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(54) Title: SELECTIVE CYPI 1B1 INHIBITORS FOR THE TREATMENT OF CORTISOL DEPENDENT DISEASES

(57) Abstract: The present invention relates to compounds which selectively inhibit CYPI 1B1. Preferably, the compounds of the present invention do not substantially inhibit CYP1 1B2. Moreover, the compounds of the present invention do not substantially inhibit CYPI 7 and/or CYPI 9, either. Amongst other applications of the compounds of the present invention, they can be used for the treatment of Cushing’s syndrome or metabolic disease.
SELECTIVE CYP11B1 INHIBITORS FOR THE TREATMENT OF CORTISOL DEPENDENT DISEASES

FIELD OF THE INVENTION

The present invention relates to compounds which selectively inhibit CYP11B1. Preferably, the compounds of the present invention do not substantially inhibit CYP11B2. Moreover, the compounds of the present invention do not substantially inhibit CYP17 and/or CYP19, either. Amongst other applications of the compounds of the present invention, they can be used for the treatment of Cushing's syndrome or metabolic disease.

BACKGROUND OF THE INVENTION

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior. Glucocorticoids such as Cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms. Mineralocorticoids such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney. Some common natural hormones are corticosterone, cortisone, 17-hydroxy-11-dehydrocorticosterone and aldosterone.

Aldosterone is mainly produced in the adrenal cortex, where its biosynthesis from the precursor cholesterol involves a number of catalytic steps and enzymes. The early steps of aldosterone biosynthesis share pathways and precursors with other steroidal hormones. The final steps of aldosterone biosynthesis are conducted by the cytochrome P450 enzymes 11B1 (Cortisol synthase or steroid-1 \(^\alpha\)-hydroxylase) and 11B2 (aldosterone synthase), which will further be denoted as CYP11B1 and CYP11B2, respectively. These enzymes catalyze the 11-hydroxylation of 11-deoxycorticosterone to corticosterone, which is then further hydroxylated by CYP11B2 to 18-hydroxycorticosterone (180H-B). Finally, CYP11B2 (but not CYP11B1) oxidizes the 18-hydroxyl group of 180H-B to the corresponding aldehyde, thus resulting in the formation of aldosterone.
CYP11B1, however, is also involved in the biosynthesis of Cortisol (hydrocortisone). Specifically, it catalyzes the conversion from 11-deoxycortisol to Cortisol, i.e. the key reaction in Cortisol biosynthesis. Cortisol is the main glucocorticoid in humans. It regulates energy mobilization and thus the stress response. In addition, it is involved in the immune response of the human body. Abnormally increased Cortisol level is the cause of a variety of diseases including Cushing's syndrome.

Endogenous Cushing's syndrome is a hormonal disorder caused by prolonged exposure to excessive levels of circulating glucocorticoids, therefore also called hypercortisolism. Signs and symptoms of this disorder vary, but most people develop central obesity, a round face and very often also diabetes and hypertension. Cushing's syndrome is the cause of considerable morbidity and mortality. In about 80% of all cases a pituitary hypersecretion of ACTH is observed, which is mostly related to an ACTH-secreting pituitary adenoma (Cushing's disease). Benign or malignant adrenocortical tumors are the most common reasons for ACTH-independent hypercortisolism. The standard treatment for most patients is the surgical removal of the tumor or radiation therapy. However, a third of all patients are not treatable with these therapies and require temporary or permanent medication. Therefore, the application of drugs lowering the elevated Cortisol levels or reducing glucocorticoid activity is considered as method of choice.

However, results with the glucocorticoid receptor antagonist mifepristone show, that administration of these agents triggers a massive secretion of Cortisol which is probably caused by the hypothalamic pituitary feedback mechanism. A decrease of glucocorticoid formation should be a better therapeutic option. The best target for such an approach is steroid-11ß-hydroxylase (CYP11B1), an adrenal CYP enzyme which directly affects Cortisol production by catalyzing the final step in Cortisol biosynthesis, namely hydroxylation of deoxycortisol in 11ß-position (Figure 1).

A major problem in the development of CYP enzyme inhibitors is the selectivity versus other CYP enzymes. Aromatase (estrogen synthase, CYP19) and 17a-hydroxylase-C17,20-lyase (CYP17) inhibitors are first line drugs for the treatment of breast cancer and upcoming therapeutics for castration refractory prostate cancer, respectively. In case of adrenal CYP11B enzymes matters are much more challenging as the homology between CYP11B1 and CYP11B2 is very high (93%) (Mornet et al. J. Biol. Chem. 1989, 264, 20961-20967) and for a long time it was considered impossible to obtain selective inhibitors. Nevertheless, CYP11B1 is the key enzyme in Cortisol biosynthesis and its inhibition with selective compounds is a promising strategy for the treatment of diseases associated with elevated Cortisol levels like Cushing's syndrome or metabolic disease which are otherwise not appropriately treatable.
Until recently, selective inhibitors of mineralo- and glucocorticoids were not in the focus of research efforts. This was due to the fact that the sequence identity between aldosterone synthase (CYP1B2) and Cortisol synthase (steroid-1 1β-hydroxylase, CYP1B1) is very high (93 %), and it was considered impossible to obtain selective inhibitors of one enzyme versus the other. Thus, although there is a high medical need for drugs interfering with excessive glucocorticoid formation resulting, for example, in Cushing's syndrome, there are only few inhibitors of CYP1B1 described so far. Because of their unselective action, their application is associated with severe side effects: The CYP19 inhibitor aminoglutethimide, metyrapone, the antimycotics ketoconazole and fluconazole, and the hypnotic etomidate are also inhibitors of other adrenal and gonadal Cytochrom P450 (CYP) enzymes. However, all of them show severe side effects due to the fact that they are unselective, i.e. they inhibit a broad range of CYP enzymes or hydroxysteroid dehydrogenases (HSDs). Some common side effects include gastrointestinal upset, edema, rash, malaise, gynecomastia and elevated transaminases (see Contemporary Endocrinology: Diagnosis and management of Pituitary Disorders, Ed. By: Swearingen and Biller, Humana Press (2008), Totowa, NJ).

Accordingly, the hypnotic and unselective CYP inhibitor etomidate was recently used as starting point in several drug discovery programs. While Roumen et al. (J. Med. Chem. 2010, 53, 1712-1725) discovered selective CYP11B2 inhibitors outgoing from etomidate and fadrozole, Zolle et al. (J. Med. Chem. 2008, 51, 2244-2253) described etomidate derived CYP1B1 inhibitors without investigating selectivity toward other CYPs. Also, WO 2007/139992 describes both CYP11B2 and CYP11B1 inhibitors based on imidazole derivatives. However, it does not provide selective CYP11B1 inhibitors.


PCT patent application publication number WO02/060877 discloses imidazole derivative which are NMDA (N-methyl-D-aspartate) receptor subtype 2B selective blockers which have as possible therapeutic indications acute forms of neurodegeneration caused, e.g., by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial or viral infections, and, in addition, depression and chronic and acute pain.
SUMMARY OF THE INVENTION

Having regard to the state of the art, there is a need to provide further, alternative selective CYP1B1 inhibitors. These inhibitors can then be applied for the treatment of medical conditions characterized by an abnormal activity or abnormal expression/level of CYP1B1 in a subject. Accordingly, the technical problem of the present invention is to comply with this need.

The present invention addresses this need and thus provides as a solution to the technical problem embodiments pertaining to novel imidazole compounds described herein, shown in the formulas and Tables and exemplified in the appended Examples. These compounds are contemplated to be selective CYP1B1 inhibitors and are, for example, illustrated in formula (1), formula (2) or formula (3). Preferably, the imidazole compounds of the present invention are for use as a medicament. Preferably, for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-11β-hydroxylase (CYP1B1). Advantageously, the compounds of the present invention can be used in treating Cortisol dependent disorders such as Cushing's syndrome or metabolic disease or metabolic syndrome.

Indeed, despite the challenging homology between CYP1B1 and CYP1B2 and overlapping ligand specificity, the present inventors have surprisingly discovered compounds which selectively inhibit CYP1B1.

Preferably, the compounds of the present invention have an IC₅₀ of less than about 200, more preferably less than about 175, more preferably less than about 150, even more preferably less than about 125, even yet more preferably less than about 115, particularly preferable less than about 105, most preferably less than about 100, 75, 50, 25 or 20 nM.

In the alternative or addition the compounds of the present invention can preferably be characterized by having a selectivity factor (SF) (IC₅₀ (CYP1B2)/IC₅₀ (CYP1B1)) of greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

Furthermore, in the alternative or addition, the compounds of the present invention can be characterized in that they selectively inhibit CYP1B1, and do not substantially inhibit CYP17 and/or CYP19. Preferably, the compounds of the present invention do not inhibit CYP17 more than 30, 25, 20, 15, 10 or 5%. Preferably, the compounds of the present invention do not inhibit CYP19 more than 30, 25, 20, 15, 10 or 5%. 
Accordingly, in some preferred embodiments, the compounds of the present invention selectively inhibit CYP1B1 and do not substantially inhibit CYP17 (not more than 30, 25, 20, 15, 10 or 5%) and/or CYP19 (not more than 30, 25, 20, 15, 10 or 5%) and can be further characterized by having a selectivity factor (IC\textsubscript{50} (CYP1B1)/IC\textsubscript{50} (CYP1B1)) greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

Accordingly, the compounds of the present invention as CYP1B1 inhibitors are also useful for the treatment of a disorder or a disease or a condition characterized by abnormal activity or abnormal level of CYP1B1. This is so because the compounds of the present invention when used as medicaments are envisaged to exhibit either reduced side effects or negligible side effects due to the fact that they are selective CYP1B1 inhibitors and hence can be used in a targeted treatment regime. For example, the compounds of the present invention can be used for the treatment of a disorder, a disease or a condition such as Cushing's syndrome, excessive CYP1B1 level, the ectopic ACTH syndrome, the change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD) Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine or cocaine withdrawal syndrome, the post-traumatic stress syndrome, the cognitive impairment after a stroke and the cortisol-induced mineralocorticoid excess, etc.

It must be noted that as used herein, the singular forms "a", "an", and "the", include plural references unless the context clearly indicates otherwise. Thus, for example, reference to "a reagent" includes one or more of such different reagents and reference to "the method" includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

All publications and patents cited in this disclosure are incorporated by reference in their entirety. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material.

Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. When used herein
the term "comprising" can be substituted with the term "containing" or sometimes when used herein with the term "having".

When used herein "consisting of" excludes any element, step, or ingredient not specified in the claim element. When used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim.

In each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms.

When used herein, the term "about" is understood to mean that there can be variation in the respective values (e.g. IC$_{50}$ or the selectivity factor) that can be to 5%, 10%, 15%, 20% or up to and including 25% of the given value.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

As described herein, "preferred embodiment" means "preferred embodiment of the present invention". Likewise, as described herein, "various embodiments" and "another embodiment" means "various embodiments of the present invention" and "another embodiment of the present invention", respectively.

In one embodiment, the present invention provides a compound of formula (1):

\[ \left\{ \frac{(R^1)_m}{A_{p}} \right\} \frac{(Q)_x}{(R^2)_y} \begin{array}{c} \text{Het} \end{array} \]  

(1)

wherein,

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoaxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoaxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl,
Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R¹ or R² can be independently H, C₁₋₅ alkyl, haloalkyl, C₆₋₁₃ aryl, naphthyl, benzo[b]thiophen, thiophen, amino, amido, C(0)R⁴, OC(0)R⁴, ester, ether, S0₂R⁴, furanyl, het, halogen, trityl, CN, N0₂ or OAc; either of which is unsubstituted or can be independently substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R³ is C₁₋₁₂ alkyl, haloalkyl, C₆₋₁₃ alkoxy, hydroxy, C₆₋₁₃ aryl, halogen, amino, amido, ester, ether, C(0)R⁴, OC(0)R⁴, S0₂R⁴, S0₂NHR⁴, trityl, CN, N0₂ or OAc,

R⁴ is H, OH, C₁₋₅ alkoxy, alkyl or aryl,

A is one or more heteroatoms independently selected from N, O, S or Se. Wherein A is N, preferably heterocycles are pyridine, pyrimidine or pyridazine; which can be further annelated by 5- or 6- membered rings.

m is selected from 0 - 3 carbons, preferably 1,

n is 0 - 6,

Q is C, O, S, CH=CH, N, CO, C0₂, CONH, S0₂, S0₂NH,

X is 1 - 3,

Y is 0 - 2,

Z is 1 - 2; if Z > 1, multi-Q can be any linker described above,

or a pharmaceutically acceptable derivative.

It is envisaged that the compounds of the present invention such as the compound of formula (1) selectively inhibit CYP1B1. Accordingly, in some preferred embodiments, said compound of formula (1) selectively inhibits CYP1B1 and has an IC₅₀ of less than about 200, more preferably less than about 175, more preferably less than about 150, even more preferably less than about 125, even yet more preferably less than about 115, particularly preferable less than about 105, most preferably less than about 100, 75, 50, 25 or 20 nM.
The compound of formula (1) of the present invention does preferably not substantially inhibit CYP17 and/or CYP19. Accordingly, in some preferred embodiments, the inhibition of CYP17 and/or 19 is not more than 30, 25, 20, 15 or 10 or 5%.

In a preferred embodiment for the compounds of formula (1), the compound is characterized by having a selectivity factor ($IC_{50}$ (CYP11B2)/$IC_{50}$ (CYP11B1)) greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

In certain embodiments, provided that in said compound of formula (1), when Het is imidazolyl, $Q$ is C, $z$ is 1, $R^2$ is H, $y$ is 2, $m$ is 1, $A$ is N and $n$ is 1—if $R^1$ is $C_6-C_{13}$ aryl it cannot be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In a further embodiment, the compound of formula 1 has $Q = C$, $z = 1$, $R^2 = H$, $y = 2$, $x = 1$, $m = 1$, $A = N$ and $n = 1-3$, more preferably 2, most preferably 1.

In another embodiment, the present invention provides a compound of formula (2):

\[
\begin{align*}
\text{het} & \quad \text{R}^3 \\
\text{R}^5 & \quad \text{het} \\
\text{R}^6 & \quad \text{het}
\end{align*}
\]

wherein,

$R^3$ is $C_1-C_2$ alkyl, haloalkyl, $C_1-C_5$ alkoxy, hydroxy, $C_6-C_{13}$ aryl, halogen, amino, amido, ester, ether, $C(0)R^4$, $C(0)R^4$, $SO_2R^4$, $SO_2NR^4$, $CN$, $N_2O$ or OAc,

$R^4$ is H, OH, $C_1-C_5$ alkoxy, alkyl or aryl,

$R^5$ is H, $C_1-C_2$ alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, $C_6-C_{13}$ aryl, naphthyl, $C_1-C_5$ alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, $N_2O$, OAc, amino, amido, $C(0)R^4$, $OC(0)R^4$, trityl or Het; which may be unsubstituted or substituted further with $R^3$ (wherein where multiple substitution with $R^3$ is possible, the substituents can be independently selected from $R^3$),

Het is heteroaryl, heteroarylylum, heterocyclyl, heteroaralkyl, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl,
benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxyopyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzooxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6-membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R⁶ is H, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₅-C₁₃ alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, C₂-C₁₃ aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO₃, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R⁷ is H, Halogen, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₂-C₁₂ alkenyl, cycloalkylene, alkynyl, C₆-C₁₃ aryl, C₅-C₁₃ alkoxy, hydroxy, thiophen, het, furanlyl, benzo[b]thiophen, naphthyl, CN, NO₃, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

or a pharmaceutically acceptable derivative.

It is envisaged that the compounds of the present invention such as the compound of formula (2) selectively inhibit CYP1B1. Accordingly, in some preferred embodiments, said compound of formula (2) selectively inhibits CYP1B1 and has an IC₅₀ of less than about 200, more preferably less than about 175, more preferably less than about 150, even more preferably less than about 125, even yet more preferably less than about 115, particularly preferable less than about 105, most preferably less than about 100, 75, 50, 25 or 20 nM.

The compound of formula (2) of the present invention does preferably not substantially inhibit CYP17 and/or CYP19. Accordingly, in some preferred embodiments, the inhibition of CYP17 and/or 19 is not more than 30, 25, 20, 15 or 10 or 5%.
In a preferred embodiment for the compounds of formula (2), the compound is characterized by having a selectivity factor \((\text{IC}_{50} \text{ (CYP1B2)})/\text{IC}_{50} \text{ (CYP1B1)})\) greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

In certain embodiments, provided that in said compound of formula (2), when \(R^5\) is C\(_6\)-C\(_{13}\) aryl it cannot be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In other embodiments, provided that in said compound of formula (2), when \(R^7\) is H and that one or both of \(R^5\) or \(R^6\) are independently either H, aryl or heteroaryl; wherein aryl or heteroaryl may be unsubstituted or substituted further with \(R^3\) (wherein where multiple substitution with \(R^3\) is possible, the substituents can be independently selected from \(R^3\)). If only one of \(R^5\) or \(R^6\) is independently either H, aryl or heteroaryl, the other \(R^5\) or \(R^6\) can be as defined herein.

In one embodiment the compounds of the present invention are the compounds of formula (2) with the exclusion of the following compounds:
In a yet further (preferred) embodiment, the present invention provides an imidazol-1-ylmethyl-pyridine compound of formula (3):

wherein,

\[ \text{R}^3 \] is C1-C12 alkyl, haloalkyl, C1-C5 alkoxy, hydroxy, C6-C13 aryl, halogen, amino, amido, ester, ether, C(0)R 4, OC(0)R 4, S0_2R 4, S0_2NHR 4, CN, N0 2 or OAc,

\[ \text{R}^4 \] is H, OH, C1-C5 alkoxy, alkyl or aryl,

\[ \text{R}^5 \] is H, C1-C12 alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkylnyl, C6-C13 aryl, naphthyl, C1-C5 alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, N0 2, OAc, amino, amido, C(0)R 4, OC(0)R 4, trityl or Het; which may be unsubstituted or substituted further with \[ \text{R}^3 \] (wherein where multiple substitution with \[ \text{R}^3 \] is possible, the substituents can be independently selected from \[ \text{R}^3 \]),

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyl, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzooxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1 H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with \[ \text{R}^3 \]. Het can also be further annelated by 5- or 6-membered rings, which can also be substituted with \[ \text{R}^3 \] (wherein where multiple substitution with \[ \text{R}^3 \] is possible, the substituents can be independently selected from \[ \text{R}^3 \]),

\[ \text{R}^6 \] is H, C1-C12 alkyl, haloalkyl, cycloalkyl, C1-C5 alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkylnyl, C6-C13 aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, N0 2, OAc, amino, amido, C(0)R 4, OC(0)R 4, trityl or het; which may be unsubstituted or
substituted further with R³ (wherein where multiple substitution with R³ is possible, the
substituents can be independently selected from R³).

R⁷ is H, Halogen, C¹-C¹² alkyl, haloalkyl, cycloalkyl, C₂-C¹₂ alkenyl, cycloalkylene, alkynyl, C₆-C₁₃ aryl, C₅ alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, N0₂, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl or het; which may be unsubstituted or
substituted further with R³ (wherein where multiple substitution with R³ is possible, the
substituents can be independently selected from R³),

or a pharmaceutically acceptable derivative.

It is envisaged that the compounds of the present invention such as the compound of formula
(3) selectively inhibit CYP1B1. Accordingly, in some preferred embodiments, said
compound of formula (3) selectively inhibits CYP1B1 and has an IC₅₀ of less than about
200, more preferably less than about 175, more preferably less than about 150, even more
preferably less than about 125, even yet more preferably less than about 115, particularly
preferable less than about 105, most preferably less than about 100, 75, 50, 25 or 20 nM.

The compound of formula (3) of the present invention does preferably not substantially inhibit
CYP17 and/or CYP19. Accordingly, in some preferred embodiments, the inhibition of CYP17
and/or 19 is not more than 30, 25, 20, 15 or 10 or 5%.

In a preferred embodiment for the compounds of formula (3), the compound is characterized
by having a selectivity factor (IC₅₀ (CYP1B2))/IC₅₀ (CYP1B1) greater than about 5, 10, 15,
20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

In certain embodiments, provided that in said compound of formula (3), when R⁵ is C₆-C₁₃
aryl it cannot be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino
substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy
substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In one embodiment the compounds of the present invention are the compounds of formula
(3) with the exclusion of the following compounds:
In some embodiments, said compound of formula (3) is for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-11β-hydroxylase (CYP11B1).

In one embodiment, the selective CYP11B1 inhibitor is a compound selected from 5-imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine, 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine, 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 2-Benzol[b]thiophen-3-yl-5-imidazol-1-ylmethyl-pyridine, 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine, 5-Imidazol-1-ylmethyl-2-thiophen-3-yl-pyridine, 3-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 2-Furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 5-Imidazol-1-ylmethyl-2-(2-methoxy-phenyl)-pyridine, 5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde, 5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 3-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 2-Bromo-3-imidazol-1-ylmethyl-pyridine, 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol, 5-Imidazol-1-ylmethyl-2-phenyl-pyridine or 5-Imidazol-1-
ylmethyl-2-naphthalen-2-yl-pyridine for use in the treatment of Cushing’s syndrome or metabolic disease or metabolic syndrome.

In a most preferred embodiment for the selective CYP1B1 inhibitor of the current invention, the compound is selected from:

In another embodiment for the selective CYP1B1 inhibitor of the current invention, the compound is 5-imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine, 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine, 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 2-Benzo[b]thiophen-3-yl-5-imidazol-1-ylmethyl-pyridine, 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine, 2-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 5-(5-imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde, 5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 3-Imidazol-1-
5 ylmethyl-2-thiophen-2-yl-pyridine, 2-Bromo-3-imidazol-1-ylmethyl-pyridine or 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol.

In some aspects of the compounds of the present invention are preferably for use as a medicament.

Similarly, a compound of the present invention is preferably present in a pharmaceutical composition comprising a therapeutically effective amount of a compound and one or more pharmaceutically acceptable carriers. In some preferred embodiments, the pharmaceutical composition comprising an additional pharmacologically active compound.

Preferably, the compounds of the present invention are for use in the treatment of a disorder characterized by an abnormal activity or abnormal expression/level of CYP1B1 in a subject.

Likewise, the compounds of the present invention may also be used in a method of treating a disorder characterized by an abnormal activity or abnormal expression/level of CYP1B1 in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of the present invention.

Also, the compounds of the present invention are for use in treating Cortisol dependent disorder. In preferred aspects, the disorder is selected from Cushing’s syndrome, excessive CYP1B1 level, the ectopic ACTH syndrome, the change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD) Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine or cocaine withdrawal syndrome, the post-traumatic stress syndrome, the cognitive impairment after stroke and the cortisol-induced mineralocorticoid excess.

More preferably, the disorder is Cushing’s syndrome or metabolic syndrome.

In other preferred embodiments, the compounds of the present invention are for use in treating weight loss.

**DETAILED DESCRIPTION OF THE INVENTION**

The present inventors have discovered imidazole compounds. These compounds are envisaged for use as a medicament or for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-11β-hydroxylase (CYP1B1). The inventors have surprisingly found that amongst other things, the compounds of the present invention can be used in treating Cortisol dependent disorders such as Cushing’s syndrome or metabolic disease or metabolic syndrome.
As used herein, the term "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder. The disease or disorder is preferably one described herein such as a Cortisol dependent disorder. In preferred aspects, the disorder is selected from Cushing’s syndrome, excessive CYP1B1 level, the ectopic ACTH syndrome, the change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD) Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine or cocaine withdrawal syndrome, the post-traumatic stress syndrome, the cognitive impairment after stroke and the cortisol-induced mineralocorticoid excess. More preferably, the disorder is Cushing’s syndrome or metabolic syndrome.

Preferably, the compounds of the present invention have an IC$_{50}$ of less than about 200, more preferably less than about 175, more preferably less than about 150, even more preferably less than about 125, even yet more preferably less than about 115, particularly preferable less than about 105, most preferably less than about 100, 75, 50, 25 or 20 nM.

As used herein, IC$_{50}$ refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, in an assay that measures such response. The IC$_{50}$ values are determined in accordance with common general knowledge and means and methods. However, preferably IC$_{50}$ values are determined in accordance with the assays described in the appended Examples.

In the alternative or addition the compounds of the present invention can preferably be characterized by having a selectivity factor (IC$_{50}$ (CYP1B2)/IC$_{50}$ (CYP1B1)) of greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

Furthermore, in the alternative or addition, the compounds of the present invention can be characterized in that they do not only selectively inhibit CYP1B1, but also do not substantially inhibit CYP17 and/or CYP19. Preferably, the compounds of the present invention do not inhibit CYP17 more than 30, 25, 20, 15, 10 or 5%. Preferably, the compounds of the present invention do not inhibit CYP19 more than 30, 25, 20, 15, 10 or 5%.
Inhibition of CYP17 or CYP19, respectively, is determined in accordance with common general knowledge and means and methods. However, preferably CYP17 and/or CYP19 inhibition is determined in accordance with the assays described in the appended Examples.

Accordingly, in some particularly preferred embodiments, the compounds of the present invention selectively inhibit CYP1 1B1 and do not substantially inhibit CYP17 (not more than 30, 25, 20, 15, 10 or 5%) and/or CYP19 (not more than 30, 25, 20, 15, 10 or 5%) and can be further characterized by having a selectivity factor (sf, i.e., IC₅₀ (CYP1 1B2)/IC₅₀ (CYP1 1B1)) greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, 49 or 50.

In one embodiment, the present invention provides a compound of formula (1):

\[
\left[ (R^1)_n \right] A \left[ (R^2)_y \right] (Q)_x \text{Het} \tag{1}
\]

wherein,

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyl, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoazoxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzooxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1 H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6-membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

R¹ or R² can be independently H, C₁-C₁₂ alkyl, haloalkyl, C₁-C₅ alkoxy, hydroxy, C₆-C₁₃ aryl, napthyl, benzo[b]thiophen, thiophen, amino, amido, C(0)R⁴, OC(0)R⁴, ester, ether, S0₂R⁴, furanyl, het, halogen, trityl, CN, NO₂ or OAc; either of which is unsubstituted or can be
independently substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R³ is C₁-C₁₂ alkyl, haloalkyl, C₁-C₅ alkoxy, hydroxy, C₆-C₁₃ aryl, halogen, amino, amido, ester, ether, C(0)R⁴, OC(0)R⁴, SO₂R⁴, SO₂NHR⁴, trityl, CN, NO₂ or OAc.

R⁴ is H, OH, C₁-C₅ alkoxy, alkyl or aryl.

A is one or more heteroatoms independently selected from N, O, S or Se. Wherein A is N, preferably heterocycles are pyridine, pyrimidine or pyridazine; which can be further annelated by 5- or 6- membered rings.

m is selected from 0 - 3 carbons, preferably 1,

n is 0 - 6,

Q is C, O, S, CH=CH, N, CO, CO₂, CONH, SO₂, SO₂NH,

X is 1 - 3,

Y is 0 - 2,

Z is 1 - 2; if z > 1, multi-Q can be any linker described above,

or a pharmaceutically acceptable derivative.

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoaxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1 H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).
As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members, more preferably 5 to about 12 members, more preferably still 5 to about 10 members, even more preferably 5 members, where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur; more preferably the heteroatom is nitrogen or sulfur, most preferably nitrogen. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, thiazolyl, isoxazolyl, triazolyl, quinolinyl|soquinolinyl, benzo[b]imidazole or 2-benzo[b]thiophene. Furthermore, heteroaryl can be further annelated by 5- or 6-membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 atoms in the ring(s), where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The term "lower heteroarylene" refers to heteroarylene groups having 5 or 6 atoms in the ring.

As used herein, "heterocycylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of
the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "alkyl," "alkenyl" and "alkynyl" carbon chains, if not specified, contain from 1 to 20 carbons, or 1 or 2 to 16 carbons, or 1 or 2 to 12 carbons, especially those having from 1 to 5 or 1 to 3 carbons, and are straight or branched. Alkyl carbon chains can also be cyclic.

Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds and alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, adamantyl, cyclo-propyl, cyclo-pentyl, cyclo-hexyl, trityl, allyl (propenyl) and propargyl (propynyl). As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond. As used herein, "cycloalkyl", "cycloalkenyl" or "cycloalkynyl" can be used interchangeably in place of "alkyl" in the compounds of the present invention.

As used herein, "cycloalkyl" refers to a saturated mono- or multi- cyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein "CrC₅ alkoxy" may be straight or branched, preferably OMe, OEt or O'Pr, most preferably OMe.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms, more preferably 6 to 13 carbon atoms. Aryl groups include, but are not limited to groups such as unsubstituted or substituted fluorenyl, unsubstituted or substituted...
phenyl and unsubstituted or substituted naphthyl. Naphthyl as used herein can be 1-naphthalene or 2-naphthalene. Preferably aryl is 1-naphthalene or phenyl, most preferably 1-naphthalene. Aryl can also be further annelated by 5- or 6- membered rings, which can also be substituted with R^3 (wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3).

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, "pseudohalides" or "pseudohalo" groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide. Accordingly, pseudohalides can also be used interchangeably in place of halogen in the compounds of the present invention.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sturffyl" refers to -S(O)\(^2\). As used herein, "sulfo" refers to -S(O)\(^2\)O-.

As used herein, "carboxy" refers to a divalent radical, -C(0)0-.

As used herein, "amino" can be either unsubstituted or mono/di-substituted with alkyl and/or aryl. In certain embodiments, aryl or alkyl can be further substituted with R^3. Wherein multiple substitution is possible, R^3 can be independently selected from R^3 as defined herein. "Amino" is preferably -NH\(_2\), -NHMe or -NMe\(_2\).

As used herein "amido" refers to the divalent group -C(0)NH- which can be either unsubstituted or mono/di-substituted with alkyl and/or aryl. In certain embodiments, aryl or alkyl can be further substituted with R^3. Wherein multiple substitution is possible, R^3 can be independently selected from R^3 as defined herein.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," "substituted cycloalkynyl," "substituted aryl," "substituted heteroaryl," "substituted heterocyclyl," "substituted alkylene," "substituted
alkenylene," "substituted alkylenylene," "substituted cycloalkylene," "substituted cycloalkenylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to alkyl, alkenyl, alkylnyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one, two, three or four substituents, where the substituents are as defined herein.

Where the number of any given substituent is not specified (e.g., haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

As used herein, the abbreviations such as those for compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, the IUPAC or IUPAC-IUB (Commission on Biochemical Nomenclature).

Some synthetic routes for preparing the compounds of the present invention are given below along with some possible testing methods. The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (≈ 20-133 mbar). The structure of final products, intermediates and starting materials was confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound.

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof.
Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethlenediamine, chloropropane, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, nitrates, borates, methanesulfonates, benzenesulfonates, toluenesulfonates, salts of mineral acids, such as but not limited to hydrochlorides, hydrobromides, hydroiodides and sulfates; and salts of organic acids, such as but not limited to acetates, trifluoroacetates, maleates, oxalates, lactates, malates, tartrates, citrates, benzoates, salicylates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=CSR where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl.

Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=COR where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl.

Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

In certain embodiments, provided that in said compound of formula (1), when Het is imidazolyl, Q is C, z is 1, R is H, y is 2, m is 1, A is N and n is 1—if R is C₆H₅aryl it cannot
be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In a further embodiment, the compound of formula (1) has \( Q = C, z = 1, R^2 = H, y = 2, x = 1, m = 1, A = N \) and \( n = 1-3 \), more preferably 2, most preferably 1.

In another embodiment, the present invention provides a compound of formula (2):

\[
\begin{align*}
&\text{R}^3 \text{ is } C_1-C_{12} \text{ alkyl, haloalkyl, } C_1-C_5 \text{ alkoxy, hydroxy, } C_6-C_{13} \text{ aryl, halogen, amino, amido, ester, ether, } C(0)R^4, OC(0)R^4, S_2NHR^4, \text{CN, } N_2O \text{ or } OAc, \\
&\text{R}^4 \text{ is } H, OH, C_1-C_5 \text{ alkoxy, alkyl or aryl,} \\
&\text{R}^5 \text{ is } H, C_1-C_{12} \text{ alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, } C_6-C_{13} \text{ aryl, naphthyl, } C_1-C_5 \text{ alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, } N_2O, \text{OAc, amino, amido, } C(0)R^4, OC(0)R^4, \text{trityl or } Het; \text{ which may be unsubstituted or substituted further with } \text{R}^3 \text{ (wherein where multiple substitution with } \text{R}^3 \text{ is possible, the substituents can be independently selected from } \text{R}^3, \\
&\text{Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyl, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzo[h]oxazolyl, benz[d]isoaxazolyl, benzo[d]isothiazoyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazoyl, 5,6,7,8-tetrahydroisoquinolinyl; more preferably het is 1-imidazoyl, 5-imidazoyl, 3-pyridiny, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxy pyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzo oxazolyl, 4-benzothiazoyl, 4-benzo[d]isoaxazolyl, 4-benzo[d]isothiazoyl, 4,5,6,7-tetrahydro-1 H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,} \\
&\text{Het can be unsubstituted or is substituted further with } \text{R}^3 \text{. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with } \text{R}^3 \text{ (wherein where multiple substitution with } \text{R}^3 \text{ is possible, the substituents can be independently selected from } \text{R}^3, \)
R is H, C1-C12 alkyl, haloalkyl, cycloalkyl, C1-C5 alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, C6-C13 aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO2, OAc, amino, amido, C(0)R4, OC(0)R4, trityl or het; which may be unsubstituted or substituted further with R3 (wherein where multiple substitution with R3 is possible, the substituents can be independently selected from R3).

R7 is H, Halogen, C1-C12 alkyl, haloalkyl, cycloalkyl, C2-C12 alkenyl, cycloalkylene, alkynyl, C6-C13 aryl, C1-C5 alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, NO2, OAc, amino, amido, C(0)R4, OC(0)R4, trityl or het; which may be unsubstituted or substituted further with R3 (wherein where multiple substitution with R3 is possible, the substituents can be independently selected from R3),

or a pharmaceutically acceptable derivative.

In a preferred embodiment, said compound of formula (2) selectively inhibits CYP1B1 (IC50 of less than 105 or 100) and does not substantially inhibit CYP17 (not more than 30, 25, 20, 15 or 10 or 5%) and/or CYP19 (not more than 30, 25, 20, 15 or 10 or 5%).

In certain embodiments, provided that in said compound of formula (2), when R5 is C6-C13 aryl it cannot be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In other embodiments, provided that in said compound of formula (2), when R7 is H and that one or both of R5 or R6 are independently either H, aryl or heteroaryl; wherein aryl or heteroaryl may be unsubstituted or substituted further with R3 (wherein where multiple substitution with R3 is possible, the substituents can be independently selected from R3). If only one of R5 or R6 is independently either H, aryl or heteroaryl, the other R5 or R6 can be as defined herein.

In a preferred embodiment, the present invention provides an imidazol-1-ylmethyl-pyridine compound of formula (3):

![Formula Image]

wherein,
5 R^3 is C_1-C_{12} alkyl, haloalkyl, CrC_5 alkoxy, hydroxy, C_6-C_{13} aryl, halogen, amino, amido, ester, ether, C(0)R^4, OC(0)R^4, S_2O_2NR^4, CN, N_2O_2 or OAc,

R^4 is H, OH, C_1-C_5 alkoxy, alkyl or aryl,

R^5 is H, C_1-C_{12} alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alknynyl, C_6-C_{13} aryl, naphthyl, C_1-C_5 alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, N_2O_2, OAc, amino, amido, C(0)R^4, OC(0)R^4, trityl or Het; which may be unsubstituted or substituted further with R^3 (wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3).

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isquinolinyl, 8-quinoxalyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoaxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with R^3. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R^3 (wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3).

R^6 is H, C_1-C_{12} alkyl, haloalkyl, cycloalkyl, C_1-C_5 alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alknynyl, C_6-C_{13} aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, N_2O_2, OAc, amino, amido, C(0)R^4, OC(0)R^4, trityl or het; which may be unsubstituted or substituted further with R^3 (wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3).

R^7 is H, Halogen, C_1-C_{12} alkyl, haloalkyl, cycloalkyl, C_2-C_{12} alkenyl, cycloalkylene, alknynyl, C_6-C_{13} aryl, C_1-C_5 alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, N_2O_2, OAc, amino, amido, C(0)R^4, OC(0)R^4, trityl or het; which may be unsubstituted or substituted further with R^3 (wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3),

or a pharmaceutically acceptable derivate.
In some embodiments, said compound of formula (3) is for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-11β-hydroxylase (CYP11B1).

In certain embodiments, provided that in said compound of formula (3), when R⁵ is C₆-C₁₃ aryl it cannot be phenyl (non-substituted), 2-methoxy substituted phenyl or a 3-amino substituted phenyl, 4-fluorine substituted phenyl, 3,4-methoxy substituted phenyl, 3-methoxy substituted phenyl, 3,4-fluorine substituted phenyl, 4-substituted methoxy phenyl.

In one embodiment, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 5. In another embodiment, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 10. In a yet further embodiment, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 20. In some embodiments, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 30. In further embodiments, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 40. In another embodiment, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) greater than about 45, 46, 47 or 48. In other embodiments, the selective CYP11B1 inhibitor is characterized by having a selectivity factor (IC₅₀ (CYP11B2)/IC₅₀ (CYP11B1)) of about 49 or 50.

In one embodiment, the selective CYP11B1 inhibitor is a compound selected from

![Chemical structures](image-url)
In one embodiment, the selective CYP1B1 inhibitor is a compound selected from 5-imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine, 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine, 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 2-Benz[b]thiophen-3-yl-5-imidazol-1-ylmethyl-pyridine, 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine, 5-Imidazol-1-ylmethyl-2-thiophen-3-yl-pyridine, 3-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 2-Furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 5-Imidazol-1-ylmethyl-2-(2-methoxy-phenyl)-pyridine, 5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde, 5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 3-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 2-Bromo-3-imidazol-1-ylmethyl-pyridine, 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol, 5-Imidazol-1-ylmethyl-2-phenyl-pyridine or 5-Imidazol-1-ylmethyl-2-naphthalen-2-yl-pyridine for use in the treatment of Cushing's syndrome or metabolic disease or metabolic syndrome.

In a most preferred embodiment for the selective CYP1B1 inhibitor of the current invention, the compound is selected from:
In another embodiment for the selective CYP11B1 inhibitor of the current invention, the compound is 5-imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine, 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine, 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 2-Benzothiophen-3-yl-5-imidazol-1-ylmethyl-pyridine, 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine, 2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde, 5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 3-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 2-Bromo-3-imidazol-1-ylmethyl-pyridine or 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol.

In some embodiments a preferred compound of the current invention is:

the compound 5-Imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine
or the compound 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine

or the compound 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine

or the compound 2-Benzo[b]thiophen-3-yl-5-imidazol-1-ylmethyl-pyridine

or the compound 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine

or the compound 2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine
or the compound 5-(5-imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde

or the compound 5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine

or the compound 3-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine

or the compound 2-Bromo-3-imidazol-1-ylmethyl-pyridine

or the compound 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol
In yet another embodiment, the present invention provides a imidazol-1-ylmethyl-pyridine
compound of formula (3):

![Chemical Structure](image)

wherein,

- $R^3$ is $C_1$-$C_{12}$ alkyl, haloalkyl, $CrC_5$ alkoxy, hydroxy, $C_6$-$C_{13}$ aryl, halogen, amino, amido, ester, ether, $C(0)R^4$, $OC(0)R^4$, $SO_2R^4$, $SO_2NH^4$, CN, $N_2O_2$ or OAc,

- $R^4$ is H, OH, alkyl or aryl,

- $R^5$ is H, $C_1$-$C_{12}$ alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, $C_6$-$C_{13}$ aryl, naphthyl, $C_1$-$C_5$ alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, $N_2O_2$, OAc, amino, amido, $C(0)R^4$, $OC(0)R^4$, trityl or Het; which may be unsubstituted or substituted further with $R^3$ (wherein where multiple substitution with $R^3$ is possible, the substituents can be independently selected from $R^3$),

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyll, benzo[axazolyl, benzo[axazolyl, benz[o][d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isquinolinyl, 8-quinazolinyll, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzo[axazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1 H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,
Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

R⁶ is H, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₁-C₅ alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkylnyl, C₆-C₁₃ aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO₂, OAc, amino, amido, C(0)R, OC(0)R, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

R⁷ is H, Halogen, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₂-C₁₂ alkenyl, cycloalkylene, alkylnyl, C₆-C₁₃ aryl, C₁-C₅ alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, NO₂, OAc, amino, amido, C(0)R, OC(0)R, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

or a pharmaceutically acceptable derivative,

for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-1α-hydroxylase (CYP1 1B1).

In some aspects, the compounds of the present invention are for use as a medicament, preferably for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-1αβ-hydroxylase (CYP1 1B1).

As used herein, the term "abnormal" refers to an activity or feature which differs from a normal activity or feature. As used herein, the term "abnormal activity" refers to an activity which differs from the activity of the wild-type or native gene or protein, or which differs from the activity of the gene or protein in a healthy subject. The abnormal activity can be stronger or weaker than the normal activity. In one embodiment, the "abnormal activity" includes the abnormal (over-) production of mRNA transcribed from a CYP1 1B1 gene. In another embodiment, the "abnormal activity" includes the abnormal (over-) production of a CYP1 1B1 polypeptide from its gene. In another embodiment, the abnormal activity refers to a level of a CYP1 1B1 mRNA or CYP1 1B1 polypeptide that is different from a normal level of said mRNA or polypeptide by about 15%, about 25%, about 35%, about 50%, about 65%, about 85%, about 100% or greater. Preferably, the abnormal level of the mRNA or polypeptide is higher or lower than the normal level of said mRNA or polypeptide. Yet in another embodiment, the abnormal activity refers to functional activity of a protein that is different from a normal activity of the wild-type protein. Preferably, the abnormal activity can be stronger than the
normal activity. For example, the abnormal activity is due to the mutations in the corresponding gene, and the mutations can be in the coding region of the gene or non-coding regions such as transcriptional promoter regions. The mutations can be substitutions, deletions, insertions.

In other aspects, the compounds of the present invention are for use in treating Cortisol dependent disorder. In further aspects, the disorder is selected from Cushing's syndrome, excessive CYP1B1 level, the ectopic ACTH syndrome, the change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine or cocaine withdrawal syndrome, the post-traumatic stress syndrome, the cognitive impairment after stroke and the cortisol-induced mineralocorticoid excess. The treatment of Cushing's syndrome by applying the compounds of the present invention is preferred. It certain preferred embodiments, the compounds of the present invention when applied for the treatment of Cushing's syndrome can be applied in combination with ketoconazole, etomidate, metyrapone, sodium-valproate, bromocriptine, octreotide, o,p'DDD, aminogluthethimide, metyrapone, retinoic acid and/or cyproheptadine.

In other aspects, the compounds of the present invention are for use in treating weight loss.

The compounds of the present invention may also be used in a method of treating a disorder characterized by an abnormal activity or abnormal expression/level of CYP1B1 in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of the present invention.

As used herein, the term "a disorder" or "a disease" refers to any derangement or abnormality of function; a morbid physical or mental state. See Dorland's Illustrated Medical Dictionary, (W.B. Saunders Co. 27th ed. 1988).

The term "therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, or ameliorate symptoms, slow or delay disease progression, or prevent a disease, etc. In a preferred embodiment, the "effective amount" refers to the amount that (selectively) inhibits or reduces activity of CYP1B1. As used herein, the term "subject" refers to an animal. Preferably, the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In a preferred embodiment, the subject is a human.
In another aspect, a compound of the present invention can be present in a pharmaceutical composition comprising a therapeutically effective amount of a compound and one or more pharmaceutically acceptable carriers.

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art; see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329. Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

In a further aspect, the pharmaceutical composition comprising an additional pharmacologically active compound.

The results obtained for some of the preferred compounds of the present invention are demonstrated below in Tables 1-3. Of note, the compounds in these Tables are compounds of the present invention, apart from MTP: metyrapone; ETO: etomidate; KTZ: ketoconazole. Likewise, also the compounds described in the appended Examples are compounds of the present invention.
Table 1. Inhibition of CYP11B2 and CYP11B1 by compounds 2 - 22

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>IC50 value (nM)</th>
<th>sf c</th>
<th>as f c</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>R5</td>
<td>R6</td>
<td>R7</td>
<td>CYP11B1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>663</td>
</tr>
<tr>
<td>3</td>
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<td>61</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Br</td>
<td></td>
<td>168</td>
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<tr>
<td>7</td>
<td>F</td>
<td></td>
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<td>9</td>
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<td>21</td>
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<td>KTZ e</td>
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<td>127</td>
</tr>
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</table>

a Mean value of at least three experiments. The deviations were within < ± 25 %.

b Hamster fibroblasts expressing human CYP11B1 or CYP11B2; substrate 11-deoxycorticosterone, 100 nM

c sf: selectivity factor: IC50 (CYP11B2)/IC50 (CYP11B1)

d n.i.: no inhibition at an inhibitor concentration of 500 nM

e MTP: metyrapone; ETO: etomidate; KTZ: ketoconazole
**Table 2. Inhibition of CYP1B2 and CYP1B1 by compounds 23 - 42**

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
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<th>sf c</th>
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<td></td>
</tr>
<tr>
<td>25</td>
<td>Ph</td>
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<td>851</td>
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<td></td>
</tr>
<tr>
<td>26</td>
<td>3-pyridine</td>
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<td>28</td>
<td>5-pyrimidine</td>
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<td>n.i. d</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3-(6-&lt;m&gt;methoxypyr&lt;/m&gt;ridine)</td>
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<td>&gt;1000</td>
<td></td>
<td></td>
</tr>
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<td>3-benzo[6]thiophene</td>
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<td>1157</td>
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<tr>
<td>39</td>
<td>2-furan</td>
<td>167</td>
<td>5159</td>
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<tr>
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<td>2832</td>
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<td>41</td>
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<td>500</td>
<td>&gt;1000</td>
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<tr>
<td>42</td>
<td>2-furan</td>
<td>29</td>
<td>830</td>
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<tr>
<td>1</td>
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<tr>
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<td>0.2</td>
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</tr>
<tr>
<td>KTZ</td>
<td>127</td>
<td>67</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Mean value of at least three experiments. The deviations were within < ± 25 %.

b Hamster fibroblasts expressing human CYP1B1 or CYP1B2; substrate 11-deoxycorticosterone, 100 nM

c sf: selectivity factor: IC50 (CYP1B2)/IC50 (CYP1B1)
d n.i.; no inhibition at an inhibitor concentration of 500 nM

e MTP: metyrapone; ETO: etomidate; KTZ: ketoconazole
Table 3: Inhibition of CYP19 and CYP17 of selected compounds

<table>
<thead>
<tr>
<th>Comp.</th>
<th>CYP 17&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>CYP 19&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>Comp.</th>
<th>CYP 17&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>CYP 19&lt;sup&gt;a,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3</td>
<td>2</td>
<td>21</td>
<td>0</td>
<td>n.d. &lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>0</td>
<td>22</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>n.d.</td>
<td>23</td>
<td>8</td>
<td>5</td>
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<tr>
<td>9</td>
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<td>n.d.</td>
<td>25</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>n.d.</td>
<td>31</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
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<td>34</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>n.d.</td>
<td>35</td>
<td>5</td>
<td>30</td>
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<tr>
<td>14</td>
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<td>n.d.</td>
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<td>19</td>
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<tr>
<td>15</td>
<td>6</td>
<td>0</td>
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</tr>
<tr>
<td>16</td>
<td>3</td>
<td>2</td>
<td>39</td>
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<td>0</td>
</tr>
<tr>
<td>17</td>
<td>4</td>
<td>1</td>
<td>40</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>0</td>
<td>42</td>
<td>6.7</td>
<td>2.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean value of at least three experiments. The deviations were within < ± 25 %.

<sup>b</sup> <i>E. coli</i> expressing human CYP17; substrate progesterone, 25 µM; inhibitor concentration 2.0 µM

<sup>c</sup> Human placental CYP19; substrate androstenedione, 500 nM; inhibitor concentration 500 nM

<sup>d</sup> n.d. = not determined

ABBREVIATIONS

- CYP: Cytochrome P450
- CYP1 1B1: Steroid-1 1/3-Hydroxylase
- CYP1 1B2: Aldosterone synthase
- CYP17: 17cr-Hydroxylase-1 7,20-lyase
- CYP19: Aromatase
- HbA1c: Glycosylated hemoglobin
- HSD: Hydroxysteroid dehydrogenase
- IC<sub>50</sub>: Concentration required for 50 % inhibition
- SAR: Structure activity relationship
- Sf: Selectivity factor
- SN: Nucleophilic substitution
Also, the following compounds are also compounds of the present invention. They illustrate the present invention and are specific embodiments encompassed at least by formula (1) and (4), shown below. Accordingly, the following compounds can thus be applied in the pharmaceutical compositions, methods of treatment and/or medical uses described herein. Accordingly, all embodiments described herein in the context of formula (1), (2) or (3), pharmaceutical compositions, methods of treatment and/or medical uses are applicable for the following compounds, mutatis mutandis.
The invention also relates to the following compounds as generalized by the following formula (4):

\[
\begin{array}{c}
\text{Het: imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, thiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl; (only } \beta \text{ and } \gamma \text{ position to methylene bridge, not a position)} \\
\text{which could be substituted by further } R^3 \text{ group if possible;}
\end{array}
\]

\[
\begin{array}{c}
\text{N Het: aromatic ring with one to four } N \text{ atoms;}
\end{array}
\]

especially pyridine, pyrimidine, pyridazine

which could be further annelated by 5- or 6-membered rings;

\[
\begin{array}{c}
\text{Ar: Benzene, naphthalene, heterocycles;}
\end{array}
\]

which could be further annelated by 5- or 6-membered rings;

\[
\begin{array}{c}
\text{R}^1, R^2: \text{ could independently be } H, \text{ Me, Et, c-Pr, c-pent and so on}
\end{array}
\]

\[
\begin{array}{c}
\text{R}^3, R^4: \text{ could independently be CF}_3, \text{ NO}_2, \text{ CN, halogen, OMe, OH, OAc, alkyl, c-alkyl, alkyloxyl, and so on}
\end{array}
\]

Thus, the compounds covered by formula (4) are also compounds of the present invention.

Accordingly, the compounds of formula (4) can thus be applied in the pharmaceutical compositions, methods of treatment and/or medical uses described herein. Accordingly, all embodiments described herein in the context of formula (1), (2) or (3), pharmaceutical compositions, methods of treatment and/or medical uses are applicable for the compounds covered by formula (4), mutatis mutandis.
FIGURES

Figure 1: Role of CYP11B1 and CYP11B2 in Cortisol and aldosterone biosynthesis

EXAMPLES

A better understanding of the present invention and of its advantages is given from the following examples, which are offered for illustrative purposes only and which are not intended to limit the scope of the present invention in any way.

Cellular assays for testing CYP11B1 and CYP11B2 inhibition

V79MZ/711B1 and V79MZ/711B2 cell lines were cultivated in Dulbecco’s modified Eagle medium supplemented with 5 % of fetal calf serum, penicillin (100 U/ml), streptomycin (100 µg/ml), glutamine (2 mM) and sodium pyruvate (1 mM) at 37°C in 5 % CO₂ in air.

V79MZ cells expressing human CYP11B1 and human CYP11B2 genes, respectively, were grown on 24-well cell culture plates (8 x 10⁵ cells per well) with 1.9 cm² culture area per well in 1 ml DMEM culture medium until confluence. Before testing, the DMEM culture medium was removed and 450 µl of fresh DMEM, containing the inhibitor in at least three different concentrations for determining the IC₅₀ value, was added to each well. Every value was determined at least three times. After a pre-incubation step of 60 min at 37°C, the reaction was started by the addition of 50 µl of DMEM containing the substrate 11-deoxycorticosterone (containing 0.15 µCi of [1,2-³H] 11-deoxycorticosterone, dissolved in ethanol, final concentration 100 nM).

The V79MZ/711B1 cells were incubated for 25 min, the V79MZ/711B2 cells were incubated for 50 min. Controls were treated in the same way without inhibitors. The maximum DMSO concentration in each well was 1 %.

Enzyme reactions were stopped by extracting the supernatant with 500 µl ethyl acetate. Samples were centrifuged (10000 x g, 2 min), and the solvent was pipetted into fresh cups. The solvent was evaporated and the steroids were redissolved in 40 µl of methanol and analyzed by HPLC using radioflow detection (Ehmer et al. J. Steroid Biochem. Mol. Biol. 2002, 81, 173-179 and Denner et al. Endocr. Res. 1995, 21, 443-448).

The above experiment was conducted at least three times and a mean value for the IC₅₀ was calculated.
17A-HYDROXYLASE/C17-20-LYASE ASSAY

Enzyme preparation of CYP17:

Recombinant E. coli pJL17/OR coexpressing human CYP17 and rat NADPH-P450-reductase were grown and stored as described by Ehmer et al. (J. Steroid Biochem. Mol. Biol., 2000, 75, 57-63)

For isolation of membrane fractions, 5 ml of bacterial suspension with an OD578 of 50 were washed using phosphate buffer (0.05 M, pH 7.4, 1 mM MgCl2, 0.1 mM EDTA and 0.1 mM dithiothreitol). Bacteria were harvested by centrifugation (2000 x g) and the pellet was resuspended in 10 ml ice-cold TES buffer (0.1 M tris-acetate, pH 7.8, 0.5 mM EDTA, 0.5 M sucrose). Lysozyme was added with 10 ml of ice-cold water resulting in a concentration of 0.2 mg/ml followed by incubation for 30 min on ice with continuous shaking. Spheroplasts were harvested by centrifugation (12000 x g, 10 min), and resuspended in 4 ml of ice-cold phosphate buffer (the same as described above plus 0.5 mM phenylmethylsulfonylfluoride (PMSF)).

After that spheroplasts were sonicated on ice (pulse 20 s on, 30 s off, five times), using a sonicator Sonopuls HD60 (Bandelin, Berlin, Germany) at maximum power. Unbroken cells and debris were pelleted at 3000 x g for 7 min, and the supernatant was centrifuged at 50000 x g for 20 min at 4°C. The membrane pellet was resuspended in 2 ml of phosphate buffer (the same as described above) with 20 % glycerol using an ultra-turrax T25 (IKA-Labortechnik, Staufen, Germany). Protein concentration was determined by the method of Lowry. Aliquots of this preparation, which generally had a content of about 5 mg protein per ml, were stored at -70°C until used.

CYP17 inhibition assay:

The assay was performed as follows: a solution of 6.25 nmol progesterone (in 5 μl methanol) in 140 μl phosphate buffer (0.05 M, pH 7.4, 1 mM MgCl2, 0.1 mM EDTA and 0.1 mM dithiothreitol), 50 μl NADPH generating system (in phosphate buffer with 10 mM NADP, 100 mM glucose-6-phosphate and 2.5 units of glucose-6-phosphate-dehydrogenase) and inhibitor (in 5 μl DMSO) was pre-incubated at 37°C for 5 min. Control cups were supplemented with 5 μl DMSO without inhibitor. The reaction was started by adding 50 μl of a 1:5 diluted membrane suspension in phosphate buffer (0.8-1.0 mg protein per ml). The maximum DMSO concentration in each sample was 2 %. After mixing, incubation was performed for 30 min at 37°C. Subsequently the reaction was stopped with 50 μl 1 N HCl.
Extraction of the steroids was performed by addition of 1.0 ml ethyl acetate and vigorous shaking for 1 min. After a centrifugation step (5 min, 2500 x g) the organic phase (0.9 ml) was transferred into a fresh cup containing 0.25 ml of incubation buffer and 50 µl 1 N HCl and mixed again. After centrifugation, 0.8 ml ethyl acetate solution was evaporated to dryness in a fresh cup. After that the steroids were redissolved in solvent for HPLC analysis (Hutschenreuter et. al. J. Enz. Inhib. Med. Chem. 2004, 19, 17-32).

The above experiment was conducted at least three times and a mean value for the CYP17 inhibition calculated.

**CYP 19 (AROMATASE) ASSAY**

*Preparation of aromatase:*

The enzyme was obtained from the microsomal fraction of freshly delivered human term placental tissue according to the procedure of Thompson and Siiteri (Thompson, E. A.; Siiteri, P. K. J. Biol. Chem. 1974, 249, 5364).

The isolated microsomes were suspended in a minimum volume of phosphate buffer (0.05 M, pH 7.4, 20 % glycerol). Additionally, DTT (dithiothreitol, 10 mM) and EDTA (1 mM) were added to protect the enzyme from degradation. The enzyme preparation was stored at -70°C.

*Inhibition of aromatase:*

The assay was performed monitoring enzyme activity by measuring the $^3$H$_2$O formed from [^- $^3$H]androstenedione during aromatization (Hartmann et al. J. Med. Chem. 1986, 29, 1362-1369). Each incubation tube contained 15 nM [^- $^3$H]androstenedione (0.08 µCi), 485 nM unlabeled androstenedione, 2 mM NADP, 20 mM glucose-6-phosphate, 0.4 units of glucose-6-phosphate-dehydrogenase and inhibitor (in at least three different concentrations for determining the IC$_{50}$ value) in phosphate buffer (0.05 M, pH 7.4). The test compounds were dissolved in DMSO and diluted with buffer. The final DMSO concentration in the control and inhibitor incubation was 2 %. Each tube was pre-incubated for 5 min at 30°C in a water bath. Microsomal protein was added to start the reaction (0.1 mg). The total volume for each incubation was 0.25 ml. The reaction was terminated by the addition of 200 µl of a cold 1 mM HgCl$_2$ solution. After addition of 200 µl of an aqueous dextran-coated charcoal (DCC) suspension (2 %), the vials were shaken for 20 min and centrifuged at 1500 x g for 5 min to separate the charcoal-absorbed steroids. The supernatant was assayed for $^3$H$_2$O by counting in a scintillation mixture using a β-counter. The calculation of the IC$_{50}$ values was performed.
by plotting the percent inhibition vs. the concentration of inhibitor on a semi-log plot. From this the molar concentration causing 50% inhibition was calculated.

The above experiment was conducted at least three times and a mean value for the CYP19 inhibition calculated.

**CHEMISTRY**

1H NMR and 13C spectra were recorded on a Bruker DRX-500 instrument. Chemical shifts are given in parts per million (ppm) and spectra are obtained as DMSO-d6 or CDCl3 solutions (reported in ppm), using chloroform as the reference standard (7.26 ppm) or DMSO-d6 (2.50 ppm). The following abbreviations are used to denote signal multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broadened. All coupling constants (J) are given in hertz (Hz). Mass spectra (LC/MS) were measured on a TSQ Quantum (Thermo Electron Corporation) instrument with a RP18 100-3 column (Macherey Nagel) and with water/acetonitrile mixtures as eluents. The purity of all compounds was ≥ 95%. Reagents were used as obtained from commercial suppliers without further purification. Yields refer to purified products and are not optimized. Solvents were distilled before use. Dry solvents were obtained by distillation from appropriate drying reagents and stored over molecular sieves. Flash chromatography was performed on silica gel 40 (35/40-63/70 μM) with petroleum ether / ethyl acetate mixtures as eluents, and the reaction progress was determined by thin-layer chromatography analyses on Alugram SIL G/UV254 (Macherey Nagel). Visualization was accomplished with UV light and KMn0₄ solution.

**Method A: Wohl Ziegler Bromination**

Methylpyridine was dissolved in 40 ml of dry carbon tetrachloride. To this solution was added β-V-bromosuccinimide (NBS) (1.1eq) and benzoyl peroxide (5 mol%) and the mixture was refluxed over night. After cooling, the succinimide was removed by filtration and the filtrate was concentrated under vacuum. The crude product was further purified by flash column chromatography on silica gel using a mixture of petroleum ether / ethyl acetate (95:5) as eluent.

**Method B: S_N2-Reaction**

The cr-brominated compounds, imidazole (2 eq), a catalytic amount of 18-crown-6 and anhydrous K₂CO₃ (1.5 eq) in dry acetonitrile were heated under reflux overnight. After cooling, water (50 ml) was added, and the aqueous layer was extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine (25 ml), dried over
Na₂S₄ and evaporated in vacuo. The crude product was purified by column chromatography on silica-gel, using 5% methanol in ethyl acetate.

**Method C: Suzuki-Coupling.**

The corresponding benzene derivative and the boronic acid were dissolved in toluene (20 ml) and aq. Na₂CO₃ (2.0 M, 5.0 ml). The mixture was deoxygenated under reduced pressure and flushed with N₂. After having repeated this cycle three times, Pd(PPh₃)₄ (5 mol%) was added, and the resulting suspension was heated under reflux for 8 h. After cooling, the phases were separated and the water phase was extracted two times with ethyl acetate. The combined organic extracts were dried over Na₂S₄, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica-gel, using 5% methanol in ethyl acetate.

**Method D: Grignard Reaction.**

To a solution of the Grignard reagent (2 eq) in dry diethyl ether the corresponding carbonyl compound (1 eq) was added dropwise. The reaction mixture was heated to reflux for 2 hours. Afterwards ice was added followed by the addition of HCl (1 M) till resulted precipitate disappeared. The phases were separated and water phase was extracted twice with diethyl ether. The combined organic layers were washed with saturated sodium hydrogen carbonate solution and brine. After drying over MgSO₄ and concentration under vacuum the crude product was purified by flash chromatography on silica-gel.

**Method E: CDI Reaction.**

To a solution of the corresponding alcohol (1 eq) in NMP or acetonitrile, CDI (5 eq) was added. Then the solution was heated to reflux for 16 hours. After cooling down to room temperature the reaction mixture was diluted with EtOAc and washed with water and brine. After drying over MgSO₄ and concentration under vacuum the crude product was purified by flash chromatography on silica-gel.

2-Bromo-5-(bromomethyl)pyridine (1b). Synthesized from 2-bromo-5-methylpyridine (3.00 g, 17.40 mmol), NBS (3.41 g, 19.20 mmol) and DBPO (230 mg, 0.80 mmol) in carbon...
tetrachloride according to Method A. Yield: 2.56 g (59 %); lachrymatory yellow needles; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 4.14\) (s, 2H), 7.47 (d, \(J = 8.2\) Hz, 1H), 7.59 (d, \(J = 8.2\) Hz, 1H), 8.38 (s, 1H); MS (ESI): \(m/z = 252.37\) [M+H]\(^+\).

5-Imidazol-1-ylmethyl-2-bromopyridine (1a). Synthesized using 1b (1.32 g, 5.26 mmol), imidazole (0.75 g, 11.00 mmol), K\(_2\)CO\(_3\) (1.13 g, 8.16 mmol) and 18-crown-6 according to Method B. Yellow solid. Yield: 0.75 g, 60 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 5.12\) (s, 2H), 6.88 (t, \(J = 1.2\) Hz, 1H), 7.13 (s, 1H), 7.28 (d, \(J = 2.5\) Hz, 1H), 7.48 (d, \(J = 8.5\) Hz, 1H), 7.56 (s, 1H), 8.28 (d, \(J = 2.5\) Hz, 1H); MS (ESI): \(m/z = 239.08\) [M+H]\(^+\).

5-Imidazol-1-ylmethyl-2-phenyl-pyridine (1). Synthesized using compound 1a (0.20 g, 0.84 mmol) and phenylboronic acid (0.20 g, 1.68 mmol) according to Method B. Yellow solid. Yield: 0.10 g, 57 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 5.19\) (s, 2H), 6.94 (t, \(J = 1.3\) Hz, 1H), 7.13 (s, 1H), 7.48-7.50 (m, 4H), 7.60 (s, 1H), 7.72 (d, \(J = 8.2\) Hz, 1H), 7.97-7.99 (m, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C (ppm) = 48.1\), 119.0, 120.6, 126.9, 128.8, 130.0, 130.4, 135.7, 137.3, 138.6, 148.6, 157.7; MS (ESI): \(m/z = 236.0\) [M+H]\(^+\).

4-Imidazol-1-ylmethyl-pyridine (2). Synthesized from 4-(bromomethyl)pyridine hydrobromide (500 mg, 1.97 mmol), imidazole (538 mg, 7.90 mmol) and K\(_2\)CO\(_3\) (1.36 g, 9.85 mmol) in DMF according to Method B. Yield: 212 mg, 1.35 mmol, 68 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 5.16\) (s, 2H), 6.91 (s, 1H), 7.01 (d, \(J = 6.3\) Hz, 2H), 7.14 (s, 1H), 7.69 (s, 1H), 8.57 (d, \(J = 6.3\) Hz, 2H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C (ppm) = 49.4\), 119.3, 121.4, 130.3, 147.6, 145.2, 150.4; MS (ESI): \(m/z = 160.08\) [M+H]\(^+\).

3-Imidazol-1-ylmethyl-pyridine (3). Synthesized from 3-(Bromomethyl)pyridine hydrobromide (500 mg, 1.97 mmol), imidazole (538 mg, 7.90 mmol) and K\(_2\)CO\(_3\) (1.36 g, 9.85 mmol) in DMF according to Method B. Yield: 246 mg, 1.55 mmol, 78 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 5.15\) (s, 2H), 6.90 (d, \(J = 0.9\) Hz, 1H), 7.11 (d, \(J = 0.9\) Hz, 1H), 7.29, (dd, \(J = 7.9, 4.7\) Hz, 1H), 7.40 - 7.43 (m, 1H), 7.56 (bs, 1H), 8.52 - 8.53 (m, 1H), 8.59 (d, \(J = 4.7\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C (ppm) = 48.3\), 119.0, 123.8, 130.3, 131.8, 134.8, 137.3, 148.7, 149.9; MS (ESI): \(m/z = 160.07\) [M+H]\(^+\).

3-Bromomethyl-pyridine-2-carbonitrile (4a). Synthesized from 3-methylpicolinonitrile (1.00 g, 8.47 mmol), NBS (1.66 g, 9.31 mmol) and DBPO (103 mg, 0.42 mmol) in CCl\(_4\) according to Method A. Yield: 616 mg, 3.12 mmol, 37 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H (ppm) = 4.63\) (s, 2H), 7.54 (dd, \(J = 7.9, 4.9\) Hz, 1H), 7.92 (dd, \(J = 7.9, 1.5\) Hz, 1H), 8.64 (dd, \(J = 4.9, 1.5\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C (ppm) = 26.8\), 115.2, 127.1, 133.2, 138.1, 138.3, 150.5; MS (ESI): \(m/z = 199.79\) [M+H]\(^+\).
3-Imidazol-1-ylmethyl-pyridine-2-carbonitrile (4). Synthesized from 4a (600 mg, 3.04 mmol), imidazole (829 mg, 12.1 mmol) and K₂CO₃ (2.07 g, 15.0 mmol) in DMF according to Method A. Yield: 476 mg, 2.58 mmol, 85%. ¹H NMR (CDCl₃, 500 MHz): δH (ppm): 5.41 (s, 2H), 6.97 (t, J = 1.3 Hz, 1H), 7.15 (t, J = 1.3 Hz, 1H), 7.36 - 7.38 (m, 1H), 7.51 (dd, J = 8.2, 4.7 Hz, 1H), 7.63 (s, 1H), 8.68 (dd, J = 4.7, 1.6 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δC (ppm) = 47.1, 115.3, 119.1, 127.4, 130.9, 132.5, 135.6, 137.0, 137.5, 150.7; MS (ESI): m/z = 185.08 [M+H]+.

2-Bromo-3-bromomethyl-pyridine (5a). Synthesized from 2-bromo-3-methylpyridine (5.00 g, 29.1 mmol), NBS (5.69 g, 32.0 mmol) and DBPO (352 mg, 1.46 mmol) in CCl₄ according to Method A. Yield: 2.87 g, 11.4 mmol, 39%. This compound was directly used in the next step without further purification.

2-Bromo-3-imidazol-1-ylmethyl-pyridine (5). Synthesized from 5a (891 mg, 2.78 mmol), imidazole (658 mg, 5.56 mmol) and K₂CO₃ (1.92 g, 13.9 mmol) according to Method B. Yield: 375 mg, 1.41 mmol, 51%. ¹H NMR (CDCl₃, 500 MHz): δH (ppm): 5.23 (s, 2H), 6.96 (t, J = 1.3 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H) 7.15 (t, J = 1.3 Hz, 1H), 7.24 (dd, J = 7.6, 4.7 Hz, 1H), 7.66 (brs, 1H), 8.32 (dd, J = 4.7, 1.9 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δC (ppm) = 49.7, 119.3, 123.4, 130.0, 133.4, 136.6, 137.6, 142.0, 149.7; MS (ESI): m/z = 239.10 [M+H]+.

3-Bromo-5-bromomethyl-2-chloro-pyridine (6a). Synthesized from 3-bromo-2-chloro-5-methylpyridine (4.00 g, 19.3 mmol), NBS (3.79 g, 21.3 mmol) and DBPO (233 mg, 0.97 mmol) in CCl₄ according to Method A. Yield: 2.38 g, 8.34 mmol, 43%. This compound was directly used in the next step without further purification.

3-Bromo-2-chloro-5-imidazol-1-ylmethyl-pyridine (6). Synthesized from 6a (2.38 g, 8.34 mmol), imidazole (1.14 g, 16.7 mmol) and K₂CO₃ (5.76 g, 41.7 mmol) according to Method B. Yield: 1.88 g, 6.90 mmol, 83%. ¹H NMR (CDCl₃, 500 MHz): δH (ppm): 5.14 (s, 2H), 6.89 (bs, 1H), 7.13 (d, J = 4.0 Hz, 1H), 7.61 - 7.63 (m, 1H), 7.70 (brs, 1H), 8.20 (brs, 1H); ¹³C NMR (CDCl₃, 125 MHz): δC (ppm) = 46.8, 118.9, 120.8, 130.5, 132.2, 137.2, 140.8, 146.3, 150.9; MS (ESI): m/z = 272.05 [M+H]+.

2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine (7). Synthesized using 2-fluorophenylboronic acid (176 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 112 mg, 0.44 mmol, 70%. ¹H NMR (500 MHz, CDCl₃): δH (ppm): 5.18 (s, 2H), 6.93 (t, J = 1.3 Hz, 1H), 7.12 (bs, 1H), 7.15 (ddd, J = 11.7, 8.2, 1.3 Hz, 1H), 7.26 (dt, J = 7.9, 1.3 Hz, 1H), 7.36 - 7.40 (m, 1H), 7.48 (dd, J = 8.2, 2.5 Hz, 1H), 7.59 (s, 1H), 7.78 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.97 (dt, J = 7.9, 1.9 Hz, 1H), 8.60 (dd, J = 2.5, 0.6 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δC (ppm) = 48.1, 116.2 (d, J = 23.0 Hz), 119.0,
2-(3-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine (8). Synthesized using 3-fluorophenylboronic acid (230 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Yellow solid. Yield: 135 mg, 0.53 mmol, 64 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm): 5.19 (s, 2H), 6.93 (s, 1H), 7.11 (dd, \(J = 8.2, 2.5, 0.9\) Hz, 1H), 7.13 (dd, \(J = 2.5, 0.9\) Hz, 1H), 7.43 (dd, \(J = 8.2, 7.9, 6.0\) Hz, 1H), 7.50 (dd, \(J = 8.2, 2.5\) Hz, 1H), 7.59 (brs, 1H), 7.69 - 7.76 (m, 3H), 8.58 (dd, \(J = 2.2, 0.6\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.0, 113.9 (d, \(J = 23.0\) Hz), 116.1 (d, \(J = 21.1\) Hz), 119.0, 120.6, 122.4 (d, \(J = 2.9\) Hz), 130.3 (d, \(J = 7.6\) Hz), 130.4, 130.7, 135.8, 137.3, 140.8 (d, \(J = 7.6\) Hz), 148.6, 156.3 (d, \(J = 2.9\) Hz), 163.5 (d, \(J = 245.7\) Hz); MS (ESI): \(m/z = 254.13\) [M+H]⁺.

2-(4-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine (9). Synthesized using 4-fluorophenylboronic acid (230 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Yellow solid. Yield: 160 mg, 0.63 mmol, 75 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm) = 5.18 (s, 2H), 6.92 (s, 1H), 7.12 (brs, 1H), 7.15 (t, \(J = 8.8\) Hz, 2H), 7.48 (dd, \(J = 8.2, 2.2\) Hz, 1H), 7.60 (s, 1H), 7.67 (d, \(J = 8.2\) Hz, 1H), 7.97 (dd, \(J = 8.8, 5.4\) Hz, 2H), 8.57 (d, \(J = 1.9\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.1, 115.7 (d, \(J = 22.1\) Hz), 119.0, 120.2, 128.7 (d, \(J = 8.6\) Hz), 130.0, 130.4, 134.7 (d, \(J = 3.9\) Hz), 135.8, 137.3, 148.6, 156.6, 163.7 (d, \(J = 249.5\) Hz); MS (ESI): \(m/z = 254.18\) [M+H]⁺.

2-(3,4-Difluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine (10). Synthesized using 3,4-difluorophenylboronic acid (270 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Yellow solid. Yield: 210 mg, 0.77 mmol, 92 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm) = 5.18 (s, 2H), 6.92 (t, \(J = 1.3\) Hz, 1H), 7.13 (t, \(J = 1.3\) Hz, 1H), 7.25 (ddd, \(J = 9.8, 8.5, 8.2\) Hz, 1H), 7.49 (dd, \(J = 8.2, 2.5\) Hz, 1H), 7.59 (s, 1H), 7.66 (dd, \(J = 8.3, 0.6\) Hz, 1H), 7.69 - 7.73 (m, 1H), 7.86 (ddd, \(J = 11.4, 7.6, 2.2\) Hz, 1H), 8.56 (dd, \(J = 2.3, 0.6\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.0, 116.0 (d, \(J = 18.2\) Hz), 117.6 (d, \(J = 17.3\) Hz), 119.0, 120.2, 122.8 (dd, \(J = 3.8, 6.7\) Hz), 130.4, 130.6, 135.6 (dd, \(J = 3.8, 5.8\) Hz), 135.9, 137.3, 148.6, 150.8 (dd, \(J = 20.2, 255.3\) Hz), 151.3 (dd, \(J = 15.4, 254.3\) Hz), 155.3; MS (ESI): \(m/z = 272.10\) [M+H]⁺.

2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol (11). Synthesized using 3-fluoro-4-hydroxyphenylboronic acid (196 mg, 2.00 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 40 mg, 0.15 mmol, 24 %. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta_H\) (ppm): 5.25 (s, 2H), 6.92 (brs, 1H), 7.03 (t, \(J = 8.8\) Hz, 1H), 7.25 (t, \(J = 1.2\) Hz, 1H), 7.69 (dd,
5-Imidazol-1-ylmethyl-2-(2-methoxy-phenyl)-pyridine (12). Synthesized using 2-methoxyphenylboronic acid (190 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Yellow solid. Yield: 210 mg, 0.79 mmol, 94 %. 1H NMR (CDCl3, 500 MHz): δH (ppm) = 3.85 (s, 3H), 5.17 (s, 2H), 6.95 (brs, 1H), 7.00 (dd, J = 8.5, 0.6 Hz, 1H), 7.08 (dt, J = 7.6, 1.1 Hz, 1H), 7.12 (s, 1H), 7.38 (ddd, J = 8.5, 7.6, 1.9 Hz, 1H), 7.44 (dd, J = 8.5, 2.2 Hz, 1H), 7.60 (s, 1H), 7.77 (dd, J = 7.6, 1.9 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 8.60 (d, J = 1.6 Hz, 1H); 13C NMR (CDCl3 125 MHz): δC (ppm) = 48.2, 55.6, 111.4, 119.1, 121.1, 125.2, 128.3, 129.5, 130.2, 130.3, 131.1, 134.6, 137.3, 148.2, 156.4, 157.0; MS (ESI): m/z = 266.28 [M+H]+.

5-Imidazol-1-ylmethyl-2-(4-methoxy-phenyl)-pyridine (13). Synthesized using 4-methoxyphenylboronic acid (380 mg, 3.35 mmol) and 1a (400 mg, 1.68 mmol) according to Method C. Yellow solid. Yield: 400 mg, 1.51 mmol, 90 %. 1H NMR (CDCl3, 500 MHz): δH (ppm) = 3.86 (s, 3H), 5.16 (s, 2H), 6.92 (t, J = 1.3 Hz, 1H), 6.99 (d, J = 9.1 Hz, 2H), 7.11 (s, 1H), 7.46 (dd, J = 8.2, 2.5 Hz, 1H), 7.59 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 9.1 Hz, 2H), 8.54 (d, J = 2.5 Hz, 1H); 13C NMR (CDCl3, 125 MHz): δC (ppm) = 48.1, 55.4, 114.2, 119.0, 119.8, 128.2, 129.2, 130.3, 131.2, 135.7, 137.3, 148.5, 157.4, 160.8; MS (ESI): m/z = 266.22 [M+H]+.

2-(3,4-Dimethoxy-phenyl)-5-imidazol-1-ylmethyl-pyridine (14). Synthesized using 3,4-dimethoxyphenylboronic acid (610 mg, 3.36 mmol) and 1a (400 mg, 1.68 mmol) according to Method C. Yellow solid. Yield: 470 mg, 1.58 mmol, 94 %. 1H NMR (CDCl3, 500 MHz): δH (ppm) = 3.93 (s, 3H), 3.98 (s, 3H), 5.16 (s, 2H), 6.92 (br, s, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.11 (bs, 1H), 7.46 (dd, J = 8.5, 2.2 Hz, 1H), 7.47 (dd, J = 8.5, 2.2 Hz, 1H), 7.58 (bs, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H); 13C NMR (CDCl3, 125 MHz): δC (ppm) = 48.1, 56.0, 56.0, 113.3, 113.0, 111.1, 119.0, 119.5, 120.0, 129.4, 130.3, 131.4, 135.7, 148.4, 149.4, 150.3, 157.3; MS (ESI): m/z = 296.17 [M+H]+.

2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine (15). Synthesized using 2-aminophenylboronic acid (173 g, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 120 mg, 0.48 mmol, 76 %. 1H NMR (500 MHz, CDCl3): δH (ppm): 5.17 (s, 2H), 6.74 - 6.79 (m, 2H), 6.93 (t, J = 1.3 Hz, 1H), 7.13 (bs, 1H), 7.16 - 7.19 (m, 1H), 7.49 - 7.53 (m, 2H), 7.62 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H);
$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.2, 117.3, 117.6, 119.1, 121.1, 122.2, 128.7, 129.3, 130.2, 130.3, 135.8, 137.3, 146.6, 146.7, 159.7; MS (ESI): m/z = 250.71 [M+H]$^+$. 

3-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine (16). Synthesized using 3-aminophenyloboronic acid 230 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Orange solid. Yield: 144 mg, 0.56 mmol, 67 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 5.11 (s, 2H), 6.72 (ddd, $J = 7.6, 2.4, 0.9$ Hz, 1H), 6.89 (brs, 1H), 7.08 (bs, 1H), 7.21 (t, $J = 7.7$ Hz, 1H), 7.28 (dt, $J = 7.8, 1.3$ Hz, 1H), 7.33 (t, $J = 2.2$ Hz, 1H), 7.41 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.55 (brs, 1H), 7.62 (d, $J = 8.2$ Hz, 1H), 8.50 (d, $J = 2.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.0, 113.3, 116.0, 117.0, 119.0, 120.5, 129.6, 129.9, 130.1, 135.6, 137.2, 139.5, 146.9, 148.3, 157.6; MS (ESI): m/z = 251.13 [M+H]$^+$. 

4-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine (17). Synthesized using 4-aminophenyloboronic acid (173 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. White solid. Yield: 35 mg, 0.14 mmol, 22 %. $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ (ppm): 5.14 (s, 2H), 6.76 (d, $J = 8.5$ Hz, 2H), 6.92 (s, 1H), 6.93 (brs, 1H), 7.12 (s, 1H), 7.43 (dd, $J = 8.5$, 2.5 Hz, 1H), 7.60 (brs, 1H), 7.62 (d, $J = 8.5$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 2H), 8.52 (d, $J = 1.5$ Hz, 1H); MS (ESI): m/z = 250.74 [M+H]$^+$. 

5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-2-methyl-phenylamine (18). Synthesized using 3-amino-4-methylphenyloboronic acid (190 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 139 mg, 0.52 mmol, 84 %. $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ (ppm): 2.22 (s, 3H), 5.16 (s, 2H), 6.92 (t, $J = 0.9$ Hz, 1H), 7.12 (t, $J = 0.9$ Hz, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 7.26 (dd, $J = 7.9, 1.9$ Hz, 1H), 7.37 (d, $J = 1.9$ Hz, 1H), 7.45 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.59 (s, 1H), 7.67 (dd, $J = 8.2, 0.6$ Hz, 1H), 8.55 (dd, $J = 2.2, 0.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 17.2, 48.2, 113.2, 117.1, 119.0, 120.4, 123.9, 129.6, 130.2, 130.9, 135.6, 137.3, 137.4, 145.1, 148.4, 157.8; MS (ESI): m/z = 264.25 [M+H]$^+$. 

3-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-benzonitrile (19). Synthesized using 3-cyanophenyloboronic acid (185 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 135 mg, 0.52 mmol, 82 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm): 5.21 (s, 2H), 6.94 (s, 1H), 7.13 (s, 1H), 7.54 (dd, $J = 8.2, 2.4$ Hz, 1H), 7.55 - 7.60 (m, 2H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 8.31 (s, 1H), 8.61 (d, $J = 1.5$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.0, 113.1, 118.6, 119.0, 120.6, 129.7, 130.4, 130.6, 131.0, 131.3, 132.5, 136.0, 137.3, 139.6, 148.77, 148.81, 155.1; MS (ESI): m/z = 264.11 [M+H]$^+$. 

4-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-benzonitrile (20). Synthesized using 4-cyanophenyloboronic acid (185 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to
Method C. Yellow solid. Yield: 110 mg, 0.42 mmol, 67 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm): 5.22 (s, 2H), 6.93 (s, 1H), 7.14 (s, 1H), 7.54 (dd, $J = 8.2$, 2.3 Hz, 1H), 7.60 (s, 1H), 7.75 - 7.78 (m, 3H), 8.11 (d, $J = 8.2$ Hz, 2H), 8.62 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.0, 112.9, 118.6, 119.0, 121.0, 127.4, 130.5, 131.5, 132.6, 136.0, 137.3, 142.6, 148.8, 150.4; MS (ESI): m/z = 261.03 [M+H]$^+$. 

4-(5-Imidazol-1-ylmethyl-2-pyridin-2-yl)-benzaldehyde (21). Synthesized using 4-formylyphenylboronic acid (252 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Brown solid. Yield: 150 mg, 0.57 mmol, 68 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm): 5.21 (s, 2H), 6.94 (t, $J = 1.3$ Hz, 1H), 7.14 (t, $J = 0.9$ Hz, 1H), 7.53 (dd, $J = 8.2$, 2.0 Hz, 1H), 7.60 (brs, 1H), 7.79 (dd, $J = 8.2$, 0.6 Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 2H), 8.16 (d, $J = 8.4$ Hz, 2H), 8.63 (d, $J = 2.0$ Hz, 1H), 10.08 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.0, 119.0, 121.2, 127.5, 130.2, 130.5, 131.3, 135.9, 136.7, 137.3, 144.0, 148.8, 156.1, 191.8; MS (ESI): m/z = 264.16 [M+H]$^+$. 

[4-(5-Imidazol-1-ylmethyl-2-pyridin-2-yl)-phenyl]-diphenyl-amine (22). Synthesized using 4-(diphenylamino)phenylboronic acid (364 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 140 mg, 0.34 mmol, 55 %. $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ (ppm): 5.16, (s, 2H), 6.93 (t, $J = 1.3$ Hz, 1H), 7.06 (t, $J = 7.3$, 1.3 Hz, 2H), 7.12 - 7.15 (m, 7H), 7.25 - 7.29 (m, 4H), 7.45 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.58 (br, s, 1H), 7.65 (dd, $J = 8.2$, 0.6 Hz, 1H), 7.83 - 7.86 (m, 2H), 8.54 (dd, $J = 2.5$, 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.2, 119.0, 119.8, 122.8, 123.4, 124.9, 127.7, 129.2, 129.3, 130.2, 132.0, 135.7, 137.3, 147.3, 148.5, 149.1, 157.3; MS (ESI): m/z = 402.94 [M+H]$^+$. 

5-Imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine (23). Synthesized using 1-naphthylboronic acid (217 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 130 mg, 0.46 mmol, 72 %. $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ (ppm): 5.25 (s, 2H), 7.00 (t, $J = 1.3$ Hz, 1H), 7.16 (t, $J = 1.3$ Hz, 1H), 7.46 - 7.52 (m, 2H), 7.54 - 7.60 (m, 4H), 7.65 (br, s, 1H), 7.90 - 7.93 (m, 2H), 8.03 - 8.05 (m, 1H), 8.70 (dd, $J = 2.5$, 0.9 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 48.19, 119.1, 125.2, 125.2, 125.3, 126.0, 126.6, 127.6, 128.4, 129.2, 130.1, 130.3, 131.0, 135.3, 137.3, 137.6, 148.3, 159.5; MS (ESI): m/z = 286.05 [M+H]$^+$. 

5-Imidazol-1-ylmethyl-2-naphthalen-2-yl-pyridine (24). Synthesized using 2-naphthylboronic acid (217 g, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 118 mg, 0.41 mmol, 66 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm): 5.23 (s, 2H), 6.97 (s, 1H), 7.17 (s, 1H), 7.50 - 7.53 (m, 2H), 7.57 (dd, $J = 8.2$, 2.4 Hz, 1H), 7.85 - 7.88 (m, 3H), 7.95 (d, $J = 8.8$ Hz, 2H), 8.11 (dd, $J = 8.5$, $J = 1.8$ Hz, 1H), 8.47 (d, $J = 0.9$ Hz, 1H).
5-Imidazol-1-ylmethyl-2,3-diphenyl-pyridine (25). Synthesized using phenylboronic acid (134 mg, 1.10 mmol) and 6 (150 mg, 0.55 mmol) according to Method C. Yellow solid. Yield: 79 mg, 0.25 mmol, 46 %. ¹H NMR (500 MHz, CDCl₃): δ_H (ppm): 5.27 (s, 2H), 7.00 (brs, 1H), 7.11 - 7.13 (m, 2H), 7.16 (brs, 1H), 7.21 - 7.28 (m, 6H), 7.32 - 7.34 (m, 2H), 7.49 (d, J = 2.1 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 48.3, 119.2, 127.6, 128.0, 128.1, 128.4, 129.2, 129.4, 129.8, 136.4, 137.1, 137.5, 139.0, 139.3, 147.1, 147.1, 157.6; MS (ESI): m/z = 285.92 [M+H]+.

5-Imidazol-1-ylmethyl-[2,3']bipyridinyl (26). Synthesized using 3-pyridylboronic acid (206 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Yellow solid. Yield: 144 mg, 0.61 mmol, 73 %. ¹H NMR (CDCl₃, 500 MHz): δ_H (ppm): 5.20 (s, 2H), 6.93 (t, J = 1.5 Hz, 1H), 7.13 (t, J = 0.9 Hz, 1H), 7.40 (ddd, J = 7.9, 4.7, 0.9 Hz, 1H), 7.52 (dd, J = 8.2, 2.2 Hz, 1H), 7.60 (s, 1H), 7.75 (d, J = 8.2 Hz), 8.29 - 8.32 (m, 1H), 8.61 (m, 1H), 8.66 (dd, J = 4.7, 1.5 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 48.0, 119.0, 120.6, 123.6, 130.5, 131.0, 134.0, 134.3, 135.9, 137.3, 148.2, 148.9, 150.3, 155.0. MS (ESI): m/z = 237.03 [M+H]+.

5-Imidazol-1-ylmethyl-[2,4']bipyridinyl (27). Synthesized using 4-pyridylboronic acid (123 mg, 1.00 mmol) and 1a (95 mg, 0.4 mmol) according to Method C. Yellow solid. Yield: 73 mg, 77 %. ¹H NMR (500 MHz, CDCl₃): δ_H (ppm): 5.22 (s, 2H), 6.94 (t, J = 1.3 Hz, 1H), 7.14 (brs, 1H), 7.54 (dd, J = 2.5, 8.2 Hz, 1H), 7.60 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.88 (dd, J = 1.6, 4.1 Hz, 2H), 8.64 (dd, J = 0.6, 2.5 Hz, 1H), 8.73 (dd, J = 1.6, 4.4 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 48.3, 119.3, 121.2, 130.8, 132.3, 136.2, 137.6, 149.1, 150.8, 155.1; MS (ESI): m/z = 237.02 [M+H]+.

5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-pyrimidine (28). Synthesized using pyrimid-5-yboronic acid (155 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 121 mg, 0.51 mmol, 81 %. ¹H NMR (500 MHz, CDCl₃): δ_H (ppm): 5.23 (s, 2H), 6.93 (t, J = 1.3 Hz, 1H), 7.12 (t, J = 1.3 Hz, 1H), 7.57 (dd, J = 8.2, 2.5 Hz, 1H), 7.67 (s, 1H), 7.74 (dd, J = 8.2, 0.9 Hz, 1H), 8.62 (m, 1H), 9.23 (s, 1H), 9.29 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 48.0, 119.0, 120.5, 130.1, 131.6, 131.8, 136.1, 136.1, 137.3, 149.2, 152.1, 155.0, 158.8; MS (ESI): m/z = 238.10 [M+H]+.

5-Imidazol-1-ylmethyl-6'-methoxy-[2,3']bipyridinyl (29). Synthesized using 2-methoxy-5-pyrid-5-yboronic acid (193 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method
C. Yellow solid. Yield: 136 mg, 0.51 mmol, 81%. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm): 3.97 (s, 3H), 5.16 (s, 2H), 6.81 (d, $J = 8.5$ Hz, 1H), 6.92 (brs, 1H), 7.11 (s, 1H), 7.46 (dd, $J = 8.2$, 2.4 Hz, 1H), 7.62 - 7.64 (m, 2H), 8.20 (dd, $J = 8.5$, 2.4 Hz, 1H), 8.53 (d, $J = 1.8$ Hz, 1H), 8.72 (d, $J = 2.1$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{C}$ (ppm) = 48.1, 53.64, 110.9, 119.0, 119.7, 127.7, 129.8, 130.0, 135.8, 137.2, 137.3, 145.6, 148.7, 155.2, 164.8; MS (ESI): m/z = 266.66 [M+H]$^+$. 

4-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-isoquinoline (30). Synthesized using 4-isoquinolinylboronic acid (218 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 97 mg, 0.34 mmol, 54 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm): 5.26 (s, 2H), 7.00 (t, $J = 1.3$ Hz, 1H), 7.16 (brs, 1H), 7.58 - 7.66 (m, 4H), 7.70 - 7.73 (m, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 8.17 (dd, $J = 8.5$, 0.6 Hz, 1H), 8.62 (s, 1H), 8.71 (d, $J = 1.6$ Hz, 1H), 9.30 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{C}$ (ppm) = 48.1, 119.1, 124.5, 125.0, 127.4, 128.0, 128.5, 130.0, 130.4, 130.8, 131.1, 133.6, 135.7, 137.4, 143.5, 148.5, 153.4, 156.6; MS (ESI): m/z = 287.10 [M+H]$^+$. 

5-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine (31). Synthesized using 2-thiophenylboronic acid (118 g, 0.92 mmol) and 1a (110 mg, 0.46 mmol) according to Method C. Yellow solid. Yield: 101 mg, 0.42 mmol, 91 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm): 5.13 (s, 2H), 6.90 (s, 1H), 7.11 (t, $J = 4.4$ Hz, 2H), 7.41 - 7.43 (m, 2H), 7.57 - 7.59 (m, 2H), 7.63 (d, $J = 8.2$ Hz, 1H), 8.45 (d, $J = 1.9$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{C}$ (ppm) = 48.1, 118.9, 119.0, 125.1, 128.13, 128.14, 129.8, 130.3, 135.7, 137.3, 144.0, 148.4, 152.9; MS (ESI): m/z = 242.10 [M+H]$^+$. 

5-Imidazol-1-ylmethyl-2-thiophen-3-yl-pyridine (32). Synthesized using 3-thiophenylboronic acid (206 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Brown solid. Yield: 144 mg, 0.61 mmol, 73 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm): 5.15 (s, 2H), 6.91 (t, $J = 1.3$ Hz, 1H), 7.12 (s, 1H), 7.40 (dd, $J = 5.0$, 3.2 Hz, 1H), 7.45 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.58 (s, 1H), 7.60 (dd, $J = 8.2$, 0.6 Hz, 1H), 7.64 (dd, $J = 5.0$, 1.3 Hz, 1H), 7.91 (dd, $J = 3.2$, 1.3 Hz, 1H), 8.51 (dd, $J = 2.2$, 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{C}$ (ppm) = 48.1, 119.0, 120.3, 124.4, 126.1, 126.5, 129.6, 130.3, 135.7, 137.3, 141.4, 148.6, 153.8; MS (ESI): m/z = 242.03 [M+H]$^+$. 

2-(5-Chloro-thiophen-2-yl)-5-imidazol-1-ylmethyl-pyridine (33). Synthesized using 5-chloro-2-thiophenylboronic acid (205 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 83 mg, 0.30 mmol, 47 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm): 5.17 (s, 2H), 6.91 - 6.92 (m, 2H), 7.13 (s, 1H), 7.33 (d, $J = 4.0$ Hz, 1H), 7.46 (dd, $J = 8.2$, 2.1 Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.80 (s, 1H), 8.42 (d, $J = 1.5$ Hz, 1H); $^{13}$C NMR
5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde (34). Synthesized using 5-formyl-2-thiophenylboronic acid (197 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 78 mg, 0.28 mmol, 46 %. \( ^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) (ppm): 5.18 (s, 2H), 6.92 (t, \( J = 1.3 \) Hz, 1H), 7.13 (t, \( J = 1.3 \) Hz, 1H), 7.47 (dd, \( J = 8.2, 2.2 \) Hz, 1H), 7.56 (brs, 1H), 7.66 (d, \( J = 4.1 \) Hz, 1H), 7.71 (dd, \( J = 8.2, 0.6 \) Hz, 1H), 7.76 (d, \( J = 4.1 \) Hz, 1H), 8.52 (dd, \( J = 2.2, 0.6 \) Hz, 1H), 9.93 (s, 1H); \( ^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) (ppm) = 48.0, 119.0, 119.8, 125.5, 130.5, 131.7, 135.8, 136.7, 137.3, 144.6, 148.7, 151.4, 152.8, 183.0; MS (ESI): \( m/z \) = 275.98 [M+H]+.

5-Imidazol-1-ylmethyl-2,3-diphenyl-pyridine (35). Synthesized using 2-thiophenylboronic acid (139 mg, 1.10 mmol) and 6 (150 mg, 0.55 mmol) according to Method C. Yellow solid. Yield: 102 mg, 0.37 mmol, 67 %. \( ^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) (ppm): 5.26 (s, 2H), 6.96 (t, \( J = 1.3 \) Hz, 1H), 7.13 (dd, \( J = 5.0, 3.5 \) Hz 1H), 7.17 (t, \( J = 1.3 \) Hz, 1H), 7.42 (dd, \( J = 3.5, 1.3 \) Hz, 1H), 7.46 (dd, \( J = 5.0, 1.3 \) Hz, 1H), 7.64 (d, \( J = 2.5 \) Hz, 1H), 8.00 (s, 1H), 8.24 (d, \( J = 2.5 \) Hz, 1H); \( ^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) (ppm) = 47.7, 119.1, 127.6, 127.8, 128.9, 129.0, 130.7, 136.9, 137.2, 138.2, 141.0, 146.6, 149.2; MS (ESI): \( m/z \) = 276.55 [M+H]+.

3-Imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine (36). Synthesized using 2-thiophenylboronic acid (161 mg, 1.26 mmol) and 5 (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 111 mg, 0.46 mmol, 73 %. \( ^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) (ppm): 5.39 (s, 2H), 6.88 (t, \( J = 1.3 \) Hz, 1H), 7.13 - 7.15 (m, 2H), 7.17 (dd, \( J = 7.9, 1.9 \) Hz, 1H), 7.20 (dd, \( J = 7.9, 4.4 \) Hz, 1H), 7.23 (dd, \( J = 3.8, 1.3 \) Hz, 1H), 7.50 (dd, \( J = 5.0, 1.3 \) Hz, 1H), 7.51 (brs, 1H), 8.60 (dd, \( J = 4.4, 1.9 \) Hz, 1H); \( ^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) (ppm) = 48.4, 119.3, 122.5, 127.2, 127.8, 128.5, 128.6, 130.3, 136.1, 137.5, 142.7, 149.0, 150.8; MS (ESI): \( m/z \) = 241.79 [M+H]+.

2-Benzo[\( C\)]thiophen-2-yl-5-imidazol-1-ylmethyl-pyridine (37). Synthesized using benzo[\( C\)]thiophen-2-ylboronic acid (149 mg, 0.84 mmol) and 1a (100 mg, 0.42 mmol) according to Method C. Yellow solid. Yield: 46 mg, 0.16 mmol, 38 %. \( ^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) (ppm): 5.17 (s, 2H), 6.93 (t, \( J = 1.3 \) Hz, 1H), 7.35 - 7.38 (m, 2H), 7.46 (dd, \( J = 8.2, 2.2 \) Hz, 1H), 7.60 (brs, 1H), 7.79 (d, \( J = 8.2 \) Hz, 1H), 7.80 - 7.83 (m 1H), 7.84 (d, \( J = 0.6 \) Hz, 1H), 7.86 - 7.88 (m, 1H), 8.52 (d, \( J = 1.9 \) Hz, 1H); \( ^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) (ppm) = 48.1, 119.0, 119.7, 121.7, 122.6, 124.2, 123.6, 125.3, 130.4, 130.6, 135.6, 137.3, 140.3, 140.8, 143.8, 148.5, 152.8; MS (ESI): \( m/z \) = 292.04 [M+H]+.
2-Benzothiophen-3-yl-5-imidazol-1-ylmethyl-pyridine (38). Synthesized using benzo[\(\text{E}\)]thiophen-3-ylboronic acid (224 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 100 mg, 0.34 mmol, 54 %. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta_H\) (ppm): 5.27 (s, 2H), 6.99 (t, \(J = 1.3\) Hz, 1H), 7.18 (brs, 1H), 7.39 - 7.42 (m, 1H), 7.43 - 7.47 (m, 1H), 7.59 (dd, \(J = 8.2, 2.5\) Hz, 1H), 7.70 (dd, \(J = 8.2, 0.9\) Hz, 1H), 7.82 (s, 1H), 7.90 - 7.92 (m, 1H), 8.01 (s, 1H), 8.46 - 8.48 (m, 1H), 8.66 - 8.67 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 45.5, 119.3, 122.6, 122.8, 124.1, 124.7, 124.8, 127.1, 128.7, 129.4, 135.7, 135.9, 137.0, 137.1, 140.9, 148.6, 155.0; MS (ESI): \(m/z = 292.05\) [M+H]^+.

2-Furan-2-yl-5-imidazol-1-ylmethyl-pyridine (39). Synthesized using 2-furanylboronic acid (141 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 127 mg, 0.56 mmol, 89 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm): 5.12 (s, 2H), 6.52 (dd, \(J = 3.4, 1.5\) Hz, 1H), 6.89 (t, \(J = 1.2\) Hz, 1H), 7.05 (dd, \(J = 3.4, 0.6\) Hz, 1H), 7.09 (brs, 1H), 7.43 (dd, \(J = 8.2, 2.1\) Hz, 1H), 7.52 (dd, \(J = 1.5, 0.6\) Hz, 1H), 7.56 (s, 1H), 7.65 (d, \(J = 8.2\) Hz, 1H), 8.46 (d, \(J = 1.8\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.1, 109.2, 112.1, 118.6, 118.9, 129.7, 130.2, 135.6, 137.2, 143.6, 148.4, 149.5, 152.9; MS (ESI): \(m/z = 225.93\) [M+H]^+.

2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine (40). Synthesized using 3-furanylboronic acid (188 mg, 1.68 mmol) and 1a (200 mg, 0.84 mmol) according to Method C. Brown solid. Yield: 144 mg, 0.61 mmol, 73 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm): 5.13 (s, 2H), 6.87 (dd, \(J = 1.9, 0.9\) Hz, 1H), 6.90 (t, \(J = 1.3\) Hz, 1H), 7.10 (s, 1H), 7.41 (dd, \(J = 8.2, 2.2\) Hz, 1H), 7.43 (dd, \(J = 8.2, 1.3\) Hz, 1H), 7.49 (t, \(J = 1.6\) Hz, 1H), 7.56 (brs, 1H), 8.02 (dd, \(J = 0.7\) Hz, \(J = 1.4\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.1, 108.5, 118.9, 120.1, 126.5, 129.5, 130.3, 135.6, 137.3, 141.5, 144.0, 148.6, 152.1; MS (ESI): \(m/z = 226.15\) [M+H]^+.

2-Benzothiophen-3-yl-5-imidazol-1-ylmethyl-pyridine (41). Synthesized using benzo[\(\text{E}\)]furan-2-ylboronic acid (204 mg, 1.26 mmol) and 1a (150 mg, 0.63 mmol) according to Method C. Yellow solid. Yield: 71 mg, 0.26 mmol, 41 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta_H\) (ppm): 5.18 (s, 2H), 6.93 (s, 1H), 7.13 (s, 1H), 7.25 - 7.28 (m, 2H), 7.35 (dt, \(J = 8.2, 1.2\) Hz, 1H), 7.44 (d, \(J = 0.9\) Hz, 1H), 7.51 (dd, \(J = 8.2, 2.1\) Hz, 1H), 7.56 (dd, \(J = 8.2, 0.9\) Hz, 1H), 7.60 (s, 1H), 7.65 (d, \(J = 7.3\) Hz, 1H), 7.88 (d, \(J = 8.2\) Hz, 1H), 8.56 (d, \(J = 2.1\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta_C\) (ppm) = 48.1, 105.5, 111.5, 119.0, 119.8, 121.8, 123.3, 125.5, 128.6, 130.4, 130.8, 135.7, 137.3, 148.7, 149.4, 154.3, 155.4; MS (ESI): \(m/z = 276.03\) [M+H]^+.

2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine (42). Synthesized using 2-furanylboronic acid (123 mg, 1.10 mmol) and 6 (150 mg, 0.55 mmol) according to Method C. Yellow solid.
Yield: 108 mg, 0.37 mmol, 67 %.

\[ \text{H NMR (500 MHz, CDCl}_3\]: } \delta_{\text{H}} \text{ (ppm)}: 5.19 \text{ (s, 2H), 6.26 (dd, } J = 3.5, 0.6 \text{ Hz, 1H), 6.41 (dd, } J = 3.5, 0.9 \text{ Hz, 1H), 6.41 - 6.48 (m, 2H), 6.93 (t, } J = 1.3 \text{ Hz, 1H), 7.12 (bs, 1H), 7.49 - 7.50 \text{ (m, 2H), 7.60 (bs, 1H), 7.61 (d, } J = 2.2 \text{ Hz, 1H), 8.50 (d, } J = 2.2 \text{ Hz, 1H); } \text{lC NMR (CDCl}_3\), 125 MHz): } \delta_{\text{C}} \text{ (ppm)} = 47.9, 110.0, 111.6, 111.7, 111.7, 119.0, 124.8, 130.0, 130.4, 136.0, 137.3, 142.8, 143.3, 146.8, 147.4, 149.9, 151.7; \text{ MS (ESI): } m/z = 292.09 \text{ [M+H]}.\]

6-Bromonicotinaldehyde (43c). To a suspension of 2,5-dibromopyridine (2.00 g, 8.44 mmol) in dry diethyl ether (25 mL) was added n-BuLi (3.55 mL, 8.87 mmol, 2.5 M solution in hexane) at -80°C under a nitrogen atmosphere. After stirring for 1 h at -80°C dry DMF (0.68 mg, 9.28 mmol) was added. After stirring for an additional hour at -80°C the reaction mixture was allowed to warm to 0°C and HCl (18.0 mL, 1 M) was added. After stirring for 15 minutes the phases were separated and aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over MgSO\(_4\). The organic phase was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:1) as eluent. White solid. Yield: 1.03 g, 66 %. \[ \text{H NMR (CDCl}_3\), 500 MHz): } \delta_{\text{H}} \text{ (ppm)} = 7.67 - 7.71 \text{ ppm (m, 1H), 8.02 (dd, } J = 8.2, 2.5 \text{ Hz, 1H), 8.84 (dd, } J = 2.5, 0.6 \text{ Hz, 1H), 10.10 (s, } 1H); \text{lC NMR (CDCl}_3\), 125 MHz): } \delta_{\text{C}} \text{ (ppm)} = 129.0, 130.6, 137.5, 148.3, 152.5, 189.4; \text{ MS (ESI): } m/z = 187.19 \text{ [M+H]}.\]

6-Phenylnicotinaldehyde (43b). Synthesized using compound 43c (1.20 g, 6.44 mmol) and phenylboronic acid (1.18 g, 9.65 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (10:1) as eluent. Light yellow solid. Yield: 1.10 g, 94 %. \[ \text{H NMR (CDCl}_3\), 500 MHz): } \delta_{\text{H}} \text{ (ppm)} = 7.44 - 7.52 \text{ ppm (m, 3H), 7.87 (d, } J = 8.2 \text{ Hz, 1H), 8.04 - 8.08 \text{ (m, 2H), 8.20 (dd, } J = 8.2, 2.2 \text{ Hz, 1H), 9.10 (dd, } J = 2.2, 0.6 \text{ Hz, 1H), 10.11 (s, } 1H); \text{lC NMR (CDCl}_3\), 125 MHz): } \delta_{\text{C}} \text{ (ppm)} = 120.5, 127.5, 129.0, 129.8, 130.4, 136.5, 138.0, 152.4, 162.2, 190.4; \text{ MS (ESI): } m/z = 184.31 \text{ [M+H]}.\]

2-Methyl-1-(6-phenylpyridin-3-yl)propan-1-ol (43a). Synthesized using compound 43b (283 mg, 1.55 mmol) and isopropylmagnesium chloride (1.55 mL, 3.10 mmol, 2 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel
using a mixture of hexane / ethyl acetate (4:1) as eluent. Orange solid. Yield: 138 mg, 40 %.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 0.82 - 0.93 (m, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 1.95 - 2.08 (m, 1H), 4.46 (d, $J = 6.6$ Hz, 1H), 7.39 - 7.44 (m, 1H), 7.45 - 7.50 (m, 2H), 7.68 - 7.75 (m, 2H), 7.96 - 8.01 (m, 2H), 8.57 (d, $J = 1.9$ Hz, H); MS (ESI): $m/z = 228.26$ [M+H]$^+$. 

2-Methyl-1-(6-phenylpyridin-3-yl)propyl 1H-imidazole-1-carboxylate (43). Synthesized using compound 43a (81 mg, 0.36 mmol), CDI (289 mg, 1.78 mmol) and acetonitrile (5 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (4:1) as eluent. White solid. Yield: 90.0 mg, 90 %.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 0.95 (d, $J = 6.9$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 2.37 (m, 1H), 5.70 (d, $J = 8.2$ Hz, 1H), 7.09 (dd, $J = 1.6$, 0.6 Hz, 1H), 7.40 - 7.51 (m, 4H), 7.72 - 7.79 (m, 2H), 7.98 - 8.03 (m, 2H), 8.19 (t, $J = 0.9$ Hz, 1H), 8.71 (dd, $J = 2.2$, 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 18.7, 18.8, 33.6, 83.7, 117.2, 120.4, 127.1, 129.0, 129.5, 131.1, 131.8, 135.6, 137.2, 138.8, 148.7, 158.0; MS (ESI): $m/z = 322.32$ [M+H]$^+$. 

1-(6-phenylpyridin-3-yl)propan-1-ol (44a). Synthesized using compound 43b (313 mg, 1.71 mmol) and ethylmagnesium bromide (3.42 ml, 3.42 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 298 mg, 82 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 0.90 - 0.95 (m, 3H), 1.71 - 1.88 (m, 2H), 4.62 (t, $J = 6.62$ Hz, 1H) 7.38 - 7.43 (m, 1H) 7.43 - 7.49 (m, 2H), 7.64 - 7.67 (m, 1H), 7.69 - 7.73 (m, 1H), 7.92 - 7.96 (m, 2H), 8.54 (d, $J = 2.21$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 9.9, 31.7, 73.2, 120.3, 126.8, 128.7, 128.8, 134.5, 138.3, 139.0, 147.7, 156.5; MS (ESI): $m/z = 214.28$ [M+H]$^+$. 

1-(6-phenylpyridin-3-yl)propyl 1H-imidazole-1-carboxylate (44). Synthesized using compound 44a (150 mg, 0.70 mmol), CDI (570 mg, 3.52 mmol) and acetonitrile (9 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. White solid. Yield: 116 mg, 54 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 1.04 (t, $J = 7.4$ Hz, 3H), 2.01 - 2.15 (m, 1H), 2.22 (dt, $J = 14.3, 7.2$ Hz, 1H), 5.92 (t, $J = 7.1$ Hz, 1H), 7.09 (dd, $J = 1.6$, 0.6 Hz, 1H), 7.41 - 7.51 (m, 4H), 7.75 - 7.80 (m, 2H), 7.98 - 8.03 (m, 2H), 8.17 - 8.19 (m, 1H), 8.74 - 8.77 (m, 1H); $^{13}$C NMR
(CDCl₃, 125 MHz): δ_C (ppm) = 9.8, 28.7, 79.8, 117.0, 120.3, 126.9, 128.8, 129.3, 130.8, 132.3, 135.0, 137.0, 138.6, ... 3.6, 19.0, 75.9, 120.3, 126.8, 128.7, 128.8, 134.5, 137.7, 139.1, 147.6, 156.5; MS (ESI): m/z = 226.28 [M+H]+.

1-(6-phenylpyridin-3-yl)ethanol (45a). Synthesized using compound 43b (210 mg, 1.15 mmol) and methylmagnesium bromide (2.29 mL, 2.29 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. Light yellow solid. Yield: 201 mg, 88 %. ¹H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 1.51 (d, J = 6.6 Hz, 3H), 3.05 (br, s, 1H), 4.92 (q, J = 6.6 Hz, 1H), 7.38 - 7.50 (m, 3H), 7.65 (d, J = 7.9 Hz, 1H), 7.74 (dd, J = 8.2, 2.2 Hz, 1H), 7.91 - 7.97 (m, 2H), 8.58 (d, J = 2.2 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 25.0, 67.8, 120.4, 126.9, 128.7, 128.9, 134.0, 139.0, 139.5, 147.2, 156.6; MS (ESI): m/z = 200.32 [M+H]+.

1-(6-phenylpyridin-3-yl)ethyl 1H-imidazole-1-carboxylate (45). Synthesized using compound 45a (170 mg, 0.85 mmol), CDI (692 mg, 4.27 mmol) and acetonitrile (10 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. White solid. Yield: 107 mg, 43 %. ¹H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 1.82 (d, J = 6.9 Hz, 3H), 6.16 (q, J = 6.6 Hz, 1H), 7.08 (dd, J = 1.7, 0.8 Hz, 1H), 7.41 - 7.53 (m, 4H), 7.76 - 7.85 (m, 2H), 7.98 - 8.03 (m, 2H), 8.17 (d, J = 1.3 Hz, 1H), 8.78 (d, J = 1.9 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 21.5, 74.9, 117.1, 120.4, 126.9, 128.8, 129.3, 130.8, 133.3, 134.7, 137.0, 138.6, 147.9, 148.0, 158.0; MS (ESI): m/z = 294.28 [M+H]+.

Cyclopropyl(6-phenylpyridin-3-yl)methanol (46a). Synthesized using compound 43b (227 mg, 1.24 mmol) and cyclopropylmagnesium bromide (4.96 mL, 2.48 mmol, 0.5 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 234 mg, 84 %. ¹H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 0.35 - 0.44 (m, 1H), 0.49 (dq, J = 9.4, 4.7 Hz, 1H), 0.55 - 0.68 (m, 2H), 1.21 (qt, J = 8.1, 5.0 Hz, 1H), 3.00 (br, s, 1H), 4.05 (d, J = 8.2 Hz, 1H), 7.38 - 7.44 (m, 1H), 7.44 - 7.50 (m, 2H), 7.66 - 7.70 (m, 1H), 7.80 - 7.85 (m, 1H), 7.94 - 8.00 (m, 2H), 8.64 - 8.69 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 2.8, 3.6, 19.0, 75.9, 120.3, 126.8, 128.7, 128.8, 134.5, 137.7, 139.1, 147.6, 156.5; MS (ESI): m/z = 226.28 [M+H]+.
5-(Cyclopropyl(1H-imidazol-1-yl)methyl)-2-phenylpyridine (46). Synthesized using compound 46a (200 mg, 0.89 mmol), CDI (720 mg, 4.44 mmol) and acetonitrile (12 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:3) as eluent. White solid. Yield: 40 mg, 24%. \( ^{1}H \) NMR (CDCl\(_3\), 500 MHz): \( \delta \)\(_{H}\) (ppm) = 5.00 - 0.61 (m, 2H), 0.81 - 0.95 (m, 2H), 1.58 (m, 1H).

6-(Furan-3-yl)nicotinaldehyde (47b). Synthesized using compound 43c (976 mg, 5.25 mmol) and 3-furanboronic acid (881 mg, 7.87 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (10:1) as eluent. White solid. Yield: 770 mg, 85%. \( ^{1}H \) NMR (CDCl\(_3\), 500 MHz): \( \delta \)\(_{H}\) (ppm) = 6.94 (dd, \( J = 1.9 \), 0.9 Hz, 1H), 7.51 - 7.55 (m, 1H), 7.58 (dd, \( J = 8.2 \), 0.6 Hz, 1H), 8.11 - 8.17 (m, 2H), 9.00 (dd, \( J = 2.2 \), 0.9 Hz, 1H), 10.06 (s, 1H); \( ^{13}C \) NMR (CDCl\(_3\), 125 MHz): \( \delta \)\(_{C}\) (ppm) = 108.5, 120.0, 126.5, 129.6, 136.3, 143.2, 144.4, 152.6, 156.8, 190.1; MS (ESI): \( m/z = 276.28 \) [M+H]+.

1-(6-(Furan-3-yl)pyridin-3-yl)ethanol (47a). Synthesized using compound 47a (200 mg, 1.16 mmol) and methylmagnesium bromide (2.31 ml, 2.31 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. Orange oil. Yield: 141 mg, 65%. \( ^{1}H \) NMR (CDCl\(_3\), 500 MHz): \( \delta \)\(_{H}\) (ppm) = 1.50 (d, \( J = 6.6 \) Hz, 3H), 4.91 (q, \( J = 6.3 \) Hz, 1H), 6.87 (dd, \( J = 1.9 \), 0.6 Hz, 1H), 7.41 (d, \( J = 8.2 \) Hz, 1H), 7.48 (t, \( J = 1.7 \) Hz, 1H), 7.70 (dd, \( J = 8.2 \), 2.2 Hz, 1H), 7.97 - 8.04 (m, 1H), 8.46 (d, \( J = 2.2 \) Hz, 1H); \( ^{13}C \) NMR (CDCl\(_3\), 125 MHz): \( \delta \)\(_{C}\) (ppm) = 25.0, 67.8, 108.6, 119.9, 126.7, 133.9, 139.1, 141.1, 143.8, 147.2, 150.9; MS (ESI): \( m/z = 190.29 \) [M+H]+.

1-(6-(Furan-3-yl)pyridine-3-yl)ethyl 1H-imidazole-1-carboxylate (47). Synthesized using compound 47a (110 mg, 0.58 mmol), CDI (471 mg, 2.91 mmol) and acetonitrile (7 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:2) as eluent. White solid. Yield: 40 mg, 24%. \( ^{1}H \)
NMR (CDCl₃, 500 MHz): δ_H (ppm) = 1.78 (d, J = 6.6 Hz, 3H), 6.11 (q, J = 6.7 Hz, 1H), 6.89 (dd, J = 1.9, 0.9 Hz, 1H), 7.07 (dd, J = 1.6, 0.6 Hz, 1H), 7.40 - 7.44 (m, 1H), 7.46 - 7.52 (m, 2H), 7.74 (dd, J = 8.4, 2.7 Hz, 1H), 8.04 (dd, J = 1.4, 0.8 Hz, 1H), 8.12 - 8.18 (m, 1H), 8.67 (d, J = 2.2 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 21.4, 74.9, 108.5, 117.0, 119.9, 126.5, 130.8, 132.8, 134.6, 137.0, 141.6, 144.0, 147.9, 148.0, 152.4; MS (ESI): m/z = 284.25 [M+H]+.

1-(6-(Furan-3-yl)pyridine-3-yl)propan-1-ol (48a). Synthesized using compound 47b (194 mg, 1.12 mmol) and ethylmagnesium bromide (2.24 mL, 2.24 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Yellow solid. Yield: 73 mg, 32%. MS (ESI): m/z = 204.30 [M+H]+.

1-(6-(Furan-3-yl)pyridin-3-yl)ethyl 1H-imidazole-1-carboxylate (48). Synthesized using compound 48a (73.0 mg, 0.36 mmol), CDI (291 mg, 1.80 mmol) and acetonitrile (4 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Green oil. Yield: 62 mg, 67%. ¹H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 1.00 (t, J = 7.4 Hz, 3H), 1.96 - 2.08 (m, 1H), 2.12 - 2.24 (m, 1H), 5.85 (t, J = 7.1 Hz, 1H), 6.88 (dd, J = 1.9, 0.6 Hz, 1H), 7.04 - 7.09 (m, 1H), 7.42 (t, J = 1.4 Hz, 1H), 7.45 - 7.51 (m, 2H), 7.69 (dd, J = 8.2, 2.2 Hz, 1H), 8.01 - 8.06 (m, 1H), 8.15 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 9.7, 28.6, 79.8, 108.5, 117.0, 119.8, 126.5, 130.7, 131.8, 134.9, 136.9, 141.5, 144.0, 148.0, 148.3, 152.3; MS (ESI): m/z = 298.27 [M+H]+.

1-(6-(Furan-3-yl)pyridin-3-yl)-2-methylpropan-1-ol (49a). Synthesized using compound 47b (160 mg, 0.92 mmol) and isopropylmagnesium chloride (0.92 mL, 1.85 mmol, 2 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Yellow solid. Yield: 53 mg, 27%. MS (ESI): m/z = 218.30 [M+H]+.
1-(6-(Furan-3-yl)pyridin-3-yl)-2-methylpropyl 1H-imidazole-1-carboxylate (49).

Synthesized using compound 49a (73.0 mg, 0.36 mmol), CDI (291 mg, 1.80 mmol) and acetonitrile (4 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Green oil. Yield: 62 mg, 67 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\)H (ppm) = 0.92 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H), 2.25 - 2.44 (m, 1H), 5.63 (d, J = 7.9 Hz, 1H), 6.88 (s, 1H), 7.08 (s, 1H), 7.41 - 7.58 (m, 3H), 7.66 (dd, J = 7.9, 1.9 Hz, 1H), 8.03 (s, 1H), 8.16 (s, 1H), 8.60 (s, 1H);
\(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\)C (ppm) = 13.1, 131.4, 135.4, 137.2, 141.7, 144.2, 148.2, 148.8, 152.5; MS (ESI): \(m/z = 312.32 [M+H]^+\).

Cyclopropyl(6-(furan-3-yl)pyridin-3-yl)methanol (50a). Synthesized using compound 47b (168 mg, 0.97 mmol) and cyclopropylmagnesium bromide (3.88 ml, 1.94 mmol, 0.5 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Yellow oil. Yield: 140 mg, 67 %.
\(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\)H (ppm) = 0.35 - 0.44 (m, 1H), 0.49 (td, J = 9.6, 5.0 Hz, 1H), 0.55 - 0.70 (m, 2H), 1.16 - 1.25 (m, 1H), 2.71 (br, s, 1H), 4.04 (d, J = 8.2 Hz, 1H), 6.89 (dd, J = 1.9, 0.6 Hz, 1H), 7.44 (dd, J = 8.0, 0.8 Hz, 1H), 7.48 - 7.50 (m, 1H), 7.75 - 7.79 (m, 1H), 8.02 (dd, J = 1.4, 0.8 Hz, 1H), 8.56 (dd, J = 2.2, 0.6 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\)C (ppm) = 2.8, 3.6, 19.1, 76.0, 108.6, 119.8, 126.8, 134.4, 137.3, 141.1, 143.8, 147.6, 150.9; MS (ESI): \(m/z = 216.27 [M+H]^+\).

5-(Cyclopropyl(1H-imidazol-1-yl)methyl)-2-(furan-3-yl)pyridine (50). Synthesized using compound 50a (67.0 mg, 0.31 mmol), CDI (253 mg, 1.56 mmol) and NMP (5 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of ethyl acetate / methanol (9:1) as eluent. Brown oil. Yield: 20 mg, 24 %. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\)H (ppm) = 0.47 - 0.57 (m, 2H), 0.81 - 0.90 (m, 2H), 1.65 - 1.72 (m, 1H), 4.45 (d, J = 9.1 Hz, 1H), 6.88 (dd, J = 1.9, 0.9 Hz, 1H), 6.95 (t, J = 1.3 Hz, 1H), 7.11 (t, J = 1.1 Hz, 1H), 7.39 - 7.45 (m, 2H), 7.49 (t, J = 1.7 Hz, 1H), 7.71 (s, 1H), 8.02 (dd, J = 1.6, 0.9 Hz, 1H), 8.53 (dd, J = 1.4, 0.8 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\)C (ppm) = 4.8, 5.2, 16.2, 63.8, 108.5, 118.1, 120.0, 126.5, 129.7, 133.6, 134.7, 136.4, 141.4, 144.0, 148.0, 151.9; MS (ESI): \(m/z = 266.27 [M+H]^+\).
5-(1-(1H-imidazol-1-yl)ethyl)-2-phenylpyridine (51). Synthesized using compound 45a (164 mg, 0.82 mmol), CDI (667 mg, 4.12 mmol) and NMP (8 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of ethyl acetate / methanol (9:1) as eluent. Brown oil. Yield: 20 mg, 10 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 1.93 (d, $J = 7.3$ Hz, 3H), 5.45 (q, $J = 6.9$ Hz, 1H), 6.97 (t, $J = 1.4$ Hz, 1H), 7.11 - 7.15 (m, 1H), 7.40 - 7.51 (m, 4H), 7.64 (s, 1H); $^13$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 21.8, 54.2, 117.7, 120.5, 126.9, 128.8, 129.3, 129.9, 134.3, 135.3, 135.9, 138.5, 147.5, 157.4. MS (ESI): $m/z = 250.26$ [M+H]+.

5-(1-(1H-imidazol-1-yl)propyl)-2-phenylpyridine (52). Synthesized using compound 44a (275 mg, 1.29 mmol), CDI (1.05 g, 6.45 mmol) and NMP (10 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of ethyl acetate / methanol (9:1) as eluent. Beige solid. Yield: 114 mg, 34 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 0.76 (t, $J = 7.3$ Hz, 3H), 1.98 - 2.13 (m, 2H), 4.87 (t, $J = 7.7$ Hz, 1H), 6.75 (t, $J = 1.1$ Hz, 1H), 6.89 (s, 1H), 7.16 - 7.33 (m, 4H), 7.41 (s, 1H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.71 - 7.79 (m, 2H), 8.37 (d, $J = 2.2$ Hz, 1H); $^13$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 10.9, 28.4, 60.8, 117.4, 120.4, 126.8, 128.8, 129.2, 130.0, 134.1, 134.7, 136.3, 138.5, 148.0, 157.4; MS (ESI): $m/z = 264.37$ [M+H]+.

5-(1-(1H-imidazol-1-yl)-2-methylpropyl)-2-phenylpyridine (53). Synthesized using compound 43a (231 mg, 1.02 mmol), CDI (825 mg, 5.09 mmol) and NMP (10 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of ethyl acetate / methanol (9:1) as eluent. Beige solid. Yield: 71 mg, 25 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 0.93 - 1.02 (m, 6H), 2.59 - 2.66 (m, 1H), 4.72 (d, $J = 10.4$ Hz, 1H), 7.02 - 7.07 (m, 1H), 7.09 (s, 1H), 7.40 - 7.51 (m, 3H), 7.62 - 7.70 (m, 2H), 7.70 - 7.76 (m, 1H), 7.95 - 8.02 (m, 2H), 8.67 (d, $J = 2.2$ Hz, 1H); $^13$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 19.9, 20.2, 32.4, 66.6, 117.2, 120.5, 126.8, 128.8, 129.3, 130.0, 133.2, 135.3, 136.4, 138.5, 148.8, 157.4; MS (ESI): $m/z = 278.41$ [M+H]+.

6-(naphthalen-1-yl)nicotinaldehyde (54b). Synthesized using compound 43c (720 mg, 3.87 mmol) and 1-naphthalenboronic acid (1.00 g, 5.81 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl
acetic acid (8:1) as eluent. Orange solid. Yield: 733 mg, 81%. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) (ppm) = 7.50 - 7.62 (m, 3H), 7.65 - 7.69 (m, 1H), 7.77 - 7.81 (m, 1H), 7.92 - 8.00 (m, 2H), 8.10 - 8.14 (m, 1H), 8.31 (dd, \(J = 7.9, 2.2\) Hz, 1H), 9.25 (dd, \(J = 2.2, 0.9\) Hz, 1H), 10.22 (s, 1H); \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta \) (ppm) = 125.1, 125.2, 125.4, 126.2, 127.0, 128.0, 128.5, 129.7, 130.0, 130.7, 134.0, 136.1, 137.2, 152.1, 164.6, 190.5; MS (ESI): \(m/z = 234.29\) [M+H]⁺.

**Cyclopropyl(6-(naphthalen-1-yl)pyridin-3-yl)methanol (54a).** Synthesized using compound 54b (253 mg, 1.09 mmol) and cyclopropylmagnesium bromide (4.34 mL, 2.17 mmol, 0.5 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 239 mg, 80%. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) (ppm) = 0.39 - 0.54 (m, 2H), 0.60 - 0.72 (m, 2H), 1.22 - 1.29 (m, 1H), 4.04 - 4.14 (m, 1H), 7.42 - 7.60 (m, 5H), 7.86 - 7.92 (m, 3H), 8.04 - 8.08 (m, 1H), 8.77 (d, \(J = 2.2\) Hz, 1H); \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta \) (ppm) = 3.3, 3.9, 14.4, 60.6, 125.0, 125.5, 125.9, 126.1, 126.7, 127.7, 128.6, 129.1, 134.2, 137.8, 138.5, 147.8, 158.5, 171.4; MS (ESI): \(m/z = 276.34\) [M+H]⁺.

**5-(Cyclopropyl(1H-imidazol-1-yl)methyl)-2-(naphthalen-1-yl)pyridine (54).** Synthesized using compound 54a (210 mg, 0.76 mmol), CDI (619 mg, 3.82 mmol) and NMP (8 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using a mixture of ethyl acetate / methanol (9:1) as eluent. After flash chromatography the obtained solid was recrystallized in ethyl acetate / hexane (1:1). White solid. Yield: 38 mg, 15%. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) (ppm) = 0.54 - 0.66 (m, 2H), 0.86 - 0.98 (m, 2H), 1.61 - 1.68 (m, 1H), 4.54 (d, \(J = 9.5\) Hz, 1H), 7.06 (s, 1H), 7.17 (s, 1H), 7.46 - 7.64 (m, 6H), 7.78 (s, 1H), 7.89 - 7.97 (m, 2H), 8.06 - 8.12 (m, 1H), 8.75 (dd, \(J = 1.3, 0.6\) Hz, 1H); \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta \) (ppm) = 5.1, 5.2, 16.4, 64.0, 118.2, 125.0, 125.2, 125.4, 125.9, 126.6, 127.6, 128.4, 129.2, 129.9, 131.0, 133.9, 134.1, 134.5, 136.4, 137.7, 147.8, 159.3; (ESI): \(m/z = 325.96\) [M+H]⁺.

**1-(6-(naphthalen-1-yl)pyridin-3-yl)ethanol (55a).** Synthesized using compound 54b (231 mg, 0.99 mmol) and methylmagnesium bromide (1.98 mL, 1.98 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. White solid. Yield: 172 mg, 70%. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) (ppm) = 1.59 (d, \(J = 6.1\) Hz, 3H), 5.00 (m, 1H), 7.44 - 7.62 (m, 5H),
5-(1-(H-imidazol-1-yl)ethyl)-2-(naphthalen-1-yl)pyridine (55). Synthesized using compound 55a (147 mg, 0.59 mmol), CDI (478 mg, 2.95 mmol) and NMP (6 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. Beige solid. Yield: 59 mg, 33 %. $^1$H NMR (CDCl$_3$, 500 MHz): $^\delta$(ppm) = 1.97 (d, $J$ = 7.3 Hz, 3H), 5.50 (q, $J$ = 6.9 Hz, 1H), 7.02 - 7.06 (m, 1H), 7.16 (s, 1H), 7.45 - 7.63 (m, 6H), 7.69 (s, 1H), 7.92 (td, $J$ = 4.9, 2.5 Hz, 2H), 8.06 (dd, $J$ = 8.2, 0.9 Hz, 1H), 8.68 (d, $J$ = 2.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $^\delta$(ppm) = 22.1, 54.5, 117.9, 125.3, 125.5, 125.6, 126.2, 126.8, 127.8, 128.6, 129.4, 130.2, 131.2, 134.1, 134.5, 135.6, 136.2, 137.9, 147.6, 159.4; (ESI): m/z = 300.03 [M+H]$^+$.

6-(Thiophen-3-yl)nicotinaldehyde (56b). Synthesized using compound 43c (840 mg, 4.52 mmol) and thiophen-3-ylboronic acid (867 g, 6.77 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:2) as eluent. Orange solid. Yield: 556 mg, 65 %. $^1$H NMR (CDCl$_3$, 500 MHz): $^\delta$(ppm) = 7.45 (dd, $J$ = 5.0, 2.8 Hz, 1H), 7.72 - 7.80 (m, 2H), 8.11 (dd, $J$ = 2.8, 1.3 Hz, 1H), 8.19 (dd, $J$ = 8.2, 2.2 Hz, 1H), 9.06 (dd, $J$ = 2.2, 0.9 Hz, 1H), 10.11 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $^\delta$(ppm) = 120.3, 126.3, 126.4, 126.9, 129.6, 136.5, 141.1, 152.6, 158.0, 190.2; (ESI): m/z = 190.27 [M+H]$^+$.

1-(6-(Thiophen-3-yl)pyridin-3-yl)ethanol (56a). Synthesized using compound 56b (260 mg, 1.37 mmol) and methylmagnesium bromide (2.74 mL, 2.74 mmol, 1 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Yellow solid. Yield: 240 mg, 85 %. $^1$H NMR (CDCl$_3$, 500 MHz): $^\delta$(ppm) = 1.50 (d, $J$ = 6.6 Hz, 3H), 4.90 (q, $J$ = 6.3 Hz, 1H), 7.38 (dd, $J$ = 5.0, 2.8 Hz, 1H), 7.55 (d, $J$ = 8.2 Hz, 1H), 7.61 (dd, $J$ = 5.0, 1.3 Hz, 1H), 7.70 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.85 (dd, $J$ = 2.8, 1.3 Hz, 1H), 8.48 (d, $J$ = 2.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $^\delta$(ppm) = 25.2, 68.0, 120.4, 123.6, 126.4, 126.5, 134.3, 139.5, 142.0, 147.4, 152.9; (ESI): m/z = 206.29 [M+H]$^+$.
Cyclopropyl(6-(thiophen-3-yl)pyridin-3-yl)methanol (57a). Synthesized using compound 56b (270 mg, 1.43 mmol) and cyclopropylmagnesium bromide (5.72 ml, 2.86 mmol, 0.5 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Yellow solid. Yield: 138 mg, 42 %. 1H NMR (CDCl3, 500 MHz): δH(ppm) = 0.37 - 0.45 (m, 1H), 0.50 (dq, J = 9.7, 4.8 Hz, 1H), 0.57 - 0.71 (m, 2H), 1.18 - 1.29 (m, 1H), 2.48 (br. s., 1H), 4.06 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 5.0, 3.2 Hz, 1H), 7.60 (dd, J = 8.2, 0.6 Hz, 1H), 7.64 - 7.68 (m, 1H), 7.78 - 7.85 (m, 1H), 7.89 (dd, J = 3.0, 1.4 Hz, 1H), 8.60 - 8.64 (m, 1H); 13C NMR (CDCl3, 125 MHz): δC(ppm) = 2.8, 3.6, 19.1, 76.1, 120.0, 123.4, 126.2, 126.3, 134.5, 137.2, 141.9, 147.6, 152.8; (ESI): m/z = 232.26 [M+H]+.

5-(1-(1H-imidazol-1-yl)ethyl)-2-(thiophen-3-yl)pyridine (56). Synthesized using compound 56a (227 mg, 1.11 mmol), CDI (897.0 mg, 5.53 mmol) and NMP (8 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate / methanol (9:1) as eluent. Beige solid. Yield: 78 mg, 28 %. 1H NMR (CDCl3, 500 MHz): δH(ppm) = 1.75 (d, J = 6.9 Hz, 3H), 5.25 (q, J = 7.0 Hz, 1H), 6.79 (t, J = 1.3 Hz, 1H), 6.96 (t, J = 0.9 Hz, 1H), 7.21 - 7.28 (m, 2H), 7.40 - 7.52 (m, 3H), 7.74 (dd, J = 2.8, 1.3 Hz, 1H), 8.34 (d, J = 2.5 Hz, 1H); 13C NMR (CDCl3, 125 MHz): δC(ppm) = 21.7, 54.2, 117.6, 120.2, 123.9, 126.1, 126.5, 129.9, 134.3, 134.9, 135.9, 141.4, 147.5, 153.5; (ESI): m/z = 256.08 [M+H]+.

5-(Cyclopropyl(1H-imidazol-1-yl)methyl)-2-(thiophen-3-yl)pyridine (57). Synthesized using compound 57a (116 mg, 0.50 mmol), CDI (407 mg, 2.51 mmol) and NMP (5 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. Beige solid. Yield: 70 mg, 50 %. 1H NMR (CDCl3, 500 MHz): δH(ppm) = 0.49 - 0.60 (m, 2H), 0.83 - 0.91 (m, 2H), 1.53 - 1.64 (m, 1H), 4.47 (d, J = 9.5 Hz, 1H), 6.97 (t, J = 1.3 Hz, 1H), 7.12 (t, J = 1.1 Hz, 1H), 7.39 - 7.46 (m, 2H), 7.59 - 7.63 (m, 1H), 7.64 - 7.68 (m, 1H), 7.72 (s, 1H), 7.91 (dd, J = 3.2, 1.3 Hz, 1H), 8.56 (dd, J = 1.6, 0.6 Hz, 1H); 13C NMR (CDCl3, 125 MHz): δC(ppm) = 4.9, 5.2, 16.2, 63.8, 118.2, 120.2, 123.9, 126.1, 126.5, 129.8, 133.7, 134.9, 136.4, 141.4, 148.0, 153.5; (ESI): m/z =282.30 [M+H]+.

Phenyl(6-phenylpyridin-3-yl)methanol (58a). Synthesized using compound 43b (300 mg, 1.73 mmol) and phenylmagnesium bromide (1.73 ml, 3.46 mmol, 2 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture
of hexane / ethyl acetate (3:1) as eluent. Yellow solid. Yield: 138 mg, 42 %. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta_H\) (ppm) = 5.91 (s, 1H), 7.29 - 7.34 (m, 1H), 7.35 - 7.50 (m, 7H), 7.68 (dd, \(J = 8.2, 0.6\) Hz, 1H), 7.73 - 7.78 (m, 1H), 7.94 - 7.99 (m, 2H), 8.68 (dd, \(J = 1.6, 0.6\) Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta_C\) (ppm) = 74.1, 120.3, 126.5, 126.9, 128.0, 128.7, 128.7, 128.9, 135.0, 137.6, 139.0, 143.0, 148.2, 156.7; (ESI): \(m/z = 261.97\) [M+H]\textsuperscript{+}.

**5-((1-H-imidazol-1-yl)(phenyl)methyl)-2-phenylpyridine (58).** Synthesized using compound 58a (299 mg, 1.14 mmol), CDI (928 mg, 5.72 mmol) and NMP (8 mL) according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. Beige solid. Yield: 75 mg, 21 %. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta_H\) (ppm) = 6.58 (s, 1H), 6.87 - 6.91 (m, 1H), 7.11 - 7.19 (m, 3H), 7.34 - 7.54 (m, 8H), 7.73 (d, \(J = 8.2\) Hz, 1H), 7.98 - 8.04 (m, 2H), 8.49 (d, \(J = 2.5\) Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta_C\) (ppm) = 62.6, 119.0, 120.2, 126.8, 127.8, 128.7, 128.8, 129.0, 129.3, 129.8, 133.1, 136.1, 137.2, 138.0, 138.3, 149.2, 157.4; (ESI): \(m/z = 312.01\) [M+H]\textsuperscript{+}.

**Methyl 6-phenylnicotinate (59a).** To a solution of 43b (350 mg, 1.91 mmol) in acetonitrile (20 mL) were added NIS (1.29 g, 5.73 mmol), K\textsubscript{2}C\textsubscript{2}O\textsubscript{4} (787 mg, 5.73 mmol) and CH\textsubscript{3}OH (0.39 mL, 9.55 mmol). After stirring the reaction mixture for 15 h aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (1 g Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} in 10 mL water) was added. The resultant mixture was extracted with a solution of 50 % ether in hexane (4x 20 mL). The combined organic phases were washed with brine and solvent was removed under vacuum. The crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (6:1) as eluent. White solid. Yield: 297 mg, 73 %. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta_H\) (ppm) = 3.75 (s, 3H), 7.22 - 7.30 (m, 3H), 7.59 (dd, \(J = 8.5, 0.9\) Hz, 1H), 7.82 - 7.86 (m, 2H), 8.12 (dd, \(J = 8.5, 2.2\) Hz, 1H), 9.06 (dd, \(J = 2.2, 0.9\) Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta_C\) (ppm) = 52.3, 119.8, 124.2, 127.3, 128.9, 129.9, 137.8, 138.3, 150.9, 160.9, 165.9; (ESI): \(m/z = 214.02\) [M+H]\textsuperscript{+}.

**2-(6-Phenylpyridin-3-yl)propan-2-ol (59).** Synthesized using compound 59a (240 mg, 1.13 mmol) and methylmagnesium bromide (3.38 mL, 3.38 mmol, 1 M in THF) according to Method D. Purification by flash chromatography was not necessary. White solid. Yield: 193 mg, 80 %. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta_H\) (ppm) = 1.65 (s, 6H), 7.39 - 7.45 (m, 1H), 7.45 - 7.51 (m, 2H), 7.70 (dd, \(J = 8.2, 0.9\) Hz, 1H), 7.89 (dd, \(J = 8.2, 2.5\) Hz, 1H), 7.97 - 8.02 (m,
2H), 8.81 (dd, J = 2.5, 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{c}$ (ppm) = 31.7, 71.4, 119.9, 126.8, 128.7, 128.8, 133.2, 139.1, 142.5, 146.4, 155.9; (ESI): m/z = 214.08 [M+H]$^+$.  

**Furan-2-yl(6- phenylpyridin-3-yl)methanol (60a).** Synthesized using compound 43b (650 mg, 3.75 mmol) and furan-2-ylmagnesium bromide (1.85 g, 10.8 mmol, 2 M in THF) according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (6:1) as eluent. Yellow solid. Yield: 631 mg, 67 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{h}$ (ppm) = 3.62 (br. s., 1H), 5.86 (s, 1H), 6.17 (d, J = 3.4 Hz, 1H), 6.33 (dd, J = 3.0, 1.8 Hz, 1H), 7.33 - 7.51 (m, 4H), 7.69 (d, J = 7.9 Hz, 1H), 7.83 (dd, J = 8.2, 1.8 Hz, 1H), 7.88 - 7.99 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{c}$ (ppm) = 66.7, 106.7, 109.3, 119.4, 126.0, 127.7, 128.0, 134.0, 134.3, 137.9, 141.8, 147.1, 154.1 , 156.1 ; (ESI): m/z = 251.87 [M+H]$^+$.  

$^{5}$-(Furan-2-yl(1 H-imidazol-1-yl)methyl)-2-phenylpyridine (60). Synthesized using compound 60a (631 mg, 2.51 mmol), CDI (2.04 g, 12.56 mmol) and NMP (4 ml) according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate / methanol (9:1) as eluent. Brown Oil. Yield: 276 mg, 37 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{h}$ (ppm) = 6.25 - 6.29 (m, 1H), 6.42 (dd, J = 3.5, 1.9 Hz, 1H), 6.55 (s, 1H), 6.95 (t, J = 1.3 Hz, 1H), 7.14 (t, J = 1.1 Hz, 1H), 7.42 - 7.57 (m, 6H), 7.75 (dd, J = 8.5, 0.6 Hz, 1H), 7.97 - 8.04 (m, 2H), 8.54 (dt, J = 1.6, 0.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{c}$ (ppm) = 56.6, 110.7, 110.8, 118.6, 120.4, 126.9, 128.8, 129.4, 129.9, 131.6, 135.4, 136.8, 138.4, 143.9, 148.4, 150.1, 157.8; (ESI): m/z = 301.96 [M+H]$^+$.  

5-Methyl-2-phenylpyrididine (61b). Synthesized using 2-bromo-5-methyl-pyridine (2.92 g, 16.95 mmol) and phenylboronic acid (3.09 g, 25.4 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:1) as eluent. White solid. Yield: 1.99 g, 70 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{h}$ (ppm) = 2.38 (s, 3H), 7.37 - 7.43 (m, 1H), 7.44 - 7.51 (m, 2H), 7.54 - 7.60 (m, 1H), 7.60 - 7.67 (m, 1H), 7.95 - 8.00 (m, 2H), 8.51 - 8.55 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_{c}$ (ppm) = 18.1, 120.0, 126.7, 128.6, 128.7, 131.5, 137.3, 139.4, 150.1, 154.8; (ESI): m/z = 169.97 [M+H]$^+$.  

70
5-(Bromomethyl)-2-phenylpyridine (61a). Synthesized using compound 61b (760 mg, 4.49 mmol), NBS (878 mg, 4.93 mmol) and DBPO (54 mg, 0.23 mmol) in carbon tetrachloride according to Method A. Crude product was purified by flash chromatography on silica-gel using hexane / ethyl acetate (8:1) as eluent. White solid. Yield: 297 mg, 73 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$$_H$ (ppm) = 4.54 (s, 2H), 7.42 - 7.53 (m, 3H), 7.71 - 7.77 (m, 1H), 7.80 - 7.85 (m, 1H), 7.98 - 8.04 (m, 2H), 8.72 - 8.76 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$$_C$ (ppm) = 29.7, 120.6, 127.0, 128.4, 128.8, 130.1, 137.6, 138.5, 149.6, 157.36; (ESI): $m/z$ = 246.98 [M+H]$^+$. 

2-Phenyl-5-(pyridin-3-ylmethyl)pyridine (61). Synthesized using compound 61a (355 mg, 1.43 mmol) and 4-pyridineboronic acid (264 mg, 2.15 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. Beige solid. Yield: 140 mg, 40 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$$_H$ (ppm) = 3.77 (s, 2H), 6.88 - 6.93 (m, 2H), 7.15 - 7.21 (m, 1H), 7.21 - 7.31 (m, 3H), 7.45 (dd, $J$ = 8.2, 0.9 Hz, 1H), 7.72 - 7.78 (m, 2H), 8.28 - 8.33 (m, 2H), 8.33 - 8.37 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$$_C$ (ppm) = 38.0, 120.3, 124.0, 126.7, 128.7, 128.9, 132.7, 137.1, 138.9, 148.7, 149.9, 150.0, 156.0; (ESI): $m/z$ = 246.85 [M+H]$^+$. 

2-Phenyl-5-(pyridin-3-ylmethyl)pyridine (62). Synthesized using compound 61a (100 mg, 0.40 mmol) and 3-pyridineboronic acid (74 mg, 0.61 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. Beige solid. Yield: 32 mg, 32 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$$_H$ (ppm) = 3.80 (s, 2H), 6.99 - 7.06 (m, 1H), 7.15 - 7.20 (m, 1H), 7.21 - 7.35 (m, 4H), 7.45 (d, $J$ = 8.2 Hz, 1H), 7.72 - 7.77 (m, 2H), 8.28 (dd, $J$ = 4.7, 1.3 Hz, 1H), 8.36 (d, $J$ = 1.9 Hz, 1H), 8.33 (d, $J$ = 1.9 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$$_C$ (ppm) = 35.9, 120.4, 123.6, 126.8, 128.7, 128.9, 133.6, 135.4, 136.2, 137.0, 139.0, 148.1, 149.9, 150.1, 155.9; (ESI): $m/z$ = 246.98 [M+H]$^+$. 

71
4-((6-Phenylpyridin-3-yl)methyl)isoquinoline (63). Synthesized using compound 61a (109 mg, 0.44 mmol) and isoquinolin-4-ylboronic acid (114 mg, 0.66 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$ solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. Beige solid. Yield: 20 mg, 19 %. $^1$H NMR (CDCl$_3$, 500 MHz): δ$_H$ (ppm) = 4.43 (s, 2H), 7.37 - 7.54 (m, 4H), 7.59 - 7.65 (m, 2H), 7.65 - 7.75 (m, 1H), 7.89 - 8.07 (m, 4H), 8.48 (s, 1H), 8.65 - 8.70 (m, 1H), 9.23 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ$_C$ (ppm) = 33.2, 120.3, 123.1, 126.7, 127.2, 128.4, 128.6, 128.8, 128.9, 130.7, 133.6, 134.6, 136.7, 139.0, 143.7, 149.7, 152.3, 155.7; (ESI): m/z = 296.95 [M+H]$^+$.  

5-Methyl-2-phenylpyrimidine (64b). To a solution of benzamidine hydrochloride (500 mg, 3.19 mmol) and 3-ethoxy-2-methylacrylaldehyde (400 mg, 3.51 mmol) in Methanol (10 mL) was added a NaOMe-solution (30 percent in methanol) dropwise under stirring over 30 minutes. After stirring for 4 hours water (20 mL) was added and mixture was stirred for further 30 minutes at room temperature. After filtration the obtained precipitate was washed with water and dried. White solid. Yield: 220 mg, 41 %. $^1$H NMR (CDCl$_3$, 500 MHz): δ$_H$ (ppm) = 2.34 (s, 3H), 7.44 - 7.54 (m, 3H), 8.37 - 8.45 (m, 2H), 8.64 (d, J = 0.6 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ$_C$ (ppm) = 15.7, 128.1, 128.5, 128.8, 130.6, 137.9, 157.6, 162.7; (ESI): m/z = 170.97 [M+H]$^+$.  

5-(Bromomethyl)-2-phenylpyrimidine (64a). Synthesized using compound 64b (205 mg, 1.20 mmol), NBS (236 mg, 1.32 mmol) and DBPO (14.6 mg, 0.06 mmol) in carbon tetrachloride according to Method A. Crude product was purified by flash chromatography on silica-gel using hexane / ethyl acetate (10:1) as eluent. Product was used directly in the next step without further characterization. White solid. Yield: 89 mg, 30 %. (ESI): m/z = 250.68 [M+H]$^+$.  

5-((1 $H$-imidazol-1-yl)methyl-2-phenylpyrimidine (64). Synthesized using compound 64a (70 mg, 0.28 mmol), imidazole (76 mg, 1.12 mmol) and K$_2$CO$_3$ (195 mg, 1.41 mmol) in acetonitrile according to Method B. Crude product was purified by flash chromatography on
silica-gel using ethyl acetate as eluent. After flash chromatography the product was recrystallized in ethyl acetate. Light yellow solid. Yield: 62 mg, 94 %. $^1$H NMR (CDCl$_3$, 500 MHz): \( \delta_H \) (ppm) = 5.17 (s, 2H), 6.94 (t, \( J = 1.3 \text{ Hz}, 1H \)), 7.15 (t, \( J = 1.1 \text{ Hz}, 1H \)), 7.47 - 7.54 (m, 3H), 7.61 (s, 1H), 8.41 - 8.46 (m, 2H), 8.63 (s, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): \( \delta_C \) (ppm) = 46.0, 118.8, 127.0, 128.2, 128.7, 130.7, 131.1, 136.8, 137.2, 156.2, 164.8; (ESI): \( m/z = 236.91 \) [M+H]$^+$.

**3-Methyl-6-Phenylpyridazine (65b).** Synthesized using 3-chloro-6-methylpyridazine (1.00 g, 7.78 mmol) and phenylboronic acid (1.42 g, 11.67 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. White solid. Yield: 1.00 g, 76 %. $^1$H NMR (CDCl$_3$, 500 MHz): \( \delta_H \) (ppm) = 2.76 (s, 3H), 7.39 (d, \( J = 8.5 \text{ Hz}, 1H \)), 7.46 - 7.55 (m, 3H), 7.76 (d, \( J = 8.5 \text{ Hz}, 1H \)), 8.03 - 8.09 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): \( \delta_C \) (ppm) = 22.0, 123.9, 126.9, 127.2, 128.9, 129.7, 134.4, 136.4, 157.2, 158.5; (ESI): \( m/z = 170.96 \) [M+H]$^+$. 

**3-(Bromomethyl)-6-phenylpyridazine (65a).** Synthesized using compound 65b (982 mg, 5.77 mmol), NBS (1.13 g, 6.35 mmol) and DBPO (70 mg, 0.29 mmol) in carbon tetrachloride according to Method A. Crude product was purified by flash chromatography on silica-gel using hexane / ethyl acetate (4:1) as eluent. Product was used directly in the next step without further characterization. Orange solid. Yield: 53 mg, 4 %. (ESI): \( m/z = 250.67 \) [M+H]$^+$. 

**3-(1H-imidazol-1-yl)methyl)-6-phenylpyridazine (65).** Synthesized using compound 65a (40 mg, 0.16 mmol), imidazole (44 mg, 0.64 mmol) and K$_2$CO$_3$ (111 mg, 0.80 mmol) in acetonitrile according to Method B. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. After flash chromatography the solid was washed with ethyl acetate. Light orange solid. Yield: 22 mg, 58 %. $^1$H NMR (CDCl$_3$, 500 MHz): \( \delta_H \) (ppm) = 5.58 (s, 2H), 7.08 (s, 1H), 7.17 - 7.26 (m, 2H), 7.55 - 7.61 (m, 3H), 7.72 (s, 1H), 7.88 (d, \( J = 8.8 \text{ Hz}, 1H \)), 8.09 - 8.14 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): \( \delta_C \) (ppm) = 50.9, 119.6, 125.1, 125.5, 127.4, 129.4, 130.7, 130.8, 135.8, 137.8, 157.2, 159.3; (ESI): \( m/z = 236.91 \) [M+H]$^+$. 
5-((6-Phenylpyridin-3-yl)methyl)pyrimidine (66). Synthesized using compound 61a (219 mg, 0.88 mmol) and pyrimidine-5-boronic acid (164 mg, 1.32 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. White solid. Yield: 43 mg, 20 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm) = 4.02 (s, 2H), 7.39 - 7.44 (m, 1H), 7.44 - 7.56 (m, 3H), 7.70 (dd, $J$ = 8.2, 0.9 Hz, 1H), 7.95 - 8.00 (m, 2H), 8.58 - 8.67 (m, 3 H), 9.13 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 33.4, 120.5, 126.8, 128.8, 129.1, 132.2, 133.3, 136.9, 138.7, 149.7, 156.4, 156.9, 157.3; (ESI): m/z = 247.83 [M+H]$^+$. 

2-Phenyl-5-(pyridin-4-ylmethyl)pyrimidine (67). Synthesized using compound 64a (102 mg, 0.41 mmol) and 4-pyridineboronic acid (76 mg, 0.61 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:2) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. White solid. Yield: 57 mg, 56 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm) = 3.98 (s, 2H), 7.10 - 7.16 (m, 2H), 7.46 - 7.53 (m, 3H), 8.41 - 8.46 (m, 2H), 8.54 - 8.60 (m, 2H), 8.64 (s, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 35.6, 123.8, 128.0, 128.5, 128.6, 129.6, 130.7, 137.1, 147.5, 150.2, 157.4, 163.4; (ESI): m/z = 247.80 [M+H]$^+$. 

2-Phenyl-5-(pyrimidin-5-ylmethyl)pyrimidine (68). Synthesized using compound 64a (102 mg, 0.41 mmol) and pyrimidine-5-boronic acid (76 mg, 0.61 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:2) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. White solid. Yield: 41 mg, 40 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_{H}$ (ppm) = 4.00 (s, 2H), 7.46 - 7.55 (m, 3H), 8.39 - 8.47 (m, 2H), 8.63 - 8.71 (m, 4H), 9.15 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 31.1, 128.1, 128.6, 129.1, 130.9, 132.2, 137.0, 156.9, 157.2, 157.6, 163.7; (ESI): m/z = 248.83 [M+H]$^+$. 

74
2-Phenyl-5-(pyridin-3-ylmethyl)pyrimidine (69). Synthesized using compound 64a (100 mg, 0.41 mmol) and pyridine-3-boronic acid (74 mg, 0.60 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:2) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na₂CO₃ solution (2M). After extraction with ethyl acetate and drying over MgSO₄ the solvent was removed under vacuum. Light orange solid. Yield: 72 mg, 71 %. ¹H NMR (CDCl₃, 500 MHz):  δ_H (ppm) = 3.76 (s, 2H), 7.00 - 7.05 (m, 1H), 7.23 - 7.29 (m, 4H), 8.16 - 8.22 (m, 2H), 8.27 - 8.36 (m, 2H), 8.40 - 8.43 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz):  δ_C (ppm) = 33.5, 123.7, 128.0, 128.6, 130.5, 130.7, 134.2, 136.1, 137.2, 148.4, 150.0, 157.3, 163.3; (ESI): m/z = 247.92 [M+H]^+.

4-((2-Phenylpyrimidin-5-yl)methyl)isoquinoline (70). Synthesized using compound 64a (85 mg, 0.34 mmol) and isoquinolin-4-ylboronic acid (104 mg, 0.60 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na₂CO₃ solution (2M). After extraction with ethyl acetate and drying over MgSO₄ the solvent was removed under vacuum. Orange solid. Yield: 68 mg, 67 %. ¹H NMR (CDCl₃, 500 MHz):  δ_H (ppm) = 4.40 (s, 2H), 7.44 - 7.51 (m, 3H), 7.61 - 7.67 (m, 1H), 7.67 - 7.74 (m, 1H), 7.87 (dd, J = 8.4, 0.8 Hz, 1H), 8.02 - 8.06 (m, 1H), 8.37 - 8.42 (m, 2H), 8.49 (s, 1H), 8.66 (s, 2H), 9.24 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz):  δ_C (ppm) = 30.9, 122.8, 127.4, 127.5, 127.9, 128.6, 128.6, 128.6, 130.4, 130.6, 131.0, 134.3, 137.2, 143.6, 152.7, 157.0, 163.1; (ESI): m/z = 297.91 [M+H]^+.

2-Methyl-5-phenylpyrazine (71b). To a stirred solution of propylenediamine (2.94 g, 0.04 mol) in ethanol was added phenylglyoxal-monohydrate (5.00 g, 0.03 mol) at 0°C within 30 minutes. After stirring for 1.5 hours at room temperature KOH (2.10 g, 0.04 mol) was added and the reaction mixture was refluxed for 12 hours. Then the solvent was removed under vacuum and the residue was extracted with ether. The organic phases were washed with brine and dried over MgSO₄. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (7:3→3:7) as eluent. After flash chromatography the product was recrystallized from hexane. White solid. Yield: 780 mg, 15 %. ¹H NMR
2-(Bromomethyl)-5-phenylpyrazine (71a). Synthesized using compound 71b (724 mg, 4.25 mmol), NBS (832 mg, 4.68 mmol) and DBPO (52 mg, 0.21 mmol) in carbon tetrachloride according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Product was used directly in the next step without further characterization. Yellow solid. Yield: 571 mg, 54 %. (ESI): m/z = 250.80 [M+H]+.

2-((1 H-imidazol-1-yl)methyl)-5-phenylpyrazine (71). Synthesized using compound 71a (100 mg, 0.40 mmol), imidazole (109 mg, 1.60 mmol) and K₂C₃O₃ (276 mg, 2.00 mmol) in DMF according to Method B. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. Light yellow solid. Yield: 69 mg, 73 %. ^1H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 5.50 (s, 2H), 7.24 (t, J = 1.3 Hz, 1H), 7.33 (t, J = 1.1 Hz, 1H), 7.64 - 7.74 (m, 3H), 7.86 (s, 1H), 8.17 - 8.23 (m, 2H), 8.63 (d, J = 1.3 Hz, 1H), 9.18 (d, J = 1.6 Hz, 1H); ^13C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 50.0, 119.2, 126.9, 129.1, 130.2, 130.3, 135.7, 137.5, 141.5, 142.3, 152.3; (ESI): m/z = 236.91 [M+H]+.

5-((4-Methylpyridin-3-yl)methyl)-2-phenylpyridine (72). Synthesized using compound 61a (100 mg, 0.40 mmol) and 4-methylpyridine-3-boronic acid (83 mg, 0.61 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na₂CO₃ solution (2M). After extraction with ethyl acetate and drying over MgSO₄ the solvent was removed under vacuum. Light yellow solid. Yield: 54 mg, 52 %. ^1H NMR (CDCl₃, 500 MHz): δ_H (ppm) = 2.22 - 2.29 (m, 3H), 4.02 (s, 2H), 7.11 (d, J = 5.0 Hz, 1H), 7.37 - 7.51 (m, 4H), 7.64 (dd, J = 8.2, 0.6 Hz, 1H), 7.95 - 8.01 (m, 2H), 8.38 - 8.46 (m, 2H), 8.52 - 8.57 (m, 1H); ^13C NMR (CDCl₃, 125 MHz): δ_C (ppm) = 19.3, 33.8, 120.5, 125.7, 126.9, 129.0, 129.1, 133.2, 133.8, 136.8, 139.2, 146.1, 148.7, 149.9, 150.7, 155.9; (ESI): m/z = 260.85 [M+H]+.
5-((5-Methylpyridin-3-yl)methyl)-2-phenylpyridine (73). Synthesized using compound 61a (70 mg, 0.28 mmol) and 5-methylpyridine-3-boronic acid (58 mg, 0.42 mmol) according to Method C. Crude product was purified by flash chromatography on silica-gel ethyl acetate as eluent. After flash chromatography the product was solved in ethyl acetate and a few drops of cone. HCl and water were added. After stirring for 30 minutes the phases were separated and water phase was neutralized with aqueous Na$_2$CO$_3$-solution (2M). After extraction with ethyl acetate and drying over MgSO$_4$ the solvent was removed under vacuum. Light yellow solid. Yield: 56 mg, 77 %. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta_H$ (ppm) = 2.30 (d, $J = 0.6$ Hz, 3H), 3.98 (s, 2H), 7.28 - 7.32 (m, 1H), 7.38 - 7.44 (m, 1H), 7.44 - 7.55 (m, 3H), 7.67 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.96 - 8.01 (m, 2H), 8.36 (d, $J = 1.6$ Hz, 1H), 8.33 (d, $J = 1.6$ Hz, 1H), 8.58 (dd, $J = 1.6$, 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta_C$ (ppm) = 18.3, 35.7, 120.4, 126.7, 128.7, 128.9, 133.1, 133.8, 134.8, 136.8, 137.0, 139.0, 147.2, 148.6, 149.8, 155.8; (ESI): $m/z = 260.84 \ [M+H]^+$. 

+++
Claims

1. A compound of formula (1):

   \[
   \begin{array}{c}
   (R^1)_m \underbrace{A}_{(Q)_x} (R^2)_y \\
   \text{Het}
   \end{array}
   \]

   wherein,

   \text{Het is heteroarylium, heterocycl, heteroaralkyl, heteroareylene, heterocyclylene or an heteroaryl selected from 5-imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;}

   more preferably \text{Het is 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoaxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;}

   Het can be unsubstituted or is substituted further with \(R^3\), Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with \(R^3\) wherein where multiple substitution with \(R^3\) is possible, the substituents can be independently selected from \(R^3\),

   \(R^1\) or \(R^2\) can be independently \(H, C_1-C_{12}\) alkyl, haloalkyl, \(C_1-C_5\) alkoxy, hydroxy, \(C_6-C_{13}\) aryl, napthyl, benzo[b]thiophen, thiophen, amino, amido, C(0)R, OC(0)R, ester, ether, S02R, furanyl, het, halogen, trityl, CN, N02 or OAc; either of which is unsubstituted or can be independently substituted further with \(R^3\) wherein where multiple substitution with \(R^3\) is possible, the substituents can be independently selected from \(R^3\),

   \(R^3\) is \(C_1-C_{12}\) alkyl, haloalkyl, CrC5 alkoxy, hydroxy, \(C_6-C_{13}\) aryl, halogen, amino, amido, ester, ether, C(0)R, OC(0)R, S02R, S02NHR, trityl, CN, N02 or OAc,

   \(R^4\) is \(H, OH, C_1-C_5\) alkoxy, alkyl or aryl,
A is one or more heteroatoms independently selected from N, O or Se wherein when A is N, preferably heterocycles are pyridine, pyrimidine or pyridazine; which can be further annelated by 5- or 6- membered rings

m is selected from 0 - 3 carbons, preferably 1,

n is 0 - 6,

Q is C, O, S, CH=CH, N, CO, C0₂, CONH, S0₂, S0₂NH,

X is 1 - 3,

Y is 0 - 2,

Z is 1 - 2; if z > 1, multi-Q can be any linker described above,

or a pharmaceutically acceptable derivative.

2. A compound of formula (2"):

\[
\begin{array}{c}
\text{het} \\
R^5 \rightarrow R^6 \\
\end{array}
\]

\[
(2")
\]

wherein,

R² can be C₁₋C₁₂ alkyl, haloalkyl, C₁₋C₅ alkoxy, hydroxy, C₆₋C₁₃ aryl, napthyl, benzo[b]thiophen, thiophen, amino, amido, C(0)R², OC(0)R², ester, ether, S₀₂R², furanyl, het, halogen, trityl, CN, N₀₂ or OAc; which is unsubstituted or can be substituted further with R³ wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³,

R² can be H, C₁₋C₁₂ alkyl, haloalkyl, C₁₋C₅ alkoxy, hydroxy, C₆₋C₁₃ aryl, napthyl, benzo[b]thiophen, thiophen, amino, amido, C(0)R², OC(0)R², ester, ether, S₀₂R², furanyl, het, halogen, trityl, CN, N₀₂ or OAc; which is unsubstituted or can be substituted further with
R\(^3\) wherein where multiple substitution with R\(^3\) is possible, the substituents can be independently selected from R\(^3\),

R\(^3\) is C\(_1\)-C\(_{12}\) alkyl, haloalkyl, CrC\(_5\) alkoxy, hydroxy, C\(_6\)-C\(_{13}\) aryl, halogen, amino, amido, ester, ether, C(0)R\(^4\), OC(0)R\(^4\), S\(_2\)O\(_2\)R\(^4\), S\(_2\)O\(_2\)NHR\(^4\), CN, N\(_2\)O or OAc,

R\(^4\) is H, OH, C\(_1\)-C\(_5\) alkoxy, alkyl or aryl,

R\(^5\) is H, C\(_1\)-C\(_{12}\) alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, C\(_6\)-C\(_{13}\) aryl, naphthyl, C\(_1\)-C\(_5\) alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, N\(_2\)O, OAc, amino, amido, C(0)R\(^4\), OC(0)R\(^4\), trityl or Het; which may be unsubstituted or substituted further with R\(^3\) wherein where multiple substitution with R\(^3\) is possible, the substituents can be independently selected from R\(^3\),

Het is heteroaryl, heteroarylmethylen, heterocyclyl, heteroaralkyl, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzoisothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isquinolinol, 8-quinoxalinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with R\(^3\) Het can also be further annelated by 5- or 6-membered rings, which can also be substituted with R\(^3\) wherein where multiple substitution with R\(^3\) is possible, the substituents can be independently selected from R\(^3\),

R\(^6\) is H, C\(_1\)-C\(_{12}\) alkyl, haloalkyl, cycloalkyl, C\(_1\)-C\(_5\) alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, C\(_6\)-C\(_{13}\) aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, N\(_2\)O, OAc, amino, amido, C(0)R\(^4\), OC(0)R\(^4\), trityl or het; which may be unsubstituted or substituted further with R\(^3\) (wherein where multiple substitution with R\(^3\) is possible, the substituents can be independently selected from R\(^3\)),

R\(^7\) is H, Halogen, C\(_1\)-C\(_{12}\) alkyl, haloalkyl, cycloalkyl, C\(_2\)-C\(_{12}\) alkenyl, cycloalkylene, alkynyl, C\(_6\)-C\(_{13}\) aryl, C\(_1\)-C\(_5\) alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, N\(_2\)O, OAc, amino, amido, C(0)R\(^4\), OC(0)R\(^4\), trityl or het; which may be unsubstituted or
substituted further with $R^3$, wherein where multiple substitution with $R^3$ is possible, the substituents can be independently selected from $R^3$,

or a pharmaceutically acceptable derivative

3. A compound of formula (2):

$$\begin{array}{c}
\text{Het} \\
\text{R}^5 \\
\text{R}^6 \\
\text{R}^7 \\
\text{R}^8 \\
\text{R}^9 \\
\text{R}^{10}
\end{array}$$

(2)

wherein,

$R^3$ is C1-C12 alkyl, haloalkyl, C1-C5 alkoxy, hydroxy, C6-C13 aryl, halogen, amino, amido, ester, ether, C(0)R 4 , OC(0)R 4 , S0 2 R 4 , S0 2 NHR 4 , CN, N0 2 or OAc,

$R^4$ is H, OH, C1-C5 alkoxy, alkyl or aryl,

$R^5$ is H, C1-C12 alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, C6-C13 aryl, naphthyl, C1-C5 alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, N0 2 , OAc, amino, amido, C(0)R 4 , OC(0)R 4 , trityl or Het; which may be unsubstituted or substituted further with $R^3$ wherein where multiple substitution with $R^3$ is possible, the substituents can be independently selected from $R^3$,

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyli, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzo[iso]xazolyl, 4-benzo[iso]thiazolyl, 4-benzo[iso]azolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,
Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6-membered rings, which can also be substituted with R³ wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³.

R⁶ is H, C₁₋₁₂ alkyl, haloalkyl, cycloalkyl, C₁₋₅ alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO₂, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl; which may be unsubstituted or substituted further with R³, wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³.

R⁷ is H, Halogen, C₁₋₁₂ alkyl, haloalkyl, cycloalkyl, C₂₋₁₂ alkenyl, cycloalkylene, alkynyl, C₆₋₁₃ aryl, C₁₋₅ alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, NO₂, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl or het; which may be unsubstituted or substituted further with R³, wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³.

or a pharmaceutically acceptable derivative

provided that the compound of formula (2) is not one of the following compounds
4. An imidazol-1-ylmethyl-pyridine compound of formula (3):

\[
\begin{align*}
R^6 & \quad R^7 & \quad R^8 \\
\text{Het} & \quad \text{Het} & \quad \text{Het}
\end{align*}
\]

wherein,

\( R^3 \) is C1-C12 alkyl, haloalkyl, CrC₅ alkoxy, hydroxy, C₆-C₁₃ aryl, halogen, amino, amido, ester, ether, C(0)R⁴, OC(0)R⁴, S₀₂R⁴, S₀₂NHR⁴, CN, N₀₂ or OAc,

\( R^4 \) is H, OH, C₁-C₅ alkoxy, alkyl or aryl,

\( R^5 \) is H, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, C₆-C₁₃ aryl, naphthyl, C₁-C₅ alkoxy, hydroxy, halogen, furanyl, benzothiophen, thiophen, CN, N₀₂, OAc, amino, amido, C(0)R⁴, OC(0)R⁴, trityl or Het; which may be unsubstituted or substituted further with \( R^3 \) wherein where multiple substitution with \( R^3 \) is possible, the substituents can be independently selected from \( R^3 \),

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazoliny, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxy-pyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzooxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl,
Het can be unsubstituted or is substituted further with R^3 Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R^3, wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3,

R^6 is H, C1-C12 alkyl, haloalkyl, cycloalkyl, C1-C_5 alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, N0_2, OAc, amino, amido, C(0)R^4, OC(0)R^4, trityl or ; which may be unsubstituted or substituted further with R^3, wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3,

R^7 is H, Halogen, C1-C12 alkyl, haloalkyl, cycloalkyl, C2-C12 alkenyl, cycloalkylene, alkynyl, C_6-C_13 aryl, C1-C_5 alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, N0_2, OAc, amino, amido, C(0)R^4, OC(0)R^4, trityl or het; which may be unsubstituted or substituted further with R^3 wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3,

or a pharmaceutically acceptable derivative

provided that the compound of formula (3) is not one of the following compounds
5. A compound selected from:

- [Chemical structure 1]
- [Chemical structure 2]
- [Chemical structure 3]
- [Chemical structure 4]
- [Chemical structure 5]
6. The compound according to any one of claims 3 to 4, wherein the compound is 5-imidazol-1-ylmethyl-2-naphthalen-1-yl-pyridine, 2-Furan-3-yl-5-imidazol-1-ylmethyl-pyridine, 2,3-Di-furan-2-yl-5-imidazol-1-ylmethyl-pyridine, 2-Benzo[b]thiophen-3-yl-5-imidazol-1-ylmethyl-pyridine, 2-(2-Fluoro-phenyl)-5-imidazol-1-ylmethyl-pyridine, 2-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-phenylamine, 5-(5-Imidazol-1-ylmethyl-pyridin-2-yl)-thiophene-2-carbaldehyde, 5-imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 5-imidazol-1-ylmethyl-2-thiophen-2-yl-pyridine, 2-Bromo-3-imidazol-1-ylmethyl-pyridine or 2-Fluoro-4-(5-imidazol-1-ylmethyl-pyridin-2-yl)-phenol.

7. A compound according to any one of claims 1 to 6 for use as a medicament.

8. A compound of formula (1'):

\[
\begin{align*}
(\text{Het})_{x} \quad (R_{1})_{m} \quad (R_{2})_{y} \\
\end{align*}
\]

\[
(\text{Het}) \quad \text{H} \\
\]

wherein,

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclylene; preferably Het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzooxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably Het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with R^3, Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R^3 wherein where multiple substitution with R^3 is possible, the substituents can be independently selected from R^3

R^1 or R^2 can be independently H, C_1-C_12 alkyl, haloalkyl, C_1-C_5 alkoxy, hydroxy, C_6-C_13 aryl, naphthyl, benzo[b]thiophen, thiophen, amino, amid, C(0)R, OC(0)R, ester, ether, SO_2 R, furanyl, het, halogen, trityl, CN, NO_2 or OAc; either of which is unsubstituted or can be
independently substituted further with $R^3$ (wherein where multiple substitution with $R^3$ is possible, the substituents can be independently selected from $R^3$).

$R^3$ is $C_1$-$C_{12}$ alkyl, haloalkyl, $CrC_5$ alkoxy, hydroxy, $C_6$-$C_{13}$ aryl, halogen, amino, amido, ester, ether, $C(0)R^4$, $OC(0)R^4$, $S0_2R^4$, $S0_2NHR^4$, trityl, CN, NO$_2$ or OAc,

$R^4$ is H, OH, $C_1$-$C_5$ alkoxy, alkyl or aryl,

$A$ is one or more heteroatoms independently selected from N, O, S or Se, wherein $A$ is N, preferably heterocycles are pyridine, pyrimidine or pyridazine which can be further annelated by 5- or 6-membered rings

$m$ is selected from 0 - 3 carbons, preferably 1,

$n$ is 0 - 6,

$Q$ is C, O, S, CH=CH, N, CO, CO$_2$, CONH, S0$_2$, S0$_2$NH,

$X$ is 1 - 3,

$Y$ is 0 - 2,

$Z$ is 1 - 2; if $Z > 1$, multi-$Q$ can be any linker described above,

or a pharmaceutically acceptable derivative

for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-1^-hydroxylase (CYP1B1).

9. A compound of formula (2'):

\[
\begin{array}{c}
\text{het} \\
\text{R}^5 \\
\text{R}^5 \\
\text{N} \\
\text{R}^7
\end{array}
\]

(2')

wherein,
R³ is C₁₋₁₂ alkyl, haloalkyl, CrC₅ alkoxy, hydroxy, C₆₋₁₃ aryl, halogen, amino, amido, ester, ether, C(0)R₄, OC(0)R₄, S0₂R₄, S0₂NHR₄, CN, NO₂ or OAc,

R⁴ is H, OH, C₁₋₅ alkoxy, alkyl or aryl,

R⁶ is H, C₁₋₁₂ alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, C₆₋₁₃ aryl, naphthyl, C₁₋₅ alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, CN, NO₂, OAc, amino, amido, C(0)R₄, OC(0)R₄, trityl or Het; which may be unsubstituted or substituted further with R³ wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³,

Het is heteroaryl, heteroarylium, heterocyclyl, heteroaralkyi, heteroarylene, heterocyclylene; preferably het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzo[c]oxazolyl, benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably het is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-isoaxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoaxazolyl, 4-benzothiazolyl, 4-benzo[d]isoxazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1H-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

Het can be unsubstituted or is substituted further with R³. Het can also be further annelated by 5- or 6- membered rings, which can also be substituted with R³ wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³,

R⁶ is H, C₁₋₁₂ alkyl, haloalkyl, cycloalkyl, C₁₋₅ alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, C₆₋₁₃ aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO₂, OAc, amino, amido, C(0)R₄, OC(0)R₄, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),

R⁷ is H, Halogen, C₁₋₁₂ alkyl, haloalkyl, cycloalkyl, C₂₋₁₂ alkenyl, cycloalkylene, alkynyl, C₆₋₁₃ aryl, C₁₋₅ alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, NO₂, OAc, amino, amido, C(0)R₄, OC(0)R₄, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³),
or a pharmaceutically acceptable derivative

for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-1\(^\lambda\)-hydroxylase (CYP1\(\text{B1}\)).

10. An imidazol-1-ylmethyl-pyridine compound of formula (3'):

\[
\begin{array}{c}
\text{N} \\
\text{R}^5 \\
\text{R}^4 \\
\text{N} \\
\text{R}^5
\end{array}
\]

(3')

wherein,

\(R^3\) is \(C_1\text{-}C_{12}\) alkyl, haloalkyl, \(CrC_5\) alkoxy, hydroxy, \(C_6\text{-}C_{13}\) aryl, halogen, amino, amido, ester, ether, \(C(0)R^4\), \(OC(0)R^4\), \(SO_2R^4\), \(SO_2\text{NHR}^4\), \(CN\), \(N\text{O}_2\) or \(\text{OAc}\),

\(R^4\) is \(H\), \(OH\), alkyl or aryl,

\(R^5\) is \(H\), \(C_1\text{-}C_{12}\) alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, \(C_5\text{-}C_{13}\) aryl, naphthyl, \(C_1\text{-}C_5\) alkoxy, hydroxy, halogen, furanyl, benzo[b]thiophen, thiophen, \(\text{CN}\), \(\text{N}\text{O}_2\), \(\text{OAc}\), amino, amido, \(C(0)R^4\), \(OC(0)R^4\), trityl or \(\text{Het}\); which may be unsubstituted or substituted further with \(R^3\) (wherein where multiple substitution with \(R^3\) is possible, the substituents can be independently selected from \(R^3\)),

\(\text{Het}\) is heteroaryl, heteroarylilum, heterocyclic, heteroaralkyli, heteroarylene, heterocyclylene; preferably \(\text{het}\) is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzotriazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl, benzothiazolyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1\(H\)-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl;

more preferably \(\text{het}\) is 1-imidazolyl, 5-imidazolyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, 3-(6-methoxypyridinyl), 4-isoquinolinyl, 8-quinazolinyl, or benzo[b]imidazolyl, 4-oxazolyl, 4-oxazolyl, 4-thiazolyl, 4-isothiazolyl, 4-benzoxazolyl, 4-benzothiazolyl, 4-benzoxazolyl, 4-benzothiazolyl, 4-benzo[d]isothiazolyl, 4,5,6,7-tetrahydro-1\(H\)-benzo[d]imidazolyl, 5,6,7,8-tetrahydroisoquinolinyl,

\(\text{Het}\) can be unsubstituted or substituted further with \(R^3\) \(\text{Het}\) can also be further annelated by 5- or 6- membered rings, which can also be substituted with \(R^3\) (wherein where multiple substitution with \(R^3\) is possible, the substituents can be independently selected from \(R^3\),

90
R³ is H, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₆-C₅ alkoxy, hydroxy, halogen, alkenyl, cycloalkylene, alkynyl, C₆-C₃ aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, N₂O₂, OAc, amino, amido, C(0)R₄, OC(0)R₄, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

R⁷ is H, Halogen, C₁-C₁₂ alkyl, haloalkyl, cycloalkyl, C₂-C₁₂ alkenyl, cycloalkylene, alkynyl, C₆-C₁₃ aryl, C₆-C₅ alkoxy, hydroxy, thiophen, het, furanyl, benzo[b]thiophen, naphthyl, CN, N₂O₂, OAc, amino, amido, C(0)R₄, OC(0)R₄, trityl or het; which may be unsubstituted or substituted further with R³ (wherein where multiple substitution with R³ is possible, the substituents can be independently selected from R³).

or a pharmaceutically acceptable derivative,

for use in the treatment of a condition characterized by abnormal activity or abnormal expression/level of steroid-1^-hydroxylase (CYP1B1).


12. The compound according to any one of claims 1 to 11 for use in treating Cortisol dependent disorder.

13. The compound according to claim 12, wherein the disorder is selected from Cushing's syndrome, excessive CYP1B1 level, the ectopic ACTH syndrome, the change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD) Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine or cocaine
withdrawal syndrome, the post-traumatic stress syndrome, the cognitive impairment after stroke and the cortisol-induced mineralocorticoid excess.

14. The compound according to any one of claims 1 to 11 for use in treating Cushing’s syndrome or metabolic disease or metabolic syndrome or in treating weight loss.

15. A compound of formula (4)

\[
\begin{array}{c}
\text{Het} \\
\text{N} \\
\text{Ar} \\
\text{R}^3 \\
\end{array}
\]

for use in treating Cortisol dependent disorder,

wherein

Het is imidazolyl, pyridyl, pyrimidyl, triazolyl, oxazolyl, thiazolyl, benzotriazolyl, benzoimidazolyl, quinoliny1, isoquinoliny1; (only \(\beta\) and \(\gamma\) position to methylene bridge, not a position);

which could be substituted by further \(R^3\) group;

\(N\) Het is aromatic ring with one to four \(N\) atoms,

in particular pyridine, pyrimidine, pyridazine

which could be further annelated by 5- or 6- membered rings;

Ar is Benzene, naphthalene, heterocycles,

which could be further annelated by 5- or 6- membered rings;

\(R^1, R^2\) could independently be \(H, \text{Me, Et, c-Pr, c-pent}\);

\(R^3, R^4\) could independently be \(\text{CF}_3, \text{NO}_2, \text{CN, halogen, OMe, OH, OAc, alkyl, c-alkyl, alkoxyloxy}\).
Figure 1

Cholesterol → 11-deoxycorticosterone → corticosterone → 18-hydroxycorticosterone → aldosterone

11-deoxycortisol

cortisol

CYP11B2
CYP11B1

11-deoxycorticosterone

corticosterone

18-hydroxycorticosterone

aldosterone
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/06 C07D409/14 A61K31/4164 A61P25/28
ADD.

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

B. FIELDS SEARCHED

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

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 database and, where practical, search terms used)

EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>wo 02/060877 AI (F. HOFFMANN-LA ROCHE AG, SWITZ.) 8 August 2002 (2002-08-08) pages 1-8; claims 1,2,3,6,9,12,15,18,21,24</td>
<td>1-3, 8</td>
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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 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 document 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

"I": 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: 7 December 2011

Date of mailing of the international search report: 23/12/2011

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer:
Goss, Ilaria
### Category* Citation of document, with indication, where appropriate, of the relevant passages

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<td>X,P</td>
<td>Ulrike E. Hille, Christina Zimmer, Carsten A. Vock, and Rolf W. Hartmann: &quot;First selective CYP11B1 inhibitors for the Treatment of Cortisol-Dependent Diseases&quot;, Medicinal Chemistry Letters, vol. 2, 22 October 2010 (2010-10-22), pages 2-6, XP002635800, web. Abstract; page 5, left-hand column; table 3; compounds 33,34.</td>
<td>1-5,8,9,11-15</td>
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<td>EP 2 095 819 AI (MAASTRICHT UNIVERSITY [NL]; STICHTING VOOR DE TECH WET [NL]; UNIV) 2 September 2009 (2009-09-02) the whole document.</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II**  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III**  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

   see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☑ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  
☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 7, 8, 12-15
   A compound of formula (1) and its medical use

2. claims: 2, 7, 12-15
   A compound of formula (2") and its medical use

3. claims: 3, 6, 7, 9, 12-15
   A compound of formula (2) and its medical use

4. claims: 4, 6, 7, 10-15
   A compound of formula (3) and its medical use

5. claims: 5, 7, 12-15
   A compound selected from the list presented in claim 5 and its medical use
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