



(51) International Patent Classification:

C07D 413/06 (2006.01) A61K 31/538 (2006.01)
 C07D 401/06 (2006.01) A61K 31/4709 (2006.01)
 C07D 471/04 (2006.01) A61K 31/4375 (2006.01)
 C07D 405/14 (2006.01) A61K 31/498 (2006.01)
 C07D 403/06 (2006.01) A61K 31/501 (2006.01)
 C07D 413/14 (2006.01) A61K 31/4439 (2006.01)
 C07D 401/14 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

PCT/FI2021/050828

(22) International Filing Date:

30 November 2021 (30.11.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

20206226 01 December 2020 (01.12.2020) FI

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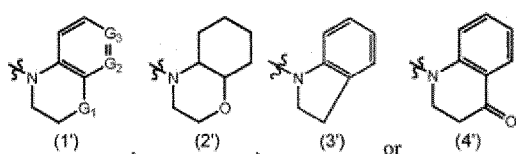
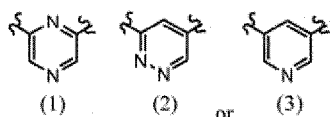
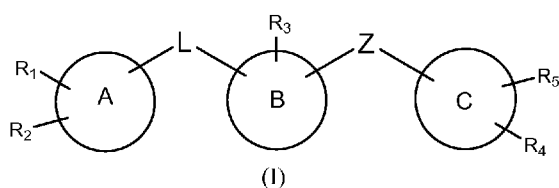
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

(54) Title: 2,3-DIHYDRO-4H-BENZO[B][1,4]OXAZIN-4-YL(5-(PHENYL)-PYRIDIN-3-YL)METHANONE DERIVATIVES AND SIMILAR COMPOUNDS AS CYP11A1 INHIBITORS FOR THE TREATMENT OF PROSTATE CANCER



(57) Abstract: The present invention relates to compounds of formula (I) wherein A is a 3-10 membered carbocyclyl or a 4-12 membered heterocyclyl containing 1-4 heteroatoms selected from O, N or S; B is any of the following groups (1) (2) or (3); C is any of the following groups (1') (2') (3') or (4') G₁ is CH₂, NH or O; G₂ and G₃ are, independently, is CH or N; Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-; L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-. The compounds of formula (I) are cytochrome P450 monooxygenase 11A1 (CYP11A1) inhibitors. The compounds are useful as medicaments in the treatment of steroid receptor, for example androgen receptor or estrogen receptor, dependent diseases and conditions, such as cancer including prostate cancer and estrogen cancer.

Published:

- *with international search report (Art. 21(3))*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

2,3-DIHYDRO-4H-BENZO[B][1,4]OXAZIN-4-YL)(5-(PHENYL)-PYRIDIN-3-YL)METHANONE
DERIVATIVES AND SIMILAR COMPOUNDS AS CYP11A1 INHIBITORS FOR THE
TREATMENT OF PROSTATE CANCER

Technical field

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The present invention relates to therapeutically active compounds useful in the treatment of a steroid receptor, such as androgen receptor (AR) or estrogen receptor (ER), dependent conditions and diseases, and to pharmaceutical compositions containing such compounds.

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Background of the invention

Treatments for steroid receptor dependent diseases such as androgen receptor (AR) dependent cancers and estrogen receptor (ER) dependent cancers have been investigated extensively. Prostate cancer, for example, is worldwide one of the most common cancers in men. Even though the 5-year survival rate of patients with localized prostate cancer is high, the prognosis for those patients, who develop castration-resistant prostate cancer (CRPC) within that 5-year follow-up period, is poor.

20

The androgen receptor (AR) signalling axis is critical in all stages of prostate cancer. In the CRPC stage (castration resistant prostate cancer), disease is characterized by high AR expression, AR amplification and persistent activation of the AR signalling axis by residual tissue/tumor androgens and by other steroid hormones and intermediates of steroid biosynthesis. Thus, treatment of advanced prostate cancer involves androgen deprivation therapy (ADT) such as hormonal manipulation using gonadotropin-releasing hormone (GnRH) agonists/antagonists or surgical castration, AR antagonists or CYP17A1 inhibitors (such as abiraterone acetate in combination with prednisone).

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Although therapies can initially lead to disease regression, eventually majority of the patients develop a disease that is refractory to currently available therapies. Increased progesterone levels in patients treated with abiraterone acetate has been hypothesized to be one of the resistance mechanisms. Several nonclinical and clinical

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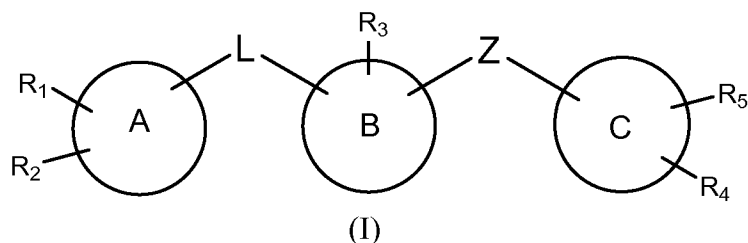
studies have indicated upregulation of enzymes that catalyse steroid biosynthesis at the late stage of CRPC. Very recently it has been published that 11 β -OH androstenedione can be metabolized into 11-ketotestosterone (11-K-T) and 11-ketodehydrotestosterone (11-K-DHT) which can bind and activate AR as efficiently as testosterone and dihydrotestosterone. It has been shown that these steroids are found in high levels in plasma and tissue in prostate cancer patients, suggesting their role as AR agonists in CRPC. Furthermore, it has been addressed that prostate cancer resistance to CYP17A1 inhibition may still remain steroid dependent and responsive to therapies that can further suppress de novo intratumoral steroid synthesis upstream of CYP17A1, such as by CYP11A1 inhibition therapy (Cai, C. et al, Cancer Res., 71(20), 6503-6513, 2011).

Cytochrome P450 monooxygenase 11A1 (CYP11A1), also called cholesterol side chain cleavage enzyme, is a mitochondrial monooxygenase which catalyses the conversion of cholesterol to pregnenolone, the precursor of all steroid hormones. By inhibiting CYP11A1, the key enzyme of steroid biosynthesis upstream of CYP17A1, the total block of the whole steroid biosynthesis can be achieved. CYP11A1 inhibitors may therefore have a great potential for treating steroid hormone dependent cancers, including prostate cancer, even in advanced stages of the disease, and especially in those patients who appear to be hormone refractory. It has been shown that a compound having CYP11A1 inhibitory effect significantly inhibited tumor growth in vivo in a murine CRPC xenograft model (Oksala, R. et al, Annals of Oncology, (2017) 28 (suppl. 5): Abstract/Poster 28P). CYP11A1 inhibitors have been described earlier in WO 2018/115591.

Summary of the invention

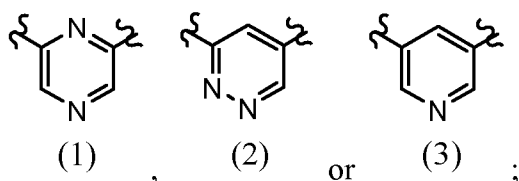
It has been found that compounds of formula (I) are potent CYP11A1 inhibitors. The compounds of the invention are therefore particularly useful as medicaments in the treatment of steroid hormone dependent conditions and diseases where CYP11A1 inhibition is desired. Such conditions and diseases include, but are not limited to, endocrine cancers and diseases, such as prostate cancer and breast cancer. In particular, the compounds of the invention are useful in the treatment of AR dependent conditions and diseases including prostate cancer.

The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof



5 wherein

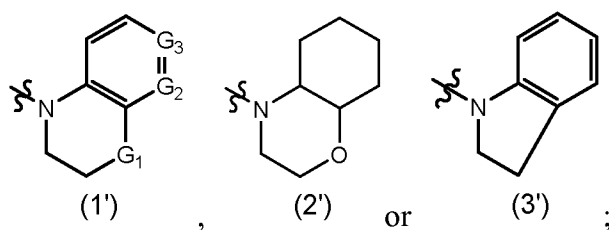
B is any of the following groups



wherein when B is group (1) or (2) then

10 A is a 3-10 membered carbocyclic ring or a 4-12 membered heterocyclic ring containing 1-4 heteroatoms selected from O, N or S;

C is any of the following groups



15 G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, nitro, halogen C₁₋₇

20 alkyl,

hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl or -X-NR₆R₇;

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R_4 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy, hydroxy C_{1-7} alkyl, halogen C_{1-7} alkyl or $-C(O)-O-C_{1-7}$ alkyl;

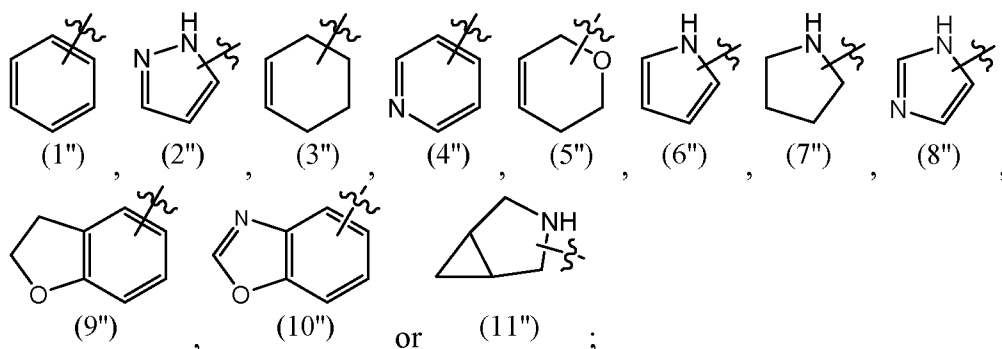
R_5 is hydrogen, halogen, C_{1-7} alkoxy or C_{1-7} alkyl;

X is a bond or C_{1-7} alkyl;

5 R_6 and R_7 are, independently, hydrogen or C_{1-7} alkyl;

wherein when B is group (3) then

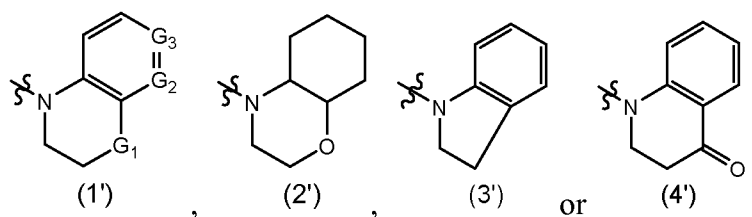
A is any one of the following groups



10

provided that when C is ring (3') then A is not ring (2'') or ring (7'');

C is any of the following groups



15

G_1 is CH_2 , NH or O;

G_2 and G_3 are, independently, is CH or N;

Z is $-C(O)-$, $-SO_2-$, $-C_{1-3}$ alkyl- or $-CH_2-C(O)-$;

L is a bond, $-C_{1-7}$ alkyl- or $-C_{1-7}$ alkenyl-;

20

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy, halogen C_{1-7} alkyl, hydroxy C_{1-7} alkyl, $-O$ -halogen C_{1-7} alkyl, $-X-NR_6R_7$,

R_2 is hydrogen, hydroxy, C_{1-7} alkyl or halogen;

R_3 is hydrogen, C_{1-7} alkyl or amino;

R_4 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy C_{1-7} alkyl, halogen C_{1-7} alkyl or $-C(O)-O-C_{1-7}$ alkyl;

25

R_5 is hydrogen, halogen, C_{1-7} alkoxy or C_{1-7} alkyl;

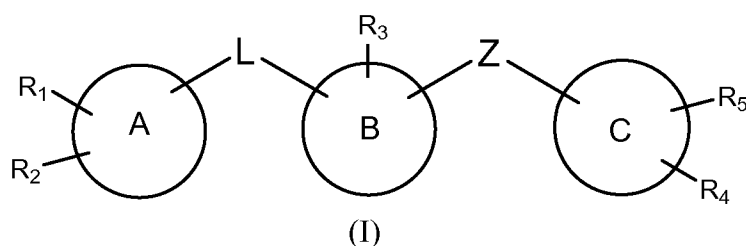
X is a bond or C₁₋₇ alkyl;

R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl;

with the proviso that compound of formula (I) is not

- (7-Methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)-
 5 pyrazin-2-yl)methanone;
 (8-Fluoro-3,4-dihydro-3-hydroxymethyl-1(2H)-quinoliny)(6-(1-pyrrolidinyl)-2-
 pyrazinyl)methanone;
 (3,4-Dihydro-3-methoxy-1(2H)-quinoliny)(6-phenyl-4-pyridazinyl)methanone;
 (6-Fluoro-3,4-dihydro-4-methyl-1(2H)-quinoxaliny)(5-phenyl-3-pyridinyl)-
 10 methanone;
 (3,4-Dihydro-1(2H)-quinoliny)(5-phenyl-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(3,4-dihydro-1(2H)-quinoliny)-
 methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(7-fluoro-2,3-dihydro-4H-1,4-
 15 benzoxazin-4-yl)methanone;
 (6,8-Difluoro-3,4-dihydro-1(2H)-quinoliny)(5-(4-(dimethylamino)phenyl)-3-
 pyridinyl)methanone;
 (3,4-Dihydro-1(2H)-quinoliny)(5-(1-pyrrolidinyl)-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-
 20 yl)methanone;
 (5-(4-Methoxyphenyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-yl)-
 methanone; or
 (2,3-Dihydro-1H-indol-1-yl)(5-phenyl-3-pyridinyl)methanone.

- 25 According to one embodiment, the invention provides a method for the treatment of a steroid receptor dependent condition or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof

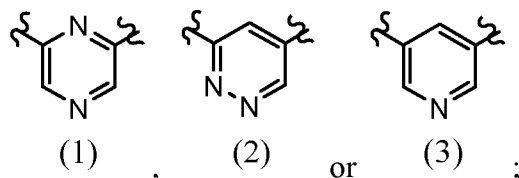


wherein

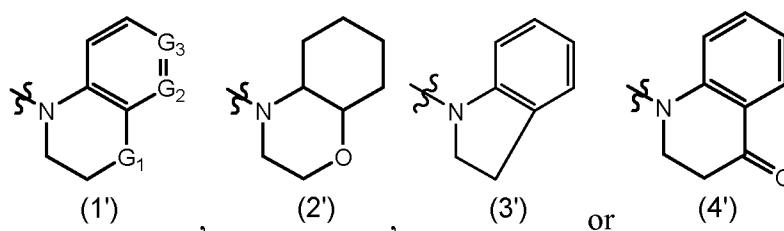
A is a 3-10 membered carbocyclic ring or a 4-12 membered heterocyclic ring containing 1-4 heteroatoms selected from O, N or S;

B is any of the following groups

5



C is any of the following groups



G₁ is CH₂, NH or O;

10

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, nitro, halogen C₁₋₇ alkyl,

15

hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl or -X-NR₆R₇;

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

20

R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;

X is a bond or C₁₋₇ alkyl;

R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl.

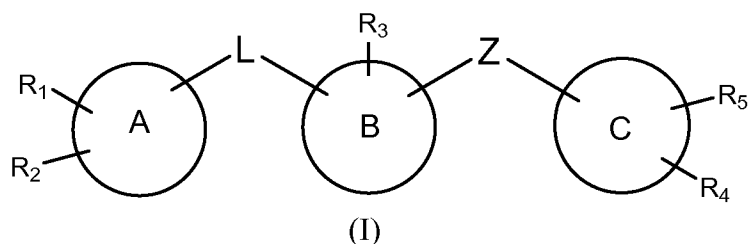
25 According to one embodiment, the steroid receptor dependent conditions or diseases include, but are not limited to, endocrine cancers and diseases, such as prostate cancer, particularly castration resistant prostate cancer (CRPC), and breast cancer.

According to one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

5 Detailed description of the invention

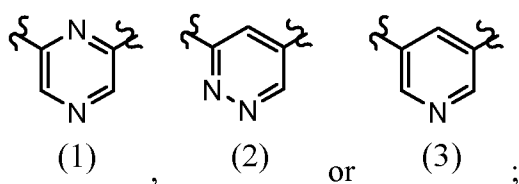
The present application provides novel compounds of formula (I) or pharmaceutically acceptable salts thereof which are useful as CYP11A1 inhibitors.

10 One of the embodiments of the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

B is any of the following groups



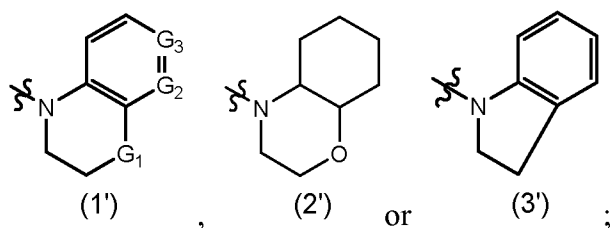
15

wherein when B is group (1) or (2) then

A is a 3-10 membered carbocyclic ring or a 4-12 membered heterocyclic ring containing 1-4 heteroatoms selected from O, N or S;

20

C is any of the following groups



G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, nitro, halogen C₁₋₇ alkyl,

5 hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl or -X-NR₆R₇;

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

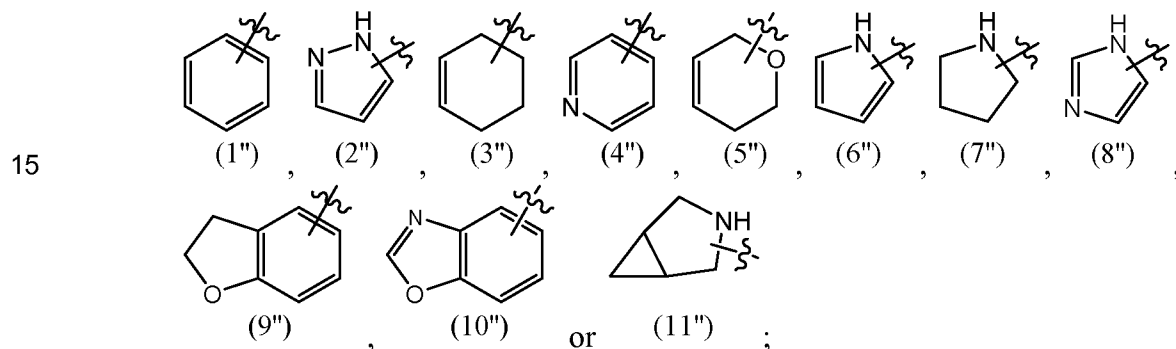
10 R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;

X is a bond or C₁₋₇ alkyl;

R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl;

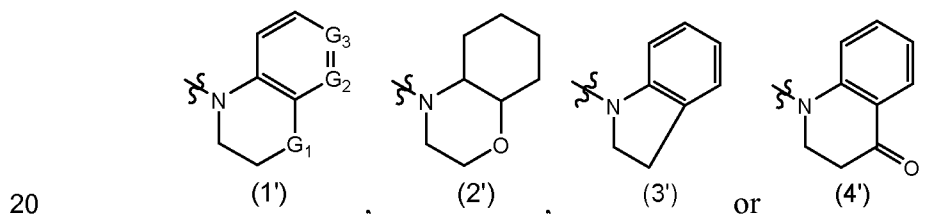
wherein when B is group (3) then

A is any one of the following groups



provided that when C is ring (3') then A is not ring (2'') or ring (7'');

C is any of the following groups



G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

25 L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

- R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy, halogen C_{1-7} alkyl, hydroxy C_{1-7} alkyl, -O-halogen C_{1-7} alkyl, -X-NR₆R₇,
 R_2 is hydrogen, hydroxy, C_{1-7} alkyl or halogen;
 R_3 is hydrogen, C_{1-7} alkyl or amino;
 5 R_4 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy C_{1-7} alkyl, halogen C_{1-7} alkyl or -C(O)-O- C_{1-7} alkyl;
 R_5 is hydrogen, halogen, C_{1-7} alkoxy or C_{1-7} alkyl;
 X is a bond or C_{1-7} alkyl;
 R_6 and R_7 are, independently, hydrogen or C_{1-7} alkyl;
- 10 with the proviso that compound of formula (I) is not
 (7-Methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)-pyrazin-2-yl)methanone;
 (8-Fluoro-3,4-dihydro-3-hydroxymethyl-1(2H)-quinoliny)(6-(1-pyrrolidinyl)-2-pyrazinyl)methanone;
 15 (3,4-Dihydro-3-methoxy-1(2H)-quinoliny)(6-phenyl-4-pyridazinyl)methanone;
 (6-Fluoro-3,4-dihydro-4-methyl-1(2H)-quinoxaliny)(5-phenyl-3-pyridinyl)-methanone;
 (3,4-Dihydro-1(2H)-quinoliny)(5-phenyl-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(3,4-dihydro-1(2H)-quinoliny)-
 20 methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(7-fluoro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methanone;
 (6,8-Difluoro-3,4-dihydro-1(2H)-quinoliny)(5-(4-(dimethylamino)phenyl)-3-pyridinyl)methanone;
 25 (3,4-Dihydro-1(2H)-quinoliny)(5-(1-pyrrolidinyl)-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-yl)methanone;
 (5-(4-Methoxyphenyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-yl)-methanone or
 30 (2,3-Dihydro-1H-indol-1-yl)(5-phenyl-3-pyridinyl)methanone.

It is to be understood that the left bond of Z is attached to the ring B of formula (I). The wavy line in group A denotes the site of attachment to L. The wavy line in

group C denotes the site of attachment to Z. The left wavy line in group B denotes the site of attachment to L and the right wavy line in group B denotes the site of attachment to Z.

- 5 According to one embodiment, specifically provided is a compound according to formula (I) wherein B is group (1) or group (3), for example B is group (1), or as another example B is group (3).

- According to yet one embodiment, specifically provided are compounds
10 according to any of the above embodiments wherein Z is -C(O)-, -SO₂-, -CH₂- or -CH₂-C(O)-. According to another embodiment, specifically provided are compounds according to any of the above embodiments wherein Z is -C(O)-. According to yet one embodiment, specifically provided are compounds according to any of the above
15 embodiments wherein L is a bond, -C₁₋₃ alkyl- or -C₁₋₃ alkenyl-. In a subgroup of the preceding embodiment L is a bond, -CH₂- or -C(CH₂)-. According to yet one embodiment, specifically provided are compounds according to any of the above
20 embodiments wherein L is a bond. According to yet one embodiment, specifically provided are compounds according to any of the above embodiments wherein C is group (1') or (2'). According to yet one embodiment, specifically provided are
20 compounds according to any of the above embodiments wherein C is group (1').

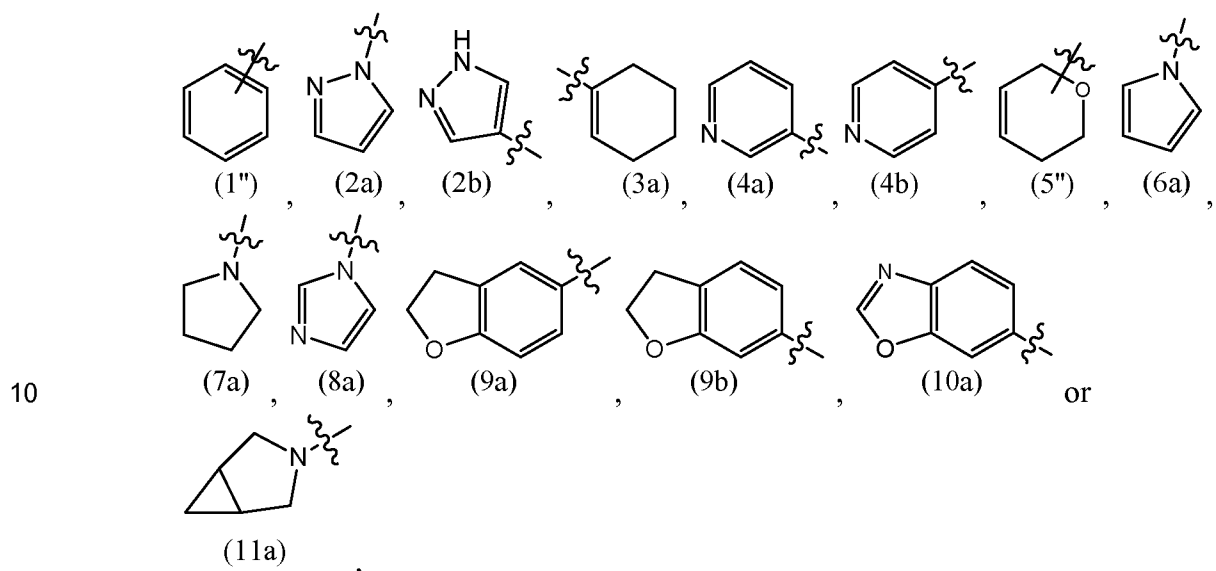
- According to yet one embodiment, specifically provided are compounds
25 according to any of the above embodiments wherein G₁ is CH₂ or O, for example G₁ is CH₂ or as another example G₁ is O. In one aspect, provided are compounds according to any of the above embodiments wherein G₂ is N and G₃ is CH, or wherein G₂ is CH and G₃ is N.

- According to one embodiment, specifically provided are compounds according
30 to any of the above embodiments wherein R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy C₁₋₇ alkyl or halogen C₁₋₇ alkyl. According to another embodiment, specifically provided are compounds according to any of the above embodiments wherein R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen. According to another

embodiment, specifically provided are compounds according to any of the above embodiments wherein R_3 is hydrogen. According to another embodiment, specifically provided are compounds according to any of the above embodiments wherein R_4 is hydrogen, C_{1-7} alkyl, halogen or $-C(O)-O-C_{1-7}$ alkyl.

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According to one embodiment, specifically provided is a compound according to any of the above embodiments of formula (I) wherein when B is group (3) then A is any one of the following groups:



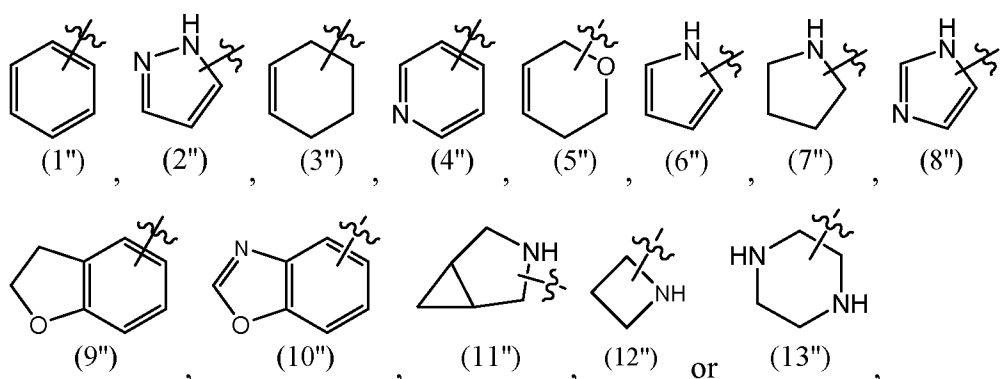
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R_1 and R_2 being attached to the above A-rings, and the wavy line denoting the site of attachment to L.

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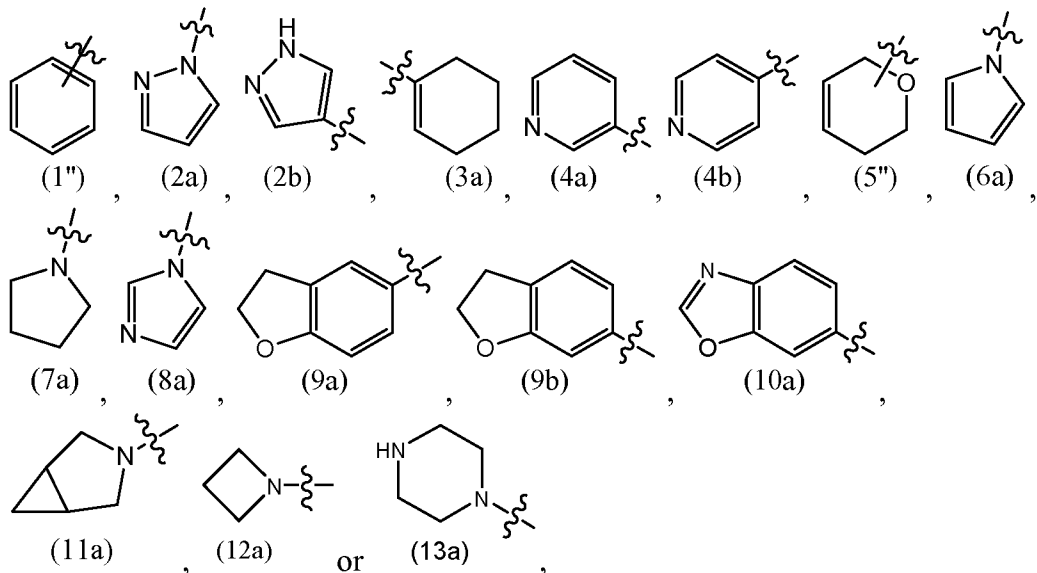
According to one embodiment, specifically provided is a compound according to any of the above embodiments of formula (I) wherein when B is group (1) or (2) then A is any one of the following groups:

20



R_1 and R_2 being attached to the above A-rings, and the wavy line denoting the site of attachment to L.

In a subclass of the above embodiment are compounds wherein A is any one of the following groups:

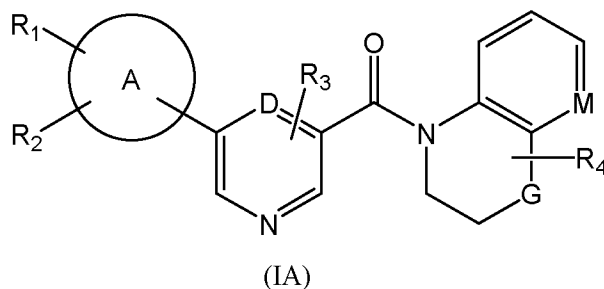


R_1 and R_2 being attached to the above A-rings, and the wavy line denoting the site of attachment to L.

According to one embodiment, specifically provided is a compound according to any of the above embodiments of formula (I) wherein A is group (1''), (2''), (3''), (6''), (8''), (9'') or (10'').

According to one embodiment, specifically provided is a compound according to any of the above embodiments of formula (I) wherein A is group (1''), (2a), (2b), (3a), (6a), (8a), (9b) or (10a).

According to one embodiment, the compound of the present invention is represented by formula (IA) or a pharmaceutically acceptable salt thereof



wherein

D is N or CH;

G is CH₂, NH or O;

5 M is CH or N;

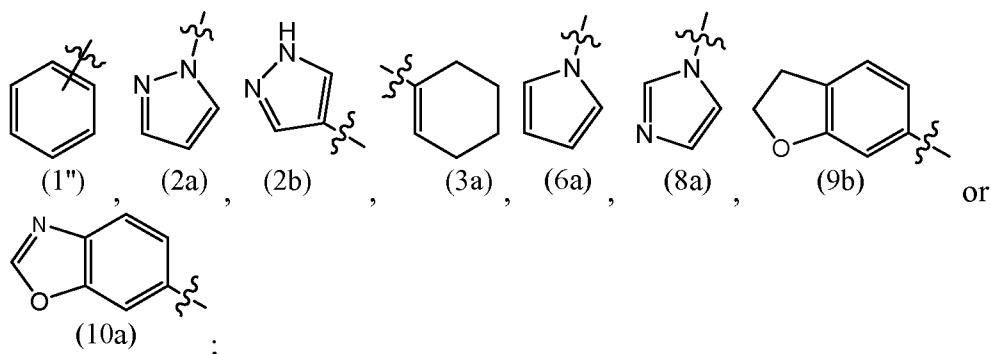
R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

R₂ is hydrogen or halogen;

R₃ is hydrogen or C₁₋₇ alkyl;

R₄ is hydrogen, C₁₋₇ alkyl, halogen or -C(O)-O-C₁₋₇ alkyl;

10 A is any one of the following groups:



with the proviso that compound of formula (I) is not

(3,4-Dihydro-1(2H)-quinolinyl)(5-phenyl-3-pyridinyl)methanone;

15 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(3,4-dihydro-1(2H)-quinolinyl)-methanone or

(5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(7-fluoro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methanone.

20 In a subclass of the above embodiment are compounds of formula (IA), wherein R₁ is hydrogen, methyl, methoxy or halogen; R₃ is hydrogen or methyl; R₄ is hydrogen, methyl or halogen; and A is group (1''), (2a), (3a), (9b) or (10a).

According to still one embodiment, the present invention provides a method for the treatment of a steroid receptor dependent conditions and diseases, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) as defined in any of the above embodiments.

5

According to one embodiment, the steroid receptor dependent disease or condition is androgen receptor or estrogen receptor dependent disease or condition including endocrine cancers and diseases, for example prostate cancer or breast cancer, particularly castration-resistant prostate cancer (CRPC). According to one embodiment
10 of the invention, the CRPC to be treated is refractory to CYP17A1 inhibitor treatment. According to another embodiment, the androgen receptor dependent disease or condition is endocrine cancer which is dependent upon CYP11A1 activation.

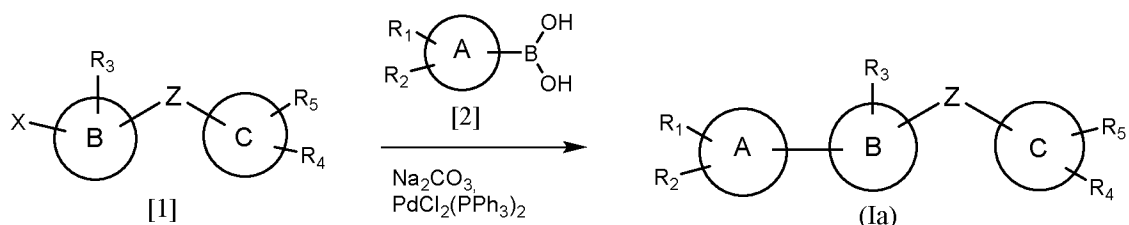
The compounds of the invention can be prepared by a variety of synthetic routes
15 analogously to the methods known in the literature using suitable starting materials. The compounds according to formula (I) can be prepared e.g. analogously or according to the following reaction Schemes. Some compounds included in the formula (I) can be obtained by converting the functional groups of the other compounds of formula (I) obtained in accordance with the following Schemes, by well known reaction steps such
20 as oxidation, reduction, hydrolysis, acylation, alkylation, amidation, amination, sulfonation and others. It should be noted that any appropriate leaving groups, e.g. N-protecting groups, such as a t-butoxycarbonyl (t-BOC) group or a phenylsulfonyl group, can be used in well known manner during the syntheses in order to improve the selectivity of the reaction steps.

25

Compounds of formula (I) wherein L is a bond can be prepared according to Scheme 1, wherein wherein X is a halogen, preferably chloro or bromo, and A, B, C, Z, R₁, R₂, R₃, R₄ and R₅ are as defined above. In the method of Scheme 1, the compound of formula [1] is coupled with a boronic acid derivative of formula [2] in a suitable
30 solvent, such as a mixture of ethanol, toluene and water, in the presence of a base such as sodium carbonate and a catalyst such as bis(triphenylphosphine)palladium (II) dichloride at elevated temperature to produce a compound of formula [Ia]. Instead of

boronic acid derivative [2] a corresponding boronic ester such as boronic acid pinacol ester can also be used.

SCHEME 1.

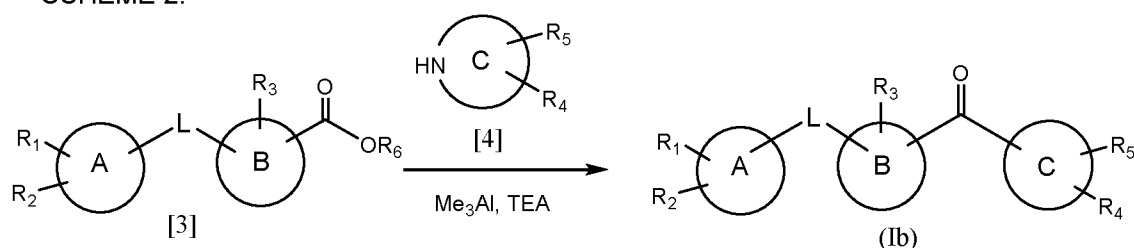


5

Compounds of formula (I) wherein Z is -C(O)- can also be prepared according to Scheme 2, wherein A, B, C, L, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 2) and R₆ is methyl or ethyl. In the method of Scheme 2, the compound of formula [3] is coupled with a compound of formula [4] in a suitable solvent such as toluene in the presence of trimethylaluminum and a base such as triethylamine (TEA) to produce a compound of formula [Ib].

10

SCHEME 2.

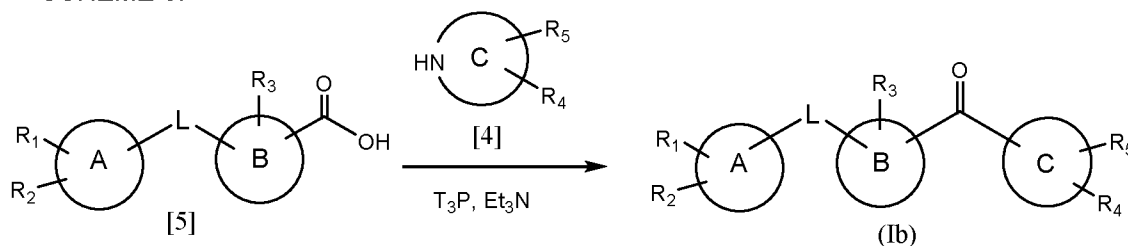


15

Alternatively, compounds of formula (I) wherein Z is -C(O)- can be prepared according to Scheme 3, wherein A, B, C, L, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 3). In the method of Scheme 3, the compound of formula [5] is coupled with a compound of formula [4] in a suitable solvent such as DMF in the presence of a base such as triethylamine (TEA) and optionally a coupling reagent such as propylphosphonic anhydride (T₃P) to produce a compound of formula [Ib].

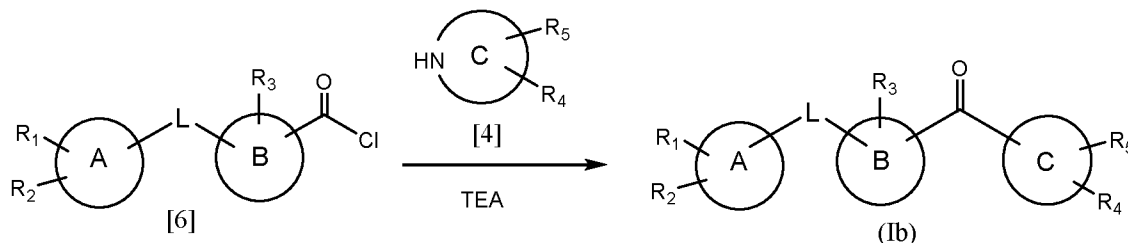
20

SCHEME 3.



Alternatively, compounds of formula (I) wherein Z is -C(O)- can be prepared according to Scheme 4, wherein A, B, C, L, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 4). In the method of Scheme 4, the compound of formula [6] is coupled with a compound of formula [4] in a suitable solvent such as DCM in the presence of a base such as triethylamine (TEA) to produce a compound of formula [Ib].

SCHEME 4.

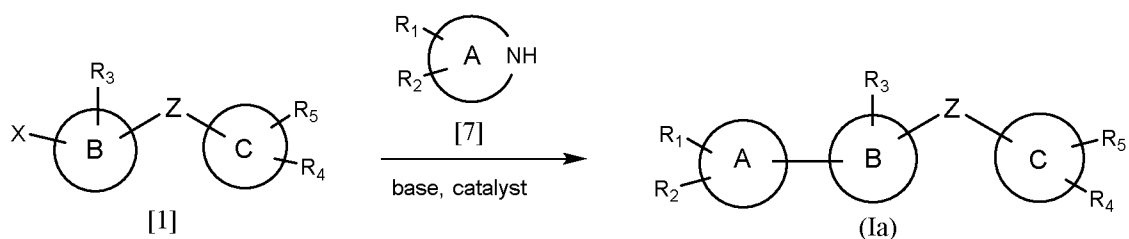


10

Compounds of formula (I) wherein L is a bond and A contains a -NH group (for example A is pyrrolidine, imidazole or pyrazole) can also be prepared according to Scheme 5, wherein X is a halogen, preferably chloro or bromo, and A, B, C, Z, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [7] is depicted in Scheme 5). In the method of Scheme 5, the compound of formula [1] can be coupled with a compound of formula [7] in a suitable solvent such as dry toluene or dry DMSO in the presence of a base such as sodium *tert*-butoxide (STB), DIPEA or potassium phosphate and optionally a catalyst such as tris(dibenzylideneacetone)dipalladium Pd₂(dba)₃ at elevated temperature to produce a compound of formula [Ia].

20

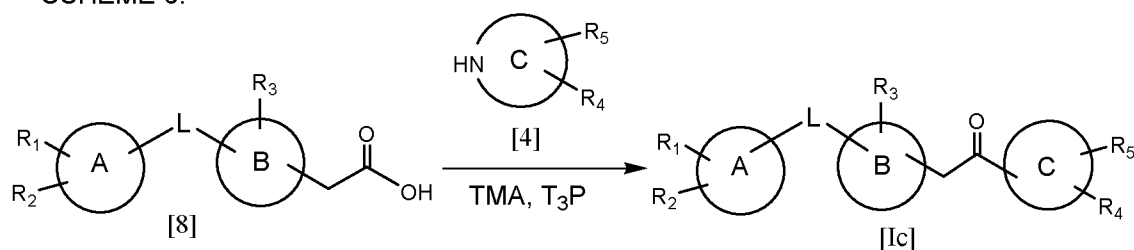
SCHEME 5.



Compounds of formula (I) wherein Z is -CH₂-C(O)- can also be prepared according to Scheme 6, wherein A, B, C, L, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 6). In the method of Scheme 6, the compound of formula [8] is coupled with a compound of formula [4] in a suitable solvent such as DMF in the presence of a base such as trimethylamine (TMA) and optionally a coupling reagent such as propylphosphonic anhydride (T₃P) and to produce a compound of formula [Ic].

10

SCHEME 6.

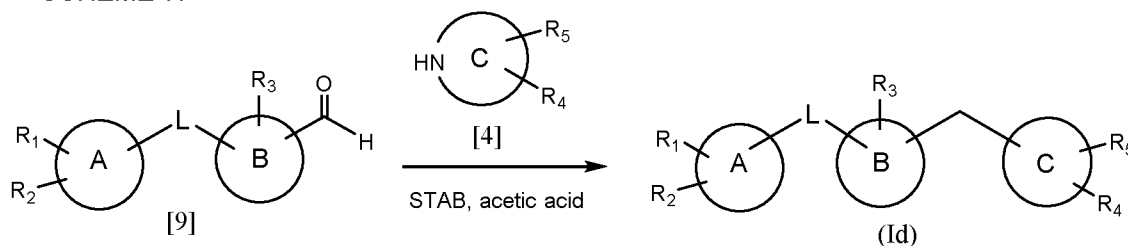


15

Compounds of formula (I) wherein Z is -C₁₋₃ alkyl- can also be prepared according to Scheme 7, wherein A, B, C, L, R₁, R₂, R₃, R₄ and R₅ are as defined above (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 7). In the method of Scheme 7, the aldehyde compound of formula [9] is reacted with a compound of formula [4] in a suitable solvent such as 1,2-dichloroethane in the presence of acetic acid and a reducing agent such as sodium triacetoxy borohydride (STAB) to produce a compound of formula [Id].

20

SCHEME 7.



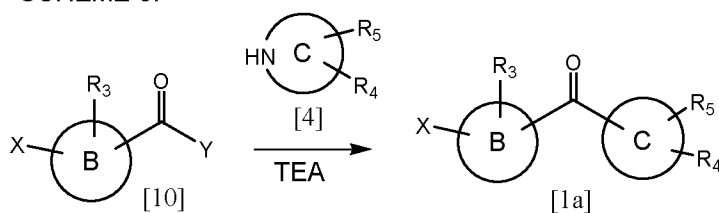
Intermediate compounds can be prepared according to the methods disclosed in the literature or as disclosed in the present disclosure.

5

For example, intermediate compounds of formula [1a] can be prepared according to Scheme 8, wherein B, C, R₃, R₄ and R₅ are as defined above, and X and Y are halogen, preferably chloro or bromo (for clarity, the ring nitrogen atom of compound [4] is depicted in Scheme 8). In the method of Scheme 8, a compound of formula [10] is coupled with a compound of formula [4] in a suitable solvent such as DCM in the presence of a base such as TEA to produce a compound of formula [1a].

10

SCHEME 8.

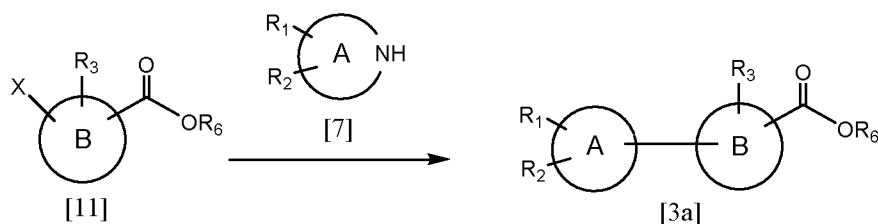


15

Intermediate compounds of formula [3a] wherein A contains a -NH group (for example A is pyrrolidine, imidazole or pyrazole) can be prepared, for example, according to Scheme 9, wherein A, B, R₁, R₃, R₂ and R₃ are as defined above, and X is halogen, preferably chloro or bromo (for clarity, the ring nitrogen atom of compound [7] is depicted in Scheme 9). In the method of Scheme 9, a compound of formula [11] is coupled with a compound of formula [7] in a suitable solvent such as toluene-dioxane in the presence of a base such as potassium phosphate and a catalyst such as the mixture of tris(dibenzylideneacetone)dipalladium and 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl to produce a compound of formula [3a].

20

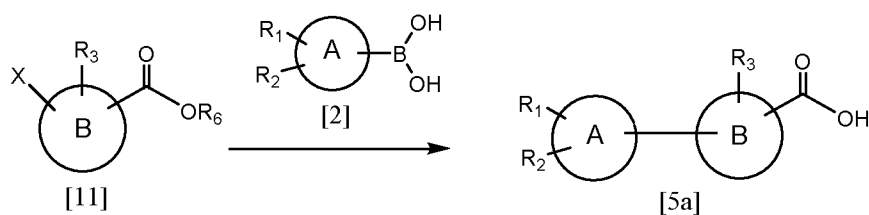
SCHEME 9.



Intermediate compounds of formula [5a] can be prepared, for example, according to Scheme 10, wherein A, B, R₁, R₂ and R₃ are as defined above, X is
 5 halogen, preferably chloro or bromo, and R₆ is methyl or ethyl. In the method of Scheme 10, a compound of formula [11] is coupled with a compound of formula [2] in a suitable solvent such as acetonitrile/ethanol/water in the presence of a base such as sodium carbonate and a catalyst such as PdCl₂(PPh₃)₂ at elevated temperature to produce a compound of formula [3a].

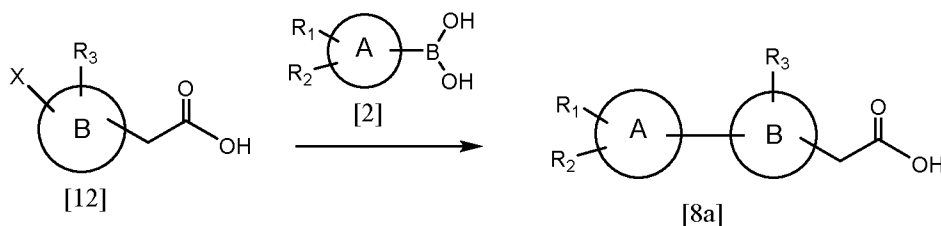
10

SCHEME 10.



Intermediate compounds of formula [8a] can be prepared, for example, according to Scheme 11, wherein A, B, R₁, R₂, R₃ are as defined above, and X is
 15 halogen, preferably chloro or bromo. In the method of Scheme 11, a compound of formula [12] is coupled with a compound of formula [2] in a suitable solvent such as DME-water in the presence of a base such as cesium carbonate and a catalyst such as added tetrakis(triphenylphosphine)palladium to produce a compound of formula [8a].

SCHEME 11.



Alternatively, the compounds of formula (I) can be prepared as disclosed in the specific Examples of the present disclosure.

5

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

10

The term “subject”, as employed herein, refers to humans and animals.

The term “steroid receptor” refers to receptor which binds to and is activated by a steroid hormone. Examples of steroid receptors include, but are not limited to, androgen, estrogen, glucocorticoid, and progesterone receptors.

15

The term “endocrine cancer” refers to partially or completely unregulated growth of one or more cellular components of the endocrine system, including, but not limited to, cancers of one or more of the adrenal glands.

20

The term “elevated temperature” refers to a temperature higher than room temperature, typically from about 30 to about 120 °C, from example from about 40 to about 100 °C or from about 50 to about 80 °C.

25

The term “halo” or “halogen”, as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

The term “C₁₋₇ alkyl”, as employed herein as such or as part of another group, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4, 5, 6 or 7 carbon atom(s). Representative examples of C₁₋₇ alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl and *n*-hexyl. One preferred embodiment of “C₁₋₇ alkyl” is C₁₋₃ alkyl. The term “C₁₋₃ alkyl” refers to a preferred embodiment of “C₁₋₇ alkyl” having 1, 2 or 3 carbon atoms.

The term “C₂₋₇ alkenyl”, as employed herein as such or as part of another group, refers to an aliphatic hydrocarbon group having 2, 3, 4, 5, 6 or 7 carbon atoms and containing one or several double bonds. Representative examples include, but are not limited to, ethenyl, propenyl and cyclohexenyl.

The term “C₃₋₇ cycloalkyl”, as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3, 4, 5, 6 or 7 carbon atoms. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term “hydroxy”, as employed herein as such or as part of another group, refers to an –OH group.

The term “cyano”, as employed herein as such or as part of another group, refers to a –CN group.

The term “carboxy”, as employed herein as such or as part of another group, refers to –COOH group.

The term “carbonyl”, as employed herein as such or as part of another group, refers to a carbon atom double-bonded to an oxygen atom (C=O).

30

The term “oxo”, as employed herein as such or as part of another group, refers to oxygen atom linked to another atom by a double bond (=O).

The term “C₁₋₇ alkoxy”, as employed herein as such or as part of another group, refers to C₁₋₇ alkyl, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of C₁₋₇ alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

5

The term “hydroxy C₁₋₇ alkyl”, as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of hydroxy C₁₋₇ alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl and 1-methyl-1-hydroxypropyl.

10

The term “halogen C₁₋₇ alkyl”, as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of halo C₁₋₇ alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl and 3-bromopropyl.

15

The term “cyano C₁₋₇ alkyl”, as employed herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of cyano C₁₋₇ alkyl include, but are not limited to, cyanomethyl, 1-cyanoethyl, 1-cyanopropyl and 2-cyanopropyl.

20

The term “halogen C₁₋₇ alkoxy”, as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkoxy group, as defined herein.

25

The term “phenyl C₁₋₇ alkyl”, as employed herein, refers to at least one phenyl group appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein.

30

The term “C₁₋₇ alkyl carbonyl”, as employed herein as such or as part of another group, refers to a C₁₋₇ alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

The term "C₁₋₇ alkoxy C₁₋₇ alkyl", as employed herein as such or as part of another group, refers to at least one C₁₋₇ alkoxy group, as defined herein, appended to the parent molecular moiety through an C₁₋₇ alkyl group, as defined herein.

5 The term "4-12 membered heterocyclyl" as employed herein, refers to a saturated, partially saturated or aromatic ring with 4-12 ring atoms, of which 1-4 atoms are heteroatoms selected from a group consisting of N, O and S. One embodiment of a "4-12 membered heterocyclyl" is a "4-10 membered heterocyclyl" which refers to a saturated, partially saturated or aromatic ring with 4-10 ring atoms, of which 1-4 atoms
10 are heteroatoms selected from a group consisting of N, O and S. Representative examples of a 4-12 membered heterocyclic ring include, but are not limited to, oxetanyl, azetidiny, pyrazolyl, 1,2,4-triazol-1-yl, 1,2,3-triazol-1-yl, pyrimidinyl, pyridinyl, piperidinyl, tetrazolyl, piperazinyl, furanyl, morpholinyl, piperidinyl, pyrrolidinyl, thiazolyl, isoxazolyl, pyrazinyl tetrahydropyranyl, 1,2,4-oxadiazolyl, oxazolyl,
15 imidazolyl, indolyl and 4,5-dihydroimidazolyl rings.

 The term "3-10 membered carbocyclyl", as employed herein, refers to a saturated, partially saturated or aromatic ring with 3 to 10 ring atoms consisting of carbon atoms only. One embodiment of a "3-10 membered carbocyclyl" is a "3-6
20 membered carbocyclyl" which refers to a saturated, partially saturated or aromatic ring with 3 to 6 ring atoms consisting of carbon atoms only. Representative examples of a 3-10 membered carbocyclyl group include, but are not limited to, phenyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl and cyclobutyl rings.

25 The term "substituted" as used herein in connection with various residues refers to, if not otherwise defined, to halogen substituents, such as fluorine, chlorine, bromine, iodine, or C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxy, amino, nitro, cyano, thiol C₁₋₇ alkyl, methylsulfonyl, C₁₋₇ alkoxy, halo C₁₋₇ alkyl, hydroxy C₁₋₇ alkyl or amino C₁₋₇ alkyl substituents. Preferred are halogen, C₁₋₇ alkyl, hydroxy, amino, halo C₁₋₇ alkyl, C₁₋₇
30 alkoxy and methylsulfonyl substituents. In one group of preferred substituents are 1-2 substituents selected from C₁₋₇ alkyl or halogen substituents, particularly C₁₋₃ alkyl or halogen substituents, particularly methyl, ethyl, chloro, fluoro or bromo substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, of the above mentioned substituents, if not otherwise defined.

Optically active enantiomers or diastereomers of compounds of formula (I) can be prepared e.g. by resolution of the racemic end product by known methods or by using suitable optically active starting materials. Similarly, racemic compounds of formula (I) can be prepared by using racemic starting materials. Resolution of racemic compounds of formula (I) or a racemic starting material thereof can be carried out, for example, by converting the racemic compound into its diastereomeric salt mixture by reaction with an optically active acid and subsequent separation of the diastereomers by crystallization. Representative examples of said optically active acids include, but are not limited to, D-tartaric acid and dibenzoyl-D-tartaric acid. Alternatively, preparative chiral chromatography may be used for resolution of the racemic mixture.

Pharmaceutically acceptable salts are well known in the field of pharmaceuticals. Non-limiting examples of suitable salts include metal salts, ammonium salts, salts with an organic base, salts with an inorganic acid, salts with organic acid, and salts with basic or acidic amino acid. Non-limiting examples of metal salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt, and magnesium salt. Non-limiting examples of salts with inorganic or organic acids include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates, acetates, oxalates, fumarates, hemifumarates, and succinates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

30

The definition of formula (I) above is inclusive of all the possible isotopes and isomers, such as stereoisomers, of the compounds, including geometric isomers, for example *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g.

diastereomers and enantiomers, and prodrug esters, e.g. phosphate esters and carbonate esters.

It will be appreciated by those skilled in the art that the present compounds may
5 contain at least one chiral center. Accordingly, the compounds may exist in optically active or racemic forms. It is to be understood that the formula (I) includes any racemic or optically active form, or mixtures thereof. In one embodiment, the compounds are the pure (R)-isomers. In another embodiment, the compounds are the pure (S)-isomers. In another embodiment, the compounds are a mixture of the (R) and the (S) isomers. In
10 another embodiment, the compounds are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. The compounds may contain two chiral centers. In such case, according to one embodiment, the compounds are a mixture of diastereomers. According to another embodiment, the compounds of the invention are a mixture of enantiomers. According to still another embodiment, the compounds are pure
15 enantiomers. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers or diastereomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

20

The present compounds may also exist as tautomers or equilibrium mixtures thereof wherein a proton of a compound shifts from one atom to another. Examples of tautomerism include, but are not limited to, amido-imido, keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine, annular tautomerism of heterocyclic rings such
25 as pyrazole ring, and the like. Tautomeric forms are intended to be encompassed by compounds of formula (I), even though only one tautomeric form may be depicted.

Examples of preferred compounds of one group of formula (I) include
(2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(3-(trifluoromethoxy)phenyl)-
30 pyridin-3-yl)methanone (Compound 1);
(7-Fluoro-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridin-3-yl)methanone (Compound 2);

- (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(4-methyl-5-phenylpyridin-3-yl)-methanone (Compound 3);
- (3,4-Dihydroquinolin-1(2*H*)-yl)(4-methyl-5-phenylpyridin-3-yl)methanone (Compound 4);
- 5 (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)-4-methylpyridin-3-yl)methanone (Compound 5);
- (4-Amino-5-phenylpyridin-3-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (Compound 6);
- (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridazin-3-yl)-methanone (Compound 7);
- 10 (6-(Benzo[*d*]oxazol-6-yl)pyrazin-2-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methanone (Compound 8);
- (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(6-(3-(trifluoromethoxy)phenyl)-pyrazin-2-yl)methanone (Compound 9);
- 15 (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-phenylpyridin-3-yl)methanone (Compound 10);
- (5-(4-Chlorophenyl)pyridin-3-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-methanone (Compound 11);
- (6-(2,3-Dihydrobenzofuran-6-yl)pyrazin-2-yl)(3,4-dihydroquinolin-1(2*H*)-yl)-methanone (Compound 12);
- 20 (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(6-(2,3-dihydrobenzofuran-6-yl)pyrazin-2-yl)methanone (Compound 13);
- (3,4-Dihydroquinolin-1(2*H*)-yl)(6-(4-methoxyphenyl)pyrazin-2-yl)methanone (Compound 14);
- 25 (3,4-Dihydroquinolin-1(2*H*)-yl)(6-phenylpyrazin-2-yl)methanone (Compound 15);
- (3,4-Dihydroquinolin-1(2*H*)-yl)(5-(4-fluorophenyl)pyridin-3-yl)methanone (Compound 16);
- (5-(4-Chlorophenyl)pyridin-3-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-methanone (Compound 17);
- 30 (3,4-Dihydroquinolin-1(2*H*)-yl)(5-(4-methoxyphenyl)pyridin-3-yl)methanone (Compound 18);

- (5-(3,4-Difluorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 19);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-fluorophenyl)pyrazin-2-yl)-methanone (Compound 20);
- 5 (6-(4-Fluorophenyl)pyrazin-2-yl)(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-methanone (Compound 21);
- (6-(4-Fluorophenyl)pyrazin-2-yl)(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-methanone (Compound 22);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-methoxyphenyl)pyridin-3-yl)-
- 10 methanone (Compound 23);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridin-3-yl)-methanone (Compound 24);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(3-methoxyphenyl)pyrazin-2-yl)methanone (Compound 25);
- 15 (6-(4-Fluorophenyl)pyrazin-2-yl)(3-methyl-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 26);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-3-hydroxyphenyl)pyridin-3-yl)methanone (Compound 27);
- (5-(2,4-Difluorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-
- 20 methanone (Compound 28);
- (6-(2,3-Dihydrobenzofuran-6-yl)pyrazin-2-yl)(octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 29);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-fluorophenyl)pyridazin-4-yl)methanone (Compound 30);
- 25 (5-(4-Fluorophenyl)pyridin-3-yl)(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-methanone (Compound 31);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-nitrophenyl)pyridin-3-yl)-methanone (Compound 32);
- (5-(Cyclohex-1-en-1-yl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-
- 30 yl)methanone (Compound 33);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-(4-methoxyphenyl)pyridin-3-yl)-methanone (Compound 34);

- Ethyl 4-(6-(4-fluorophenyl)pyrazine-2-carbonyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine-2-carboxylate (Compound 35);
- 1-(5-Phenylnicotinoyl)-2,3-dihydroquinolin-4(1H)-one (Compound 36);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(6-phenylpyrazin-2-yl)methanone
- 5 (Compound 37);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(3-methoxyphenyl)pyridin-3-yl)methanone (Compound 38);
- (5-(1H-Pyrrol-1-yl)pyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 39);
- 10 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-fluorophenyl)pyridazin-4-yl)-methanone (Compound 40);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(2-fluorophenyl)pyridin-3-yl)-methanone (Compound 41);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-(4-fluorophenyl)pyridin-3-yl)-
- 15 methanone (Compound 42);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(1-methyl-1H-pyrazol-4-yl)-pyrazin-2-yl)methanone (Compound 43);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone (Compound 44);
- 20 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-2-methoxyphenyl)-pyridin-3-yl)methanone (Compound 45);
- 4-((5-(4-Fluorophenyl)pyridin-3-yl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine (Compound 46);
- 1-((5-(4-Fluorophenyl)pyridin-3-yl)sulfonyl)-1,2,3,4-tetrahydroquinoline
- 25 (Compound 47);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone (Compound 48);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6'-fluoro-[3,3'-bipyridin]-5-yl)-methanone (Compound 49);
- 30 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(3-methoxyphenyl)pyridin-3-yl)-methanone (Compound 50);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(1-phenylvinyl)pyridin-3-yl)methanone (Compound 51);

- (3,4-Dihydroquinolin-1(2H)-yl)(6-phenylpyridazin-4-yl)methanone (Compound 52);
- (6-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 53);
- 5 (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-(hydroxymethyl)phenyl)pyridin-3-yl)-methanone (Compound 54);
- (5-(4-Fluorophenyl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 55);
- (5-(4-Fluorophenyl)pyridin-3-yl)((4aS,8aS)-octahydro-4H-benzo[b][1,4]oxazin-
- 10 4-yl)methanone (Compound 56);
- (5-(4-Fluorophenyl)pyridin-3-yl)((4aR,8aR)-octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 57);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-3-nitrophenyl)pyridin-3-yl)methanone (Compound 58);
- 15 (5-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 59);
- (5-(4-Fluorophenyl)pyridin-3-yl)(indolin-1-yl)methanone (Compound 60);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 61);
- 20 [3,4'-Bipyridin]-5-yl(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 62);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(1-methyl-1H-pyrazol-5-yl)-pyrazin-2-yl)methanone (Compound 63);
- (6-(4-Fluorophenyl)pyridazin-4-yl)(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-methanone (Compound 64);
- 25 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-(hydroxymethyl)phenyl)pyridin-3-yl)methanone (Compound 65);
- (5-(3,6-Dihydro-2H-pyran-4-yl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone (Compound 66);
- Methyl 1-(5-phenylnicotinoyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate
- 30 (Compound 67);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-((dimethylamino)methyl)phenyl)pyridin-3-yl)methanone (Compound 68);

- (7-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 69);
- [3,3'-Bipyridin]-5-yl(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 70);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(p-tolyl)pyridin-3-yl)methanone
- 5 (Compound 71);
- (5-(2,3-Dihydrobenzofuran-6-yl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone (Compound 72);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl)methanone (Compound 73);
- 10 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(pyrrolidin-1-yl)pyridin-3-yl)-methanone (Compound 74);
- 2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(6,6-dimethyl-3-azabicyclo[3.1.0]-hexan-3-yl)pyridin-3-yl)methanone (Compound 75);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)pyrazin-2-yl)-
- 15 methanone (Compound 76);
- (6-(3,3-Difluoroazetidin-1-yl)pyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 77);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)methanone (Compound 78);
- 20 1-(3,4-Dihydroquinolin-1(2H)-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 79);
- 1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-methoxyphenyl)pyridin-3-yl)ethan-1-one (Compound 80);
- 4-((5-Phenylpyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine
- 25 (Compound 81);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)-methanone (Compound 82);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl)-methanone (Compound 83);
- 30 (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-methyl-1H-pyrazol-1-yl)pyrazin-2-yl)-methanone (Compound 84);
- (6-Benzylpyrazin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 85);

1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 86);

(3,4-Dihydroquinolin-1(2H)-yl)(6-(3,5-dimethyl-1H-pyrazol-1-yl)pyrazin-2-yl)-methanone (Compound 87);

5 (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)-methanone (Compound 88);

1-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)-1,2,3,4-tetrahydroquinoline (Compound 89); or

1-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)indoline (Compound 90);

10 and tautomers and pharmaceutically acceptable salts thereof.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.5 to about 2000 mg, more typically from about 1 to about 500 mg, for example from about 2 to about 100 mg, daily
15 depending on the age, sex, weight, ethnic group, condition of the patient, condition to be treated, administration route and the active ingredient used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. The compound can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories,
20 emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. Suitable carriers, solvents, gel-forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may also be used. The compositions containing the active compound can be given enterally or
25 parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, typically from about 0.5 to about 20 %, per weight of the total composition.

The compounds of the invention can be given to the subject as the sole active
30 ingredient or in combination with one or more other active ingredients for treatment of a particular disease.

In the treatment of a steroid receptor dependent disease or condition, such as endocrine cancers and disorders including prostate cancer and breast cancer, a combination of therapeutic agents and/or other treatments (e.g., radiation therapy) is often advantageous. The second (or third) agent to be administered may have the same or different mechanism of action than the primary therapeutic agent.

Accordingly, a compound of the invention may be administered in combination with other anti-cancer treatments useful in the treatment of cancers such as prostate cancer or breast cancer. For example, a compound of the invention can be packaged together with instructions that the compound is to be used in combination with other anti-cancer agents and treatments for the treatment of cancer. The present invention further comprises combinations of a compound of the invention and one or more additional agents in kit form, for example, where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is co-administered with a glucocorticoid and/or a mineralocorticoid and, optionally, with one or more anti-cancer agents.

Examples of suitable glucocorticoids include, but are not limited to, hydrocortisone, prednisone, prednisolone, methylprednisolone and dexamethasone. Examples of suitable mineralocorticoids include, but are not limited to, fludrocortisone, deoxycorticosterone, 11-desoxycortisone and deoxycorticosterone acetate.

The optional other anti-cancer agents which can be administered in addition to a compound of formula (I) or a pharmaceutically acceptable salt thereof include, but are not limited to,

- non-steroidal androgen receptor antagonists (e.g. enzalutamide, apalutamide and darolutamide);
- steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel);

- chemotherapeutic agents (e.g. docetaxel and paclitaxel);
- antiestrogens (e.g. tamoxifen and fulvestrant);
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors);
- mTOR inhibitors (e.g. everolimus);
- 5 - AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribociclib).

10

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof in addition to a therapeutically effective amount of one or more anti-cancer agents selected from the list consisting of

- 15 - non-steroidal androgen receptor antagonists (e.g. enzalutamide, apalutamide and darolutamide);
- steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel);
- chemotherapeutic agents (e.g. docetaxel and paclitaxel);
- 20 - antiestrogens (e.g. tamoxifen and fulvestrant);
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors);
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- 25 - GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribociclib).

30 According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof in addition to a therapeutically effective amount of a steroidogenesis inhibitor (e.g. a CYP17A1 inhibitor). Examples of suitable CYP17A1 inhibitors include, but are not limited to, abiraterone acetate and seviteronel.

According to another embodiment of the invention, the therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof in addition to a therapeutically effective
5 amount of a non-steroidal androgen receptor antagonist. Examples of suitable non-steroidal androgen receptor (AR) antagonists include, but are not limited to, enzalutamide, apalutamide and darolutamide.

According to still another embodiment, the present invention provides a
10 pharmaceutical combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one additional active ingredient selected from the list consisting of

- a glucocorticoid,
- a mineralocorticoid,
- 15 - a steroidogenesis inhibitor (e.g. a CYP17A1 inhibitor),
- a non-steroidal androgen receptor antagonist,
- chemotherapeutic agents (e.g. docetaxel and paclitaxel),
- antiestrogens (e.g. tamoxifen and fulvestrant),
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors),
- 20 - mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- 25 - CDK4/6 inhibitors (e.g. ribociclib)

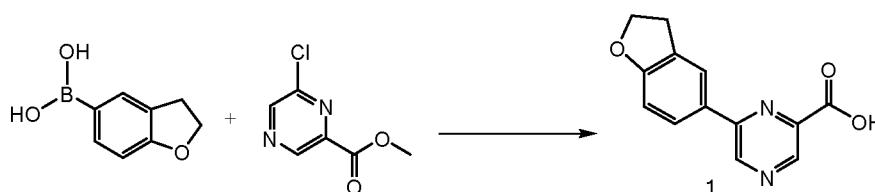
for simultaneous, separate or sequential administration.

The above other therapeutic agents, when employed in combination with a compound of the invention can be used, for example, in those amounts indicated in the
30 Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The present invention will be explained in more detail by the following experiments and examples. The experiments and examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXAMPLES:

Intermediate 1: 6-(2,3-Dihydrobenzofuran-5-yl)pyrazine-2-carboxylic acid



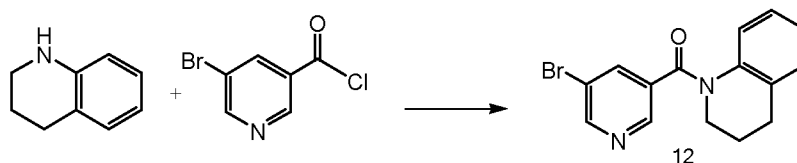
A mixture of methyl-6-chloro-2-pyrazinecarboxylate (0.5 g, 2.90 mmol), 2,3-dihydrobenzofuran-5-boronic acid (0.47 g, 2.90 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (102.0 mg, 0.145 mmol) and sodium carbonate (0.30 g, 2.90 mmol) in acetonitrile/ethanol/water (2 ml / 2 ml / 2 ml) was degassed and heated at 100° C in microwave oven for 1.5 h. After cooling to RT, the reaction mixture was diluted with EtOAc (10 ml) and filtered. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography to afford the title compound. LC-MS: m/z 243.1 $[\text{M}+\text{H}]^+$

The following intermediates were prepared according to the procedure described for Intermediate 1 from the starting materials indicated on the table.

No.	Structure	LC-MS	Starting material
Int-2		m/z 231.0 $[\text{M}+\text{H}]^+$	4-Methoxyphenylboronic acid and Methyl-6-chloro-2-pyrazine-carboxylate

Int-3		m/z 201.1 [M+H] ⁺	Methyl 6-phenylpyrazine-2-carboxylate
Int-4		m/z 229.1 [M+H] ⁺	4-Methoxyphenylboronic acid and 5-Bromopyridine-3-carboxylic acid
Int-5		m/z 231.0 [M+H] ⁺	3-Methoxyphenylboronic acid and Methyl-6-chloro-2-pyrazine-carboxylate
Int-6		m/z 201.1 [M+H] ⁺	3-Chloropyridazine-5-carboxylic acid and (4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzene
Int-7		m/z 219.0 [M+H] ⁺	3-Chloropyridazine-5-carboxylic acid and 4-Fluorobenzeneboronic acid
Int-8		m/z 226.4 [M+H] ⁺	1-Phenylvinylboronic acid pinacol ester and 5-Bromopyridine-3-carboxylic acid
Int-9		m/z 219.0 [M+H] ⁺	6-Chloropyrazine-2-carboxylic acid and 4-Fluorobenzeneboronic acid
Int-10		m/z 218.0 [M+H] ⁺	5-Bromopyridine-3-carboxylic acid and 4-Fluorobenzeneboronic acid

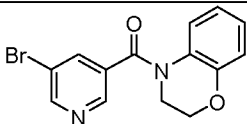
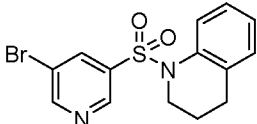
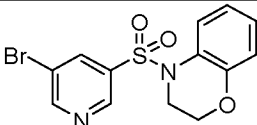
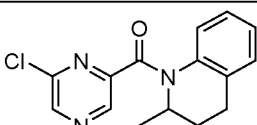
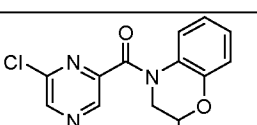
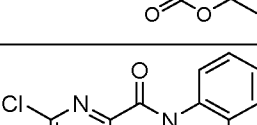
Intermediate 11: (5-Bromopyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone



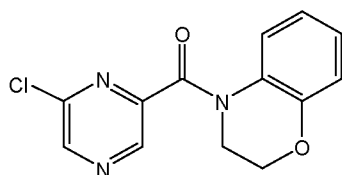
To a mixture of 5-bromopyridine-3-carbonylchloride (1.0 g, 4.54 mmol) and 1,2,3,4-tetrahydroquinoline (0.60 g, 4.54 mmol) in DCM (5 ml) at 0° C was added TEA (1.80 ml, 13.61 mmol). The reaction mixture was stirred at RT for 5 h. Water (10 ml) was added and the product was extracted with DCM, washed with brine, dried with anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by column chromatography to afford the title compound. LC-MS: *m/z* 317.4 [M+H]⁺

The following intermediates were prepared according to the procedure described for Intermediate 12 from the starting materials indicated on the table.

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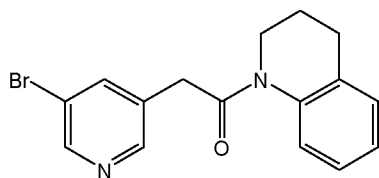
No.	Structure	LC-MS	Starting material
Int-12		<i>m/z</i> 321.0 [M+H] ⁺	2,3-Dihydro-1,4-benzoxazine and 5-Bromopyridine-3-carbonylchloride
Int-13		<i>m/z</i> 354.6 [M+H] ⁺	5-Bromo-3-(chlorosulphonyl)pyridine and 1,2,3,4-Tetrahydroquinoline
Int-14		<i>m/z</i> 356.9 [M+H] ⁺	5-Bromo-3-(chlorosulphonyl)pyridine and 2,3-Dihydro-1,4-benzoxazine
Int-15		<i>m/z</i> 288.0 [M+H] ⁺	6-Chloropyrazine-2-carbonylchloride and 2-Methyl-1,2,3,4-tetrahydroquinoline
Int-16		<i>m/z</i> 348.0 [M+H] ⁺	6-Chloropyrazine-2-carbonylchloride and Ethylbenzomorpholine-2-carboxylate
Int-17		<i>m/z</i> 290.0 [M+H] ⁺	6-Chloropyrazine-2-carbonyl chloride and 3-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine

Intermediate 18: (6-Chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone



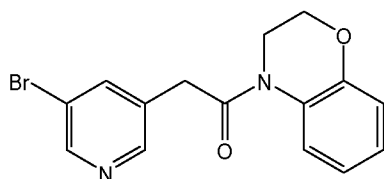
To a mixture of 6-chloropyrazine-2-carboxylic acid (0.793 g, 5.0 mmol) in dry
5 DCM (10 ml) was added few drops of DMF and oxalyl chloride (0.858 ml, 10.0 mmol).
The mixture was stirred at RT for 2 h. Solvents were evaporated and fresh DCM (10
ml) was added. Mixture was cooled to 0-5 °C (ice cooling) and DIPEA (1.742 ml, 10.0
mmol) and 3,4-dihydro-2H-benzo[b][1,4]oxazine (0.676 g, 5.0 mmol) were added. The
mixture was stirred at RT overnight. The mixture was diluted with DCM, washed with
10 water and brine, dried and evaporated. Crude product was purified by flash
chromatography to afford 0.92 g of the title compound. ¹H NMR (400 MHz, *d*₆-
DMSO): δ 8.95 (s, 2H), 7.5-8.5 (br, 1H), 7.00-7.17 (m, 1H), 6.94 (dd, 1H), 6.65-6.95
(br, 1H), 4.14-4.52 (m, 2H), 3.74-4.08 (m, 2H).

Intermediate 19: 2-(5-Bromopyridin-3-yl)-1-(3,4-dihydroquinolin-1(2H)-yl)-
15 ethan-1-one



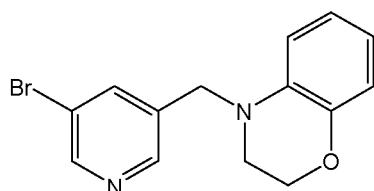
To an ice-cooled mixture of 5-bromo-3-pyridinecarboxylic acid (0.216 g, 1.00
mmol), 1,2,3,4-tetrahydroquinoline (0.147 g, 1.10 mmol) and trimethylamine (0.558
ml, 4.00 mmol) in dry DMF (5.5 ml) was added 1-propanephosphonic acid cyclic
20 anhydride (50 % in EtOAc, 0.795 ml, 1.35 mmol). The mixture was stirred overnight at
RT. The mixture was diluted with EtOAc and water and phases were separated. Organic
phase was washed with water and brine, dried and evaporated. Crude product was
purified by flash chromatography to afford 0.27 g of the title compound. ¹H NMR (400
MHz, CDCl₃): δ 8.53 (d, 1H), 8.23 (br s, 1H), 7.74 (br s, 1H), 6.98-7.26 (m, 4H), 3.83
25 (s, 2H), 3.81 (t, 2H), 2.52-2.70 (m, 2H), 1.94 (quint, 2H).

Intermediate 20: 2-(5-Bromopyridin-3-yl)-1-(2,3-dihydro-4H-benzo[b][1,4]-oxazin-4-yl)ethan-1-one



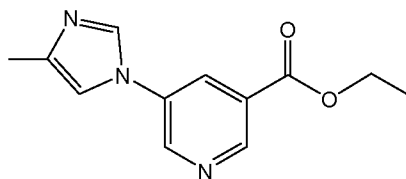
The compound was prepared according to the procedure described for
5 Intermediate 19 starting from 5-bromo-3-pyridinecarboxylic acid and 3,4-dihydro-2H-benzo[b][1,4]oxazine. Yield: 0.24 g. ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, 1H), 8.35 (br s, 1H), 7.78-7.85 (m, 1H), 6.99-7.22 (m, 2H), 6.89-6.98 (m, 2H), 4.24-4.32 (m, 2H), 3.83-4.05 (m, 4H).

Intermediate 21: 4-((5-Bromopyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b]-
10 [1,4]oxazine



A mixture of 3,4-dihydro-2H-benzo[b][1,4]oxazine (0.170 g, 1.259 mmol), 3-bromo-5-(chloromethyl)pyridine (0.260 g, 1.259 mmol), cesium carbonate (0.821 g, 2.52 mmol) and potassium iodide (0.021 g, 0.126 mmol) in dry acetonitrile (5.0 ml) was
15 stirred at 90 °C until the reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. Filtrate was evaporated and crude product was purified by flash chromatography to afford 0.12 g of the title compound. ¹H NMR (400 MHz, *d*₆-DMSO): δ 8.61 (d, 1H), 8.54 (d, 1H), 7.95-8.00 (m, 1H), 6.63-6.75 (m, 3H), 6.52-6.59 (m, 1H), 4.53 (s, 2H), 4.20-4.27 (m, 2H), 3.38-3.45
20 (m, 2H).

Intermediate 22: Ethyl 5-(4-methyl-1H-imidazol-1-yl)nicotinate

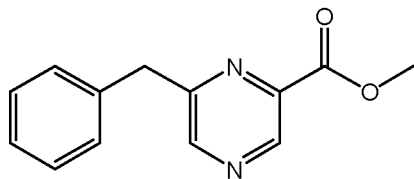


A mixture of tris(dibenzylideneacetone)dipalladium (7.33 mg, 0.008 mmol) and 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (8.65 mg, 0.018 mmol) in degassed toluene-dioxane (5:1, 1.0 ml) under nitrogen atmosphere was stirred at 120 °C for 10 min. Ethyl 5-bromonicotinate (0.23 g, 1.00 mmol), 4-methylimidazole (0.099 g, 1.20 mmol) and potassium phosphate (0.425 g, 2.00 mmol) were added and the mixture was stirred at 120 °C until reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. Filtrate was dried and evaporated. Crude product was purified by flash chromatography to afford the pure compound. ¹H NMR (400 MHz, CDCl₃): δ 9.18 (dd, 1H), 8.88 (dd, 1H), 8.28 (dd, 1H), 7.85 (d, 1H), 7.07-7.10 (m, 1H), 4.47 (q, 2H), 2.33 (d, 3H), 1.45 (t, 3H).

The following intermediates were prepared according to the procedure described for Intermediate 22 from the starting materials indicated on the table.

No.	Structure	¹ H NMR	Starting material
Int-23		¹ H NMR (400 MHz, <i>d</i> ₆ DMSO): δ 9.39 (d, 1H), 9.10 (d, 1H), 8.56 (d, 1H), 7.74-7.76 (m, 1H), 3.96 (s, 3H), 2.20 (d, 3H)	Methyl 6-chloro-pyrazine-2-carboxylate and 4-Methylimidazole
Int-24		¹ H NMR (400 MHz, CDCl ₃): δ 9.47 (d, 1H), 9.11 (d, 1H), 8.38-8.40 (m, 1H), 7.63-7.64 (m, 1H), 4.05 (s, 1H), 2.16-2.19 (m, 3H)	Methyl 6-chloro-pyrazine-2-carboxylate and 4-Methylpyrazole

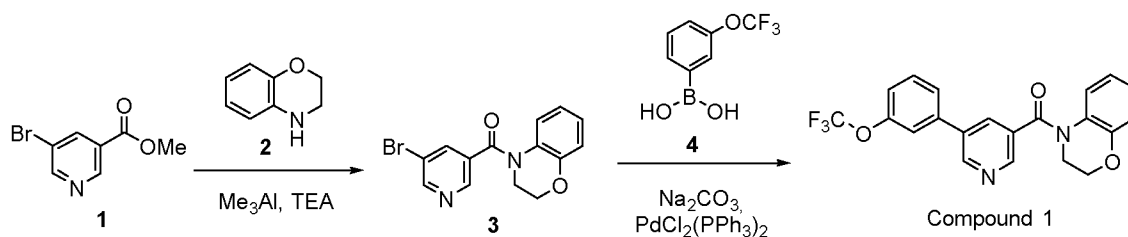
Intermediate 25: Methyl 6-benzylpyrazine-2-carboxylate



To a mixture of methyl 6-chloropyrazine-2-carboxylate (0.173 g, 1.00 mmol), potassium phosphate (0.637 g, 3.00 mmol), dicyclohexylphosphino-2,6-dimethoxybiphenyl (0.041 g, 0.10 mmol) and palladium acetate (0.011 g, 0.05 mmol) in degassed THF (10 ml) under nitrogen atmosphere was added B-benzyl-9-borabicyclo[3.3.1]nonane (0.5 M in THF, 2.5 ml, 5.0 mmol). The mixture was stirred at 65 °C until reaction was completed. Cooled mixture was diluted with DCM and filtered through a short plug of Celite. Filtrate was washed with aqueous 5 % Na₂CO₃ solution, water and brine, dried and evaporated. Crude product was purified by flash chromatography to afford 0.16 g of the title compound. ¹H NMR (400 MHz, CDCl₃): δ 9.14 (d, 1H), 8.57 (d, 1H), 7.23-7.37 (m, 5H), 4.31 (s, 2H), 4.05 (s, 3H).

Example 1.

(2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(3-(trifluoromethoxy)phenyl)pyridin-3-yl)methanone (Compound 1)



a) (5-Bromopyridin-3-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methanone (3)

20

Methyl 5-bromonicotinate (8.0 g, 37.0 mmol) was treated with 4-dihydro-2*H*-benzo[*b*][1,4]oxazine (7.5 g, 56.0 mmol) in the presence of triethylamine (11.0 g, 15 mL, 0.11 mol), trimethylaluminum (28.0 ml, 2 M in toluene, 56.0 mmol) in 40 ml of toluene at 25 °C for 16 h. Purification by combi-flash chromatography afforded 9.5 g of the title compound. ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 8.80 (d, 1H), 8.68 (d, 1H), 8.20

25

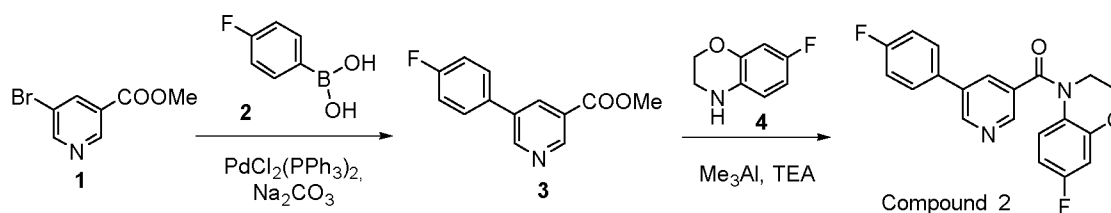
– 8.26 (m, 1H), 7.20 – 7.45 (m, 1H), 7.04 (t, 1H), 6.92 (d, 1H), 6.70 – 6.80 (m, 1H), 4.31 – 4.40 (m, 2H), 3.82 – 3.90 (m, 2H). MS (ESI) m/z $[M+1]^+$: 318.99.

b) (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(3-(trifluoromethoxy)phenyl)-pyridin-3-yl)methanone (Compound 1)

To a solution of methyl (5-bromopyridin-3-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]-oxazin-4-yl)methanone (200 mg, 0.627 mmol) in mixture of 2.5 ml of ethanol, 10 ml of toluene and 2.5 ml of water were added 3-(trifluoromethoxy)phenylboronic acid (142 mg, 0.689 mmol) and sodium carbonate (133 mg, 1.25 mmol) under inert atmosphere. Reaction mixture was degassed for 10 min followed by addition of bis(triphenylphosphine)palladium(II) dichloride. Degassing was continued for another 10 minutes. Resulting reaction mixture was stirred at 100 °C for 16 h. After completion of the reaction as indicated by TLC, the mixture was filtered through celite bed. Obtained filtrate was diluted with water (10 ml) and EtOAc (21 ml), and extracted with EtOAc (3 × 10 ml). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by combi-flash chromatography using 5-40 % EtOAc in heptane as an eluent to afford 0.08 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.05 (d, 1H), 8.73 (s, 1H), 8.28 (s, 1H), 7.81 (d, 1H), 7.76 (s, 1H), 7.65 (t, 1H), 7.45 (dd, 1H), 7.10 – 7.30 (m, 1H), 7.03 (dt, 1H), 6.94 (dd, 1H), 6.70 – 6.80 (m, 1H), 4.32 – 4.40 (m, 2H), 3.86 – 3.95 (m, 2H). MS (ESI) m/z $[M+1]^+$: 401.13.

Example 2.

(7-Fluoro-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridin-3-yl)methanone (Compound 2)



a) Methyl 5-(4-fluorophenyl)nicotinate (3)

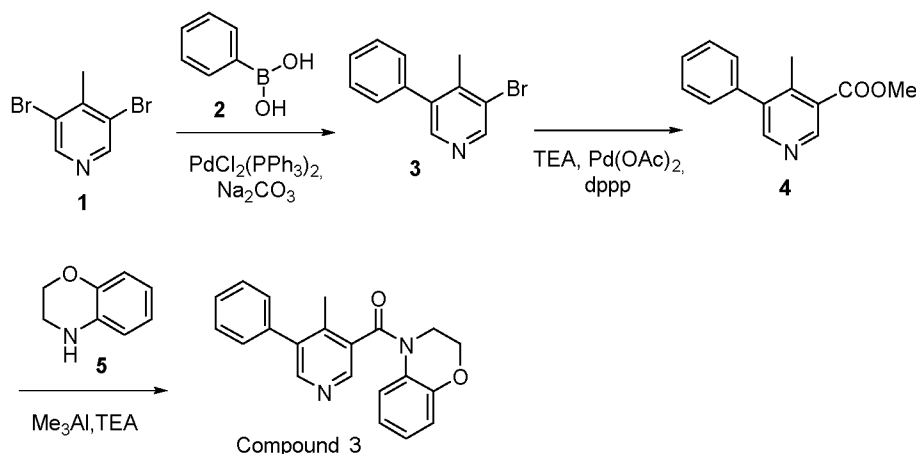
Methyl 5-bromonicotinate (2.0 g, 9.3 mmol) was treated with (4-fluorophenyl)-boronic acid (1.4 g, 10.0 mmol) in the presence of sodium carbonate (2.0 g, 19.0 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.65 g, 0.93 mmol) in 40 ml of DME and 20 ml water at 90 °C for 4 h. Purification by combi-flash using 5-30 % EtOAc in heptane as an eluent afforded 1.7 g of the title compound. ¹H-NMR (400 MHz, DMSO-d₆): δ: 9.13 (s, 1H), 9.07 (s, 1H), 8.47 (d, 1H), 7.87 (t, 2H), 7.37 (t, 2H), 3.93 (s, 3H). MS (ESI) m/z [M+1]⁺: 232.06.

b) (7-Fluoro-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)-pyridin-3-yl)methanone (Compound 2)

Methyl 5-(4-fluorophenyl)nicotinate (200 mg, 0.865 mmol) was treated with 7-fluoro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (199 mg, 1.30 mmol) in the presence of TEA (0.36 ml, 2.59 mmol) and trimethylaluminum (0.65 ml, 2.0 M in toluene, 1.30 mmol) in 8 ml toluene at 25 °C for 16 h. Purification by combi-flash chromatography using 5-25 % EtOAc in heptane as eluent afforded 0.235 g of the title compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.99 (d, 1H), 8.69 (s, 1H), 8.22 (s, 1H), 7.00 – 7.90 (m, 5H), 6.84 (dd, 1H), 6.67 (m, 1H), 4.30 – 4.40 (m, 2H), 3.84 – 3.93 (m, 2H). MS (ESI) m/z [M+1]⁺: 352.11.

Example 3.

(2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(4-methyl-5-phenylpyridin-3-yl)-methanone (Compound 3)



a) 3-Bromo-4-methyl-5-phenylpyridine (3)

5 3,5-Dibromo-4-methylpyridine (5.0 g, 20.0 mmol) was treated with (phenyl-
boronic acid (2.7 g, 22.0 mmol) in the presence of sodium carbonate (4.2 g, 40.0 mmol)
and bis(triphenylphosphine)palladium(II) dichloride (1.4 g, 2.0 mmol) in 60 ml of DME
and 30 ml of water at 90 °C for 6 h. Purification by combi-flash using 5-30 % EtOAc in
heptane as an eluent afforded 3.1 g of the title compound. $^1\text{H-NMR}$ (400 MHz, DMSO-
10 d_6): δ : 8.69 (s, 1H), 8.35 (s, 1H), 7.43 – 7.54 (m, 3H), 7.38 – 7.44 (m, 2H), 2.30 (s, 3H).
MS (ESI) m/z $[\text{M}+1]^+$: 248.01.

b) 4-Methyl-5-phenylnicotinate (4)

15 To a solution of 3-bromo-4-methyl-5-phenylpyridine (2.8 g, 11.0 mmol) in
MeOH : DMSO (1 : 1) was added triethylamine (7.8 ml, 56.0 mmol). The reaction
mixture was degassed with argon for 10 min followed by addition of palladium(II)
acetate (0.51 g, 2.3 mmol) and 1,3-bis(diphenylphosphino)propane (0.93 g, 2.3 mmol)
and CO gas. The resulting reaction mixture was stirred at 100 °C for 16 h. After
20 completion of the reaction as indicated by TLC, all volatile were evaporated under
reduced pressure. Obtained residue was diluted with water (20 ml) and EtOAc (30 ml),
and extracted with EtOAc (3 $\times$ 30 ml). The combined organic layer was washed with
water and brine, dried over anhydrous sodium sulphate and concentrated under reduced
pressure. The residue was purified by combi-flash chromatography using 5-40 %
25 EtOAc in heptane as an eluent to afford 2.3 g of the title compound. $^1\text{H-NMR}$ (400

MHz, DMSO- d_6): δ : 8.87 (s, 1H), 8.52 (s, 1H), 7.41 – 7.53 (m, 3H), 7.36 – 7.41 (m, 2H), 3.89 (s, 3H), 2.39 (s, 3H). MS (ESI) m/z $[M+1]^+$: 228.03.

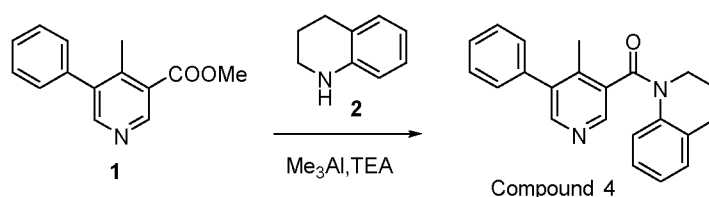
c) (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(4-methyl-5-phenylpyridin-3-yl)methanone (Compound 3)

4-Methyl-5-phenylnicotinate (500 mg, 2.20 mmol) was treated with 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (446 mg, 3.30 mmol) in the presence of triethylamine (0.93 ml, 6.60 mmol) and trimethylaluminum (1.65 ml, 2.0 M in toluene, 3.30 mmol) in 12 ml of toluene at 100 °C for 16 h. Purification by combi-flash chromatography using 5-40 % EtOAc in heptane as eluent afforded 0.05 g of the title compound. R_f (50 % EtOAc/heptane) = 0.2. 1H NMR (400 MHz, DMSO- d_6) δ : 8.48 (s, 1H), 8.40 (s, 1H), 7.26 – 7.54 (m, 6H), 7.06 (s, 1H), 6.92 (d, 1H), 6.75 – 6.84 (m, 1H), 4.31 – 4.40 (m, 2H), 3.31 – 3.40 (m, 2H), 2.16 (s, 1H). MS (ESI) m/z $[M+1]^+$: 330.97.

15

Example 4.

(3,4-Dihydroquinolin-1(2*H*)-yl)(4-methyl-5-phenylpyridin-3-yl)methanone (Compound 4)

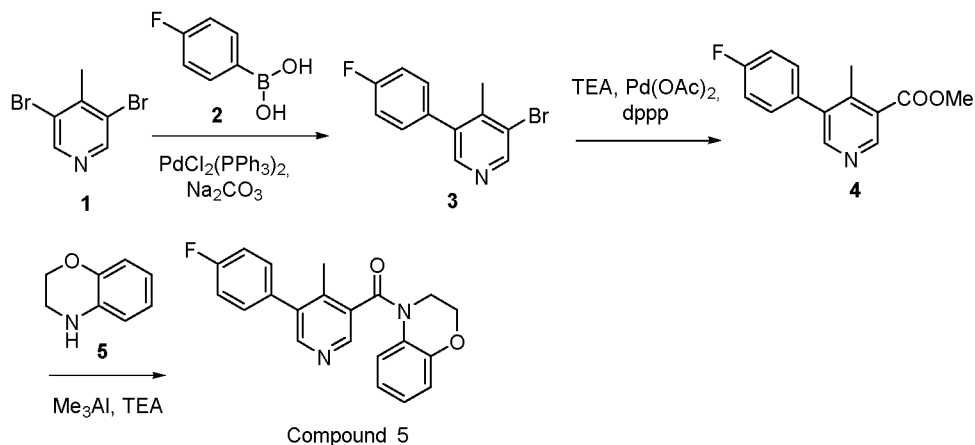


4-Methyl-5-phenylnicotinate (500 mg, 2.20 mmol) was treated with 1,2,3,4-tetrahydroquinoline (440 mg, 3.30 mmol) in the presence of triethylamine (0.93 ml, 6.60 mmol) and trimethylaluminum (1.65 ml, 2.0 M in toluene, 3.30 mmol) in 15 ml toluene at 100 °C for 16 h. Purification by combi-flash chromatography using 5-30 % EtOAc in heptane as eluent afforded 0.15 g of the title compound. R_f (50 % EtOAc/heptane) = 0.2. 1H NMR (400 MHz, DMSO- d_6) δ : 8.35 (s, 2H), 7.40 – 7.55 (m, 3H), 7.25 – 7.35 (m, 2H), 7.18 – 7.22 (m, 1H), 6.98 – 7.07 (m, 2H), 3.74 – 3.80 (m, 2H), 2.84 (t, 2H), 2.09 (s, 3H), 1.94 – 2.03 (m, 2H). MS (ESI) m/z $[M+1]^+$: 329.15.

25

Example 5.

(2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)-4-methylpyridin-3-yl)methanone (Compound 5)



5 a) 3-Bromo-5-(4-fluorophenyl)-4-methylpyridine (3)

3,5-Dibromo-4-methylpyridine (5.0 g, 0.02 mol) was treated with (4-fluorophenyl)boronic acid (3.0 g, 0.02 mol), Na₂CO₃ (6.0 g, 0.06 mol) and Pd(PPh₃)₂Cl₂ (1.0 g, 2.0 mmol) in 60 ml of DME and 30 ml of water at 100 °C for 16 h. Purification by
10 combi-flash chromatography using 5-40 % ethyl acetate in heptane as an eluent afforded 4.2 g of the title compound. ¹H-NMR (400 MHz, DMSO-*d*₆): δ: 8.65 (s, 1H), 8.31 (s, 1H), 7.23 - 7.30 (m, 2H), 7.10 - 7.20 (m, 2H), 2.33 (s, 3H). MS (ESI) *m/z* [M+1]⁺: 265.90.

15 b) Methyl 5-(4-fluorophenyl)-4-methylnicotinate (4)

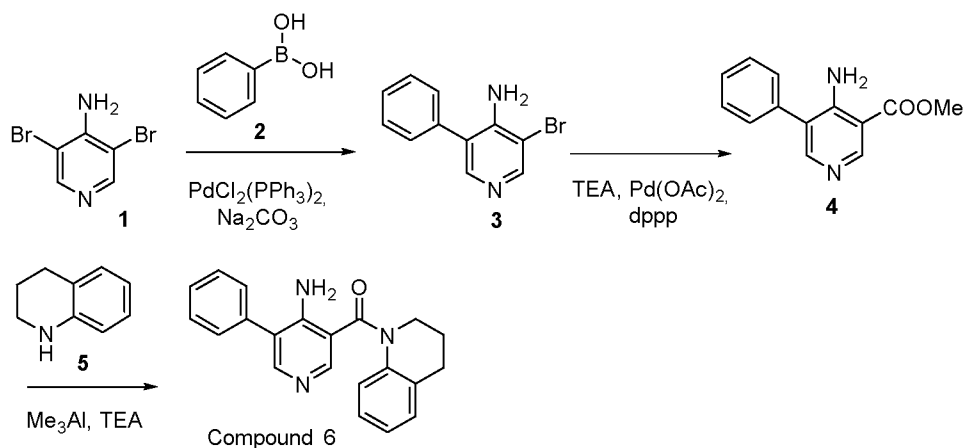
3-Bromo-5-(4-fluorophenyl)-4-methylpyridine (5.0 g, 0.02 mol) was treated with triethylamine (8.0 g, 11 ml, 79.0 mmol), palladium(II) acetate (0.71 g, 3.2 mmol), 1,3-bis(diphenylphosphino)propane (1.3 g, 3.2 mmol) and CO gas in 60 ml of DMSO
20 and 60 ml of MeOH at 100 °C for 16 h. Purification by combi-flash chromatography using 10-40 % ethyl acetate in heptane as an eluent afforded 3.2 g of the title compound. ¹H-NMR (400 MHz, DMSO-*d*₆): δ: 8.87 (s, 1H), 8.52 (s, 1H), 7.41 - 7.50 (m, 2H), 7.30 - 7.37 (m, 2H), 3.89 (s, 3H), 2.38 (s, 3H). MS (ESI) *m/z* [M+1]⁺: 343.10.

c) (2,3-Dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(4-fluorophenyl)-4-methylpyridin-3-yl)methanone (Compound 5)

Methyl 5-(4-fluorophenyl)-4-methylnicotinate (400 mg, 1.63 mmol) was treated with 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (331 mg, 2.45 mmol) in the presence of triethylamine (0.68 ml, 4.89 mmol) and trimethylaluminum (1.22 ml, 2 M in toluene, 2.45 mmol) in 10 ml of toluene at 95 °C for 18 h. Purification by combi-flash chromatography using 5-40 % ethyl acetate in heptane as an eluent afforded 0.118 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.18 – 8.57 (m, 2H), 7.41 – 7.55 (m, 2H), 7.34 (t, 2H), 7.00 – 7.10 (m, 1H), 6.93 (d, 2H), 6.30 – 6.60 (m, 1H), 4.20 – 4.50 (m, 2H), 3.54 – 3.80 (m, 2H), 2.16 (s, 3H). MS (ESI) *m/z* [M+1]⁺: 349.12.

Example 6.

(4-Amino-5-phenylpyridin-3-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (Compound 6)



a) 3-Bromo-5-phenylpyridin-4-amine (3)

3,5-Dibromopyridin-4-amine (6.0 g, 24.0 mmol) was treated with phenylboronic acid (3.2 g, 26.0 mmol), Na_2CO_3 (5.0 g, 48.0 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.7 g, 2.4 mmol) in 12 ml of DME and 6 ml of water at 90 °C for 4 h. Purification by combi-flash chromatography using 5-40 % ethyl acetate in heptane as an eluent afforded 3.6 g of the title compound. ¹H-NMR (400 MHz, DMSO-*d*₆): δ: 8.29 (s, 1H), 7.91 (s, 1H), 7.47 – 7.55 (m, 2H), 7.38 – 7.47 (m, 3H), 5.73 (bs, 2H). MS (ESI) *m/z* [M+1]⁺: 248.97.

b) Methyl 4-amino-5-phenylnicotinate (4)

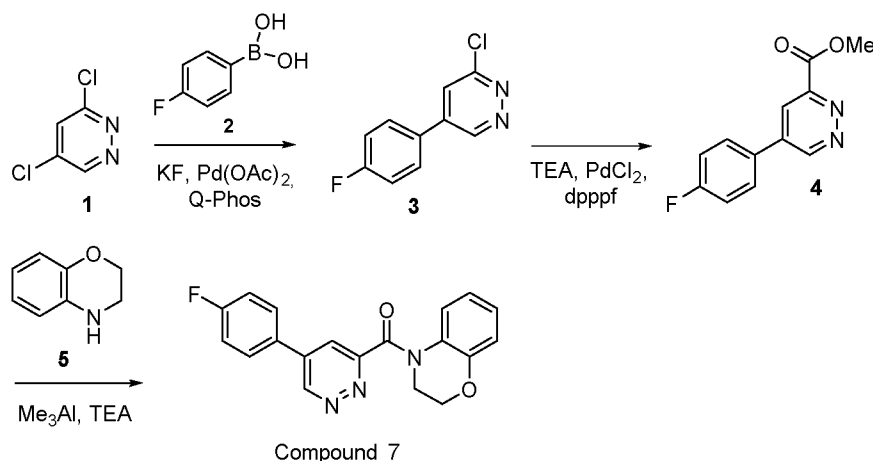
3-Bromo-5-phenylpyridin-4-amine (2.8 g, 11.0 mmol) was treated with
5 triethylamine (5.7 g, 7.8 ml, 56.0 mmol), palladium(II) acetate (1.0 g, 4.5 mmol), 1,3-
bis(diphenylphosphino)propane (1.9 g, 4.5 mmol) and CO gas in 50 ml of MeOH and
50 ml of DMSO at 80 °C for 12 h. Purification by combi-flash chromatography using
10-40 % ethyl acetate in heptane as an eluent afforded 1.6 g of the title compound. ¹H-
NMR (400 MHz, DMSO-d₆): δ 8.74 (s, 1H), 8.03 (s, 1H), 7.48 – 7.55 (m, 2H), 7.38 –
10 7.48 (m, 3H), 6.87 (bs, 2H), 3.85 (s, 3H). MS (ESI) m/z [M+1]⁺: 229.19.

c) (4-Amino-5-phenylpyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone
(Compound 6)

15 Methyl 4-amino-5-phenylnicotinate (500 mg, 2.19 mmol) was treated with
1,2,3,4-tetrahydroquinoline (438 mg, 3.29 mmol), triethylamine (0.92 ml, 6.57 mmol)
trimethylaluminum (1.64 ml, 2.0 M in toluene, 3.29 mmol) in 20 ml of toluene at 100
°C for 16 h. Purification by combi-flash chromatography using 5-30 % ethyl acetate in
heptane as an eluent afforded 0.025 g of the title compound. (NMR/MS data in Table
20 2). ¹H NMR (400 MHz, DMSO-d₆) δ: 7.90 (s, 1H), 7.79 (s, 1H), 7.51 (t, 2H), 7.37 –
7.47 (m, 3H), 7.20 (d, 1H), 6.92 – 7.06 (m, 3H), 5.83 (bs, 2H), 3.78 (t, 2H), 2.82 (t, 2H),
1.96 (q, 2H). MS (ESI) m/z [M+1]⁺: 302.20.

Example 7.

25 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridazin-3-yl)-
methanone (Compound 7)



a) 3-Chloro-5-(4-fluorophenyl)pyridazine (3)

- 5 3,5-Dichloropyridazine (3.0 g, 20.1 mmol) was treated with (4-fluorophenyl)-boronic acid (3.10 g, 22.2 mmol), KF (2.93 g, 50.3 mmol), diacetoxypalladium (226 mg, 1.01 mmol) and Q-PHOS (716 mg, 1.01 mmol) in 40 ml of toluene and 10 ml of water at 80 °C for 16 h. Purification by combi-flash chromatography using 5-40 % ethyl acetate in heptane as an eluent afforded 1.0 g of the title compound. R_f (70 %
- 10 EtOAc/heptane) = 0.4. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 9.68 (d, 1 H), 8.29 (d, 1 H), 8.09 (dt, 2H), 7.43 (dd, 2H). MS (ESI) m/z $[\text{M}+1]^+$: 209.02.

b) Methyl 5-(4-fluorophenyl)pyridazine-3-carboxylate (4)

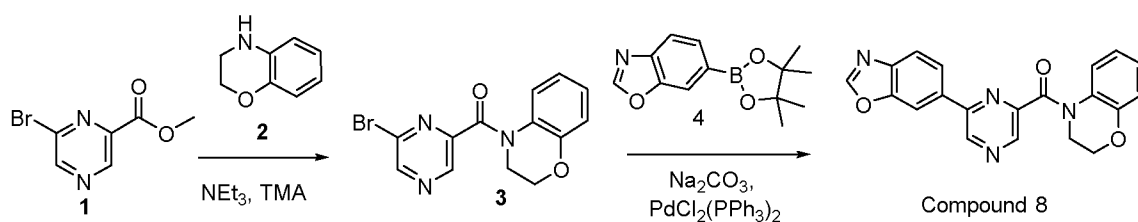
- 15 3-Chloro-5-(4-fluorophenyl)pyridazine (850 mg, 4.07 mmol) was treated with triethylamine (1.14 ml, 8.15 mmol), $\text{PdCl}_2(\text{dppf})$ (298 mg, 0.407 mmol) and CO gas in 50 ml of MeOH at 100 °C for 16 h. Purification by combi-flash chromatography using 10-40 % ethyl acetate in heptane as an eluent afforded 0.87 g of the title compound. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 9.86 (d, 1 H), 8.45 (d, 1 H), 8.11 (dd, 2H), 7.44 (dd,
- 20 2H), 3.99 (s, 3H). MS (ESI) m/z $[\text{M}+1]^+$: 233.02.

c) (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridazin-3-yl)methanone (Compound 7)

Methyl 5-(4-fluorophenyl)pyridazine-3-carboxylate (500 mg, 2.15 mmol) was treated with 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (437 mg, 3.23 mmol), triethylamine (0.91 ml, 6.46 mmol) and trimethylaluminum (1.61 ml, 2.0 M in toluene, 3.23 mmol) in 15 ml toluene at 100 °C for 16 h. Purification by combi-flash chromatography using 5-
 5 40 % ethyl acetate in heptane as an eluent afforded 0.142 g of the title compound. *R_f* (50 % EtOAc/heptane) = 0.2.

Example 8.

(6-(Benzo[*d*]oxazol-6-yl)pyrazin-2-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-
 10 yl)methanone (Compound 8)



a) (6-Bromopyrazin-2-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methanone
 (3)

15

Methyl 5-(4-fluorophenyl)pyridazine-3-carboxylate (20 mg, 0.086 mmol) was treated with 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (18.2 mg, 0.129 mmol), triethylamine (36 μl, 0.258 mmol) and trimethylaluminum (65 μl, 2.0 M in toluene, 0.129 mmol) in 5 ml of toluene at 100 °C for 16 h. Purification by combi-flash
 20 chromatography using 20-60 % ethyl acetate in heptane as an eluent afforded 0.025 g of the title compound. *R_f* (50 % EtOAc/heptane) = 0.2. Yield: 70 %. ¹H-NMR (400 MHz, DMSO-*d*₆): δ: 9.01 (s, 1H), 8.96 (s, 1H), 7.50 – 8.50 (m, 1H), 7.08 (t, 1H), 6.93 (d, 1H), 6.70 – 6.90 (m, 1H), 4.20 – 4.48 (m, 2H), 3.80 – 3.92 (m, 2H). MS (ESI) *m/z* [M+1]⁺: 320.05.

25

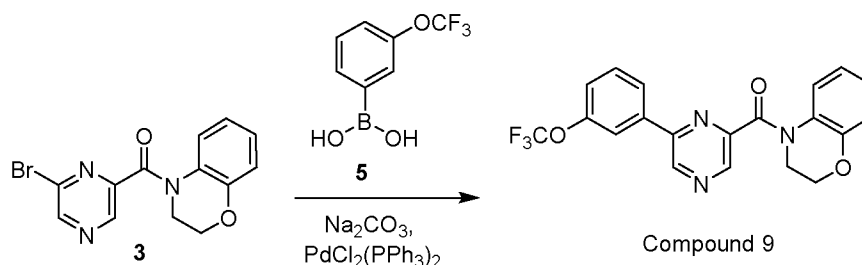
b) (6-(Benzo[*d*]oxazol-6-yl)pyrazin-2-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methanone (Compound 8)

(6-Bromopyrazin-2-yl)(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methanone
 30 (500 mg, 1.56 mmol) was treated with 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

benzo[d]oxazole (383 mg, 1.56 mmol), sodium carbonate (331 mg, 3.12 mmol) and Pd(PPh₃)₂Cl₂ (110 mg, 0.156 mmol) in 2.5 ml of ethanol, 10 ml of toluene and 2.5 ml of water at 90 °C for 16 h. Purification by combi-flash chromatography using 0-50 % ethyl acetate in heptane as an eluent afforded 0.3 g of the title compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.41 (s, 1H), 8.92 (s, 1H), 8.77 (s, 1H), 8.36 (s, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.41 – 7.51 (m, 1H), 7.06 (t, 1H), 6.96 (d, 1H), 6.78 (t, 1H), 4.39 (t, 2H), 4.05 (t, 2H). MS (ESI) m/z [M+1]⁺: m/z 359.15.

Example 9.

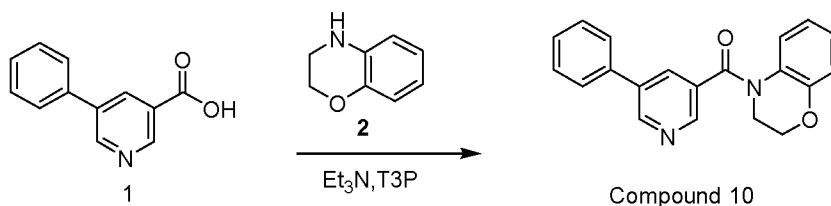
(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(3-(trifluoromethoxy)phenyl)-pyrazin-2-yl)methanone (Compound 9)



(6-Bromopyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (500 mg, 1.56 mmol) was treated with (3-(trifluoromethoxy)phenyl)boronic acid (354 mg, 1.72 mmol), sodium carbonate (331 mg, 3.12 mmol) and Pd(PPh₃)₂Cl₂ (110 mg, 0.156 mmol) in 0.63 ml of ethanol, 2.5 ml of toluene and 0.63 ml of water at 90 °C for 16 h. Purification by combi-flash chromatography using 0-35 % ethyl acetate in heptane as an eluent afforded 0.4 g of the title compound. ¹H NMR (400 MHz, DMSO-d₆) δ 9.37 (s, 1H), 8.96 (s, 1H), 8.07 (d, 1H), 7.89 (s, 1H), 7.65 (t, 1H), 7.48 (d, 1H), 7.35 – 7.46 (m, 1H), 7.05 (t, 1H), 6.94 (d, 1H), 6.77 (t, 1H), 4.38 (t, 2H), 4.03 (t, 2H). MS (ESI) m/z [M+1]⁺: m/z 402.12.

Example 10.

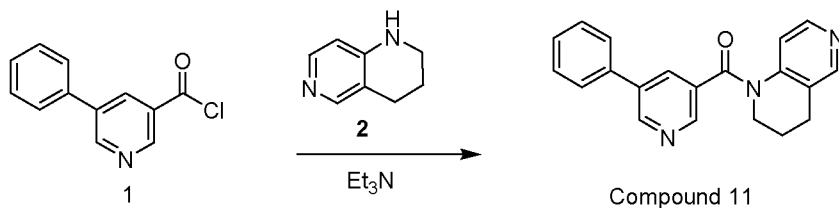
(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-phenylpyridin-3-yl)methanone (Compound 10)



A solution of 50 % propylphosphonic anhydride (T3P) in EtOAc (0.6 ml, 1.0 mmol) was added to a mixture of 5-phenylnicotinic acid (0.10 g, 1.50 mmol), 2,3-dihydro-1,4-benzoxazine (0.07 g, 0.50 mmol) and Et₃N (0.41 ml, 4.02 mmol) in DMF (2 ml). The mixture was stirred over night at RT under N₂. The mixture was diluted with EtOAc (10 ml) and 5 % Na₂CO₃ (5 ml) and extracted with EtOAc. The combined extracts were washed with brine, dried with Na₂SO₄ filtered and evaporated. The crude product was purified by column chromatography to afford the title compound. ¹H NMR (Chloroform-d, 400 MHz) δ: 8.88 (d, 1H), 8.69 (d, 1H), 7.99 (t, 1H), 7.4-7.5 (m, 5H), 6.8-7.1 (m, 3H), 6.6-6.8 (m, 1H), 4.3-4.5 (m, 2H), 4.0-4.1 (m, 2H).

Example 11.

(5-(4-Chlorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 11)



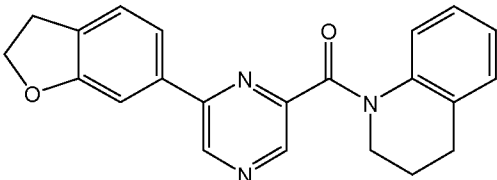
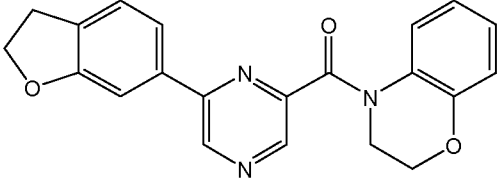
A mixture of 5-(4-chlorophenyl)pyridin-3-yl)pyridin-3-yl)methanone (0.1 g, 0.46 mmol), 1,2,3,4-tetrahydro-1,6-naphthyridine (61.6 mg, 0.46 mmol) in DCM (5 ml) was cooled to 0° C followed by addition of Et₃N (0.2 ml, 1.38 mmol). The mixture was stirred at RT for 12 h. Water (10 ml) was added followed by extraction with DCM. The combined organic layer was washed with brine, dried with anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by column chromatography to afford the title compound. ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.99 (d, 1H), 8.63 (d, 1H), 8.39 (s, 1H), 8.17 (t, 1H), 8.13 (d, 1H), 7.72 (d, 2H), 7.51 (t, 2H), 7.4-7.5 (m, 1H), 7.20 (br d, 1H), 3.8-3.8 (m, 2H), 2.86 (t, 2H), 1.99 (quin, 2H). LC-MS: *m/z* 316.4 (M+H)⁺.

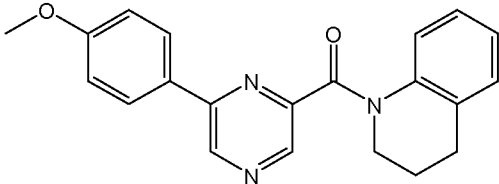
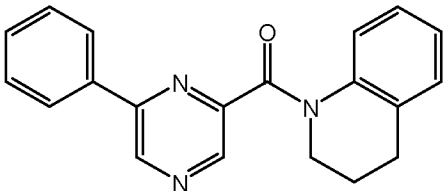
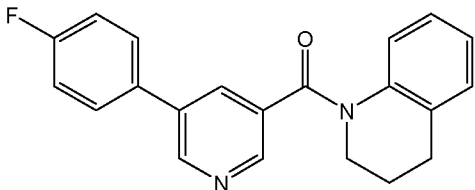
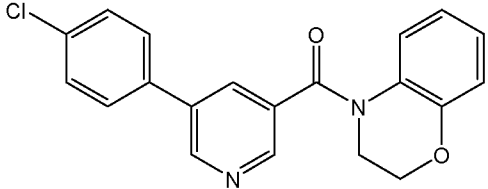
The following compounds were prepared according to the procedures described above. The compound number, characterization data, starting materials, reaction conditions (Example number referred to) and purification method are indicated on the table.

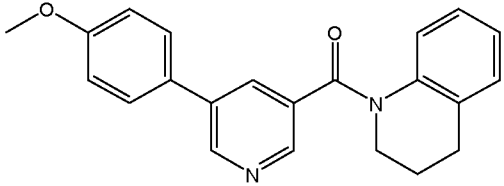
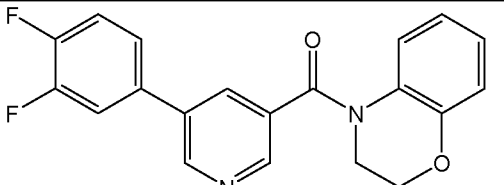
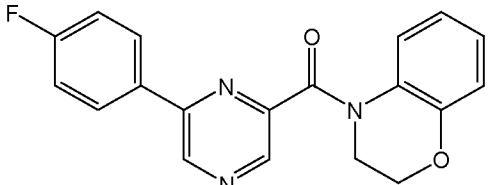
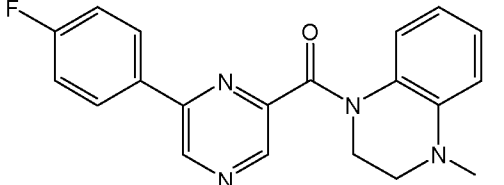
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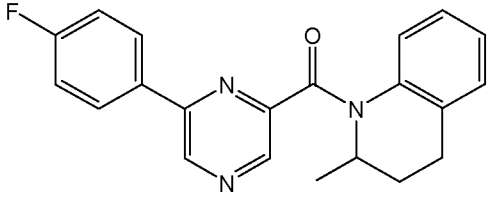
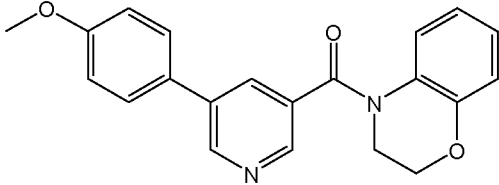
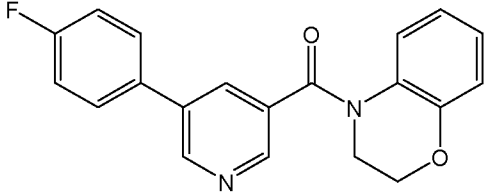
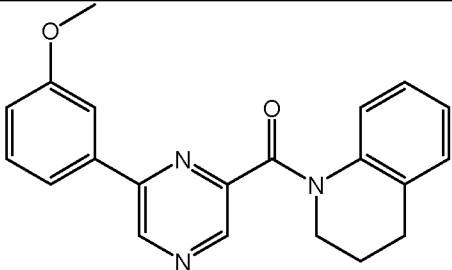
Purification methods used:

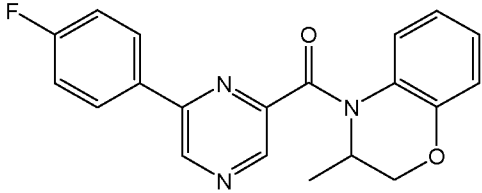
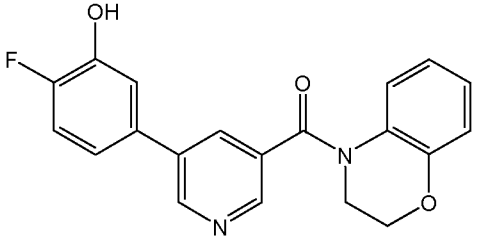
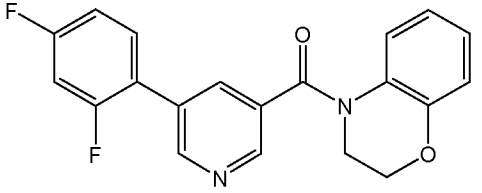
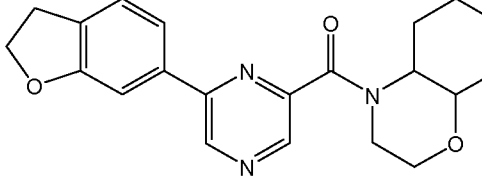
- a) Crystallization
 b) Column chromatography
 c) Precipitation in aqueous media
 10 d) Semipreparative HPLC
 e) Trituration
 f) Salt formation

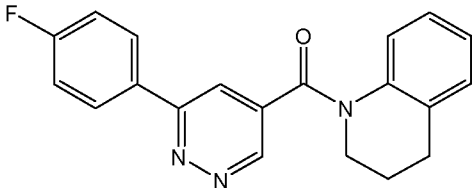
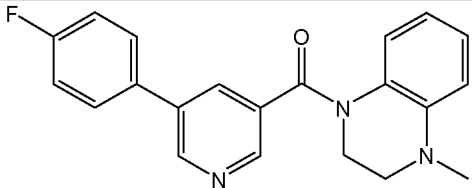
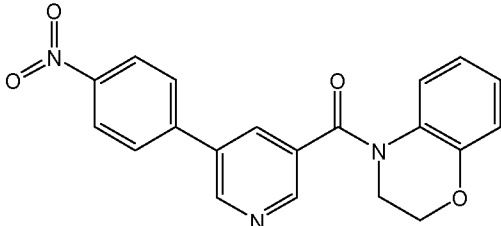
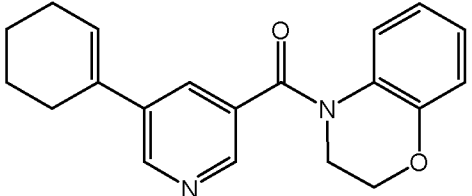
No	Structure and starting material	Reaction conditions, purification method, ¹ H NMR / LC-MS
12	 Starting materials: 6-(2,3-Dihydrobenzofuran-6-yl)pyrazine-2-carboxylic acid and 1,2,3,4-tetrahydroquinoline	Conditions: Ex.10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.88 (br s, 1H), 8.68 (s, 1H), 7.45 (td, 2H), 7.22 (d, 1H), 7.04 (br t, 1H), 6.8-7.0 (m, 1H), 6.7-6.8 (m, 1H), 4.62 (t, 2H), 3.99 (br t, 2H), 3.22 (br t, 2H), 2.89 (t, 2H), 2.11 (quin, 2H), 2.00 (s, 1H). LC-MS: m/z 359.1 (M+H)⁺.
13	 Starting materials: 6-(2,3-Dihydrobenzofuran-6-yl)pyrazine-2-carboxylic acid and 2,3-Dihydro-1,4-benzoxazine	Conditions: Ex. 10, purification b), ¹H NMR (400 MHz, Chloroform-d) δ: 3.30 (br s, 2H), 4.13 (br s, 2H), 4.43 (br s, 2H), 4.64 (t, 2H), 6.78-7.12 (m, 5H), 7.40-7.94 (m, 2H), 8.77-8.88 (m, 1H), 8.95-9.04 (m, 1H). LC-MS: m/z 361.1 (M+H)⁺.

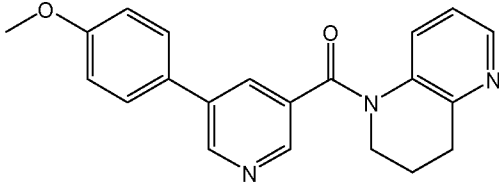
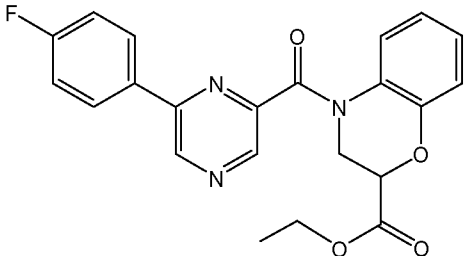
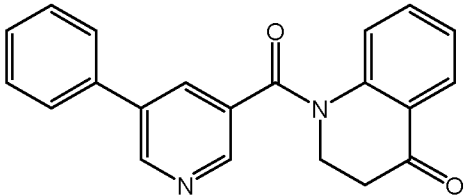
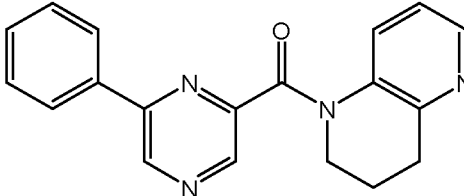
14	 Starting materials: 6-(4-Methoxyphenyl)pyrazine-2-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 2.12 (quin, 2H), 2.90 (t, 2H), 3.79-3.92 (m, 4H), 3.95-4.07 (m, 2H), 6.65-7.14 (m, 5H), 7.16-7.25 (m, 1H), 7.52 (br s, 1H), 7.59 (br s, 1H), 8.70 (s, 1H), 8.91 (br s, 1H). LC-MS: <i>m/z</i> 346.1 (M+H)⁺.
15	 Starting materials: 6-Phenylpyrazine-2-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.26 (br s, 1H), 8.79 (br s, 1H), 8.16 (s, 1H), 7.7-7.9 (m, 1H), 7.48 (br s, 3H), 7.27 (d, 1H), 7.0-7.1 (m, 1H), 6.8-7.0 (m, 1H), 3.86 (br s, 2H), 2.86 (t, 2H), 2.08 (s, 1H), 2.02 (quin, 2H). LC-MS: <i>m/z</i> 316.3 (M+H)⁺.
16	 Starting materials: (Fluorophenyl)-nicotinic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 8.88 (d, 1H), 8.45 (br s, 1H), 7.98 (br s, 1H), 7.70 (br dd, 2H), 7.33 (t, 2H), 7.25 (d, 1H), 7.05 (t, 1H), 6.9-7.0 (m, 1H), 6.86 (br s, 1H), 3.82 (t, 2H), 2.86 (t, 2H), 2.00 (quin, 2H). LC-MS: <i>m/z</i> 334.1 (M+H)⁺.
17	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[<i>b</i>][1,4]-oxazin-4-yl)methanone and 4-Chlorophenylboronic acid	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.00 (d, 1H), 8.71 (s, 1H), 8.23 (br s, 1H), 7.78 (br d, 2H), 7.58 (d, 2H), 7.03 (t, 1H), 6.94 (dd, 1H), 6.76 (br s, 1H), 4.3-4.4 (m, 2H), 3.93 (br s, 2H). LC-MS: <i>m/z</i> 351.8 (M+H)⁺.

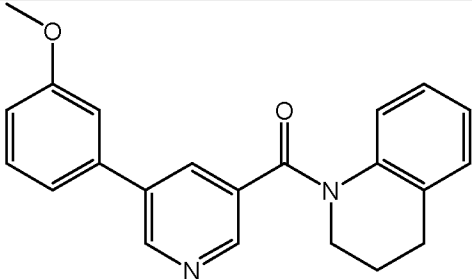
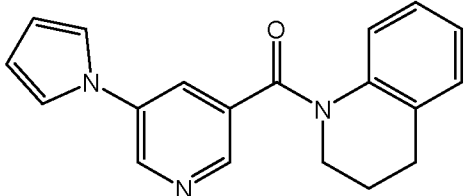
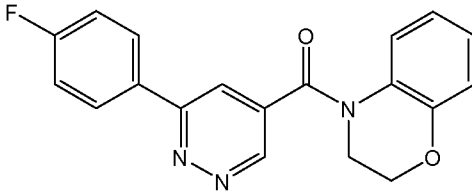
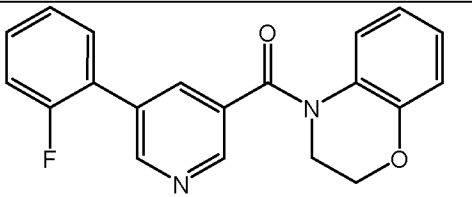
18	 Starting materials: 5-(4-Methoxyphenyl)nicotinic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 2.01-2.15 (m, 2H), 2.87 (t, 2H), 3.76-4.03 (m, 5H), 6.70 (br s, 1H), 6.88-7.08 (m, 4H), 7.21 (d, 1H), 7.37 (d, 2H), 7.81 (t, 1H), 8.44 (d, 1H), 8.75 (d, 1H). LC-MS: <i>m/z</i> 346.1 (M+H)⁺.
19	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone and 3,4-Difluorophenyl boronic acid	Conditions: Ex. 1, purification b), ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 3.93 (br s, 2H), 4.37 (br s, 2H), 6.76 (br s, 1H), 6.94 (dd, 1H), 7.04 (t, 1H), 7.55-7.67 (m, 3H), 7.86-7.98 (m, 1H), 8.26 (br s, 1H), 8.71 (br s, 1H), 9.03 (d, 1H). LC-MS: <i>m/z</i> 354.1 (M+H)⁺.
20	 Starting materials: 6-(4-Fluorophenyl)pyrazine-2-carboxylic acid and 2,3-Dihydro-1,4-benzoxazine	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.3-9.4 (m, 1H), 8.9-9.0 (m, 1H), 7.9-8.4 (m, 2H), 7.36 (br s, 2H), 7.0-7.1 (m, 1H), 6.9-7.0 (m, 2H), 4.35 (br s, 2H), 3.9-4.1 (m, 2H). LC-MS: <i>m/z</i> 336.3 (M+H)⁺.
21	 Starting materials: 6-(4-Fluorophenyl)pyrazine-2-carboxylic acid and 1,2,3,4-Tetrahydro-1-methylquinoxaline	Conditions: Ex. 10, purification b), ¹H NMR (Chloroform-<i>d</i>, 400 MHz) δ: 8.91 (br s, 2H), 8.73 (br s, 1H), 7.59 (br s, 2H), 7.09 (br s, 3H), 7.01 (br d, 2H), 6.74 (d, 2H), 6.25 (br s, 2H), 4.14 (br s, 3H), 3.57 (br s, 3H), 3.04 (br s, 4H). LC-MS: <i>m/z</i> 349.4 (M+H)⁺.

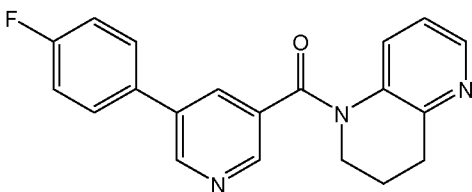
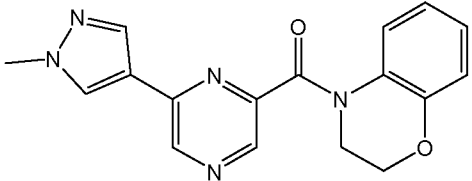
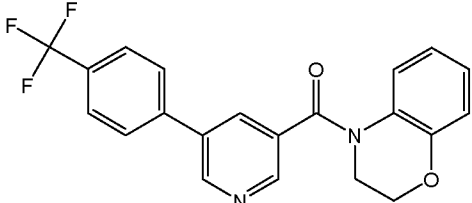
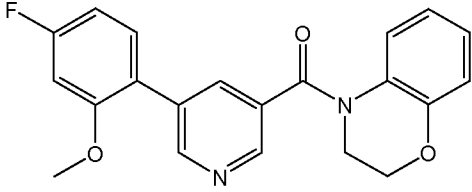
22	 Starting materials: (6-Chloropyrazin-2-yl)(2-methyl-3,4-dihydroquinolin-1(2H)-yl)methanone and 4-Fluorobenzene boronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.21 (br s, 1H), 8.72 (br s, 1H), 7.83 (br s, 2H), 7.2-7.4 (m, 3H), 7.04 (br t, 1H), 6.89 (br s, 1H), 4.70 (br s, 1H), 2.7-2.8 (m, 2H), 2.3-2.5 (m, 1H), 1.44 (br s, 1H), 1.23 (d, 3H). LC-MS: <i>m/z</i> 348.4 (M+H)⁺.
23	 Starting materials: 5-(4-Methoxyphenyl)nicotinic acid and 2,3-Dihydro-1,4-benzoxazine	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.96 (d, 1H), 8.64 (s, 1H), 8.15 (br s, 1H), 7.69 (br d, 2H), 7.0-7.1 (m, 3H), 6.94 (dd, 1H), 6.7-6.8 (m, 1H), 4.38 (br s, 2H), 3.94 (br s, 2H), 3.82 (s, 3H), 0.93 (s, 1H). LC-MS: <i>m/z</i> 348.1 (M+H)⁺.
24	 Starting materials: 5-(4-Fluorophenyl)nicotinic acid and 2,3-Dihydro-1,4-benzoxazine	Conditions: Ex.10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.91 (d, 1H), 8.62 (s, 1H), 8.13 (br s, 1H), 7.7-7.8 (m, 2H), 7.28 (t, 2H), 6.96 (t, 1H), 6.86 (dd, 1H), 6.69 (br s, 1H), 4.30 (br s, 2H), 3.86 (br s, 2H). LC-MS: <i>m/z</i> 336.1 (M+H)⁺.
25	 Starting materials: 6-(3-Methoxyphenyl)pyrazine-2-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex.10, purification b), ¹H NMR (600 MHz, DMSO-d₆) δ: 1.98-2.08 (m, 2H), 2.85 (t, 2H), 3.32 (br s, 4H), 3.77 (s, 3H), 3.86 (br s, 2H), 6.89 (br s, 1H), 7.03 (br d, 2H), 7.18-7.31 (m, 2H), 7.37 (br t, 2H), 7.47 (br s, 1H), 8.81 (s, 1H), 9.26 (br s, 1H). LC-MS: <i>m/z</i> 347.3 (M+H)⁺.
26		Conditions: Ex. 1, purification b),

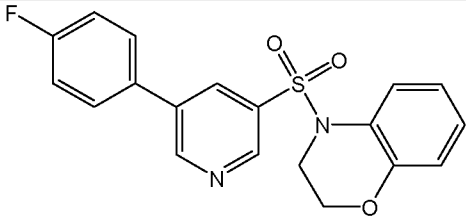
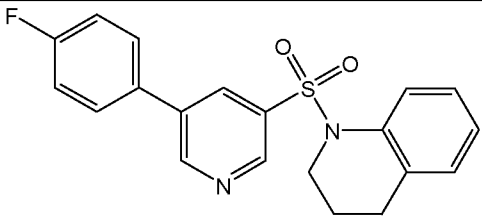
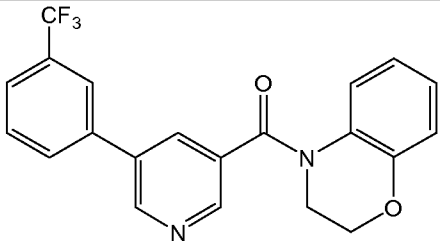
	 Starting materials: (6-Chloropyrazin-2-yl)(3-methyl-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Fluorobenzene boronic acid	¹ H NMR (DMSO-d ₆ , 600 MHz) δ: 9.38 (br s, 1H), 8.90 (s, 1H), 8.16 (br s, 2H), 7.39 (br s, 2H), 7.08 (br s, 1H), 6.97 (d, 1H), 6.7-6.9 (m, 1H), 4.26 (br s, 1H), 4.20 (br s, 1H), 1.3-1.4 (m, 3H). LC-MS: <i>m/z</i> 350.4 (M+H) ⁺ .
27	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Fluoro-3-hydroxyphenylboronic acid	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO-d ₆ , 600 MHz) δ: 10.11 (br s, 1H), 8.89 (s, 1H), 8.67 (br s, 1H), 8.11 (br s, 1H), 7.2-7.3 (m, 2H), 7.13 (br s, 1H), 7.03 (t, 1H), 6.93 (dd, 1H), 6.75 (br s, 1H), 4.37 (br s, 2H), 3.93 (br s, 2H), 2.1-2.1 (m, 1H). LC-MS: <i>m/z</i> 351.1 (M+H) ⁺ .
28	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 2,4-Difluorophenyl boronic acid	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO-d ₆ , 600 MHz) δ: 8.84 (s, 1H), 8.75 (s, 1H), 8.10 (br s, 1H), 7.6-7.7 (m, 1H), 7.45 (t, 1H), 7.26 (dt, 1H), 7.03 (t, 1H), 6.93 (dd, 1H), 6.76 (br s, 1H), 4.37 (br s, 2H), 3.93 (br s, 2H). LC-MS: <i>m/z</i> 354.1 (M+H) ⁺ .
29	 Starting materials: 6-(2,3-Dihydrobenzofuran-6-yl)pyrazine-2-carboxylic acid and Octahydro-2H-benzo[b][1,4]oxazin-4-ylmethanone	Conditions: Ex. 10, purification b), ¹ H NMR (Chloroform-d, 400 MHz) δ: 9.0-9.0 (m, 1H), 8.7-8.8 (m, 1H), 7.8-7.9 (m, 2H), 6.91 (d, 1H), 4.6-4.7 (m, 2H), 3.9-4.1 (m, 4H), 3.31 (t, 3H), 2.44 (br s, 1H), 1.9-2.1 (m, 2H), 1.7-

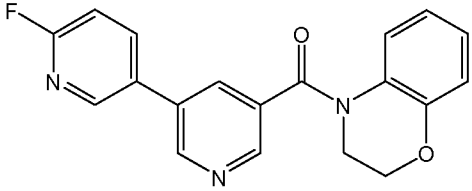
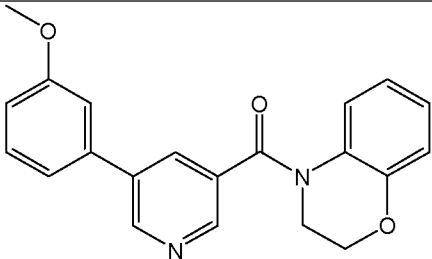
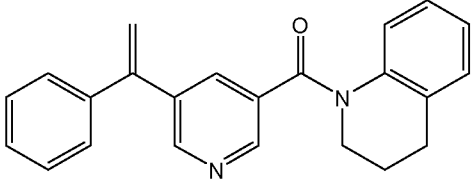
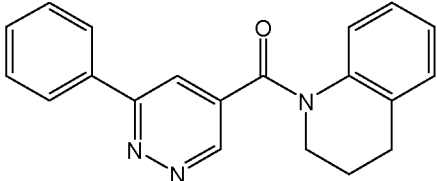
	oxazine	1.9 (m, 2H), 1.5-1.6 (m, 1H), 1.3-1.5 (m, 3H). LC-MS: m/z 466.5 (M+H) ⁺ .
30	 Starting materials: 6-(4-Fluorophenyl)pyridazine-4-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.9-9.2 (m, 1H), 8.16 (br s, 2H), 7.40 (t, 3H), 7.26 (d, 2H), 7.07 (br t, 1H), 6.9-7.0 (m, 1H), 3.82 (br s, 2H), 2.88 (t, 2H), 2.01 (br s, 2H). LC-MS: m/z 334.1 (M+H)⁺.
31	 Starting materials: 5-(4-Fluorophenyl)nicotinic acid and 1,2,3,4-Tetrahydro-1-methylquinoxaline	Conditions: Ex.10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.75 (d, 1H), 8.58 (d, 1H), 7.81 (t, 1H), 7.38 (dd, 2H), 7.0-7.2 (m, 3H), 6.6-6.8 (m, 1H), 6.2-6.6 (m, 2H), 4.09 (t, 2H), 3.54 (t, 2H), 3.03 (s, 3H). LC-MS: m/z 348.1 (M+H)⁺.
32	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Nitrophenylboronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.11 (s, 1H), 8.78 (br s, 1H), 8.3-8.4 (m, 3H), 8.0-8.1 (m, 2H), 7.04 (t, 1H), 6.94 (dd, 1H), 6.6-6.8 (m, 1H), 4.37 (br s, 2H), 3.94 (br s, 2H), 3.2-3.3 (m, 1H), 2.5-2.5 (m, 1H). LC-MS: m/z 362.0 (M+H)⁺.
33	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxa-	Conditions: Ex. 1, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.68 (d, 1H), 8.5-8.6 (m, 1H), 7.77 (t, 1H), 7.0-7.1 (m, 1H), 6.93 (dd, 1H), 6.6-6.8 (m, 1H), 6.15 (br s, 1H), 4.3-4.5 (m, 2H), 3.9-4.1 (m, 2H), 2.3-2.4

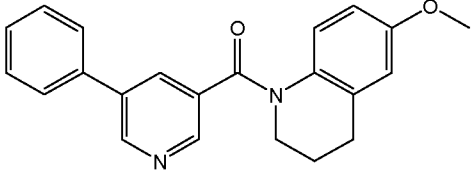
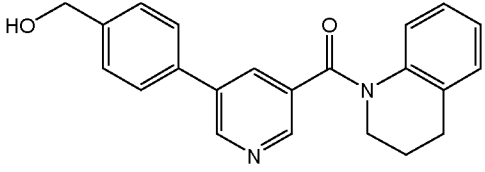
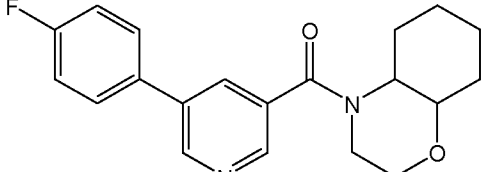
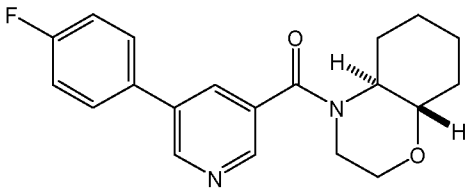
	zin-4-yl)methanone and Cyclohexen-1-ylboronic acid	(m, 2H), 2.2-2.3 (m, 2H), 1.7-1.8 (m, 2H), 1.6-1.7 (m, 2H). LC-MS: m/z 321.1 (M+H) ⁺ .
34	 Starting materials: 5-(4-Methoxyphenyl)nicotinic acid and 1,2,3,4-Tetrahydro-[1,5]naphthyridine	Conditions: Ex. 10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.8-8.9 (m, 1H), 8.5-8.6 (m, 1H), 8.31 (dd, 1H), 7.9-7.9 (m, 1H), 7.0-7.0 (m, 2H), 6.7-6.8 (m, 2H), 6.6-6.7 (m, 2H), 4.2-4.3 (m, 2H), 3.9-3.9 (m, 3H), 3.4-3.4 (m, 2H), 3.11 (t, 2H). LC-MS: m/z 346.5 (M+H)⁺.
35	 Starting materials: Ethyl 4-(6-chloropyrazine-2-carbonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate and 4-Fluorobenzeneboronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.33 (br s, 1H), 8.18 (br s, 1H), 7.87 (br s, 1H), 7.29 (br s, 3H), 7.00 (br d, 3H), 5.25 (br s, 1H), 3.98 (br s, 4H), 0.95 (br t, 5H). LC-MS: m/z 408.1 (M+H)⁺.
36	 Starting materials: 5-Phenylnicotinic acid and 2,3-Dihydro-1H-quinolin-4-one	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.98 (d, 1H), 8.71 (d, 1H), 8.20 (s, 1H), 7.92 (dd, 1H), 7.67 (d, 2H), 7.4-7.6 (m, 5H), 7.26 (t, 1H), 7.15 (br s, 1H), 4.27 (t, 2H), 3.4-3.5 (m, 1H), 2.96 (t, 2H). LC-MS: m/z 329.4 (M+H)⁺.
37		Conditions: Ex. 10, purification b), ¹H NMR (400 MHz, Chloroform-d) δ: 2.19 (quin, 2H), 3.14 (t, 2H), 4.00 (br t, 2H), 6.87-7.15 (m, 1H), 7.47 (br s,

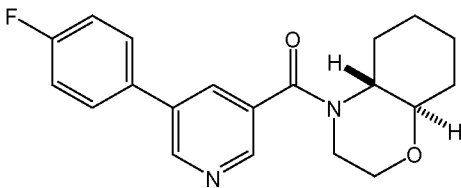
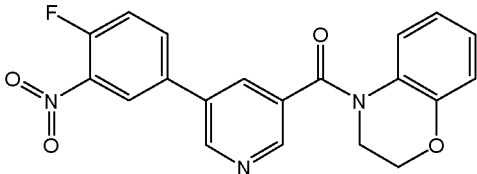
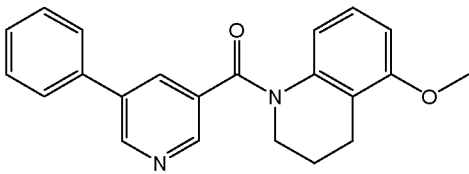
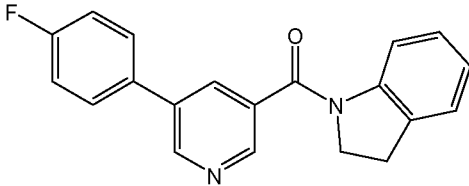
	Starting materials: 6-Phenylpyrazine-2-carboxylic acid and 1,2,3,4-Tetrahydro-[1,5]naphthyridine	3H), 7.79 (br s, 2H), 8.32 (br s, 1H), 8.93 (s, 1H), 9.08 (s, 1H). LC-MS: m/z 317.4 (M+H) ⁺ .
38	 Starting materials: 5-(3-Methoxyphenyl)nicotinic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ : 2.10 (quin, 2H), 2.87 (t, 2H), 3.83 (s, 3H), 3.97 (t, 2H), 6.68 (br s, 1H), 6.86-7.08 (m, 5H), 7.21 (d, 1H), 7.35 (t, 1H), 7.81 (t, 1H), 8.53 (d, 1H), 8.78 (d, 1H). LC-MS: m/z 346.1 (M+H) ⁺ .
39	 Starting materials: 5-(1H-Pyrrol-1-yl)-nicotinic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹ H NMR (DMSO- <i>d</i> ₆ , 600 MHz) δ : 8.90 (d, 1H), 8.28 (br s, 1H), 7.98 (br s, 1H), 7.41 (br s, 2H), 7.24 (d, 1H), 7.04 (t, 1H), 6.93 (br t, 2H), 6.31 (t, 2H), 3.80 (t, 2H), 2.85 (t, 2H), 2.07 (s, 1H), 1.99 (quin, 2H). LC-MS: m/z 303.1 (M+H) ⁺ .
40	 Starting materials: 6-(4-Fluorophenyl)pyridazine-4-carboxylic acid and 2,3-Dihydro-1,4-benzoxazine	Conditions: Ex. 10, purification b), ¹ H NMR (DMSO- <i>d</i> ₆ , 600 MHz) δ : 9.2-9.4 (m, 1H), 8.1-8.5 (m, 3H), 7.3-7.5 (m, 3H), 7.0-7.1 (m, 1H), 6.9-7.0 (m, 2H), 4.2-4.5 (m, 2H), 3.8-4.0 (m, 2H). LC-MS: m/z 336.0 (M+H) ⁺ .
41	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-2-yl)-	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO- <i>d</i> ₆ , 600 MHz) δ : 8.86 (s, 1H), 8.75 (s, 1H), 8.11 (br s, 1H), 7.59 (br t, 1H), 7.5-7.6 (m, 1H), 7.3-7.4 (m, 3H), 7.05 (s, 1H), 6.93 (dd, 1H), 6.7-6.8 (m, 1H), 4.37 (br s, 2H),

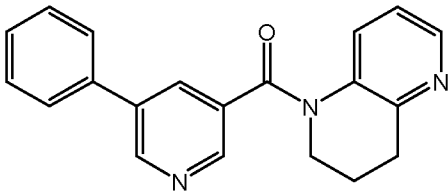
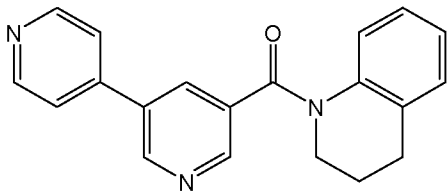
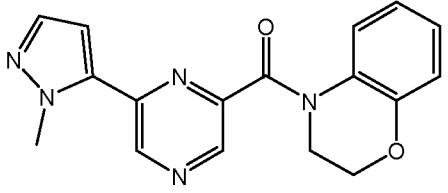
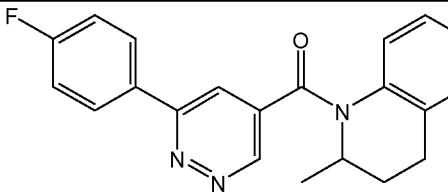
	zin-4-yl)methanone and 2-Fluorophenylboronic acid	3.93 (br s, 2H). LC-MS: m/z 335.4 (M+H) ⁺ .
42	 Starting materials: 5-(4-Fluorophenyl)nicotinic acid and 1,2,3,4-Tetrahydro-[1,5]naphthyridine	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.95 (d, 1H), 8.58 (br s, 1H), 8.23 (dd, 1H), 8.12 (br s, 1H), 7.77 (dd, 2H), 7.5-7.7 (m, 1H), 7.3-7.4 (m, 2H), 7.06 (br s, 1H), 3.81 (t, 2H), 2.99 (t, 2H), 2.05 (quin, 2H). LC-MS: m/z 334.4 (M+H)⁺.
43	 Starting materials: (6-Chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.07 (br s, 1H), 8.68 (br s, 1H), 8.43 (br s, 1H), 8.0-8.2 (m, 1H), 7.06 (br s, 1H), 6.95 (d, 2H), 4.33 (br s, 2H), 3.96 (br s, 2H), 3.90 (s, 4H). LC-MS: m/z 322.3 (M+H)⁺.
44	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-(Trifluoromethyl)phenylboronic acid	Conditions: Ex.1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.0-9.1 (m, 1H), 8.76 (br s, 1H), 8.31 (br s, 1H), 7.98 (br d, 2H), 7.87 (d, 2H), 7.04 (t, 1H), 6.9-7.0 (m, 1H), 6.7-6.8 (m, 1H), 4.37 (br s, 2H), 3.94 (br s, 2H). LC-MS: m/z 385.0 (M+H)⁺.
45	 Starting materials: (5-Bromopyridin-3-	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.75 (d, 1H), 8.67 (s, 1H), 7.99 (br s, 1H), 7.38 (br t, 1H), 7.08 (dd, 1H), 7.04 (t, 1H), 6.9-7.0 (m, 2H), 6.77 (br

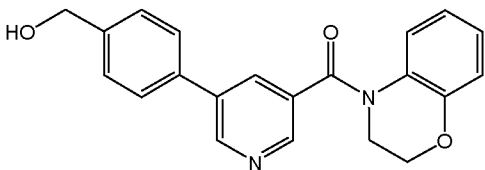
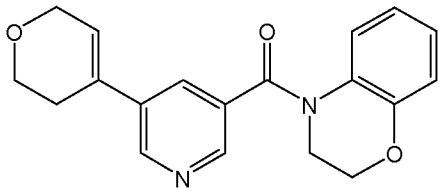
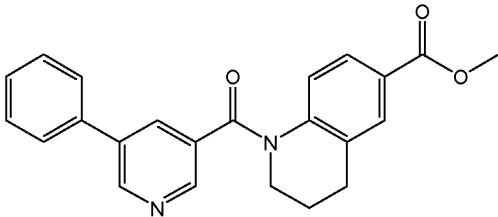
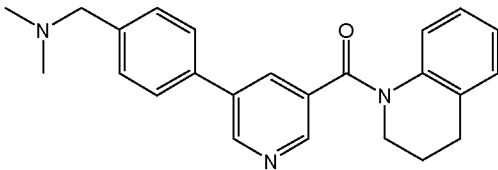
	yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Fluoro-2-methoxyphenylboronic acid	s, 1H), 4.36 (br s, 2H), 3.9-4.0 (m, 2H), 3.78 (s, 3H). LC-MS: m/z 365.4 (M+H) ⁺ .
46	 Starting materials: 4-((5-Bromopyridin-3-yl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine and 4-Fluorobenzene boronic acid	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO-d ₆ , 600 MHz) δ : 9.14 (d, 1H), 8.70 (d, 1H), 8.07 (t, 1H), 7.7-7.7 (m, 3H), 7.3-7.4 (m, 2H), 7.2-7.3 (m, 1H), 7.1-7.2 (m, 2H), 3.9-3.9 (m, 2H), 2.41 (t, 2H), 1.65 (quin, 2H). LC-MS: m/z 370.3 (M+H) ⁺ .
47	 Starting materials: 1-((5-Bromopyridin-3-yl)sulfonyl)-1,2,3,4-tetrahydroquinoline and 4-Fluorobenzene boronic acid	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO-d ₆ , 600 MHz) δ : 9.14 (d, 1H), 8.70 (d, 1H), 8.07 (t, 1H), 7.7-7.7 (m, 3H), 7.36 (t, 2H), 7.2-7.3 (m, 1H), 7.1-7.2 (m, 2H), 3.9-3.9 (m, 2H), 2.41 (t, 2H), 1.65 (quin, 2H). LC-MS: m/z 369.0 (M+H) ⁺ .
48	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 3-(Trifluoromethyl)phenyl boronic acid	Conditions: Ex. 1, purification b), ¹ H NMR (DMSO-d ₆ , 600 MHz) δ : 9.08 (s, 1H), 8.75 (br s, 1H), 8.33 (br s, 1H), 8.07 (br d, 2H), 7.82 (d, 1H), 7.7-7.8 (m, 1H), 7.04 (t, 1H), 6.94 (dd, 1H), 6.7-6.8 (m, 2H), 4.37 (br s, 2H), 3.94 (br s, 2H). LC-MS: m/z 385.4 (M+H) ⁺ .

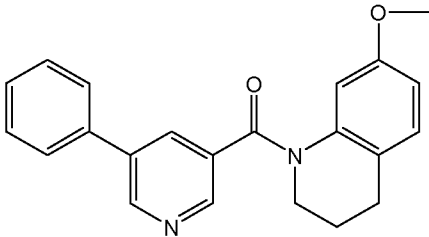
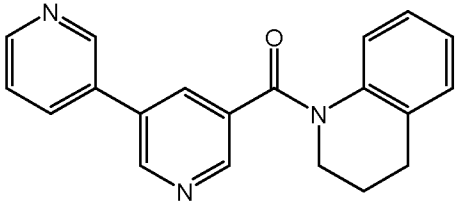
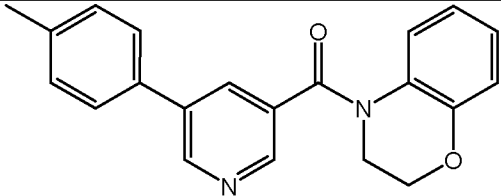
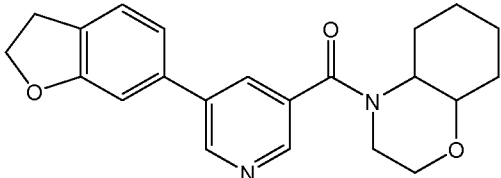
49	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Conditions: Ex. 1, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.8-8.9 (m, 1H), 8.7-8.8 (m, 1H), 8.32 (br s, 1H), 7.95 (s, 1H), 7.6-7.7 (m, 2H), 6.9-7.2 (m, 3H), 6.68 (br s, 1H), 4.46 (br t, 2H), 4.0-4.2 (m, 2H). LC-MS: <i>m/z</i> 336.0 (M+H)⁺.
50	 Starting materials: 5-(3-Methoxyphenyl)nicotinic acid and 2,3-Dihydro-1,4-benzoxazin	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.0-9.0 (m, 1H), 8.70 (s, 1H), 8.19 (br s, 1H), 7.42 (t, 1H), 7.2-7.3 (m, 2H), 6.9-7.1 (m, 4H), 6.6-6.8 (m, 1H), 4.38 (br s, 2H), 3.94 (br s, 2H), 3.83 (s, 3H). LC-MS: <i>m/z</i> 347.4 (M+H)⁺.
51	 Starting materials: 5-(1-Phenylvinyl)nicotinic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex.10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.55 (dd, 2H), 7.52 (t, 1H), 7.0-7.4 (m, 7H), 6.9-7.0 (m, 1H), 6.64 (br s, 1H), 5.53 (d, 1H), 5.3-5.4 (m, 1H), 3.92 (t, 2H), 2.80 (t, 2H), 2.0-2.1 (m, 2H). LC-MS: <i>m/z</i> 342.1 (M+H)⁺.
52	 Starting materials: 6-Phenylpyridazine-4-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.0-8.2 (m, 5H), 7.5-7.6 (m, 6H), 7.27 (d, 2H), 7.08 (br t, 2H), 6.8-7.0 (m, 2H), 3.83 (br s, 4H), 2.89 (t, 4H), 2.08 (s, 1H), 2.02 (br s, 4H). LC-MS: <i>m/z</i> 316.3 (M+H)⁺.

53	 Starting materials: 5-Phenylnicotinic acid and 1,2,3,4-Tetrahydro-6-methoxyquinoline	Conditions: Ex. 10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.75 (d, 1H), 8.58 (d, 1H), 7.81 (t, 1H), 7.3-7.4 (m, 2H), 7.0-7.2 (m, 3H), 6.73 (d, 1H), 6.48 (br s, 1H), 6.3-6.4 (m, 1H), 4.09 (t, 2H), 3.54 (t, 2H), 3.03 (s, 3H). LC-MS: <i>m/z</i> 345.1 (M+H)⁺.
54	 Starting materials: (5-Bromopyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)-methanone and 4-(Hydroxymethyl)-benzeneboronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.87 (d, 1H), 8.44 (br s, 1H), 7.95 (br s, 1H), 7.5-7.6 (m, 2H), 7.42 (d, 2H), 7.25 (d, 1H), 7.04 (t, 1H), 6.93 (br t, 2H), 4.54 (s, 2H), 3.82 (t, 2H), 2.85 (t, 2H), 2.00 (quin, 2H). LC-MS: <i>m/z</i> 345.1 (M+H)⁺.
55	 Starting materials: 5-(4-Fluorophenyl)nicotinic acid and Octahydro-2H-benzo[b][1,4]oxazine	Conditions: Ex.10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.96 (d, 1H), 8.61 (d, 1H), 8.10 (t, 1H), 7.85 (t, 2H), 7.36 (t, 2H), 3.7-3.8 (m, 3H), 3.66 (dt, 1H), 3.5-3.5 (m, 1H), 3.3-3.4 (m, 1H), 2.3-2.4 (m, 1H), 1.9-1.9 (m, 1H), 1.6-1.7 (m, 2H), 1.4-1.5 (m, 1H), 1.2-1.4 (m, 3H).
56	 Starting materials: (5-(4-Fluorophenyl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone	Conditions: purification d), ¹H NMR (600 MHz, DMSO-d₆) δ: 1.11 (t, 1 H), 1.17-1.36 (m, 5H), 1.43-1.50 (m, 1H), 1.62-1.73 (m, 2H), 1.85-1.92 (m, 1H), 2.33-2.38 (m, 1H), 3.34-3.40 (m, 1H), 3.43-3.56 (m, 2H), 3.62-3.69 (m, 1H), 3.71-3.84 (m, 4H), 7.35 (t, 2H), 7.85 (t, 2H), 8.09 (t, 1H), 8.60

		(d, 1H), 8.96 (d, 1H).
57	 Starting materials: (5-(4-Fluorophenyl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone	Conditions: purification d), ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.21-1.36 (m, 3H), 1.42-1.51 (m, 1H), 1.63-1.72 (m, 2H), 1.86-1.92 (m, 1H), 2.33-2.38 (m, 1H), 3.34-3.40 (m, 1H), 3.45-3.53 (m, 1H), 3.66 (td, 1H), 3.72- 3.84 (m, 3H), 7.35 (t, 2H), 7.85 (t, 2H), 8.09 (t, 1H), 8.60 (d, 1H), 8.96 (d, 1H).
58	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Fluoro-3-nitrophenylboronic acid	Conditions: Ex.1, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.08 (s, 1H), 8.75 (br s, 1H), 8.50 (br d, 1H), 8.35 (br s, 1H), 8.2-8.3 (m, 1H), 7.76 (dd, 1H), 7.04 (br t, 1H), 6.9-7.0 (m, 1H), 6.77 (br s, 2H), 4.37 (br s, 2H), 3.93 (br s, 2H). LC-MS: <i>m/z</i> 380.0 (M+H)⁺.
59	 Starting materials: 5-Phenylnicotinic acid and 5-Methoxy-1,2,3,4-tetrahydroquinoline	Conditions: Ex.10, purification b), ¹H NMR (Chloroform-<i>d</i>, 400 MHz) δ: 8.80 (d, 1H), 8.5-8.5 (m, 1H), 7.92 (t, 1H), 7.4-7.5 (m, 6H), 6.88 (t, 1H), 6.6- 6.6 (m, 1H), 3.9-4.0 (m, 2H), 3.85 (s, 3H), 2.83 (t, 2H), 2.0-2.1 (m, 2H). LC-MS: <i>m/z</i> 345.1 (M+H)⁺.
60	 Starting materials: 5-(4-Fluorophenyl)nicotinic acid and indoline	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.02 (s, 1H), 8.78 (br s, 1H), 8.32 (br s, 1H), 8.14 (br s, 1H), 7.87 (br dd, 2H), 7.37 (t, 2H), 7.30 (d, 1H), 7.24 (br s, 1H), 7.08 (br s, 1H), 4.09 (br t, 2H), 3.11 (t, 2H). LC-MS: <i>m/z</i> 320.1

		(M+H) ⁺ .
61	 Starting materials: 5-Phenylnicotinic acid and 1,2,3,4-Tetrahydro-[1,5]-naphthyridine	Conditions: Ex.10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.96 (d, 1H), 8.59 (s, 1H), 8.24 (br s, 1H), 8.13 (br d, 1H), 7.70 (br d, 2H), 7.51 (t, 2H), 7.4-7.5 (m, 1H), 7.08 (br s, 1H), 3.82 (t, 2H), 2.99 (t, 2H), 2.05 (quin, 2H), 1.5-1.6 (m, 1H), 0.9-1.0 (m, 1H). LC-MS: <i>m/z</i> 316.1 (M+H)⁺.
62	 Starting materials: [3,4'-Bipyridine]-5-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex.10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 9.01 (d, 1H), 8.67 (d, 2H), 8.5-8.6 (m, 1H), 8.15 (br s, 1H), 7.70 (br d, 2H), 7.1-7.3 (m, 1H), 7.04 (t, 1H), 6.92 (br t, 1H), 6.86 (br s, 1H), 3.82 (t, 2H), 2.86 (t, 2H), 2.0-2.0 (m, 2H). LC-MS: <i>m/z</i> 316.1 (M+H)⁺.
63	 Starting materials: (6-Chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 1-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole	Conditions: Ex. 1, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.94 (s, 2H), 7.4-7.7 (m, 2H), 6.9-7.1 (m, 2H), 6.5-6.8 (m, 2H), 4.4-4.6 (m, 2H), 4.14 (br s, 2H), 3.3-3.8 (m, 3H). LC-MS: <i>m/z</i> 322.0 (M+H)⁺.
64	 Starting materials: 6-(4-Fluorophenyl)pyridazine-4-carbonyl	Conditions: Ex. 11, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.73 (br s, 1H), 7.9-8.0 (m, 2H), 7.73 (d, 1H), 7.1-7.3 (m, 4H), 6.93 (br t, 1H), 6.52 (br s, 1H), 4.88 (br s, 1H), 2.7-2.9 (m, 2H), 2.5-2.7 (m, 2H), 1.2-

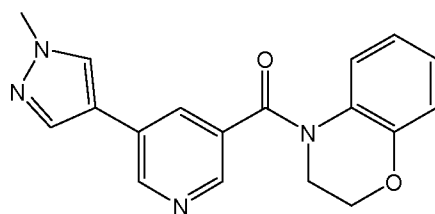
	chloride and 2-Methyl-1,2,3,4-tetrahydroquinoline	1.6 (m, 4H). LC-MS: m/z 348.1 (M+H) ⁺ .
65	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-(Hydroxymethyl)benzene boronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.99 (d, 1H), 8.68 (s, 1H), 8.19 (br s, 1H), 7.69 (br d, 2H), 7.44 (d, 3H), 7.03 (t, 1H), 6.94 (dd, 1H), 6.6-6.8 (m, 1H), 5.27 (t, 1H), 4.56 (d, 2H), 4.37 (br s, 2H), 3.94 (br s, 2H). LC-MS: m/z 347.1 (M+H)⁺.
66	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 3,6-Dihydro-2H-pyran-4-boronic acid pinacol ester	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.78 (d, 1H), 8.58 (br s, 1H), 7.97 (br s, 1H), 7.0-7.1 (m, 1H), 6.93 (dd, 1H), 6.7-6.8 (m, 1H), 6.44 (br s, 1H), 5.6-5.8 (m, 1H), 4.35 (br s, 2H), 4.23 (q, 2H), 3.89 (br s, 2H), 3.82 (t, 2H), 2.45 (br s, 2H). LC-MS: m/z 324.4 (M+H)⁺.
67	 Starting materials: 5-Phenylpyridin-3-ylmethanone and Methyl-1,2,3,4-tetrahydroquinoline-6-carboxylate	Conditions: Ex. 10, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.93 (d, 1H), 8.50 (d, 1H), 8.08 (t, 1H), 7.84 (d, 1H), 7.67 (d, 2H), 7.4-7.5 (m, 4H), 7.11 (br d, 1H), 3.8-3.8 (m, 5H), 2.93 (t, 2H), 2.00 (quin, 2H). LC-MS: m/z 373.1 (M+H)⁺.
68	 Starting materials: (5-Bromopyridin-3-yl)(2,3,4,5-tetrahydro-1H-benzo[b]pyridin-6-yl)methanone and N,N-dimethylaniline	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.88 (d, 1H), 8.44 (br s, 1H), 7.96 (br s, 1H), 7.5-7.6 (m, 2H), 7.39 (d, 2H), 7.25 (d, 1H), 7.04 (t, 1H), 6.93 (br t, 2H), 3.82 (t, 2H), 3.42 (s, 2H), 2.85 (t, 2H), 2.15 (s, 6H), 2.00 (quin, 2H).

	methanone and (4-[(Dimethylamino)-methyl]phenyl)boronic acid	LC-MS: m/z 372.2 (M+H) ⁺ .
69	 Starting materials: 5-Phenylnicotinic acid and 7-Methoxy-1,2,3,4-tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.91 (br s, 2H), 8.73 (br s, 1H), 7.59 (br s, 2H), 7.09 (br s, 3H), 7.01 (br d, 2H), 6.74 (d, 2H), 6.25 (br s, 2H), 4.14 (br s, 3H), 3.57 (br s, 3H), 3.04 (br s, 4H). LC-MS: m/z 345.1 (M+H)⁺.
70	 Starting materials: [3,3'-Bipyridine]-5-carboxylic acid and 1,2,3,4-Tetrahydroquinoline	Conditions: Ex. 10, purification b), ¹H NMR (Chloroform-d, 400 MHz) δ: 8.79 (d, 1H), 8.6-8.7 (m, 2H), 8.58 (d, 1H), 7.82 (t, 1H), 7.75 (d, 1H), 7.3-7.4 (m, 1H), 7.0-7.3 (m, 3H), 6.92 (t, 1H), 6.65 (br s, 1H), 3.99 (t, 2H), 3.7-3.9 (m, 1H), 2.8-2.9 (m, 2H), 2.72 (br t, 1H), 2.23 (s, 1H), 2.11 (quin, 2H), 1.9-2.0 (m, 1H). LC-MS: m/z 317.0 (M+H)⁺.
71	 Starting materials: (5-Bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 4-Methylbenzene boronic acid	Conditions: Ex. 1, purification b), ¹H NMR (DMSO-d₆, 600 MHz) δ: 8.97 (d, 1H), 8.67 (s, 1H), 8.17 (br s, 1H), 7.63 (br d, 2H), 7.32 (d, 2H), 7.03 (t, 1H), 6.94 (dd, 1H), 6.75 (br s, 1H), 4.37 (br s, 2H), 3.93 (br s, 2H), 2.36 (s, 3H). LC-MS: m/z 331.4 (M+H)⁺.
72		Conditions: Ex.10, purification b) ¹H NMR (400 MHz, Chloroform-d) δ: 1.29-1.58 (m, 4H), 1.75-1.86 (m, 2H), 1.91-2.10 (m, 1H), 2.47-2.57 (m, 1H),

	Starting materials: 5-(2,3-Dihydro-benzofuran-6-yl)nicotinic acid and octahydro-2H-benzo[b][1,4]oxazine	3.29 (t, 2H), 3.45-3.71 (m, 4H), 3.73-3.95 (m, 4H), 4.64 (t, 2H), 6.89 (d, 1H), 7.31-7.57 (m, 2H), 7.91 (t, 1H), 8.60 (d, 1H), 8.83 (d, 1H).
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Example 12.

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl)methanone (Compound 73)



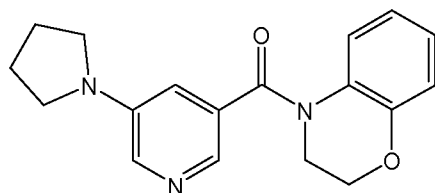
5

To a mixture of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.091 g, 0.438 mmol), (5-bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (0.112 g, 0.35 mmol) and cesium carbonate (0.319 g, 0.98 mmol) in degassed DME-water (2.5:1, 3.5 ml) under nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium (0.040 g, 0.035 mmol). The mixture was stirred at 90 °C until the reaction was completed. Cooled reaction mixture was diluted with EtOAc and filtered through a short plug of Celite. The filtrate was washed with water and brine, dried and evaporated. Crude was purified by reverse phase flash chromatography to afford 0.083 g of the title compound. ¹H NMR (400 MHz, CDCl₃): δ 8.78 (d, 1H), 8.51 (d, 1H), 7.88 (t, 1H), 7.74 (d, 1H), 7.65 (s, 1H), 7.00-7.06 (m, 1H), 6.94 (dd, 1H), 6.64-6.74 (m, 1H), 6.60-6.70 (m, 1H), 4.37-4.48 (m, 2H), 4.03-4.11 (m, 2H), 3.97 (s, 3H). LC-MS: *m/z* 321.8 (M+H).

15

Example 13.

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(pyrrolidin-1-yl)pyridin-3-yl)methanone (Compound 74)

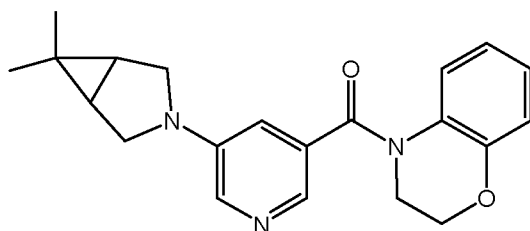


20

A mixture of pyrrolidine (0.067 ml, 0.80 mmol), (5-bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (0.128 g, 0.40 mmol), sodium *tert*-butoxide (0.050g, 0.52 mmol), tris(dibenzylideneacetone)dipalladium (0.018 g, 0.020 mmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.025 g, 0.10 mmol) in
5 dry toluene (1.5 ml) under nitrogen atmosphere was stirred at 100 °C until the reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. The filtrate was evaporated. Crude product was purified by reverse phase flash chromatography to afford 0.046 g of the title compound. ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, 1H), 7.93 (d, 1H), 7.00-7.17 (br, 1H), 6.97-7.04 (m, 1H), 6.94 (dd,
10 1H), 6.91 (dd, 1H), 6.66-6.77 (m, 1H), 4.33-4.42 (m, 2H), 3.98-4.07 (m, 2H), 3.24-3.35 (m, 4H), 1.99-2.09 (m, 4H). LC-MS: *m/z* 310.7 (M+H).

Example 14.

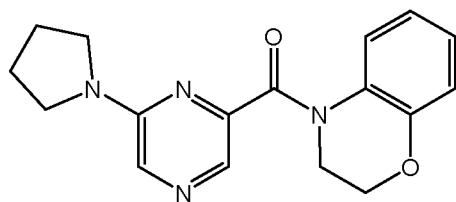
2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(6,6-dimethyl-3-azabicyclo[3.1.0]-
15 hexan-3-yl)pyridin-3-yl)methanone (Compound 75)



The compound was prepared according to the procedure of **Example 13** starting from 6,6-dimethyl-3-azabicyclo[3.1.0]hexane (0.047 g, 0.42 mmol) and (5-bromopyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (0.112 g, 0.35 mmol).
20 Yield 0.028 g. ¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, 1H), 7.92 (d, 1H), 6.58-7.20 (m, 5H), 4.30-4.44 (m, 2H), 3.95-4.08 (m, 2H), 3.37-3.47 (m, 2H), 3.21 (d, 2H), 1.49-1.56 (m, 2H), 1.08 (s, 3H), 0.84 (s, 3H). LC-MS: *m/z* 350.9 (M+H).

Example 15.

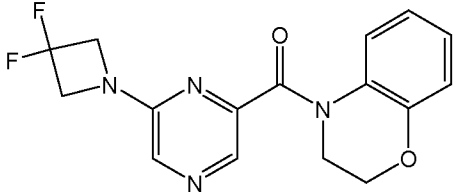
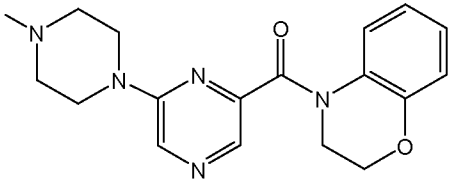
25 (2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)pyrazin-2-yl)-methanone (Compound 76)



A mixture of (6-chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (0.096 g, 0.35 mmol) and pyrrolidine (0.146 ml, 1.75 mmol) in dry DMSO (1.0 ml) was stirred at 90 °C until the reaction was completed. Cooled mixture was
 5 diluted with EtOAc, washed with water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the pure compound. ¹H NMR (400 MHz, CDCl₃): δ 8.09 (br s, 1H), 7.89 (s, 1H), 6.96-7.07 (m, 1H), 6.97-6.96 (m, 1H), 6.3-6.87 (m, 2H), 4.24-4.49 (m, 2H), 3.90-4.14 (m, 2H), 3.15-3.63 (m, 4H), 1.85-2.12 (m, 4H). LC-MS: *m/z* 311.8 (M+H).

10

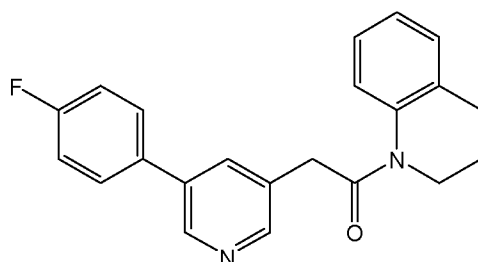
The following compounds were prepared according to the procedure of Example 15. The compound number, characterization data, deviating reaction conditions and starting materials are indicated on the table.

No	Structure and starting material	Reaction conditions, ¹ H NMR / LC-MS
77	 Starting materials: (6-Chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 3,3-Difluoroazetidine hydrochloride (1.25 equiv.).	Conditions: DIPEA (2.5 equiv.). ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 7.92 (s, 1H), 6.97-7.13 (m, 1H), 6.87-6.97 (m, 1H), 6.0-6.87 (m, 2H), 4.14-4.58 (m, 6H), 3.88-4.14 (m, 2H). LC-MS: <i>m/z</i> 333.6 (M+H).
78		¹H NMR (400 MHz, CDCl₃): δ 8.22 (s, 1H), 8.16 (s, 1H), 6.94-7.10 (m, 1H), 6.85-6.94 (m, 1H), 6.02-6.85 (m, 2H), 4.24-4.54 (m, 2H), 3.90-4.18 (m,

	Starting materials: (6-Chloropyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone and 1-Methylpiperazine (2.0 equiv.).	2H), 3.15-3.76 (m, 4H), 2.35-2.61 (m, 4H), 2.32 (s, 3H). LC-MS: <i>m/z</i> 340.7 (M+H).
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Example 16.

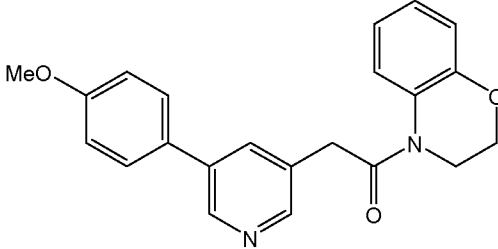
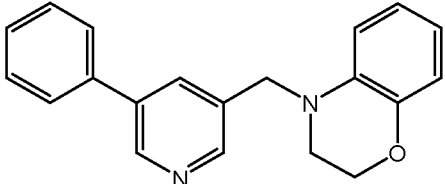
1-(3,4-Dihydroquinolin-1(2H)-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 79)



To a mixture of 2-(5-bromopyridin-3-yl)-1-(3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (0.116 g, 0.35 mmol), 4-fluorobenzeneboronic acid (0.059 g, 0.42 mmol) and sodium carbonate (0.104 g, 0.98 mmol) in degassed DME-water (6:1, 1.75 ml) under nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium (0.030 g, 0.026 mmol). The mixture was stirred at 90 °C until reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. Filtrate was washed with water and brine, dried and evaporated. Crude was purified by reverse phase flash chromatography to afford the pure compound. ¹H NMR (400 MHz, CDCl₃): δ 8.66 (d, 1H), 8.28 (br s, 1H), 7.75 (br s, 1H), 7.47-7.56 (m, 2H), 7.01-7.27 (m, 6H), 3.92 (s, 2H), 3.82 (t, 2H), 2.52-2.71 (m, 2H), 1.93 (quint, 2H). LC-MS: *m/z* 347.9 (M+H).

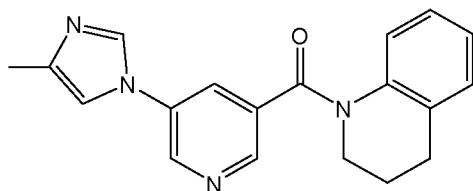
The following compounds were prepared according to the procedure of Example 16. The compound number, characterization data and starting materials are indicated on the table.

No	Structure and starting material	¹ H NMR / LC-MS
----	---------------------------------	----------------------------

80	 Starting material: 2-(5-Bromopyridin-3-yl)-1-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one	¹ H NMR (400 MHz, CDCl ₃): δ 8.71 (s, 1H), 8.36 (s, 1H), 7.77 (s, 1H), 7.44-7.57 (m, 2H), 7.06-7.25 (m, 2H), 6.97-7.04 (m, 2H), 6.86-6.97 (m, 2H), 4.19-4.34 (m, 2H), 3.91-4.10 (m, 4H), 3.85 (s, 3H). LC-MS: <i>m/z</i> 361.8 (M+H).
81	 Starting material: 4-((5-Bromopyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine	¹ H NMR (400 MHz, CDCl ₃): δ 8.76 (d, 1H), 8.55 (d, 1H), 7.79-7.83 (m, 1H), 7.52-7.57 (m, 2H), 7.43-7.50 (m, 2H), 7.37-7.43 (m, 1H), 6.77-6.86 (m, 2H), 6.65-6.72 (m, 2H), 4.51 (s, 2H), 4.27-4.33 (m, 2H), 3.37-3.42 (m, 2H). LC-MS: <i>m/z</i> 303.8 (M+H).

Example 17.

(3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)-methanone (Compound 82)



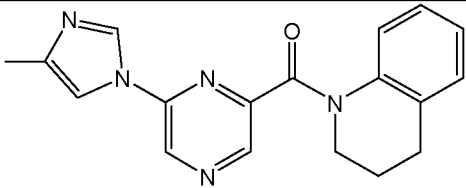
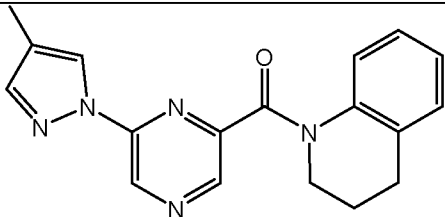
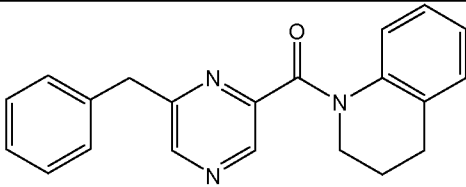
5

A mixture of ethyl 5-(4-methyl-1H-imidazol-1-yl)nicotinate (0.080 g, 0.346 mmol), 1,2,3,4-tetrahydroquinoline (0.043 ml, 0.346 mmol) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (0.071 g, 0.277 mmol) in dry toluene (0.5 ml) was stirred at 120 °C until the reaction was completed. Cooled mixture was quenched with aqueous 2 M HCl and then extracted with DCM. Organic phase was dried and evaporated. Crude was purified by reverse phase flash chromatography to afford the pure compound. ¹H NMR (600 MHz, *d*₆-DMSO): δ 8.91 (d, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.06 (s, 1H), 7.50 (s, 1H), 7.24 (d, 1H), 7.04 (t, 1H),

10

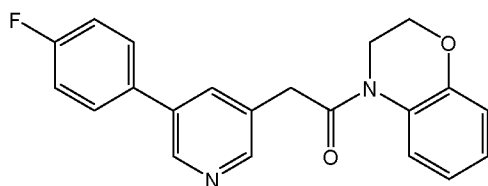
6.65-7.00 (m, 2H), 3.80 (t, 2H), 2.85 (t, 2H), 2.16 (s, 3H), 1.99 (quint, 2H). LC-MS: m/z 319.7 (M+H).

- The following compounds were prepared according to the procedure of Example 17. The compound number, characterization data and starting materials are indicated on the table.

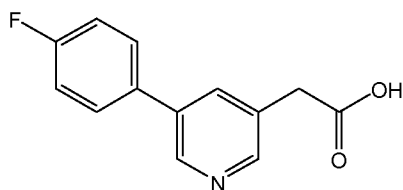
No	Structure and starting material	¹ H NMR / LC-MS
83	 Starting material: Methyl 6-(4-methyl-1H-imidazol-1-yl)pyrazine-2-carboxylate	¹ H NMR (400 MHz, CDCl ₃): δ 8.80 (s, 1H), 8.63 (s, 1H), 7.47-7.77 (m, 1H), 7.21-7.27 (m, 1H), 7.06 (t, 1H), 6.74-7.04 (m, 2H), 6.17-6.55 (m, 1H), 3.87-4.08 (m, 2H), 2.88 (t, 2H), 2.25 (s, 3H), 2.12 (quint, 2H). LC-MS: m/z 320.7 (M+H).
84	 Starting material: Methyl 6-(4-methyl-1H-pyrazol-1-yl)pyrazine-2-carboxylate	¹ H NMR (400 MHz, CDCl ₃): δ 9.21 (s, 1H), 8.62 (s, 1H), 7.46-7.78 (m, 2H), 7.18-7.26 (m, 1H), 6.77-7.12 (m, 2H), 6.08-6.68 (m, 1H), 3.88-4.09 (m, 2H), 3.89 (t, 2H), 2.05-2.19 (m, 5H). LC-MS: m/z 320.7 (M+H).
85	 Starting material: Methyl 6-benzylpyrazine-2-carboxylate	¹ H NMR (400 MHz, CDCl ₃): δ 8.57 (br s, 1H), 8.38 (s, 1H), 7.13-7.32 (m, 4H), 6.94-7.13 (m, 3H), 6.03-6.94 (m, 2H), 4.03 (s, 2H), 3.76-4.03 (m, 2H), 2.85 (t, 2H), 1.96-2.17 (m, 2H). LC-MS: m/z 330.7 (M+H).

Example 18.

1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 86)

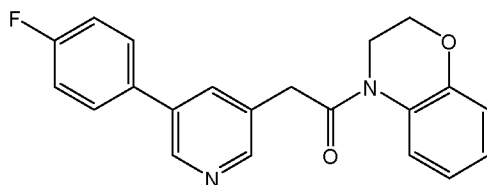


5 a) 2-(5-(4-Fluorophenyl)pyridin-3-yl)acetic acid



To a mixture of 5-bromo-3-pyridineacetic acid (0.216 g, 1 mmol), 4-fluoro-benzeneboronic acid (0.175 g, 1.25 mmol), cesium carbonate (0.912 g, 2.80 mmol) in degassed DME-water (3:1, 8 ml) under nitrogen atmosphere was added tetrakis(tri-
10 phenylphosphine)palladium (0.116 g, 0.10 mmol). The mixture was stirred at 90 °C until reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. Phases were separated and pH of the aqueous phase was adjusted to 6 with aqueous 2 M NaOH solution. Aqueous phase was extracted with EtOAc. Organic phase was dried and evaporated to afford 0.10 g of the
15 title compound. ¹H NMR (400 MHz, *d*₆-DMSO): δ 12.56 (s, 1H), 8.77 (d, 1H), 8.46 (d, 1H), 7.97 (t, 1H), 7.74-7.81 (m, 2H), 7.31-7.40 (m, 2H), 3.73 (s, 2H).

b) 1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 85)



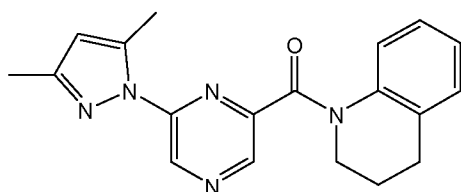
20

The compound was prepared according to the procedure of Intermediate 19 starting from 2-(5-(4-fluorophenyl)pyridin-3-yl)acetic acid (0.090 g, 0.35 mmol) and 3,4-dihydro-2H-benzo[b][1,4]oxazine (0.052 g, 0.385 mmol). Crude product was purified by reverse phase flash chromatography. Yield: 0.039 g. ¹H NMR (400 MHz, CDCl₃): δ 8.70 d (1H), 8.40 (br s, 1H), 7.78 (br s, 1H), 7.48-7.58 (m, 2H), 7.00-7.24 (m,
25

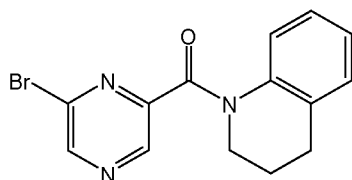
4H), 6.87-6.99 (m, 2H), 4.21-4.34 (m, 2H), 3.89-4.11 (m, 4H). LC-MS: m/z 349.9 (M+H).

Example 19.

5 (3,4-Dihydroquinolin-1(2H)-yl)(6-(3,5-dimethyl-1H-pyrazol-1-yl)pyrazin-2-yl)-methanone (Compound 87)



a) (6-Bromopyrazin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone

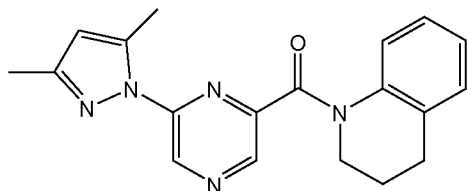


10

The compound was prepared according to the procedure of Example 17 starting from methyl 6-bromopyrazine-2-carboxylate (0.217 g, 1.00 mmol) and 1,2,3,4-tetrahydroquinoline (0.126 ml, 1.00 mmol). Crude product was purified by flash chromatography to afford 0.080 g of the title compound. ^1H NMR (400MHz, CDCl_3): δ 8.30-8.88 (m, 2H), 7.15-7.22 (m, 1H), 7.07 (t, 1H), 6.77-7.07 (br, 1H), 6.0-6.75 (br, 1H), 3.76-4.12 (m, 2H), 2.87 (t, 2H), 2.09 (quint., 2H).

15

b) (3,4-Dihydroquinolin-1(2H)-yl)(6-(3,5-dimethyl-1H-pyrazol-1-yl)pyrazin-2-yl)methanone (Compound 86)



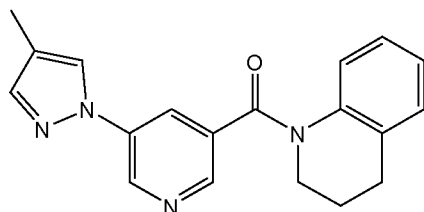
20

The compound was prepared according to the procedure of Intermediate 22 starting from (6-bromopyrazin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (0.080 g, 0.251 mmol) and 3,5-dimethylpyrazole (0.024 g, 0.251 mmol). Crude product was purified by reverse phase flash chromatography to afford 0.012 g of

the title compound. ^1H NMR (400 MHz, CDCl_3): δ 9.26 (s, 1H), 8.72 (d, 1H), 7.12-7.18 (m, 1H), 6.99 (t, 1H), 6.76-6.93 (m, 1H), 6.19-6.6 (m, 1H), 5.90 (s, 1H), 3.97 (t, 2H), 2.84 (t, 2H), 2.26 (s, 3H), 2.10 (quint, 2H), 1.98 (br s, 3H). LC-MS: m/z 334.7 (M+H).

5 **Example 20.**

(3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)-methanone (Compound 88)

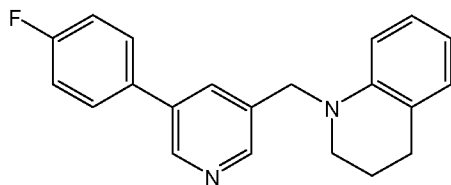


A mixture of (5-bromopyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)-methanone (0.111 g, 0.35 mmol), 4-methylpyrazole (0.035 ml, 0.438 mmol), potassium phosphate (0.097 g, 0.455 mmol), copper iodide (0.013 g, 0.070 mmol) and N,N'-dimethylenediamine (0.015 ml, 0.140 mmol) in dry toluene (1.0 ml) was stirred at 110 °C until reaction was completed. Cooled mixture was diluted with EtOAc and filtered through a short plug of Celite. Filtrate was washed with aqueous NH_4Cl - NH_3 solution (4:1) and water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford 0.016 g of the title compound. ^1H NMR (400 MHz, CDCl_3): δ 8.94 (d, 1H), 8.27 (s, 1H), 8.06 (dd, 1H), 7.63-7.67 (m, 1H), 7.56 (s, 1H), 7.17-7.23 (m, 1H), 7.05 (td, 1H), 6.87-6.94 (m, 1H), 6.60-6.80 (m, 1H), 3.95 (t, 2H), 3.86 (t, 2H), 2.16 (s, 3H), 2.09 (quint, 2H). LC-MS: m/z 319.7 (M+H).

20

Example 21.

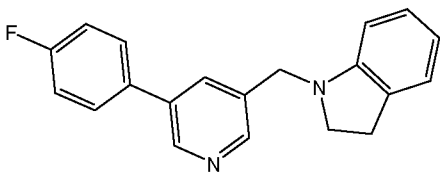
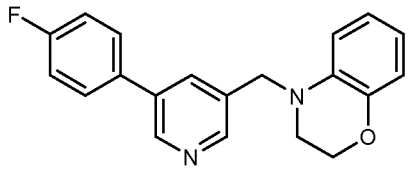
1-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)-1,2,3,4-tetrahydroquinoline (Compound 89)



25 To a mixture of 1,2,3,4-tetrahydroquinoline (0.050 ml, 0.40 mmol) in 1,2-dichloroethane (1.0 ml) and acetic acid (0.25 ml) was added 5-(4-fluorophenyl)nicotin-

aldehyde (0.089 g, 0.44 mmol) dissolved in 1,2-dichloroethane (1.0 ml). The mixture was stirred at RT for 6 h. Sodium triacetoxy borohydride (0.1287 g, 0.88 mmol) was added and the mixture was stirred overnight at RT. The mixture was diluted with DCM and basified with saturated aqueous NaHCO₃ solution. Phases were separated and aqueous phase was extracted with DCM. Combined organic phases were dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the pure compound. ¹H NMR (400 MHz, CDCl₃): δ 8.69 (d, 1H), 8.51-8.54 (m, 1H), 7.70-7.73 (m, 1H), 7.46-7.53 (m, 2H), 7.10-7.18 (m, 2H), 6.97-7.03 (m, 2H), 6.62 (td, 1H), 6.51-6.55 (m, 1H), 4.54 (s, 2H), 3.36-3.42 (m, 2H), 2.83 (t, 2H), 2.00-2.08 (m, 2H). LC-MS: *m/z* 319.8 (M+H).

The following compounds were prepared according to the procedure of Example 21. The compound number, characterization data and starting materials are indicated on the table.

No	Structure and starting material	¹ H NMR / LC-MS
90	 Starting material: 5-(4-Fluorophenyl)-nicotinaldehyde and indoline	¹ H NMR (400 MHz, CDCl ₃): δ 8.73 (d, 1H), 8.59 (d, 1H), 7.84-7.88 (m, 1H), 7.51-7.58 (m, 2H), 7.05-7.20 (m, 4H), 6.72 (td, 1H), 6.55 (d, 1H), 4.31 (s, 2H), 3.34 (t, 2H), 3.00 (t, 2H). LC-MS: <i>m/z</i> 305.7 (M+H).
91	 Starting material: 5-(4-Fluorophenyl)-nicotinaldehyde and 3,4-Dihydro-2H-benzo[b][1,4]oxazine	¹ H NMR (400 MHz, CDCl ₃): δ 8.72 (d, 1H), 8.55 (d, 1H), 7.73-7.78 (m, 1H), 7.47-7.55 (m, 2H), 7.12-7.19 (m, 2H), 6.77-6.87 (m, 2H), 6.64-6.72 (m, 2H), 4.51 (s, 2H), 4.28-4.33 (m, 2H), 3.37-3.43 (m, 2H). LC-MS: <i>m/z</i> 321.8 (M+H).

Abbreviations

- DCM - Dichloromethane
DIPEA - N,N-diisopropylethylamine
DME - Dimethoxyethane
DMF - N,N-Dimethylformamide
5 DMSO – Dimethylsulfoxide
dppp - 1,3-Bis(diphenylphosphino)propane
HPLC - High-performance liquid chromatography
LC-MS - Liquid chromatography–mass spectrometry
PdCl₂(dppf) - [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
10 Pd(OAc)₂ - Palladium(II) acetate
Pd₂(dba)₃ - Tris(dibenzylideneacetone)dipalladium
PdCl₂(PPh₃)₂ - Bis(triphenylphosphine)palladium(II) dichloride
Q-PHOS - 1,2,3,4,5-Pentaphenyl-1'-(di-tert-butylphosphino)ferrocene
RT - Room temperature
15 STB- Sodium *tert*-butoxide
STAB - Sodium triacetoxo borohydride
TEA – Triethylamine
T₃P - Propylphosphonic anhydride
THF – Tetrahydrofuran
20 TLC – Thin layer chromatography
TMA - Trimethylamine

EXPERIMENTS

25 Experiment 1. CYP11A1 inhibition

The ability of the test compounds to inhibit pregnenolone biosynthesis was measured by enzyme-linked immunosorbent assay (ELISA) detecting pregnenolone (Abnova Pregnenolone ELISA Kit, KA1912). Human adrenocortical carcinoma cell line
30 NCI-H295R that has been shown to express all the key steroidogenic enzymes was used as a enzyme source. To determine the half maximal inhibitory concentration (IC₅₀) of the test compounds on CYP11A1 inhibition, the cells were treated for 24 hours with increasing concentrations of the test compound. The final DMSO concentration was 0.4

%. Medium samples were diluted 1:6 and pregnenolone amounts determined with ELISA. Manufacturer's recommended protocols were used and pregnenolone (Sigma-Aldrich, P9129) standards were prepared in cell culture medium. Absorbance (A450) was measured with Envision plate reader (PerkinElmer). All the test compounds were
 5 studied at 10 concentrations in duplicates.

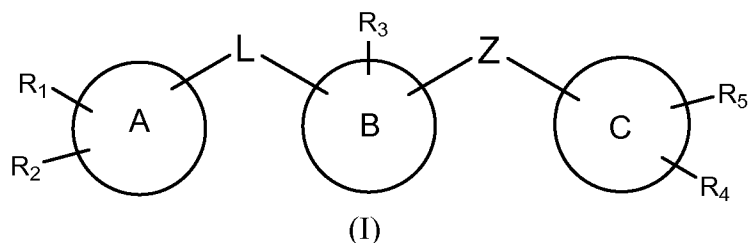
The compounds of the invention were screened in the above mentioned assay and the IC₅₀ values of the compounds are set forth in Table 1 below wherein "A" refers to an IC₅₀ value of less than 50 nM, "B" refers to IC₅₀ value in range of 51 to 200 nM
 10 and "C" refers to IC₅₀ value in range of 201 nM to 2500 nM.

Table 1.

Group	Compound No.
A	2, 5, 8, 10, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 83, 84 and 88.
B	3, 4, 9, 11, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 87, 89 and 90.
C	1, 6, 7, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 85, 86 and 91.

Claims

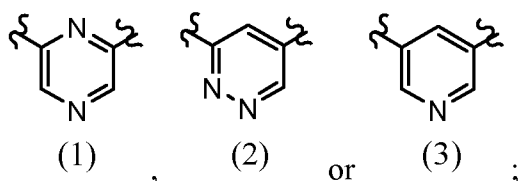
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



5

wherein

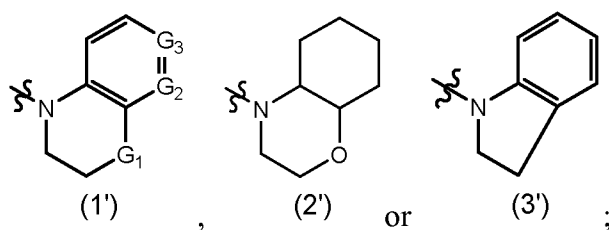
B is any of the following groups



10 wherein when B is group (1) or (2) then

A is a 3-10 membered carbocyclyl or a 4-12 membered heterocyclyl containing 1-4 heteroatoms selected from O, N or S;

C is any of the following groups



15

G_1 is CH_2 , NH or O;

G_2 and G_3 are, independently, is CH or N;

Z is $-C(O)-$, $-SO_2-$, $-C_{1-3}$ alkyl- or $-CH_2-C(O)-$;

L is a bond, $-C_{1-7}$ alkyl- or $-C_{1-7}$ alkenyl-;

20 R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy, nitro, halogen C_{1-7} alkyl,

hydroxy C_{1-7} alkyl, $-O$ -halogen C_{1-7} alkyl or $-X-NR_6R_7$;

R_2 is hydrogen, hydroxy, C_{1-7} alkyl or halogen;

R_3 is hydrogen, C_{1-7} alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

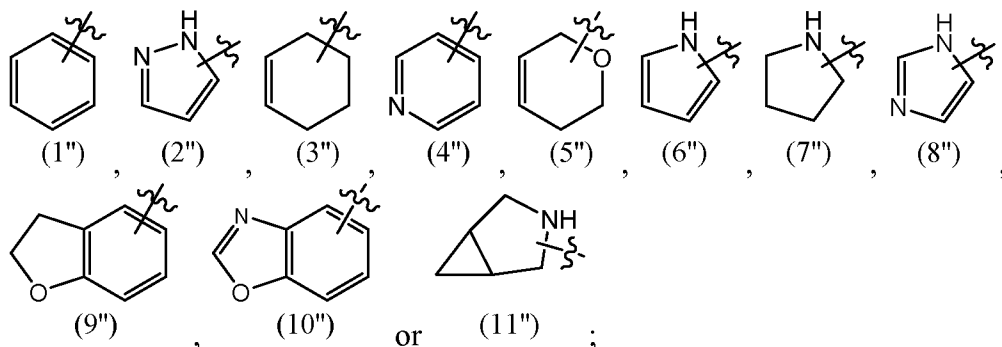
R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;

X is a bond or C₁₋₇ alkyl;

5 R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl;

wherein when B is group (3) then

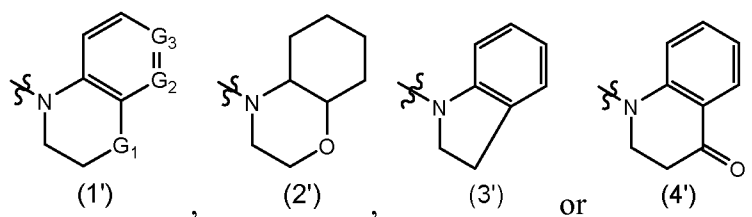
A is any one of the following groups



10

provided that when C is ring (3') then A is not ring (2'') or ring (7'');

C is any of the following groups



15

G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

20 R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, halogen C₁₋₇ alkyl, hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl, -X-NR₆R₇,

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

25

R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;

X is a bond or C₁₋₇ alkyl;

R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl;

with the proviso that compound of formula (I) is not

- (7-Methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)-
 5 pyrazin-2-yl)methanone;
 (8-Fluoro-3,4-dihydro-3-hydroxymethyl-1(2H)-quinoliny)(6-(1-pyrrolidinyl)-2-
 pyrazinyl)methanone;
 (3,4-Dihydro-3-methoxy-1(2H)-quinoliny)(6-phenyl-4-pyridazinyl)methanone;
 (6-Fluoro-3,4-dihydro-4-methyl-1(2H)-quinoxaliny)(5-phenyl-3-pyridinyl)-
 10 methanone;
 (3,4-Dihydro-1(2H)-quinoliny)(5-phenyl-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(3,4-dihydro-1(2H)-quinoliny)-
 methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(7-fluoro-2,3-dihydro-4H-1,4-
 15 benzoxazin-4-yl)methanone;
 (6,8-Difluoro-3,4-dihydro-1(2H)-quinoliny)(5-(4-(dimethylamino)phenyl)-3-
 pyridinyl)methanone;
 (3,4-Dihydro-1(2H)-quinoliny)(5-(1-pyrrolidinyl)-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-
 20 yl)methanone;
 (5-(4-Methoxyphenyl)-3-pyridinyl)(octahydro-4H-1,4-benzoxazin-4-yl)-
 methanone or
 (2,3-Dihydro-1H-indol-1-yl)(5-phenyl-3-pyridinyl)methanone.

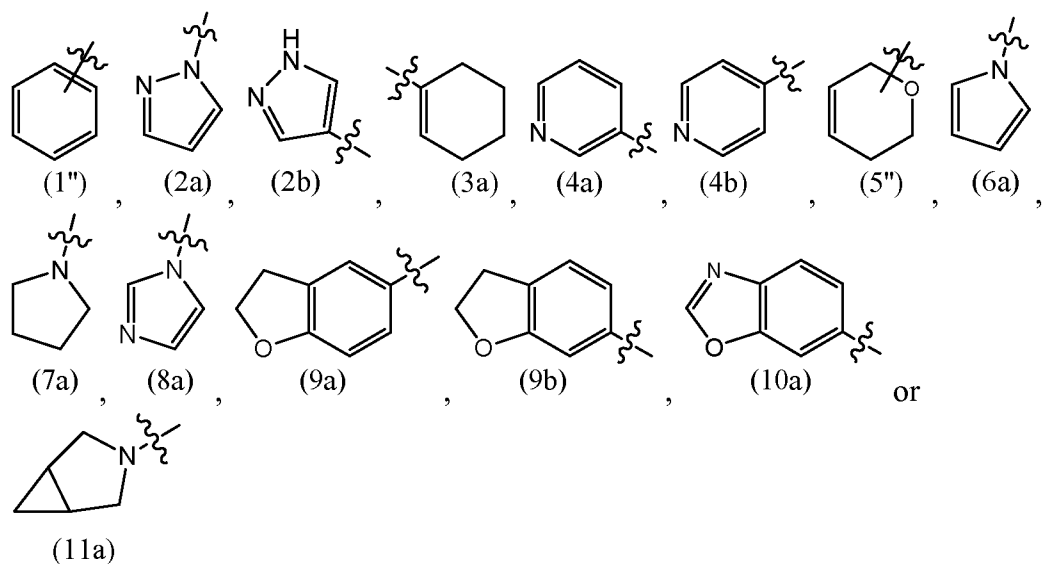
25 2. A compound according to claim 1, wherein B is group (1) or group (3).

3. A compound according to claim 1 or 2, wherein Z is -C(O)-.

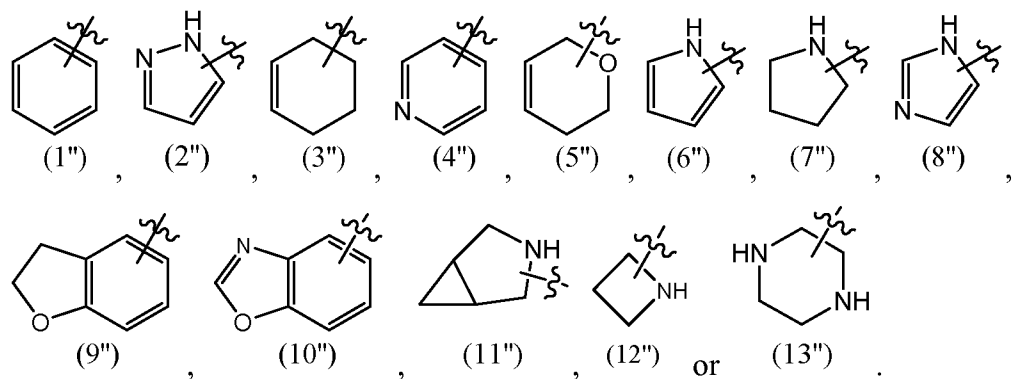
30 4. A compound according to any one of the preceding claims, wherein L is a bond.

5. A compound according to any one of the preceding claims, wherein group C is (1').

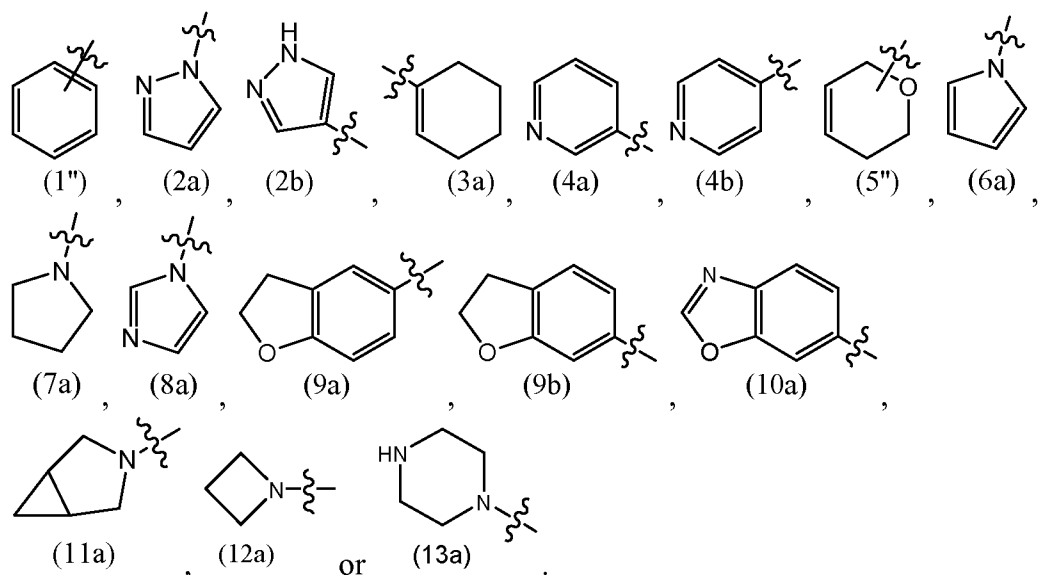
6. A compound according to claim 5, wherein G_1 is CH_2 or O.
7. A compound according to claim 5 or 6, wherein G_2 is N and G_3 is CH.
- 5 8. A compound according to claim 5 or 6, wherein G_2 is CH and G_3 is N.
9. A compound according to any one of the preceding claims, wherein R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, hydroxy C_{1-7} alkyl or halogen C_{1-7} alkyl.
- 10 10. A compound according to any one of the preceding claims, wherein R_2 is hydrogen, hydroxy, C_{1-7} alkyl or halogen.
11. A compound according to any one of the preceding claims, wherein R_3 is
- 15 hydrogen.
12. A compound according to any one of the preceding claims, wherein R_4 is hydrogen, C_{1-7} alkyl, halogen or $-C(O)-O-C_{1-7}$ alkyl.
- 20 13. A compound according to any one of the preceding claims, wherein R_5 is hydrogen.
14. A compound according to any one of the preceding claims, wherein when B is group (3) then A is any one of the following groups:



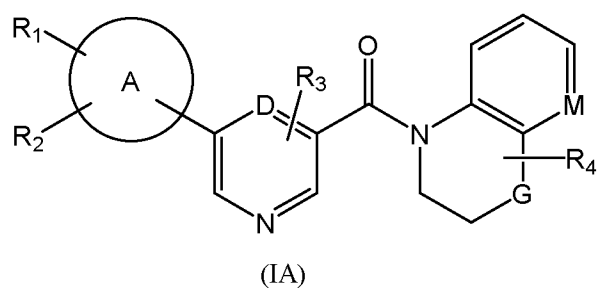
- 5 15. A compound according to any one of the preceding claims, wherein when B is group (1) or (2) then A is any one of the following groups:



- 10 16. A compound according to claim 15, wherein A is any one of the following groups:

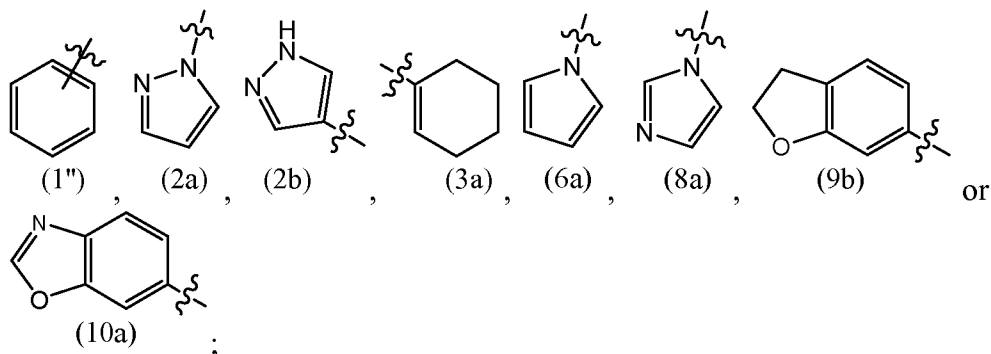


- 5 17. A compound according to any one of the preceding claims, which is represented by formula (IA) or a pharmaceutically acceptable salt thereof



wherein

- 10 D is N or CH;
 G is CH₂, NH or O;
 M is CH or N;
 R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;
 R₂ is hydrogen or halogen;
 15 R₃ is hydrogen or C₁₋₇ alkyl;
 R₄ is hydrogen, C₁₋₇ alkyl, halogen or -C(O)-O-C₁₋₇ alkyl;
 A is any one of the following groups:



with the proviso that compound of formula (I) is not

- 5 (3,4-Dihydro-1(2H)-quinolinyl)(5-phenyl-3-pyridinyl)methanone;
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(3,4-dihydro-1(2H)-quinolinyl)-
 methanone or
 (5-(2,3-Dihydro-5-benzofuranyl)-3-pyridinyl)(7-fluoro-2,3-dihydro-4H-1,4-
 benzoxazin-4-yl)methanone.

10

18. A compound according to claim 17, wherein A is group (1''), (2a), (3a), (9b)
 or (10a).

19. A compound according to any one of claims 1-18, wherein the compound is
 15 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(3-(trifluoromethoxy)phenyl)-
 pyridin-3-yl)methanone (Compound 1);

(7-Fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridin-
 3-yl)methanone (Compound 2);

- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(4-methyl-5-phenylpyridin-3-yl)-
 20 methanone (Compound 3);

(3,4-Dihydroquinolin-1(2H)-yl)(4-methyl-5-phenylpyridin-3-yl)methanone
 (Compound 4);

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)-4-
 methylpyridin-3-yl)methanone (Compound 5);

- 25 (4-Amino-5-phenylpyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone
 (Compound 6);

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridazin-3-yl)-
 methanone (Compound 7);

- (6-(Benzo[d]oxazol-6-yl)pyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 8);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(3-(trifluoromethoxy)phenyl)-pyrazin-2-yl)methanone (Compound 9);
- 5 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-phenylpyridin-3-yl)methanone (Compound 10);
- (5-(4-Chlorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 11);
- (6-(2,3-Dihydrobenzofuran-6-yl)pyrazin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)-methanone (Compound 12);
- 10 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(2,3-dihydrobenzofuran-6-yl)pyrazin-2-yl)methanone (Compound 13);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-methoxyphenyl)pyrazin-2-yl)methanone (Compound 14);
- 15 (3,4-Dihydroquinolin-1(2H)-yl)(6-phenylpyrazin-2-yl)methanone (Compound 15);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-fluorophenyl)pyridin-3-yl)methanone (Compound 16);
- (5-(4-Chlorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 17);
- 20 (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methoxyphenyl)pyridin-3-yl)methanone (Compound 18);
- (5-(3,4-Difluorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 19);
- 25 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-fluorophenyl)pyrazin-2-yl)-methanone (Compound 20);
- (6-(4-Fluorophenyl)pyrazin-2-yl)(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-methanone (Compound 21);
- (6-(4-Fluorophenyl)pyrazin-2-yl)(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-methanone (Compound 22);
- 30 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-methoxyphenyl)pyridin-3-yl)-methanone (Compound 23);

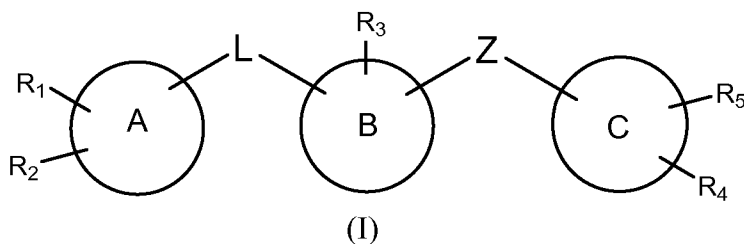
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluorophenyl)pyridin-3-yl)-methanone (Compound 24);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(3-methoxyphenyl)pyrazin-2-yl)methanone (Compound 25);
- 5 (6-(4-Fluorophenyl)pyrazin-2-yl)(3-methyl-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 26);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-3-hydroxyphenyl)pyridin-3-yl)methanone (Compound 27);
- (5-(2,4-Difluorophenyl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 28);
- 10 (6-(2,3-Dihydrobenzofuran-6-yl)pyrazin-2-yl)(octahydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone (Compound 29);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-fluorophenyl)pyridazin-4-yl)methanone (Compound 30);
- 15 (5-(4-Fluorophenyl)pyridin-3-yl)(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-methanone (Compound 31);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-nitrophenyl)pyridin-3-yl)-methanone (Compound 32);
- (5-(Cyclohex-1-en-1-yl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 33);
- 20 (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-(4-methoxyphenyl)pyridin-3-yl)-methanone (Compound 34);
- Ethyl 4-(6-(4-fluorophenyl)pyrazine-2-carbonyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine-2-carboxylate (Compound 35);
- 25 1-(5-Phenylnicotinoyl)-2,3-dihydroquinolin-4(1H)-one (Compound 36);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(6-phenylpyrazin-2-yl)methanone (Compound 37);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(3-methoxyphenyl)pyridin-3-yl)methanone (Compound 38);
- 30 (5-(1H-Pyrrol-1-yl)pyridin-3-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 39);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-fluorophenyl)pyridazin-4-yl)-methanone (Compound 40);

- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(2-fluorophenyl)pyridin-3-yl)-methanone (Compound 41);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-(4-fluorophenyl)pyridin-3-yl)-methanone (Compound 42);
- 5 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(1-methyl-1H-pyrazol-4-yl)-pyrazin-2-yl)methanone (Compound 43);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone (Compound 44);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-2-methoxyphenyl)-pyridin-3-yl)methanone (Compound 45);
- 10 4-((5-(4-Fluorophenyl)pyridin-3-yl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine (Compound 46);
- 1-((5-(4-Fluorophenyl)pyridin-3-yl)sulfonyl)-1,2,3,4-tetrahydroquinoline (Compound 47);
- 15 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone (Compound 48);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6'-fluoro-[3,3'-bipyridin]-5-yl)-methanone (Compound 49);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(3-methoxyphenyl)pyridin-3-yl)-methanone (Compound 50);
- 20 (3,4-Dihydroquinolin-1(2H)-yl)(5-(1-phenylvinyl)pyridin-3-yl)methanone (Compound 51);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-phenylpyridazin-4-yl)methanone (Compound 52);
- 25 (6-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 53);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-(hydroxymethyl)phenyl)pyridin-3-yl)-methanone (Compound 54);
- (5-(4-Fluorophenyl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]oxazin-4-yl)-methanone (Compound 55);
- 30 (5-(4-Fluorophenyl)pyridin-3-yl)((4aS,8aS)-octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 56);

- (5-(4-Fluorophenyl)pyridin-3-yl)((4aR,8aR)-octahydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 57);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-fluoro-3-nitrophenyl)pyridin-3-yl)methanone (Compound 58);
- 5 (5-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 59);
- (5-(4-Fluorophenyl)pyridin-3-yl)(indolin-1-yl)methanone (Compound 60);
- (3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 61);
- 10 [3,4'-Bipyridin]-5-yl(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 62);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(1-methyl-1H-pyrazol-5-yl)-pyrazin-2-yl)methanone (Compound 63);
- (6-(4-Fluorophenyl)pyridazin-4-yl)(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-methanone (Compound 64);
- 15 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(4-(hydroxymethyl)phenyl)pyridin-3-yl)methanone (Compound 65);
- (5-(3,6-Dihydro-2H-pyran-4-yl)pyridin-3-yl)(2,3-dihydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone (Compound 66);
- Methyl 1-(5-phenylnicotinoyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate
- 20 (Compound 67);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-((dimethylamino)methyl)phenyl)pyridin-3-yl)methanone (Compound 68);
- (7-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(5-phenylpyridin-3-yl)methanone (Compound 69);
- 25 [3,3'-Bipyridin]-5-yl(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 70);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(p-tolyl)pyridin-3-yl)methanone (Compound 71);
- (5-(2,3-Dihydrobenzofuran-6-yl)pyridin-3-yl)(octahydro-4H-benzo[b][1,4]-oxazin-4-yl)methanone (Compound 72);
- 30 (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl)methanone (Compound 73);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(pyrrolidin-1-yl)pyridin-3-yl)-methanone (Compound 74);

- 2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(5-(6,6-dimethyl-3-azabicyclo[3.1.0]-hexan-3-yl)pyridin-3-yl)methanone (Compound 75);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(pyrrolidin-1-yl)pyrazin-2-yl)-methanone (Compound 76);
- 5 (6-(3,3-Difluoroazetidin-1-yl)pyrazin-2-yl)(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methanone (Compound 77);
- (2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)methanone (Compound 78);
- 10 1-(3,4-Dihydroquinolin-1(2H)-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 79);
- 1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-methoxyphenyl)pyridin-3-yl)ethan-1-one (Compound 80);
- 4-((5-Phenylpyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (Compound 81);
- 15 (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)-methanone (Compound 82);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl)-methanone (Compound 83);
- (3,4-Dihydroquinolin-1(2H)-yl)(6-(4-methyl-1H-pyrazol-1-yl)pyrazin-2-yl)-methanone (Compound 84);
- 20 (6-Benzylpyrazin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (Compound 85);
- 1-(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-(5-(4-fluorophenyl)pyridin-3-yl)ethan-1-one (Compound 86);
- 25 (3,4-Dihydroquinolin-1(2H)-yl)(6-(3,5-dimethyl-1H-pyrazol-1-yl)pyrazin-2-yl)-methanone (Compound 87);
- (3,4-Dihydroquinolin-1(2H)-yl)(5-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl)-methanone (Compound 88);
- 1-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)-1,2,3,4-tetrahydroquinoline (Compound 89); or
- 30 1-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)indoline (Compound 90);
- or a tautomer or a pharmaceutically acceptable salts thereof.

20. A compound of formula (I) or a pharmaceutically acceptable salt thereof

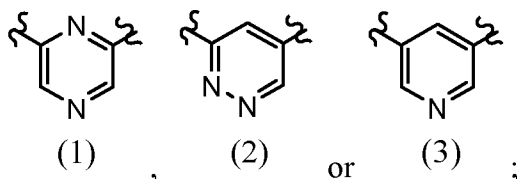


wherein

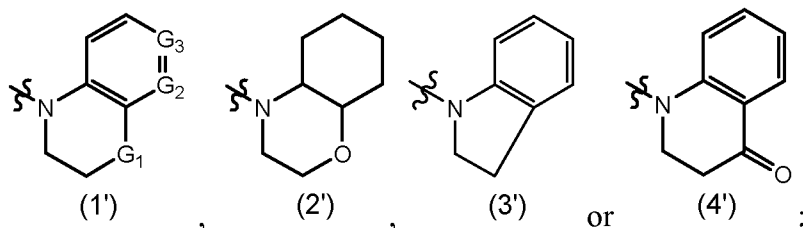
A is a 3-10 membered carbocyclyl or a 4-12 membered heterocyclyl containing

5 1-4 heteroatoms selected from O, N or S;

B is any of the following groups



C is any of the following groups



10

G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

15

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, nitro, halogen C₁₋₇ alkyl,

hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl or -X-NR₆R₇;

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

20

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;

X is a bond or C₁₋₇ alkyl;

R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl;

for use as a medicament.

5 21. A compound for use according to claim 20, for use in the treatment of a steroid receptor dependent condition or disease.

22. A compound for use according to claim 21, wherein the steroid receptor dependent condition or disease is cancer.

10

23. A compound for use according to claim 22, wherein the steroid receptor dependent condition or disease is prostate cancer or breast cancer.

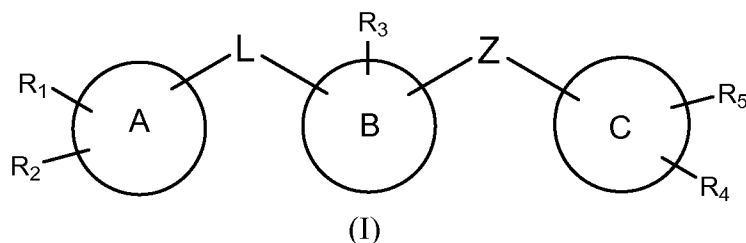
24. A compound for use according to any of claims 20-23 wherein the
15 compound of formula (I) is administered in addition to a glucocorticoid and/or a mineralocorticoid and, optionally, one or more anti-cancer agent.

25. A compound for use according to any of claims 20-24 wherein the
20 compound of formula (I) is administered in addition to one or more anti-cancer agents selected from the group consisting of

- non-steroidal androgen receptor antagonists;
- steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- 25 - epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- 30 - PI3K inhibitors; and
- CDK4/6 inhibitors,

for simultaneous, separate or sequential administration.

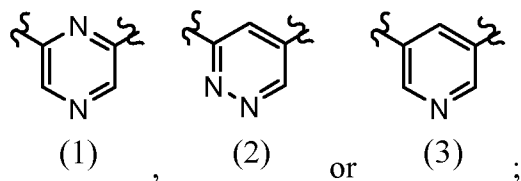
26. A method for the treatment of a steroid receptor dependent condition or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof



5 wherein

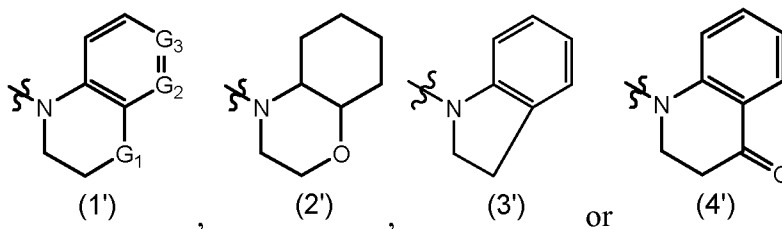
A is a 3-10 membered carbocyclyl or a 4-12 membered heterocyclyl containing 1-4 heteroatoms selected from O, N or S;

B is any of the following groups



10

C is any of the following groups



G₁ is CH₂, NH or O;

G₂ and G₃ are, independently, is CH or N;

15

Z is -C(O)-, -SO₂-, -C₁₋₃ alkyl- or -CH₂-C(O)-;

L is a bond, -C₁₋₇ alkyl- or -C₁₋₇ alkenyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, nitro, halogen C₁₋₇ alkyl,

hydroxy C₁₋₇ alkyl, -O-halogen C₁₋₇ alkyl or -X-NR₆R₇;

20

R₂ is hydrogen, hydroxy, C₁₋₇ alkyl or halogen;

R₃ is hydrogen, C₁₋₇ alkyl or amino;

R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxy, hydroxy C₁₋₇ alkyl, halogen C₁₋₇ alkyl or -C(O)-O-C₁₋₇ alkyl;

R₅ is hydrogen, halogen, C₁₋₇ alkoxy or C₁₋₇ alkyl;
X is a bond or C₁₋₇ alkyl;
R₆ and R₇ are, independently, hydrogen or C₁₋₇ alkyl.

5 27. A method according to claim 26 wherein the steroid receptor dependent condition or disease is cancer.

 28. A method according to claim 27 wherein the steroid receptor dependent condition or disease is prostate cancer or breast cancer.

10

 29. A method according to any of claims 26-28 wherein a therapeutically effective amount of a compound of formula (I) is administered in addition to a glucocorticoid and/or a mineralocorticoid and, optionally, one or more anti-cancer agent.

15

 30. A method according to any of claims 26-29 wherein a therapeutically effective amount of a compound of formula (I) is administered in addition to one or more anti-cancer agents selected from the group consisting of

- non-steroidal androgen receptor antagonists;
- 20 - steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- 25 - AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuporelin);
- PI3K inhibitors; and
- CDK4/6 inhibitors,

30 for simultaneous, separate or sequential administration.

 31. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically acceptable carrier.

32. Pharmaceutical combination comprising a compound according to claim 1 and at least one additional active ingredient selected from the list consisting of

- glucocorticoids;
- 5 - mineralocorticoids;
- non-steroidal androgen receptor antagonists;
- steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- 10 - epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- 15 - PI3K inhibitors; and
- CDK4/6 inhibitors;

for simultaneous, separate or sequential administration.

INTERNATIONAL SEARCH REPORT

International application No

PCT/FI2021/050828

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/06 C07D401/06 C07D471/04 C07D405/14 C07D403/06
 C07D413/14 C07D401/14 A61K31/538 A61K31/4709 A61K31/4375
 A61K31/498 A61K31/501 A61K31/4439 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MURINEDDU GABRIELE ET AL: "Novel N-aryl nicotinamide derivatives: Taking stock on 3,6-diazabicyclo[3.1.1]heptanes as ligands for neuronal acetylcholine receptors", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 180, 5 July 2019 (2019-07-05), pages 51-61, XP085819381, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2019.06.079	20
A	abstract page 54; compound 47 -----	1-19, 21-32
A	WO 2018/115591 A1 (ORION CORPORATION [FI]) 28 June 2018 (2018-06-28) cited in the application claims 1, 3, 13-15, 27, 29-32, 36-39 -----	1-32



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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 February 2022

Date of mailing of the international search report

23/02/2022

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/FI2021/050828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018115591 A1	28-06-2018	AR 110412 A1	27-03-2019
		AU 2017380282 A1	01-08-2019
		AU 2021203497 A1	01-07-2021
		BR 112019012906 A2	03-12-2019
		CA 3047370 A1	28-06-2018
		CL 2019001728 A1	27-09-2019
		CN 110139861 A	16-08-2019
		CO 2019007321 A2	31-07-2019
		DK 3558981 T3	26-07-2021
		EA 201991513 A1	29-11-2019
		EP 3558981 A1	30-10-2019
		EP 3868756 A1	25-08-2021
		ES 2880151 T3	23-11-2021
		HR P20211255 T1	12-11-2021
		IL 267484 A	30-09-2021
		JP 2020502229 A	23-01-2020
		KR 20190095950 A	16-08-2019
		LT 3558981 T	25-08-2021
		PE 20191137 A1	02-09-2019
		PH 12019550111 A1	09-03-2020
		PL 3558981 T3	06-12-2021
		PT 3558981 T	06-07-2021
		SI 3558981 T1	30-09-2021
		TN 2019000189 A1	05-10-2020
		TW 201835072 A	01-10-2018
		UA 124640 C2	20-10-2021
		US 2019359601 A1	28-11-2019
		US 2020299280 A1	24-09-2020
		US 2021347765 A1	11-11-2021
		WO 2018115591 A1	28-06-2018