidic solvent, such as acetic acid, or in a solvent, such as acetonitrile, methanol or ethanol, in the presence of an acid catalyst, such as acetic acid or p-toluenesulfonic acid, at a suitable temperature of typically between room temperature and reflux and in the presence of a suitable oxidant, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), iron (III) chloride or manganese dioxide.

Aniline (14) can be prepared by reduction of the corresponding nitro derivative (13) under hydrogen at a pressure of typically between 50psi and 100psi, in the presence of a catalyst, such as Raney Nickel, and a solvent, such as methanol or ethanol.

Alternatively, aniline derivative (14) is prepared by reaction with a reductive agent, such as sodium dithionite ($Na_2S_2O_4$), in a mixture of water and an organic solvent, such as dichloromethane, methanol or ethanol. A phase transfer catalyst may also be added.

Scheme 6



Metallated imidazole (21) is formed from haloimidazole derivative (20) using a suitable organometallic reagent, such as butyllithium or isopropylmagnesium chloride (optionally used as the lithium chloride complex), in a suitable solvent, such as THF or diethyl ether, at a temperature of between -78 °C and room temperature. The resulting species can be further converted into another metallated species, such as an organozinc species, by further reaction with zinc chloride, or preferentially into an organoboronate, by reaction with a trialkylborate (such as trimethylborate), followed by hydrolysis with water or dilute base/acid.

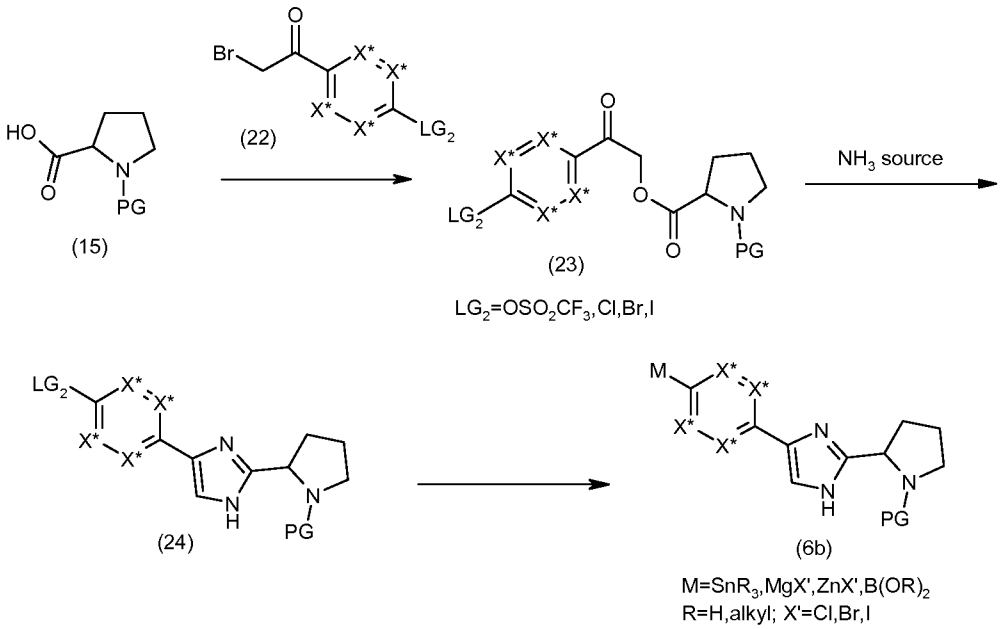
Haloimidazole (20) is formed from derivative (19) using a source of halogen, such as bromine, N-bromosuccinimide, iodine or N-iodosuccinimide, in a suitable solvent, such as dichloromethane or acetonitrile at a temperature of typically between 0 °C and reflux.

The imidazole (19) is protected, preferentially with a SEM group, using standard literature methods, such as reaction with a suitable base (e.g. sodium hydride), in a solvent, such as NMP or DMF, followed by

addition of 2-(triethylsilyl)ethoxymethyl chloride at a temperature of typically between 0 °C and room temperature.

Formation of imidazole (18) from derivative (17) is carried out with glyoxal and ammonium hydroxide in a suitable solvent, such as methanol, at a temperature of typically between 0 °C and room temperature (the pyrrolidine nitrogen is preferably protected as a Boc or CBZ derivative).

Scheme 7



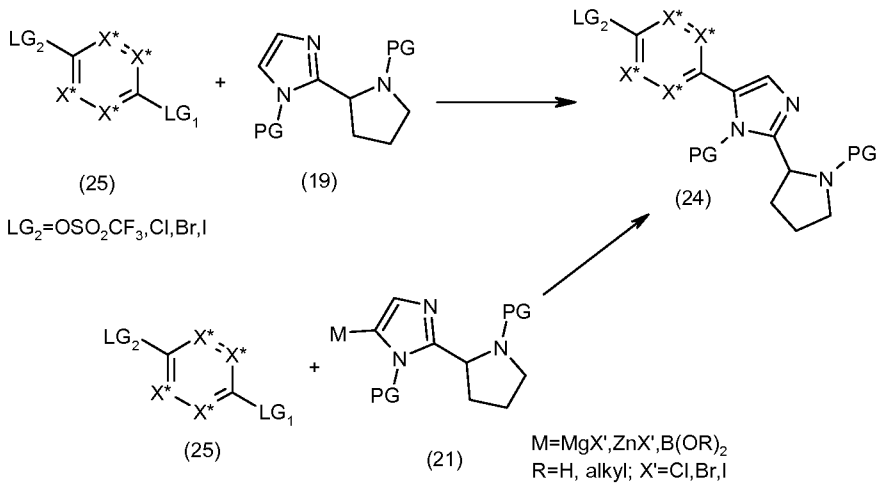
Organometallated derivative (6b) (in this case without the imidazole protecting group i.e. PG=H on imidazole as previously described for Scheme 3) is formed from derivative (24) using a suitable organometallic reagent, such as butyllithium or isopropylmagnesium chloride (optionally used as the lithium chloride complex), in a suitable solvent, such as THF or diethylether, at a temperature of between -78 °C and room temperature. The resulting species can be further converted into an organoboronate by reaction with a trialkylborate (such as trimethylborate) followed by hydrolysis with water or dilute base/acid. It may also be made by palladium coupling with a suitable boron source, such as bis(pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, using a suitable palladium catalyst, such as palladium acetate or (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, and a suitable base, such as sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate, in a suitable solvent, such as 1,4-dioxane or DME, at a temperature of typically around 80 °C to 120 °C.

Alternatively, derivative (6b) may also be made by a palladium coupling of derivative (24) with a suitable stannane source, such as hexamethylditin, using a suitable palladium catalyst, such as tetrakis(triphenylphosphine)palladium, in a suitable solvent, such as 1,4-dioxane or toluene, at a temperature of typically around 80 °C to 120 °C.

Formation of imidazole derivative (24) from ester (23) is carried out using a suitable ammonia source, typically ammonium acetate, in a solvent, such as toluene, trifluorotoluene or xylene, at a temperature of typically around 100 °C to 150 °C.

Ester (23) may be prepared using bromoketone (22) and protected carboxylic acid (15) with a suitable base, such as triethylamine or diisopropylethylamine, in a suitable solvent, such as dichloromethane, acetonitrile or methyl-THF, at a temperature of typically between 0 °C and room temperature (the pyrrolidine protecting group is preferably BOC or CBZ).

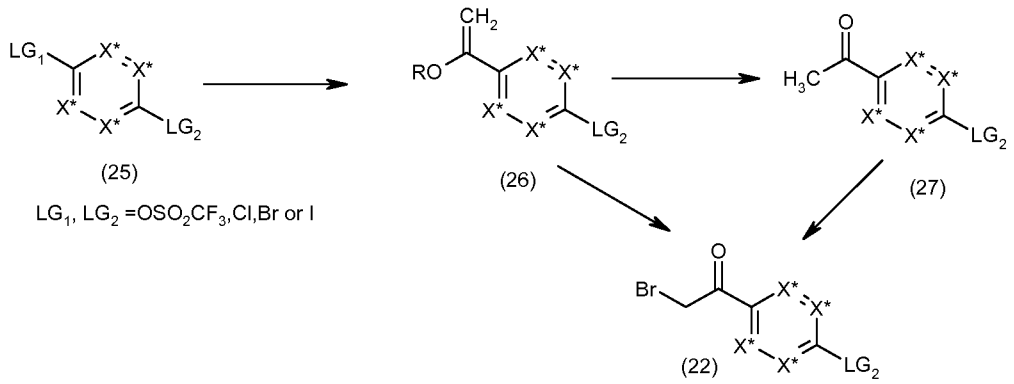
Scheme 8



Halogenated derivative (24) may be also be formed by a palladium catalysed CH activation between protected imidazole (19) and derivative (25) (i.e. LG_1 = Cl/Br/I or OSO_2CF_3). The reaction is typically carried out using a suitable palladium catalyst, such as palladium acetate, a suitable phosphine base, such as tricyclohexylphosphine (typically used as the tetrafluoroborate salt), an acid source, such as 2,2-dimethylpropionic acid (pivalic acid), and a suitable base, such as potassium carbonate, in the presence of a suitable solvent, such as *N*,*N*-dimethylacetamide or *N*,*N*-dimethylformamide, at a temperature of typically around 140 °C.

Derivative (24) may also be formed by a palladium catalysed coupling of heterocycle (25) (LG_1=Cl,Br,I,OSO_2CF_3) with metallated imidazole (21). For example, the reaction can be carried out using a suitable palladium catalyst, such as palladium acetate, palladium bis(triphenylphosphine)dichloride, tetrakis(triphenylphosphine)palladium, or (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, and a suitable base, such as sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate, in a suitable solvent, such as 1,4-dioxane or DME, at a temperature of typically around 80 °C to 120 °C.

Scheme 9

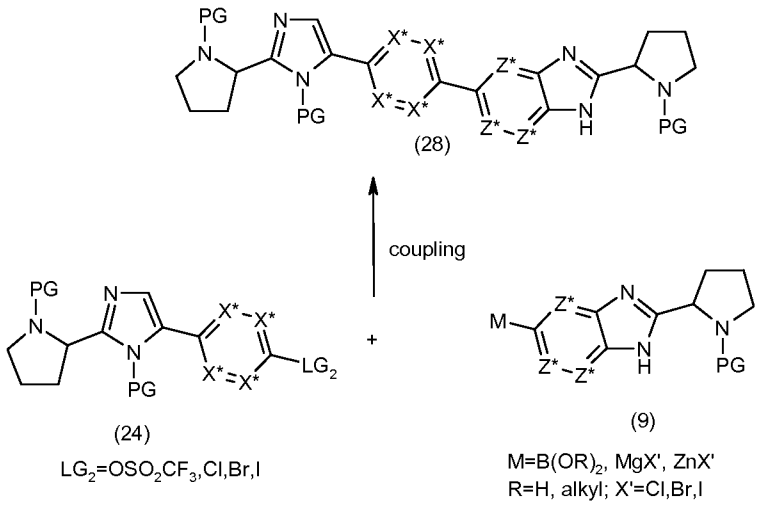


Conversion of derivative (25) (i.e. LG_1, LG_2 = OSO_2CF_3 or Cl/Br/I) to the ketone (27) can typically be carried out via formation of an enol ether (26) followed by hydrolysis under acidic conditions. Formation of the enol ether (26) is typically carried out using tributyl(1-ethoxy)vinyltin and a palladium catalyst, such as palladium bis(triphenylphosphine)dichloride or tetrakis(triphenylphosphine)palladium, in a suitable solvent such as DMF, 1,4-dioxane or acetonitrile, at a temperature of typically between 80 °C and 120 °C.

Alternatively, enol ether (26) can be reacted directly with bromine or N-bromosuccinimide, in a suitable solvent system, such as THF/water, at a temperature of typically between 0 °C and room temperature, to provide a direct route to derivative (22) (i.e. LG_2 = OSO_2CF_3 or Cl/Br/I).

As an alternative method to provide derivative (22), bromination of (27) may also be carried out using standard literature methods, such as using bromine in acetic acid, with either hydrochloric or hydrobromic acid present. The reaction is typically carried out at room temperature. Alternatively, the reaction can be carried out with tetrabutylammonium tribromide, in a suitable solvent, such as acetonitrile or methanol, at a temperature of typically between room temperature and 70 °C. The reaction can also be carried out using copper (II) bromide in a suitable solvent, such as 1,4-dioxane, typically at reflux.

Scheme 10

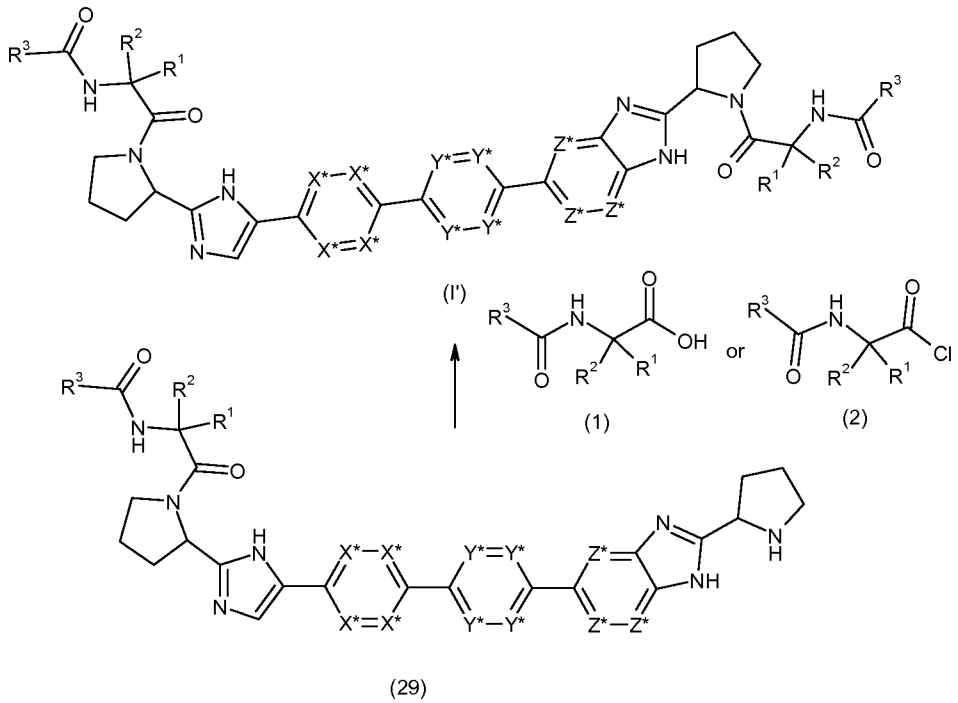


Protected amine (28) may be formed by a palladium coupling between a metallated derivative (9) and derivative (24) (i.e. LG_2 = OSO_2CF_3 or Cl/Br/I). For example, the reaction can be carried out using a suitable palladium catalyst, a suitable base, in a suitable solvent such as 1,4-dioxane or DME at a temperature of typically around 80 °C to 120 °C.

Suitable palladium catalysts are palladium acetate, palladium bis(triphenylphosphine)dichloride, tetrakis(triphenylphosphine)palladium, or (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium

Suitable bases are sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate.

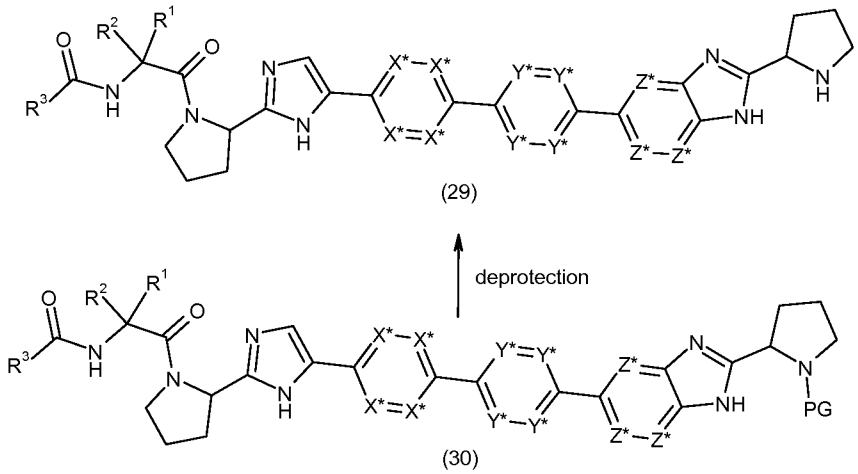
Scheme 11



(29)

The compound of formula (I') may be prepared from amine (29), according to Scheme 11, using suitable coupling conditions such as those described in Scheme 1.

Scheme 12

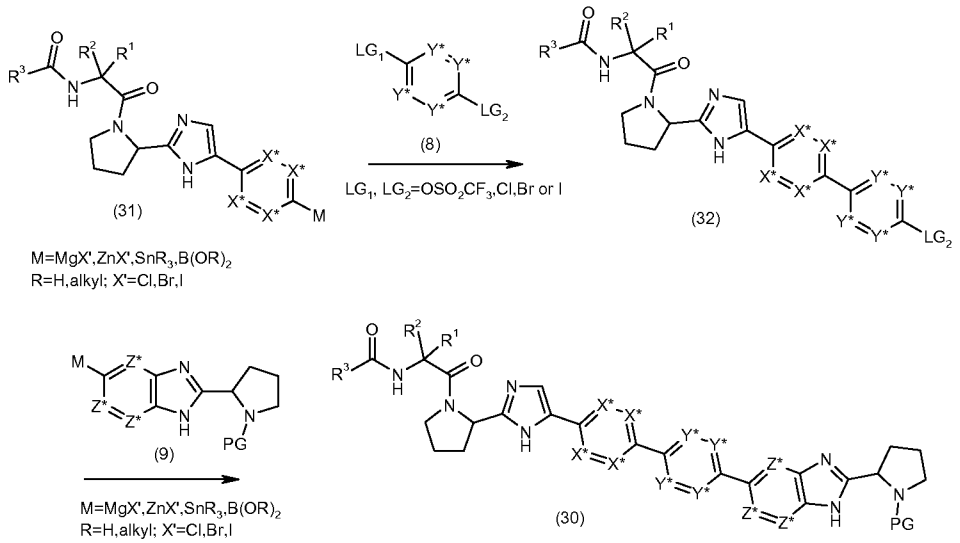


(29)

(30)

Amine (29) may be formed from protected amine (30), according to Scheme 12, using known literature methods such as reaction with an acid (*e.g.* hydrochloric acid or trifluoracetic acid), in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux.

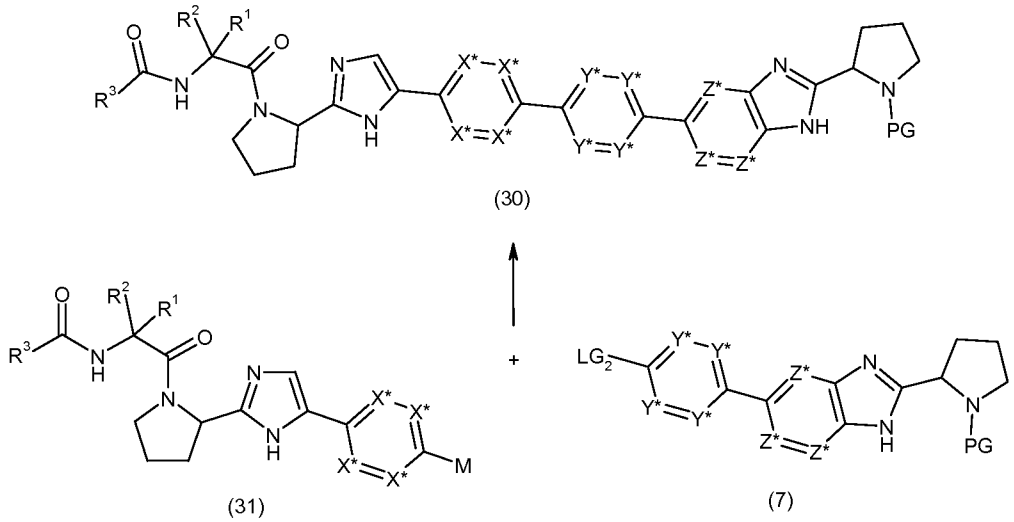
Scheme 13



Protected amine (30) may be formed by a palladium catalysed coupling between a metallated derivative of general formula (9) and derivative (32) (i.e. LG_2= OSO_2CF_3 or Cl/Br/I). Preferably, the reaction is carried out between derivative (9) (M=$B(OR)_2$) and a halide imidazole derivative (12) (LG_2=OSO_2CF_3, Cl, Br or I) using a suitable palladium catalyst, such as (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, a suitable base, such as potassium phosphate or potassium carbonate, in the presence of a suitable solvent, such as 1,4-dioxane, THF/water or toluene/ethanol/water, at a temperature of typically around 60 °C to 120 °C.

Halide imidazole derivative (32) may be prepared by a palladium catalysed coupling between a metallated aryl imidazole (31), and aryl of general formula (8) (where Aryl-LG_1 (i.e. LG_1= OSO_2CF_3 or Cl/Br/I) is assumed to be a more reactive bond than aryl-LG_2 (i.e. LG_2= OSO_2CF_3 or Cl/Br/I)) using conditions such as those above described for Scheme 3.

Scheme 14

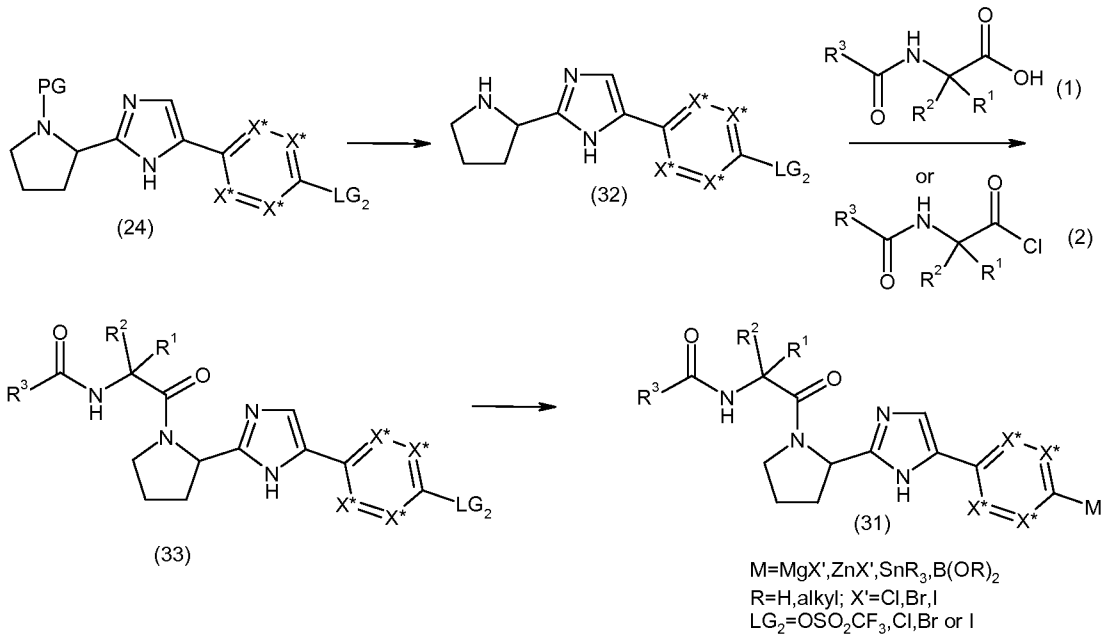


Alternatively, protected amine (30) may be formed by a palladium catalysed coupling between a metallated imidazole (31) and derivative (7).

Preferably, the reaction is carried out between the boronate ester (31) ($M=B(OR)_2$) and a halide derivative (7) ($LG_2= OSO_2CF_3$, Cl, Br or I) using a suitable palladium catalyst, a suitable phosphine base and a suitable base in the presence of a suitable solvent at a temperature of typically around reflux.

A suitable palladium catalyst is tris(dibenzylideneacetone)dipalladium, bis (dibenzylideneacetone) palladium, palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium. A suitable phosphine base is tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxylbiphenyl. A suitable base is potassium carbonate, potassium phosphate or sodium hydrogen carbonate and solvents are DME, 1,4-dioxane or THF/water.

Scheme 15



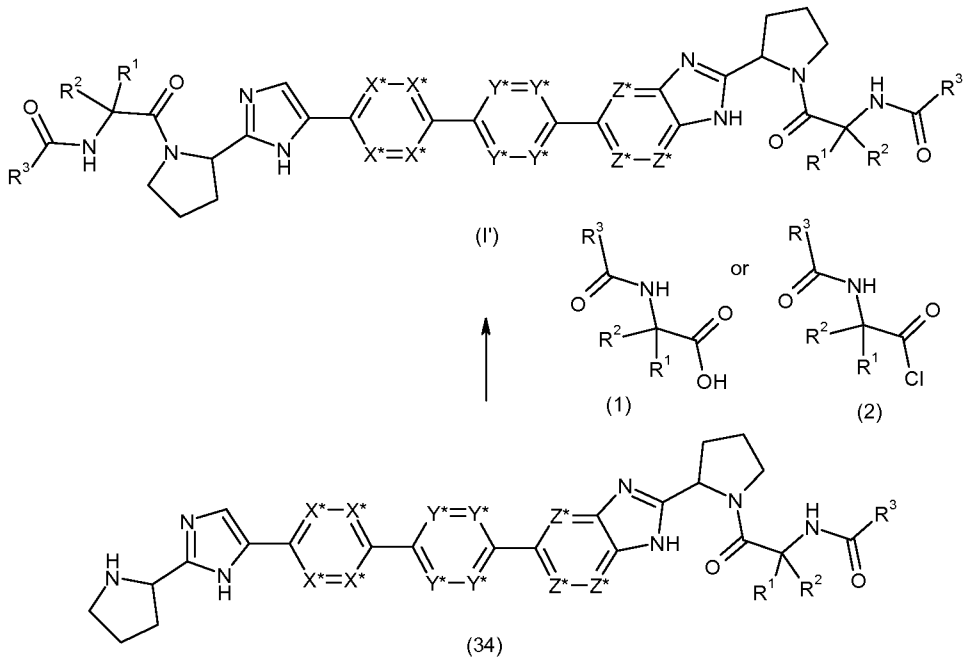
Organometallated derivative (31) may be formed from derivative (33) by palladium coupling with a suitable boron source, such as bis(pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, using a suitable palladium catalyst, such as palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene)dichloropalladium, and a suitable base, such as sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate, in a suitable solvent, such as 1,4-dioxane or DME, at a temperature of typically around 80 °C to 120 °C.

Amide derivative (33) may be formed using standard literature conditions. The acid (1) can be converted to the acid chloride (2) using a suitable chlorinating agent, such as oxalyl chloride or thionyl chloride, in a suitable solvent, such as dichloromethane or toluene, optionally in the presence of catalytic DMF, at a suitable temperature, typically of between 0 °C and room temperature. The acid chloride (2) can then be reacted with the amine (32) in the presence of a base, such as triethylamine or diisopropylethylamine, in a suitable solvent, such as dichloromethane or toluene, at a temperature of between 0 °C and room temperature. Alternatively, the acid (1) can be converted to a suitable activated species with a coupling agent, such as EDCI.HCl, EDCI.MeI, HBTU, HATU, PyBop, DCC, or CDI, in a suitable solvent, such as dichloromethane, acetonitrile or DMF. In the presence of EDCI.HCl or EDCI.MeI, HOBT is optionally added. A suitable base, such as triethylamine or diisopropylethylamine, is also used and the reaction is typically carried out at room temperature.

Amine (32) may be formed from protected amine (24) using known literature methods such as reaction with an acid (*e.g.* hydrochloric acid or trifluoracetic acid), in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux.

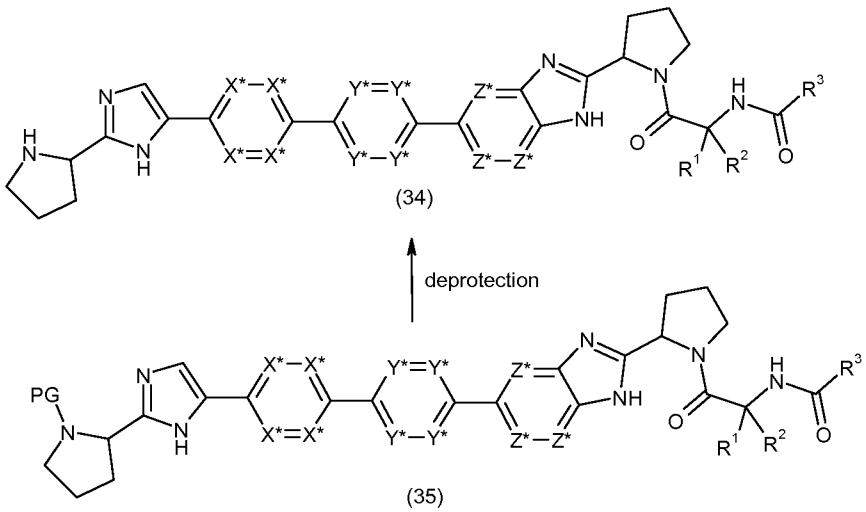
Compounds of formula (I') may also be formed according to Scheme 16:

Scheme 16



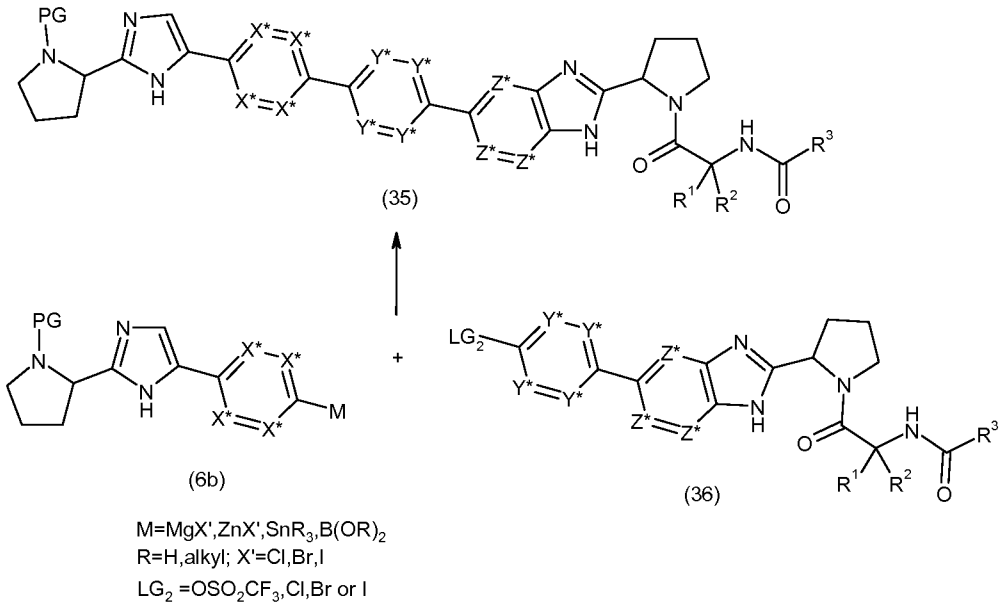
The compound of formula (I') may be prepared from amine (34), according to Scheme 16, using suitable coupling conditions such as those described in Scheme 1.

Scheme 17



Amine (34) may be formed from protected amine (35), according to Scheme 17, using known literature methods such as reaction with an acid (*e.g.* hydrochloric acid or trifluoracetic acid), in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux.

Scheme 18



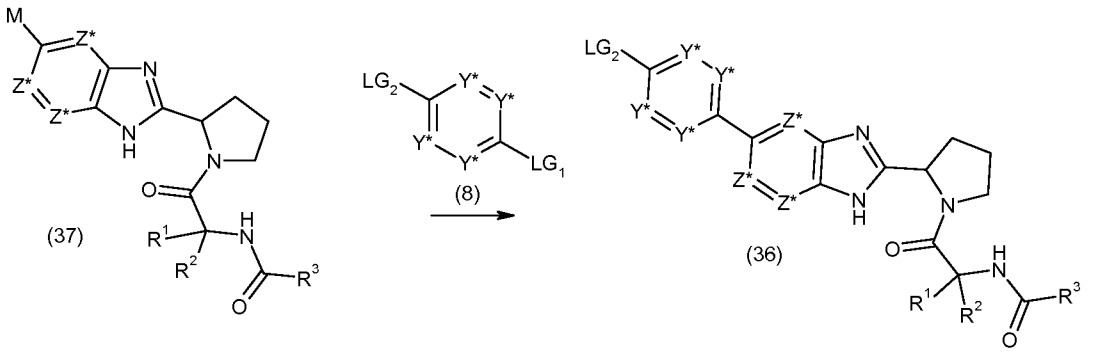
M=MgX',ZnX',SnR_3,$B(OR)_2$
R=H,alkyl; X'=Cl,Br,I
LG_2 =OSO_2CF_3,Cl,Br or I

Protected amine (35) may be formed by a palladium catalysed coupling between a metallated imidazole (6b) and derivative (36).

Preferably, the reaction is carried out between the boronate ester (6b) (M=$B(OR)_2$) and a halide derivative (36) (LG_2= OSO_2CF_3, Cl, Br or I) using a suitable palladium catalyst, a suitable phosphine base and a suitable base in the presence of a suitable solvent at a temperature of typically around.

A suitable palladium catalyst is tris(dibenzylideneacetone)dipalladium, bis (dibenzylideneacetone) palladium, palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium. A suitable phosphine base is tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxylbiphenyl. A suitable base is potassium carbonate, potassium phosphate or sodium hydrogen carbonate and solvents are DME, 1,4-dioxane or THF/water.

Scheme 19



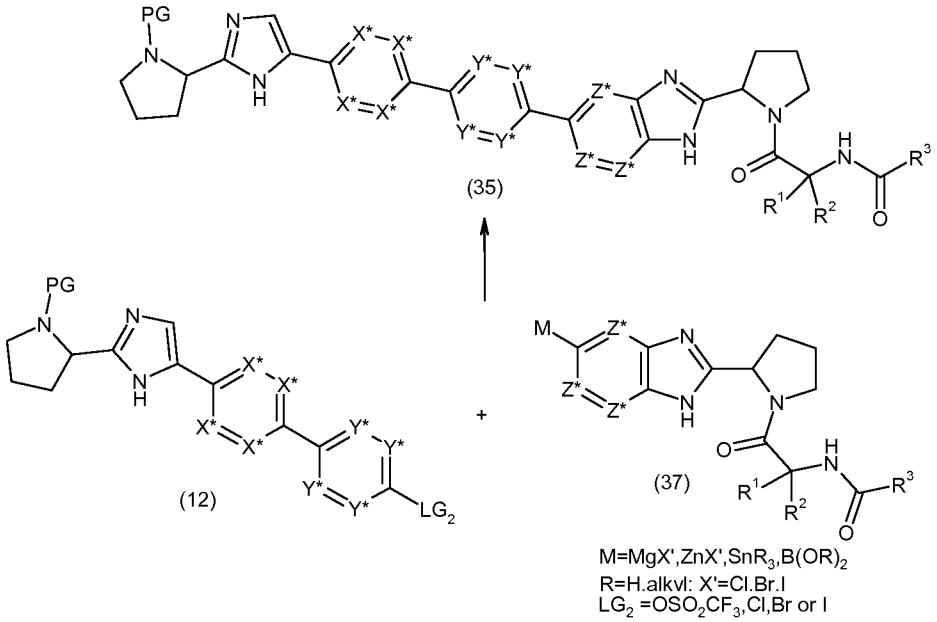
M=MgX',ZnX',SnR_3,$B(OR)_2$
R=H,alkyl; X'=Cl,Br,I
LG_1, LG_2 =OSO_2CF_3,Cl,Br or I

Derivative (36) (LG_2=OSO_2CF_3, Cl, Br, I) may be formed by the reaction of metallated derivative (37) (M=$B(OH)_2$ or $B(OR)_2$) with derivative (8) using a suitable palladium catalyst, a suitable phosphine base, an

optional copper (I) source, and a suitable base in the presence of a suitable solvent at a temperature of typically around reflux.

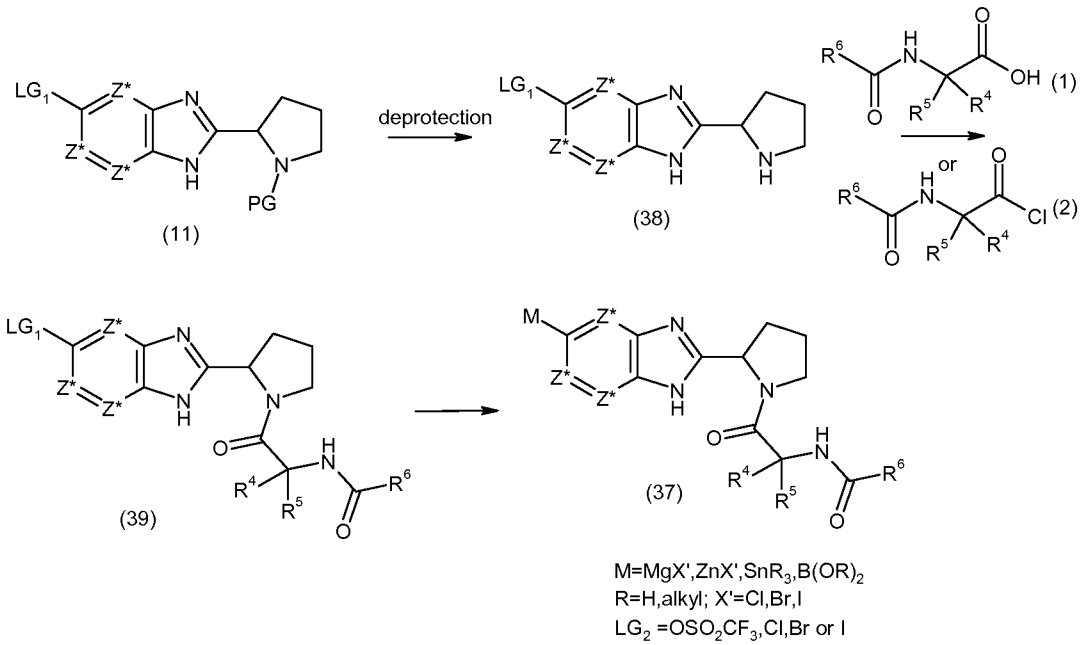
Suitable palladium catalysts are tris(dibenzylideneacetone)dipalladium, bis(dibenzylidene acetone)palladium, palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium. Suitable phosphine bases are tricyclohexylphosphine or 2-dicyclohexylphosphino-2',6'-dimethoxylbiphenyl. Suitable bases are potassium carbonate or sodium hydrogen carbonate. Suitable solvents are DME, 1,4-dioxane or THF/water.

Scheme 20



Alternatively, protected amine (35) may also be formed by a palladium catalysed coupling between a metallated derivative of general formula (37) and derivative (12) (i.e. LG_2= OSO_2CF_3 or Cl/Br/I). Preferably, the reaction is carried out between derivative (37) ($M=B(OR)_2$) and a halide imidazole derivative (12) ($LG_2=OSO_2CF_3$, Cl, Br or I) using a suitable palladium catalyst, such as (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium, a suitable base, such as potassium phosphate or potassium carbonate, in the presence of a suitable solvent, such as 1,4-dioxane, THF/water or toluene/ethanol/water, at a temperature of typically around 60 °C to 120 °C.

Scheme 21

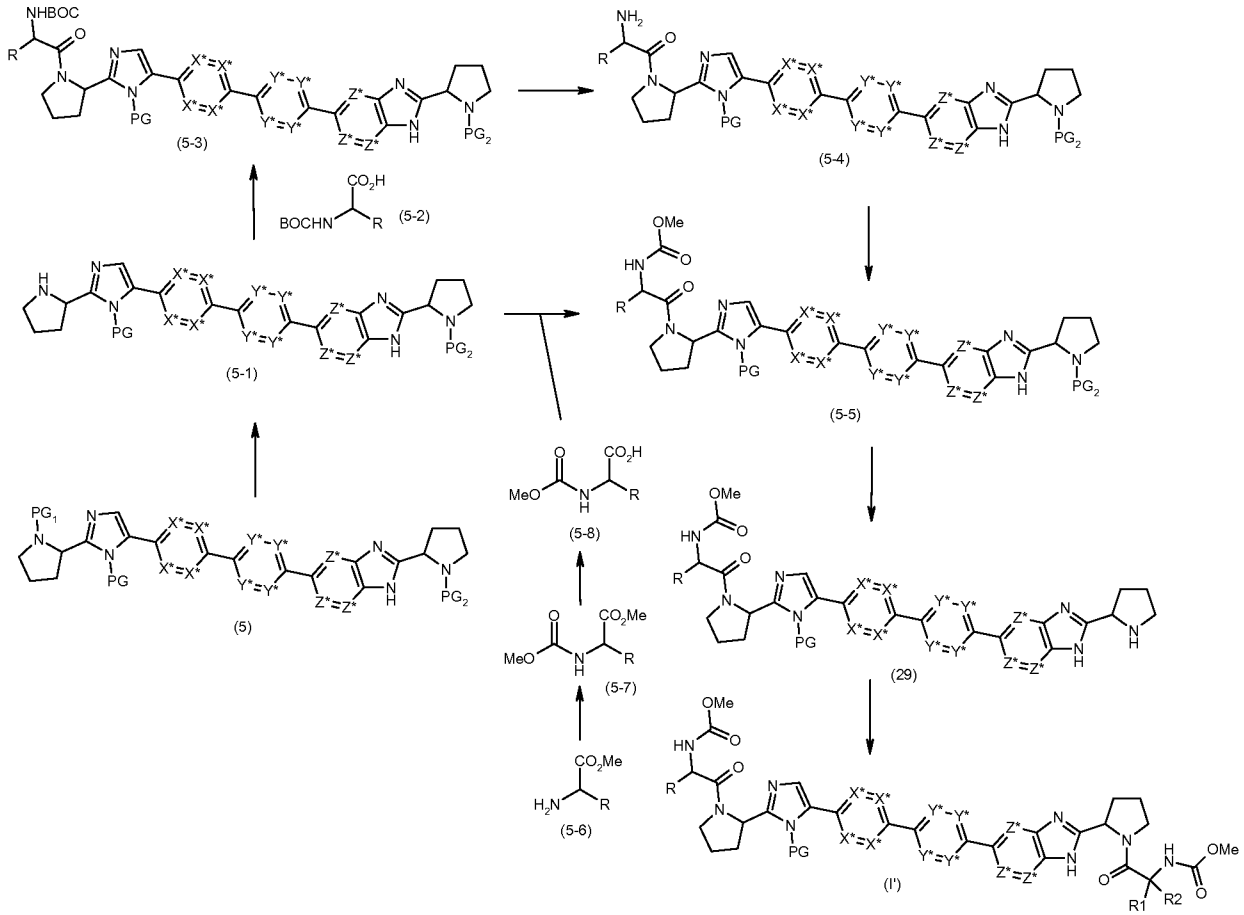


Organometallated derivative (37) may be formed from derivative (39) by palladium coupling with a suitable boron source, such as bis(pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, using a suitable palladium catalyst, such as palladium acetate or (1,1'-bis(diphenylphosphino) ferrocene)dichloropalladium, and a suitable base, such as sodium carbonate, sodium hydrogen carbonate, potassium acetate or potassium phosphate, in a suitable solvent, such as 1,4-dioxane or DME, at a temperature of typically around 80 °C to 120 °C.

Amide derivative (39) may be formed using standard literature conditions. The acid (1) can be converted to the acid chloride (2) using a suitable chlorinating agent, such as oxalyl chloride or thionyl chloride, in a suitable solvent, such as dichloromethane or toluene, optionally in the presence of catalytic DMF, at a suitable temperature, typically of between 0 °C and room temperature. The acid chloride (2) can then be reacted with the amine (38) in the presence of a base, such as triethylamine or diisopropylethylamine, in a suitable solvent, such as dichloromethane or toluene, at a temperature of between 0 °C and room temperature. Alternatively, the acid (1) can be converted to a suitable activated species with a coupling agent, such as EDCI.HCl, EDCI.MeI, HBTU, HATU, PyBop, DCC, or CDI, in a suitable solvent, such as dichloromethane, acetonitrile or DMF. In the presence of EDCI.HCl or EDCI.MeI, HOBT is optionally added. A suitable base, such as triethylamine or diisopropylethylamine, is also used and the reaction is typically carried out at room temperature.

Amine (38) may be formed from protected amine (11) using known literature methods such as reaction with an acid (*e.g.* hydrochloric acid or trifluoracetic acid), in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux.

Scheme 22



Pyrrolidine substituents based on amino acid derivatives may be synthesised according to the route described in Scheme 22.

The protected amine (5) may be prepared in such a way that the two pyrrolidine ring N atoms are differentially protected with two orthogonal protecting groups, PG1 and PG2. Suitable protecting groups include, but are not limited to, t-butyloxycarbonyl (t-BOC), allyloxycarbonyl (alloc) and benzyloxycarbonyl (Cbz).

For illustrative purposes, if in Scheme 22 PG1=t-BOC and PG2=Cbz, the t-BOC protecting group may be selectively removed using a suitable reagent described in the literature for this purpose such as a strong acid (e.g. hydrochloric acid or trifluoroacetic acid) in a suitable solvent, such as methanol, ethanol or 1,4-dioxane, at a temperature typically of between room temperature and reflux, to give the amine (5-1). This amine may then be reacted with a range of t-BOC protected amino acids (5-2), be they commercially available or prepared using methods described in the literature. Thus, the acid (5-2) can be converted to a suitable activated species with a coupling agent, such as EDCI.HCl, EDCI.MeI, HBTU, HATU, PyBop, DCC, or CDI, in a suitable solvent, such as dichloromethane, acetonitrile or DMF. In the presence of EDCI.HCl or EDCI.MeI, HOBT is optionally added. A suitable base, such as triethylamine or diisopropylethylamine, is also used and the reaction is typically carried out at room temperature to give the amide derivative (5-3). The t-BOC protecting group may then be removed using standard methodology to give the amine (5-4), and then

reacted with a suitable reagent for the formation of the methyl carbamate (5-5), for example methyl chloroformate. Alternatively, a range of amino acid methyl esters (5-6), be they commercially available or prepared using methods described in the literature, may be converted into the corresponding methyl carbamate (5-7) using a suitable reagent, for example methyl chloroformate. Ester hydrolysis, carried out according to standard methods, for example by using a strong base such as lithium or sodium hydroxide, may then provide the corresponding acid (5-8). This can then be coupled directly to the amine (5-1) using the methods indicated above. The second protecting group may then be removed. Continuing with the same example as above, if PG2=Cbz, the Cbz group may be removed using a suitable reagent described in the literature for this purpose such as hydrogen gas in the presence of a heterogeneous palladium or platinum catalyst, which would provide a derivative that is entirely analogous to intermediate (29) described in Scheme 11. This could then be treated in exactly the same ways described above to provide compounds of the general formula (I').

It will be appreciated by those skilled in the art that several of the above described steps may be performed in one-pot and that many similar reaction sequences may be carried out in parallel, for example in multi-well plates. Similarly, it will be appreciated by those skilled in the art that several of the above described steps may be carried out sequentially with no purification.

As an example of a telescoped procedure, compounds of general formula (5-1) or (29) can be reacted with an acid of general formula (5-2) and the reaction mixture extracted with a suitable solvent, for example ethyl acetate or t-butyl methyl ether. The extract may then be dried over a suitable reagent, for example sodium or magnesium sulfate, and the solvent evaporated. The crude material may then be dissolved in a suitable solvent, for example methanol or 1,4-dioxane, and treated with a strong acid such as hydrochloric acid or trifluoroacetic acid. After a sufficient time has passed for completion of the ensuing reaction, the mixture may be evaporated under reduced pressure and then immediately treated with a mixture of methyl chloroformate in a suitable solvent such as dichloromethane or dichloroethane and a suitable base such as triethylamine or *N*-methyl morpholine. The mixture may then be finally concentrated under reduced pressure and purified by preparative HPLC to provide compounds of the formula (5-6) or (I').

Similarly, the amine (5-6) may be converted into the acid (5-8) in a telescoped procedure, before reaction with the amine (5-1) according to the standard methods described above to provide derivatives (5-6) or (I').

Cyclic cores of derivatives of generic formula (8),(10),(13), (22) and (25) can be prepared by one skilled in the art and carried out according to literature methods detailed in suitable reference books such as Heterocyclic Chemistry, J.A. Joule and K. Mills, 4th edition, Wiley-Blackwell (2000) or Heterocyclic Chemistry, T.L. Gilchrist, 3rd edition, Prentice-Hall, 1997.

In a second aspect, the present invention provides a pharmaceutical composition including a compound of formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient.

The term 'excipient' is used herein to describe any ingredient other than the compound of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in "Remington's Pharmaceutical Sciences", 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include both solid and liquid formulations.

Solid formulations include tablets, capsules (containing particulates, liquids, or powders), lozenges (including liquid-filled lozenges), chews, multi- and nano-particulates, gels, solid solutions, liposomal preparations, films, ovules, and sprays.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11(6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form.

In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may

comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function. The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %. Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents. Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular

and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of the compound of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus the compound of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve

their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective, or have other more useful properties than the compounds in the art.

As demonstrated by the results of biological testing (described in greater detail below), the compounds of formula (I) are potent inhibitors of HCV replication. Preferably, the compounds of formula (I) are potent inhibitors of HCV replication which show activity against multiple HCV genotypes. More preferably, the compounds of formula (I) are potent inhibitors of HCV replication which show balanced activity against both genotype 1a and 1b.

Thus, in a third aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

A specific embodiment of this aspect of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease for which an inhibitor of HCV replication is indicated.

Another specific embodiment of this aspect of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of HCV infection.

In a fourth aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament to treat a disease for which an inhibitor of HCV replication is indicated.

A specific embodiment of this aspect of the invention is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of HCV infection.

In a fifth aspect, the present invention provides a method of treatment of a mammal, including a human being, to treat a disease for which an inhibitor of HCV replication is indicated, including administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A specific embodiment of this aspect of the invention is a method of treatment of a mammal, including a human being, to treat HCV infection, including administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The term 'treatment' as used herein includes both preventative and curative treatment of a disease or disorder. It also includes slowing, interrupting, controlling or stopping the progression of a disease or

disorder. It also includes preventing, curing, slowing, interrupting, controlling or stopping the symptoms of a disease or disorder.

The compound of the present invention may be administered in combination with one or more additional agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HCV virus, or any other disease or condition which is related to infection with the HCV virus. The agents that may be used in combination with the compounds of the present invention include, but are not limited to, cyclophilin inhibitors (such as NIM-811, Debio-025 and SCY-635), immunomodulators (such as Zadaxin, Ceplene, Cellcept, Civacir and Zadazim), TLR9 agonists (such as Actilon), antisense agents (such as ISIS14803), NS4A inhibitors (such as ACH-806), NS5A inhibitors (such as A831, BMS-790052 and A689), inosine monophosphate dehydrogenase inhibitors (such as Levovirin, Miremepodib, Viramidine and Ribavirin), inhibitors of HCV entry (such as XTL-6865), NS3 serine protease inhibitors (such as Telapravir, Boceprevir, TMC-435350, MK-7009, BI-201335, ABT-450, ITMN-191 and BILN-2061; and also compounds described in Reiser and Timm, Expert Rev. Anti Infect. Ther. 7(5), 537-547, (2009)), TLR7 agonists (such as N-(4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl)methanesulfonamide, ANA-971 and ANA-773), NS5B RNA-polymerase inhibitors (such as Filibuvir, HCV-796, Valopicitabine, GL-59728, GL-60667, PSI-6130, R1626, R7128, JTK-003 GL-59728 and GS-9190; and also compounds described in Beaulieu, Expert Opin. Ther. Patents, 19(2), 145-164 (2009)), caspase inhibitors (such as IDN-6556), glucosidase inhibitors (such as Celgosivir), inhibitors of NS4B and other compounds described in Holler et al. Expert Opin. Drug Discov. 4(3), 293-314 (2009). Preferably the compound of the present invention may be administered in combination with one or more additional agents selected from NS3 serine protease inhibitors (such as Telapravir, Boceprevir, TMC-435350, MK-7009, BI-201335, ABT-450, ITMN-191 and BILN-2061; and also compounds described in Reiser and Timm, Expert Rev. Anti Infect. Ther. 7(5), 537-547, (2009)) and/or NS5B RNA-polymerase inhibitors (such as Filibuvir, HCV-796, Valopicitabine, GL-59728, GL-60667, PSI-6130, R1626, R7128, JTK-003 GL-59728 and GS-9190; and also compounds described in Beaulieu, Expert Opin. Ther. Patents, 19(2), 145-164 (2009)).

Compounds of the present invention can also be combined with inhibitors of the hepatitis C structural proteins such as nucleocapsid or core proteins. Compounds of the present invention can also be combined with an interferon, or an interferon derivative (such as Albuferon, AlbInterferon, BLX-883 (locteron), Infergen A, Omega IFN, IFN beta, Rebif, Roferon A, Intron A, Rebetron, Actimmune, Multiferon, Wellferon, Omniferon, Pegasys, Pegasys+Ribavirin, and Pegintron+Ribavirin).

Such a combination may be administered such that the compound of the present invention is present in the same pharmaceutical composition as the additional agent(s) described above. Alternatively, such a combination may be administered such that the compound of the present invention is present in a pharmaceutical composition that is separate from the pharmaceutical composition in which the additional agent(s) is(are) found. If the compound of the present invention is administered separately from the additional agent(s), such administration may take place concomitantly or sequentially with an appropriate period of time in between.

Additionally, the compound of the present invention may be administered in combination with one or more additional agents that have the effect of increasing the exposure of the mammal to the compound of the invention. The term 'exposure', as used herein, refers to the concentration of the compound of the invention in the plasma of a mammal as measured over a period of time. The exposure of a mammal to a particular compound can be measured by administering the compound of the invention to a mammal in an appropriate form, withdrawing plasma samples at predetermined times, and measuring the amount of a compound of the invention in the plasma using an appropriate analytical technique, such as liquid chromatography or liquid chromatography/mass spectroscopy. The amount of the compound of the invention present in the plasma at a certain time is determined and the concentration and time data from all the samples are plotted to afford a curve. The area under this curve is calculated and affords the exposure of the mammal to the compound. The terms 'exposure', 'area under the curve', and 'area under the concentration/time curve' are intended to have the same meaning and may be used interchangeably.

Among the agents that may be used to increase the exposure of a mammal to a compound of the present invention are those that can act as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP3A4 include, but are not limited to, ritonavir, delavirdine, N-(3,4-difluorobenzyl)-2-{[(4-methoxypyridin-3-yl)amino]sulfonyl}-N-methylbenzamide, and N-(1-(5-(4-fluorobenzyl)-3-(pyridin-4-yl)-1H-pyrazole-1-carbonyl)piperidin-4-yl)methanesulfonamide.

Such a combination may be administered such that the compound of the present invention is present in the same formulation as the additional agent(s) described above. Alternatively, such a combination may be administered such that the compound of the present invention is present in a pharmaceutical composition that is separate from the pharmaceutical composition in which the additional agent(s) is(are) found. If the compound of the present invention is administered separately from the additional agent(s), such administration may take place concomitantly or sequentially with an appropriate period of time in between.

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for co-administration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

The invention provides:

(i) a compound of formula (I) or a pharmaceutically acceptable salt thereof, as herein defined;

(ii) processes for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as herein defined;

(iii) a pharmaceutical formulation including a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein defined, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament;

(v) a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein defined for use in the treatment of a disease for which an inhibitor of HCV replication is indicated;

(vi) a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein defined for use in the treatment of HCV infection;

(vii) a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease for which an inhibitor of HCV replication is indicated;

(viii) a method of treatment of a mammal, including a human being, to treat a disease for which an inhibitor of HCV replication is indicated, including administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof;

(ix) a method of treatment of a mammal, including a human being, to treat HCV infection, including administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof;

(x) a compound of formula (I) or a pharmaceutically acceptable salt thereof, in combination with one or more other pharmacologically active agents;

(xi) a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more other agents which are useful for the treatment of HCV infection;

(xii) a product comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more other pharmacologically active agents as a combined preparation for simultaneous, separate or sequential use in therapy;

(xiii) a kit comprising two or more pharmaceutical compositions, at least one of which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient, and means for separately retaining said compositions;

(xiv) novel intermediates as disclosed herein.

Other aspects of the invention will be apparent from the claims.

The following procedures illustrate the preparation of specific examples of compounds of the formula (I). ^{1}H-NMR spectra were recorded on a Varian Mercury 400MHz, Bruker Avance 400 MHz NMR or Jeol ECX 400MHz. NMR spectra were obtained as DMSO-d_6 solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm). Other NMR solvents were used as needed. When peak

multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets.

Microwave experiments were carried out using a Biotage initiator 8.

The mass spectra were obtained using:
System A: Waters ZQ ESCI 2 minutes LC-MS
System B: Waters ZQ ESCI 6 minutes LC-MS
System C: Applied Biosystem API-2000 5 minutes LC-MS
System D: Waters Alliance 2795 with ZQ2000 (ESI) 5 minutes LC-MS
System E: Waters Alliance 2695 with ZQ2000 (ESI) 25 minutes LC-MS
System F: Waters Acquity ZQD (ESI) 1.5 minutes LC-MS
System G: Agilent technologies 6890N with Agilent 5975 inert mass selective detector GC-MS
System J: Waters micromass ZQ2000 (ESI) 4.5 minutes LC-MS
System K: Waters micromass ZQ2000 (ESI) 25 minutes LC-MS
System L: Waters micromass ZQ2000 (ESI) 4.5 minutes LC-MS
System M: Shimadzu 2010 ESI 2 minutes LC-MS
System N: Agilent 1200 HPLC with 6140 (ESI) 4.7 minutes LC-MS
System O: Agilent 1200 HPLC with 6140 (ESI) 4.7 minutes LC-MS
System P: Agilent 1200 HPLC with 6140 (ESI) 4.7 minutes LC-MS

System A:
2 minute LC-MS gradient and instrument conditions:
Acid run:
A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile
Column: C18 phase Phenomenex 20 x 4.0mm with 3 micron particle size
Gradient: 70-2% A over 1.5 min, 0.3 min hold, 1.8 mL/min
UV: 210nm - 450nm DAD
Temperature: 75 °C

System B:
6 minute LC-MS gradient and instrument conditions:
Acid run:
A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile
Column: C18 phase Fortis 50 x 4.6mm with 5 micron particle size
Gradient: 95-5% A over 3min, 1 min hold, 1 mL/min

UV: 210nm - 450nm DAD

Temperature: 50 °C

System C:

5 minute LC-MS gradient and instrument conditions:

Acid Run:

A: 0.05% trifluoroacetic acid/0.05% formic acid/10mM ammonium acetate

B: Acetonitrile

Column: C18 phase Phenomenex Gemini 50 x 4.6mm with 5 micron particle size

Gradient: 90-10% A over 3 min, 1 min hold, 1.2 mL/min

UV: 220nm, 260nm

Temperature: 50 °C

System D:

5 minute LC-MS gradient and instrument conditions:

Acid run:

A: water

B: Methanol

C: 2% formic acid in water

Column: XBridge C18 2.1 x 30mm with 5 micron particle size

Gradient table:

minutes	%A	%B	%C
0	90	5	5
0.1	90	5	5
3	0	95	5
3.9	0	95	5
4	90	5	5

Flow: 1 mL/min

UV: 215nm - 350nm DAD

Temperature: 25 °C

Base run:

B: methanol

C: 10mM ammonium bicarbonate @ pH10

Column: XBridge C18 2.1 x 30mm with 5 micron particle size

Gradient table:

minutes	%A	%B	%C
0		5	95
0.1		5	95
3		95	5
3.9		95	5
4		5	95

Flow: 0.5 mL/min

UV: 215nm - 350nm DAD

Temperature: 25 °C

System E:

25 minute LC-MS gradient and instrument conditions:

Acid run:

A: water

B: acetonitrile

C: 2% formic acid in water

Column: XBridge C18 3 x 150mm with 5 micron particle size

Gradient table:

minutes	%A	%B	%C
0	90	5	5
15	0	95	5
25	0	95	5

Flow: 0.5 mL/min

UV: 215nm - 350nm DAD

Temperature: 30 °C

Base run:

B: acetonitrile

C: 10mM ammonium bicarbonate @ pH10

Column: XBridge C18 3 x 150mm with 5 micron particle size

Gradient table:

minutes	%A	%B	%C
0		5	95
15		95	5
25		95	5

Flow: 0.5 mL/min

UV: 215nm - 350nm DAD

Temperature: 30 °C

System F:

1.5 minute LC-MS gradient and instrument conditions:

Acid run:

A: 0.1% formic acid in water

B: Acetonitrile

Column: XBridge C18 2.1 x 50mm with 2.5 micron particle size

Gradient table:

minutes	%A	%B
0	98	2
0.8	2	98
1.2	2	98
1.25	98	2

Flow: 0.8 mL/min

UV: 215nm - 350nm DAD

Temperature: 30 °C

Base run:

A: 10mM ammonium bicarbonate @ pH10

B: acetonitrile

Column: XBridge C18 2.1 x 50mm with 2.5 micron particle size

Gradient table:

minutes	%A	%B
0	98	2
0.8	2	98
1.2	2	98
1.25	98	2

Flow: 0.8 mL/min

UV: 215nm - 350nm DAD

Temperature: 30 °C

Accurate mass spectra were obtained using a Bruker micrOTOF mass spectrometer.

loop: 1mL/min 1.5min runtime.

A: 0.1% formic acid +H_20

B: 0.1% formic acid +MeCN

Sodium formate used as calibrant.

System G:

GC-MS instrument conditions:

Column: HP-5MSi 30m x 0.250mm x 0.25μm

Flow: 0.9 mL/minute

Oven temperature gradient:

Initial Temp (°C)	Rate (°C/min)	Final Temp (°C)	Hold Time (min)
50	-	-	1.00
50	20	280	1.00

Run time	13.50 min
Injection Volume	1 μl
Inlet Mode	Split
Inlet temperature	250 °C
Split ratio	100:1
Gas type	Helium
FID Temperature	300 °C
FID Hydrogen Flow	30.0 ml/min
FID Air flow	400 ml/min
FID Make up gas	Nitrogen
FID Make up flow	25.0 ml/min
MS Acquisition mode	Scan
MS Solvent Delay	4.00 min
MS Quad temperature	100 °C
MS Source Temperature	230 °C
MS Transfer line temperature	280 °C

Preparative HPLC was carried out using Waters Purification Systems with either PDA / mass spec or UV detection: (System H) or (System I).

System H: gradient and instrument conditions:

Column: XBridge C18 19 x 100mm or 19 x 150mm or 30 x 150mm with 5 micron particle size

Eluent: Methanol / 0.1% ammonia in water

Flow: 20 or 50 mL/min

Temperature: 25 °C

Gradient Table:

minutes	% A	% B
0	90	10
3	70	30
8	50	50
18	20	80
19	5	95
20	5	95
21	90	10
25	90	10

System I: gradient and instrument conditions:

Column: XTerra C18, 19 x 250mm, 10 micron particle size

Eluent: (A) Acetonitrile / (B) 0.05% ammonia in water (pH=10.5)

Flow: 16 mL/min

Temperature: 25 °C

Gradient Table:

minutes	% A	% B
0	90	10
3	70	30
8	50	50
18	20	80
19	5	95
20	5	95
21	90	10
25	90	10

System J:

4.5 minutes LC-MS gradient and instrument conditions:

Acid run:

A: 0.05 % formic acid in water

B: 0.05% formic acid in acetonitrile

Column: C18 phase Phenomenex Gemini, 50 x 4.60 mm with 3 micron particle size.

Gradient: 5% B to 95% B over 3.5 minutes. Hold to 4.5 minutes. 2.0 mL/min

UV: 200 nm, 400 nm

Temperature: 40 °C.

System K:

25 minutes LC-MS gradient and instrument conditions:

Basic run:

A: 10mM ammonium bicarbonate @ pH10

B: acetonitrile

Column: C18 phase XBridge, 3.0 x 150 mm with 5 micron particle size

Gradient: 3% B to 95% B over 13.00 minutes. Hold to 22.60 minutes. 22.60 minutes 3% B, hold to 25.00 minutes. 0.5 mL/min

UV: 215 nm, 350 nm

Temperature: 25 °C.

System L:

4.5 minute LC-MS gradient and instrument conditions:

Acid run:

A: water

B : Acetonitrile

D: Acetonitrile 1% formic acid

Column: XBridge C18 2.1 x 30 mm with 5 micron particle size

Gradient table:

minutes	%A	%B	%D
0	95	0	5
2.30	0	95	5
3.50	0	95	5
3.60	95	0	5

Flow: 1 mL/min

UV: 215nm - 350nm DAD

Temperature: 25 °C

Basic run:

B : Acetonitrile

C: Ammonium hydrogen carbonate buffer pH 10

Column: XBridge C18 2.1 x 30 mm with 5 micron particle size

Gradient table:

minutes	%B	%C
0	0	100
2.30	95	5
3.50	95	5
3.60	0	100

Flow: 1 mL/min

UV: 215nm - 350nm DAD

Temperature: 25 °C

IPC Acid:

12 minutes LC-MS gradient and instrument conditions:

A: 0.05% TFA in water

B: Acetonitrile

Column: SB-C18 3.0x50 1.8um

Flow: 1.2 mL/min

UV: 210, 225, 254nm

Temperature: 50 °C.

minutes	% A	% B
0	95	5
1	95	5
9	0	100
11.5	0	100
11.6	100	0
12	100	0

IPC Neutral:

12 minutes LC-MS gradient and instrument conditions:

A: 5% MeCN; 10 mM NH_4OAc in water

B: Acetonitrile

Column: Extend-C18 3.0x50 1.8um

Flow: 1.2 mL/min

UV: 210, 225, 254nm

Temperature: 50 °C.

minutes	% A	% B
0	100	0
1	100	0
9	0	100
11.5	0	100
11.6	100	0
12	100	0

System M:

2 minute LC-MS gradient and instrument conditions:

Acid run:

A: 1.5ml TFA in 4L water

B: 0.75ml TFA in 4L acetonitrile

Column: C18 phase Xtimate 2.1*30mm with 3 micron particle size

Gradient: 90-20% A over 0.9 min, 0.6 min hold, 1.2 mL/min

UV: 210nm - 370nm

Temperature: 50 °C

System N:

4.7 minute LC-MS gradient and instrument conditions:

Acid run:

A: 0.0375% TFA in water (V/V)

B: 0.01875% TFA in acetonitrile (V/V)

Column: XBridge C18 2.1 x 50mm with 5 micron particle size

Gradient table:

minutes	%A	%B
0	99	1
0.6	95	5
4	0	100
4.3	99	1
4.7	99	1

Flow: 0.8 mL/min

UV: 210nm DAD

Temperature: 40 °C

System O:

4.7 minute LC-MS gradient and instrument conditions:

Acid run:

A: 0.0375% TFA in water (V/V)

B: 0.01875% TFA in acetonitrile (V/V)

Column: XBridge C18 2.1 x 50mm with 5 micron particle size

Gradient table:

minutes	%A	%B
0	90	10
0.5	90	10
4	0	100
4.3	90	10
4.7	90	10

Flow: 0.8 mL/min

UV: 210nm DAD

Temperature: 40 °C

System P:

4.7 minute LC-MS gradient and instrument conditions:

Base run:

A: 0.05% NH4OH in water (V/V)

B: Acetonitrile

Column: XBridge C18 2.1 x 50mm with 5 micron particle size

Gradient table:

minutes	%A	%B
0	95	5
0.5	95	5
3.4	0	100
4.2	0	100
4.21	95	5
4.7	95	5

Flow: 0.8 mL/min

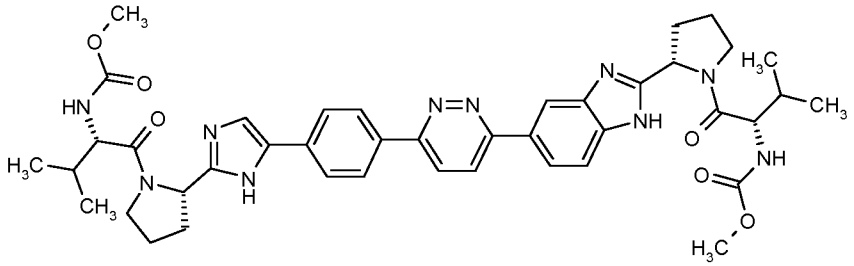
UV: 210nm DAD

Temperature: 40 °C

Abbreviations

EDCI.HCl	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
HATU	2-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBT	*N*-Hydroxybenzotriazole
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
DIPEA	Diisopropylethylamine
Sphos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
DMF	*N*,*N*-Dimethylformamide
$MgSO_4$	Magnesium sulphate
Na_2SO_4	Sodium sulphate
K_3PO_4	Potassium phosphate tribasic
tBME	tert Butyl methyl ether

Example 1: Methyl {(2*S*)-1-[(2*S*)-2-{5-[6-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridazin-3-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

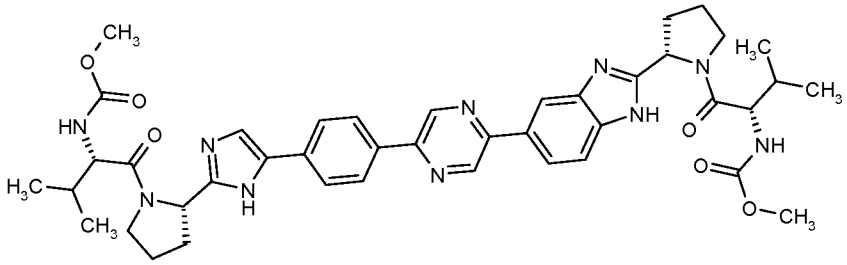


N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (131 mg, 0.746 mmol), HOBT (119 mg, 0.778 mmol) and EDCI.HCl (143 mg, 0.746 mmol) in acetonitrile (5 mL) were stirred at room temperature for 40 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[6-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridazin-3-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 9** (170 mg, 0.311 mmol) was added, followed by the dropwise addition of diisopropylethylamine (0.45 mL, 2.49 mmol). The mixture was then stirred at room temperature for 72 hours. After this time, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 98:2 to 90:10), followed by preparative HPLC (System H) (60:40 (v/v) methanol/ 0.1% NH_3 in water, flow rate 20 mL/min), to give the title compound as a white solid (32 mg).

LCMS (run time = 25 minutes, System E): R_t = 9.02 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.35-7.40 (m, 10H), 5.30 (m, 1H), 5.15 (m, 1H), 4.25 (m, 2H), 4.15-3.85 (m, 4H), 3.65 (s, 6H), 2.50-1.95 (m, 10H), 1.00-0.85 (m, 12H).

Example 2: Methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Method A:

N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (47 mg, 0.271 mmol), HOBT (43 mg, 0.283 mmol) and EDCI.HCl (52 mg, 0.271 mmol) in acetonitrile (8 mL) were stirred at room temperature for 40 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 13** (62 mg, 0.113 mmol) was added, followed by the dropwise addition of DIPEA (0.15 mL, 0.904 mmol). The reaction mixture was then stirred at room temperature for 18 hours. After this time, the solvent was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5), followed by preparative HPLC (System H) (60:40 to 65:35 (v/v) methanol/ 0.1% NH_3 in water, flow rate 50 mL/min), to give the title compound as a white solid (13.79 mg).

LCMS (run time = 25 minutes, System E): R_t = 9.45 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.30-7.25 (m, 9H), 7.10-7.00 (m, 1H), 5.35-5.10 (m, 2H), 4.35-4.20 (m, 2H), 4.15-3.85 (m, 4H), 3.65 (s, 6H), 2.50-1.90 (m, 10H), 1.00-0.80 (m, 12H).

Method B:

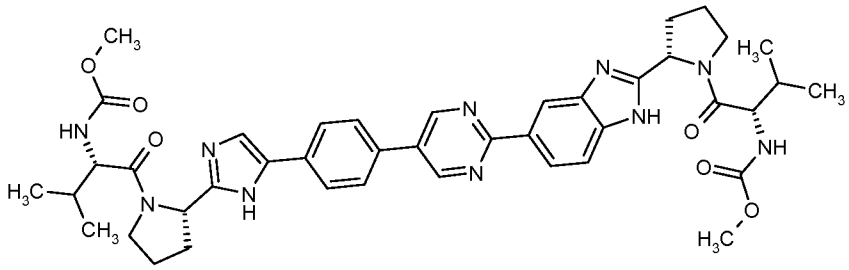
To a slurry of *N*-(methoxycarbonyl)-L-valine obtained from **Preparation 58** (144 g, 0.819 mol) and 1-hydroxybenzotriazole monohydrate (132 g, 0.860mol) in acetonitrile (3.19 L) at 0°C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (161 g, 0.840 mol). The reaction was maintained <5°C for 30 minutes then 2-[(2*S*)-pyrrolidin-2-yl]-6-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 13** (232 g, 396 mmol) was added, followed by DIPEA (357 mL, 2.05 mol) dropwise over 15 minutes. The solution was maintained at 0°C until reaction completion was observed, then the crude reaction mixture was reduced in *vacuo* to an orange oil. The oil was dissolved in dichloromethane (1.92 L) and washed with sodium hydrogen carbonate (sat. aq) (1.44 L) then water (1.44 L). The organic layer was reduced in *vacuo* to a yellow foam, then re-dissolved in dichloromethane (0.75L) and purified by flash chromatography (heptane:acetone 20:80 to 0:100). The product-containing fractions were reduced in *vacuo* to a yellow foam which was granulated in tBME (2.5

L) for 2 hours then reduced in *vacuo*. The resulting solid was granulated in water (2.5 L) overnight then filtered under reduced pressure to give the title compound as a yellow powder (260 g)

LCMS (IPC_ACID): Rt = 3.83 minutes; m/z 791 [MH^+]

^{1}H NMR (DMSO-d_6 + TFA): δ = 9.46-9.37 (s, 2H), 8.59-8.50 (m, 1H), 8.43-8.29 (m, 3H), 8.19-8.10 (m, 1H), 8.01-7.89 (m, 3H), 5.81-5.08 (m, 2H), 4.18-4.07 (dd, 2H), 3.86-3.72 (m, 2H), 3.61-3.46 (s, 6H), 2.50-1.89 (m, 12H), 0.94-0.66 (m, 12H).

Example 3: Methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

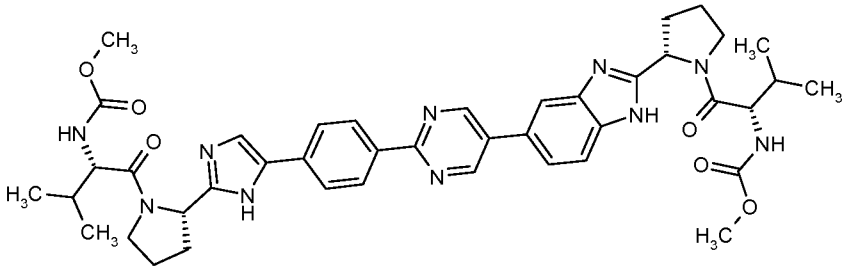


N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (143 mg, 0.816 mmol), HOBT (130 mg, 0.85 mmol) and EDCI.HCl (156 mg, 0.816 mmol) in acetonitrile (20 mL) were stirred at room temperature for 40 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 16** (186 mg, 0.340 mmol) was added, followed by the dropwise addition of DIPEA (0.48 mL, 2.72 mmol). The resulting reaction mixture was stirred at room temperature for 18 hours. After this time, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5), followed by preparative HPLC (System H) (60:40 to 65:35 (v/v) methanol/ 0.1% NH_3 in water, flow rate 50 mL/min), to give the title compound as a white solid (50.5 mg).

LCMS (run time = 25 minutes, System E): R_t = 9.36 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.10-7.35 (m, 8H), 7.30-7.15 (m, 2H), 5.30-5.10 (m, 2H), 4.30-3.80 (m, 6H), 3.65 (s, 6H), 2.50-2.00 (m, 10H), 1.00-0.80 (m, 12H).

Example 4: Methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Method A:

N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (46 mg, 0.266 mmol), HOBT (42 mg, 0.2775 mmol) and EDCI.HCl (51 mg, 0.266 mmol) in acetonitrile (8 mL) were stirred at room temperature for 40 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[2-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 19** (61 mg, 0.110 mmol) was added, followed by the dropwise addition of DIPEA (0.15 mL, 0.88 mmol). The reaction mixture was stirred at room temperature for 18 hours. After this time, the solvent was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5), followed by preparative HPLC (System H) (60:40 to 65:35 (v/v) methanol/ 0.1% NH_3 in water, flow rate 50 mL/min), to give the title compound as a white solid (18 mg).

LCMS (run time = 25 minutes, System E): R_t = 9.36 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.10-8.95 (m, 2H), 8.45-8.25 (m, 2H), 7.90-7.30 (m, 6H), 5.35-5.15 (m, 2H), 4.25 (t, 2H), 4.10-3.80 (m, 4H), 3.65 (s, 6H), 2.45-1.90 (m, 10H), 1.00-0.85 (m, 12H).

Method B:

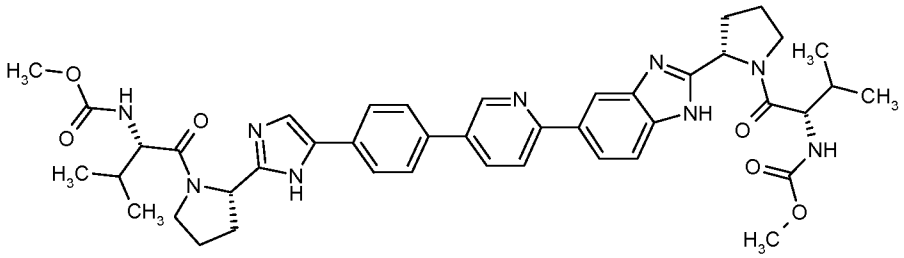
A slurry of *N*-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (3.41 g, 19.46 mmol) and HOBT (3.13 g, 20.43 mmol) in acetonitrile (76 mL) was cooled to 0 °C with an ice bath. EDCI.HCl (3.82 g, 19.92 mmol) was added in one portion. Once a clear solution was obtained, the reaction mixture was stirred at 0 °C for 40 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[2-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazole hydrochloride salt (5.7 g, 9.73 mmol) obtained from **Preparation 19** was added in one portion, forming a thick slurry. After 5 minutes, diisopropylethylamine (8.48 mL, 48.65 mmol) was added dropwise over a period of 10-15 minutes. The ice bath was removed and the mixture was stirred for another 30 minutes. The reaction mixture was concentrated under reduced pressure, and then the residue was diluted with dichloromethane (150 mL) and sodium bicarbonate (sat. aq.) (100 mL). The mixture was thoroughly mixed for 30 minutes. The two phases were separated and the organic layer was washed with water (100 mL). The layers were separated and the organic layer was concentrated under reduced pressure

to an orange foam. The crude product was purified by flash chromatography (heptane:acetone, 40:60 to 15:85) to give the title compound as a pale yellow solid (2.03 g).

LC (run time = 30 minutes, System E): R_t = 9.29 minutes; m/z = 791 [MH^+]

^{1}H NMR (400 MHz, CD_3OD + 3 drops TFA-*d*): δ = 9.23 (s, 2H), 8.66-8.63 (m, 2H), 8.17 (s, 1H), 8.02-7.87 (m, 5H), 5.40-5.24 (m, 2H), 4.30-4.23 (m, 2H), 4.29-4.08 (m, 2H), 4.03-3.85 (m, 2H), 3.66 (s, 6H), 2.70-2.55 (m, 2H), 2.44-2.02 (m, 8H), 1.01-086 (m, 12H)

Example 5: Methyl {(2*S*)-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

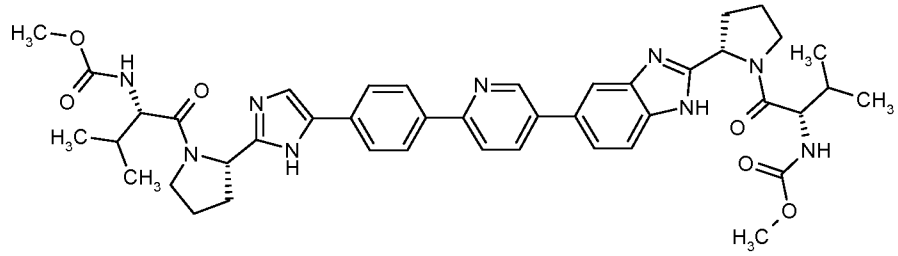


To a stirred solution of *N*-(methoxycarbonyl)-L-valine obtained from **Preparation 58** (14 mg, 0.082 mmol) in dry acetonitrile (1 mL) were added HOBT (15 mg, 0.098 mmol) and EDCI.HCl (18 mg, 0.094 mmol). The reaction mixture was stirred at room temperature for 45 minutes. 2-[(2S)-Pyrrolidin-2-yl]-5-[5-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 22** (24 mg, 0.039 mmol) was then added, followed by the dropwise addition of DIPEA (68 μL, 0.39 mmol). The reaction mixture was stirred at room temperature for 4.5 hours. After this time, the solvent was evaporated under reduced pressure and the resulting crude material was purified by flash chromatography (dichloromethane : methanol : ammonia, 98:2:0.2 to 93:7:0.7) to give the title compound as a pale yellow solid (14 mg).

LCMS (run time = 6 minutes, System B): R_t = 1.81 minutes; m/z 790 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.97-10.51 (m, 2H), 8.95-8.82 (m, 1H), 8.33-7.38 (m, 9H), 7.21-7.09 (m, 1H), 5.72 (m, 1H), 5.60 (m, 1H), 5.46 (m, 1H), 5.29 (m, 1H), 4.26 (m, 2H), 3.90 (m, 2H), 3.71 (m, 8H), 3.05-2.95 (m, 2H), 2.47-2.34 (m, 2H), 2.30-2.11 (m, 4H), 2.02-1.96 (m, 2H), 0.96-0.83 (m, 12H).

Example 6: Methyl {(2*S*)-1-[(2*S*)-2-{5-[6-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-3-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

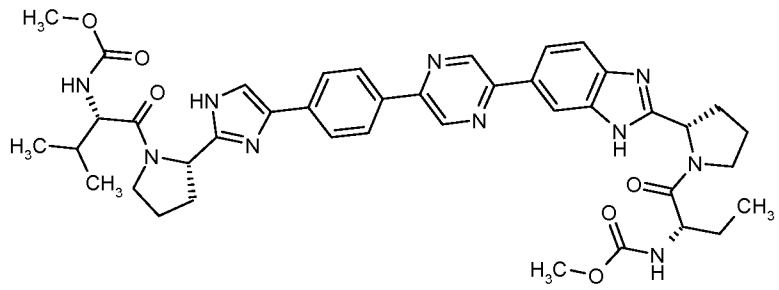


To a stirred solution of *N*-(methoxycarbonyl)-L-valine obtained from **Preparation 58** (48 mg, 0.271 mmol) in dry acetonitrile (2 mL) were added HOBT (50 mg, 0.323 mmol) and EDCI.HCl (59 mg, 0.310 mmol). The reaction mixture was stirred at room temperature for 45 minutes. 2-[(2S)-Pyrrolidin-2-yl]-5-[6-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-3-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 25** (80 mg, 0.13 mmol) was added, followed by the dropwise addition of DIPEA (225 μL, 1.29 mmol). The resulting mixture was stirred at room temperature for 16 hours. After this time, the solvent was evaporated under reduced pressure and the resulting crude material was purified by flash chromatography (dichloromethane : methanol : ammonia, 98:2:0.2 to 90:10:1) to give the title compound as a pale yellow solid (50 mg).

LCMS (run time = 6 minutes, System B): R_t = 1.58 minutes; m/z 790 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.96-10.50 (m, 2H), 8.97-8.84 (m. 1H), 8.06-7.34 (m, 9H), 7.19-6.97 (m, 1H), 5.60-5.49 (m, 2H), 5.45 (d, 1H), 5.37-5.26 (m, 1H), 4.43-4.33 (m, 2H), 3.99-3.83 (m, 2H), 3.80-3.69 (m, 8H), 3.10-2.85 (m, 2H), 2.47-1.96 (m, 8H), 0.96-0.87 (m, 12H).

Example 7: Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



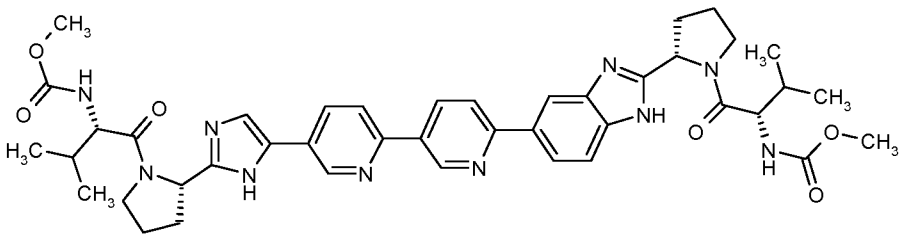
(2*S*)-2-[(Methoxycarbonyl)amino]butanoic acid obtained from **Preparation 74** (98 mg, 0.061 mmol) in acetonitrile (10 mL) was treated with EDCI.HCl (116 mg, 0.61 mmol) and HOBT (100 mg, 0.66 mmol) at room

temperature. After 30 minutes Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-indol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate (350 mg, 0.55 mmol) from **Preparation 64** and DIPEA (0.765 mL, 4.4 mmol) were added and the reaction was stirred at room temperature for 4 hours. The reaction was diluted with ethyl acetate (20 mL) and washed with saturated sodium hydrogen carbonate (2 x 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 100:0 to 96:4) to give the title compound as a yellow solid (120 mg).

LCMS (run time = 25 minutes, System L): R_t = 11.87 minutes; m/z 777 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.35, 12.30 (2 x s, 1H), 11.84 (s, 1H), 9.30-9.28 (m, 2H), 8.22 (s, 1H), 8.16-8.13 (m, 2H), 7.99-7.97 (m, 1H), 7.88-7.84 (m, 2H), 7.59-7.56 (m, 1H), 7.29-7.27 (m, 1H), 5.22-5.20 (m, 1H), 5.08-5.05 (m, 1H), 4.24-4.19 (m, 1H), 4.07-4.03 (m, 1H), 3.79-3.77 (m, 4H), 3.52 (s, 6H), 2.25-2.11 (m, 6H), 2.05-1.91 (m, 8H), 1.73-1.64 (m, 1H), 1.51-1.46 (m, 1H), 0.90-0.81 (m, 6H).

Example 8: Methyl [(2*S*)-1-{(2*S*)-2-[5-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-2,3'-bipyridin-6'-yl)-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

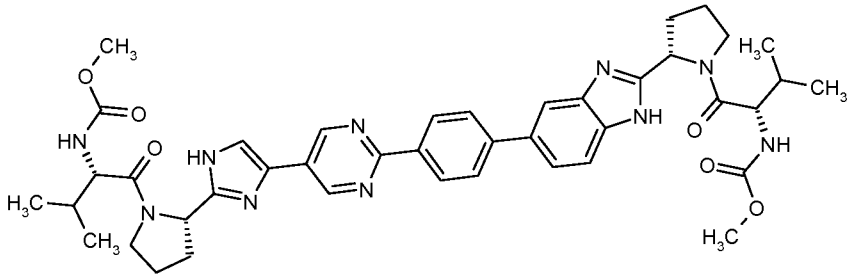


To a stirred solution of *N*-(methoxycarbonyl)-L-valine obtained from **Preparation 58** (0.089 g, 0.51 mmol) in dry acetonitrile (2.5 mL), were added HOBT (0.082 g, 0.53 mmol) and EDCI.HCl (0.097 g, 0.51 mmol). The resulting solution was stirred at room temperature for 1 hour. After this time, 6'-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-2,3'-bipyridine hydrochloride salt obtained from **Preparation 30** (0.088 g, 0.13 mmol) was added, followed by DIPEA (0.3 mL, 1.52 mmol). The resulting reaction mixture was stirred at room temperature. After 16 hours, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (dichloromethane : methanol : ammonia, 97.5:2.5:0.3 to 95:5:0.3) to give the title compound as a yellow solid (42 mg).

LCMS (run time = 5 minutes, System D): R_t = 2.01 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.37-9.34 (m, 1H), 9.07-9.06 (m, 1H), 8.54-8.47 (m, 1H), 8.36-8.04 (m, 4H), 7.71-7.32 (m, 3H), 5.27-5.22 (m, 2H), 4.09-4.05 (m, 2H), 3.90-3.79 (m, 4H), 3.54 (s, 6H), 2.29-1.91 (m, 10H), 0.93-0.82 (m, 12H).

Example 9: Methyl {(2*S*)-1-[(2*S*)-2-{4-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

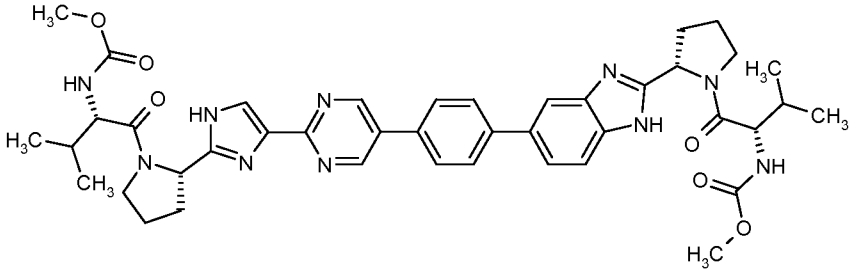


N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (147 mg, 0.84 mmol), HOBT (134 mg, 0.875 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (161 mg, 0.84 mmol) in acetonitrile (5 mL) were stirred at room temperature for 20 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 40** (350 µmol) was added, followed by the dropwise addition of diisopropylethylamine (488 µL, 2.80 mmol). The resulting mixture was stirred at room temperature for 18 hours. After this time, the reaction was diluted with ethyl acetate and washed with sodium bicarbonate (sat. aq.), then brine. The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC (System H) (60:40 to 35:75 methanol/ 0.1% NH_3 in water over 10 minutes) to give the title compound as a yellow solid (114.7 mg).

LCMS (run time = 25 minutes, System E): R_t = 10.24 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, MeOD) δ = 9.11-9.05 (m, 3H), 8.41-8.36 (m, 3H), 7.75-7.68 (m, 3H), 7.54-7.48 (m, 1H), 5.27-5.22 (m, 2H), 4.25 (t, 2H), 4.10-3.89 (m, 4H), 3.64 (s, 6H), 2.50-2.01 (m, 10H), 0.97-0.92 (m, 12H).

Example 10: Methyl {(2*S*)-1-[(2*S*)-2-{4-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



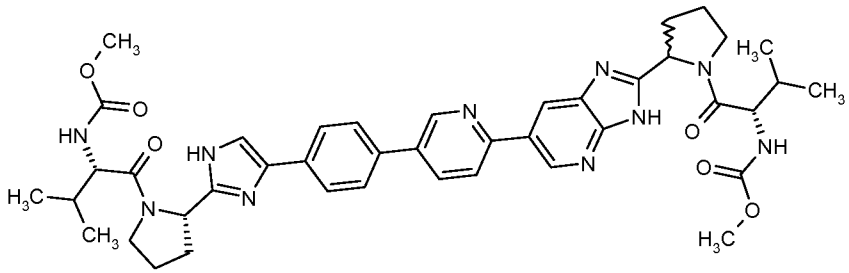
N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (64 mg, 366 µmol), HOBT (58 mg, 381 µmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70 mg, 366 µmol) in acetonitrile (5 mL) were stirred at room temperature for 20 minutes. 2-[(2*S*)-Pyrrolidin-2-yl]-5-[4-(2-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}pyrimidin-5-yl)phenyl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 43** (152

μmol) was added, followed by the dropwise addition of diisopropylethylamine (210 μL, 1.22 mmol). The resulting mixture was stirred at room temperature for 18 hours. After this time, the reaction was diluted with ethyl acetate and washed with sodium bicarbonate (sat. aq.), then brine. The organic extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by preparative HPLC (System H) (60:40 to 35:75 methanol/ 0.1% NH_3 in water over 10 minutes) to give the title compound as a white solid (39mg).

LCMS (run time = 25 minutes, System E): R_t = 9.68 minutes; m/z 791 [MH^+]

^{1}H NMR (400 MHz, MeOD) δ = 9.05-9.02 (m, 3H), 7.80-7.78 (m, 7H), 5.27-5.25 (m, 2H), 4.24 (m, 2H), 4.10-3.80 (m, 4H), 3.64 (s, 6H), 2.45-2.02 (m, 10H), 0.93-0.86 (m, 12H).

Example 11: Methyl [(2*S*)-1-(2-{6-[5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyridin-2-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamate

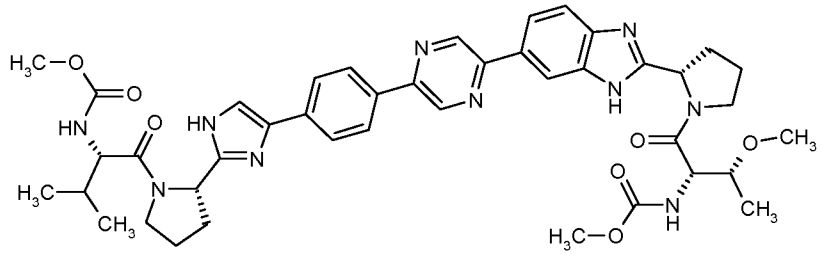


N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (40 mg, 230 μmol), HOBT (37 mg, 240 μmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 230 μmol) in acetonitrile (5 mL) were stirred at room temperature for 20 minutes. 2-(Pyrrolidin-2-yl)-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 57** (96 μmol) was added, followed by the dropwise addition of diisopropylethylamine (134 μL, 770 μmol). The resulting mixture was stirred at room temperature for 16 hours. After this time, the reaction mixture was diluted with ethyl acetate and washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC (System H) (45:55 to 65:35 (v/v) methanol/ 0.1% ammonia in water, flow rate 50 mL/min) to give the title compound as an off-white solid (14 mg).

LCMS (run time = 30 minute method): R_t = 9.35 minutes (57.6%); m/z 791 [MH^+], 9.60 minutes (41.4%); m/z 791 [MH^+]

^{1}H NMR (400 MHz, DMSO) δ = 9.10-8.97 (m, 2H), 8.20-8.08 (m, 2H), 7.87-7.70 (m, 4H), 7.33-7.22 (m, 2H), 5.10-5.03 (m, 2H), 4.11-3.97 (m, 2H), 3.89-3.70 (m, 4H), 3.60-3.54 (m, 6H), 2.35-1.80 (m, 10 H), 0.95-0.77 (m, 12H).

Example 12: Methyl (2*S*,3*R*)-3-methoxy-2-{[(2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidin-1-yl]carbonyl}butanoate

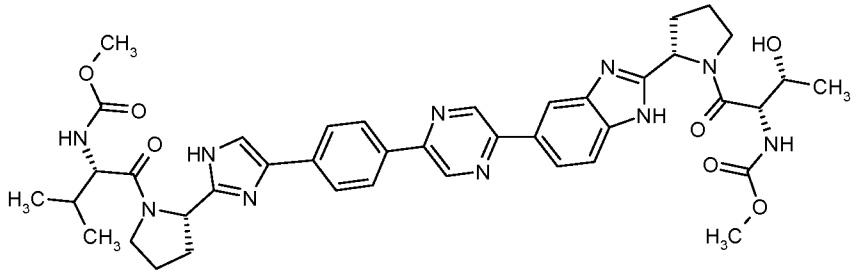


N-(Methoxycarbonyl)-*O*-methyl-L-threonine obtained from **Preparation 72** (130 mg, 0.682 mmol), HOBt (109 mg, 0.710 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (131 mg, 0.682 mmol) in acetonitrile (15 mL) were stirred at room temperature for 30 minutes. After this time, a solution of methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-indol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate obtained from **Preparation 64** (360 mg, 0.568 mmol) in acetonitrile (5.0 mL) was added, followed by dropwise addition of diisopropylethylamine (594 µL, 0.568 mmol) and the reaction mixture was stirred at room temperature for 48 hours. After this time, the solvent was removed under reduced pressure to give a brown oil which was partitioned between saturated sodium hydrogen carbonate solution (100 mL) and dichloromethane (50 mL). The layers were separated and the aqueous phase extracted again with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulphate and filtered. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (dichloromethane : methanol with 1N ammonia, 100:0 to 90:10) to give an off white solid. The solid was further purified by preparative HPLC (30:70 acetonitrile/ water with ammonium hydrogen carbonate buffer pH 10 over 20 minutes) to a white solid that was loaded on a SCX column (20.0 g), eluting with 7N ammonia in methanol (2 x 20 mL). The elute was concentrated under reduced pressure to give the title compound as an off white solid (90 mg).

LCMS (run time = 25 minutes, System K): R_t = 14.44 minutes, m/z 805.83 [M-H$^-$]; LCMS (run time = 5 minutes, System C): R_t = 1.71 minutes, m/z 807.42 [MH$^+$]

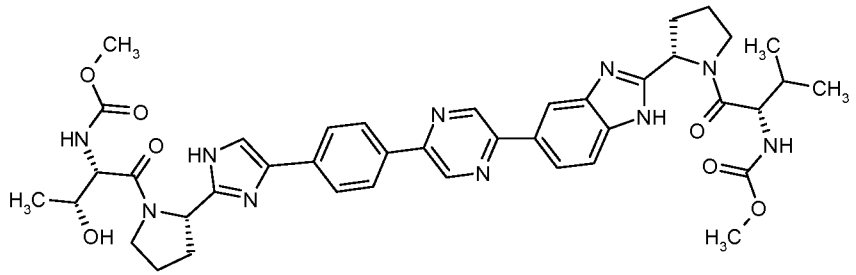
^{1}H NMR (400 MHz, DMSO-d_6 + 1 drop of TFA): δ= 9.44-9.42 (m, 2H), 8.56 (s, 1H); 8.38-8.33 (m, 3H); 8.25 (s, 1H); 7.96-7.80 (m, 3H); 5.31-5.27 (m, 1H); 5.14-5.10 (m, 1H); 4.32-4.30 (m, 1H); 4.17-4.09 (m, 1H) 3.95-3.75 (m, 5H); 3.53-3.50 (m, 9H);2.45-2.34 (m, 1H); 2.26-1.90 (m, 9H);1.00 (d, 3H); 0.83 (d, 3H); 0.79 (d, 3H).

Example 13: Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*,3*R*)-3-hydroxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



N-(Methoxycarbonyl)-L-threonine obtained from **Preparation 70** (94 mg, 0.53 mmol), HOBT (169 mg, 1.10 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (101 mg, 0.53 mmol) in acetonitrile (15 mL) were stirred at room temperature for 20 minutes. A suspension of methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-indol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate obtained from **Preparation 64** (278 mg, 0.44 mmol) in acetonitrile (5 mL) was added, followed by the dropwise addition of diisopropylethylamine (306 µL, 1.76 mmol). The resulting mixture was stirred at room temperature for 18 hours. After this time, the reaction was diluted with dichloromethane and washed with brine (sat. aq.). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC (System H) (50:50 to 5:95 methanol/ 0.1% NH_3 in water over 15 minutes) to give the title compound as a yellow solid (130 mg).
LCMS (run time = 25 minutes, System E): R_t = 9.30 minutes; m/z 793 [MH^+].
^{1}H NMR (400 MHz, MeOD) δ = 9.27-8.73 (m, 2H), 8.38-6.89 (m, 8H), 5.45-4.97 (m, 2H), 4.59-2.99 (m, 17H), 2.65-1.74 (m, 10H), 1.42-0.60 (m, 9H).

Example 14: Methyl {(2*S*,3*R*)-3-hydroxy-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate



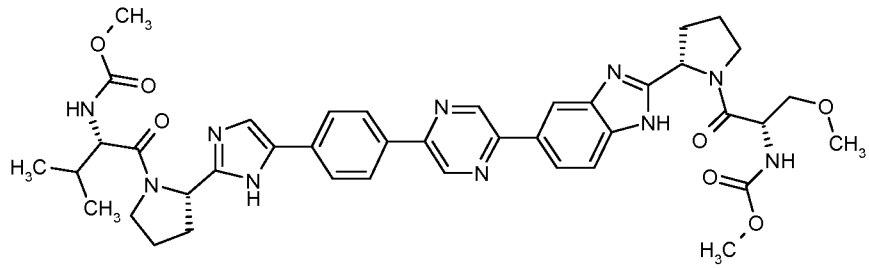
N-(Methoxycarbonyl)-L-threonine obtained from **Preparation 70** (160 mg, 0.90 mmol), HOBT (289 mg, 1.18 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (173 mg, 0.90 mmol) in acetonitrile (20 mL) were stirred at room temperature for 30 minutes. Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{5-[5-(4-{2-

[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate obtained from **Preparation 69** (476 mg, 0.75 mmol) in acetonitrile (5 mL) was added, followed by the dropwise addition of diisopropylethylamine (522 µL, 3.00 mmol). The resulting mixture was stirred at room temperature for 16 hours. After this time, the reaction was diluted with dichloromethane and washed with brine (sat. aq.). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC (System H) (50:50 to 5:95 methanol/ 0.1% NH_3 in water over 15 minutes) to give the title compound as a yellow solid (255 mg).

LCMS (run time = 30 minutes, System E): R_t = 8.59 minutes; m/z 793 [MH^+].

^{1}H NMR (400 MHz, DMSO) δ = 12.24-12.19 (d, 1H), 11.65 (s, 1H), 9.23 (s, 2H), 8.29 (d, 1H), 8.13 (d, 2H), 7.96 (dd, 1H), 7.86 (d, 2H), 7.61 (d, 1H), 7.54 (s, 1H), 7.03 (br s, 1H), 6.76 (br s, 1H), 5.21-5.13 (m, 2H), 4.87 (br m, 1H), 4.29-4.10 (m, 2H), 3.91-3.70 (m, 5H), 3.54 (s, 6H), 2.27-1.82 (m, 9H), 1.08 (s, 3H), 0.86-0.80 (m, 6H).

Example 15: Methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-3-methoxy-2-[(methoxycarbonyl)amino]propanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

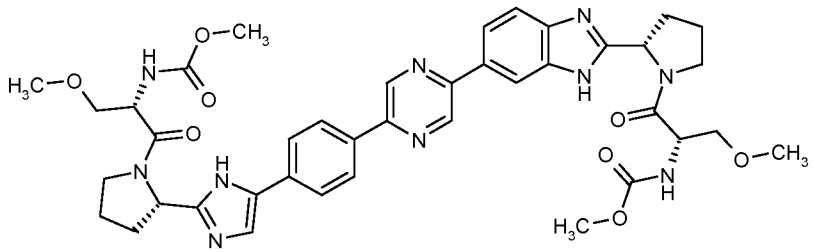


N-(Methoxycarbonyl)-*O*-methyl-L-serine obtained from **Preparation 77** (103 mg, 0.583 mmol), HOBT (93 mg, 0.607 mmol), EDCI.HCl (112 mg, 0.583 mmol) and DIPEA (0.508 mL, 2.916 mmol) were stirred in acetonitrile (5 mL) at room temperature for 30 minutes. Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-indol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate obtained from **Preparation 64** (308 mg, 0.486 mmol) was then added to the reaction mixture. It was then stirred at room temperature for 16 hours. After this time, the reaction mixture was diluted with ethyl acetate (60 mL) and the organic layer was washed with sodium hydrogen carbonate saturated solution (80 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and then the combined organic layers were washed with brine (100 mL) and dried over sodium sulphate. The solvent was evaporated under reduced pressure to give a yellow solid. The crude product was purified by flash chromatography (dichloromethane : methanol, 100 to 95:5) to give the title compound as a pale yellow solid (190 mg).

LCMS (run time = 25 minutes, System K): R_t = 10.66 minutes; m/z 791 [MH^-]

^{1}H NMR (400 MHz, CD_3OD+TFA-d): δ = 9.32-9.29 (m, 2H), 8.56 (d, 1H), 8.40 (d, 1H), 8.37-8.33 (m, 2H), 7.98-7.89 (m, 4H), 5.48-5.40 (m, 1H), 5.26 (t, 1H), 4.78-4.70 (m, 1H), 4.24 (d, 1H), 4.16-3.83 (m, 4H), 3.67-3.60 (m, 8H), 3.37, 3.34 (2s, 3H), 2.70-2.54 (m, 2H), 2.33-2.13 (m, 6H), 2.06 (m, 1H), 0.99, 0.93 (2d, 6H).

Example 16: Methyl {(2*S*)-3-methoxy-1-[(2*S*)-2-(5-{4-[5-(2-{(2*S*)-1-[N-(methoxycarbonyl)-*O*-methyl-L-seryl]pyrrolidin-2-yl}-1*H*-benzimidazol-6-yl)pyrazin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-1-oxopropan-2-yl}carbamate

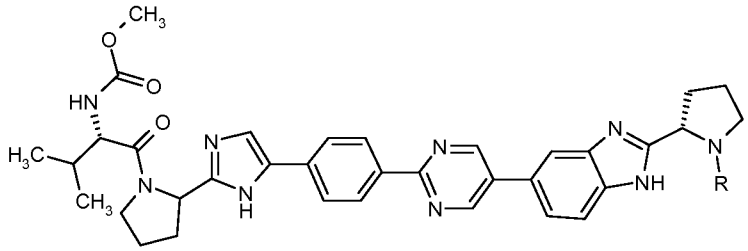


A solution of *N*-(methoxycarbonyl)-*O*-methyl-L-serine obtained from **Preparation 77** (141 mg, 0.794 mmol), HOBT (127 mg, 0.827 mmol) and EDCI.HCl (152 mg, 0.794 mmol) was stirred in acetonitrile (5 mL) at room temperature for 20 minutes. DIPEA (0.46 mL, 2.65 mmol) and 2-[(2*S*)-pyrrolidin-2-yl]-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazole hydrochloride salt obtained from **Preparation 13** (158 mg, 0.331 mmol) were then added. The reaction mixture was stirred at room temperature for 3 hours. The crude product was then purified by preparative HPLC (system H) (methanol/ 0.1% NH_3 in water, 55:45 to 65:35, 10 minutes), to give the title compound (45 mg).

LCMS (run time = 25 minutes, system E, base run); Rt = 8.68 minutes; m/z 795 [MH^+].

^{1}H NMR (400 MHz, CD_3OD): δ = 9.02-8.99 (m, 3H), 8.03-7.61 (m, 6H), 7.36-7.29 (m, 1H), 5.22-5.21 (m, 2H), 4.72-4.71 (m, 1H), 4.47-4.46 (m, 1H), 3.89 (d, 2H), 3.59 (s, 6H), 3.58-3.57 (m, 2H), 3.35 (s, 6H), 2.38-2.06 (m, 12H).

Examples 17 to 24 of general structure:



were synthesised *via* general method A or B and data for these are described in the table below.

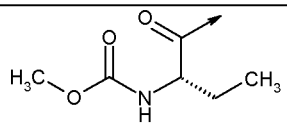
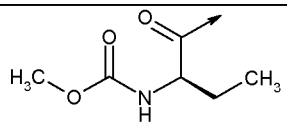
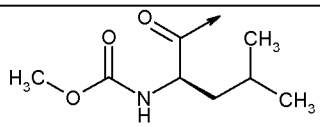
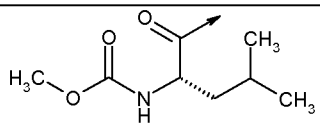
General method A:

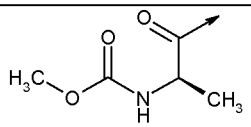
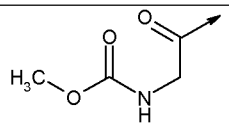
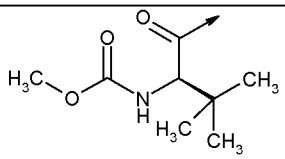
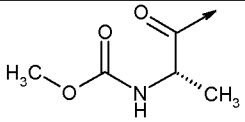
To a solution of methyl {(2S)-3-methyl-1-oxo-1-[(2S)-2-{5-[4-(5-{2-[(2S)-pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate, obtained from **Preparation 86,** in DMSO (0.1 M) was added the corresponding *tert*-butyl carboxylate amino acid (1.3 equivalents), triethylamine (2.0 equivalents) and HATU (1.3 equivalents). The resulting reaction mixture was stirred at room temperature for 16 hours. After this time, the mixture was diluted with saturated aq. Na_2CO_3 solution (3

mL) and extracted with ethyl acetate (4 x 1 mL). The combined ethyl acetate layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude intermediate was dissolved in methanol (0.750 mL) and to this solution was added 4M HCl in dioxane (0.250 mL). The resulting mixture was stirred at room temperature for 2 hours. After this time, the reaction mixture was concentrated under reduced pressure. The crude intermediate which was obtained was treated with a solution of methyl chloroformate in dichloromethane (1.0 equivalent of 0.1 M solution). The reaction mixture was then cooled to 0°C and triethylamine (2.0 equivalents) was added dropwise followed by stirring at 0°C for 10 minutes. It was then allowed to warm up to room temperature and stirred at this temperature for 1 hour. 7M Ammonia in methanol (1 mL) was then added to the reaction mixture and it was stirred at room temperature for a further 16 hours. The resulting mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC to give the pure final compound.

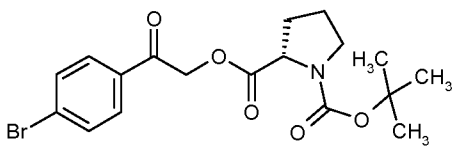
General method B:

A solution of methyl chloroformate in dichloromethane (1.25 equivalents of 0.1 M solution) was added to the amino acid methyl ester (1.0 equivalents). Triethylamine (1.1 equivalents) was then added at 0°C and the reaction mixture was stirred at 0°C for 10 minutes. After this time the mixture was allowed to warm up to room temperature and was stirred at this temperature for 1 hour. It was then concentrated under reduced pressure. The crude residue which was obtained was dissolved in methanol and 2M aqueous lithium hydroxide (16 equivalents) was then added. This mixture was then stirred at room temperature for 16 hours. After this time, the mixture was adjusted to pH 5-6 by addition of 2M HCl, evaporated under reduced pressure and then lyophilized to give the crude intermediate. To this intermediate was added a solution of methyl {(2S)-3-methyl-1-oxo-1-[(2S)-2-{5-[4-(5-{2-[(2S)-pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate, obtained from **Preparation 86**, in DMSO (0.7 equivalents of 0.1 M), triethylamine (0.7 equivalents) and HATU (1.0 equivalents). The reaction mixture was then stirred at 50°C for 16 hours. After this time, it was evaporated under reduced pressure and the residue was purified by preparative HPLC to give pure final compound.

Ex No.	R =	HPLC method	HPLC rtntn /mins	m/z	Method
17	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	N	2.386	777	A
18	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	N	2.43	777	A
19	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	O	2.069	805	B
20	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	O	2.396	805	B

21	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]propanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	N	2.344	763	B
22	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{[(methoxycarbonyl)amino]acetyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	N	2.301	749	B
23	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	P	2.551	805	B
24	 Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]propanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate	N	2.388	763	B

Preparation 1: 2-[2-(4-Bromophenyl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate



Method A:

2,4'-dibromoacetophenone (23.7 g, 85.4 mmol) was added to a stirred solution of 1-(*tert*-butoxycarbonyl)-L-proline (17.5 g, 81.3 mmol) in dichloromethane (175 mL) at 0 °C. DIPEA (15.6 mL, 89.4 mmol) was added

dropwise to the mixture and the resulting yellow solution was allowed to warm to room temperature and stirred for a further 2.5 hours. After this time, the mixture was washed successively with water (200 mL), sodium bicarbonate solution (sat.)(100 mL), water (200 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a viscous yellow oil (33.6 g).

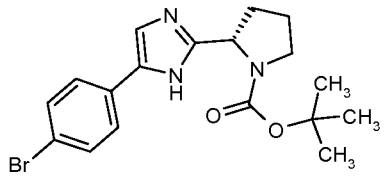
LCMS (run time = 6 minutes, System B): R_t = 3.40 minutes; m/z 312 and 314 [(M-Boc)H^+]

^{1}H NMR (400 MHz, T = 90 °C, DMSO-d_6): δ = 7.91-7.85 (m, 2H), 7.77-7.71 (m, 2H), 5.48 (d, 1H), 5.41 (d, 1H), 4.34 (dd, 1H), 3.40-3.35 (m, 2H), 2.34-2.23 (m, 1H), 2.14-2.05 (m, 1H), 1.96-1.84 (m, 2H), 1.40 (s, 9H).

Method B:

2,4'-dibromoacetophenone (13.09 Kg, 47.1 mol) was added to a stirring solution of 1-(*tert*-butoxycarbonyl)-L-proline (9.67 Kg, 44.9 mol) in dichloromethane (48 L) at 5°C. DIPEA (6.38 Kg, 49.4 mol) was added dropwise to the mixture and the resulting yellow solution was allowed to warm to room temperature and stirred for a further 2.5 hours. The mixture was washed with water (25 L), saturated sodium bicarbonate solution (25 L), water (25 L) and brine (25 L). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give a viscous yellow oil (18.51 Kg).

Preparation 2: *tert*-Butyl (2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate



Method A:

Ammonium acetate (44.6 g, 0.58 mmol) was added to a solution of 2-[2-(4-bromophenyl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate obtained from **Preparation 1** (53 g, 130 mmol) in xylenes (250 mL) and the resulting mixture was heated at 150 °C for 5 hours. After this time, the reaction mixture was cooled to room temperature. The suspension was filtered and the solvent was evaporated under reduced pressure. The resulting yellow solid was stirred in t-butylmethylether (75 mL) for 1 hour, then collected by filtration and dried to give the title compound as a white solid (29.1 g).

LCMS (run time = 6 minutes, System B): R_t = 2.48 minutes; m/z 391 and 393 [MH^+]

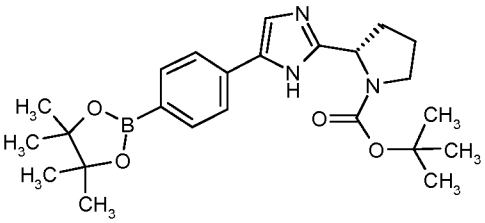
^{1}H NMR (400 MHz, T = 90 °C, DMSO-d_6): δ = 7.68 (d, 2H), 7.55 (s, 1H), 7.47 (d, 2H), 4.86-4.76 (m, 1H), 3.58-3.48 (m, 1H), 3.45-3.34 (m, 1H), 2.24-2.15 (m, 1H), 2.06-1.99 (m, 2H), 1.91-1.79 (m, 1H), 1,29 (s, 9H).

Method B:

Ammonium acetate (17.30 Kg, 224.4 mol) was added to a solution of the compound obtained from **Preparation 1** (18.51 Kg, 44.9 mol) in xylenes (92.5 L) and the resulting mixture was heated at 130-135°C for

5 hours. After cooling, the mixture was washed with water (22.5 L) and the aqueous was back extracted with ethyl acetate (22.5 L). The combined organics were washed with water (22.5 L), dried (Na_2SO_4), filtered and evaporated. The residue was suspended in tBME (100 L) and the resulting yellow solid was filtered off, washed with tBME (22.5 L) and dried to give 13.0 Kg of the title compound as a white solid.

Preparation 3: *tert*-Butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



Method A:

A mixture of *tert*-butyl (2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 2** (3.00 g, 7.65 mmol), bis(pinacolato)diboron (3.88 g, 15.3 mmol), and potassium acetate (1.88 g, 19.1 mmol) were dissolved in 1,4-dioxane (15.3 mL). The mixture was purged with nitrogen before adding (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (191 mg, 0.77 mmol). The reaction was purged again with nitrogen before heating at reflux for 2 hours. After this time, the resulting suspension was cooled to room temperature and the reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The pH of the aqueous layer was adjusted to around 8 by addition of a 2N aqueous sodium hydroxide solution and the phases were then separated. The aqueous layer was extracted again with ethyl acetate (100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (heptane : ethyl acetate, 50:50 to 40:60) to give the desired compound as a white foam. This material was dissolved in ethanol (10 mL) and heated to reflux. Water (20 mL) was added and the cloudy suspension was allowed to cool to room temperature slowly. The precipitate formed was collected by filtration, rinsing with water and dried to give the title compound as a white solid (2.54 g).

LCMS (run time = 6 minutes, System B): R_t = 3.46 minutes; m/z 440 [MH^+]

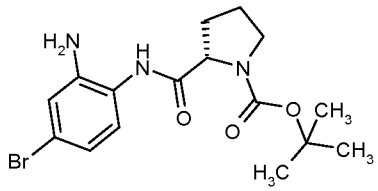
Method B:

A mixture of the bromide obtained from **Preparation 3** (12.1 Kg, 30.84 mol), bis(pinacolato)diboron (8.224 Kg, 32.38 mol), and potassium acetate (7.57 Kg, 77.1 mol) were dissolved in 1,4-dioxane (85 L). The mixture was degassed and then nitrogen filled three times.

(1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II), complex with dichloromethane (1:1) (918 g, 1.124 mol) was added and the reaction mixture was degassed and put under nitrogen twice more. The mixture was refluxed for 2 hours and then allowed to cool. The solvent was evaporated and the residue was partitioned with ethyl acetate (120 L) and water (120 L). The biphasic mixture was filtered and then

separated. The pH of the aqueous was adjusted to around 8 by the addition of 1M aqueous sodium hydroxide solution and extracted twice with ethyl acetate (2x60 L). The combined organic phases were washed with water (60 L), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was triturated in hexanes (20 L) filtered and washed with further hexanes (20 L). The product was dried to give 10.79 Kg of the title compound as a white solid.

Preparation 4: *tert*-Butyl (2S)-(2-amino-4-bromophenylcarbamoyl)pyrrolidine-1-carboxylate



Method A:

4-bromobenzene-1,2-diamine (8.2 g, 43.8 mmol) was added to a solution of *tert*-(butoxycarbonyl)-L-proline (9.42 g, 43.8 mmol), HATU (20 g, 52.6 mmol), and DIPEA (19.1 mL, 109.6 mmol) in dichloromethane (100 mL). The dark red reaction mixture was stirred under argon and at room temperature for 18 hours. After this time, the mixture was washed with sodium bicarbonate (sat. aq.), dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting brown oil was purified by flash chromatography (heptane : ethyl acetate, 60:40 to 0:100) to give the title compound as a pink solid (15.35 g).

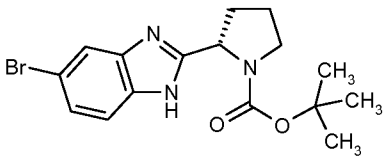
LCMS (run time = 5 minutes, System D): R_t = 2.85 minutes, m/z 384 and 386 [MH^+] (^{79}Br and ^{81}Br)

^1H NMR (400 MHz, CD_3OD): δ = 7.30-6.60 (m, 3H), 4.30 (m, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 2.30 (m, 1H), 2.10-1.80 (m, 3H), 1.50 (s, 9H).

Method B:

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (196 g, 1.022 mol) was added to a mixture of *tert*-(butoxycarbonyl)-L-proline (200 g, 0.929 mol), 4-bromobenzene-1,2-diamine (182.5 g, 0.976 mol) and DIPEA (240 mL, 1.858 mol) in acetonitrile (2000 mL). The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (1000 mL) and saturated aqueous sodium bicarbonate (1000 mL). The organic layer was further washed with saturated aqueous sodium bicarbonate (1000 mL) then saturated aqueous brine (1000 mL). The solvent was evaporated under reduced pressure to give the title compound as a beige solid (357 g).

Preparation 5: *tert*-Butyl (2*S*)-2-(5-bromo-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate



Method A:

A solution of *tert*-butyl (2S)-(2-amino-4-bromophenylcarbamoyl)pyrrolidine-1-carboxylate obtained from **Preparation 4** (15.35 g, 39.9 mmol) in acetic acid (65 mL) was heated at 70 °C. After 2 hours, the acetic acid was evaporated under reduced pressure and the resulting residue was diluted with dichloromethane (60 mL). The organic layer was washed with sodium bicarbonate (sat. aq.), then brine. It was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (12.82 g).

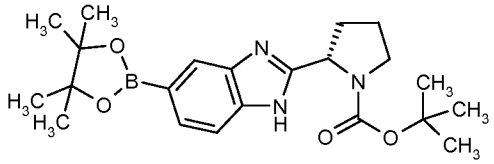
LCMS (run time = 6 minutes, System B): R_t = 2.50 minutes; m/z 366 and 368 [MH^+] (^{79}Br and ^{81}Br)

^1H NMR (400 MHz, DMSO-d_6): δ = 7.70-7.60 (m, 1H), 7.45-7.35 (d, 1H), 7.20 (t, 1H), 4.80-4.50 (m, 1H), 3.50-3.35 (m, 2H), 2.30 (m, 2H), 1.95 (br, 2H), 1.35, 1.00 (2xs, 9H).

Method B:

A solution of *tert*-butyl (2S)-(2-amino-4-bromophenylcarbamoyl)pyrrolidine-1-carboxylate obtained from **Preparation 4** (360 g, 0.93 mol) in acetic acid (1870 mL) was heated at 70 °C. After 2 hours, the acetic acid was evaporated under reduced pressure and the resulting residue was diluted with dichloromethane (1500 mL). The organic layer was washed sequentially with 2M aqueous potassium carbonate (1000 mL), 1M aqueous hydrochloric acid (1000 mL), 0.5M aqueous hydrochloric acid (1000 mL), 2M aqueous potassium carbonate (1000 mL) and water (1000 mL). The solvent was evaporated under reduced pressure to give the title compound as a brown solid (340 g).

Preparation 6: *tert*-Butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl] pyrrolidine-1-carboxylate



Method A:

To *tert*-butyl (2*S*)-2-(5-bromo-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 5** (6g, 16.40 mmol) in 1,4-dioxane (100 mL), were added dichloro(1,1'-bis(diphenylphosphino)ferrocene) palladium(II) (1.34 g, 1.64 mmol), potassium acetate (3.6 g, 36.08 mmol), and bis(pinacolato)diboron (8.33 g, 32.80 mmol). The reaction mixture was heated at 120 ºC for 16 hours. After this time, the reaction was cooled to room temperature and diluted with ethyl acetate (30 mL). The solution was washed with water, then

sodium bicarbonate (sat. aq.), and brine. The organic layer was dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude oil obtained was purified by flash chromatography (heptane:ethyl acetate, 50:50 to 0:100) to give the title compound as a pink solid (0.79 g).

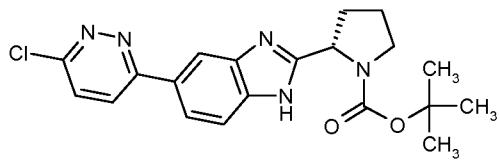
LCMS (run time = 5 minutes, System D): R_t = 2.93 minutes; m/z 414 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 7.95 (s, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 4.95 (m, 1H), 4.90 (m, 2H), 3.70 (m, 1H), 3.50 (m, 1H), 2.40 (m, 1H), 2.00 (m, 1H), 1.35 (s, 12H), 1.10 (s, 9H).

Method B:

To *tert*-butyl (2*S*)-2-(5-bromo-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 5** (208.6 g, 0.569 mol) in 1,4-dioxane (2086 mL), were added dichloro(1,1'-bis(diphenylphosphino) ferrocene)palladium(II) (23.3 g, 28.5 mmol), potassium acetate (139.7 g, 1.42 mol), and bis(pinacolato)diboron (188 g, 0.74 mol). The reaction mixture was heated at 100 °C for 16 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (1000 mL) and water (1000 mL). The organic layer was washed twice with water (1000 mL) and the solvent was removed under reduced pressure. The crude oil obtained was purified by flash chromatography (heptane:ethyl acetate, 60:40 to 20:80) to give a beige solid. This solid was slurried in heptane (1000 mL), collected by filtration and dried to give the title compound as a white solid (159.5 g)

Preparation 7: *tert*-Butyl (2*S*)-2-[5-(6-chloropyridazin-3-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate

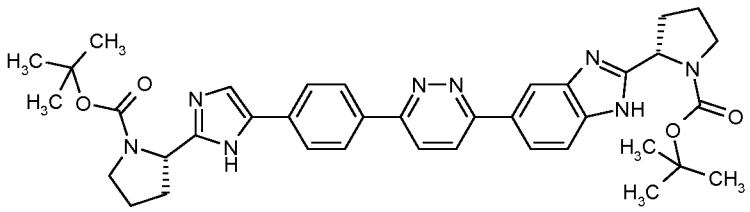


To *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (500 mg, 1.21 mmol) and 3,6-dichloropyridazine (160 mg, 1.10 mmol) in 1,4-dioxane (20 mL) / water (1.9 mL), were added tris(dibenzylideneacetone)dipalladium(0) (10 mg, 11.0 µmol), tricyclohexylphosphine (7 mg, 27.5 µmol) and potassium phosphate (397 mg, 1.87 mmol) and the resulting mixture was heated at 120 °C for 16 hours. After this time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water. The aqueous layer was extracted again with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5) to give the title compound as a yellow solid (295 mg).

LCMS (run time = 5 minutes, System D): R_t = 2.55 minutes; m/z 400 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.30 (m, 1H), 8.25 (d, 1H), 7.90 (br, 1H), 7.80 (d, 1H), 7.75 (m, 1H), 5.10-5.00 (m, 1H), 3.75 (m, 1H), 3.55 (m, 1H), 2.45 (br, 1H), 2.10-1.90 (m, 3H), 1.20 (s, 9H).

Preparation 8: *tert*-Butyl (2*S*)-2-{5-[4-(6-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridazin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

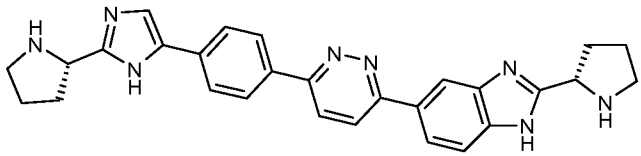


To *tert*-butyl (2S)-2-[5-(6-chloropyridazin-3-yl)-1H-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 7** (150 mg, 369 µmol) and *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (175 mg, 406 µmol) in 1,4-dioxane (6 mL) / water (0.6 mL), were added $Pd_2(dba)_3$ (3.4 mg, 3.69 µmol), tricyclohexylphosphine (2.6 mg, 9.23 µmol) and potassium phosphate (176 mg, 625 µmol). The reaction mixture was heated at 120 ºC for 16 hours. After this time, the resulting mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed with water. The aqueous layer was extracted again with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5) to give the title compound as a yellow solid (148 mg).

LCMS (run time = 1.5 minutes, System F): R_t = 0.69 minutes; m/z 677 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.40-7.35 (m, 10H), 5.00 (m, 2H), 3.75 (m, 2H), 3.55 (m, 2H), 2.50-2.25 (br m, 2H), 2.10-1.85 (br m, 6H), 1.10 (s, 18H).

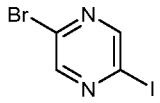
Preparation 9: 2-[(2*S*)-pyrrolidin-2-yl]-5-[6-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridazin-3-yl]-1*H*-benzimidazole hydrochloride salt



4M HCl in 1,4-dioxane (0.95 mL, 28.0 mmol) was added to *tert*-butyl (2*S*)-2-{5-[4-(6-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridazin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 8** (148 mg, 311 µmol) in ethanol (0.5 mL) and the reaction mixture was stirred at room temperature for 16 hours. After this time, the solvent was evaporated under reduced pressure and azeotroped with toluene to give the title compound as a yellow solid (170 mg).

^{1}H NMR (400 MHz, D_2O): δ = 8.25 (d, 2H), 8.10 (s, 1H), 7.90 (d, 2H), 7.80 (d, 1H), 7.70 (d, 4H), 5.00 (m, 2H), 3.40 (m, 4H), 2.45 (m, 2H), 2.30-2.00 (m, 6H).

Preparation 10: 2-Bromo-5-iodopyrazine

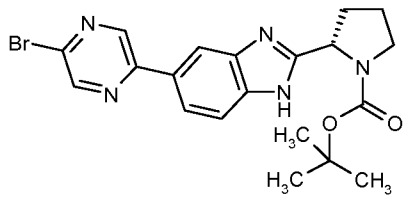


To a solution of 5-bromopyrazin-2-amine (25.95 g, 147.13 mmol) in 1,2-dimethoxyethane (500 mL) was added cesium iodide (38.75 g, 147.13 mmol), copper (I) iodide (8.52 g, 44.74 mmol) and iodine (18.93 g, 74.57 mmol). Isoamyl nitrite (120 mL, 894.8 mmol) was then added dropwise via a dropping funnel and the reaction mixture was heated at 60 °C for 1 hour. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (200 mL), washed with ammonium chloride (sat. aq .200 mL), then sodium thiosulphate (sat. aq.3 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by silica column (heptane : ethyl acetate, 100:0 to 85:15) to give the title compound as a off-white solid (35.38 g).

LCMS (run time = 5 minutes, System D): R_t = 2.09 minutes.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.50 (s, 1H).

Preparation 11: *tert*-Butyl (2*S*)-2-[5-(5-bromopyrazin-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate

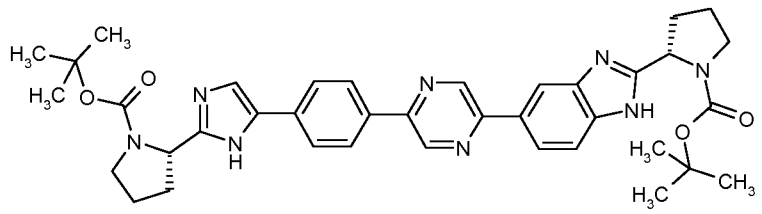


To *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (500 mg, 1.21 mmol) and 2-bromo-5-iodopyrazine obtained from **Preparation 10** (310 mg, 1.10 mmol) in toluene (12.5 mL) and ethanol (1.6 mL), were added [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 55 µmol) and sodium carbonate (1.1 mL, 1M aqueous solution, 1.1 mmol). The reaction mixture was heated at 60 ºC for 16 hours. After this time, the resulting mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water. The aqueous layer was extracted again with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography (ethyl acetate : dichloromethane, 1:1) to give the title compound as a yellow solid (385 mg).

LCMS (run time = 5 minutes, System D): R_t = 2.92 minutes; m/z 444 and 446 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.40-7.00 (br, 5H), 5.10-5.00 (m, 1H), 3.75 (m, 1H), 3.55 (m, 1H), 2.55-2.35 (m, 1H), 2.15-1.95 (m, 3H), 1.10 (s, 9H).

Preparation 12: *tert*-Butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



Method A:

To *tert*-butyl (2S)-2-[5-(5-bromopyrazin-2-yl)-1H-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 11** (145 mg, 327 µmol) and *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (158 mg, 360 µmol) in 1,4-dioxane (6 mL) / water (0.6 mL), were added $Pd_2(dba)_3$ (3.0 mg, 3.27 µmol), tricyclohexylphosphine (2.3 mg, 8.18 µmol) and potassium phosphate (117 mg, 0.556 mmol). The reaction mixture was heated at 120 °C for 16 hours. After this time, the resulting mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). It was washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography (acetone : dichloromethane, 1:1) to give the title compound as a yellow solid (103 mg).

LCMS (run time = 1.5 minutes, System F): R_t = 0.78 minutes; m/z 677 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.10-7.30 (m, 10H), 5.00 (m, 2H), 3.70 (br, 2H), 3.50 (br, 2H) 2.50-2.20 (m, 2H), 2.15-1.85 (m, 6H), 1.30-1.10 (m, 18H).

Method B:

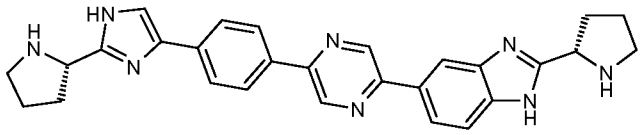
A solution of sodium carbonate (147 g, 1.39mol) in water (1.09 L) was added to a mixture of *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (192 g, 0.463 mol) and *tert*-Butyl (2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 67** (218 g, 0.463 mol), in 1,4-dioxane (2.18 L). The mixture was heated at reflux with nitrogen, sparging with nitrogen for 20 minutes. After this time, bis(diphenylphosphino)ferrocene)palladium(II) chloride (3.78 g, 4.63 mmol) was added and the reaction was stirred at reflux with continual nitrogen sparging for 3 hours. After this time, the reaction mixture was distilled and replaced with toluene under atmospheric pressure, removing the water azeotropically using Dean-Stark apparatus. The resulting residue was diluted with methanol (1 L) then reduced in *vacuo* to an olive-coloured foam. The foam was granulated in 10% methanol in dichloromethane (2.2 L) for 20 minutes then filtered under reduced pressure. The resulting filtrate was reduced in *vacuo* then re-dissolved in 10% methanol in dichloromethane (1.8 L). This solution was filtered through a bed of silica, eluting with 10% methanol in dichloromethane. The liquors were reduced in *vacuo* to a green foam which was dissolved in refluxing ethanol (1.5 L). To the ethanolic solution was added water (1.5 L) over 20 minutes and allowed to stir at reflux

for 90 minutes, then cooled to 40°C. The resulting slurry was filtered under reduced pressure, washing the filter cake with ethanol:water 1:1 to give a dense clay. The solid was re-crystallised from ethanol:water 1:1 in the same way to give the title compound as a solid (257 g).

LCMS (IPC_NEUT): Rt = 6.13 minutes; m/z 677 [MH^+]

^{1}H NMR (DMSO-d_6): δ = 12.54-12.26 (m, 1H), 12.26-11.75 (m, 1H), 9.34-9.17 (m, 2H), 8.40-8.06 (m, 3H), 8.05-7.92 (m, 1H), 7.92-7.73 (m, 2H), 7.69-7.29 (m, 2H), 5.05-4.67 (m, 2H), 3.67-3.46 (m, 2H), 3.45-3.28 (m, 2H), 2.41-2.09 (m, 2H), 2.09-1.72 (m, 6H), 1.50-0.95 (m, 18H).

Preparation 13: 2-[(2*S*)-pyrrolidin-2-yl]-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazole hydrochloride salt



Method A:

4M HCl in 1,4-dioxane (3.42 mL, 30.6 mmol) was added to *tert*-butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 12** (103 mg, 152 µmol) in ethanol (4 mL) and the reaction mixture was stirred at room temperature for 16 hours. After this time, the solvent was evaporated under reduced pressure and azeotroped with toluene to give the title compound as a yellow solid (186 mg).

LCMS (run time = 5 minutes, System D): R_t = 2.77 minutes; m/z 477 [MH^+].

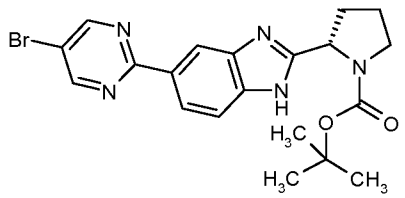
Method B:

tert-Butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 12** (257 g, 0.380 mol) was suspended in ethanol (2.57 L) and 12M aqueous HCl (231 mL, 2.77 mol) was added. The resulting solution was heated at reflux for 90 minutes. After this time, the resulting slurry was cooled to 30°C and filtered under reduced pressure, washing the filter cake with ethanol then tBME to give the title compound as a yellow solid (223 g).

LCMS (IPC_ACID): Rt = 3.65 minutes; m/z 477 [MH^+]

^{1}H NMR (DMSO-d_6): δ = 10.74-10.30 (m, 2H), 10.18-9.88 (br s, 1H), 9.75-9.47 (br s, 1H), 9.43-9.33 (s, 2H), 8.49-8.43 (s, 1H), 8.36-8.28 (d, 2H), 8.28-8.23 (s, 1H), 8.21-8.14 (d, 1H), 8.14-8.06 (d, 2H), 7.82-7.75 (d, 1H), 5.17-4.95 (m, 2H), 3.60-3.26 (m, 4H), 2.59-2.41 (m, 3H), 2.39-2.26 (m, 1H), 2.26-1.90 (m, 4H).

Preparation 14: *tert*-Butyl (2*S*)-2-[5-(5-bromopyrimidin-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate

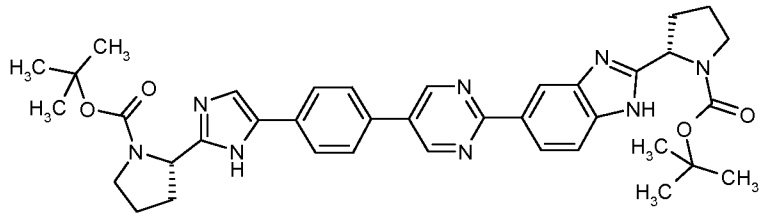


To *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (500 mg, 1.21 mmol) and 5-bromo-2-iodopyrimidine (310 mg, 1.10 mmol) in DMF (16 mL) / water (4 mL), were added tetrakis(triphenylphosphine)palladium(0) (25 mg, 22.0 µmol), and potassium carbonate (300 mg, 2.20 mmol). The reaction mixture was heated at 60 ºC for 16 hours. After this time, the resulting mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water. The aqueous layer was extracted again with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate : dichloromethane, 1:1) to give the title compound as a yellow solid (315 mg).

LCMS (run time = 5 minutes, System D): R_t = 2.99 minutes; m/z 444 & 446 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 8.85 (s, 1H), 8.59 (br s, 0.5H, rotamers), 8.33 (br s, 0.5H, rotamers), 7.70-7.45 (m, 3H), 5.10-4.94 (m, 1H), 3.78-3.67 (m, 1H), 3.60-3.50 (m, 1H), 2.50-2.35 (m, 1H), 2.12 -1.90 (m, 3H), 1.13 (s, 9H).

Preparation 15: *tert*-Butyl (2*S*)-2-{5-[4-(2-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-5-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



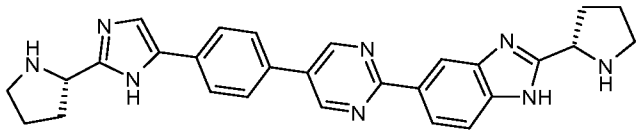
To a solution of *tert*-butyl (2*S*)-2-[5-(5-bromopyrimidin-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 14** (315 mg, 709 µmol) and *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (342 mg, 780 µmol) in 1,4-dioxane (12 mL) / water (1.2 mL), were added $Pd_2(dba)_3$ (6.5 mg, 7.09 µmol), tricyclohexylphosphine (5.0 mg, 17.73 µmol) and potassium phosphate (256 mg, 1.21 mmol). The reaction mixture was heated at 120 ºC for 16 hours. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). It was washed with sodium bicarbonate (sat. aq.), then brine. The organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product

was purified by flash chromatography (dichloromethane:methanol, 98:2 to 90:10), followed by trituration with hexane and diethyl ether to give the title compound as a yellow solid (230 mg).

LCMS (run time = 5 minutes, System D): R_t = 3.14 minutes; m/z 677 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.10-7.35 (m, 10H), 5.00 (m, 2H), 3.80-3.70 (m, 2H), 3.60-3.40 (m, 2H), 2.50-2.30 (m, 2H), 2.20-1.90 (m, 6H), 1.30-1.10 (m, 18H).

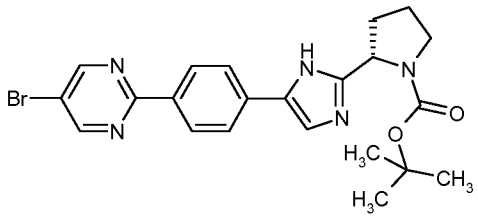
Preparation 16: 2-[(2*S*)-pyrrolidin-2-yl]-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-2-yl]-1*H*-benzimidazole hydrochloride salt



4M HCl in 1,4-dioxane (7.65 mL, 30.6 mmol) was added to *tert*-butyl (2*S*)-2-{5-[4-(2-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-5-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 15** (230 mg, 340 µmol) in ethanol (8 mL), and the reaction mixture was stirred at room temperature for 16 hours. After this time, the solvent was evaporated under reduced pressure and azeotroped with toluene to give the title compound as a yellow solid (186 mg).

^{1}H NMR (400 MHz, D_2O): δ = 9.00-7.60 (m, 10H), 5.10-5.00 (m, 2H), 3.45 (m, 4H), 2.70-2.50 (m, 2H), 2.35-2.00 (m, 6H).

Preparation 17: *tert*-Butyl (2*S*)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



Method A:

To *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (250 mg, 0.57 mmol) and 5-bromo-2-iodopyrimidine (145 mg, 0.518 mmol) in toluene (10 mL) and ethanol (1.25 mL), were added [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25 mg, 26.0 µmol) and potassium carbonate (1M solution, 0.52 mL, 0.518 mmol). The reaction mixture was heated at 60 °C under argon for 16 hours. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water. The aqueous layer was extracted again with ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate : dichloromethane, 1:1) to give the title compound as a yellow solid (197 mg).

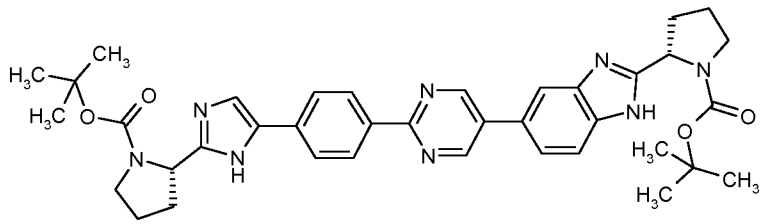
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.81 (d, 2H), 8.39 (d, 2H), 7.88-7.69 (m, 2H), 7.33 (s, 1H), 4.99 (br d, 1H), 3.48-3.38 (m, 2H), 3.10-3.00 (m, 1H), 2.24-2.10 (m, 2H), 2.10-1.94 (m, 1H), 1.49 (s, 9H).

Method B:

To *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (14.43 g, 40.4 mmol) and 2-iodo-5-bromo pyrimidine (10.5 g, 36.7 mmol) in Toluene (330 mL) and ethanol (40 mL) were added [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) 1.89 g, 2.20 mmol) (25 mg, 26.0 µmol) and potassium carbonate (1M solution, 5.08 g, 36.7 mmol). The reaction mixture was sparged with nitrogen and heated at 60 °C for 10 hours. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (400 mL) and washed with saturated sodium bicarbonate (250 mL). water. The aqueous layer was extracted again with ethyl acetate. The layers were separated and the organic phase was washed with brine (200ml). It was then dried over Na_2SO_4 and evaporated under reduced pressure. The pale yellow residue was purified by flash chromatography (redisep 330g, silica preabsorption) eluting heptane:EtOAc (80:20 to 30:70) to give the title compound as a white solid (8.45 g).

LCMS (run time = 30minutes, System E): Rt=11.20minutes, m/z 492 and 494 [MNa^+]

Preparation 18: *tert*-Butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



Method A:

To *tert*-butyl (2*S*)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 17** (197 mg, 419 µmol) and *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (190 mg, 461 µmol) in 1,4-dioxane (8 mL) / water (0.7 mL), were added $Pd_2(dba)_3$ (3.7 mg, 4.189 µmol), tricyclohexylphosphine (3.0 mg, 10.47 µmol) and potassium phosphate (151 mg, 0.712 mmol). The reaction mixture was heated at 120 °C for 16 hours. After this time, the resulting mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 98:2 to 90:10) to give the title compound as a yellow solid. A further purification by flash chromatography (dichloromethane : acetone, 60:40) gave the title compound as a pale yellow solid (75 mg).

LCMS (run time = 5 minutes, System D): R_t = 3.16 minutes; m/z 677 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.10-7.35 (m, 10H), 5.10-5.00 (m, 2H), 3.75-3.65 (m, 2H), 3.60-3.45 (m, 2H), 2.50-1.90 (m, 8H), 1.30-1.10 (m, 18H).

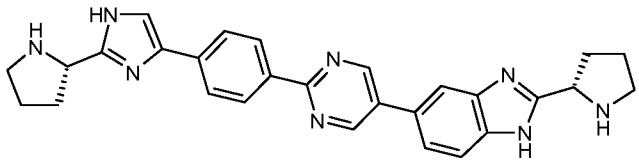
Method B:

To a solution of *tert*-butyl (2*S*)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 17** (7.85 g, 16.69 mmol) and *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (7.26 g, 17.56 mmol) in 1,4-dioxane (314 mL) were added $Pd_2(dba)_3$ (157 mg, 0.171 mmol), tricyclohexylphosphine (110 mg, 0.392 mmol) and K_3PO_4 (1M solution, 28.5 mL). After sparging with nitrogen, the reaction mixture was heated at 110 °C for 16 hours. After this time, the resulting mixture was cooled to room temperature and partitioned between ethyl acetate (600 mL) and water (300 mL). The organic layer was washed with sodium bicarbonate (sat. aq.) (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a light brown solid. The crude residue was purified by flash chromatography (heptane: acetone, 60:40 to 25:75) to give the title compound as a pale yellow solid (6.69 g).

LC-MS (run time = 25 minutes, System E): R_t = 20.48 minutes; m/z = 677.31 [MH^+]

^{1}H NMR (400 MHz, CD_3OD + 3 drops TFA-*d*): δ = 9.25 (s, 2H), 8.68-8.65 (m, 2H), 8.20-8.15 (m, 1H), 8.05-7.89 (m, 5H), 5.32-5.28 (m, 1H), 5.15-5.10 (m, 1H), 3.79-3.56 (m, 4H), 2.71-2.50 (m, 2H), 2.28-2.05 (m, 6H), 1.48-1.21 (m, 18H)

Preparation 19: 2-[(2*S*)-pyrrolidin-2-yl]-5-[2-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl} phenyl)pyrimidin-5-yl]-1*H*-benzimidazole hydrochloride salt



Method A:

4M HCl in 1,4-dioxane (2.5 mL, 9.99 mmol) was added to *tert*-butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 18** (75 mg, 111 µmol) in ethanol (3 mL), and the reaction mixture was stirred at room temperature for 6 hours. After this time, the solvent was evaporated under reduced pressure and azeotroped with toluene to give the title compound as a yellow solid (61 mg).

^{1}H NMR (400 MHz, D_2O): δ = 8.95-7.60 (m, 10H), 5.10-5.00 (m, 2H), 3.55-3.45 (m, 4H), 2.55-2.00 (m, 8H).

Method B:

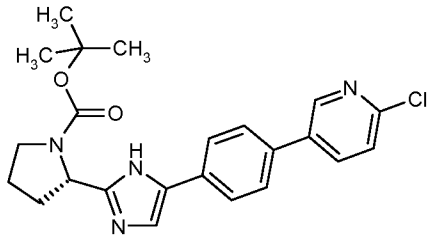
4M HCl in 1,4-dioxane (29.5 mL, 118 mmol) was added to *tert*-butyl (2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 18** (6.69 g, 9.88 mmol) in ethanol (74 mL). The mixture was stirred at

50°C under nitrogen for 3 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, azeotroped twice with toluene, and dried under vacuum overnight to give the title compound as a yellow solid (5.7 g).

LC-MS (run time = 4.5 minutes, System J): R_t = 1.43 minutes; m/z = 477 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.55-10.36 (br, 2H), 10.10-9.88 (br, 1H), 9.68-9.50 (br, 1H), 9.33 (s, 2H), 8.57-8.54 (m, 2H), 8.25 (s, 1H), 8.16-8.11 (m, 3H), 7.83-7.81 (m, 2H), 5.12-5.00 (m, 2H), 3.51-3.32 (m, 4H), 2.55-2.47 (m, 2H), 2.36-1.96 (m, 6H)

Preparation 20: *tert*-Butyl (2S)-2-{5-[4-(6-chloropyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

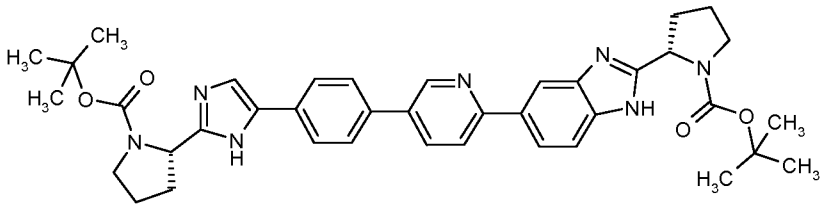


To *tert*-butyl (2S)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 2** (200 mg, 0.510 mmol) and 2-chloro-5-pyridine boronic acid (88 mg, 0.561 mmol) in 1,4-dioxane (2 mL), were added $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and tricyclohexylphosphine (4 mg, 0.012 mmol). A solution of potassium phosphate (184 mg, 0.867 mmol) in water (683 µL) was added and the resulting mixture was heated at 100 °C for 16 hours under nitrogen. After this time, the resulting mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 70:30 to 10:90) to give the title compound as a yellow solid (183 mg).

LCMS (run time = 2 minutes, System A): R_t = 1.24 minutes; m/z 425, 427 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, 1H), 7.86 (dd, 1H), 7.77 (m, 2H), 7.56 (d, 2H), 7.40 (d, 1H), 7.30 (s, 1H), 5.01 (d, 1H), 3.48-3.41 (m, 2H), 3.09-2.98 (m, 1H), 2.25-2.13 (m, 2H), 2.05-1.96 (m, 1H), 1.51 (s, 9H).

Preparation 21: *tert*-Butyl (2S)-2-{5-[4-(6-{2-[(2S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



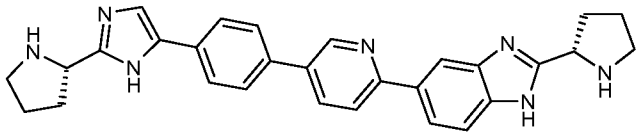
To *tert*-butyl (2S)-2-{5-[4-(6-chloropyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 20** (50 mg, 0.12 mmol) and *tert*-butyl (2S)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (54 mg, 0.13 mmol) in 1,4-

dioxane (1 mL), were added SPhos (10 mg, 0.024 mmol) and $Pd_2(dba)_3$ (6 mg, 0.006 mmol). The mixture was purged with nitrogen and a solution of potassium phosphate (50 mg, 0.236 mmol) in water (186 uL) was added. The mixture was purged again with nitrogen and heated at 110 °C for 16 hours. After this time, the resulting suspension was cooled to room temperature. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (heptane : ethyl acetate : methanol, 50:50:0 to 0:70:30) to give the title compound as a yellow solid (37 mg).

LCMS (run time = 2 minutes, System A): R_t = 1.25 minutes; m/z 676 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.83 (br, 1H), 10.55 (br, 1H), 8.33-8.20 (m, 1H), 8.02-7.51 (m, 8H), 7.28 (s, 1H), 5.17-5.16 (m, 1H), 5.00 (d, 1H), 3.65-3.44 (m, 4H), 3.08-2.98 (m, 2H), 2.29-2.12 (m, 4H), 2.03-1.95 (m, 2H), 1.53-1.48 (m, 18H).

Preparation 22: 2-[(2S)-pyrrolidin-2-yl]-5-[5-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazole hydrochloride salt

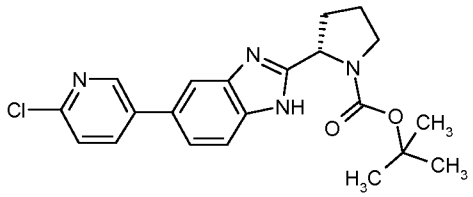


4N HCl in 1,4-dioxane (1.17 mL, 4.68 mmol) was added to a stirred solution of *tert*-butyl (2S)-2-{5-[4-(6-{2-[(2S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 21** (35 mg, 0.05 mmol) in ethanol (1 mL). After stirring at room temperature for 16 hours, the resulting suspension was diluted with t-butylmethylether (10 mL) and the solid was collected by filtration then dried *in vacuo* at 60 °C to give the title compound as a dark orange solid (24 mg).

LCMS (run time = 2 minutes, System A): R_t = 1.01 minutes; m/z 476 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.17 (d, 1H), 8.99 (dd, 1H), 8.54 (d, 1H), 8.40 (s, 1H), 8.14 (s, 1H), 8.13-8.07 (m, 4H), 8.00 (dd, 1H), 7.96 (s, 1H), 7.93 (d, 1H), 5.25-5.20 (m, 1H), 5.16 (d, 1H), 3.67-3.53 (m, 4H), 2.76-2.70 (m, 2H), 2.62-2.56 (m, 1H), 2.45-2.38 (m, 2H), 2.33-2.24 (m, 2H).

Preparation 23: *tert*-Butyl (2S)-2-[5-(6-chloropyridin-3-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate



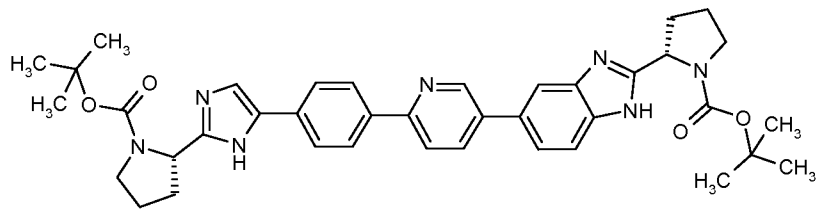
To *tert*-butyl (2S)-2-(5-bromo-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 6** (187 mg, 0.510 mmol) and 2-chloro-5-pyridine boronic acid (88 mg, 0.561 mmol) in 1,4-dioxane (2 mL), were added $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and tricyclohexylphosphine (4 mg, 0.012 mmol). A solution of potassium

phosphate (184 mg, 0.867 mmol) in water (683 uL) was added and the resulting reaction mixture was heated at 110 °C for 16 hours. After this time, the suspension formed was cooled to room temperature and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography (heptane : ethyl acetate, 70:30 to 20:80) to give the title compound as a white solid (143 mg).

LCMS (run time = 2 minutes, System A): R_t = 1.29 minutes; m/z 399, 401 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, 1H), 7.87 (dd, 1H), 7.76-7.66 (br, 2H), 7.42 (s, 1H), 7.40 (d, 1H), 5.15 (dd, 1H), 3.47-3.44 (m, 2H), 3.09-3.02 (m, 1.5H), 2.08-2.01 (m, 1.5H), 1.53 (s, 9H).

Preparation 24: *tert*-Butyl (2S)-2-{5-[4-(5-{2-[(2S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

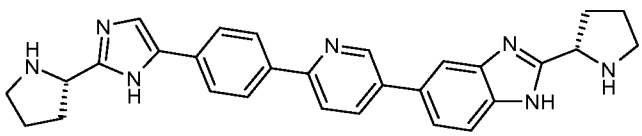


To *tert*-butyl (2S)-2-[5-(6-chloropyridin-3-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 23** (90 mg, 0.23 mmol) and *tert*-butyl (2S)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (109 mg, 0.25 mmol) in 1,4-dioxane (2 mL), were added SPhos (19 mg, 0.045 mmol) and $Pd_2(dba)_3$ (10 mg, 0.011 mmol). The reaction mixture was purged with nitrogen and a solution of potassium phosphate (96 mg, 0.452 mmol) in water (356 μL) was added. The resulting reaction mixture was heated at 110 °C for 16 hours. After this time, the suspension was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate : methanol, 100:0 to 50:50) to give the title compound as a yellow solid (121 mg).

LCMS (run time = 2 minutes, System A): R_t = 1.30 minutes; m/z 676 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.88 (br, 2H), 8.94 (s, 1H), 8.03 (d, 2H), 7.93 (d, 1H), 7.84-7.60 (m, 4H), 7.53-7.42 (m, 2H), 7.29 (s, 1H), 5.18 (d, 1H), 5.03 (d, 1H), 3.56-3.38 (m, 4H), 3.08-2.90 (m, 2H), 2.29-2.14 (m, 4H), 2.03-1.93 (m, 2H), 1.53 (s, 9H), 1.52 (s, 9H).

Preparation 25: 2-[(2S)-pyrrolidin-2-yl]-5-[6-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-3-yl]-1*H*-benzimidazole hydrochloride salt



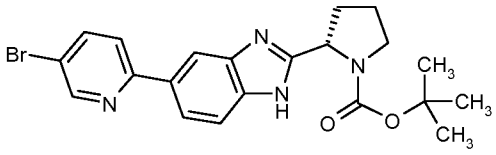
4N HCl in 1,4-dioxane (4.00 mL, 16.0 mmol) was added to a stirred solution of *tert*-butyl (2S)-2-{5-[4-(5-{2-[(2S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyridin-2-yl)phenyl]-1*H*-imidazol-2-

yl}pyrrolidine-1-carboxylate obtained from **Preparation 24** (120 mg, 0.178 mmol) in ethanol (2 mL), and the reaction was stirred at room temperature for 4.5 hours. After this time, the resulting suspension was diluted with t-butylmethylether (10 mL). The solid was collected by filtration and dried *in vacuo* at 60 °C to give the title compound as a dark orange solid (88 mg).

LCMS (run time = 2 minutes, System A): R_t = 0.98 minutes; m/z 476 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.21 (d, 1H), 9.02 (dd, 1H), 8.54 (d, 1H), 8.27 (s, 1H), 8.21 (s, 4H), 8.20 (s, 1H), 7.93 (s, 2H), 5.23-5.18 (m, 2H), 3.67-3.54 (m. 4H), 2.76-2.68 (m, 2H), 2.62-2.21 (m, 6H).

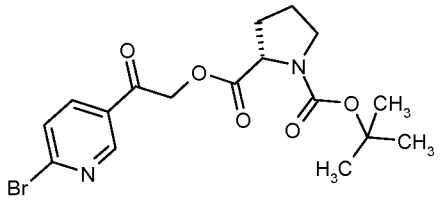
Preparation 26: *tert*-Butyl (2*S*)-2-[5-(5-bromopyridin-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate



5-Bromo-2-iodopyridine (0.29 g, 1.01 mmol), *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (350mg, 0.85 mmol) and [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.12 g, 0.14 mmol) were loaded into a microwave vial, followed by dimethoxyethane (3.5 mL) and sodium carbonate (2 M aqueous solution, 1.06 mL). The vial was sealed and heated at 120 °C under microwave irradiation for 1 hour. After this time, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through Arbocel®. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (heptane : ethyl acetate, 70:30 to 30:70) to give the title compound as a white solid (55 mg).

LCMS (run time = 5 minutes, System C): R_t = 2.54 minutes; m/z 443 & 445 [MH^+]

Preparation 27: 2-[2-(6-Bromopyridin-3-yl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate

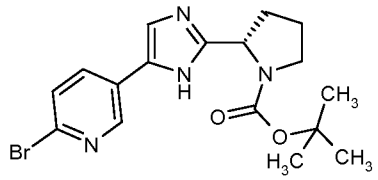


To a stirred solution of 1-(*tert*-butoxycarbonyl)-L-proline (3.64 g, 16.9 mmol) in dichloromethane (50 mL), cooled to 0 °C, were added 2-bromo-1-(6-bromopyridin-3-yl)ethanone (4.96 g, 17.8 mmol) and DIPEA (6.2 mL, 35.5 mmol). The reaction mixture was allowed to warm to room temperature and left stirring at room temperature for 16 hours. After this time, the mixture was washed with water (100 mL), then sodium bicarbonate (sat. aq., 150 mL), and brine (150 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil (7.1 g).

LCMS (run time = 5 minutes, System C): R_t = 3.17 minutes; m/z 413 and 415 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (s, 1H), 8.03 (dt, 1H), 7.66 (dd, 1H), 5.32 (m, 2H), 4.45 (m, 1H), 3.57 (m, 1H), 3.44 (m, 1H), 2.29 (m, 2H), 2.05 (m, 1H), 1.94 (m, 1H) 1.46 (m, 9H).

Preparation 28: *tert*-Butyl (2*S*)-2-[5-(6-bromopyridin-3-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate

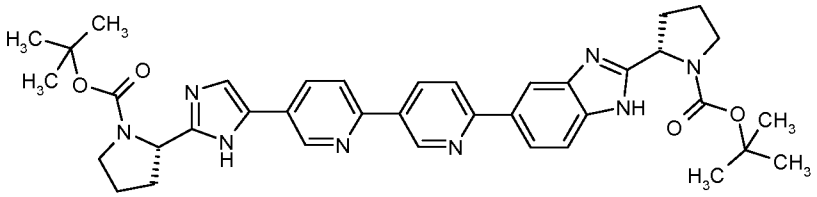


To a stirred solution of 2-[2-(6-bromopyridin-3-yl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate obtained from **Preparation 27** (7.0 g, 16.9 mmol) in xylenes (40 mL), was added ammonium acetate (6.5 g, 84.7 mmol) and the resulting mixture was heated at 150 °C for 6 hours. After this time, the reaction mixture was cooled to room temperature and then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was further washed with water (2 x 100 mL), then brine (150 mL). It was then dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (heptane : ethyl acetate, 50:50 to 30:70) to give the title compound as an off-white foam (5.3 g).

LCMS (run time = 5 minutes, System C): R_t = 2.02 minutes; m/z 393 and 395 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.06 (m, 1H), 8.74 (d, 1H), 8.03 (dd, *J*=2.7 Hz, 1H), 7.68 (m, 1H), 7.58 (d, 1H), 4.80 (m, 1H), 3.52 (m, 1H), 3.35 (m, 1H), 2.21 (m, 1H), 1.91 (m, 3H), 1.25 (m, 9H).

Preparation 29: *tert*-Butyl (2*S*)-2-[5-(6'-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-2,3'-bipyridin-5-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate

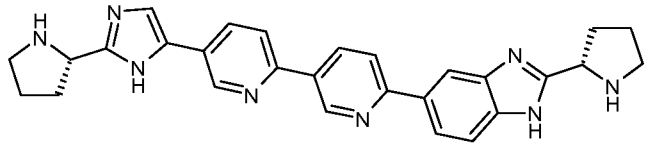


To a stirred solution of *tert*-butyl (2*S*)-2-[5-(6-bromopyridin-3-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 28** (0.11 g, 0.27 mmol) in dry dioxane (2 mL), were added hexamethylditin (0.088 g, 0.27 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.077 g, 0.078 mmol). The reaction mixture was degassed with nitrogen and heated at 100 °C for 2 hours. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The organic layer was washed with ammonium chloride (sat. aq., 10 mL), then water (10 mL) and brine (10 mL). It was then dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was dissolved in DMF (2mL) and *tert*-butyl (2*S*)-2-[5-(5-bromopyridin-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 26** (0.12 g, 0.27 mmol), cesium fluoride (0.073 g, 0.48 mmol), copper (I) chloride (0.026 g, 0.27 mmol) and

tetrakis(triphenylphosphine)palladium (0) (0.04 g, 0.04 mmol) were added. The resulting reaction mixture was degassed with nitrogen and stirred at 110 °C for 5 hours. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). The resulting suspension was washed with ammonia (0.880 solution, 50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (dichloromethane : methanol : ammonia, 98:2:0.3 to 95:5:0.3) to give the title compound as an orange solid (78 mg).

LCMS (run time = 6 minutes, System B): R_t = 2.14 minutes; m/z 677 [MH^+]

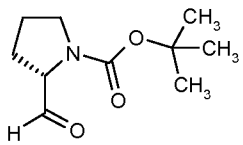
Preparation 30: 6'-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-2,3'-bipyridine hydrochloride salt



4 M HCl in dioxane (0.6 mL) was added to a stirred solution of *tert*-butyl (2*S*)-2-[5-(6'-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-2,3'-bipyridin-5-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 29** (0.078 g, 0.12 mmol) in methanol (1 mL), and the reaction mixture was stirred at room temperature for 2 hours. After this time, it was further stirred at 50 °C for 1 hour. The reaction was cooled to room temperature and the solvent was evaporated under reduced pressure to give the title compound as an orange solid (80 mg).

LCMS (run time = 6 minutes, System B): R_t = 1.48 minutes; m/z 477 [MH^+]

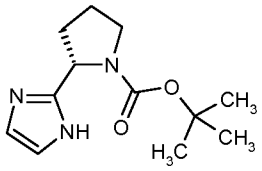
Preparation 31: *tert*-Butyl (2*S*)-2-formylpyrrolidine-1-carboxylate



To a solution of *tert*-butyl (2*S*)-2-formylpyrrolidine-1-carboxylate (198.7 g, 987.1 mmol) in dichloromethane (596 mL), were added sodium bromide (12.2 g, 119 mmol), sodium bicarbonate (12.44 g, 148.1 mmol), water (257 mL) and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) (1.54 g, 9.87 mmol). The reaction mixture was cooled to 0 °C and 1.35M sodium hypochlorite aqueous solution (794 mL, 1066 mmol) was added over 90 minutes. After this time, the layers were separated and the aqueous layer was extracted with dichloromethane (200ml). The combined organic layers were washed with 1M sodium thiosulfate aqueous solution (1.07 L), then water (500 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as an orange oil (148.6 g).

GCMS (run time = 13.5 minutes, System G): R_t = 8.61 minutes; m/z 200 [MH^+]

Preparation 32: *tert*-Butyl (2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

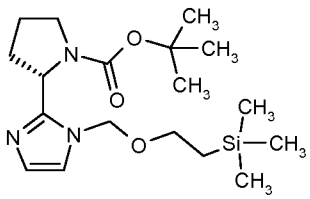


Glyoxal (264 mL, 40% in water) was added dropwise, over 15 minutes, to a cooled (ice/ water) solution of *tert*-butyl (2*S*)-2-formylpyrrolidine-1-carboxylate obtained from **Preparation 31** (104.4 g, 523.9 mmol) in ammonia (28% w/w aqueous solution, 230 mL) and methanol (418 mL). After 10 minutes, the reaction mixture was allowed to warm to room temperature and stirred for a further 19 hours. After this time, the solvent was were removed under reduced pressure. The residue was dissolved in dichloromethane (200 mL), filtered through a pad of silica gel and the solvent was evaporated under reduced pressure. The residue was triturated with *tert*-butyl methyl ether (500 mL) and collected by filtration, then dried *in vacuo* to give to give the title compound as a white solid (86.1 g).

LRMS: m/z 238 [MH^+]

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 11.71/11.63 (br s, 1H), 6.96 (s, 1H), 6.77 (s, 1H), 4.77 (m, 1H), 3.49 (m, 1H), 3.31 (m, 1H), 2.19-1.80 (m, 4H), 1.39/1.14 (s, 9H, rotamers).

Preparation 33: *tert*-Butyl (2*S*)-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

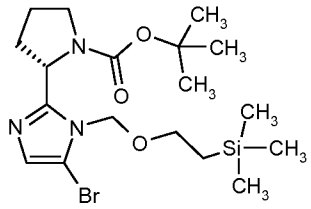


Sodium hydride (160 g, 398.9 mmol, 60% dispersion in oil) was added portionwise to a stirred solution of *tert*-butyl (2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 32** (86.1 g, 362.6 mmol) in THF (860 mL), at 0 °C. After stirring for 20 minutes, 2-(trimethylsilyl)ethoxymethyl chloride (68.8 mL, 388.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature before stirring for 16 hours at room temperature. After this time, the reaction was quenched with water (172 mL) and stirred for 30 minutes before diluting with water (200 mL) and *tert*-butyl methyl ether (400 mL). The layers were separated and the organic layer was washed with water (2x200 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude material was dissolved in dichloromethane (200 mL), filtered through a plug of silica and washed through with *tert*-butyl methyl ether (1000 mL). The *tert*-butyl methyl ether washings were combined and concentrated under reduced pressure to give the title compound as a straw coloured oil that crystallized on standing (133.2 g).

LRMS: m/z 368 [MH^+].

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.17 (m, 1H), 6.81 (m, 1H), 5.62- 5.40 (m, 1H), 5.27 (d, 1H), 4.92 (dd, 1H), 3.53-3.36 (m, 4H), 2.15 (m, 2H), 1.85 (m, 2H), 1.35-1.14 (s, 9H rotamer), 0.88 (m, 2H), 0.00 (s, 9H).

Preparation 34: *tert*-Butyl (2*S*)-2-(5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

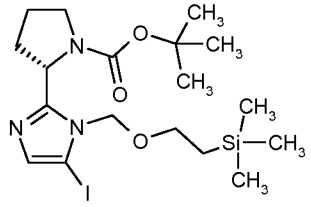


To a stirred solution of *tert*-butyl (2*S*)-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 33** (850 g, 2.31 mol) in dichloromethane (8.5 L) was added *N*-bromosuccinimide (411.6 g, 2.31 mol) as a solution in acetonitrile (4.25L), over 1 hour. Once added, the reaction was stirred at room temperature for an additional 1 hour. An aqueous solution of sodium metabisulfite (10% wt/vol, 2.2 L) was added to the reaction and the resulting mixture was stirred for 30 minutes. After this time, the layers were separated. Triethylamine (322.3 mL, 2.31 mol) and water (2.1 L) were added to the organic layer and the resulting mixture was stirred for 30 minutes. The layers were separated and the organic phase was washed with water (2 x 2.1 L), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil (1004 g).

LRMS: m/z 446 and 448 [MH^+].

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.96 (d, 1H), 5.60-5.53 (m, 1H), 5.29 (m, 1H), 4.97(m, 1H), 3.62-3.35 (m, 4H), 2.28-1.81 (m, 4H), 1.32 and 1.15 (s, 9H, rotamers), 0.85 (m, 2H), 0.00 (s, 9H).

Preparation 35: *tert*-Butyl (2*S*)-2-(5-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl) pyrrolidine-1-carboxylate



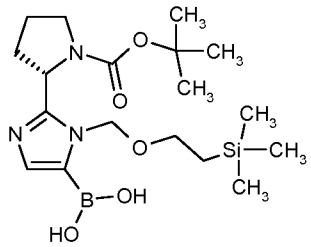
Iodine (3.08 g, 12.1 mmol) was added to a stirring solution of *tert*-butyl (2*S*)-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 33** (7.44 g, 20.2 mmol), in acetonitrile (125 mL), at room temperature. (Diacetoxyiodo)benzene (7.82 g, 24.3 mmol) was added and the mixture was stirred for 16 hours in the dark. The solvent was removed under reduced pressure and the resulting orange oil was dissolved in *tert*-butyl methyl ether (100 mL). The mixture was washed with sodium thiosulphate (saturated solution, 2 x 100 mL) and the layers were separated. The

organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude compound was purified by flash chromatography (heptane : ethyl acetate, 90:10 to 70:30) to give the title compound as a yellow oil (5.83 g).

LCMS (run time = 6 minutes, System B): R_t = 3.54 minutes; m/z 494 [MH^+].

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.95 (m, 1H), 5.58-5.23 (br m, 2H), 5.02-4.92 (m, 1H), 3.57-3.50 (m, 2H), 3.46-3.30 (br m, 2H), 2.20-1.97 (br m, 2H), 1.89-1.77 (m, 2H), 1.35 and 1.12 (2xs, 9H, rotamers), 0.93-0.80 (m, 2H), -0.03 (s, 9H).

Preparation 36: (2-[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-1-{[2(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-5-yl)boronic acid



The boronic acid above was made in two different ways (if the bromide of **Preparation 34** is used, it must be used immediately on formation):

Method A:

tert-Butyl (2*S*)-2-(5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 34** (4.8 g, 10.75 mmol) was dissolved in THF (120 mL), and cooled to 0 °C. The solution was placed under nitrogen and isopropylmagnesium chloride-lithium chloride complex (14% solution in THF, 16.1 mL, 16.1 mmol) was added dropwise. The mixture was stirred at this temperature for 1 hour. Trimethyl borate (1.92 mL, 17.2 mmol) was added and the resulting mixture was allowed to warm up to room temperature and stirred for 16 hours. After this time, water (60 mL) was added, followed by sodium bicarbonate (sat. solution) (40 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) and the combined organic fractions were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 3.4 g of the title compound as a yellow solid.

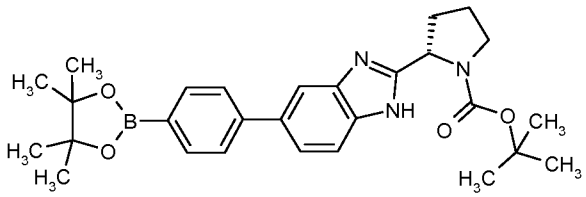
Method B:

tert-Butyl (2*S*)-2-(5-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 35** (3.28 g, 6.65 mmol) was dissolved in THF (35 mL) and cooled to 0 °C. The mixture was placed under nitrogen and isopropylmagnesium chloride-lithium chloride complex (14% solution in THF, 9.97 mL, 9.97 mmol) was added dropwise. The mixture was stirred at this temperature for 1 hour. Trimethyl borate (1.19 mL, 10.6 mmol) was added and the resulting mixture was allowed to warm to room temperature and stirred for 16 hours. After this time, water (60 mL) was added, followed by sodium bicarbonate (sat. solution) (40 mL). The mixture was extracted with ethyl acetate (3 x 60mL) and the

combined organic fractions were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 2.72 g of the title compound as a yellow solid.

LCMS (run time = 2 min, System A): R_t = 1.34 min; m/z 412 [MH^+]

Preparation 37: *tert*-Butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate

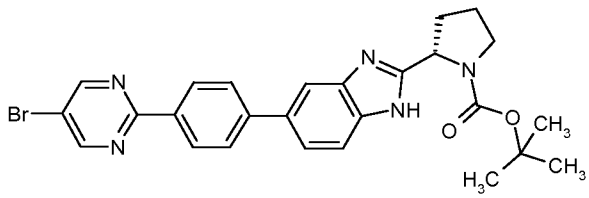


To *tert*-butyl (2*S*)-2-[5-(4-bromophenyl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 20** (1.89 g, 4.27 mmol) in cyclopentyl methyl ether (35 mL), were added dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(0) (349 mg, 427 µmol), potassium acetate (922 mg, 9.40 mmol) and bis(pinacolato)diboron (2.17 g, 8.55 mmol). The reaction mixture was heated at 110 ºC for 16 hours. After this time, the reaction was cooled to room temperature, diluted with ethyl acetate (15 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5x15 mL). The combined organic layers were washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 50:50 to 0:100) to give the title compound as a brown foam (1.67 g).

LCMS: (run time = 5 minutes, System C): R_t = 3.33 minutes; m/z 490 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, 3H), 7.63 (d, 3H), 7.49 (d, 1H), 5.12-5.10 (m, 1H), 3.42-3.40 (m, 2H), 3.03-3.00 (m, 1H), 2.20-2.15 (m, 2H), 2.03-2.00 (m, 2H), 1.50 (s, 9H), 1.35 (s, 12H).

Preparation 38: *tert*-Butyl (2*S*)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate

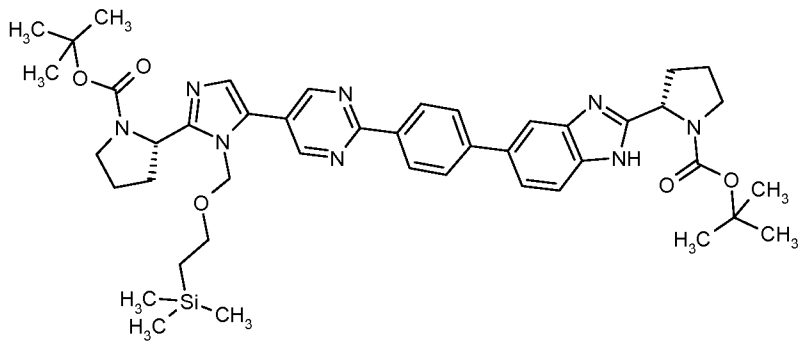


To *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-benzimidazol-2-yl} pyrrolidine-1-carboxylate obtained from **Preparation 37** (1.0 g, 2.04 mmol) and 5-bromo-2-iodopyrimidine (640 mg, 2.25 mmol) in *N,N*-dimethylformamide (16 mL) and water (4 mL), were added tetrakis(triphenylphosphine)palladium(0) (47 mg, 41 µmol) and potassium carbonate (565 mg, 4.09 mmol). The resulting mixture was heated at 60 ºC for 23 hours. After this time, the reaction was cooled to room temperature and diluted with ethyl acetate (15 mL) and water (15 mL). The layers were separated and the

organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 98:2) to give the title compound as a cream foam (538 mg).

LCMS: (run time = 5 minutes, System C): R_t = 3.46 minutes; m/z 520 and 522 [MH^+]

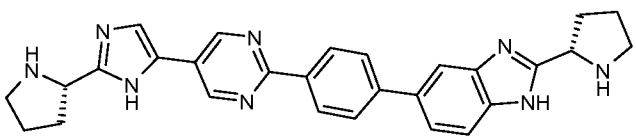
Preparation 39: *tert*-Butyl (2*S*)-2-(5-[2-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-5-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate



To *tert*-butyl (2*S*)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 38** (357 mg, 686 µmol) and (2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1-{[2(trimethylsilyl)ethoxy]methyl }-1*H*-imidazol-5-yl)boronic acid obtained from **Preparation 36** (480 mg, 1.17 mmol) in cyclopentyl methyl ether (10 mL), were added tris(dibenzylideneacetone)dipalladium(0) (6 mg, 7.0 µmol), tricyclohexylphosphine (5 mg, 17.0 µmol) and potassium phosphate (1M (aq), 1.2 mL, 1.17 mmol). The resulting mixture was heated at 110 ºC for 16 hours. After this time, the reaction was cooled to room temperature, diluted with ethyl acetate (15 mL) and water (15 mL). The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 50:50 to 0:100) to give the title compound as a brown gum (479 mg).

LCMS (run time = 5 minutes, System C): R_t = 3.65 minutes; m/z 807 [MH^+]

Preparation 40: 2-[(2*S*)-pyrrolidin-2-yl]-5-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}pyrimidin-2-yl) phenyl]-1*H*-benzimidazole hydrochloride salt

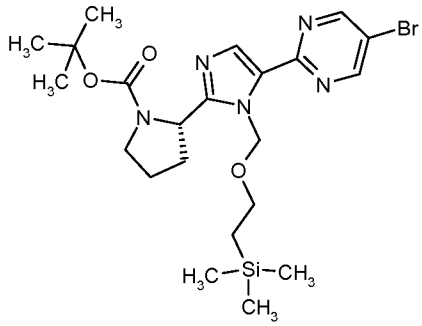


4M HCl in industrial methylated spirit (4 mL) was added to *tert*-butyl (2*S*)-2-(5-[2-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-5-yl]-1-{[2-

(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 39** (283 mg, 350 µmol) in industrial methylated spirit (10 mL), and the reaction mixture was stirred at 70 °C for 3 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound that was taken directly into the next step.

LCMS (run time = 5 minutes, System C): R_t = 2.03 minutes; m/z 477 [MH^+]

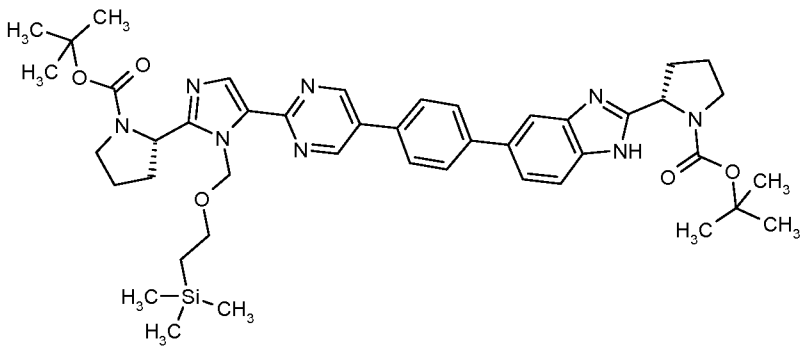
Preparation 41: *tert*-Butyl (2*S*)-2-[5-(5-bromopyrimidin-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate



To (2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1-{[2(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-5-yl)boronic acid obtained from **Preparation 36** (470 mg, 1.14 mmol) in 1,2 dimethoxyethane (5 mL), were added dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium (55 mg, 67 µmol), sodium carbonate (214 mg, 2.02 mmol), and 5-bromo-2-iodopyrimidine (191 mg, 672 µmol). The resulting mixture was heated at 60 ºC for 5 hours. After this time, the reaction was cooled to room temperature, diluted with ethyl acetate (6 mL) and water (10 mL). The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 60:40 to 0:100) to give the title compound as a brown gum (235 mg).

LCMS: (run time = 5 minutes, System C): R_t = 3.43 minutes; m/z 524 and 526 [MH^+]

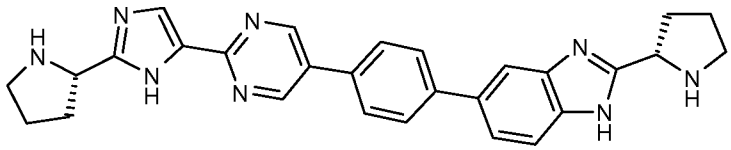
Preparation 42: *tert*-Butyl (2*S*)-2-(5-[5-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-2-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate



To *tert*-butyl (2*S*)-2-[5-(5-bromopyrimidin-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 41** (185 mg, 353 µmol) and *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 37** (190 mg, 388 µmol) in 1,4-dioxane (10 mL), were added tris(dibenzylideneacetone) dipalladium(0) (3 mg, 4.0 µmol), tricyclohexylphosphine (3 mg, 9.0 µmol) and potassium phosphate (1M (aq), 0.6 mL). The resulting reaction mixture was heated at 120 ºC for 16 hours. After this time, the reaction was cooled to room temperature and diluted with ethyl acetate (15 mL) and water (15 mL). The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 100:0 to 95:5) to give the title compound as a beige gum (123 mg).

LCMS (run time = 5 minutes, System C): R_t = 3.61 minutes; m/z 807 [MH^+]

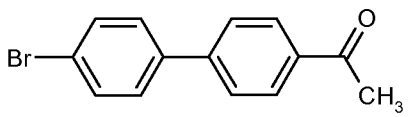
Preparation 43: 2-[(2*S*)-pyrrolidin-2-yl]-5-[4-(2-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}pyrimidin-5-yl) phenyl]-1*H*-benzimidazole hydrochloride salt



4M HCl in industrial methylated spirit (2 mL) was added to *tert*-butyl (2*S*)-2-(5-[5-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}phenyl)pyrimidin-2-yl]-1-{[2-(trimethylsilyl)ethoxy] methyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 42** (123 mg, 152 µmol) in industrial methylated spirit (10 mL), and the resulting reaction mixture was stirred at 70 °C for 3 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound which was taken directly into the next step.

LCMS (run time = 5 minutes, System C): R_t = 2.06 minutes; m/z 477 [MH^+]

Preparation 44: 1-(4'-bromobiphenyl-4-yl)ethanone

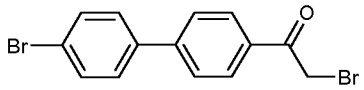


Acetyl chloride (366 µL, 5.15 mmol) was added dropwise to a solution of aluminium trichloride (858 mg, 6.44 mmol) in dichloromethane (6 mL). The solution was cooled to 0 °C and 4'-bromobiphenyl (1.0 g, 4.29 mmol) in dichloromethane (4 mL) was added dropwise. The reaction mixture was left to warm up to room temperature and left stirring at this temperature for 18 hours. After this time, the reaction was poured into ice / hydrochloric acid (conc.), then extracted with dichloromethane. The organic extracts were washed with

sodium hydroxide (2 M, aq.), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid (1.09 g).

^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (dd, 2H), 7.64 (dd, 1H), 7.60 (dd, 2H), 7.47 (dd, 2H), 2.61 (s, 3H).

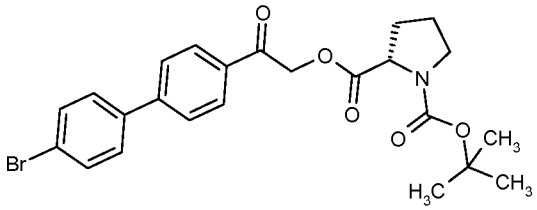
Preparation 45: 2-Bromo-1-(4'-bromobiphenyl-4-yl)ethanone



Bromine (164 µL, 3.19 mmol) was added dropwise to 1-(4'-bromobiphenyl-4-yl)ethanone obtained from **Preparation 44** (871 mg, 3.16 mmol) in dichloromethane (20 mL). After stirring at room temperature for 18 hours, the reaction mixture was diluted with dichloromethane and washed with sodium thiosulfate (aq.). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (heptane : ethyl acetate, 90:10) to give the title compound as a white solid (506 mg).

^1H NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, 2H), 7.67 (d, 2H), 7.60 (d, 2H), 7.49 (d, 2H), 4.47 (s, 2H).

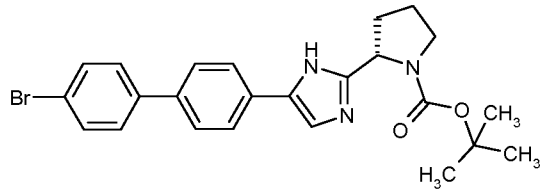
Preparation 46: 2-[2-(4'-Bromobiphenyl-4-yl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate



2-Bromo-1-(4'-bromobiphenyl-4-yl)ethanone obtained from **Preparation 45** (500 mg, 1.41 mmol), 1-(*tert*-butoxycarbonyl)-L-proline (290 mg, 1.35 mmol) and diisopropylethylamine (260 µL, 1.49 mmol) in dichloromethane (10 mL), were stirred at room temperature for 16 hours. After this time, the reaction was diluted with dichloromethane, washed with sodium bicarbonate (aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil (624 mg).

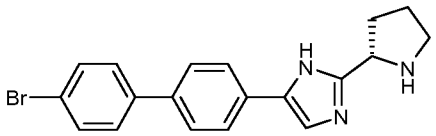
^1H NMR (400 MHz, $CDCl_3$) δ = 8.00-7.94 (m, 2H), 7.70-7.62 (m, 2H), 7.58 (d, 2H), 7.48 (d, 2H), 5.65-5.20 (m, 2H), 4.52-4.48 (m, 0.5H), 4.41 (t, 0.5H), 3.64-3.51 (m, 1H), 3.51-3.37 (m, 1H), 2.40-2.26 (m, 2H), 2.14-2.02 (m, 1H), 2.02-1.88 (m, 1H), 1.44 (d, 9H).

Preparation 47: *tert*-Butyl (2*S*)-2-[5-(4'-bromobiphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate



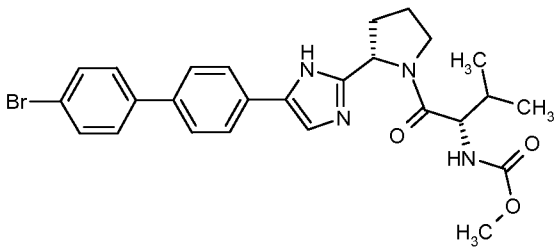
2-[2-(4'-Bromobiphenyl-4-yl)-2-oxoethyl] 1-*tert*-butyl (2*S*)-pyrrolidine-1,2-dicarboxylate obtained from **Preparation 46** (620 mg, 1.27 mmol), ammonium acetate (2.0 g, 25.4 mmol) and 4 Å molecular sieves (2 g) in toluene (10 mL), were heated at 120 °C for 16 hours. After this time, the reaction was filtered through a pad of celite, rinsing with ethyl acetate. The filtrate was washed with water, then brine. It was then dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a brown foam (458 mg).
LCMS: (run time = 5 minutes, System C): R_t = 3.36 minutes; m/z 468 and 470 [MH^+]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75-7.62 (m, 1H), 7.54 (d, 4H), 7.47 (d, 2H), 7.26 (d, 2H), 5.03-4.98 (m, 1H), 3.50-3.40 (m, 2H), 3.08-2.96 (m, 1H), 2.27-2.11 (m, 2H), 2.02-1.92 (m, 1H), 1.50 (s, 9H).

Preparation 48: 5-(4'-Bromobiphenyl-4-yl)-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole hydrochloride salt



4M HCl in 1,4-dioxane (10.0 mL, 2.5 mmol) was added to *tert*-butyl (2*S*)-2-[5-(4'-bromobiphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 47** (450 mg, 0.96 mmol) in ethanol (10 mL), and the reaction mixture was stirred at room temperature for 4 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound used crude into the next step.
LCMS: (run time = 5 minutes, System C): R_t = 3.22 minutes; m/z 368 and 370 [MH^+]

Preparation 49: Methyl [(2*S*)-1-{(2*S*)-2-[5-(4'-bromobiphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate



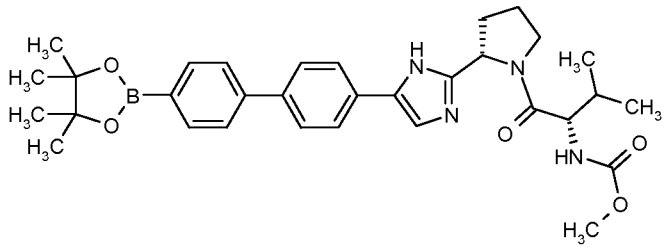
N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (202 mg, 1.15 mmol), HOBT (184 mg, 1.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (220 mg, 1.15 mmol) in acetonitrile (10 mL), were stirred at room temperature for 20 min. 5-(4'-Bromobiphenyl-4-yl)-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-

imidazole hydrochloride salt obtained from **Preparation 48** was added, followed by the dropwise addition of diisopropylethylamine (0.669 mL, 3.84 mmol). The resulting mixture was stirred at room temperature for 18 hours. After this time, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a beige foam (459 mg).

LCMS: (run time = 5 minutes, System C): R_t = 3.25 minutes; m/z 525 and 527 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60-7.49 (m, 5H), 7.49-7.39 (m, 3H), 7.23 (s, 1H), 5.46-5.36 (m, 1H), 5.30-5.20 (m, 1H), 4.39-4.29 (m, 1H), 3.95-3.79 (m, 1H), 3.79-3.60 (m, 2H), 3.68 (s, 3H), 2.45-2.28 (m, 1H), 2.28-2.14 (m, 1H), 2.14-2.05 (m, 1H), 2.05-1.90 (m, 1H), 0.92-0.79 (m, 6H).

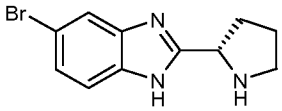
Preparation 50: Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{5-[4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-4-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate



To methyl [(2*S*)-1-{(2*S*)-2-[5-(4'-bromobiphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate obtained from **preparation 49** (448 mg, 0.85 mmol) in 1,4-dioxane (10 mL), were added dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium (70 mg, 0.12 mmol), potassium acetate (183 mg, 1.86 mmol), and bis(pinacolato)diboron (433 mg, 1.71 mmol). The resulting mixture was heated at 120 ºC for 16 hours. After this time, the reaction was cooled to room temperature, filtered through celite and rinsed through with ethyl acetate (30 mL). The filtrate was washed with water, sodium bicarbonate (sat. aq.), then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude oil obtained was purified by flash chromatography (dichloromethane : methanol, 95:5) to give the title compound as a brown foam (487 mg).

LCMS: (run time = 5 minutes, System C): R_t = 3.25 minutes; m/z 573 [MH^+]

Preparation 51: 5-Bromo-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole hydrochloride salt

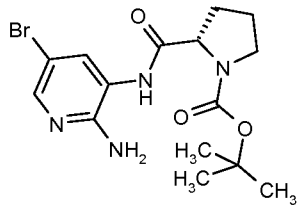


4M HCl in ethanol (20 mL, 5 mMol) was added to *tert*-butyl (2*S*)-2-(5-bromo-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 5** (1.0 g, 2.73 mmol) in ethanol (10 mL), and the reaction mixture

was stirred at room temperature for 5 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound used crude into the next step.

^{1}H NMR (400 MHz, D_2O) δ = 7.78 (s, 1H), 7.49 (s, 2H), 5.15 (t, 1H), 3.56-3.42 (m, 2H), 2.71-2.62 (m, 1H), 2.48-2.34 (m, 1H), 2.34-2.21 (m, 1H), 2.21-2.09 (m, 1H).

Preparation 52: *tert*-Butyl (2*S*)-2-[(2-amino-5-bromopyridin-3-yl)carbamoyl]pyrrolidine-1-carboxylate

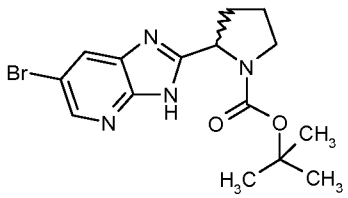


To 1-(*tert*-butoxycarbonyl)-L-proline (5.7 g, 26.6 mmol) in *N*,*N*-dimethylformamide (125 mL) were added *O*-(7-azabenzotriazole-1-yl)-*N*, *N*, *N*', *N*'-tetramethyluronium hexafluorophosphate (11.1 g, 29.3 mmol) and diisopropylethyl amine (9.7 mL, 55.8 mmol). After stirring for 15 minutes at room temperature, 5-bromo-2,3-diaminopyridine (5 g, 26.6 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. After this time, the reaction was diluted with ethyl acetate and water. The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 3:1) to give the title compound as an orange foam (7.02 g).

LCMS: (run time = 5 minutes, System C): R_t = 2.57 minutes; m/z 385 and 387 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.01 (br s, 1H), 8.05, 7.90 (2 x s, 1H, rotamers), 4.41 (m, 1H), 3.46-3.31 (m, 2H), 2.46 (m, 1H), 2.02-1.90 (m, 3H), 1.46 (s, 9H).

Preparation 53: t*ert*-Butyl 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)pyrrolidine-1-carboxylate

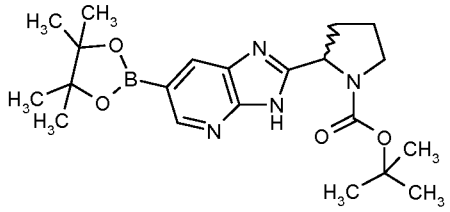


tert-Butyl (2*S*)-2-[(2-amino-5-bromopyridin-3-yl)carbamoyl]pyrrolidine-1-carboxylate obtained from **Preparation 52** (4 g, 10.38 mmol) in acetic acid (20 mL) was heated at 70 °C for 16 hours. After this time, the reaction mixture was heated for a further 3 hours at 100 °C. After this time, the reaction was cooled to room temperature and the acetic acid was removed under reduced pressure. The residue was partitioned between ethyl acetate and sodium bicarbonate (sat. aq.). The organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (heptane : ethyl acetate, 1:2) to give the title compound as a yellow oil (689 mg).

LCMS: (run time = 5 minutes, System C): R_t = 2.64 minutes; m/z 367 and 369 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.10 (br s, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 5.15-5.08 (m, 1H), 3.43-3.36 (m, 2H), 2.23-2.13 (m, 1H), 2.06-1.98 (m, 2H), 1.60 (m, 1H), 1.49 (s, 9H).

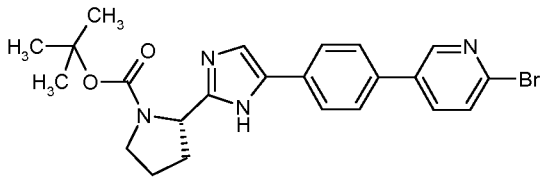
Preparation 54: *tert*-Butyl 2-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]pyrrolidine-1-carboxylate



To *tert*-butyl 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 53** (680 mg, 1.85 mmol) in 1,4-dioxane (10 mL), were added dichloro(1,1'-bis(diphenylphosphino) ferrocene)palladium (151 mg, 185 µmol), potassium acetate (400 mg, 4.07 mmol) and bis(pinacolato)diboron (940 mg, 3.70 mmol). The resulting mixture was heated at 110 °C for 16 hours. After this time, the solution was cooled to room temperature and partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5) to give the title compound as an orange oil (140 mg).

LCMS: (run time = 5 minutes, Method C): R_t = 1.69 minutes, m/z 333.1 [MH^+] (boronic acid).

Preparation 55: *tert*-Butyl (2*S*)-2-{5-[4-(6-bromopyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

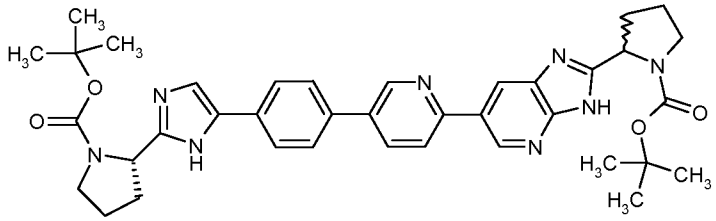


To *tert*-butyl (2*S*)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (250 mg, 569 µmol) and 2-bromo-5-iodopyridine (150 mg, 517 µmol) in DMF (8 mL) / water (2 mL), were added tetrakis(triphenylphosphine)palladium(0) (12 mg, 11 µmol) and potassium carbonate (146 mg, 1.06 mmol). The resulting mixture was heated at 60 °C for 16 hours. After this time, the reaction was cooled to room temperature and diluted with ethyl acetate (30 mL) and water (30 mL). The layers were separated and the organic phase was washed with sodium bicarbonate (sat. aq.), then brine. The ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5) to give the title compound as an off-white solid (243 mg).

LCMS (run time = 5 minutes, System C): R_t = 3.04 minutes, m/z 469 and 470 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.06, 10.55 (2 x br s, 1H), 8.60 (s, 1H), 7.90-7.81 (m, 1H), 7.88-7.72 (m, 1H), 7.57-7.50 (m, 4H), 7.30-7.24 (m, 1H), 5.02-4.95 (m, 1H), 3.45-3.36 (m, 2H), 2.24-2.08 (m, 1H), 2.04-1.93 (m, 3H), 1.49 (s, 9H).

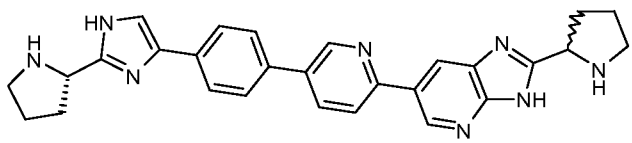
Preparation 56: *tert*-Butyl 2-{6-[5-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyrrolidine-1-carboxylate



To a solution of *tert*-butyl (2*S*)-2-{5-[4-(6-bromopyridin-3-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 55** (159 mg, 334 µmol) and *tert*-butyl 2-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 54** (140 mg, 368 µmol) in 1,4-dioxane (4 mL) and water (0.8 mL), were added tris(dibenzylideneacetone)dipalladium(0) (3 mg, 3.3 µmol), tricyclohexylphosphine (2.3 mg, 8.0 µmol) and potassium phosphate (122 mg, 569 µmol). The resulting mixture was heated at 120 °C for 16 hours. After this time, the reaction was cooled to room temperature and partitioned between ethyl acetate (15 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 95:5 to 93:7) to give the title compound as an orange foam (65 mg).

LCMS (run time = 5 minutes, Method C): R_t = 3.13 minutes, m/z 677 [MH^+]

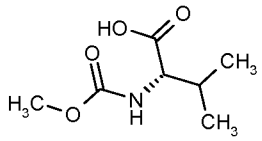
Preparation 57: 2-(Pyrrolidin-2-yl)-5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyridin-2-yl]-1*H*-benzimidazole hydrochloride salt



4M HCl in industrial methylated spirit (1 mL) was added to *tert*-butyl 2-{6-[5-(4-{2-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyridin-2-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 56** (65 mg, 96 µmol) in industrial methylated spirit (3 mL), and the resulting solution was stirred at 50 °C for 2 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound which was taken crude into the next step.

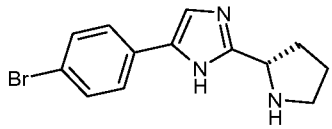
LCMS (run time = 5 minutes, Method C): R_t = 1.96 minutes, m/z 477 [MH^+]

Preparation 58: *N*-(methoxycarbonyl)-L-valine



L-Valine (200 g, 1.707 mol) was added to a stirred mixture of sodium hydroxide (150.2 g, 3.755 mol), water (1000 mL) and toluene (1000 mL), then cooled to 0 °C. Methylchloroformate (145.3 mL, 1.880 mol) was added over 30 minutes, and the resulting mixture was stirred overnight at room temperature. The layers were separated and the aqueous layer was acidified with 5M sulfuric acid (800 mL, 4.0 mol), then extracted with ethyl acetate (2 x 500 mL). The combined organic phase was washed with water (500 mL) and the solvent was evaporated under reduced pressure. The solid obtained was dried *in vacuo* at 45 °C to give the title compound as a white solid (216 g).

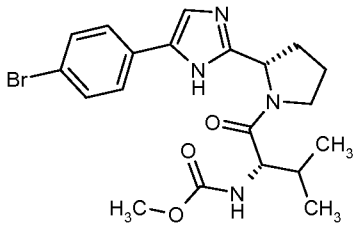
Preparation 59: 5-(4-Bromophenyl)-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole hydrochloride salt



HCl/EtOAc (500 mL) was added to a stirred solution of *tert*-butyl (2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 2** (160 g, 0.41 mol) in ethyl acetate (500 mL) at 30°C and the reaction mixture was stirred at room temperature for 16 hours. After this time, the solid formed was collected by filtration, rinsing with ethyl acetate to give the title compound as a yellow solid (135 g).

^{1}H NMR (400 Hz, DMSO-d_6): δ = 10.44-9.97 (m, 1H), 8.17 (s, 1H), 7.89 (d, 2H), 7.70 (d, 2H), 5.03 (t, 1H), 3.55-3.36 (m, 2H), 2.49-2.45 (m, 2H), 2.23-2.14 (m, 1H), 2.04-1.90 (m, 1H).

Preparation 60: Methyl [(2*S*)-1-{(2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate



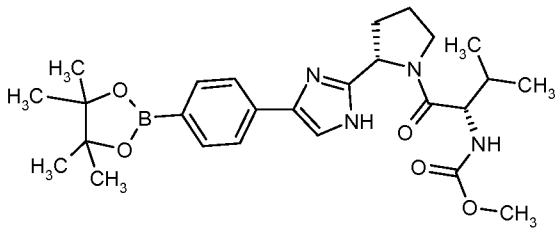
N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (68 g, 0.39 mol), HATU (154 g, 0.41 mol) and 5-(4-bromophenyl)-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole hydrochloride salt obtained from **Preparation 59** (135 g, 0.41 mol)in anhydrous DMF (1500 mL) were treated with DIPEA (239 g, 1.85 mol) at 30°C. After 2 hours, brine (1 L) and Na_2CO_3 (saturated solution, 500 mL) were added. The product was extracted with EtOAc (3 x

1 L). The combined organic layers were washed with brine (4x 1 L), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (Petroleum ether : EtOAc, 4:1 to 1:2) to give the title compound as a yellow solid (125 g).

^{1}H NMR (400 Hz, DMSO-d_6): δ = 12.38-11.82 (m, 1H), 7.69-7.65 (m, 2H), 7.52-7.47 (m, 3H), 7.30-6.89 (m, 1H), 5.06-5.04 (m, 1H), 4.07-4.03 (m, 1H), 3.79-3.78 (m, 2H), 3.54 (s, 3H), 2.13-2.10 (t, 1H), 1.99-1.91 (m, 3H), 0.88-0.81 (m, 6H)

LCMS (run time = 6 minutes): R_t = 2.87 minutes; m/z 449 and 451 [MH^+]

Preparation 61: Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate

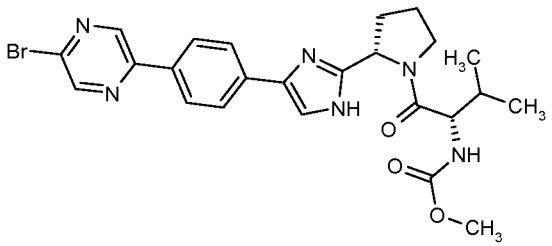


To a solution of methyl [(2*S*)-1-{(2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate obtained from **Preparation 60** (40.00 g, 88.62 mmol) in 1,4-dioxane (300 mL) were added potassium acetate (22.70 g, 23.16 mmol) and bis(pinacolato)diboron (23.80 g, 93.72 mmol). The mixture was sparged with nitrogen for 30 minutes. 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.20 g, 2.69 mmol) was added to the suspension and the reaction mixture sparged again with nitrogen for 10 minutes before heating to reflux for 3 hours under nitrogen. After this time, the mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to give a black gum. The residual gum was partitioned between ethyl acetate (250 mL) and water (250 mL), the layers were separated, the organic layer was washed with brine (500 mL), dried over magnesium sulphate and filtered. Silica (10.00 g) and charcoal (10.00 g) were added to the filtrate and the mixture heated to reflux for 30 minutes, then allowed to cool to room temperature. The mixture was filtered and the solvent removed under reduced pressure. The residue obtained was triturated with heptane (2x 400 mL) to give the title compound as a pale brown solid (33.00 g).

LCMS (run time = 5 minutes, System J): R_t=3.14 minutes, m/z 497 [MH^+]

^{1}H NMR (400 MHz, CD_3OD+drop of TFA): δ= 7.72 (m, 2H), 7.64 (d, 2H), 7.35 (s, 1H), 5.17-5.14 (m, 1H), 4.24-4.19 (m, 1H), 3.89-3.82 (m, 1H), 3.64 (s, 3H), 2.35-2.19 (m, 3H), 2.06-1.98 (m, 3H), 1.35 (s, 12H), 0.94-0.88 (m, 6H).

Preparation 62: Methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Method A:

To a solution of methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate obtained from **Preparation 61** (33.00 g, 66.53 mmol) and 2-bromo-5-iodopyrazine obtained from **Preparation 10** (24.70 g, 86.67 mmol) in 1,4-dioxane (600 mL) and water (150 mL), were added potassium phosphate (28.20 g, 133.01 mmol) and tetrakis(triphenylphosphine)palladium (0) (2.30 g, 1.99 mmol). The mixture was sparged with nitrogen for 10 minutes before heating to reflux for 16 hours. After this time, the reaction was allowed to cool to room temperature, the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (250 mL) and water (250 mL). The layers were separated and the organic layer was washed with brine (500 mL), dried over magnesium sulphate. The solvent was removed under reduced pressure to give a black gum. The crude product was purified by flash chromatography (heptane : acetone, 20:80) to give the title compound as a foam (22.00 g).

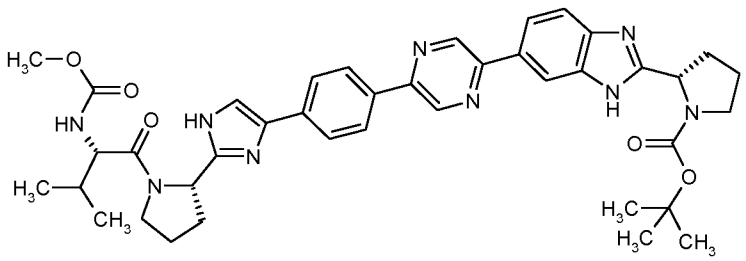
LCMS (run time = 25 minutes, System K) R_t= 13.19; m/z 527 and 529 [MH^+]

^{1}H NMR (400 MHz, CD_3OD+drop of TFA) : δ= 8.99 (s, 1H), 8.81 (s, 1H), 8.25 (d, 2H), 7.94 (s, 1H) 7.86 (d, 2H), 5.27-5.23 (m, 1H), 4.24 (d, 1H), 4.13-4.08 (m, 1H), 3.88 (m, 1H), 3.65 (s, 3H), 2.62-2.54 (m, 1H), 2.31-2.24 (m, 1H), 2.20-2.14 (m, 2H), 2.09-2.00 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

Method B:

N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (85.3 g, 487 mmol), EDCI (95.7 g, 499 mmol) and HOBT hydrate (78.3 g, 512 mmol) were combined in acetonitrile (3644 mL) at 0°C and (2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine methane sulfonate salt (274 g, 487 mmol) obtained from **Preparation 73** was added. DIPEA (340 mL, 1949 mmol) was added dropwise and the reaction was stirred for 16 hours. The acetonitrile was removed by distillation at reduced pressure and the residue was partitioned with DCM (2192 mL) and saturated sodium hydrogen carbonate solution (1644 mL). The organic phase was washed with water (1644 mL) and concentrated to give the title compound (305 g) as a yellow oil. The crude oil was used directly in the subsequent reaction without further purification

Preparation 63: *tert*-Butyl (2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidine-1-carboxylate



Method A:

To a solution of methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate obtained from **Preparation 62** (22.0 g, 41.74 mmol) and *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (17.20 g, 41.65 mmol) in 1,4-dioxane (200 mL) and water (50 mL) was added sodium carbonate (13.30 g, 125.47 mmol) and the mixture was sparged with nitrogen for 30 minutes. 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (341 mg, 0.417 mmol) was added and the mixture was sparged with nitrogen for 10 minutes before heating the reaction to reflux for 16 hours. After this time, the reaction mixture was allowed to cool to room temperature, the solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (250 mL) and water (250 mL). The layers were separated, the organic layer was washed with brine (500 mL) and the solvent removed under reduced pressure to give a black solid. The crude material was purified by flash chromatography (heptane: acetone, 50:50 to 10:90) to give the title compound as a yellow solid (24.9 g).

LCMS (run time = 25 minutes, System K): R_t = 14.62 minutes, m/z 734 [MH^+]

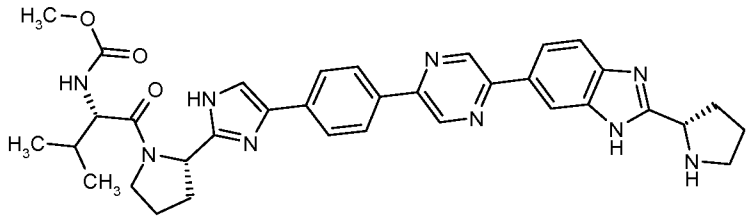
^{1}H NMR (400 MHz, DMSO-d_6+drop of TFA): δ = 9.46 (s, 2H), 8.56 (s, 1H), 8.39 (m, 3H), 8.21 (s, 1H), 7.98 (m, 3H), 5.23-5.19 (m, 1H), 5.16-5.13 (m, 1H), 4.12-4.09 (m, 1H), 3.88-3.82 (m, 2H), 3.67-3.62 (m, 1H), 3.53 (s, 3H), 3.49-3.43 (m, 1H), 2.43-2.38 (m, 1H), 2.19-1.98 (m, 8H), 1.39-1.08 (2xs, 9H), 0.82 (d, 3H), 0.76 (d, 3H).

Method B:

To a solution of methyl {(2*S*)-1-[(2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate obtained from **Preparation 62** (234 g, 444 mmol) and *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (184 g, 444 mmol) in 1,4-dioxane (2790 mL) and water (1395 mL) was added sodium carbonate (141 g, 1333 mmol) and the mixture was sparged with nitrogen for 30 minutes at 60°C. 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3.63 g, 4.44 mmol) was added and sparged with nitrogen was continued whilst further heating the reaction to reflux for 3 hours. After this time, the reaction mixture was allowed to cool to room temperature, the solvents were removed under reduced pressure and

the residue was azeotropically dried by distillation of toluene. The crude material was purified by flash chromatography (heptane: acetone, 30:70 to 0:100) to give the title compound as a yellow solid (298 g).
LCMS (run time = 25 minutes, System K): R_t = 14.62 minutes, m/z 734 [MH^+]

Preparation 64: Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{4-[4-(5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-indol-6-yl} pyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate



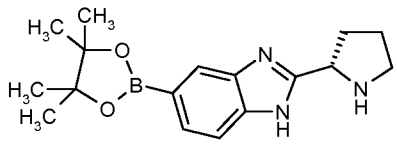
Method A:

Trifluoroacetic acid (52 mL) was added to a solution of *tert*-butyl (2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 63** (24.9 g, 33.97 mmol) in dichloromethane (200 mL) at 0°C. The reaction was then allowed to warm to room temperature and stirred for 6 hours. After this time, the solvent was removed under reduced pressure and the crude material was quenched by slow addition of a saturated solution of sodium hydrogen carbonate. Ethyl acetate (300 mL) was added and the layers were separated. The aqueous layer was extracted again with dichloromethane/methanol (90/10, 2 x 400 mL). The combined organic layers were concentrated under reduced pressure, azeotroping with toluene (300 mL). The crude material was preabsorbed onto silica and purified by flash chromatography (dichloromethane : methanol : ammonia, 97 : 3 : 1 to 85 : 15 : 1) to give the title compound as a yellow solid (18.80 g).
LCMS (run time = 25 minutes, System K): 14.62 minutes, m/z 634 [MH^+].
^{1}H NMR (400 MHz, DMSO-d_6+drop of TFA): δ= 9.37 (s, 2H), 8.42 (s, 1H), 8.35 (d, 2H), 8.17 (s, 1H), 8.12 (d, 1H), 7.93 (d, 2H), 7.75 (d, 1H), 5.12-5.09 (m, 1H), 5.01-4.97 (m, 1H), 4.10-4.07 (m, 1H), 3.86-3.75 (m, 2H), 3.49 (s, 3H), 3.44-3.28 (m, 2H), 2.40-2.37 (m, 1H), 2.21-1.96 (m, 8H), 0.78 (d, 3H), 0.73 (d, 3H).

Method B:

To a solution of *tert*-butyl (2*S*)-2-(6-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrazin-2-yl}-1*H*-indol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 63** (296 g, 403 mmol) in ethanol (3000 mL) was added 4M HCl in1,4-dioxane (303 mL, 1210 mmol). The reaction was heated at reflux for 16 hours, then allowed to cool room temperature. The solvent was removed by distillation at reduced pressure to give the title compound as a yellow solid (285 g) and as a hydrochloride salt.
^{1}H NMR (400 MHz, DMSO-d_6): δ= 10.57 (br s, 1H), 9.58 (br s, 1H), 9.42 (s, 2H), 8.50 (s, 1H), 8.35 (d, 2H), 8.22-8.19 (m, 2H), 8.12-8.10 (d, 2H), 7.82-7.80 (d, 1H), 7.30-7.27 (m, 1H), 5.27-5.20 (m, 1H), 5.09-5.01 (m, 1H), 4.18-4.11 (m, 1H), 4.08-4.00 (m, 1H), 3.89-3.80 (m, 1H), 3.58 (s, 3H), 3.42-3.34 (m, 2H), 2.59-2.51 (m, 1H), 2.44-1.97 (m, 8H), 0.98-0.90 (m, 1H), 0.89-0.85 (d, 3H), 0.79-0.75 (d, 3H).

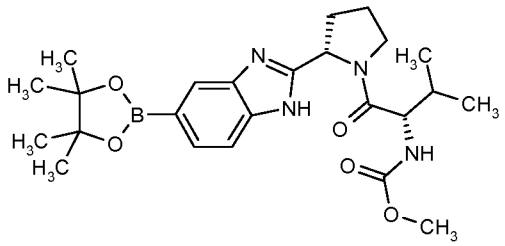
Preparation 65: 2-[(2*S*)-Pyrrolidin-2-yl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazole



4M HCl in 1,4-dioxane (10 mL, 40 mmol) was added to *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 6** (745 mg, 1.80 mmol) and the reaction mixture was heated to 50°C for 3 hours. After this time, the mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure to give the title compound, which was used crude in the next step.

LCMS (run time = 5 minutes, System D): R_t = 2.62 minutes; m/z 314 [MH^+].

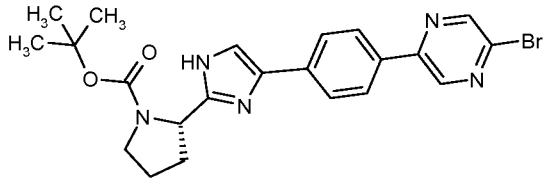
Preparation 66: Methyl [(2*S*)-3-methyl-1-oxo-1-{(2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate



N-(Methoxycarbonyl)-L-valine obtained from **Preparation 58** (378 mg, 2.16 mmol), HOBT (693 mg, 4.50 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (414 mg, 2.16 mmol) in acetonitrile (15 mL) were stirred at room temperature for 30 minutes. A suspension of 2-[(2*S*)-pyrrolidin-2-yl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazole obtained from **Preparation 65** (563 mg, 1.80 mmol) in acetonitrile (10 mL) was added, followed by the dropwise addition of diisopropylethylamine (1.25 mL, 7.20 mmol). The resulting mixture was stirred at room temperature for 16 hours. After this time, the reaction was diluted with dichloromethane and washed with brine (sat. aq.). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 50:1 to 20:1) to give the title compound as a white foam (668 mg).

LCMS (run time = 5 minutes, System D): R_t = 1.81 minutes; m/z 389.2 [MH^+] boronic acid; R_t = 2.81 minutes; m/z 471 [MH^+] boronate ester.

Preparation 67: *tert*-Butyl (2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate



Method A:

Potassium phosphate (7.39 g, 34.81 mmol) was added to a stirred solution of 2-bromo-5-iodopyrazine obtained from **Preparation 10** (7.65 g, 17.41 mmol) and tert-butyl (2S)-2-{4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 3** (6.45 g, 22.63 mmol) in a mixture of 1,4-dioxane : water (3:7, 500 mL). The mixture was degassed for 20 minutes after which time tetrakis(triphenylphosphine)palladium (0) (2.00 g, 1.74 mmol) was added and the reaction heated to 90°C for 2 hours. After this time, the reaction mixture was cooled to room temperature and poured into a saturated solution of sodium bicarbonate (500 mL). The product was extracted with ethyl acetate (3 x 500 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed under reduced pressure to a brown crude oil. The crude product was purified by flash chromatography (ethyl acetate:dichloromethane, 50 : 50 to 100 : 0) to give the title compound as a pale yellow solid (5.56 g).

LCMS: (run time = 4.5 minutes, System J): R_t = 2.22 minutes; m/z 470.19 and 472.07 [MH^+]

^{1}H NMR (400 MHz, CD_3OD) δ = 8.95 (s, 1H), 8.75 (s, 1H), 8.1 (d, 2H), 7.85 (d, 2H), 7.50-7.40 (m, 1H), 4.90-4.80 (m, 1H), 3.75-3.65 (m, 1H), 3.55-3.45 (m, 1H), 2.40-2.30 (br. m, 1H), 2.10-1.90 (m, 3H), 1.25 (s, 9H)

Method B:

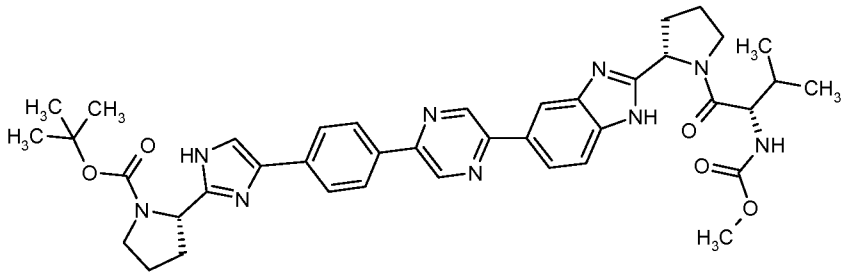
tert-Butyl (2*S*)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate obtained from **Preparation 2** (380 g, 0.969 mol), potassium acetate (285 g, 2.90 mol) and bis(pinacolato)diboron (246 g, 0.969 mol) were combined in 1,4-dioxane (3.8 L). The mixture was heated to 80°C and sparged with nitrogen for 10 minutes. To the mixture was added (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) chloride (7.92 g, 9.68 mmol) and the reaction was heated at reflux with continual nitrogen sparging for 90 minutes. To the reaction mixture was added a solution of 2,5-dibromopyrazine (300 g, 1.26 mol) in 1,4-dioxane (0.95 L), followed by a solution of sodium carbonate (308 g, 2.90 mol) in water (1.9 L). The mixture was sparged with nitrogen at 85°C for 10 minutes then bis(diphenylphosphino)ferrocene)palladium(II) chloride (7.92 g, 9.68 mmol) was added and the reaction was heated at reflux for 7 hours. After this time the reaction mixture was distilled and replaced with toluene at atmospheric pressure, removing the water azeotropically using Dean-Stark apparatus. The resulting slurry was cooled to 25°C and diluted with dichloromethane (2.5 L), then filtered under reduced pressure washing the inorganic filter cake with dichloromethane (0.5 L). The filtrate was evaporated under reduced pressure. The crude black oil was purified by flash chromatography (heptane:acetone 3:1 to 1:1). The product-containing fractions were evaporated under reduced pressure and the resulting solid was

granulated in t-butylmethylether (1.5 L), collected by filtration under reduced pressure to give the title compound as a beige solid (112 g).

LCMS (IPC_NEUT): Rt = 6.48 minutes; m/z 470 and 472 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.36-11.88 (m, 1H), 9.35-9.05 (m, 1H), 8.93-8.83 (m, 1H), 8.23-8.04 (m, 2H), 7.97-7.79 (m, 2H), 7.73-7.60 (m, 1H), 4.93-4.72 (m, 1H), 3.66-3.46 (m, 1H), 3.45-3.34 (m, 1H), 2.36-2.11 (m, 1H), 2.11-1.74 (m, 3H), 1.47-1.10 (m, 9H).

Preparation 68: *tert*-Butyl (2*S*)-2-(4-{4-[5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrazin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

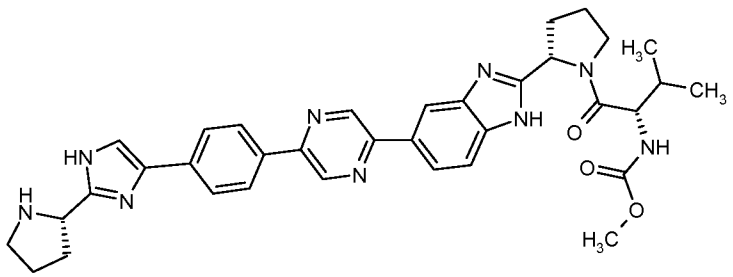


Methyl [(2*S*)-3-methyl-1-oxo-1-{(2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate obtained from **Preparation 66** (668 mg, 1.42 mmol), *tert*-butyl (2*S*)-2-(4-{4-[5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrazin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 67** (668 mg, 1.42 mmol), $Pd(PPh_3)_4$ (164 mg, 0.14 mmol) and K_2CO_3 (2.0 M in water, 1.42 mL, 2.84 mmol) in *N*,*N*'-dimethylformamide (10 mL) were stirred at room temperature and sparged with Argon for 10 minutes. The reaction mixture was then heated to 60°C for 16 hours. After this time, the mixture was diluted with ethyl acetate and washed with brine (sat. aq.). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane : methanol, 97:3 to 90:10) to give the title compound as a pale yellow foam (551 mg).

LCMS (run time = 5 minutes, System D): R_t = 3.08 minutes; m/z 340 [M-^{t}Bu]H+$2H^+$/2.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.09-8.75 (m, 2H), 8.37-6.70 (m, 9H), 5.50-5.29 (m, 2H), 5.02-4.85 (m, 1H), 4.39-4.10 (m, 1H), 3.90-3.38 (m, 5H), 3.70 (s, 3H), 3.06-1.51 (m, 9H), 1.50-0.74 (m, 15H).

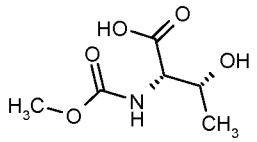
Preparation 69: Methyl {(2*S*)-3-methyl-1-oxo-1-[(2*S*)-2-{5-[5-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrazin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate



tert-Butyl (2*S*)-2-(4-{4-[5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl) pyrazin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate obtained from **Preparation 68** (551 mg, 0.75 mmol) and 4 M HCl in 1,4-dioxane (5 mL, 20.0 mmol) in industrial methylated spirits (5 mL) were stirred at 50°C for 3 hours. After this time, the solvent was evaporated under reduced pressure to give the title compound as a yellow solid (476 mg), which was used crude in the next step.

LCMS (run time = 5 minutes, System D): R_t = 2.89 minutes; m/z 318 [MH^+]/2.

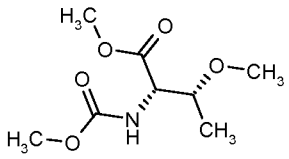
Preparation 70: *N*-(Methoxycarbonyl)-L-threonine



Methyl chloroformate (7.1 mL, 92.34 mmol) was added dropwise to a solution of *L*-threonine (10 g, 83.94 mmol) and sodium carbonate (4.44 g, 41.97 mmol) in 1M NaOH (100 mL) at 0°C. Once added, the reaction was left to stir at room temperature for 3 hours. After this time, the reaction was acidified to pH 1 with concentrated hydrochloric acid and the product was extracted with 2-methyltetrahydrofuran (3 x 300 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed under reduced pressure to a yellow gum. The residue was azeotroped with dichlomethane/heptane and then dried under vacuum to give the title compound as a white foam (14.77 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.10-5.80 (br. m, 3H), 4.40 (m, 1H), 4.35 (m, 1H), 3.70 (s, 3H), 1.25 (d, 3H)

Preparation 71: Methyl *N*-(methoxycarbonyl)-*O*-methyl-L-threoninate

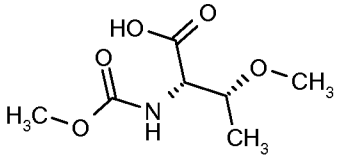


Iodomethane (5.1 mL, 81.85 mmol) and silver (I) oxide (20.9 g, 90.03 mmol) were added to a stirred solution of *N*-(methoxycarbonyl)-L-threonine obtained from **Preparation 70** (2.90 g, 16.37 mmol) in acetone (100 mL). The reaction was left to stir at room temperature for 24 hours. After this time, the reaction was heated to 50°C

and stirred at this temperature for a further 24 hours. After this time, the reaction was cooled to room temperature, the solid formed was removed by filtration through a pad of celite, rinsing with acetone (2 x 500 mL). The filtrate was concentrated under reduced pressure to an orange oil. The crude product was purified by flash chromatography (heptane : ethyl acetate, 50:50 to 30:70) to give the title compound as a colourless solid (657 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.40 (br s, 1H), 4.30 (dd, 1H), 4.00-3.90 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.30 (s, 3H), 1.20 (d, 3H).

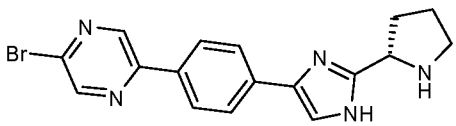
Preparation 72: *N*-(Methoxycarbonyl)-*O*-methyl-L-threonine



Lithium hydroxide (80 mg, 3.36 mmol) was added to a solution of methyl *N*-(methoxycarbonyl)-*O*-methyl-L-threoninate obtained from **Preparation 71** (657 mg, 3.20 mmol) in a methanol:water:tetrahydrofuran (1:1:1, 6 mL) mixture. After stirring at room temperature for 16 hours, a further equivalent of lithium hydroxide (80 mg, 3.36 mmol) was added. The reaction mixture was stirred at room temperature for a further 16 hours. After this time, the reaction was acidified to pH 3 with 2M HCl (aq). The product was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were dried over sodium sulphate. The solvent was removed under reduced pressure to give a crude brown oil. The crude product was purified by flash chromatography (dichloromethane : methanol : acetic acid, 100:0:0 to 90:9:1) to give the title compound as a colourless oil (469 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.25 (br s, 1H), 4.20 (dd, 1H), 4.00 (m, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 1.20 (d, 3H).

Preparation 73: (2*S*)-2-{4-[4-(5-Bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine methane sulfonate salt

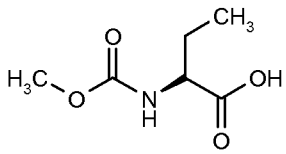


To a solution of *tert*-butyl (2*S*)-2-{4-[4-(5-bromopyrazin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate obtained from **Preparation 67** (257g, 546 mmol) in ethanol (2570 mL) was added methane sulfonic acid (143 mL, 2186 mmol). The mixture was heated at reflux for 16 hours. After this time, the reaction was allowed to cool to room temperature and the solid was collected by filtration, washed with ethanol and dried to give the title compound as a white solid (275 g).

LCMS (run time = 13 minutes, System E) R_t= 4.08; m/z 370 and 372 [MH^+]

^{1}H NMR (400 MHz, DMSO-d_6) : δ= 9.60-9.75 (br. s, 1H), 9.25-9.55 (br s, 1H), 9.18 (s, 1H) 8.93 (s, 1H), 8.26-8.28 (d, 2H), 8.22 (s, 1H), 8.01-8.03 (d, 2H), 4.95-5.06 (m, 1H), 3.37-3.48 (m, 2H), 2.46 (s, 6H), 2.45-2.56 (m, 1H), 2.33-2.42 (m, 1H), 2.15-2.27 (m, 1H), 1.98-2.11 (m, 1H).

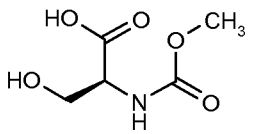
Preparation 74: (2*S*)-2-[(Methoxycarbonyl)amino]butanoic acid



To a solution of 2-aminobutanoic acid (2.0 g, 19.4 mmol) in 1M NaOH (20 mL) was added sodium carbonate (1.0 g, 9.7 mmol) and methyl chloroformate (1.6 mL, 21.3 mmol). The reaction was stirred at room temperature for 72 hours. After this time, it was acidified to pH 2.0 using 1M hydrochloric acid, then extracted with ethyl acetate (3 x 50 mL). The organic layers were combined and washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the title compound as an oil (1.9 g).

^{1}H NMR (400 MHz, CD_3OD): δ =4.09-4.06 (m, 1H), 3.64 (s, 3H), 1.91-1.81 (m, 1H), 1.76-1.63 (m, 1H), 0.99-0.96 (m, 3H).

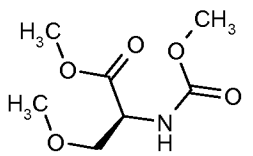
Preparation 75: *N*-(methoxycarbonyl)-L-serine



Methyl chloroformate (3.79 mL, 49.19 mmol) was added dropwise to a solution of L-serine (4.7 g, 44.72 mmol) and sodium carbonate (2.37 g, 22.36 mmol) in 1M NaOH (60 mL) at 0 °C. Once added, the reaction was left to stir at room temperature for 16 hours. After this time, the reaction was acidified to pH 1 with concentrated hydrochloric acid and the product was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulphate and the solvent was evaporated under reduced pressure to give a colourless oil. The residue was azeotroped with dichlomethane/heptane and then dried under vacuum to give the title compound as a colourless oil (1.44 g).

^{1}H NMR (400 MHz, CD_3OD) δ = 4.23 (t, 1H), 3.88-3.79 (m, 2H), 3.64 (s, 3H).

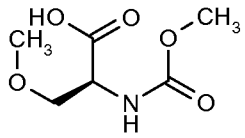
Preparation 76: Methyl *N*-(methoxycarbonyl)-*O*-methyl-L-serinate



Iodomethane (6.23g, 2.73 mL, 44.1 mmol) and silver (I) oxide (11.2 g, 44.1 mmol) were added to a stirred solution of *N*-(methoxycarbonyl)-L-serine obtained from **Preparation 75** (1438 mg, 8.82 mmol) in acetone (70 mL) at 60 °C. The reaction mixture was left to stir at room temperature for 16 hours. After this time, it was cooled to room temperature and the solid which had formed was removed by filtration through a pad of celite, rinsing with acetone (2 x 50 mL). The filtrate was concentrated under reduced pressure to give a colourless oil. The crude product was purified by flash chromatography (heptane : ethyl acetate, 60:40 to 40:60) to give the title compound as a white solid (887 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.50 (br s, 1H), 4.55 (br s, 1H), 3.79 (dd, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.59 (dd, 1H), 3.32 (s, 3H).

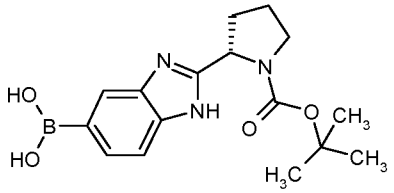
Preparation 77: *N*-(methoxycarbonyl)-*O*-methyl-L-serine



Lithium hydroxide (117 mg, 4.87 mmol) was added to a solution of methyl *N*-(methoxycarbonyl)-*O*-methyl-L-serinate obtained from **Preparation 76** (887 mg, 4.64 mmol) in a methanol : water : tetrahydrofuran (3:3:1, 7 mL) mixture. After stirring at room temperature for 16 hours, lithium hydroxide (11 mg, 0.464 mmol) was added. The reaction mixture was stirred at room temperature for a further 2 hours. After this time, the solvent was removed under reduced pressure to give an oil which was partitioned between water (20 mL) and 2-methyl tetrahydrofuran (20 mL). The pH of the water layer was adjusted to pH 2-3 by slow addition of 1.0 M HCl. The organic layer was separated and the aqueous layer was extracted with 2-methyl tetrahydrofuran (2 X 20 mL). The combined organic extracts were dried over sodium sulphate. The solvent was removed under reduced pressure to give a colourless oil (455 mg) which was used without further purification into the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.56 (d, 1H), 4.50 (br s, 1H), 3.86 (dd, 1H), 3.71 (s, 3H), 3.63 (dd, 1H), 3.37 (s, 3H).

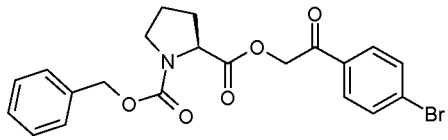
Preparation 78: {2-[(2S)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}boronic acid



To a solution of *tert*-butyl (2*S*)-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-2-yl]pyrrolidine-1-carboxylate (46 g, 0.119 mol), obtained from **Preparation 6,** in acetone (500 mL) was added $NaIO_4$ (103.6 g, 0.484 mol) and 1M aqueous NH_4OAc (55.9, 0.727 mol). The resulting mixture was stirred at room temperature for 16 hours. After this time, it was concentrated under reduced pressure and the residue was diluted with ethyl acetate (300 mL), washed with water (400 mL), and then with brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the title compound (40 g).

LCMS (run time = 2 minutes, System M): Rt = 0.915 minutes, m/z 332.2 [MH^+]

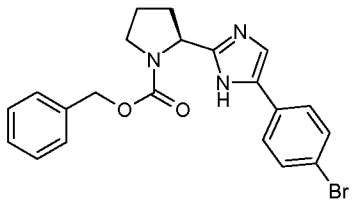
Preparation 79: 1-Benzyl 2-[2-(4-bromophenyl)-2-oxoethyl] (2*S*)-pyrrolidine-1,2-dicarboxylate



2,4'-Dibromoacetophenone (58.6 g, 0.21 mol) was added to a stirred solution of 1-[(benzyloxy)carbonyl]-L-proline (50 g, 0.20 mmol) in dichloromethane (370 mL) at 0°C. Diisopropylethylamine (38.4mL, 0.22 mmol) was added dropwise to the mixture and the resulting yellow solution was allowed to warm to room temperature and then stirred for 16 hours. After this time, the reaction was washed successively with water (200 mL), saturated $NaHCO_3$ (100 mL), water (200 mL) and brine (200 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give the title compound (98 g), which was used in the next step without further purification.

LCMS (run time = 2 minutes, System M): Rt = 1.208 minutes, m/z 446 and 448 [MH^+]

Preparation 80: Benzyl (2S)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate

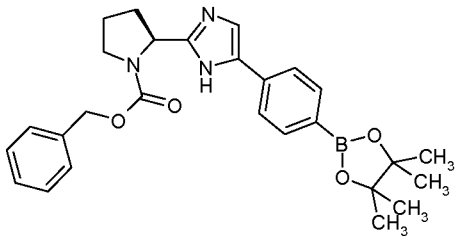


Ammonium acetate (76 g, 0.990 mol) was added to a solution of 1-benzyl 2-[2-(4-bromophenyl)-2-oxoethyl] (2S)-pyrrolidine-1,2-dicarboxylate (98 g, 0.219 mol), obtained from **Preparation 79,** in xylene (1000 mL). The resulting mixture was heated to 150 °C for 5 hours. After this time, it was cooled to room temperature, filtered and the filtrate was evaporated under reduced pressure. The resulting yellow solid was stirred in *tert*-butyl

methyl ether (100 mL) for 1 hour and then the resulting precipitate was collected by filtration and dried under vacuum to give the title compound (73 g) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.12 (m, 10H), 5.09 (s, 2H), 4.94-9.93 (d, 1H), 3.45-3.42 (t, 2H), 2.90 (s, 1H), 2.12-2.11 (d, 2H), 1.92-1.90 (m, 1H).

Preparation 81: Benzyl (2S)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

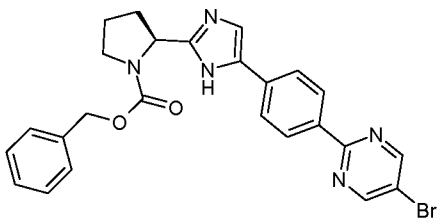


A mixture of benzyl (2S)-2-[5-(4-bromophenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate (30 g, 0.07 mol) obtained from **Preparation 80**, bis(pinacolato)diboron (35.6 g, 0.14 mol), and potassium acetate (17.3 g, 0.17 mol) were dissolved in 1,4-dioxane (300 mL). The mixture was sparged with nitrogen before adding (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (5.73 g, 7 mmol). The resulting solution was sparged again with nitrogen before heating to reflux for 2 hours. After this time, it was cooled to room temperature and the mixture was partitioned between ethyl acetate (200 mL) and water (100 mL). The pH of the aqueous layer was adjusted to around 8 by addition of 2M aqueous NaOH solution. The aqueous layer was further extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography (petroleum ether: ethyl acetate, 50:50 to 40:60) to give the title compound (50 g) as a white solid.

LCMS (run time = 2 minutes, System M): Rt = 1.157 minutes, m/z 474.1 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 7.77-7.68 (m, 4H), 7.39-7.35 (m, 3H), 7.11-6.97 (m, 3H), 5.15-5.12 (d, 2H), 5.04 (s, 1H), 3.77-3.57 (m, 2H), 2.45-2.03 (m, 4H).

Preparation 82: Benzyl (2S)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate

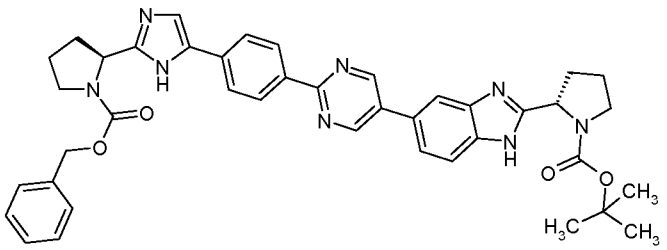


To a solution of benzyl (2S)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate (50 g, 0.105 mol) obtained from **Preparation 81** and 5-bromo-2-iodopyrimidine (35.3 g, 0.126 mol) in toluene (1000 mL) and ethanol (120 mL) was added K_2CO_3 (17.5 g, 0.126 mol) in water (127 mL). The resulting mixture was sparged with nitrogen before adding bis(diphenylphosphino)

ferrocene)dichloropalladium(II) (8.6 g, 10.5 mmol). It was sparged again with nitrogen before heating to 80 °C for 16 hours. After this time, it was cooled to room temperature, diluted with ethyl acetate (500 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (300 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate: dichloromethane, 50:50) to give the title compound (31 g) as a yellow solid.

LCMS (run time = 2 minutes, System M): Rt = 1.127 minutes, m/z 526 and 528 [MNa^+]

Preparation 83: *tert*-Butyl (2S)-2-(5-{2-[4-(2-{(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrimidin-5-yl}-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate

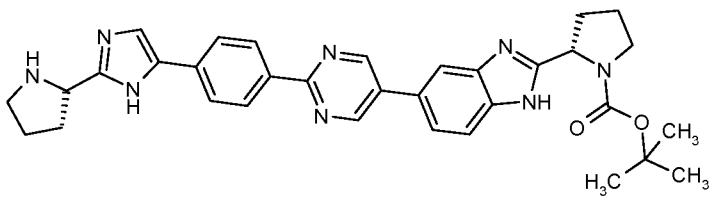


A mixture of benzyl (2S)-2-{5-[4-(5-bromopyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidine-1-carboxylate (25 g, 0.049 mol) from **Preparation 82**, (2-{(2S)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)boronic acid (20.5 g, 0.049 mol) from **Preparation 78** and K_3PO_4 (17.7 g, 0.084 mol) in dioxane (250 mL) and water (25 mL) was sparged with nitrogen before $Pd_2(dba)_3$ (453 mg) and $P(Cy)_3$ (1347 mg) were added. The reaction mixture was heated to 80 °C. After 16 hours, it was cooled to room temperature, diluted with ethyl acetate (150 mL), and washed with saturated $NaHCO_3$ (aq.)(150 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane: MeOH, 10:1) to give the title compound (28 g) as a yellow solid.

LCMS (run time = 2 minutes, System M): Rt = 0.920 minutes; m/z 711 [MH^+]

^{1}H NMR (400 MHz, CD_3OD): δ = 9.17 (s, 2H), 8.50-8.48 (d, 2H), 7.87-7.44 (m, 8H), 7.13-7.02 (m, 3H), 5.14 (s, 2H), 5.07 (s,2H), 3.78-3.77 (d, 2H), 3.62-3.60 (m, 2H), 2.17-2.09 (m, 2H), 2.05-2.02 (m, 6H), 1.50 (s, 3H), 1.22-1.19 (d, 6H).

Preparation 84: *tert*-Butyl (2S)-2-{5-[2-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate

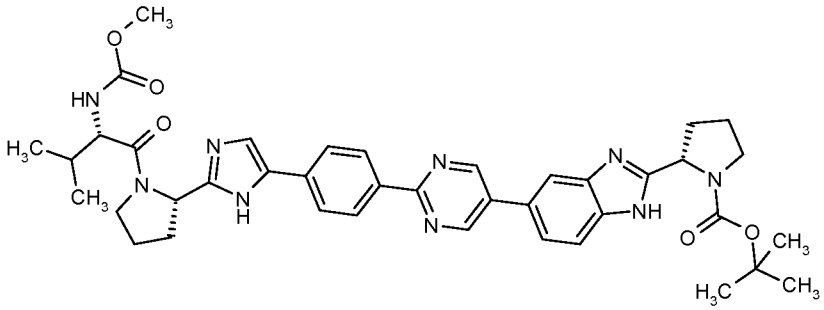


To a solution of *tert*-butyl (2S)-2-(5-{2-[4-(2-{(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrimidin-5-yl}-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate (28 g, 0.039 mol) obtained from **Preparation 83** in methanol (300 mL) was added $Pd(OH)_2/C$(8 g), under an atmosphere of nitrogen. The resulting mixture was hydrogenated at 45 Psi and 50°C for 16 hours. After this time, it was evaporated under reduced pressure to give the title compound as a light yellow solid (19.8 g).

^{1}H NMR: (400MHz, DMSO-d_6): 12.54 (b, 1H), 9.28 (s, 2H), 8.48-8.13 (s, 2H), 7.91-7.64 (m, 6H), 5.07-4.99 (m, 1H) ,4.27-4.25 (m, 1H), 3.51-3.22 (m, 4H), 3.06-2.96 (m, 2H), 2.41-2.35 (m, 1H), 2.97-2.00 (m, 6H), 1.50-1.02 (d, 9H).

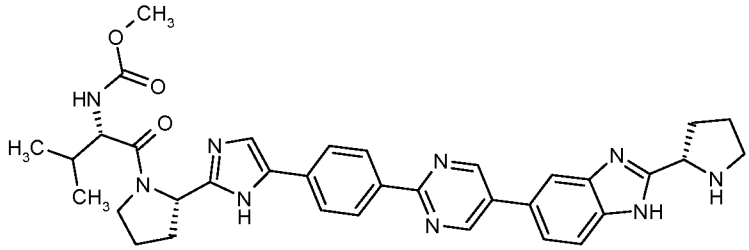
LRMS: m/z 577 [MH^+]

Preparation 85: *tert*-Butyl (2S)-2-(5-{2-[4-(2-{(2S)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrimidin-5-yl}-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate



To a solution of *tert*-butyl (2S)-2-{5-[2-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)pyrimidin-5-yl]-1*H*-benzimidazol-2-yl}pyrrolidine-1-carboxylate (7 g, 0.012 mol) obtained from **Preparation 84** in dichloromethane/acetonitrile (800 mL, 1:1 mixture) were added *N*-(methoxycarbonyl)-L-valine (2.5 g, 0.0145 mol) obtained from **Preparation 58**, triethylamine (50 mL, 0.360 mol) and HATU (5.5g, 0.0145 mol). The resulting reaction mixture was stirred at room temperature for 16 hours. After this time, it was evaporated under reduced pressure and the residue was purified by column chromatography (ethyl acetate: methanol, 30:1 to 5:1) to give the title compound (5 g) which was used without further purification in the next step.

Preparation 86: Methyl {(2S)-3-methyl-1-oxo-1-[(2S)-2-{5-[4-(5-{2-[(2S)-pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrimidin-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]butan-2-yl}carbamate hydrochloride salt



To a solution of *tert*-butyl (2S)-2-(5-{2-[4-(2-{(2S)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrimidin-5-yl}-1*H*-benzimidazol-2-yl)pyrrolidine-1-carboxylate (5 g, 0.0068 mol) obtained from **Preparation 85** in methanol (400 mL) was added 4M HCl in dioxane (100 mL). The reaction mixture was stirred at room temperature for 2 hours. After this time, it was evaporated under reduced pressure to give the title compound (4.5 g) as an hydrochloride salt.

^{1}H NMR: (400MHz, CD_3OD): δ = 8.89 (s, 2H), 8.24 (d, 2H), 7.80-7.70 (m, 1H), 7.69-7.52 (m, 3H), 7.43 (d, 1H), 7.39 (s, 1H), 5.21-5.10 (m, 1H), 5.01-4.91 (m, 1H), 4.24 (d, 1H), 4.10-3.97 (m, 1H), 3.95-3.82 (m, 1H), 3.64 (s, 3H), 3.61-3.45 (m, 2H), 2.59-2.50 (m, 1H), 2.42-2.29 (m, 2H), 2.29-1.97 (m, 6H), 0.96 (d, 3H), 0.90 (d, 3H)

LRMS: m/z 634 [MH^+]

Determination of HCV replicon inhibitory activity

The ability of the compounds of the formula (I) to inhibit HCV replication may be measured using the assays described below:

Test compound preparation

Test compounds were solubilised to 4mM in 100% DMSO. Dilutions were made to the desired starting concentration in 100% DMSO and then 1 in 3 dilutions made, again in 100% DMSO. 0.5μl of each sample was added to 384-well assay plates. White Lumitrac (Greiner) plates were used for the 1a and 1b replicon assays and black, clear bottomed (Greiner) plates were used for the WST-1 cytotoxity assay.

Determination of HCV 1a replicon inhibitory activity

1a-H77 replicon cells (licensed from Apath LLC) were resuspended to a concentration of 1.4 x 10^5cells/ml by addition of pre-warmed assay medium (Dulbecco's Modified Eagle's Medium (DMEM) + 10% fetal calf serum (FCS)). 45μl of this suspension was added to each well of a 384-well assay plate (Lumitrac, Greiner), already containing 0.5μl of test compound.

All plates were covered with gas permeable seals and incubated at 37°C, 5% CO_2 for 48 hours. After 48 hours, the assay plate was removed from the incubator and left to cool to room temperature for 15-30 mins. Medium was removed from the wells and 5μl 1X lysis buffer (from Promega's Renilla Luciferase assay

kit, E2820) was added to each well. The plate was incubated at room temperature on a rocker for 15 mins then 15µl 1X Assay Substrate (from the same kit) was added to each well. Luminescence was read immediately using an EnVision (Perkin Elmer) plate reader. The half maximal effective concentration (EC50) values were calculated by constructing log concentration-response curves for each compound.

Determination of HCV 1b replicon inhibitory activity

1b (con1) replicon cells (pFKI389lucubineo/NS3-3'/ET/9B, licensed from Ralf Bartenschlager, University of Heidelberg) were resuspended to a concentration of 1.4 x 10^5cells/ml by addition of pre-warmed medium (DMEM + 10% FCS). 45µl of this suspension was added to each well of a 384-well assay plate (Lumitrac, Greiner) already containing 0.5µl of test compound.

All plates were covered with gas permeable seals and incubated at 37ºC, 5% CO_2 for 48 hours. After 48 hours, the plate was removed from the incubator and left to cool to room temperature for 15-30mins. An equal volume of reconstituted Lyophilised Britelite Plus Substrate (PerkinElmer, 6016767) to medium was added to each well. Luminescence was read after 1 min but before 15 mins on an EnVision (Perkin Elmer) plate reader. The half maximal effective concentration (EC50) values were calculated by constructing log concentration-response curves for each compound.

Determination of compound induced cytotoxicity in HCV replicon cell lines (as measured using WST-1 reagent)

1b (con1) replicon cells were resuspended to a concentration of 1.4 x 10^5cells/ml by addition of pre-warmed medium (DMEM +10% FCS). 45µl of this suspension was added to each well of a 384-well assay plate (Black, clear bottomed, Greiner) already containing 0.5µl of test compound.

All plates were covered with gas permeable seals and incubated at 37ºC, 5% CO_2 for 48 hours. After 48 hours, 5µl WST-1 reagent (Roche, 11 644 807 001) was added to each well and the plate returned to the incubator for 1 hour. After this incubation period absorbance was read at 450nm on an EnVision (Perkin Elmer) plate reader. The half maximal cytotoxic concentration (CC50) values were calculated for each compound by constructing log concentration-response curves.

Table 1: Data for Replicon 1a and Replicon 1b in vitro pharmacology assays detailing geometric means from IC50 values generated. 95% confidence intervals are shown in parentheses followed by the respective n value.

Example number	Replicon 1a IC50 (95% CI) n	Replicon 1b IC50 (95% CI) n
1	6.95E-010 (3.14E-010 - 1.54E-009) 6	4.04E-011 (2.10E-011 - 7.75E-011) 7
2	3.18E-011 (2.41E-011 - 4.18E-011) 23	6.61E-012 (5.16E-012 - 8.46E-012) 20
3	1.08E-010 (8.25E-011 - 1.41E-010) 13	9.42E-012 (6.72E-012 - 1.32E-011) 10
4	7.05E-011 (5.64E-011 - 8.81E-011) 16	7.80E-012 (6.64E-012 - 9.17E-012) 11
5	1.28E-010 (8.55E-011 - 1.92E-010) 11	1.63E-011 (1.11E-011 - 2.40E-011) 8
6	1.01E-010 (8.03E-011 - 1.26E-010) 6	5.90E-012 (3.12E-012 - 1.11E-011) 5
7	6.85E-011 (3.69E-011 - 1.27E-010) 4	7.75E-012 (6.37E-012 - 9.44E-012) 4
8	1.18E-010 (9.46E-011 - 1.46E-010) 11	2.05E-011 (1.35E-011 - 3.12E-011) 9
9	1.61E-010 (1.20E-010 - 2.16E-010) 13	9.17E-012 (7.16E-012 - 1.17E-011) 10
10	2.53E-010 (1.82E-010 - 3.52E-010) 10	2.99E-011 (2.50E-011 - 3.57E-011) 8
11	5.24E-011 (3.98E-011 - 6.90E-011) 11	3.67E-011 (3.21E-011 - 4.19E-011) 11
12	5.75E-011 (3.97E-011 - 8.33E-011) 7	1.50E-011 (1.11E-011 - 2.04E-011) 7
13	4.41E-011 (2.34E-011 - 8.32E-011) 7	1.55E-011 (8.27E-012 - 2.90E-011) 7
14	4.89E-011 (3.53E-011 - 6.76E-011) 7	1.88E-011 (1.49E-011 - 2.38E-011) 7
15	2.91E-010 (1.78E-010 - 4.78E-010) 5	2.34E-011 (1.42E-011 - 3.84E-011) 5
16	4.37E-010 (2.09E-010 - 9.14E-010) 4	8.13E-011 (5.91E-011 - 1.12E-010) 4
17	9.74E-010 (5.82E-010 - 1.63E-009) 7	5.31E-011 (3.79E-011 - 7.44E-011) 6
18	1.15E-010 (7.89E-011 - 1.67E-010) 8	8.38E-012 (3.03E-012 - 2.32E-011) 6
19	2.71E-010 (2.05E-010 - 3.58E-010) 6	5.39E-012 (2.77E-012 - 1.05E-011) 4
20	8.98E-010 (2.59E-010 - 3.11E-009) 3	1.37E-011 (9.66E-012 - 1.95E-011) 3
21	1.83E-010 (1.09E-010 - 3.09E-010) 8	2.55E-011 (1.57E-011 - 4.16E-011) 5
22	4.73E-009 (1.58E-009 - 1.42E-008) 4	5.71E-011 (3.49E-011 - 9.35E-011) 6
23	> 1.00E-008 3	2.48E-011 (2.09E-011 - 2.93E-011) 3
24	7.63E-009 (6.73E-009 - 8.64E-009) 2	4.47E-011 (2.55E-011 - 7.84E-011) 5

Table 2: Compound Induced Cytotoxicity in HCV Replicon Cell Lines

Example number	WST-1 IC50 (95% CI) n
1	> 1.000E-008 4
2	9.798E-006 (6.937E-006 - 1.384E-005) 7
3	> 1.000E-008 5
4	> 1.000E-008 9
5	> 1.000E-008 7
6	1.934E-006 (4.192E-009 - 8.917E-004) 4
7	> 1.330E-005 3
8	> 1.000E-008 11
9	1.468E-005 2
10	> 1.000E-008 11
11	1.482E-005 (1.210E-005 - 1.816E-005) 3
12	> 1.330E-005 4
13	7.105E-006 2
14	5.391E-006 1
15	> 1.330E-005 2
16	> 1.000E-008 4
17	1.298E-005 2
18	1.173E-005 1
19	1.320E-005 2
20	> 1.330E-005 2
21	3.834E-005 1
22	4.843E-006 2
23	> 1.330E-005 2
24	> 4.440E-006 7

Estimation of f_u - Equilibrium Dialysis.

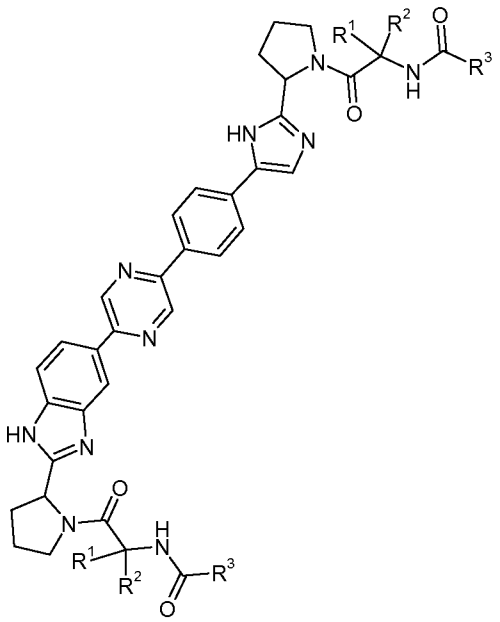
Plasma binding free fractions (f_u) were determined using a proprietary validated Rapid Equilibrium Dialysis (RED) device (Thermofisher). The analyte was spiked to a concentration of 2µM in pre-prepared male CD rat plasma and 220 µl aliquots (n=4) were loaded into a RED device. The samples were dialysed vs. 350µl of dulbeccos phosphate buffered saline (dPBS) for 4h at 37°C in a CO_2 incubator in order to reach equilibrium.

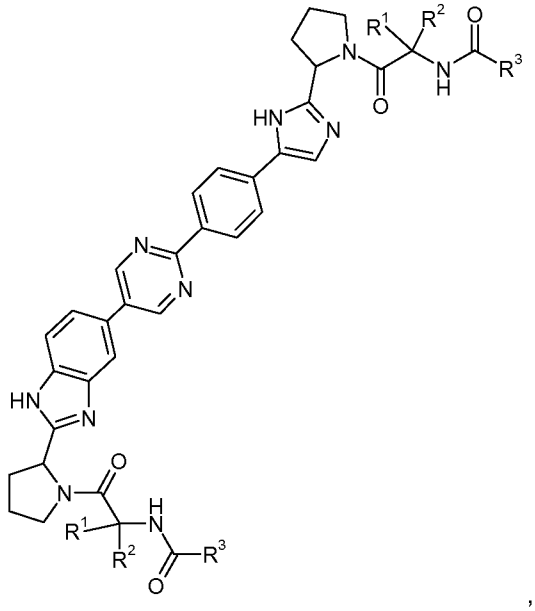
After 4 hours, 45µl buffer and 15µl plasma aliquots were taken and added to a 200 µl 384-well polypropylene plate. Respective volumes of control buffer were added to the plasma or control plasma was added to the buffer samples to give an identical matrix between samples. The samples were then crashed in 120 µl of acetonitrile and analysed via LC-MS/MS.

Compounds of the present invention may exhibit a high degree of binding to human plasma proteins (for example, the plasma protein binding for Examples 2 and 4 is 98.90%, and 98.90% respectively). For highly bound compounds in the potency assay, which includes 10% foetal calf serum, measured potencies may not reflect real intrinsic potency due to a significant degree of compound binding. True *in vitro* activity for compounds of this type could be significantly greater, when adjustments are made for unbound compound.

Claims

1. A compound selected from:



, or 

,

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is H;

each R^2 is independently selected from H, C_{1-4} alkyl, halogen, and C_{1-4} alkoxyalkyl;

said C_{1-4} alkyl being optionally substituted by NR^cR^d;

said R^c and R^d being each independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxyalkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxycarbonyl; and

each R^3 is independently C_{1-4} alkoxy.

2. A compound according to claim 1, wherein:

each R^2 is independently selected from C_{1-4} alkyl and C_{1-4} alkoxyalkyl.

3. A compound according to claim 2 wherein:

at least one R^2 is isopropyl.

4. A compound according to claim 2 wherein:

at least one R^2 is 1-methoxyethyl.

5. A compound according to any of claims 1 to 4 wherein:
each R^3 is methoxy.

6. A pharmaceutical composition comprising a compound according to any of the preceding claims, together with a pharmaceutically acceptable excipient.

7. A compound according to any of claims 1 to 5 for use as a medicament.

8. A compound according to any of claims 1 to 5 for use in the treatment of a disease for which an inhibitor of HCV replication is indicated.

9. A compound according to any of claims 1 to 5 for use in the treatment of HCV infection.

10. A method of treatment of a mammal, including a human being, to treat a disease for which an inhibitor of HCV replication is indicated, comprising administering to said mammal an effective amount of a compound according to any of claims 1 to 5, or a composition according to claim 6.

11. A method of treatment of a mammal, including a human being, to treat HCV infection, comprising administering to said mammal an effective amount of a compound according to any of claims 1 to 5, or a composition according to claim 6.

12. A compound according to any of claims 1 to 5, in combination with one or more other pharmacologically active agents.

13. A compound according to any of claims 1 to 5, in combination with one or more other agents which are useful for the treatment of HCV infection.

14. A product comprising a compound according to any of claims 1 to 5, and one or more other pharmacologically active agents as a combined preparation for simultaneous, separate or sequential use in therapy.

15. A compound according to claim 13 or a product according to claim 14, wherein at least one of the one or more other agents is a NS5B RNA-polymerase inhibitor.

16. A compound or product according to claim 15, wherein the NS5B RNA-polymerase inhibitor is selected from Filibuvir, HCV-796, Valopicitabine, GL-59728, GL-60667, PSI-6130, R1626, R7128, JTK-003 GL-59728 and GS-9190.

17. A compound or product according to claim 15 or 16, wherein the NS5B RNA-polymerase inhibitor is Filibuvir.

18. A kit comprising two or more pharmaceutical compositions, at least one of which comprises a compound according to any of claims 1 to 5 with a pharmaceutically acceptable excipient, and means for separately retaining said compositions.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052392

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4164 C07D403/14 A61P31/22
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/102318 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 20 August 2009 (2009-08-20) the whole document	1-18
A	WO 2008/021936 A2 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 21 February 2008 (2008-02-21) the whole document	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 2011	11/08/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/052392

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