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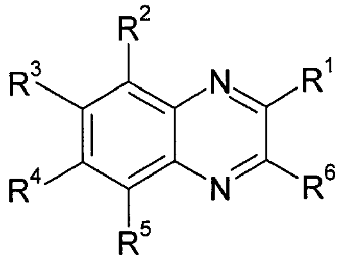
(54) Title: QUINOXALINE DERIVATIVES AS INHIBITORS OF THE TYROSINE KINASE ACTIVITY OF JANUS KINASES


(I)

(57) Abstract: The present invention relates to quinoxaline compound of the formula (I): wherein R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; R^2 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^8; R^3, R^4, R^5 and R^6 are each independently hydrogen or R^9; and R^7, R^8 and R^9 are each independently selected from organic and inorganic substituents, their use in therapy of diseases, in particular diseases mediated by the tyrosine kinase activity of Janus kinases, including JAK-2 and JAK-3 kinases.

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Quinoxaline Derivatives as Inhibitors of the Tyrosine Kinase Activity of Janus Kinases

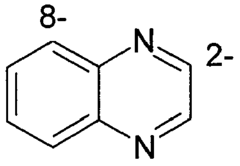
Field of the Invention

The present invention relates to compounds, their use in therapy and to other subject matter. In particular, the present invention concerns compounds which may be useful as inhibitors of the tyrosine kinase activity of Janus kinases, including JAK-2 and JAK-3 kinases

Background to the Invention

US 5721248 and EP-A-0630895 disclose dihydropyridine compounds which are substituted at the 4-position by a bicyclic group, which may be a quinoxaline. The compounds are described as being suitable for use in the treatment of cardiovascular disease.

The 2- and 8- positions of quinoxaline are shown below:



Summary of the Invention

The invention provides quinoxaline compounds in which the 2- and 8- positions of the quinoxaline ring are substituted by cyclic groups. The compounds may be useful as inhibitors of the tyrosine kinase activity of Janus kinases, including JAK-2 and JAK-3 kinases. Consequently, the compounds may be useful in the therapy of proliferative diseases such as tumor diseases, leukaemias, polycythemia vera, essential thrombocythemia, and myelofibrosis with myeloid metaplasia. Through the inhibition of JAK-3 kinase, compounds of the invention also have utility as immunosuppressive agents, for example for the treatment of diseases such as organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes.

Compounds of the invention may exist in different forms, such as free acids, free bases, esters and other prodrugs, salts and tautomers, for example, and the claims embrace all variant forms of the compounds.

The extent of protection includes counterfeit or fraudulent products which contain or purport to contain a compound of the invention irrespective of whether they do in fact contain such a compound and irrespective of whether any such compound is contained in a therapeutically effective amount.

Included in the scope of protection are packages which include a description or instructions which indicate that the package contains a species or pharmaceutical formulation of the invention and a product which is or comprises, or purports to be or comprise, such a formulation or species. Such packages may be, but are not necessarily, counterfeit or fraudulent.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

Description of Various Embodiments

Embodiments of the invention are described below. It will be appreciated that the features specified in each embodiment may be combined with other specified features, to provide further embodiments.

The term “hydrocarbyl” as used herein includes reference to a moiety consisting exclusively of hydrogen and carbon atoms; such a moiety may comprise an aliphatic and/or an aromatic moiety. The moiety may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Examples of hydrocarbyl groups include C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl); C_{1-6} alkyl substituted by aryl (e.g. benzyl) or by cycloalkyl (e.g cyclopropylmethyl); cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl); aryl (e.g. phenyl, naphthyl or fluorenyl) and the like.

The terms “alkyl” and "C_{1-8} alkyl" as used herein include reference to a straight or branched chain alkyl moiety having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. This term includes reference to groups such as methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, sec-butyl or tert-butyl), pentyl, hexyl, heptyl, octyl and the like. In particular, alkyl may have 1, 2, 3 or 4 carbon atoms.

The terms "alkenyl" and "C_{2-6} alkenyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one double bond, of either E or Z stereochemistry where applicable. This term includes reference to groups such as ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl and 3-hexenyl and the like.

The terms "alkynyl" and "C_{2-6} alkynyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one triple bond. This term includes reference to groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl and 3-hexynyl and the like.

The terms “alkoxy” and "C_{1-6} alkoxy" as used herein include reference to -O-alkyl, wherein alkyl is straight or branched chain and comprises 1, 2, 3, 4, 5 or 6 carbon atoms. In one class of embodiments, alkoxy has 1, 2, 3 or 4 carbon atoms. This term includes reference to groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like.

The term “cycloalkyl” as used herein includes reference to an alicyclic moiety having 3, 4, 5, 6, 7 or 8 carbon atoms. The group may be a bridged or polycyclic ring system. More often cycloalkyl groups are monocyclic. This term includes reference to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl and the like.

The term "aryl" as used herein includes reference to an aromatic ring system comprising 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring carbon atoms. Aryl is often phenyl but may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. This term includes reference to groups such as phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

The term "carbocyclyl" as used herein includes reference to a saturated (e.g. cycloalkyl) or unsaturated (e.g. aryl) ring moiety having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 carbon ring atoms. In particular, carbocyclyl includes a 3- to 10-membered ring or ring system and, in particular, a 5- or 6-membered ring, which may be saturated or unsaturated. A carbocyclic moiety is, for example, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl, phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

The term "heterocyclyl" as used herein includes reference to a saturated (e.g. heterocycloalkyl) or unsaturated (e.g. heteroaryl) heterocyclic ring moiety having from 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen, phosphorus, silicon and sulphur. In particular, heterocyclyl includes a 3- to 10-membered ring or ring system and more particularly a 5- or 6-membered ring, which may be saturated or unsaturated.

A heterocyclic moiety is, for example, selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholino, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl, chromanyl and the like.

The term "heterocycloalkyl" as used herein includes reference to a saturated heterocyclic moiety having 3, 4, 5, 6 or 7 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur. The group may be a polycyclic ring system but more often is monocyclic. This term includes reference to groups such as azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxiranyl, pyrazolidinyl, imidazolyl, indolizidinyl, piperazinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, quinolizidinyl and the like.

The term "heteroaryl" as used herein includes reference to an aromatic heterocyclic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen and sulphur. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic, but is more often monocyclic. This term includes reference to groups such as pyrimidinyl, furanyl, benzo[b]thiophenyl, thiophenyl, pyrrolyl, imidazolyl, pyrrolidinyl, pyridinyl, benzo[b]furanyl, pyrazinyl, purinyl, indolyl, benzimidazolyl, quinolinyl, phenothiazinyl, triazinyl, phthalazinyl, 2H-chromenyl, oxazolyl, isoxazolyl, thiazolyl, isoindolyl, indazolyl, purinyl, isoquinolinyl, quinazolinyl, pteridinyl and the like.

The term "halogen" as used herein includes reference to F, Cl, Br or I. In particular, halogen may be F or Cl, of which F is more common.

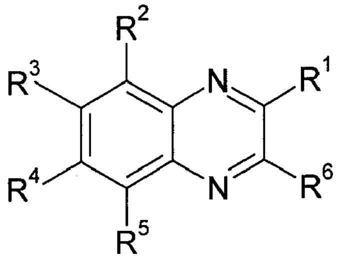
The term “substituted” as used herein in reference to a moiety means that one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of the described substituents. The term “optionally substituted” as used herein means substituted or unsubstituted. It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Additionally, it will of course be understood that the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognised by the skilled man.

The term “pharmaceutically acceptable” as used herein includes reference to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. This term includes acceptability for both human and veterinary purposes.

Where two or more moieties are described as being “each independently” selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.

The invention provides quinoxaline compounds in which the 2- and 8- positions of the quinoxaline ring are substituted by cyclic groups. The cyclic groups may be the same or different and may be substituted or unsubstituted. In embodiments, the cyclic groups are carbocyclyl or heterocyclyl and are substituted or unsubstituted.

Included in the invention are quinoxaline compounds of the formula (I):



(I)

wherein

R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^2 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^8;

R^3, R^4, R^5 and R^6 are each independently hydrogen or R^9; and

R^7, R^8 and R^9 are each independently selected from organic and inorganic substituents;

or a pharmaceutically acceptable salt or prodrug thereof.

R^1

According to formula (I), R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

In one embodiment, R^1 comprises a monocyclic ring having 3, 4, 5, 6 or 7 ring members. Alternatively, R^1 may comprise a fused ring system comprising 2 or more fused rings, for example two fused rings having 5 or 6 ring members.

In a particular embodiment, R^1 is a 5- or 6-membered carbocycle or heterocycle, and is optionally substituted with 1, 2, 3, 4 or 5 R^7. R^1 may be aromatic or heteroaromatic. Alternatively, R^1 may be saturated group, e.g. cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 R^7. R^1 may also be an unsaturated carbocyclic or unsaturated heterocyclic moiety.

Of mention are compounds in which R^1 is aryl (e.g. phenyl or naphthyl) or heteroaryl (e.g. pyridinyl or pyrazolyl), either of which is optionally substituted with one or more R^7 groups, e.g. 1, 2, 3, 4 or 5 R^7 groups. Compounds in which R^1 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7 are of particular mention. Compounds in which R^1 is pyridinyl optionally substituted with 1, 2, 3 or 4 R^7 are also of particular mention. Also of particular mention are compounds in which R^1 is pyrazolyl optionally substituted with 1, 2 or 3 R^7.

In certain compounds, R^1 is substituted with at least 1 R^7, e.g. 1, 2 or 3 R^7. Of particular mention are compounds in which R^1 is phenyl or pyridinyl or pyrazolyl, each independently substituted with 1, 2 or 3 R^7, preferably 1 or 2 R^7.

Where present, the or each R^7 is independently selected from organic or inorganic substituents.

In certain compounds, at least one R^7 is independently selected from -W-R^{10}, wherein:

W is a bond or a linker comprising 1 to 20 (e.g. 1 to 8) in-chain atoms and, for example, comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})-, hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R^{13};

R^{10} is selected from hydrogen, except when W is a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{13};

R^{11} is selected from R^{12}, -OR^{12}, -C(O)R^{12}, -C(O)OR^{12} and -S(O)$_l$$R^{12}$;

R^{12} is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{13};

R^{13} is selected from R^{14}; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{14}; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{14};

R^{14} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^{15}, -OR^{15}, -C(O)R^{15}, -C(O)N(R^{15})R^{16}, -C(O)OR^{15}, -OC(O)R^{15}, -C(NR^{15})N(R^{15})R^{16}, -S(O)$_l$$R^{15}$, -S(O)$_l$N($R^{15}$)$R^{16}$, -N($R^{15}$)$R^{16}$, -N($R^{15}$)N($R^{15}$)$R^{16}$, -N($R^{15}$)C(O)$R^{16}$ and -N(R^{15})S(O)$_l$$R^{16}$;

R^{15} and R^{16} are each independently hydrogen or selected from hydrocarbyl and -(CH$_2$)$_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6; and

l is 0, 1, or 2.

In one embodiment, W is a bond or is selected from the following linkers:

-W^1-;
-W^1-W^2-;
-W^1-W^2-W^3-;

$-W^1-W^2-W^3-W^4-$; and
$-W^1-W^2-W^3-W^4-W^5-$;

wherein W^1, W^2, W^3, W^4 and W^5 are each independently selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^{11})-$, hydrocarbylene (e.g. C_{1-6} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

Of mention are compounds in which W is $-W^1-$, $-W^1-W^2-$ or $-W^1-W^2-W^3-$.

Also of mention are compounds in which W is a bond or a linker comprising 1, 2, 3 or 4 linkages independently selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^{11})-$ and C_{1-6} alkylene (e.g. methylene or ethylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

Included are compounds in which R^{10} is hydrocarbyl, e.g. C_{1-6} alkyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}. The invention also includes compounds in which R^{10} is heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}. For example, R^{10} may be a nitrogen-containing heterocycle, e.g. piperadyl (e.g. 4-piperadyl), piperazinyl or morpholinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

In certain compounds, R^1 is substituted with at least one R^7, wherein said R^7 is selected from halogen (e.g. fluorine, chlorine or bromine), hydroxy, cyano, amino, -C(O)OH, C_{1-6} alkyl, C_{1-6} alkoxy (e.g. C_1, C_2, C_3 or C_4 alkoxy), $-C(O)-C_{1-6}$ alkyl, $-C(O)O-C_{1-6}$ alkyl, $-S(O)_l-C_{1-6}$ alkyl, $-C(O)NH-C_{1-6}$ alkyl, $-C(O)N(C_{1-6}\text{ alkyl})_2$, $-NH(C_{1-6}$ alkyl) and $-N(C_{1-6}\text{ alkyl})_2$, wherein any C_{1-6} alkyl group present is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C_{1-6} alkoxy.

Of mention are compounds in which R^1 is substituted with 1, 2 or 3 R^7, wherein at least one R^7 is selected from hydroxy, C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}, C_{1-6} alkoxy optionally substituted with 1, 2, 3, 4 or 5 R^{13}, C_{1-6} alkoxyalkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}, $-S(O)_lR^{15}$, $-S(O)_lN(R^{15})R^{16}$ and $-N(R^{15})S(O)_lR^{16}$, wherein R^{15} and R^{16} are typically each hydrogen or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

By way of example, R^1 may be phenyl substituted with 1, 2 or 3 R^7, wherein at least one R^7 is C_{1-6} alkyl, e.g. C_1, C_2, C_3 or C_4 alkyl, or C_{1-6} alkoxy, e.g. C_1, C_2, C_3 or C_4 alkoxy, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Of mention are compounds in which R^1 is phenyl substituted with 1, 2 or 3 R^7, wherein at least one R^7 is methyl or ethyl. Also of mention are compounds in which R^1 is phenyl substituted with 2 or 3 groups selected from methoxy and ethoxy. For example, R^1 may be selected from 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl and 3,4,5-trimethoxyphenyl. Of particular mention are compounds in which R^1 is 3,4,5-trimethoxyphenyl.

In certain compounds R^1 is substituted with 1, 2, or 3 R^7, wherein at least one R^7 is -W-R^{10}. By way of example, R^1 may be phenyl substituted with 1, 2, or 3 R^7, wherein at least one R^7 is -W-R^{10}. Included are compounds in which said at least one R^7 is present at the 4-position of the phenyl ring. Said W may, for example, be a bond or a linker comprising 1, 2, 3, 4 or 5 linkages independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})- and C_{1-6} alkylene (e.g. methylene or ethylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In certain compounds, said W is a bond. In other compounds, said W is selected from -C(O)-, C_{1-6} alkylene, -O-C_{1-6} alkylene- and -C_{1-6} alkylene-O-, wherein the C_{1-6} alkylene moieties (e.g. C_1, C_2, C_3 or C_4 alkylene) are optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Said R^{10} may, for example, be heterocyclyl, e.g. morpholinyl, pyrrolidinyl, piperidinyl, imidazolyl or piperazinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}. R^1 may comprise one or more further R^7 substituents, wherein said further R^7 are independently selected from, for example, C_{1-6} alkyl (e.g. methyl or ethyl), C_{1-6} alkoxy (e.g. methoxy or ethoxy) and halogen (e.g. fluorine or chlorine).

R^2

According to formula (I), R^2 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^8.

In one embodiment, R^2 comprises a monocyclic ring having 3, 4, 5, 6 or 7 ring members. Alternatively, R^2 may comprise a fused ring system comprising 2 or more fused rings, for example two fused rings having 5 or 6 ring members.

In one embodiment, R^2 is a 5- or 6-membered carbocycle or heterocycle, and is optionally substituted with 1, 2, 3, 4 or 5 R^8. R^2 may be aromatic. Alternatively, R^2 may be saturated group, e.g. cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

Of mention are compounds in which R^2 is aryl (e.g. phenyl or naphthyl) or heteroaryl (e.g. pyridinyl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R^8. Compounds in which R^2 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^8 are of particular mention.

In certain compounds, R^2 is substituted with at least 1, e.g. 1, 2 or 3, R^8. Of particular mention are compounds in which R^2 is phenyl substituted with 1, 2 or 3 R^8.

In particular compounds, R^2 is other than optionally substituted dihydropyridinyl.

Where present, the or each R^8 is independently selected from organic or inorganic substituents.

In certain compounds, at least one R^8 is independently selected from -Y-R^{17}, wherein:

> Y is a bond or a linker comprising 1 to 20 (e.g. 1 to 8) in-chain atoms and, for example, comprising one or more linkages selected from O-, -C(O)-, -S(O)$_l$-, -N(R^{11})-, hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}; and
>
> R^{17} is selected from hydrogen, except when Y is a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}; and -(CH_2)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{13};
>
> and wherein R^{11} and R^{13} are as defined elsewhere herein.

In one embodiment, Y is selected from the following linkers:
-Y^1-;
-Y^1-Y^2-;
-Y^1-Y^2-Y^3-;
-Y^1-Y^2-Y^3-Y^4-; and
-Y^1-Y^2-Y^3-Y^4-Y^5-;

wherein Y^1, Y^2, Y^3, Y^4 and Y^5 are each independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})-, hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

Of mention are compounds in which Y is -Y^1-, -Y^1-Y^2- or -Y^1-Y^2-Y^3-. Also of mention are compounds in which Y is a bond or a linker comprising 1, 2, 3 or 4 linkages independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})- and C_{1-6} alkylene optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

The invention includes compounds in which R^{17} is heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Of particular mention are compounds in which R^{17} is a nitrogen-containing heterocycle, e.g. piperazinyl or morpholinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

In certain compounds, R^2 is substituted with at least one R^8, wherein said R^8 is selected from halogen (e.g. fluorine, chlorine or bromine), hydroxy, cyano, amino, -C(O)OH, C_{1-6} alkyl, C_{1-6} alkoxy (e.g. C_1, C_2, C_3 or C_4 alkoxy), -C(O)-C_{1-6} alkyl, -C(O)O-C_{1-6} alkyl, -S(O)$_l$-C_{1-6} alkyl, -NH(C_{1-6} alkyl) and -N(C_{1-6} alkyl)$_2$, wherein any C_{1-6} alkyl group present is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C_{1-6} alkoxy.

Of mention are compounds in which R^2 is substituted with 1, 2 or 3 R^8, wherein at least one R^8 comprises a group selected from -S(O)$_l$- (e.g. -S(O)$_2$-) and -N(R^{11})-. Included are compounds in which R^2 is phenyl substituted with 1, 2 or 3 R^8, wherein at least one R^8 comprises a group selected from -S(O)$_l$- (e.g. -S(O)$_2$-) and -N(R^{11})-. For example, said at least one R^8 may be -S(O)$_l$$R^{15}$, -S(O)$_l$N($R^{15}$)$R^{16}$ or -N(R^{15})S(O)$_l$$R^{16}$, wherein R^{15} and R^{16} are typically each hydrogen or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

In other compounds R^2 is substituted with 1, 2, or 3 R^8, wherein at least one R^8 is -Y-R^{17}. Included are compounds in which R^2 is phenyl substituted with 1, 2, or 3 R^8, wherein at least one R^8 is -Y-R^{17}. Included are compounds in which said at least one R^8 is present at the 4-position of the phenyl ring. Said Y may, for example, be a bond or a linker comprising 1, 2, 3 or 4 linkages independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})- and C_{1-6} alkylene (e.g. methylene or ethylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In certain compounds, said Y is selected from -C(O)-, -C_{1-6} alkylene-, -C(O)-C_{1-6} alkylene- and -C_{1-6}

alkylene-C(O)-, wherein the C_{1-6} alkylene (e.g. C_1, C_2, C_3 or C_4 alkylene) moieties are optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In particular compounds, said Y is selected from -C(O)-, -CH_2-, -C(C_{1-6} alkyl$)_2$, -C(O)-CH_2- and -CH_2-C(O)-. Said R^{17} may, for example, be heterocyclyl, e.g. morpholinyl, thiomorpholinyl or piperazinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Included are compounds in which said R^{17} is 1,1-dioxido-thiomorpholinyl optionally substituted with 1, 2 or 3 R^{13}. Of mention are compounds in which R^2 is phenyl and said at least one R^8 is -C(O)R^{17} or -CH_2C(O)R^{17}, wherein R^{17} is heterocyclyl (e.g. morpholinyl, thiomorpholinyl or piperazinyl) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. R^2 may comprise one or more further R^8 substituents, wherein said further R^8 are each independently selected from, for example, C_{1-6} alkyl (e.g. methyl or ethyl), C_{1-6} alkoxy (e.g. methoxy or ethoxy) and halogen (e.g. fluorine or chlorine).

R^3, R^4, R^5 & R^6

According to formula (I), R^3, R^4, R^5 and R^6 are each independently hydrogen or R^9, wherein are each independently hydrogen or R^9, wherein the or each R^9 is independently selected from organic and inorganic substituents.

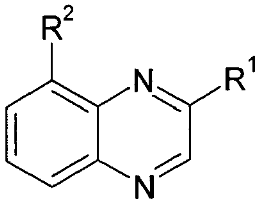
In one embodiment, R^3, R^4, R^5 and R^6 are each independently hydrogen or R^9, wherein the or each R^9 is independently selected from R^{13}, wherein R^{13} is as defined elsewhere herein.

Of mention are compounds in which R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, halogen (e.g. fluorine or chlorine), cyano, hydroxy, C_{1-8} alkyl and -N(R^{13})R^{14}, wherein R^{13} and R^{14} are each independently hydrogen or C_{1-8} alkyl.

Of further mention are compounds in which R^3 and R^4 are each independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-8} alkyl and -N(R^{13})R^{14}; and R^5 and R^6 are each independently selected from hydrogen, hydroxy and -N(R^{13})R^{14}; and wherein R^{13} and R^{14} are each independently hydrogen or C_{1-8} alkyl. In some compounds, R^4 is C_{1-6} alkyl (e.g. methyl) or halogen (e.g. fluorine or chlorine)

The invention includes compounds in which at least one of R^3, R^4, R^5 and R^6 are each hydrogen. Included are compounds in which R^3, R^4 and R^5 are each hydrogen. Also included are compounds in which R^6 is hydrogen.

Of particular mention is a compound of the following formula:

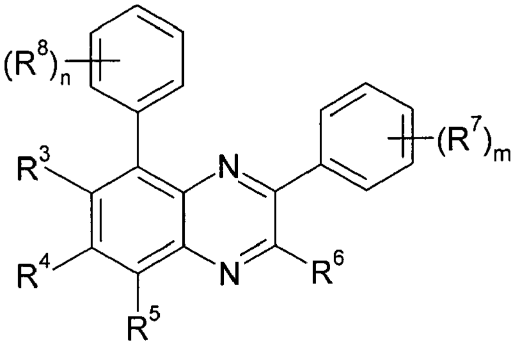


(II)

or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R^1 is substituted with at least one R^7, and R^2 is substituted with at least one R^8.

Also of mention is a compound of the following formula:

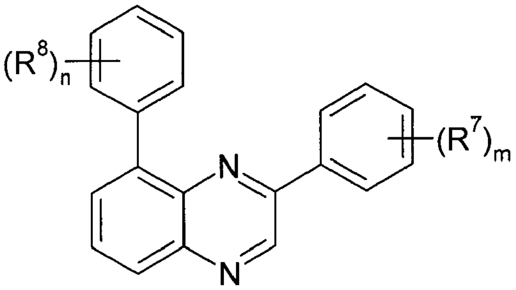


(III)

wherein m and n are each independently 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

Of particular mention is a compound of the following formula:



(IV)

wherein m and n are each independently 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

Included are compounds of said formulae in which m and n are each independently 1, 2 or 3.

In certain compounds of formulae (III) and (IV), at least one R^7 is selected from halogen (e.g. fluorine, chlorine or bromine), hydroxy, cyano, amino, -C(O)OH, C_{1-6} alkyl, C_{1-6} alkoxy (e.g. C_1, C_2, C_3 or C_4 alkoxy), -C(O)-C_{1-6} alkyl, -C(O)O-C_{1-6} alkyl, -S(O)$_l$-C_{1-6} alkyl, -C(O)NH-C_{1-6} alkyl, -C(O)N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl) and -N(C_{1-6} alkyl)$_2$, wherein any C_{1-6} alkyl group present is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C_{1-6} alkoxy.

In particular compounds of formulae (III) and (IV), at least one R^7 is selected from hydroxy, C_{1-6} alkoxy optionally substituted with 1, 2, 3, 4 or 5 R^{13}, C_{1-6} alkoxyalkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}, -S(O)$_l$$R^{15}$, -S(O)$_l$N($R^{15}$)$R^{16}$ and -N(R^{15})S(O)$_l$$R^{16}$, wherein R^{15} and R^{16} are typically each hydrogen or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In other compounds of formulae (III) and (IV), at least one R^7 is independently C_{1-6} alkoxy, e.g. C_1, C_2, C_3 or C_4 alkoxy, optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

In other compounds of said formulae, at least one R^7 is -W-R^{10}. Included are compounds in which said at least one R^7 is present at the 4- position of the phenyl ring. Said W may, for example, be a bond or a linker comprising 1, 2, 3 or 4 linkages independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})- and C_{1-6} alkylene (e.g. methylene or ethylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. . In certain compounds, said W is a bond. In other compounds, said W is selected from -C(O)-, -O-C_{1-6} alkylene-, and -C_{1-6} alkylene-O-, wherein the C_{1-6} alkylene (e.g. C_1, C_2, C_3 or C_4 alkylene) moieties are optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Said R^{10} may, for example, be heterocyclyl, e.g. morpholinyl, pyrrolidinyl, piperidinyl, imidazolyl or piperazinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}. R^1 may comprise one or more further R^7 substituents, wherein said further R^7 are independently selected from, for example, C_{1-6} alkyl (e.g. methyl or ethyl), C_{1-6} alkoxy (e.g. methoxy or ethoxy) and halogen (e.g. fluorine or chlorine).

In certain compounds of formulae (III) and (IV), at least one R^8 is selected from halogen (e.g. fluorine, chlorine or bromine), hydroxy, cyano, amino, -C(O)OH, C_{1-6} alkyl, C_{1-6} alkoxy (e.g. C_1, C_2, C_3 or C_4 alkoxy), -C(O)-C_{1-6} alkyl, -C(O)O-C_{1-6} alkyl, -S(O)$_l$-C_{1-6} alkyl, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -C(O)NH-C_{1-6} alkyl, -C(O)N(C_{1-6} alkyl)$_2$ and , -S(O)$_l$-C_{1-6} alkyl, wherein any C_{1-6} alkyl group present is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C_{1-6} alkoxy.

In other compounds of said formulae, at least one R^8 comprises a group selected from -S(O)$_l$- (e.g. -S(O)$_2$-) and -N(R^{11})-. For example, said at least one R^8 may be -S(O)$_l$$R^{15}$, -S(O)$_l$N($R^{15}$)$R^{16}$ or -N(R^{15})S(O)$_l$$R^{16}$, wherein R^{15} and R^{16} are typically each hydrogen or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{13}.

In other compounds of said formulae, at least one R^8 is -Y-R^{17}. Included are compounds in which said at least one R^8 is present at the 4- position of the phenyl ring. Said Y may, for example, be a bond or a linker comprising 1, 2, 3 or 4 linkages independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^{11})- and C_{1-6} alkylene (e.g. methylene or ethylene) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In certain compounds, said Y is selected from -C(O)-, -C_{1-6} alkylene-, -C(O)-C_{1-6} alkylene- and -C_{1-6} alkylene-C(O)-, wherein the C_{1-6} alkylene (e.g. C_1, C_2, C_3 or C_4 alkylene) moieties are optionally substituted with 1, 2, 3, 4 or 5 R^{13}. In particular compounds, said Y is selected from -C(O)-, -CH_2-, -C(C_{1-6} alkyl)$_2$, -C(O)-CH_2- and -CH_2-C(O)-. Said R^{17} may, for example, be heterocyclyl, e.g. morpholinyl, thiomorpholinyl or piperazinyl, optionally substituted with 1, 2, 3, 4 or 5 R^{13}. Included are compounds in which said R^{17} is 1,1-dioxido-thiomorpholinyl optionally substituted with 1, 2 or 3 R^{13}. Of mention are compounds in which said at least one R^8 is -C(O)R^{17} or -CH_2C(O)R^{17}, wherein R^{17} is heterocyclyl (e.g. morpholinyl, piperazinyl or 1,1-dioxido-thiomorpholinyl) optionally substituted with 1, 2, 3, 4 or 5 R^{13}. R^2 may comprise one or more further R^8 substituents, wherein said further R^8 are each independently selected from, for example, C_{1-6} alkyl (e.g. methyl or ethyl), C_{1-6} alkoxy (e.g. methoxy or ethoxy) and halogen (e.g. fluorine or chlorine).

Compounds of the invention may be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stochiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., US, 1985, p. 1418, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, "Handbook of Pharmaceutical Salts Properties Selection and Use", Verlag Helvetica Chimica Acta and Wiley-VCH, 2002.

The invention thus includes pharmaceutically acceptable salts of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. for example the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g. from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The invention includes prodrugs for the active pharmaceutical species of the invention, for example in which one or more functional groups are protected or derivatised but can be converted *in vivo* to the functional group, as in the case of esters of carboxylic acids convertible *in vivo* to the free acid, or in the case of protected amines, to the free amino group. The term "prodrug," as used herein, represents in particular compounds which are rapidly transformed *in vivo* to the parent compound, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery

Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. Synthetic Communications, 26(23), 4351-4367 (1996), each of which is incorporated herein by reference.

Prodrugs therefore include drugs having a functional group which has been transformed into a reversible derivative thereof. Typically, such prodrugs are transformed to the active drug by hydrolysis. As examples may be mentioned the following:

Functional Group	**Reversible derivative**
Carboxylic acid	Esters, including e.g. acyloxyalkyl esters, amides
Alcohol	Esters, including e.g. sulfates and phosphates as well as carboxylic acid esters
Amine	Amides, carbamates, imines, enamines,
Carbonyl (aldehyde, ketone)	Imines, oximes, acetals/ketals, enol esters, oxazolidines and thiazoxolidines

Prodrugs also include compounds convertible to the active drug by an oxidative or reductive reaction. As examples of oxidative activation may be mentioned N- and O- dealkylation, oxidative deamination, N-oxidation and epoxidation. As example of reductive activation may be mentioned azo reduction, sulfoxide reduction, disulfide reduction, bioreductive alkylation and nitro reduction.

Also to be mentioned as metabolic activations of prodrugs are nucleotide activation, phosphorylation activation and decarboxylation activation. For additional information, see "The Organic Chemistry of Drug Design and Drug Action", R B Silverman (particularly Chapter 8, pages 497 to 546), incorporated herein by reference.

The use of protecting groups is fully described in `Protective Groups in Organic Chemistry`, edited by J W F McOmie, Plenum Press (1973), and `Protective Groups in Organic Synthesis`, 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Thus, it will be appreciated by those skilled in the art that, although protected derivatives of compounds of the invention may not possess pharmacological activity as such, they may be administered, for example parenterally or orally, and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives are therefore examples of "prodrugs". All prodrugs of the described compounds are included within the scope of the invention.

Some groups mentioned herein (especially those containing heteroatoms and conjugated bonds) may exist in tautomeric forms and all these tautomers are included in the scope of the disclosure. More generally, many species may exist in equilibrium, as for example in the case of organic acids and their counterpart anions; a reference herein to a species accordingly includes reference to all equilibrium forms thereof.

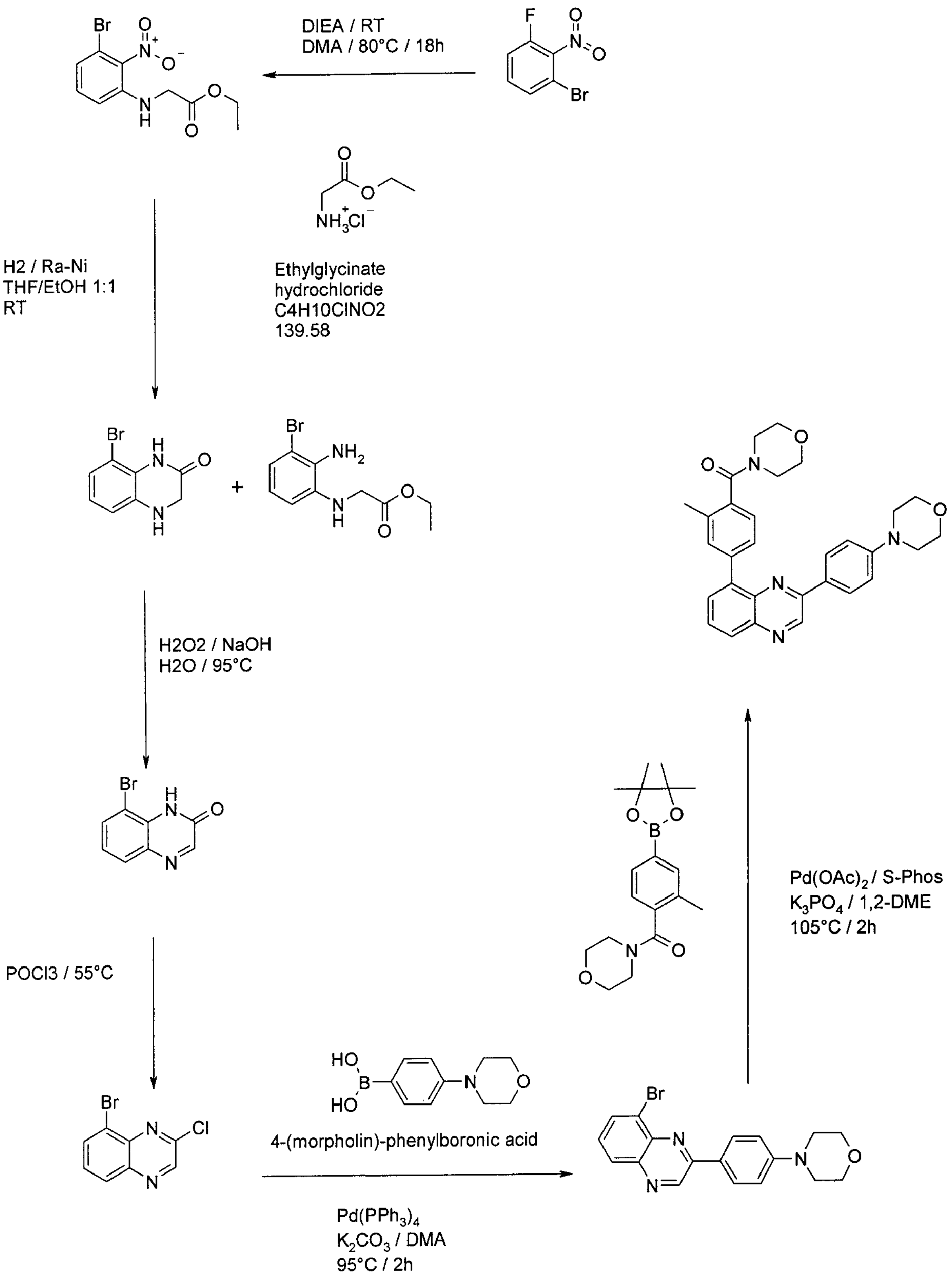
Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Such a compound may exist in optically active form or in the form of a mixture of optical isomers, e.g. in the form of a racemic mixture. All optical isomers and their mixtures, including the racemic mixtures, are part of the present invention. Thus, any given formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (i.e. cis and trans isomers), as tautomers, or as atropisomers. All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the disclosure. Where a single enantiomer or diasteromer is disclosed, the disclosure also covers the other enantiomers or diastereomers, and also racemates; in this regard, particular reference is made to the specific compounds listed herein.

Geometric isomers may also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond and designates such isomers as of the Z or E configuration, wherein the term "Z" represents substituents on the same side of the carbon--carbon double bond and the term "E" represents substituents on opposite sides of the carbon--carbon double bond.

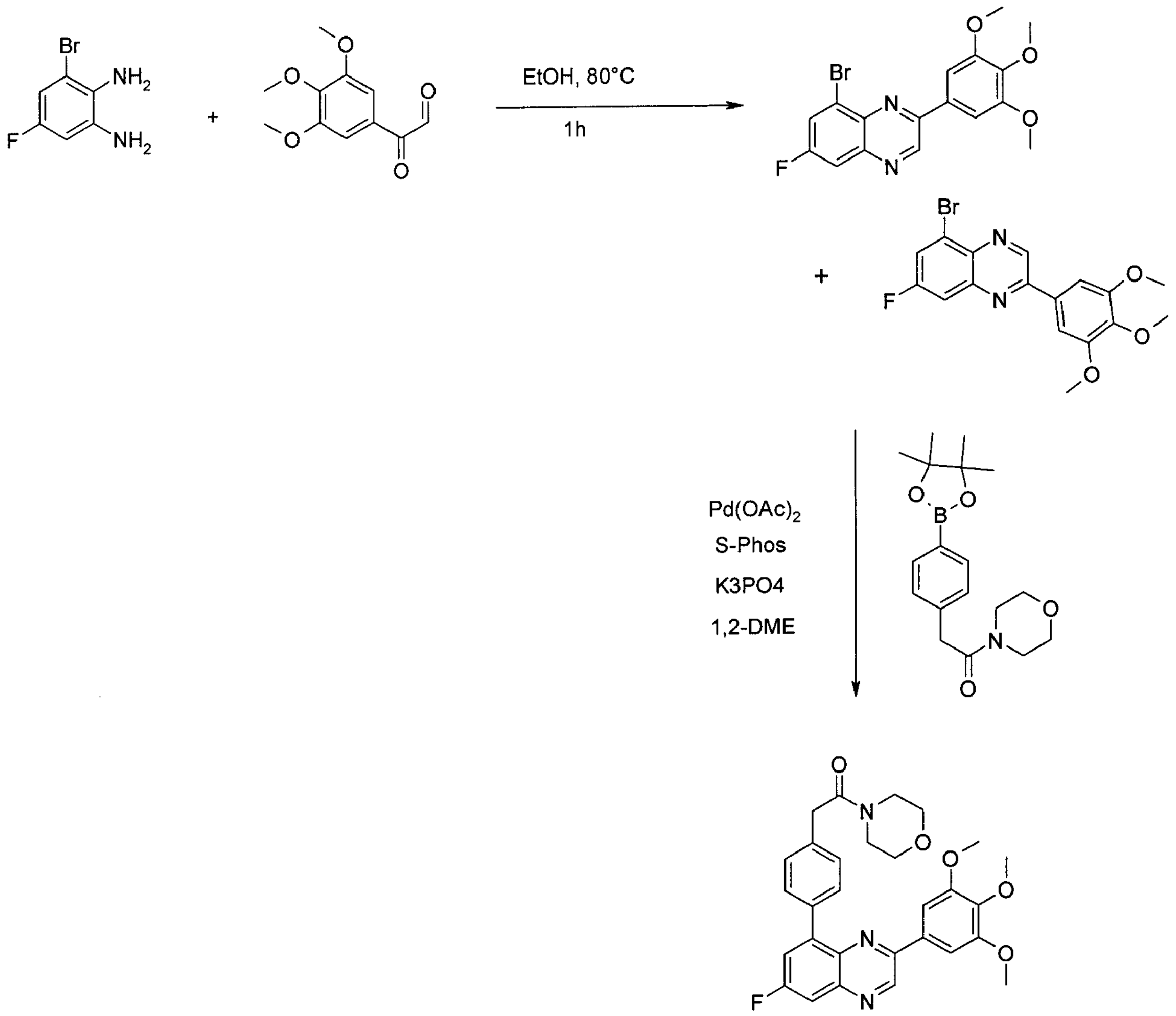
The invention therefore includes all variant forms of the defined compounds, for example any tautomer or any pharmaceutically acceptable salt, ester, acid or other variant of the defined compounds and their tautomers as well as substances which, upon administration, are capable of providing directly or indirectly a compound as defined above or providing a species which is capable of existing in equilibrium with such a compound. Furthermore, any formula given herein is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{13}C, and ^{14}C are incorporated. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a. readily available isotopically labeled reagent for a non-isotopically labeled reagent.

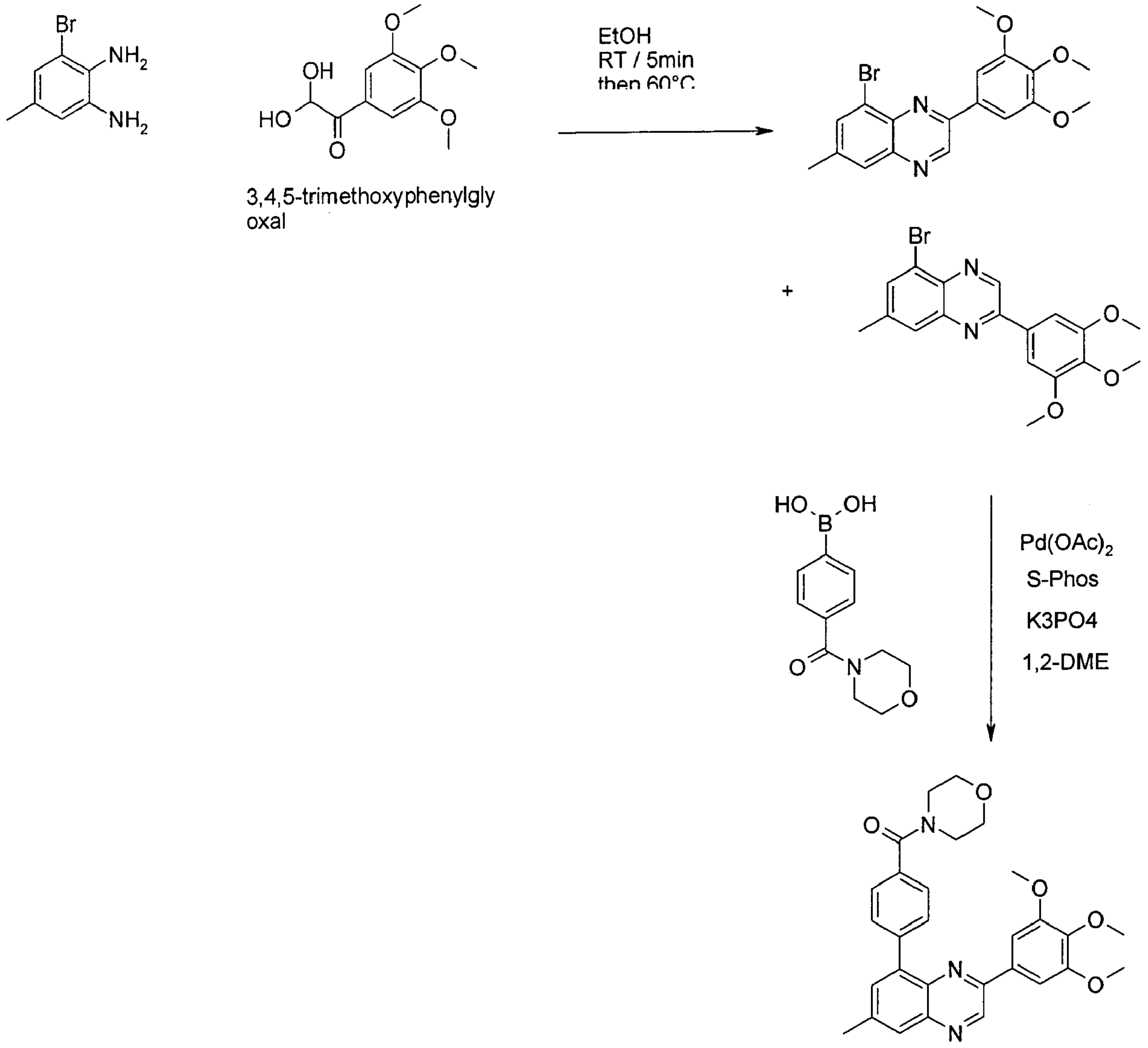
Compounds of the invention may be prepared using, for example, a Suzuki (Miyaura) or analogous coupling reaction, for example a Stille reaction. By way of illustration, a compound of the invention may be prepared according to the following Schemes:


DIEA / RT
DMA / 80°C / 18h
Ethylglycinate
hydrochloride
C4H10ClNO2
139.58
H2 / Ra-Ni
THF/EtOH 1:1
RT
+
H2O2 / NaOH
H2O / 95°C
POCl3 / 55°C
4-(morpholin)-phenylboronic acid
Pd(PPh$_3$)$_4$
K$_2$CO$_3$ / DMA
95°C / 2h
Pd(OAc)$_2$ / S-Phos
K$_3$PO$_4$ / 1,2-DME
105°C / 2h

Scheme 1


Br
NH2
NH2
F
+
O
O
O
O
O
EtOH, 80°C
1h
Br
N
N
F
+
Pd(OAc)2
S-Phos
K3PO4
1,2-DME
B
N
O

Scheme 2


EtOH
RT / 5min
then 60°C
3,4,5-trimethoxyphenylglyoxal
+
Pd(OAc)$_2$
S-Phos
K3PO4
1,2-DME

Scheme 3

It will be understood that the processes detailed above are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions (for example, an analogous base, solvent, catalyst, ligand or reaction temperature) known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

Compounds of the invention have valuable pharmacological properties, as described hereinbefore and hereinafter. The compounds may be useful in the therapy (i.e the treatment, prevention or delay of progression) of proliferative diseases and immunological diseases.

The invention therefore also relates to a method for the treatment of a proliferative disease in a patient, which comprises administering a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof, in a quantity effective against the said disease. The patient will generally be a warm-blooded animal requiring such treatment.

The invention relates also to pharmaceutical compositions comprising an effective amount, especially an amount effective in the treatment of one of the above-mentioned disorders, of compound of the invention or a pharmaceutically acceptable salt thereof together with pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration and that may be inorganic or organic, solid or liquid. Used for oral administration can be especially tablets or gelatin capsules that comprise the active ingredient together with diluents and/or lubricants. Tablets may also comprise binders, and, if desired, disintegrators and/or effervescent mixtures, or adsorbents, dyes, flavorings and sweeteners. It is also possible to use the pharmacologically active compounds of the present invention in the form of parenterally administrable compositions or in the form of infusion solutions. The present pharmaceutical compositions, which may, if desired, comprise other pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and comprise approximately from 1% to 95%, especially from approximately 1% to approximately 20%, active ingredient(s).

The dosage of the active ingredient to be administered may depend upon a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. In general, a compound of the invention may be applied in a daily dosage between about 1 mg and 1000 mg.

Compounds of the invention may be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. A compound of formula I can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

Therapeutic agents for possible combination are especially one or more antiproliferative, cytostatic or cytotoxic compounds, for example one or several agents selected from the group which includes, but is not limited to, an inhibitor of polyamine biosynthesis, an inhibitor of a protein kinase, especially of a serine/threonine protein kinase, such as protein kinase C, or of a tyrosine protein kinase, such as the EGF receptor tyrosine kinase, e.g. Iressa®, the VEGF receptor tyrosine kinase, e.g. PTK787 or Avastin®, or the PDGF receptor tyrosine kinase, e.g. STI571 (Glivec®), a cytokine, a negative growth regulator, such as TGF-ß or

IFN-ß, an aromatase inhibitor, e.g. letrozole (Femara®) or anastrozole, an inhibitor of the interaction of an SH2 domain with a phosphorylated protein, antiestrogens, topoisomerase I inhibitors, such as irinotecan, topoisomerase II inhibitors, microtubule active agents, e.g. paclitaxel or an epothilone, alkylating agents, antiproliferative antimetabolites, such as gemcitabine or capecitabine, platin compounds, such as carboplatin or cis-platin, bisphosphonates, e.g. AREDIA® or ZOMETA®, and monoclonal antibodies, e.g. against HER2, such as trastuzumab.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The following Examples illustrate the invention.

Abbreviations

The following abbreviations are used in the Examples:

AcOH	Acetic acid
DMA	*N*, *N*-Dimethylacetamide
DMF	*N*, *N*-Dimethylformamide
EtOH	ethanol
H.V.	High Vacuum
KOAc	Potassium acetate
min	minutes
$PdCl_2(dppf).CH_2Cl_2$	1,1'-bis(diphenylphosphino)ferrocenedichlropalladium(II) dichloromethane
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(OAc)_2$	Palladium (II) acetate
Ra-Ni	Raney Nickel
R_t	retention time
RT	Room temperature
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

DMAP	4-(dimethylamino)pyridine
TFA	Trifluoroacetic acid
UPLC	Ultra Performance Liquid Chromatography
HPLC	High Performance Liquid Chromatography

HPLC Conditions

A:

System	Agilent 1100 Series with Waters Micromass ZQ
Column	XBridge C18 2.5 micron, 3 x 30 mm
Eluents	A: H_2O, B: acetonitrile, both containing 0.1% TFA
Flow Rate	1.4-2.4 mL/min
Gradient	10-90% B in 2.4 min

B:

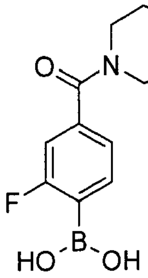
System	Agilent 1100 Series
Column	Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD
Column Temperature	30 °C
Eluents	A: H_2O, B: acetonitrile, both containing 0.1% TFA
Flow Rate	1.0 mL/min
Gradient	2-100% B in 7.0 min

Preparation of Boronic Acid and Boronic Ester Starting Compounds

The following preparations illustrate the synthesis of boronic acid or boronic esters used in the preparation of the Examples. If not specified, the boronic acids or esters are obtained from commercial source. The aryl boronic esters are prepared according to a modified procedure of Miyaura et al., *J.Org.Chem.* 1995, *60*, 7508-7510 from their corresponding haloarenes.

Preparation 1:

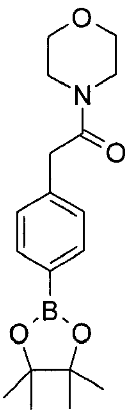
(4-Boronic acid-2-fluoro-phenyl)-morpholin-4-yl-methanone:



A microwave tube is charged with 1.499 g (5.2 mmol) of (4-Bromo-3-fluoro-phenyl)-morpholin-4-yl-methanone (CAS 897016-95-4), 1.48 g (5.71 mmol) bis(pinacolato)diboron, 127 mg (0.15 mmol) $PdCl_2(dppf).CH_2Cl_2$ and 1.02 g (10.4 mmol) of KOAc. After several cycle of vacuum/ purge with argon, 6 ml of dry DMA are added. The reaction mixture is then heated at 80°C for 15h. After cooling, the reaction mixture is partitioned between EtOAc and water. The aqueous phase is re-extracted twice with water. The combined organic layers are washed with water, saturated brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo to afford, after drying in HV, the title compound which is used in the next step without further purification. Note: the boronic ester is hydrolyzed into its corresponding boronic acid under the reaction condition.

Preparation 2:

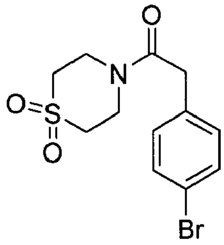
1-Morpholin-4-yl-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethanone



The title compound is obtained analogously to Preparation 1, but using 2-(4-Bromo-phenyl)-1-morpholin-4-yl-ethanone (CAS 349428-85-9).

Preparation 3:

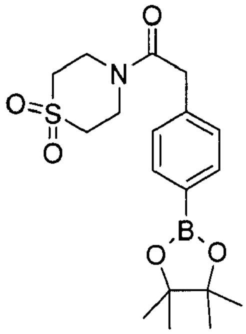
2-(4-Bromo-phenyl)-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone



A solution of 1.17 g (5 mmol) (4-Bromo-phenyl)-acetyl chloride (CAS 37859-24-8) in 25 ml CH_2Cl_2 is added dropwise to a solution of 710 mg (5.25 mmol) thiomorpholine 1,1-dioxide in 25 ml CH_2Cl_2 . After complete addition, the reaction mixture is partitioned between water and CH_2Cl_2. The aqueous phase is re-extracted twice with CH_2Cl_2. The combined organic solution is washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford the title compound as a light yellow residue.

Preparation 4

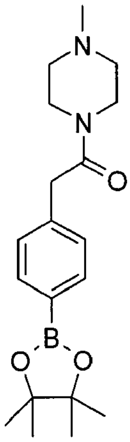
1-(1,1-Dioxido-thiomorpholin-4-yl)-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethanone



The title compound is obtained analogously to Preparation 1, but using 2-(4-Bromo-phenyl)-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone (as prepared in Preparation 3).

Preparation 5:

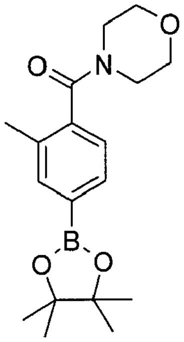
1-(4-Methyl-piperazin-1-yl)-2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethanone



The title compound is obtained analogously to Preparation 1, but using 2-(4-Bromo-phenyl)-1-(4-methyl-piperazin-1-yl)-ethanone (CAS 349430-56-4).

Preparation 6:

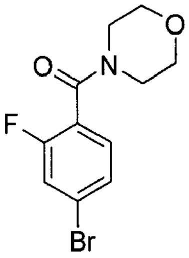
[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-morpholin-4-yl-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-methyl-phenyl)-morpholin-4-yl-methanone (CAS 276677-17-9)

Preparation 7:

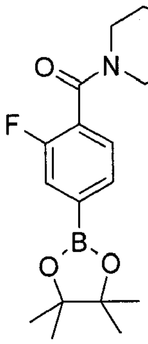
(4-Bromo-2-fluoro-phenyl)-morpholin-4-yl-methanone



A solution of 3.8 ml (44 mmol) oxalyl chloride in 30 ml CH_2Cl_2 is added dropwise to a iced-cooled solution of 4.88 g (21.9 mmol) 4-bromo-2-fluorobenzoic acid in 180 ml CH_2Cl_2. After complete addition, the cooling bath is removed and stirring maintained for 15h at RT. The solvent is evaporated to dryness, the resultant colorless residue is dried under vacuum and then diluted with 80 ml CH_2Cl_2. This solution of 2-Fluoro-4-bromobenzoyl chloride (CAS 151982-51-3) is then added dropwise to a mixture of 9.55 ml (54.7 mmol) of diisopropylethylamine, 2.01 ml (23 mmol) of morpholine in 100 ml CH_2Cl_2. After 1h30, the reaction mixture is diluted with water and the two phases are separated. The aqueous phase is re-extracted with CH_2Cl_2 and the combined organic extracts are washed with water, saturated brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo to afford, after drying in HV, the title compound which is used in the next step without further purification.

Preparation 8:

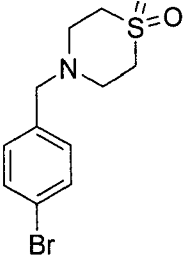
[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-morpholin-4-yl-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-fluoro-phenyl)-morpholin-4-yl-methanone (as obtained in preparation 7)

Preparation 9:

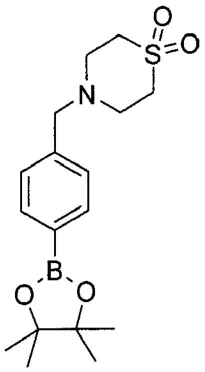
4-(4-Bromo-benzyl)-thiomorpholine-1,1-dioxide



2.18 ml (15.5 mmol) of triethylamine are added to a colorless suspension of 1.28 g (5 mmol) of 4-bromobenzyl bromide and 944 mg (5.5 mmol) thiomorpholine-1,1-dioxide hydrochloride in 15 ml DMF. After 3h at RT, the reaction mixture is partitioned between CH_2Cl_2 and H_2O. The aqueous phase is re-extracted four times with CH_2Cl_2. The combined organic extracts are washed with water, saturated brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo to afford, after drying in HV, the title compound which is used in the next step without further purification.

Preparation 10:

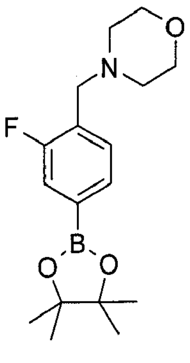
4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-benzyl)-thiomorpholine -1,1-dioxide (as obtained in preparation 9).

Preparation 11:

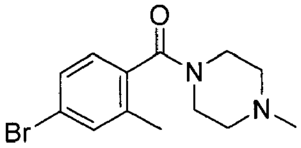
4-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-fluoro-benzyl)-morpholine (CAS 338454-98-1).

Preparation 12:

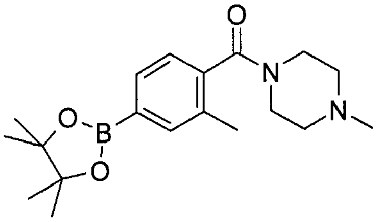
(4-Bromo-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone



A solution of 0.850 ml (10 mmol) oxalyl chloride in 20 ml CH_2Cl_2 is added dropwise to a iced-cooled solution of 1.10 g (5 mmol) 4-bromo-2-methylbenzoic acid in 30 ml CH_2Cl_2. After complete addition, the cooling bath is removed and stirring maintained for 1h at RT. The solvent is evaporated to dryness, the resultant colorless residue is dried under vacuum and then diluted with 25 ml CH_2Cl_2. This solution is then added dropwise to a mixture of 1.01 g (10 mmol) of N-methylpiperazine in 25 ml CH_2Cl_2. After 1h30, the reaction mixture is diluted with water and the two phases are separated. The aqueous phase is re-extracted with CH_2Cl_2 and the combined organic extracts are successively washed with a sat.solution of $NaHCO_3$, water, sat. brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo to afford, after drying in HV, the title compound which is used in the next step without further purification.

Preparation 13:

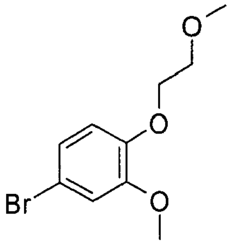
(4-Methyl-piperazin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone (as obtained in preparation 12).

Preparation 14:

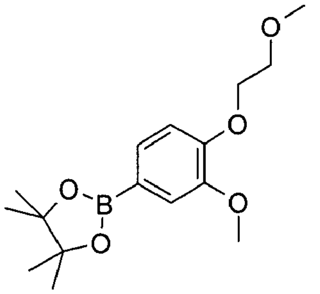
4-Bromo-2-methoxy-1-(2-methoxy-ethoxy)-benzene



2.0g (9.65 mmol) 4-bromoguaiacol and 1.89g (5.8 mmol) Cs_2CO_3 are suspended in 20.0ml dry DMF and 1.02ml (10.6 mmol) 2-bromoethylmethylether are introduced at RT under an argon flux. The resulting pale brown suspension is heated to 100°C for 15h. After cooling, the reaction mixture is partitioned between EtOAc and water. The aqueous phase is re-extracted twice with EtOAc. The combined organic solution is washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford the title compound as a light yellow residue.

Preparation 15:

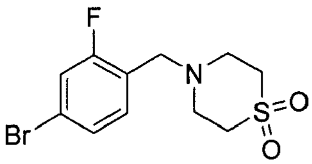
2-[3-Methoxy-4-(2-methoxy-ethoxy)-phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-2-methoxy-1-(2-methoxy-ethoxy)-benzene (as obtained in preparation 14).

Preparation 16:

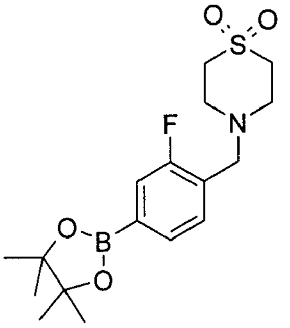
4-(4-Bromo-2-fluoro-benzyl)-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-2-fluorobenzyl bromide.

Preparation 17:

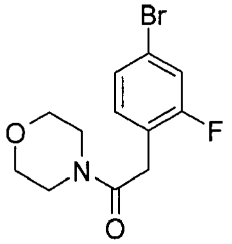
4-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-fluoro-benzyl)-thiomorpholine 1,1-dioxide (as obtained in preparation 16).

Preparation 18:

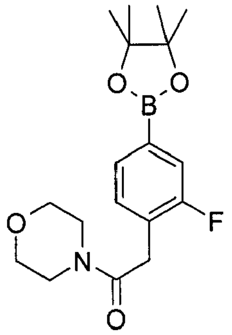
2-(4-Bromo-2-fluoro-phenyl)-1-morpholin-4-yl-ethanone



The title compound is obtained analogously to Preparation 12, but using 4-Bromo-2-fluorophenylacetic acid (CAS 114897-92-6) and morpholine.

Preparation 19:

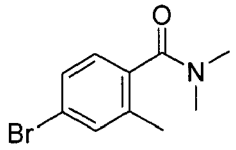
2-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1-morpholin-4-yl-ethanone



The title compound is obtained analogously to Preparation 1, but using 2-(4-Bromo-2-fluoro-phenyl)-1-morpholin-4-yl-ethanone (as obtained in preparation 18).

Preparation 20:

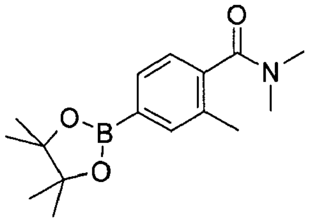
4-Bromo-2,N,N-trimethyl-benzamide



The title compound is obtained analogously to Preparation 12, but using N,N-dimethylamine.

Preparation 21:

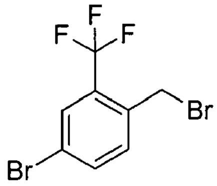
2,N,N-Trimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-2,N,N-trimethyl-benzamide (as obtained in preparation 20).

Preparation 22:

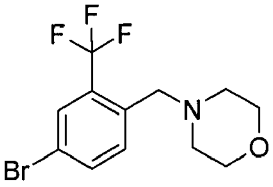
4-Bromo-1-bromomethyl-2-trifluoromethyl-benzene



4-Bromo-1-methyl-2-trifluoromethyl-benzene (3g, 12.55 mmol), N-bromosuccinimide (2.68g, 15.06 mmol, 1.2 eq) and dibenzoylperoxid (60 mg, 2.5 mmol, 0.02 eq) are stirred in carbon tetrachloride under ultraviolet light at reflux for 5h. The reaction mixtureis cooled to RT, filtered and the filtrate is concentrated in vacuo. The residue is carefully purified by chromatography (silicagel, pure hexanes) to afford the title compound as a colorless liquid.

Preparation 23:

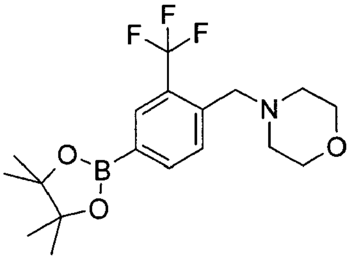
4-(4-Bromo-2-trifluoromethyl-benzyl)-morpholine



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-trifluoromethyl-benzene (as obtained in preparation 22) and morpholine.

Preparation 24:

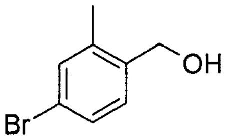
4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-trifluoromethyl-benzyl]-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-trifluoromethyl-benzyl)-morpholine (as obtained in preparation 23).

Preparation 25:

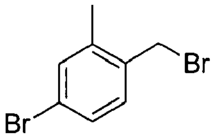
(4-Bromo-2-methyl-phenyl)-methanol



4-bromo-2-methylbenzoic acid (5g, 22.8 mmol) is dissolved in dry THF(100 ml) and cooled to 0°C. A 1M solution of BH_3.THF in THF (34mL, 34 mmol) is slowly added. The resulting colorless suspension is then stirred overnight, allowing it to gradually reach room temperature. K_2CO_3 solid (1.1g) and H_2O (100 ml) are added to the colorless solution and the mixture is stirred for an additional 30 minutes. THF is then evaporated and the residue extracted with EtOAc (30 ml). The organic phase is washed with 1N HCl (3×50 ml), dried over Na_2SO_4 and evaporated. The residue gives the title compound which is used in the next step without further purification.

Preparation 26:

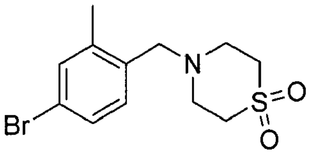
4-Bromo-1-bromomethyl-2-methyl-benzene



To a stirred solution of (4-Bromo-2-methyl-phenyl)-methanol (as obtained in preparation 25) (4.58 g, 22.8 mmol) in CH2Cl2 (50 ml) is added , under Argon and at RT, carbon tetrabromide (9.27 g, 27.4 mmol) followed by triphenylphosphine (7.25 g, 27.4 mmol). The mixture is stirred overnight and then concentrated in vacuo. The crude residue is then purified by chromatography (silicagel, hexane: EtOAc 25:1) to afford the title compound as a clear oil.

Preparation 27:

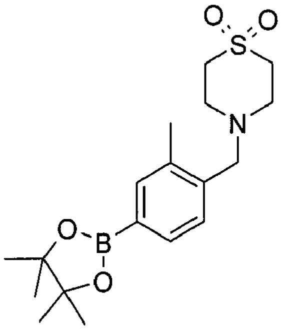
4-(4-Bromo-2-methyl-benzyl)-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-methyl-benzene (as obtained in preparation 26) .

Preparation 28:

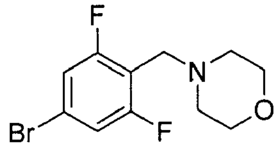
4-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-methyl-benzyl)-thiomorpholine 1,1-dioxide (as obtained in preparation 27).

Preparation 29:

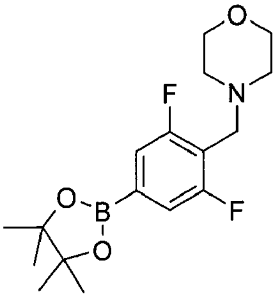
4-(4-Bromo-2,6-difluoro-benzyl)-morpholine



The title compound is obtained analogously to Preparation 9, but using 5-Bromo-2-bromomethyl-1,3-difluoro-benzene (CAS 162744-60-7) and morpholine .

Preparation 30:

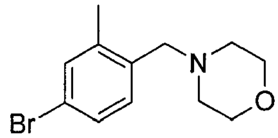
4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2,6-difluoro-benzyl)-morpholine (as obtained in preparation 29).

Preparation 31:

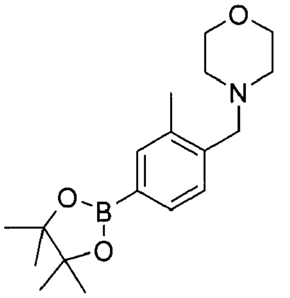
4-(4-Bromo-2-methyl-benzyl)-morpholine



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-methyl-benzene (as obtained in preparation 26) and morpholine .

Preparation 32:

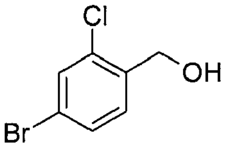
4-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-methyl-benzyl)-morpholine (as obtained in preparation 31).

Preparation 33:

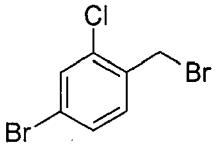
(4-Bromo-2-chloro-phenyl)-methanol



The title compound is obtained analogously to Preparation 25, but using 4-bromo-2-chlorobenzoic acid .

Preparation 34:

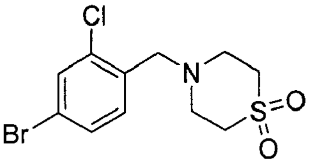
4-Bromo-1-bromomethyl-2-chloro-benzene



The title compound is obtained analogously to Preparation 26, but using (4-Bromo-2-chloro-phenyl)-methanol

Preparation 35:

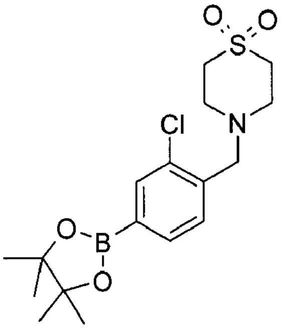
4-(4-Bromo-2-chloro-benzyl)-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-chloro-benzene (as obtained in preparation 34) .

Preparation 36:

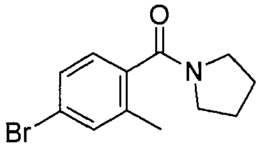
4-[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2-chloro-benzyl)-thiomorpholine 1,1-dioxide (as obtained in preparation 35).

Preparation 37:

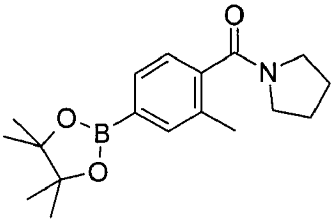
(4-Bromo-2-methyl-phenyl)-pyrrolidin-1-yl-methanone



The title compound is obtained analogously to Preparation 12, but using pyrrolidine.

Preparation 38:

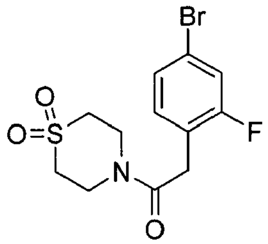
[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-1-yl-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-methyl-phenyl)-pyrrolidin-1-yl-methanone (as obtained in preparation 37).

Preparation 39:

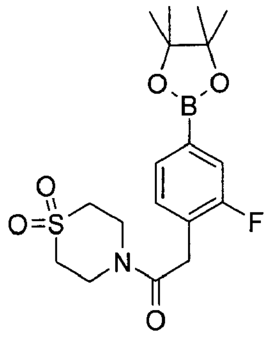
2-(4-Bromo-2-fluoro-phenyl)-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone



The title compound is obtained analogously to Preparation 12, but using 4-Bromo-2-fluorophenylacetic acid (CAS 114897-92-6) and thiomorpholine 1,1-dioxide.

Preparation 40:

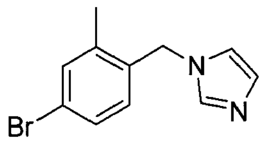
1-(1,1-Dioxido-thiomorpholin-4-yl)-2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2]dioxaborolan-2-yl)-phenyl]-ethanone



The title compound is obtained analogously to Preparation 1, but using 2-(4-Bromo-2-fluoro-phenyl)-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone (as obtained in preparation 39).

Preparation 41:

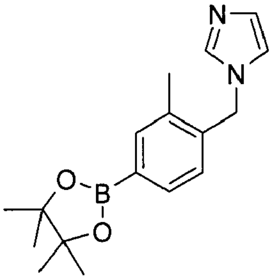
1-(4-Bromo-2-methyl-benzyl)-1H-imidazole



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-methyl-benzene (as obtained in preparation 26) and imidazole .

Preparation 42:

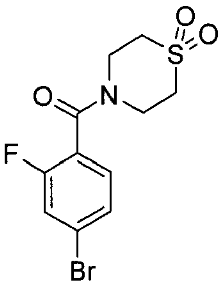
1-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-1H-imidazole



The title compound is obtained analogously to Preparation 1, but using 1-(4-Bromo-2-methyl-benzyl)-1H-imidazole (as obtained in preparation 41).

Preparation 43:

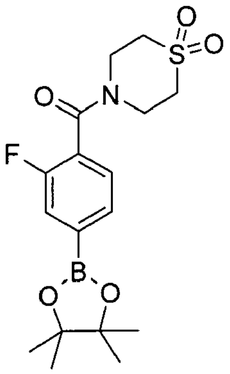
(4-Bromo-2-fluoro-phenyl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone



The title compound is obtained analogously to Preparation 7, but using thiomorpholine 1,1-dioxide

Preparation 44:

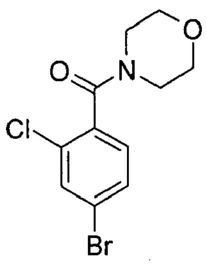
(1,1-Dioxido-thiomorpholin-4-yl)-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-fluoro-phenyl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone (as obtained in preparation 43)

Preparation 45:

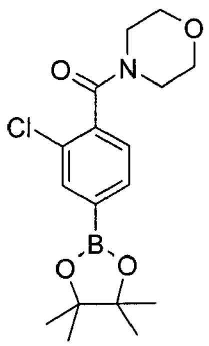
(4-Bromo-2-chloro-phenyl)-morpholin-4-yl-methanone



The title compound is obtained analogously to Preparation 7, but using 4-Bromo-2-chloro-benzoic acid (CAS 59748-90-2)

Preparation 46:

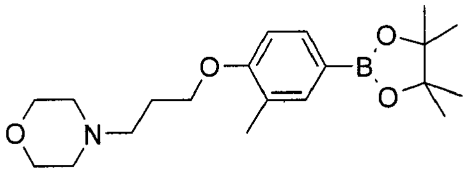
[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-morpholin-4-yl-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-chloro-phenyl)-morpholin-4-yl-methanone (as obtained in preparation 45)

Preparation 47:

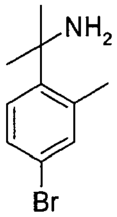
4-{3-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propyl}-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-[3-(4-Bromo-2-methyl-phenoxy)-propyl]-morpholine (CAS 434303-70-5)

Preparation 48:

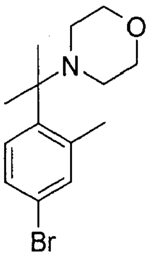
1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethylamine



In a dried apparatus, Cerium (III) trichloride ultradry (5g, 20.28 mmol) is introduced under Ar and anhydrous THF is added (40 ml). The resultant suspension gives a milky solution after 24h stirring at RT. The mixture is then cooled to -65°C and a solution of MeLi (1.6 M in Et_2O, 12.67 mL, 20.28 mmol) is added dropwise and the canary yellow suspension is stirred for 30 min. A solution of 4-bromo-2-methylbenzonitrile (1.365 g, 6.76 mmol) in THF (5 ml) is added and the reaction is further stirred at -65°C for 4h before allowing to warm to -40°C. The brown suspension is quenched by addition of 20 ml of 25% ammoniaque solution and then allow to warm to RT. The resulting solids are removed by filtration on a pad of Celite and washed three times with EtOAc. The combined filtrates are washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the desired compound as a colorless liquid. R_t = 0.735 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 211 ($M-NH_3+1$, $^{79}Br)^+$.

Preparation 49:

4-[1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethyl]-morpholine

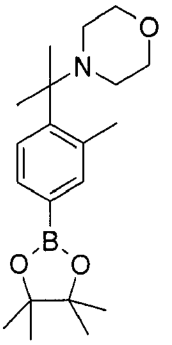


A solution of 1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethylamine (preparation 48, 544 mg, 2 mmol), 2, 2'-dibromodiethylether (579.8 mg, 2.5 mmol) and N,N-diisopropylethylamine (1.027 ml, 6 mmol) in DMF (7 ml) is heated to 100°C for 16h and then allowed to cool to RT. The reaction mixture is partitioned between water and CH_2Cl_2. The aqueous phase is re-extracted twice, the combined organic phases are dried over Na_2SO_4 and concentrated in vacuo. The residue is purified by flash chromatography (silicagel, CH_2Cl_2: EtOAc = 1:0 => 0:1) to afford the title compound as a pale yellow oil, R_t = 0.786 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100%

CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 298 (M+1, $^{79}Br)^+$.

Preparation 50:

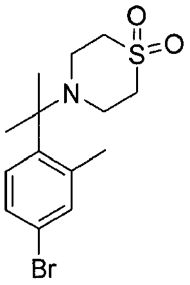
4-{1-Methyl-1-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl}-morpholine



The title compound is obtained analogously to Preparation 1, but using 4-[1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethyl]-morpholine (preparation 49)

Preparation 51:

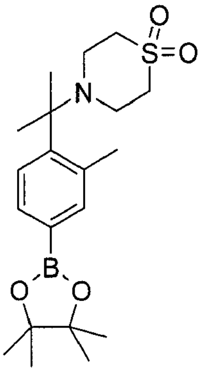
4-[1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethyl]-thiomorpholine 1,1-dioxide



A solution of 1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethylamine (preparation 48, 544 mg, 2 mmol), vinyl sulfone (200 µl, 2 mmol) in EtOH (8 ml) is heated to 100°C for 6h and then allowed to cool to RT. EtOH is removed under HV and the residue is purified by flash chromatography (silicagel, CH_2Cl_2: EtOAc = 1:0 => 0:1) to afford the title compound as a pale pink solid, R_t = 1.231 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 346 (M+1, $^{79}Br)^+$.

Preparation 52:

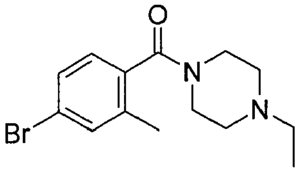
4-{1-Methyl-1-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl}-thiomorpholine 1,1-dioxide



The title compound is obtained analogously to Preparation 1, but using 4-[1-(4-Bromo-2-methyl-phenyl)-1-methyl-ethyl]-thiomorpholine 1,1-dioxide (preparation 51)

Preparation 53:

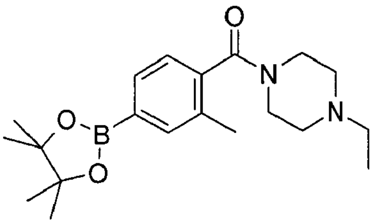
4-Bromo-2-methyl-phenyl)-(4-ethyl-piperazin-1-yl)-methanone



The title compound is obtained analogously to Preparation 12, but using N-ethylpiperazine

Preparation 54:

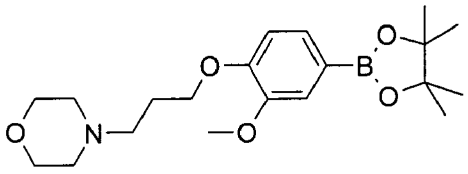
(4-Ethyl-piperazin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-2-methyl-phenyl)-(4-ethyl-piperazin-1-yl)-methanone (as obtained in preparation 53).

Preparation 55:

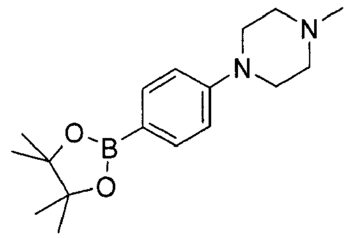
4-{3-[2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propyl}-morpholine



A solution of 4-(3-Chloro-propyl)-morpholine (460 mg, 2.75 mmol), Cs_2CO_3 (493 mg, 1.515 mmol) and 2 -Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (703 mg, 2.75 mmol) in dry DMF (15 ml) are heated at 80°C under argon for 24h and then allowed to cool to RT. DMF is removed under HV and the residue is re-taken in EtOAc and washed with de-ionized water. The aqueous phase is re-extracted with EtOAc and the combined organic extracts are washed with saturated brine, dried over Na_2SO_4, filtered and concentrated under vacuum to dryness. After drying under HV, the title compound is obtained as a solid, R_t = 0.878 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 378 $(M+1)^+$.

Preparation 56:

1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine

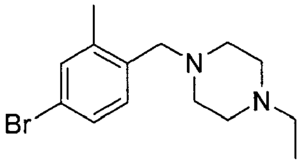


To a cooled (-78°C) solution of 1-(4-Bromo-phenyl)-4-methyl-piperazine (8.05 g, 31.54 mmol, CAS 130307-08-3) in dry THF (500 ml) are added dropwise 28ml of a solution of n-BuLi (2.5M in hexanes, 69 mmol). After 1h, of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13.1 ml, 63.1 mmol) in solution in dry THF (20 ml) are introduced. After complete addition, the reaction mixture is allowed to slowly warm up to RT. The reaction mixture is then diluted with 200 ml of a saturated solution of NH_4Cl and most of the THF is removed by evaporation. The residue is diluted with EtOAc and the phases are separated. The aqueous phase is re-extracted three times with EtOAc and the combined organic extracts are washed twice with de-ionized water, once with saturated brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2 / EtOH 9:1) to afford the title compound as a colorless solid, R_t = 0.851 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in

H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 303 $(M+1)^+$.

Preparation 57:

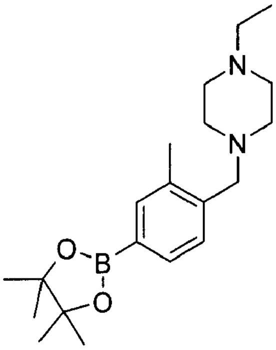
1-(4-Bromo-2-methyl-benzyl)-4-ethyl-piperazine



The title compound is obtained analogously to Preparation 9, but using 4-Bromo-1-bromomethyl-2-methyl-benzene (as obtained in preparation 26) and N-ethylpiperazine .

Preparation 58:

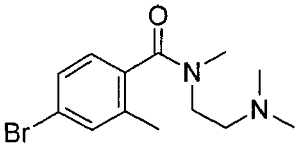
1-Ethyl-4-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine



The title compound is obtained analogously to Preparation 1, but using 1-(4-Bromo-2-methyl-benzyl)-4-ethyl-piperazine (as obtained in preparation 57).

Preparation 59:

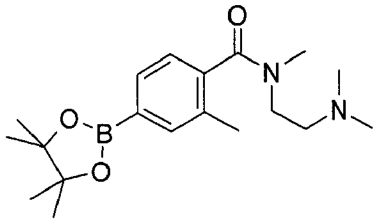
4-Bromo-N-(2-dimethylamino-ethyl)-2,N-dimethyl-benzamide



The title compound is obtained analogously to Preparation 12, but using N,N,N'-Trimethyl-ethane-1,2-diamine

Preparation 60:

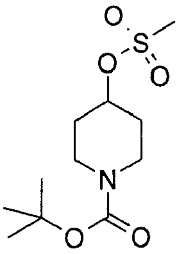
N-(2-Dimethylamino-ethyl)-2,N-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-N-(2-dimethylamino-ethyl)-2,N-dimethyl-benzamide (as obtained in preparation 59).

Preparation 61:

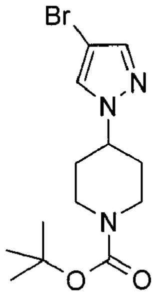
4-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester



To a stirred solution of 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (25.55 g, 123 mmol) in CH_2Cl_2 (250 ml), cooled to 0°C, is slowly added Et_3N (18.95 ml, 135.4 mmol) followed by methane sulfonyl chloride (9.569 ml, 123.14 mmol) and DMAP (152 mg, 1.23 mmol). The mixture is stirred at room temperature overnight. The suspension is diluted with CH_2Cl_2 and the phases are separated. The aqueous phase is re-extracted 3× with CH_2Cl_2. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. Upon concentration, the desired compound precipitates and is collected by filtration to afford, after drying in HV, the title compound as a colorless solid.

Preparation 62:

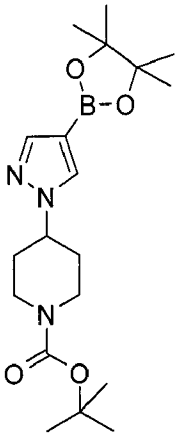
4-(4-Bromo-pyrazol-1-yl)-piperidine -1-carboxylic acid tert-butyl ester



NaH (60% in mineral oil, 1.36 g, 34 mmol) is added portionwise to a stirred solution of 4-bromopyrazole (4.58 g, 30.9 mmol) in DMF (20 ml). The resulting mixture is stirred for 1h at 0°C and 4-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 61, 8.62 g, 30.9 mmol) is added. The resulting pale suspension is heated at 100°C for 1h. The reaction is quenched with water and extracted with EtOAc several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 120 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient hexanes: TBDME from 1:0 => 0:1) to afford the title compound as a colorless solid, R_t = 1.213 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 330 $(M+1, {}^{79}Br)^+$.

Preparation 63:

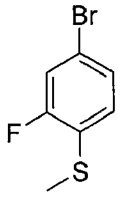
4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-pyrazol-1-yl)-piperidine -1-carboxylic acid tert-butyl ester (as obtained in preparation 62).

Preparation 64:

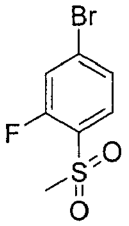
4-Bromo-2-fluoro-1-methylsulfanyl-benzene



To a stirred solution of 2-fluorothioanisole (5.12 g, 35.3 mmol) in CH_2Cl_2 (30 ml) is added dropwise a solution of dibrome (1.8 ml, 35.51 mmol) in CH_2Cl_2 (10 ml). After complete addition, the red solution is then poured onto a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography (silicagel, n-hexanes / CH_2Cl_2 9:1) to afford the title compound, R_t = 1.324 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min).

Preparation 65:

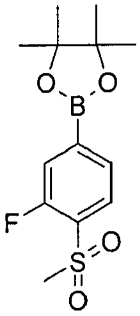
4-Bromo-2-fluoro-1-methanesulfonyl-benzene



In a 50 ml sealable tube is introduced 4-Bromo-2-fluoro-1-methylsulfanyl-benzene (as obtained in preparation 63, 5 g, 22.6 mmol) followed by 4.6 ml AcOH. 9.3 ml of a 30% H_2O_2 solution in H_2O is added at RT. The tube is sealed and the resulting colorless biphasic solution is stirred at 100°C for 2h. After cooling, the pH of the medium is set basic with solid $NaHCO_3$ and then extracted with CH_2Cl_2 several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The title compound is obtained as a colorless solid, R_t = 0.916 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min)

Preparation 66:

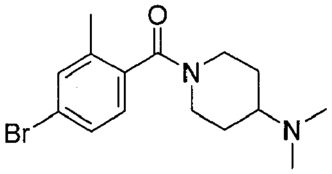
2-(3-Fluoro-4-methanesulfonyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



The title compound is obtained analogously to Preparation 56, but using 4-Bromo-2-fluoro-1-methanesulfonyl-benzene (as obtained in preparation 65).

Preparation 67:

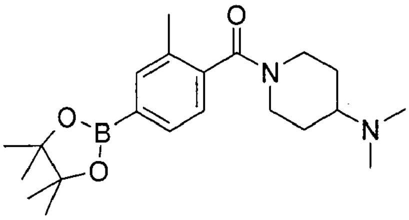
(4-Bromo-2-methyl-phenyl)-(4-dimethylamino-piperidin-1-yl)-methanone



The title compound is obtained analogously to Preparation 12, but using dimethyl-piperidin-4-yl-amine

Preparation 68:

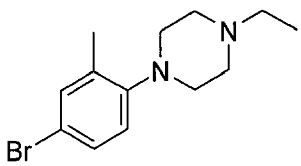
(4-Dimethylamino-piperidin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-2-methyl-phenyl)-(4-dimethylamino-piperidin-1-yl)-methanone (as obtained in preparation 67).

Preparation 69:

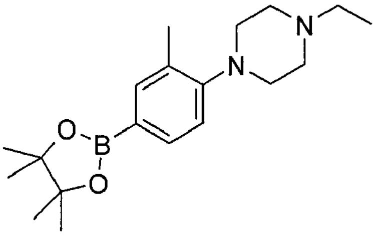
1-(4-Bromo-2-methyl-phenyl)-4-ethyl-piperazine



4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamine (1.3 g, 6 mmol) in hydrobromic acid (61% in H_2O, 9.2 ml, 70 mmol) is diazotized at 0°C with sodium nitrite (443 mg, 6.42 mmol) in 2.3 ml H_2O and the mixture is poured into a solution of copper(I) bromide (1.84 g, 12.5 mmol) in hydrobromic acid (61% in H_2O, 7.7 ml, 58.8 mmol) at 0°C. The cooling bath is then removed and the mixture is heated at 60°C for 5h. After cooling, the mixture is basified with a 2M NaOH solution and diluted with CH_2Cl_2. After separation, the aqueous phase is extracted with CH_2Cl_2 several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 120 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2 / CH_2Cl_2: EtOH :NH3 90:9:1 from 1:0 => 4:6) to afford the title compound as a pale brown solid, R_t = 0.878 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 283 (M+1, $^{79}Br)^+$.

Preparation 70:

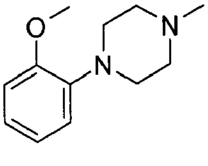
1-Ethyl-4-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine



The title compound is obtained analogously to Preparation 1, but using 1-(4-Bromo-2-methyl-phenyl)-4-ethyl-piperazine (as obtained in preparation 69).

Preparation 71:

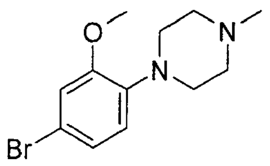
1-(2-Methoxy-phenyl)-4-methyl-piperazine



Formaldehyde (1.84 ml in solution) is added to a solution of 1-(2-methoxyphenyl)-piperazine (4.77 g, 24.3 mmol) in 1,2-dichloroethane. $NaHB(OAc)_3$ (7.59 g, 34 mmol) is then added portionwise. After stirring at RT overnight, the reaction is quenched by addition of a saturated solution of $NaHCO_3$. The mixture is extracted several times with EtOAc and the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo to afford the title compound as a colorless oil, R_t = 0.615 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 207 $(M+1)^+$.

Preparation 72:

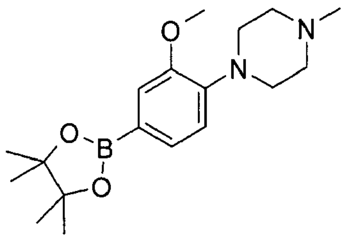
1-(4-Bromo-2-methoxy-phenyl)-4-methyl-piperazine



A bromine solution (1.24 ml, 24.2 mmol) in 9.7 ml AcOH is added dropwise to a cooled solution (ca. 5°C) of 1-(2-Methoxy-phenyl)-4-methyl-piperazine (as obtained in preparation 71, 5 g, 24.2 mmol) in AcOH (87 ml). After complete addition, the cooling bath is removed and reaction mixture allowed to warm up to RT. The dark violet solution is concentrated in vacuo, 20 ml de-ionized water is added and the pH is adjusted basic with a 20% NaOH solution. The mixture is extracted several times with CH_2Cl_2 and the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 120 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2 / CH_2Cl_2: EtOH :NH_3 90:9:1 from 1:0 => 0:1) to afford the title compound as a dark brown oil, R_t = 0.767 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 285 $(M+1, {}^{79}Br)^+$.

Preparation 73:

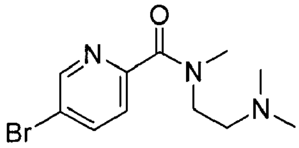
1-[2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-methyl-piperazine



The title compound is obtained analogously to Preparation 1, but using 1-(4-Bromo-2-methoxy-phenyl)-4-methyl-piperazine (as obtained in preparation 72).

Preparation 74:

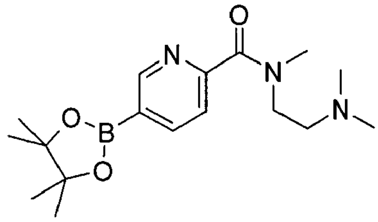
5-Bromo-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



The title compound is obtained analogously to Preparation 12, but using N,N,N'-Trimethyl-ethane-1,2-diamine and 5-Bromo-pyridine-2-carboxylic acid

Preparation 75:

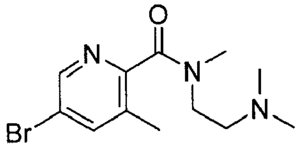
5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



The title compound is obtained analogously to Preparation 1, but using 5-Bromo-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide (as obtained in preparation 74).

Preparation 76:

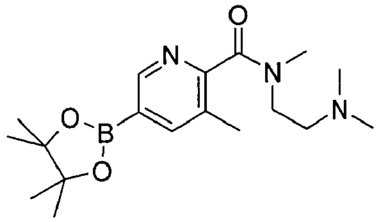
5-Bromo-3-methyl-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



The title compound is obtained analogously to Preparation 12, but using N,N,N'-Trimethyl-ethane-1,2-diamine and 5-Bromo-3-methyl-pyridine-2-carboxylic acid

Preparation 77:

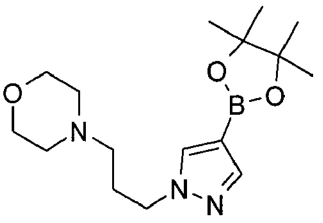
3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



The title compound is obtained analogously to Preparation 1, but using 5-Bromo-3-methyl-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide (as obtained in preparation 76).

Preparation 78:

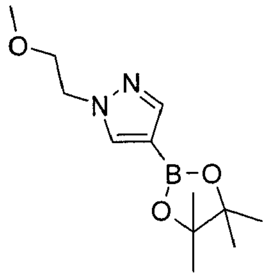
4-{3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-propyl}-morpholine



A solution of 4-(3-Chloro-propyl)-morpholine (702 mg, 4.2 mmol), Cs_2CO_3 (753 mg, 2.31 mmol) and 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (832 mg, 4.2 mmol) in 5 ml dry DMF are heated at 80°C under argon for 24h and then allowed to cool to RT. DMF is removed under HV and the residue is re-taken in EtOAc and washed with de-ionized water. The aqueous phase is re-extracted with EtOAc and the combined organic extracts are washed with saturated brine, dried over Na_2SO_4, filtered and concentrated under vacuum to dryness. After drying under HV, the title compound is obtained as a pale orange oil, R_t = 0.728 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 322 $(M+1)^+$.

Preparation 79:

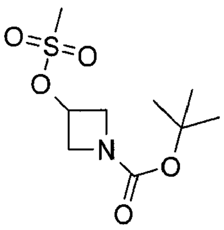
1-(2-Methoxy-ethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole



The title compound is obtained analogously to Preparation 78, but using 2-chloroethyl methyl ether.

Preparation 80:

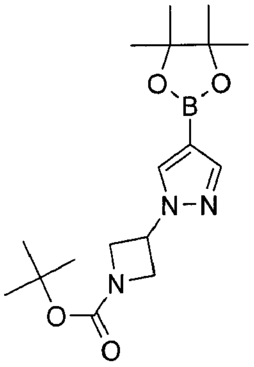
3-Methanesulfonyloxy-azetidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 61, but using 3-Hydroxy-azetidine-1-carboxylic acid tert-butyl ester.

Preparation 81:

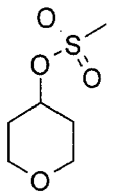
3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-azetidine-1-carboxylic acid tert-butyl ester



NaH (60% in mineral oil, 222 mg, 5.6 mmol) is added portionwise to a stirred solution of 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.10 g, 5.56 mmol) in DMF (20 ml). The resulting mixture is stirred for 1h at 0°C and then allowed to warn to RT. A solution of 3-Methanesulfonyloxy-azetidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 80, 1.39 g, 5.56 mmol) in DMF (3 ml) is then added dropwise. After complete addition, the reaction mixture is heated at 95°C for 5h. The reaction is quenched with water and extracted with EtOAc several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 40 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2: TBDME from 1:0 => 0:1) to afford the title compound as a colorless foam, R_t = 1.200 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 350 $(M+1)^+$.

Preparation 82:

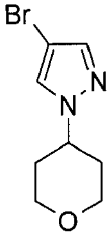
Methanesulfonic acid tetrahydro-pyran-4-yl ester



The title compound is obtained analogously to Preparation 61, but using Tetrahydro-pyran-4-ol.

Preparation 83:

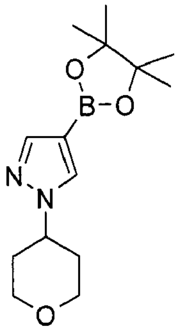
4-Bromo-1-(tetrahydro-pyran-4-yl)-1H-pyrazole



The title compound is obtained analogously to Preparation 62, but using Methanesulfonic acid tetrahydro-pyran-4-yl ester (as obtained in preparation 82).

Preparation 84:

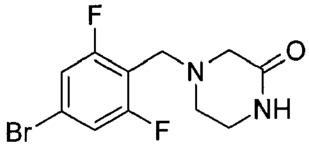
1-(Tetrahydro-pyran-4-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-1-(tetrahydro-pyran-4-yl)-1H-pyrazole (as obtained in preparation 83).

Preparation 85:

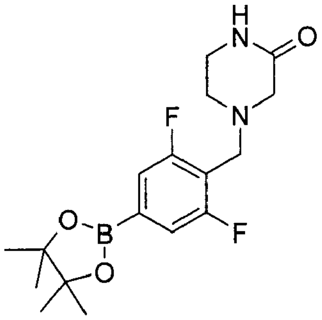
4-(4-Bromo-2,6-difluoro-benzyl)-piperazin-2-one



The title compound is obtained analogously to Preparation 9, but using 5-Bromo-2-bromomethyl-1,3-difluoro-benzene (CAS 162744-60-7) and Piperazin-2-one .

Preparation 86:

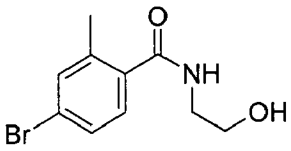
4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazin-2-one



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-2,6-difluoro-benzyl)-piperazin-2-one (as obtained in preparation 85).

Preparation 87:

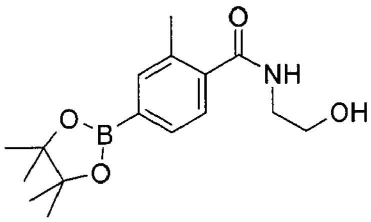
4-Bromo-N-(2-hydroxy-ethyl)-2-methyl-benzamide



The title compound is obtained analogously to Preparation 12, but using 2-aminoethanol

Preparation 88:

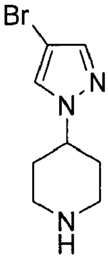
N-(2-Hydroxy-ethyl)-2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



The title compound is obtained analogously to Preparation 1, but using 4-Bromo-N-(2-hydroxy-ethyl)-2-methyl-benzamide (as obtained in preparation 87).

Preparation 89:

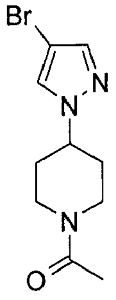
4-(4-Bromo-pyrazol-1-yl)-piperidine



A 4 M solution of HCl in 1,4-dioxane (13.5 ml, 54 mmol) is added to a solution of 4-(4-Bromo-pyrazol-1-yl)-piperidine -1-carboxylic acid tert-butyl ester (as obtained in preparation 62, 5.92 g , 17.94 mmol) in CH_2Cl_2 (50 ml) and the reaction mixture is stirred at RT for 6h. The suspension is filtered on a Por. 4 Fritte and the cake dissolved in EtOAc. A saturated solution of $NaHCO_3$ is added and the phases are separated. The aqueous phase is extracted 3× with EtOAc. The combined organic layers are washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is used without further purification in the next step, and afford the title compound as pale orange solid, R_t = 0.582 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 330 (M+1, $^{79}Br)^+$

Preparation 90:

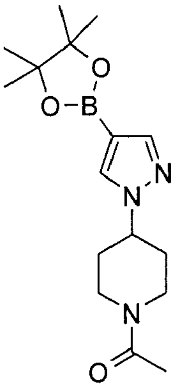
1-[4-(4-Bromo-pyrazol-1-yl)-piperidin-1-yl]-ethanone



Acetyl chloride (312 µl, 4.35 mmol) is added dropwise, under stirring at 0°C, to a solution of 4-(4-Bromo-pyrazol-1-yl)-piperidine (as obtained in preparation 89, 1 g, 4.34 mmol), Et_3N (1.824 ml, 13.04 mmol) in CH_2Cl_2. The cooling bath is then removed and the reaction mixture stirred at RT for an additional 1h. The mixture is then diluted with de-ionized water and the phases are separated. The organic phase is washed several times with de-ionized water and the aqueous layer re-extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is used without further purification in the next step, and afford the title compound as yellow solid, R_t = 0.786 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 272 (M+1, $^{79}Br)^+$

Preparation 91:

1-{4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidin-1-yl}-ethanone



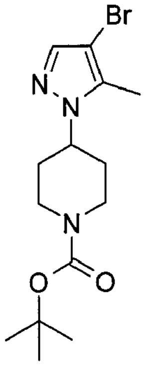
The title compound is obtained analogously to Preparation 1, but using 1-[4-(4-Bromo-pyrazol-1-yl)-piperidin-1-yl]-ethanone (as obtained in preparation 90).

Preparation 92 and 93:

NaH (60% in mineral oil, 410 mg, 10.2 mmol) is added portionwise to a stirred solution of 4-bromo-3-methylpyrazole (1.69 g, 10.2 mmol) in DMF (20 ml). The resulting mixture is stirred for 1h at 0°C and 4-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 61, 2.839 g, 10.16 mmol) is added. The resulting pale suspension is heated at 95°C for 1h. The reaction is quenched with water and extracted with EtOAc several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 120 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient hexanes: TBDME from 1:0 => 1:1) to afford the two regioisomers identified by preparation 92 and preparation 93.

Preparation 92:

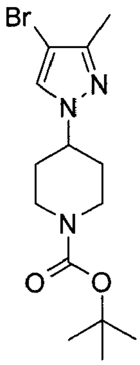
4-(4-Bromo-5-methyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



R_t = 1.252 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 344 (M+1, $^{79}Br)^+$.

Preparation 93:

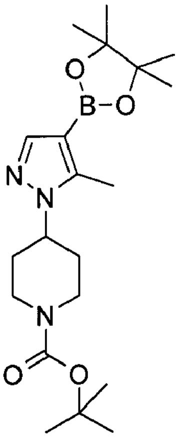
4-(4-Bromo-3-methyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



R_t = 1.247 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 344 (M+1, ^{79}Br)$^+$.

Preparation 94:

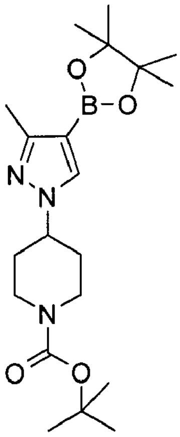
4-[5-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-5-methyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 92).

Preparation 95:

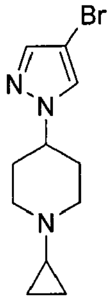
4-[3-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-3-methyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 93).

Preparation 96:

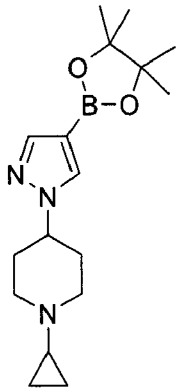
4-(4-Bromo-pyrazol-1-yl)-1-cyclopropyl-piperidine



Acetic acid (1.258 ml, 21.98 mmol) is added dropwise, under stirring at RT, to a solution of 4-(4-Bromo-pyrazol-1-yl)-piperidine (as obtained in preparation 89, 1.686 g, 7.327 mmol) and [(1-ethoxy-1-cyclopropyl)oxy]trimethylsilane (2.210 ml, 10.99 mmol) in MeOH (20 ml). Sodium cyanoborohydride (775 mg, 11.7) is then added in one portion at RT. The mixture is then heated at 60°C for 3h. After cooling, the reaction mixture is concentrated in vacuo and the residue dissolved in EtOAc and diluted with saturated $NaHCO_3$. After separation, the aqueous phase is re-extracted 3× with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is used without further purification in the next step, and afford the title compound as colorless solid, R_t = 0.618 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 270 (M+1, $^{79}Br)^+$

Preparation 97:

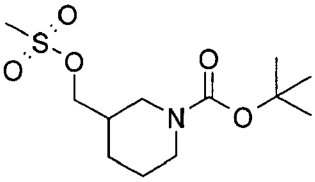
1-Cyclopropyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-pyrazol-1-yl)-1-cyclopropyl-piperidine (as obtained in preparation 96).

Preparation 98:

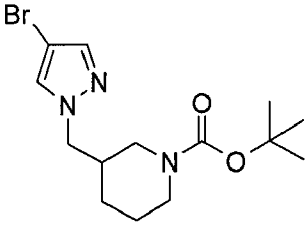
(rac)-3-Methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 61, but using 3-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester.

Preparation 99:

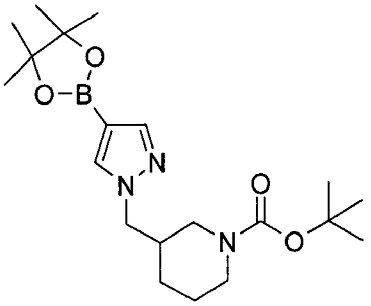
(rac)-3-(4-Bromo-pyrazol-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 62, but using (rac)-3-Methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 98).

Preparation 100:

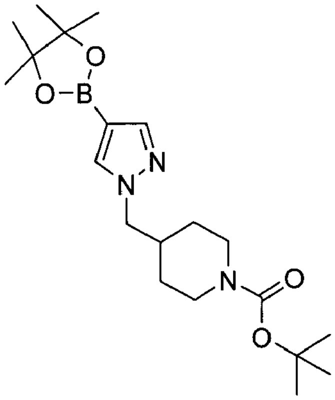
(rac)-3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 1, but using (rac)-3-(4-Bromo-pyrazol-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (as obtained in preparation 99).

Preparation 101:

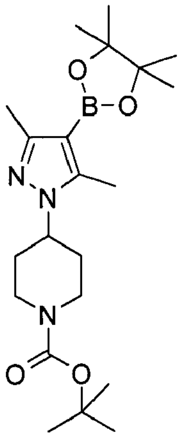
4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 100, but using 4-(4-Bromo-pyrazol-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (obtained analogously to preparation 99 from 4-Methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester).

Preparation 102:

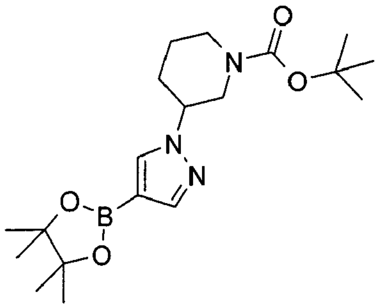
4-[3,5-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 1, but using 4-(4-Bromo-3,5-dimethyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (obtained analogously to preparation 92 from 4-Bromo-3,5-dimethyl-1H-pyrazole).

Preparation 103:

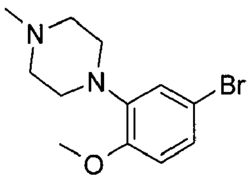
(rac)-3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is obtained analogously to Preparation 100, but using (rac)-3-(4-Bromo-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (obtained analogously to preparation 99 from (rac)-3-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester).

Preparation 104:

1-(5-Bromo-2-methoxy-phenyl)-4-methyl-piperazine

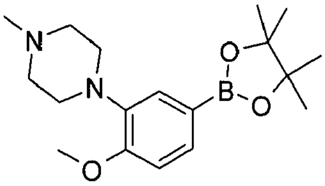


A mixture of 5-bromo-2-methoxyaniline (2.00 g, 9.60 mmol) and bis(2-chloroethyl)-methylaminde hydrochloride (2.04 g, 10.4 mmol) in xylene (40 ml) is heated to reflux (155

°C, oilbath) for 29 h. After cooling to RT, the xylene layer is washed with H_2O (3x). The organic layer is discarded and the pH of the aqueous layer is adjusted to pH > 13. The aqueous layer is extracted with CH_2Cl_2 (3x). The combined organic layers are dried (Na_2SO_4), filtered, concentrated under reduced pressure, and put under HV overnight to afford the title compound as a brown solid, R_t = 4.8 min (HPLC conditions B); MS: 287 $(M+1)^+$

Preparation 105:

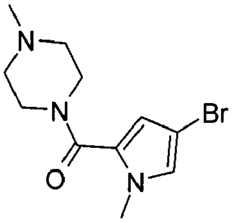
1-[2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-methyl-piperazine



The title compound is obtained analogously to Preparation 1, but using 1-(5-Bromo-2-methoxy-phenyl)-4-methyl-piperazine (as obtained in preparation 104).

Preparation 106:

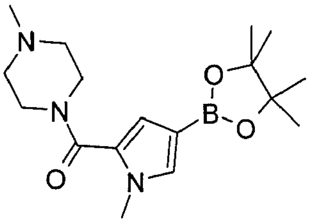
(4-Bromo-1-methyl-1H-pyrrol-2-yl)-(4-methyl-piperazin-1-yl)-methanone



The title compound is obtained analogously to Preparation 12, but using 4-Bromo-1-methyl-1H-pyrrole-2-carboxylic acid.

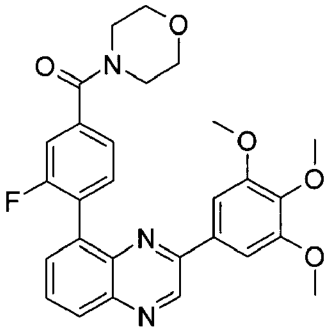
Preparation 107:

(4-Methyl-piperazin-1-yl)-[1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrol-2-yl]-methanone



The title compound is obtained analogously to Preparation 1, but using (4-Bromo-1-methyl-1H-pyrrol-2-yl)-(4-methyl-piperazin-1-yl)-methanone (as obtained in preparation 106).

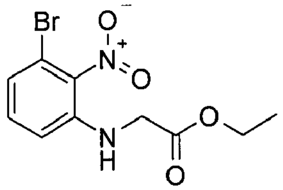
Example 1: {3-Fluoro-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone.



A microwave tube is charged with 50 mg (0.133 mmol) of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline, 50.6 mg (ca. 0.140 mmol) of (4-Boronic acid-2-fluoro-phenyl)-morpholin-4-yl-methanone, 5.1 mg (0.012 mmol) of S-Phos, 87 mg (0.4 mmol) of K_3PO_4 and 0.9 mg (0.004 mmol) of $Pd(OAc)_2$. After several cycles of vacuum/ purge with argon, 3 ml of a mixture consisting of 36 µl deionized water in 15 ml 1,2-dimethoxy-ethane, are added. The reaction mixture is then heated to 105°C for 2h30. After cooling, the reaction mixture is diluted with CH_2Cl_2, poured onto a saturated solution of Na_2CO_3 and extracted 3x with CH_2Cl_2. The combined organic layers are washed with water, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2: EtOH = 95:5 => 4:6) to afford the title compound as a yellow solid, R_t = 1.132 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 500 $(M+1)^+$.

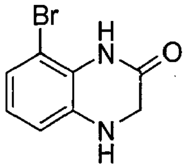
The starting materials can be prepared as follows:

Step 1.1: (3-Bromo-2-nitro-phenylamino)-acetic acid ethyl ester.



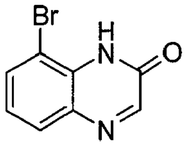
9.90 g (69.6 mmol) ethylglycinate hydrochloride are suspended under argon in 100 mL of dry DMA. 24.3 mL (139 mmol) diisopropylethylamine and 10.21 g (46.4 mmol) of 2-bromo-6-fluoronitrobenzene are then added at RT. The orange solution is then heated to 80°C for 16h. After cooling, the reaction mixture is poured onto iced-cold water and the suspension is collected by filtration to afford, after drying in HV at 50°C, the title compound as a dark orange solid, which is used in the next step without further purification.

Step 1.2: 8-Bromo-3,4-dihydro-1H-quinoxalin-2-one.



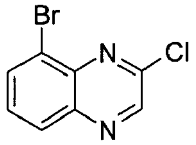
10.33 g (ca. 25.9 mmol) (3-Bromo-2-nitro-phenylamino)-acetic acid ethyl ester is hydrogenated in the presence of 2.84 g Ra-Ni (B113W EtOH, Degussa) in 340 ml of THF:EtOH = 1:1 for 20h. The reaction mixture is filtered on hyflo and the filtrate is concentrated in vacuo. A mixture of the title compound with uncyclized (2-Amino-3-bromo-phenylamino)-acetic acid ethyl ester is obtained and used as obtained in the next synthetic step.

Step 1.3: 8-Bromo-1H-quinoxalin-2-one.



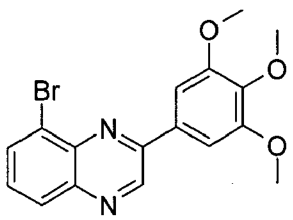
A sealable tube is charged with 4.99 g (39.549 mmol) of a mixture of 8-Bromo-3,4-dihydro-1H-quinoxalin-2-one with (2-Amino-3-bromo-phenylamino)-acetic acid ethyl ester (as obtained in step 1.2) . 50 mL of a 1M NaOH solution and 12.1 ml of a 30% H_2O_2 aqueous solution are added. The tube is sealed and heated to 95°C for 1h. After cooling, 50 mL of 1M HCl solution are added slowly and the brown solid is collected by filtration, to afford, after drying in HV at 50°C, the title compound which is used without further purification.

Step 1.4: 8-Bromo-2-chloro-quinoxaline.



A mixture of 2.0 g (ca. 7.64 mmol) 8-Bromo-1H-quinoxalin-2-one and 36 ml of $POCl_3$ is heated to 50°C for 16h. After cooling, the excess of $POCl_3$ is evaporated, water is then added and extracted 3× with CH_2Cl_2. The combined organic layers are successively washed with water, $NaHCO_3$, saturated brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography (silicagel, hexane: CH2Cl2= 7:3 => 1:1) to afford the title compound as a pale orange solid, MS: 243 $(M)^+$

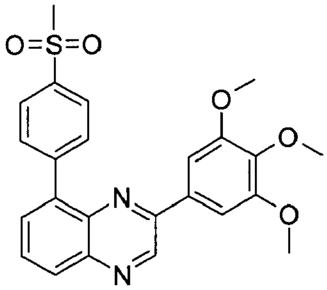
Step 1.5: 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline.



A microwave tube is charged with 30 mg (0.123 mmol) of 8-Bromo-2-chloro-quinoxaline, 26.4 mg (0.123 mmol) of 3,4,5-trimethoxyphenylboronic acid, 40 mg (0.370 mmol) of Na_2CO_3 and 4.4 mg (0.0037 mmol) of $Pd(PPh_3)_4$. After several cycles of vacuum/ purge with argon, 1.5 ml of dry DMF are added. The reaction mixture is then heated tot 105°C for 15h. After cooling, the yellow suspension is poured onto de-ionized water and filtered. After drying under H.V. at 50°C, the residue is purified by chromatography (silicagel, hexane: EtOAc = 100 => 1:1) to afford the title compound as a yellow solid, R_t = 1.294 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 375 $(M)^+$.

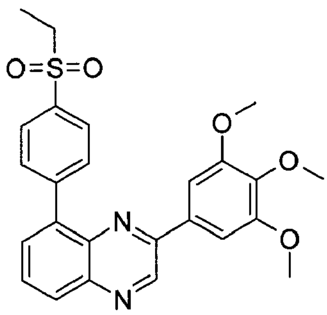
Using the same synthetic methods as described in Example 1, reaction of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples:

Example 2: 8-(4-Methanesulfonyl-phenyl)-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



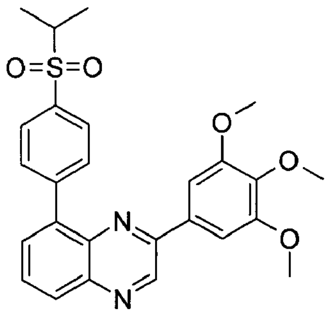
R_t = 1.142 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 451 $(M+1)^+$.

Example 3: 8-(4-Ethanesulfonyl-phenyl)-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



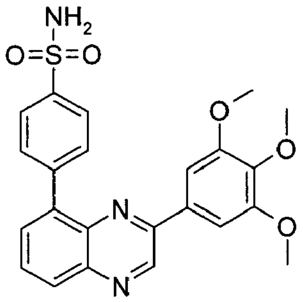
R_t = 1.061 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 465 $(M+1)^+$.

Example 4: 8-[4-(Propane-2-sulfonyl)-phenyl]-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



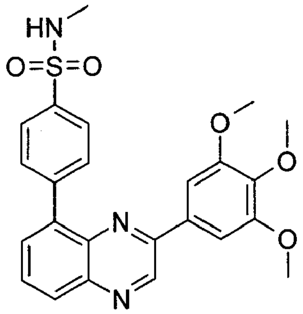
R_t = 1.217 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 479 $(M+1)^+$.

Example 5: 4-[3-(3,4,5-Trimethoxy-phenyl)-quinoxalin-5-yl]-benzenesulfonamide



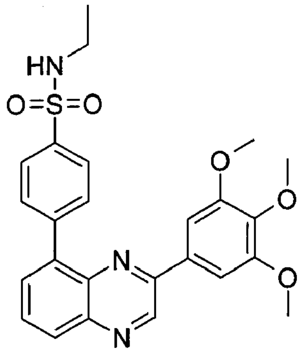
R_t = 1.049 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 452 $(M+1)^+$.

Example 6: N-Methyl-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-benzenesulfonamide



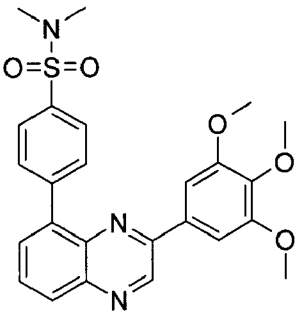
R_t = 1.144 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 466 $(M+1)^+$.

Example 7: N-Ethyl-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-benzenesulfonamide



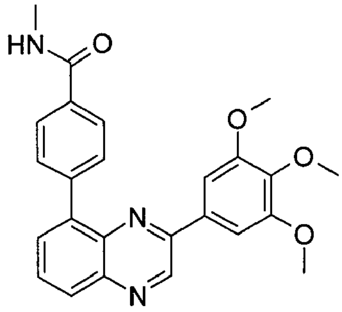
R_t = 1.061 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 480 $(M+1)^+$.

Example 8: N,N-Dimethyl-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-benzenesulfonamide



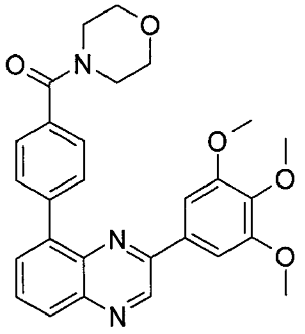
R_t = 1.061 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 480 $(M+1)^+$.

Example 9: N-Methyl-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-benzamide



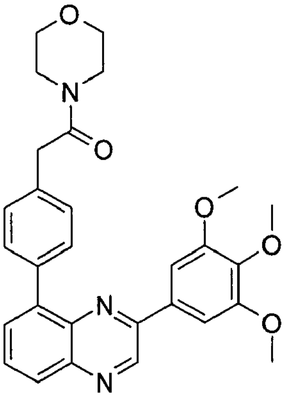
R_t = 1.063 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 430 $(M+1)^+$.

Example 10: Morpholin-4-yl-{4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-methanone



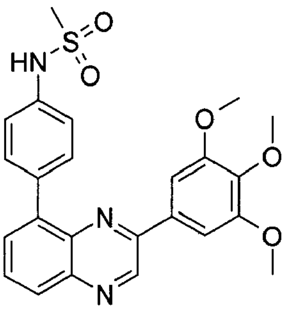
R_t = 1.093 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 486 $(M+1)^+$.

Example 11: 1-Morpholin-4-yl-2-{4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone



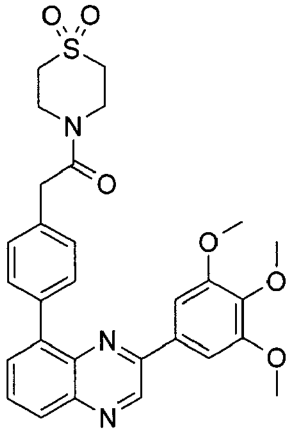
R_t = 1.113 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 500 $(M+1)^+$.

Example 12: N-{4-[3-(3,4,5-Trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-methanesulfonamide



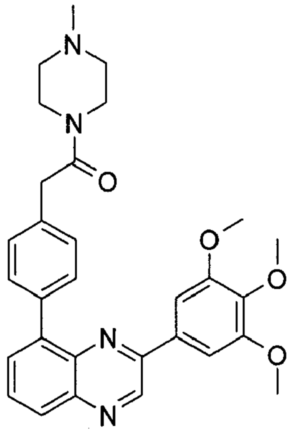
R_t = 1.122 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 466 $(M+1)^+$.

Example 13: 1-(1,1-Dioxido-thiomorpholin-4-yl)-2-{4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone.



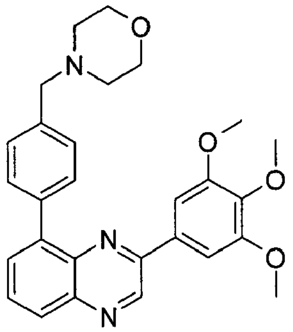
R_t = 1.079 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 548 $(M+1)^+$.

Example 14: 1-(4-Methyl-piperazin-1-yl)-2-{4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone.



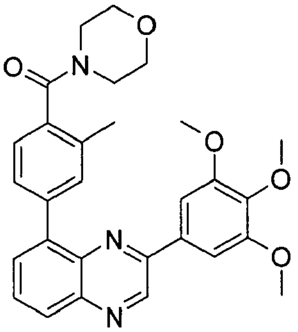
R_t = 0.917 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 513 $(M+1)^+$.

Example 15: 8-(4-Morpholin-4-ylmethyl-phenyl)-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



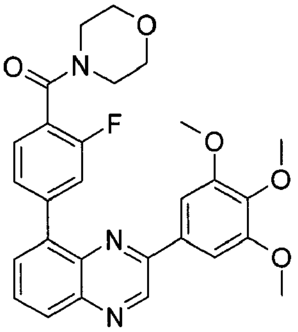
R_t = 0.920 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 472 $(M+1)^+$.

Example 16: {2-Methyl-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



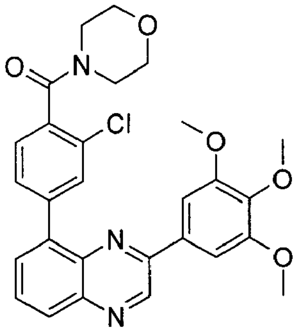
R_t = 1.155 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 500 $(M+1)^+$.

Example 17: 2-Fluoro-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



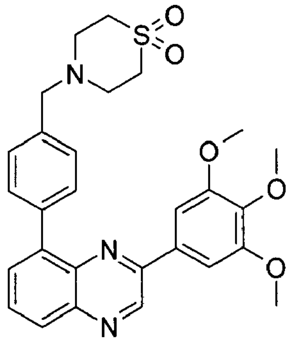
R_t = 1.158 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 504 $(M+1)^+$.

Example 18: {2-Chloro-4-[3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



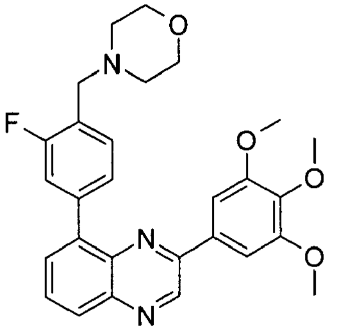
R_t = 1.184 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 520 $(M+1)^+$.

Example 19: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



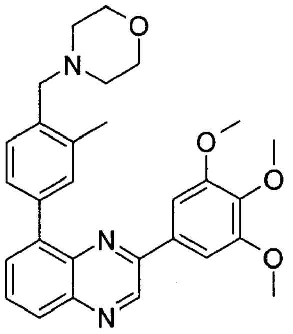
R_t = 0.969 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 520 $(M+1)^+$.

Example 20: 8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



R_t = 0.932 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 490 $(M+1)^+$.

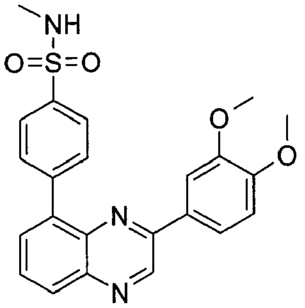
Example 21: 8-(3-Methyl-4-morpholin-4-ylmethyl-phenyl)-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



R_t = 0.947 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 486 $(M+1)^+$.

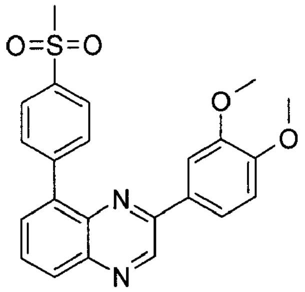
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(3,4-dimethoxy-phenyl)-quinoxaline [prepared analogously to step 1.5 but utilizing 4,5-dimethoxyphenylboronic acid in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 22: 4-[3-(3,4-Dimethoxy-phenyl)-quinoxalin-5-yl]-N-methyl-benzenesulfonamide



R_t = 1.124 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 436 $(M+1)^+$.

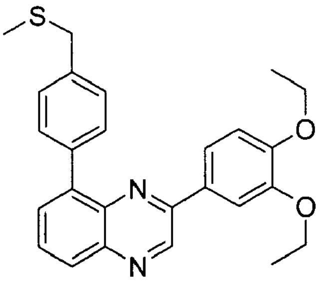
Example 23: 2-(3,4-Dimethoxy-phenyl)-8-(4-methanesulfonyl-phenyl)-quinoxaline



R_t = 1.116 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 421 $(M+1)^+$.

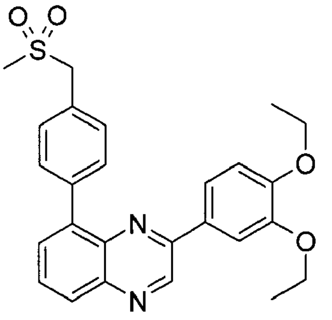
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(3,4-diethoxy-phenyl)-quinoxaline [prepared analogously to step 1.5 but utilizing 4,5-diethoxyphenylboronic acid in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 24: 2-(3,4-Diethoxy-phenyl)-8-(4-methylsulfanylmethyl-phenyl)-quinoxaline



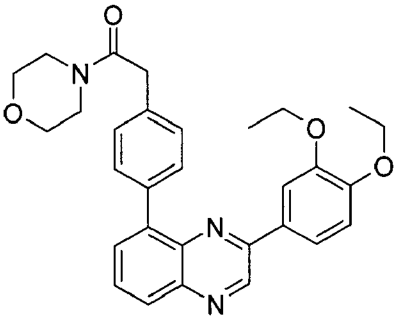
R_t = 1.550 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 431 $(M+1)^+$.

Example 25: 2-(3,4-Diethoxy-phenyl)-8-(4-methanesulfonylmethyl-phenyl)-quinoxaline



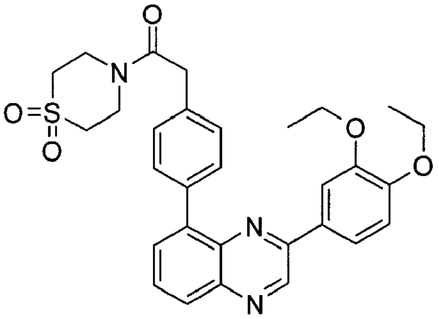
A microwave tube is charged with 23 mg (0.053 mmol) of 2-(3,4-Diethoxy-phenyl)-8-(4-methylsulfanylmethyl-phenyl)-quinoxaline, 2 ml AcOH and 20 µl (0.2 mmol) of a 30% aqueous H_2O_2 solution. The tube is sealed and heated to reflux for 30 min. After cooling, the reaction mixture is diluted with EtOAc and washed three time with 2M NaOH solution, once with a 10% $Na_2S_2O_3$ solution and finally with de-ionized water. The organic layers is washed dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by preparative HPLC (H_2O/ MeCN with 0.05% TFA 1:0 => 0:1) to afford the title compound as a yellow solid, R_t = 1.243 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 463 $(M+1)^+$.

Example 26: 2-{4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-1-morpholin-4-yl-ethanone



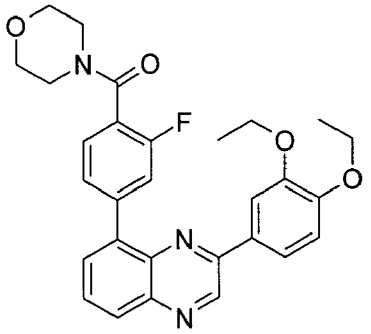
R_t = 1.260 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 498 $(M+1)^+$.

Example 27: 2-{4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone



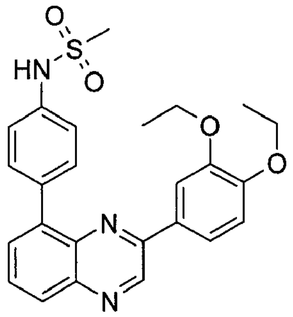
R_t = 1.212 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 546 $(M+1)^+$.

Example 28: {4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



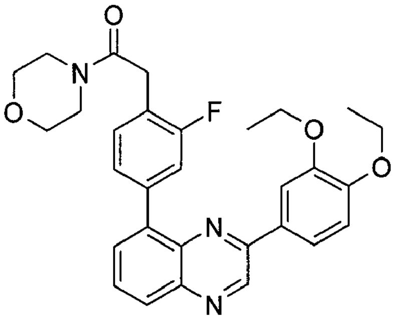
R_t = 1.276 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 502 $(M+1)^+$.

Example 29: N-{4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-methanesulfonamide



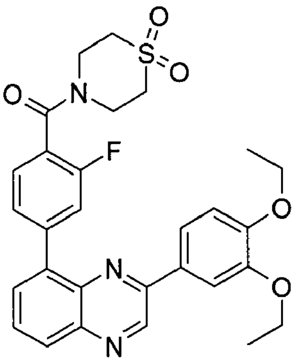
R_t = 1.254 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 464 $(M+1)^+$.

Example 30: 2-{4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-2-fluoro-phenyl}-1-morpholin-4-yl-ethanone



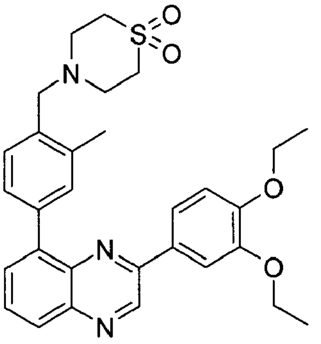
R_t = 1.291 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 516 $(M+1)^+$.

Example 31: {4-[3-(3,4-Diethoxy-phenyl)-quinoxalin-5-yl]-2-fluoro-phenyl}-(1,1-dioxido-thiomorpholin-4-yl)-methanone



R_t = 1.217 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 550 $(M+1)^+$.

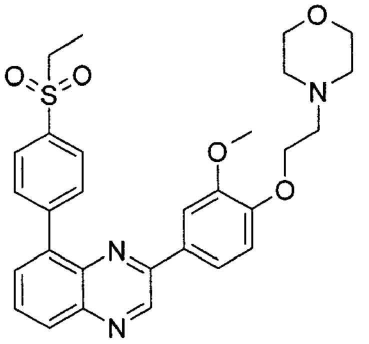
Example 32: 2-(3,4-Diethoxy-phenyl)-8-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3-methyl-phenyl]-quinoxaline



R_t = 1.153 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 532 $(M+1)^+$.

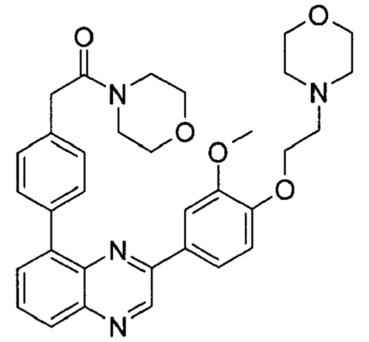
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 4-{2-[2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (CAS 864754-10-9) in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 33: 8-(4-Ethanesulfonyl-phenyl)-2-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxaline



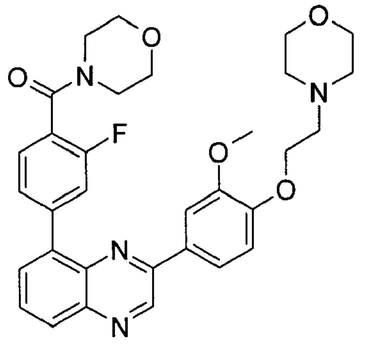
R_t = 0.923 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 534 $(M+1)^+$.

Example 34: 2-(4-{3-[3-Methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



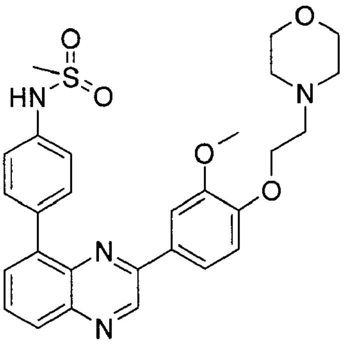
R_t = 0.905 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 569 $(M+1)^+$.

Example 35: (2-Fluoro-4-{3-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-morpholin-4-yl-methanone



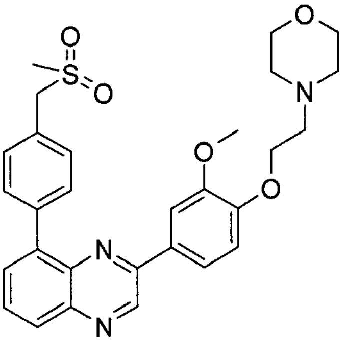
R_t = 0.900 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 573 $(M+1)^+$.

Example 36: N-(4-{3-[3-Methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-methanesulfonamide



R_t = 0.903 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 535 $(M+1)^+$.

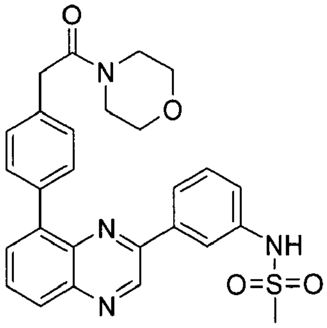
Example 37: 8-(4-Methanesulfonylmethyl-phenyl)-2-[3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-quinoxaline



R_t = 0.894 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 534 $(M+1)^+$.

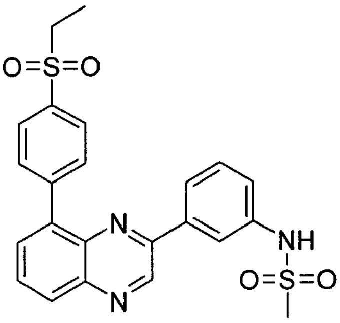
Using the same synthetic methods as described in Example 1, but utilizing N-[3-(8-Bromo-quinoxalin-2-yl)-phenyl]-methanesulfonamide [prepared analogously to step 1.1 but utilizing [3-[(Methylsulfonyl)amino]phenyl]boronic acid in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples.

Example 38: N-(3-{8-[4-(2-Morpholin-4-yl-2-oxo-ethyl)-phenyl]-quinoxalin-2-yl}-phenyl)-methanesulfonamide



R_t = 1.008 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 503 $(M+1)^+$.

Example 39: N-{3-[8-(4-Ethanesulfonyl-phenyl)-quinoxalin-2-yl]-phenyl}-methanesulfonamide

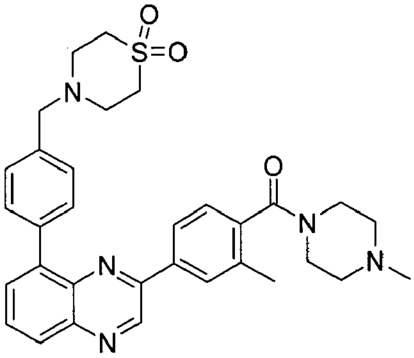


R_t = 1.056 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 468 $(M+1)^+$.

Using the same synthetic methods as described in Example 1, but utilizing [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-(4-methyl-piperazin-1-yl)-methanone [prepared analogously to step 1.5 but utilizing (4-Methyl-piperazin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone in lieu of 3,4,5-

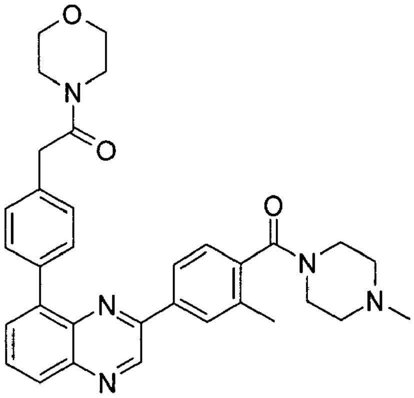
trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 40: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone



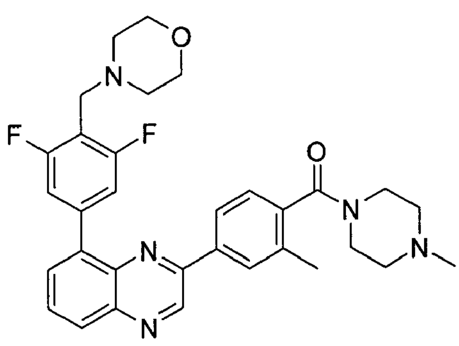
R$_t$ = 0.752 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 570 $(M+1)^+$.

Example 41: 2-(4-{3-[3-Methyl-4-(4-methyl-piperazine-1-carbonyl)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



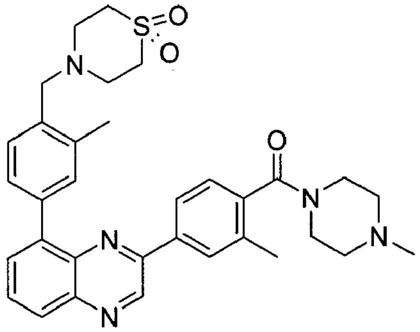
R$_t$ = 0.862 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 550 $(M+1)^+$.

Example 42: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone



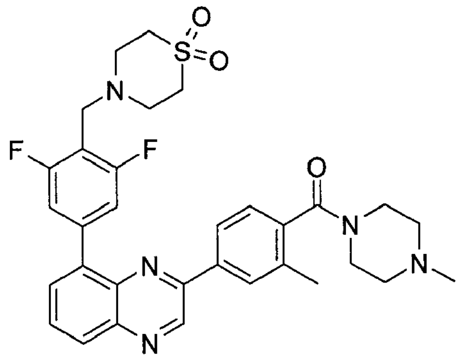
R_t = 0.706 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 558 $(M+1)^+$.

Example 43: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-methyl-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone



R_t = 0.842 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 584 $(M+1)^+$.

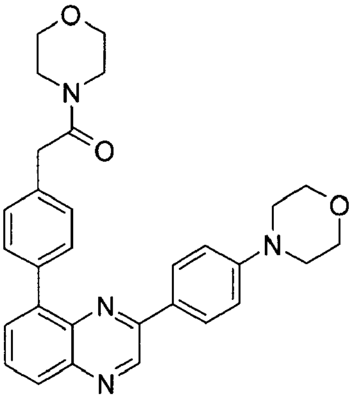
Example 44: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone



R_t = 0.852 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 606 $(M+1)^+$

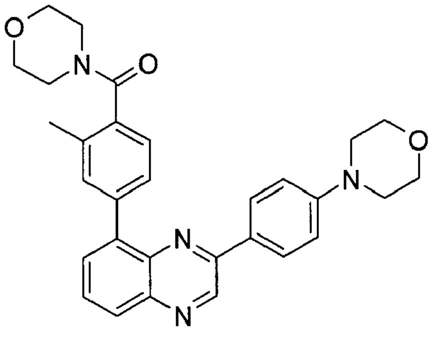
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(4-morpholin-4-yl-phenyl)-quinoxaline [prepared analogously to step 1.5 but utilizing 4-(Morpholino)phenylboronic acid in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 45: 1-Morpholin-4-yl-2-{4-[3-(4-morpholin-4-yl-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone



R_t = 1.127 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 495 $(M+1)^+$.

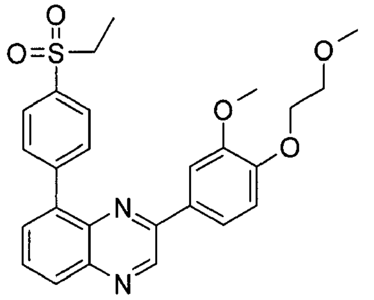
Example 46: {2-Methyl-4-[3-(4-morpholin-4-yl-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



R_t = 1.154 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 495 $(M+1)^+$.

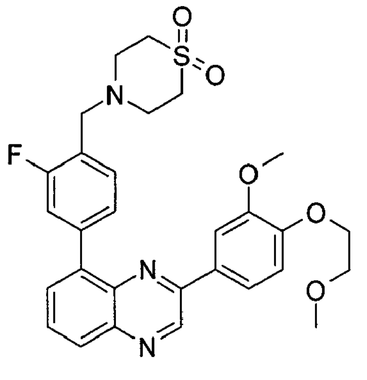
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 2-[3-Methoxy-4-(2-methoxy-ethoxy)-phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 47: 8-(4-Ethanesulfonyl-phenyl)-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



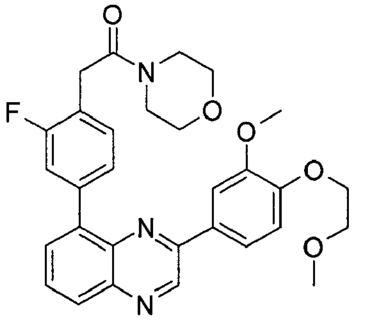
R_t = 1.209 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 479 $(M+1)^+$.

Example 48: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



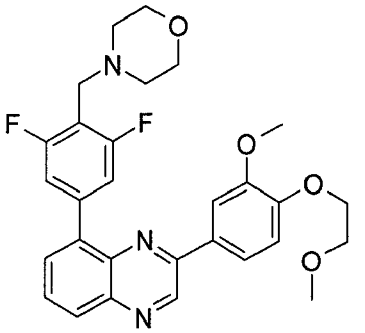
R_t = 1.025 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 552 $(M+1)^+$.

Example 49: 2-(2-Fluoro-4-{3-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



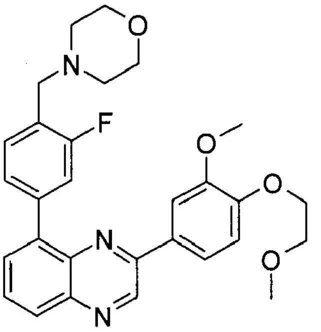
R_t = 1.162 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 532 $(M+1)^+$

Example 50: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



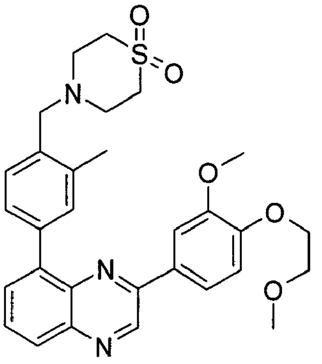
R_t = 0.958 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 522 $(M+1)^+$.

Example 51: 8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



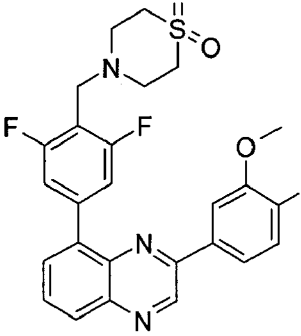
R_t = 0.955 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 504 $(M+1)^+$.

Example 52: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-methyl-phenyl]-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



R_t = 1.062 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 548 $(M+1)^+$

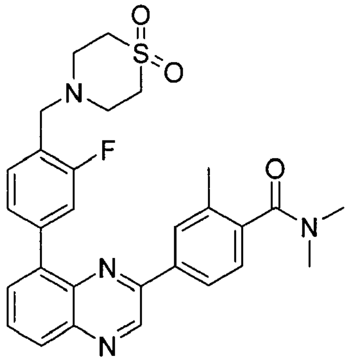
Example 53: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[3-methoxy-4-(2-methoxy-ethoxy)-phenyl]-quinoxaline



R_t = 1.145 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 570 $(M+1)^+$

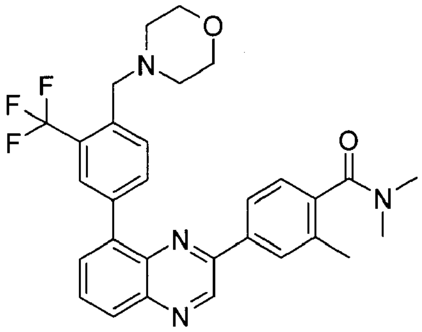
Using the same synthetic methods as described in Example 1, but utilizing 4-(8-Bromo-quinoxalin-2-yl)-2,N,N-trimethyl-benzamide [prepared analogously to step 1.5 but utilizing 2,N,N-Trimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 54: 4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-quinoxalin-2-yl}-2,N,N-trimethyl-benzamide



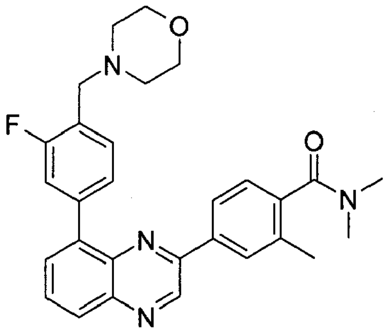
R_t = 0.934 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 533 $(M+1)^+$

Example 55: 2,N,N-Trimethyl-4-[8-(4-morpholin-4-ylmethyl-3-trifluoromethyl-phenyl)-quinoxalin-2-yl]-benzamide



R_t = 0.922 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 535 $(M+1)^+$

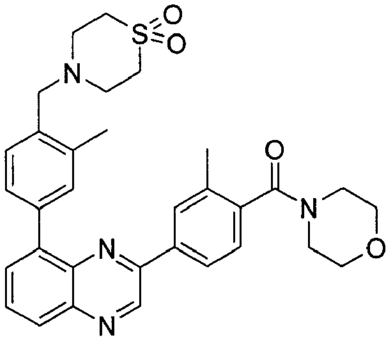
Example 56: 4-[8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2,N,N-trimethyl-benzamide



R_t = 0.934 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 533 $(M+1)^+$

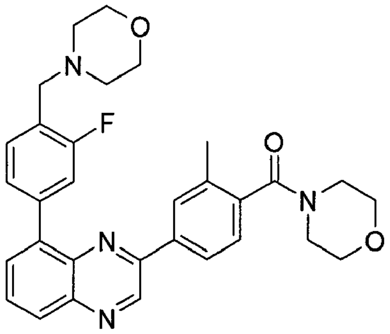
Using the same synthetic methods as described in Example 1, but utilizing [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-morpholin-4-yl-methanone [prepared analogously to step 1.5 but utilizing [2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-morpholin-4-yl-methanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 57: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-methyl-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



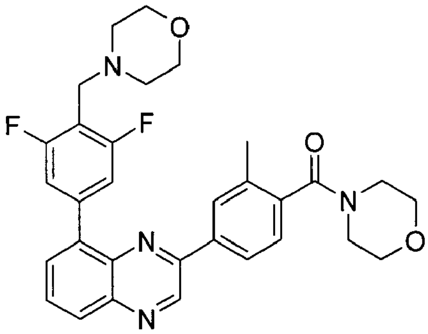
R_t = 0.939 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 571 $(M+1)^+$

Example 58: {4-[8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



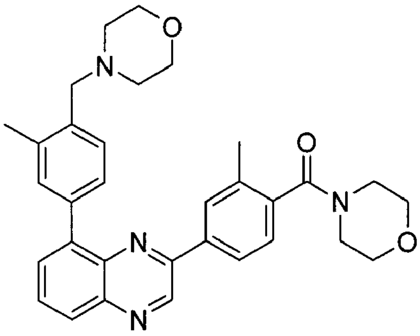
R_t = 0.844 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 527 $(M+1)^+$

Example 59: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



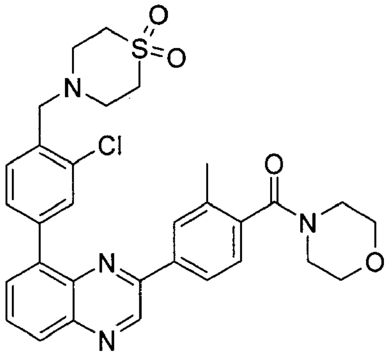
R_t = 0.844 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 545 $(M+1)^+$

Example 60: {2-Methyl-4-[8-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-phenyl}-morpholin-4-yl-methanone



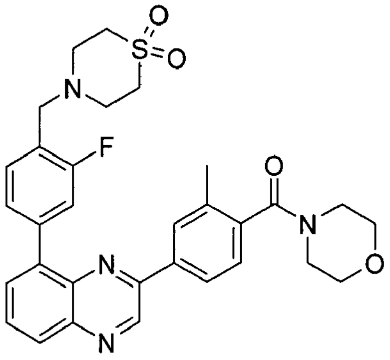
R_t = 0.868 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 523 $(M+1)^+$

Example 61: (4-{8-[3-Chloro-4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



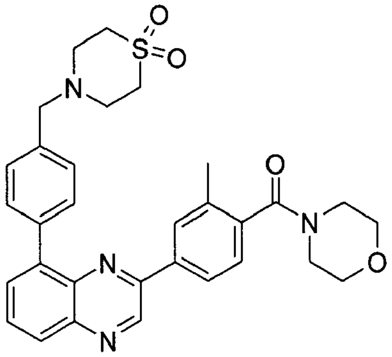
R_t = 1.016 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 591 $(M+1)^+$

Example 62: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



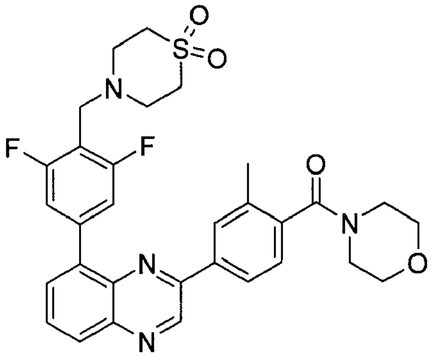
R_t = 0.924 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 575 $(M+1)^+$

Example 63: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



R_t = 0.869 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 557 $(M+1)^+$

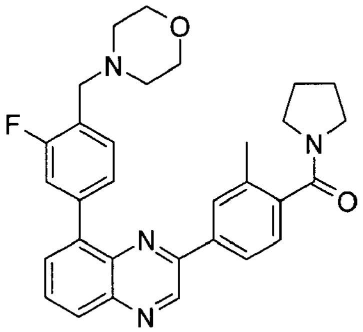
Example 64: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



R_t = 0.995 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 593 $(M+1)^+$

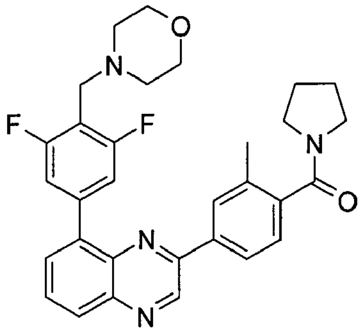
Using the same synthetic methods as described in Example 1, but utilizing [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-pyrrolidin-1-yl-methanone [prepared analogously to step 1.5 but utilizing [2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-1-yl-methanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 65: {4-[8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-pyrrolidin-1-yl-methanone



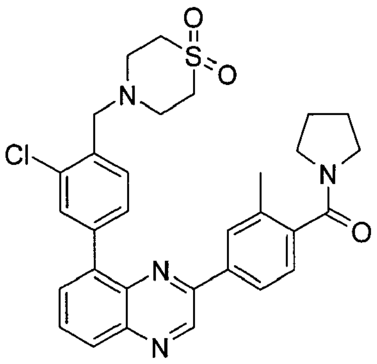
R_t = 0.897 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 511 $(M+1)^+$

Example 66: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-pyrrolidin-1-yl-methanone



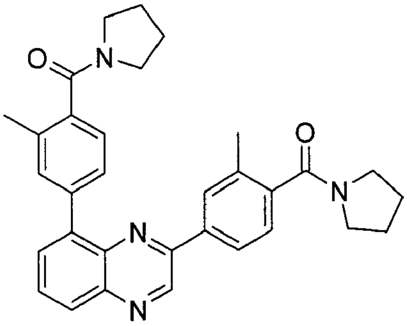
R_t = 0.897 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 529 $(M+1)^+$

Example 67: (4-{8-[3-Chloro-4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-pyrrolidin-1-yl-methanone



R_t = 1.072 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 575 $(M+1)^+$

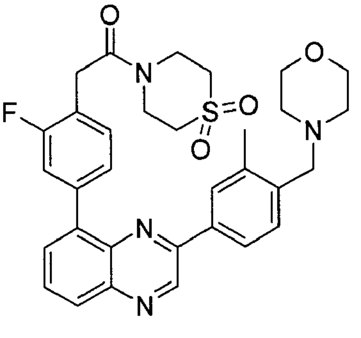
Example 68: (2-Methyl-4-{3-[3-methyl-4-(pyrrolidine-1-carbonyl)-phenyl]-quinoxalin-5-yl}-phenyl)-pyrrolidin-1-yl-methanone



R_t = 1.160 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

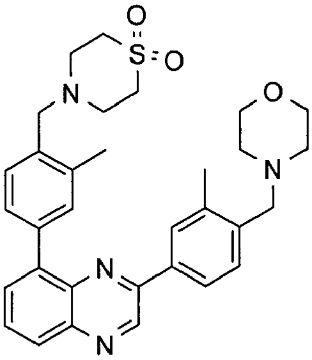
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxaline [prepared analogously to step 1.5 but utilizing 4-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-morpholine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 69: 1-(1,1-Dioxido-thiomorpholin-4-yl)-2-{2-fluoro-4-[3-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone



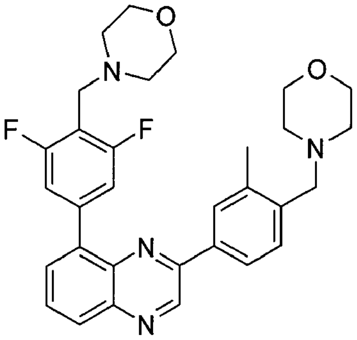
R_t =0.885 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 589 $(M+1)^+$

Example 70: 8-[4-(1,1-Dioxido--thiomorpholin-4-ylmethyl)-3-methyl-phenyl]-2-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



R_t =0.827 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 557 $(M+1)^+$

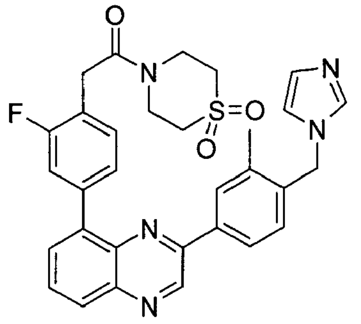
Example 71: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



R_t =0.720 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 531 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(4-imidazol-1-ylmethyl-3-methyl-phenyl)-quinoxaline [prepared analogously to step 1.5 but utilizing 1-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-1H-imidazole in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

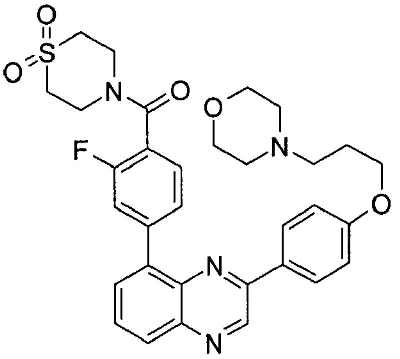
Example 72: 1-(1,1-Dioxido-thiomorpholin-4-yl)-2-{2-fluoro-4-[3-(4-imidazol-1-ylmethyl-3-methyl-phenyl)-quinoxalin-5-yl]-phenyl}-ethanone



R_t =0.905 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 570 $(M+1)^+$

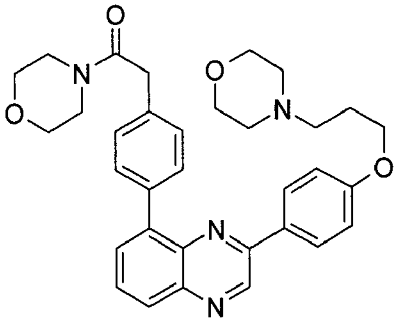
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 4-{3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propyl}-morpholine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 73: (1,1-Dioxido-thiomorpholin-4-yl)-(2-fluoro-4-{3-[4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-methanone



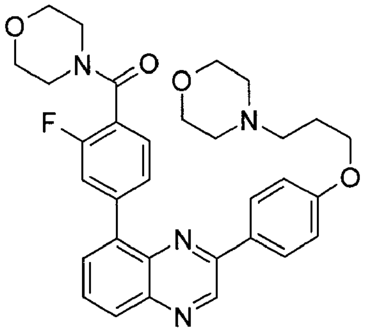
R_t = 0.897 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 605 $(M+1)^+$

Example 74: 1-Morpholin-4-yl-2-(4-{3-[4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-ethanone



R_t = 0.929 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 553 $(M+1)^+$

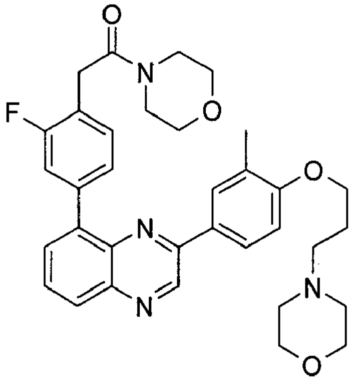
Example 75: (2-Fluoro-4-{3-[4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-morpholin-4-yl-methanone



R_t = 0.929 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 557 $(M+1)^+$

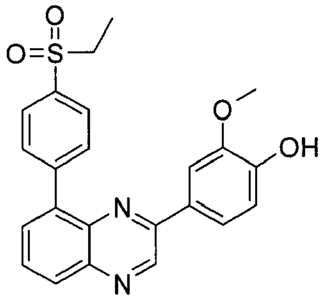
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[3-methyl-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 4-{3-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propyl}-morpholine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 76: 2-(2-Fluoro-4-{3-[3-methyl-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



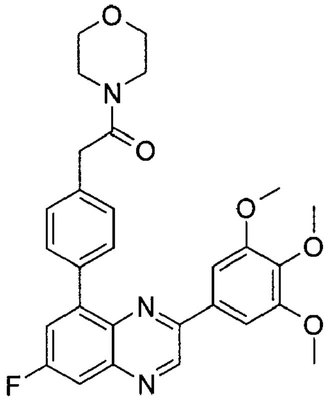
R_t = 0.982 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 585 $(M+1)^+$

Example 77: 4-[8-(4-Ethanesulfonyl-phenyl)-quinoxalin-2-yl]-2-methoxy-phenol



R_t = 1.079 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 421 $(M+1)^+$.

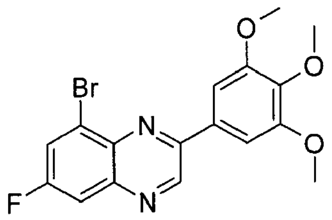
Example 78: 2-{4-[7-Fluoro-3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-1-morpholin-4-yl-ethanone



R_t = 1.164 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 518 $(M+1)^+$.

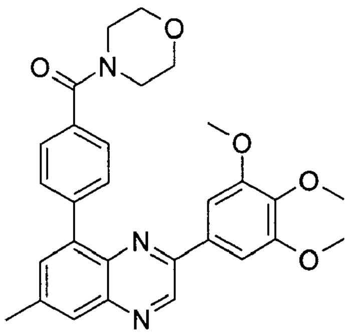
The starting materials can be prepared as follows:

a) 8-Bromo-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



A round bottom flask is charged with 1.03 g (5 mmol) 3-Bromo-5-fluoro-benzene-1,2-diamine and solved into 30 ml EtOH. 1.15 g (5.02 mmol) 3,4,5-trimethylphenylglyoxal monohydrate is then added and the mixture is heated to 80°C for 1h. After cooling to 0°C, the suspension is filtered and the residue is purified by chromatography (silicagel, hexane: EtOAc 2:1) to afford the title compound as a yellow solid.

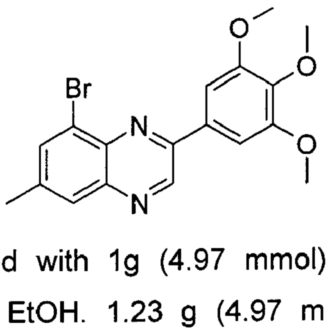
Example 79: {4-[7-Methyl-3-(3,4,5-trimethoxy-phenyl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



R_t = 1.198 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 500 $(M+1)^+$.

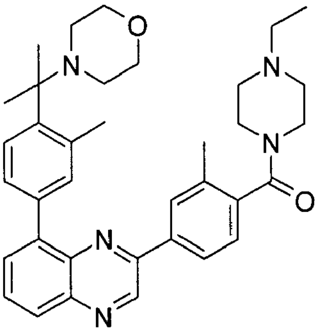
The starting materials can be prepared as follows:

a) 8-Bromo-6-methyl-2-(3,4,5-trimethoxy-phenyl)-quinoxaline



A round bottom flask is charged with 1g (4.97 mmol) 3-Bromo-5-methyl-benzene-1,2-diamine and solved into 27 ml EtOH. 1.23 g (4.97 mmol) 3,4,5-trimethylphenylglyoxal monohydrate is then added and the mixture is heated to 60°C for 1h. After cooling to 0°C, the title compound is collected by filtration and used in the next step without further purification.

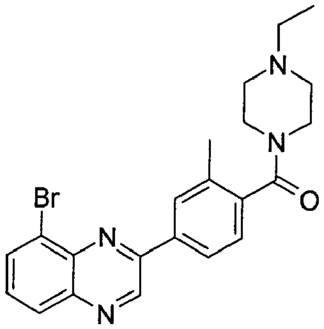
Example 80: (4-Ethyl-piperazin-1-yl)-(2-methyl-4-{8-[3-methyl-4-(1-methyl-1-morpholin-4-yl-ethyl)-phenyl]-quinoxalin-2-yl}-phenyl)-methanone.



A microwave tube is charged with of [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-(4-ethyl-piperazin-1-yl)-methanone (step 80.1, 49 mg, 0.112 mmol), 4-{1-Methyl-1-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl}-morpholine (40.4 mg, ca. 0.117 mmol), S-Phos (4.25 mg, 0.01 mmol), K_3PO_4 (72.5 mg, 0.33 mmol) and $Pd(OAc)_2$ (0.75 mg ,0.0033 mmol). After several cycles of vacuum/ purge with argon, 3 ml of a mixture consisting of 28 µl deionized water in 12 ml 1,2-dimethoxy-ethane, are added. The reaction mixture is then heated to 105°C for 5h30. After cooling, the reaction mixture is diluted with CH_2Cl_2, poured onto a saturated solution of Na_2CO_3 and extracted 3× with CH_2Cl_2. The combined organic layers are washed with water, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2 / CH_2Cl_2: EtOH :NH3 90:9:1 from 1:0 => 0:1) to afford the title compound as a pale yellow foam, R_t = 1.777 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 578 $(M+1)^+$.

The starting materials can be prepared as follows:

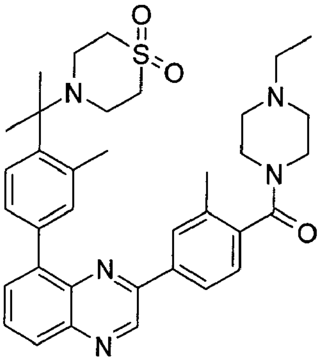
Step 80.1: [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-(4-ethyl-piperazin-1-yl)-methanone.



A microwave tube is charged with 8-Bromo-2-chloro-quinoxaline (Step 1.4, 298 mg ,1.226 mmol), (4-Ethyl-piperazin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone (439 mg, 1.226 mmol), K_3PO_4 (532 mg, 2.450 mmol) and $Pd(PPh_3)_4$ (43.8 mg ,0.0368 mmol). After several cycles of vacuum/ purge with argon, 5 ml of dry DMA are added. The reaction mixture is then heated to 105°C for 4h. After cooling, the suspension is poured onto 70 ml de-ionized water and filtered. The cake is re-taken in EtOAc, washed with saturated brine and dried over Na_2SO_4. After filtration, the mixture is concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2 / CH_2Cl_2: EtOH :NH3 90:9:1 from 1:0 => 0:1) to afford the title compound as a pale brown foam, R_t = 0.833 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 439 (M+1, $^{79}Br)^+$.

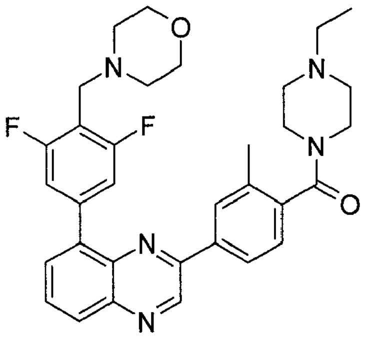
Using the same synthetic methods as described in Example 80, reaction of [4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-(4-ethyl-piperazin-1-yl)-methanone and the appropriate boronic acid or ester derivative leads to the following Examples:

Example 81: [4-(8-{4-[1-(1,1-Dioxido-thiomorpholin-4-yl)-1-methyl-ethyl]-3-methyl-phenyl}-quinoxalin-2-yl)-2-methyl-phenyl]-(4-ethyl-piperazin-1-yl)-methanone



R_t = 1.040 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 626 $(M+1)^+$.

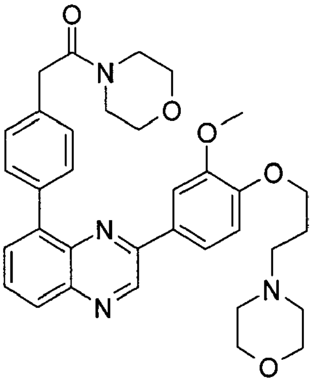
Example 82: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-(4-ethyl-piperazin-1-yl)-methanone



R_t = 0.716 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 572 $(M+1)^+$.

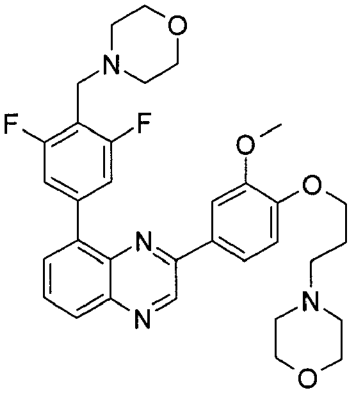
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[3-methoxy-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 4-{3-[2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propyl}-morpholine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 83: 2-(4-{3-[3-Methoxy-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



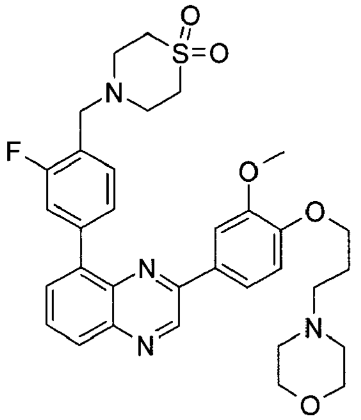
R_t =0.938 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 583 $(M+1)^+$

Example 84: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[3-methoxy-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline



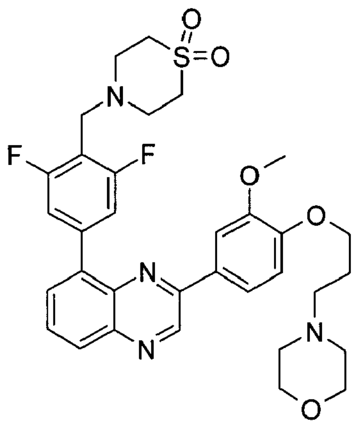
R_t =0.776 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 591 $(M+1)^+$

Example 85: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-2-[3-methoxy-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline



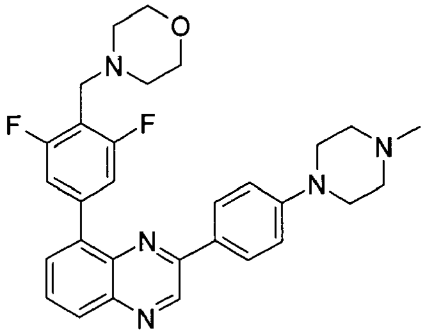
R_t =0.882 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 621 $(M+1)^+$

Example 86: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[3-methoxy-4-(3-morpholin-4-yl-propoxy)-phenyl]-quinoxaline



R_t =0.940 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 639 $(M+1)^+$

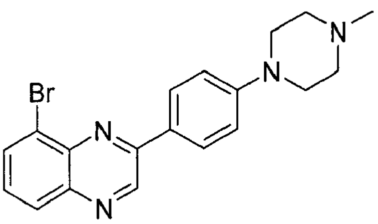
Example 87: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline.



A microwave tube is charged with 8-Bromo-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline (2.6 g ,6.783 mmol), 4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-morpholine (Step 87.1, 2.68 g, 7.12 mmol,), S-Phos (258 mg, 0.611 mmol), K_3PO_4 (4.41 g, 20.4 mmol) and $Pd(OAc)_2$ (45.68 mg, 0.203 mmol). After several cycles of vacuum/ purge with argon, a mixture of 370 µl deionized water in 30 ml 1,2-dimethoxy-ethane is added. The reaction mixture is then heated to 105°C for 12h. After cooling, the reaction mixture is diluted with CH_2Cl_2, poured onto a saturated solution of $NaHCO_3$ and extracted 3× with CH_2Cl_2. The combined organic layers are washed with water, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2 / CH_2Cl_2: EtOH :NH3 90:9:1 4:6) to afford the title compound as yellow solid, R_t = 0.742 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 516 $(M+1)^+$.

The starting materials can be prepared as follows:

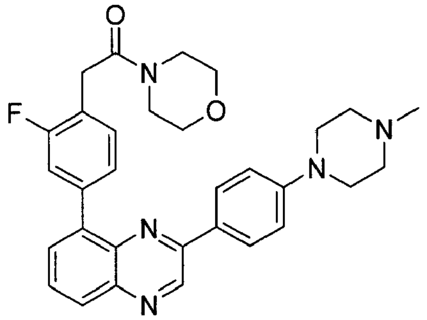
Step 87.1: 8-Bromo-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



A microwave tube is charged with 8-Bromo-2-chloro-quinoxaline (Step 1.4, 2.5 g, 10.267 mmol), 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine (2.88 g, 9.24 mmol), K_3PO_4 (6.67 g, 30.8 mmol) and $PdCl_2(PPh_3)_2$ (221 mg, 0.308 mmol). After several cycles of vacuum/ purge with argon, a mixture of 21 ml of DMA and 560 µl deionized water is added. The reaction mixture is then heated to 105°C for 4h. After cooling, the suspension is poured onto de-ionized water and diluted with EtOAc. The phases are separated and the aqueous phase re-extracted twice with EtOAc. The combined organic phases are washed with saturated brine and dried over Na_2SO_4. After filtration, the mixture is concentrated in vacuo. The residue is purified by chromatography (silicagel, CH_2Cl_2: EtOH :NH3 95:4.5:0.5 from 1:0 => 0:1) to afford the title compound as a yellow orange solid, R_t = 0.930 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 383 (M+1, $^{79}Br)^+$.

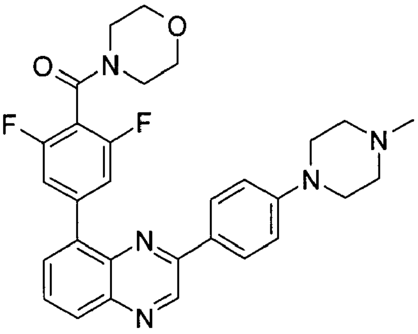
Using the same synthetic methods as described in Example 87, reaction of 8-Bromo-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline and the appropriate boronic ester derivative leads to the following Examples:

Example 88: 2-(2-Fluoro-4-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxalin-5-yl}-phenyl)-1-morpholin-4-yl-ethanone



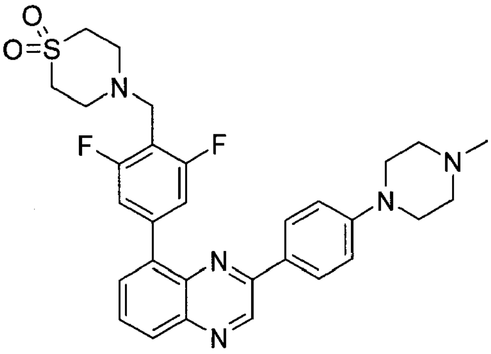
R_t =0.934 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 526 $(M+1)^+$

Example 89: (2,6-Difluoro-4-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxalin-5-yl}-phenyl)-morpholin-4-yl-methanone



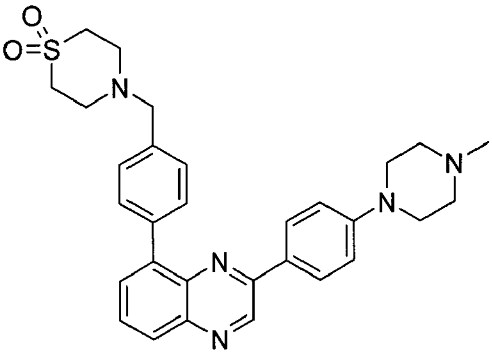
R_t =0.939 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 530 $(M+1)^+$

Example 90: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



R_t =0.913 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 564 $(M+1)^+$

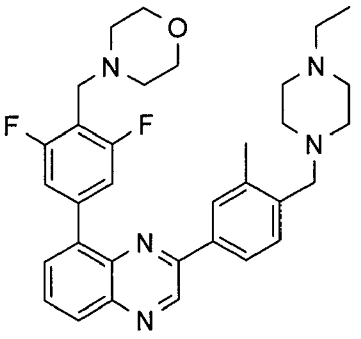
Example 91: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



R_t =0.794 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 528 $(M+1)^+$

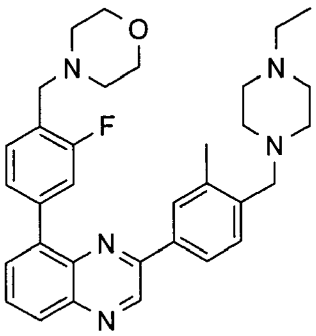
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[4-(4-ethyl-piperazin-1-ylmethyl)-3-methyl-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-Ethyl-4-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 92: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[4-(4-ethyl-piperazin-1-ylmethyl)-3-methyl-phenyl]-quinoxaline



R_t =0.743 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 558 $(M+1)^+$

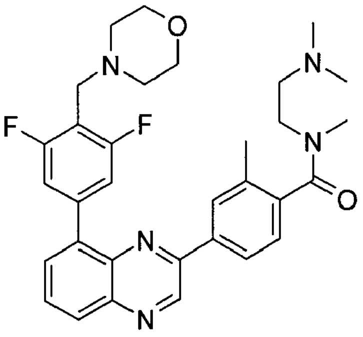
Example 93: 2-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-methyl-phenyl]-8-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



R_t =0.741 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 540 $(M+1)^+$

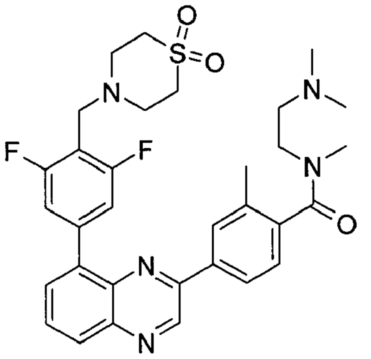
Using the same synthetic methods as described in Example 1, but utilizing 4-(8-Bromo-quinoxalin-2-yl)-N-(2-dimethylamino-ethyl)-2,N-dimethyl-benzamide [prepared analogously to step 1.5 but utilizing N-(2-Dimethylamino-ethyl)-2,N-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 94: 4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-N-(2-dimethylamino-ethyl)-2,N-dimethyl-benzamide



R_t =0.750 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 560 $(M+1)^+$

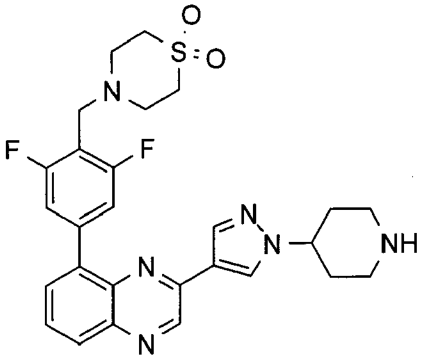
Example 95: N-(2-Dimethylamino-ethyl)-4-{8-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-2,N-dimethyl-benzamide



R_t =0.893 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 608 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline [prepared in step 94.2] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

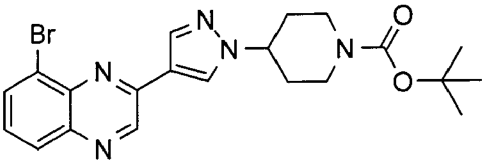
Example 96: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



R_t =0.819min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 539 $(M+1)^+$

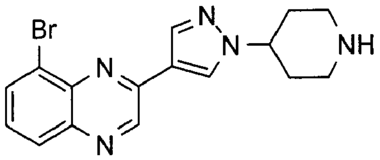
The starting materials can be prepared as follows:

Step 96.1: 4-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester



A microwave tube is charged with 8-Bromo-2-chloro-quinoxaline (Step 1.4, 1 g, 4.11 mmol), 4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (1.74 g, 3.70 mmol), K_3PO_4 (2.67 g, 12.3 mmol) and of $PdCl_2(PPh_3)_2$ (88.2 mg, 0.123 mmol). After several cycles of vacuum/ purge with argon, a mixture of 5 ml of DMA and 220 µl deionized water is added. The reaction mixture is then heated to 80°C for 3h. After cooling, the suspension is poured onto de-ionized water and diluted with EtOAc. The phases are separated and the aqueous phase re-extracted twice with EtOAc. The combined organic phases are washed with saturated brine and dried over Na_2SO_4. After filtration, the mixture is concentrated in vacuo. The residue is purified by chromatography on a 80 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient hexanes: EtOAc from 1:0 => 0:1) to afford the title compound as a yellow foam, R_t = 1.350 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 458 (M+1, $^{79}Br)^+$.

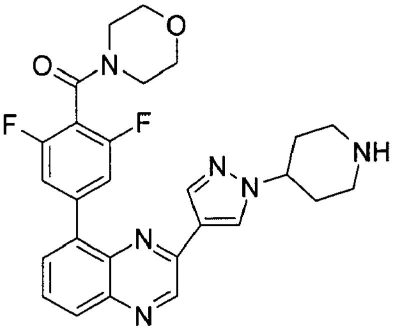
Step 96.2: 8-Bromo-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



A 1.2 M solution of HCl in EtOH (60 ml, 72 mmol) is added to 4-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Step 94.1, 1.98 g , 4.32 mmol) and the reaction mixture is heated at 50°C for 12h. After cooling, the yellow suspension is concentrated under vacuo and the residue is diluted with CH_2Cl_2, poured onto a saturated solution of $NaHCO_3$ and extracted 3× with CH_2Cl_2. The combined organic layers are washed with water, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is used without further purification in the next step, and afford the title compound as pale orange solid, R_t = 0.802 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection

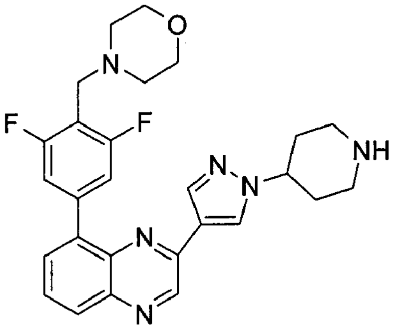
215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 358 (M+1, $^{79}Br)^+$

Example 97: {2,6-Difluoro-4-[3-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



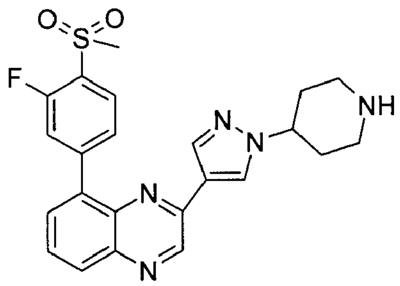
R_t =0.848 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

Example 98: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



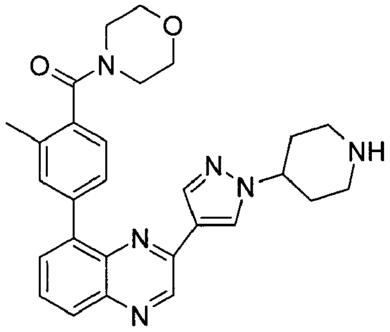
R_t =0.682 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 491 $(M+1)^+$

Example 99: 8-(3-Fluoro-4-methanesulfonyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



R_t =0.841 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 452 $(M+1)^+$

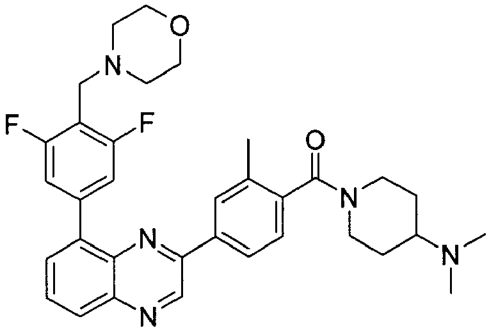
Example 100: {2-Methyl-4-[3-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxalin-5-yl]-phenyl}-morpholin-4-yl-methanone



R_t =0.883 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 483 $(M+1)^+$

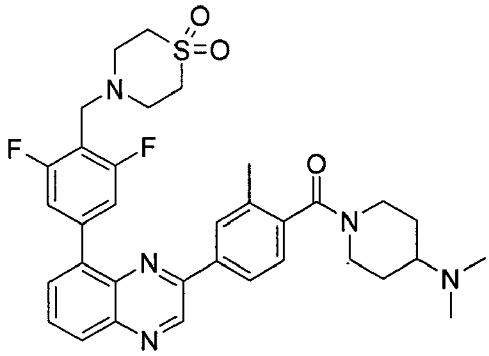
Using the same synthetic methods as described in Example 1, but utilizing 4-(8-Bromo-quinoxalin-2-yl)-2-methyl-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone [prepared analogously to step 1.5 but utilizing (4-Dimethylamino-piperidin-1-yl)-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 101: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-2-methyl-phenyl}-(4-dimethylamino-piperidin-1-yl)-methanone



R_t =0.729 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 586 $(M+1)^+$

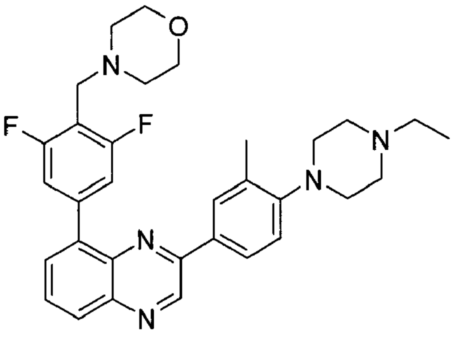
Example 102: (4-Dimethylamino-piperidin-1-yl)-(4-{8-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-2-methyl-phenyl)-methanone



R_t =0.881 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 634 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[4-(4-ethyl-piperazin-1-yl)-3-methyl-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-Ethyl-4-[2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

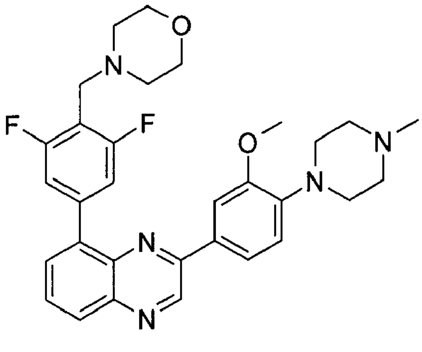
Example 103: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[4-(4-ethyl-piperazin-1-yl)-3-methyl-phenyl]-quinoxaline



R_t =0.804 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 544 $(M+1)^+$

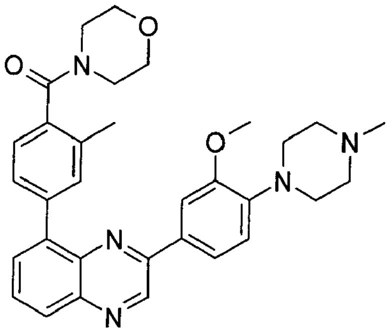
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[3-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-[2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-methyl-piperazine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 104: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[3-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



R_t =0.750 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 546 $(M+1)^+$

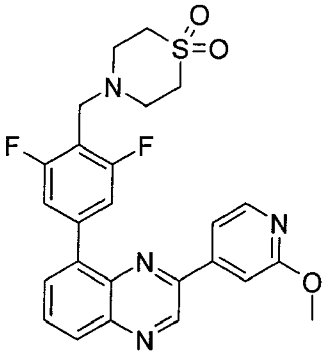
Example 105: (4-{3-[3-Methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-quinoxalin-5-yl}-2-methyl-phenyl)-morpholin-4-yl-methanone



R_t =0.912 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 538 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-(2-methoxy-pyridin-4-yl)-quinoxaline [prepared analogously to step 1.5 but utilizing 2-methoxy-pyridine 4-boronic acid in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

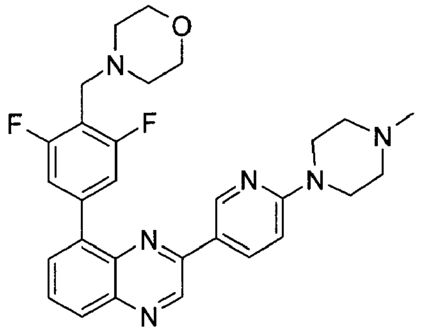
Example 106: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-(2-methoxy-pyridin-4-yl)-quinoxaline



R_t =1.058 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 497 $(M+1)^+$

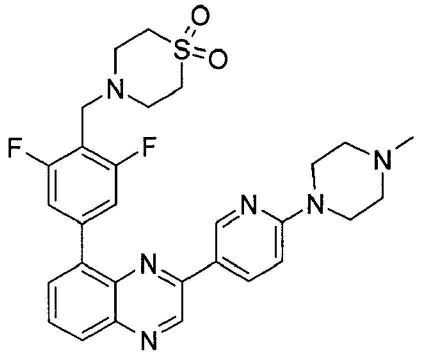
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-Methyl-4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-piperazine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 107: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinoxaline



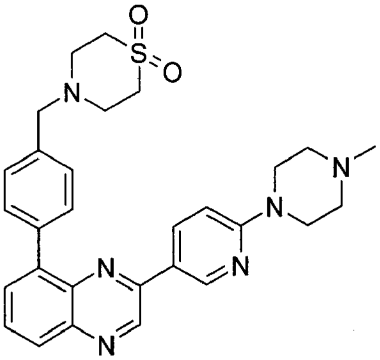
R_t =0.702 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 517 $(M+1)^+$

Example 108: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinoxaline



R_t =0.839 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 565 $(M+1)^+$

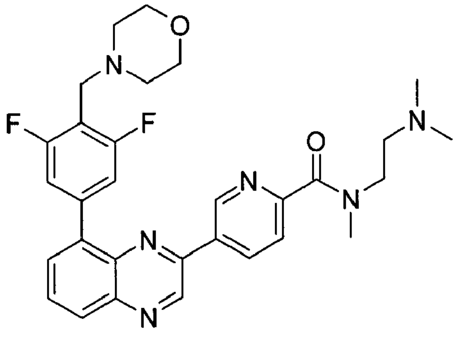
Example 109: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-quinoxaline



R_t =0.716 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 529 $(M+1)^+$

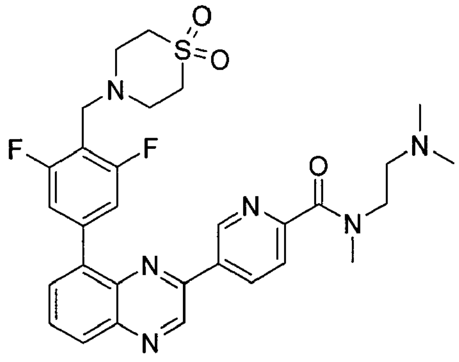
Using the same synthetic methods as described in Example 1, but utilizing 5-(8-Bromo-quinoxalin-2-yl)-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide [prepared analogously to step 1.5 but utilizing 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 110: 5-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



R_t =0.674 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 547 $(M+1)^+$

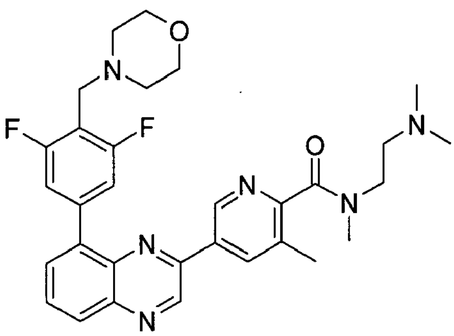
Example 111: 5-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



R_t =0.809 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 595 $(M+1)^+$

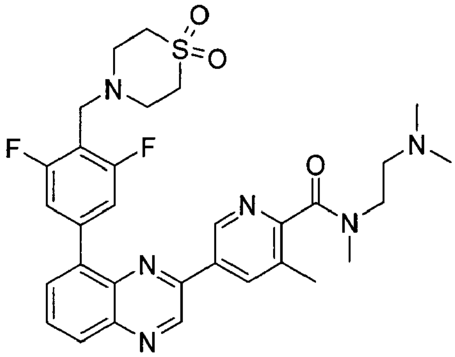
Using the same synthetic methods as described in Example 1, but utilizing 5-(8-Bromo-quinoxalin-2-yl)-3-methyl-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide [prepared analogously to step 1.5 but utilizing 3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 112: 5-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-3-methyl-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



R_t =0.697 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 561 $(M+1)^+$

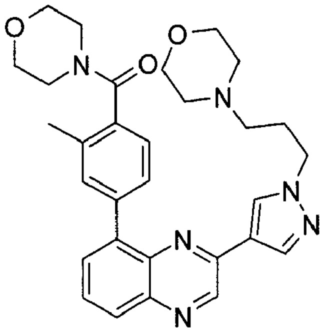
Example 113: 5-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-3-methyl-pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide



R_t =0.832 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 609 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[1-(3-morpholin-4-yl-propyl)-1H-pyrazol-4-yl]-quinoxaline [prepared analogously to step 1.5 but utilizing 4-{3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-propyl}-morpholine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

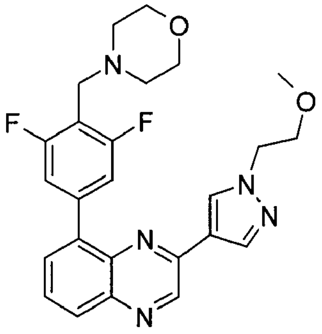
Example 114: (2-Methyl-4-{3-[1-(3-morpholin-4-yl-propyl)-1H-pyrazol-4-yl]-quinoxalin-5-yl}-phenyl)-morpholin-4-yl-methanone



R_t =0.838 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 527 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-(2-Methoxy-ethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

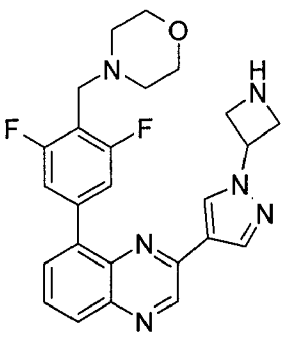
Example 115: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-quinoxaline



R_t =0.805 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 466 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 2-(1-Azetidin-3-yl-1H-pyrazol-4-yl)-8-bromo-quinoxaline [prepared analogously to the steps 94.1 and 94.2, but using 3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-azetidine-1-carboxylic acid tert-butyl ester] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

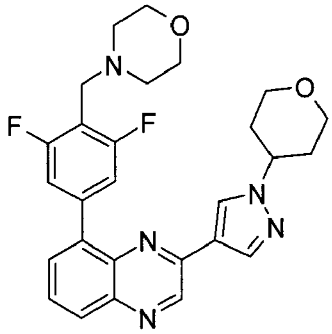
Example 116: 2-(1-Azetidin-3-yl-1H-pyrazol-4-yl)-8-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



R_t =0.664 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 463 $(M+1)^+$

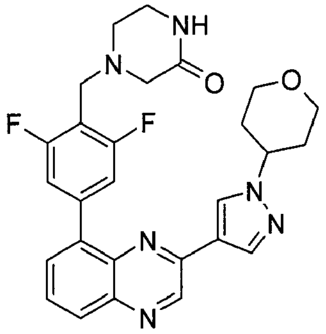
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-(Tetrahydro-pyran-4-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 117: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-quinoxaline



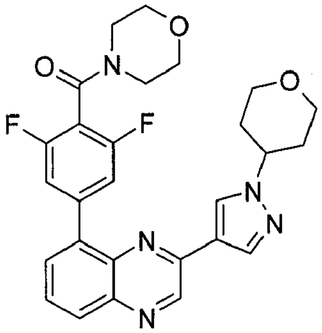
R_t =0.823 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 492 $(M+1)^+$

Example 118: 4-(2,6-Difluoro-4-{3-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-quinoxalin-5-yl}-benzyl)-piperazin-2-one



R_t =0.795 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

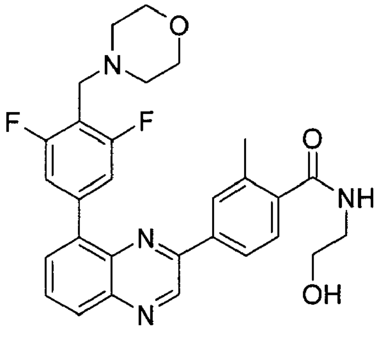
Example 119: (2,6-Difluoro-4-{3-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-quinoxalin-5-yl}-phenyl)-morpholin-4-yl-methanone



R_t =1.042 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 506 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 4-(8-Bromo-quinoxalin-2-yl)-N-(2-hydroxy-ethyl)-2-methyl-benzamide [prepared analogously to step 1.5 but utilizing N-(2-Hydroxy-ethyl)-2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

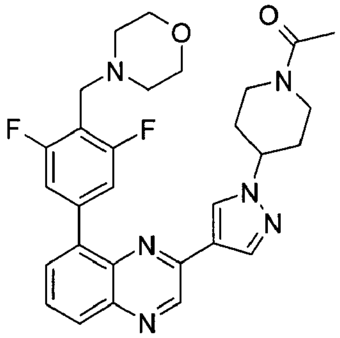
Example 120: 4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-N-(2-hydroxy-ethyl)-2-methyl-benzamide



R_t =0.769 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 519 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 1-{4-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-yl]-piperidin-1-yl}-ethanone [prepared analogously to step 1.5 but utilizing 1-{4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidin-1-yl}-ethanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

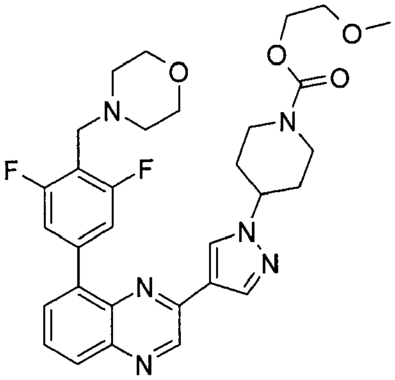
Example 121: 1-(4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidin-1-yl)-ethanone



R_t =0.792 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 533 $(M+1)^+$

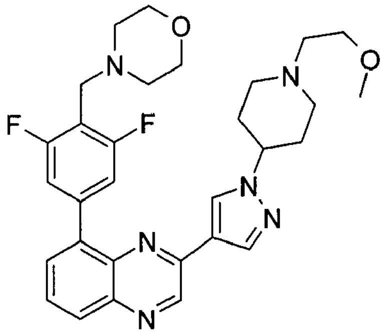
2-chloroethylmethyl ether (13.5 µl, 0.143 mmol) is added dropwise to a solution of 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline (as obtained in example 98, 67 mg, 0.137 mmol), Cs_2CO_3 (24 mg, 0.075 mmol) in DMF (0.5 ml). The resulting mixture is heated under Ar at 95°C for 17h. Two products are formed in a ratio 1:1, as identified by example 122 and example 123. The reaction is quenched with water and extracted with EtOAc several times. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography on a 40 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2/ (CH_2Cl_2: EtOH: NH_3 90:9:1) from 1:0 => 0:1) to afford example 122 and example 123.

Example 122: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid 2-methoxy-ethyl ester



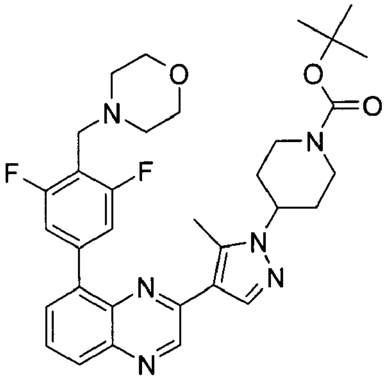
R_t =0.871 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 593 $(M+1)^+$

Example 123: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-{1-[1-(2-methoxy-ethyl)-piperidin-4-yl]-1H-pyrazol-4-yl}-quinoxaline



R_t =0.702 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 549 $(M+1)^+$

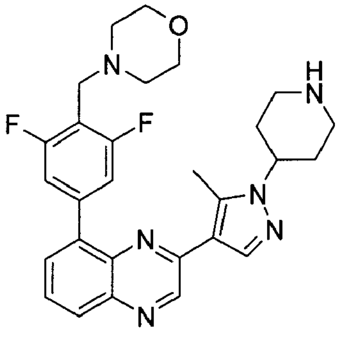
Example 124: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-5-methyl-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared using the same synthetic methods as described in Example 1, but utilizing 4-[4-(8-Bromo-quinoxalin-2-yl)-5-methyl-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester [prepared analogously to step 96.1 but utilizing 4-[5-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester.

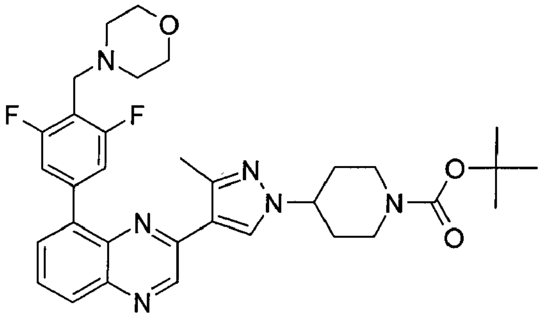
R_t =1.037 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 605 $(M+1)^+$

Example 125: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(5-methyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



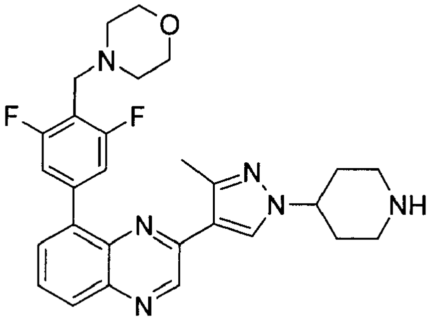
A 1.25 M solution of HCl in EtOH (5 ml, 6.26 mmol) is added to 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-5-methyl-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester (Example 121, 239 mg , 0.368 mmol) and the reaction mixture is heated at 60°C for 4h. After cooling, the yellow suspension is concentrated under vacuo and the residue is diluted with EtOAc, poured onto a saturated solution of $NaHCO_3$ and extracted 3× with EtOAc. The combined organic layers are washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and purified by chromatography on a 40 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2/ (CH_2Cl_2: EtOH: NH_3 85:13.5:1.5) from 1:0 => 1:9) to afford the title compound as a pale orange foam. R_t =0.703 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

Example 126: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-3-methyl-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



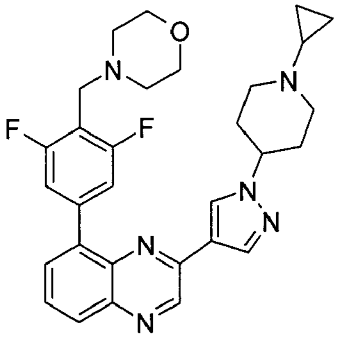
The title compound is obtained analogously to example 124 but using 4-[4-(8-Bromo-quinoxalin-2-yl)-3-methyl-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester. R_t =1.030 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 605 $(M+1)^+$

Example 127: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(3-methyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



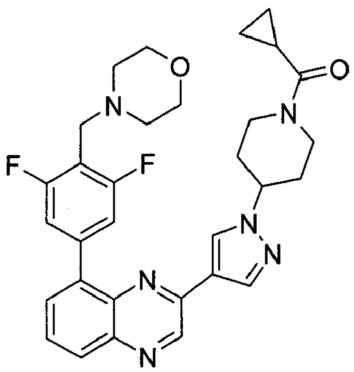
The title compound is obtained analogously to example 125 but using 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-3-methyl-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester (as obtained in example 126). R_t =0.690 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

Example 128: 2-[1-(1-Cyclopropyl-piperidin-4-yl)-1H-pyrazol-4-yl]-8-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



The title compound is obtained using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[1-(1-cyclopropyl-piperidin-4-yl)-1H-pyrazol-4-yl]-quinoxaline in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester. R_t =0.968 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 531 $(M+1)^+$

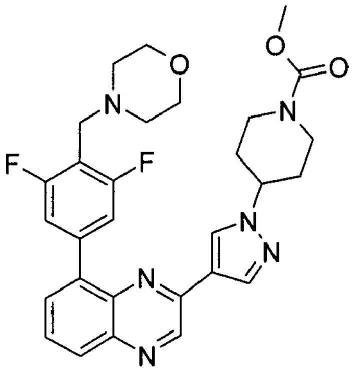
Example 129: Cyclopropyl-(4-{4-[8-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidin-1-yl)-methanone



Cyclopropanecarbonyl chloride (23 µl, 0.245 mmol) is added dropwise, under stirring at 0°C, to a solution of 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-

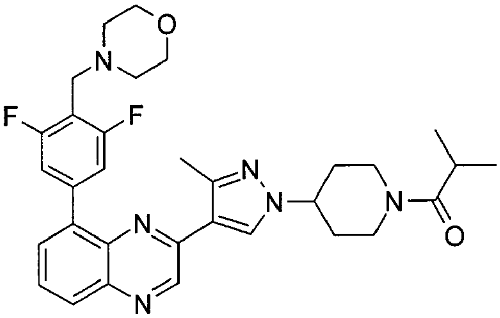
4-yl)-quinoxaline (as obtained in example 98, 120 mg, 0.245 mmol), Et_3N (103 µl, 0.734 mmol) in CH_2Cl_2. The cooling bath is then removed and the reaction mixture stirred at RT for an additional 30 min. The mixture is then diluted with de-ionized water and the phases are separated. The organic phase is washed several times with de-ionized water and the aqueous layer re-extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and purified by chromatography on a 12 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2/ (CH_2Cl_2: EtOH: NH_3 90:9:1.1) from 1:0 => 1:9) to afford the title compound as a pale yellow foam. R_t =0.852 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 559 $(M+1)^+$

Example 130: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid methyl ester



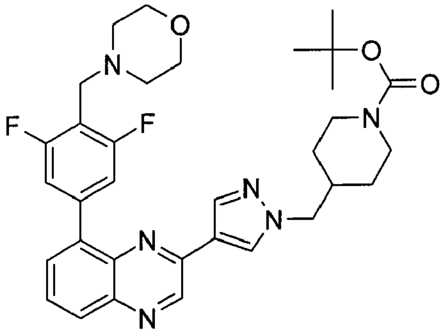
Dimethyldicarbonate (27 µl, 0.245 mmol) is added dropwise, under stirring at 0°C, to a solution of 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline (as obtained in example 98, 120 mg, 0.245 mmol) in THF. The cooling bath is then removed and the reaction mixture stirred at RT for an additional 30 min. The mixture is then diluted with de-ionized water and the phases are separated. The organic phase is washed several times with de-ionized water and the aqueous layer re-extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and purified by chromatography on a 12 g silica gel column on a Combiflash Companion™ (Isco Inc.) apparatus (gradient CH_2Cl_2/ (CH_2Cl_2: EtOH: NH_3 90:9:1.1) from 1:0 => 1:9) to afford the title compound as a pale yellow foam. R_t =0.865 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 549 $(M+1)^+$

Example 131: 1-(4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-3-methyl-pyrazol-1-yl}-piperidin-1-yl)-2-methyl-propan-1-one



The title compound is obtained analogously to example 129, but using 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(3-methyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline (as obtained in example 127) and isobutyryl chloride, R_t =0.885 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 575 $(M+1)^+$

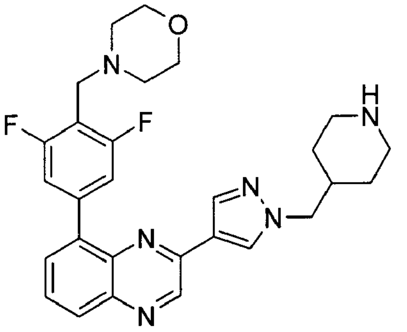
Example 132: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-ylmethyl}-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared using the same synthetic methods as described in Example 1, but utilizing 4-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester [prepared analogously to step 96.1 but utilizing 4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester, as obtained in preparation 101] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester.

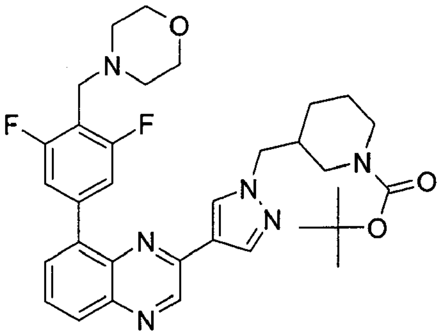
R_t =1.020 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 605 $(M+1)^+$

Example 133: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-ylmethyl-1H-pyrazol-4-yl)-quinoxaline



The title compound is obtained analogously to example 125 but using 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-ylmethyl}-piperidine-1-carboxylic acid tert-butyl ester (as obtained in example 132). R_t =0.681 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

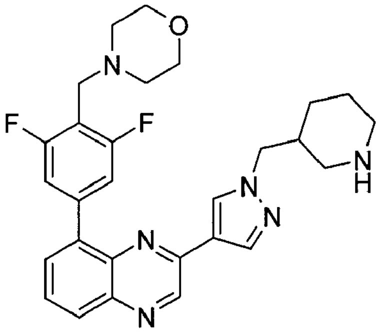
Example 134: (rac)-3-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-ylmethyl}-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared using the same synthetic methods as described in Example 1, but utilizing (rac)-3-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester [prepared analogously to step 96.1 but utilizing (rac)-3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester, as obtained in preparation 100] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester.

R_t =1.015 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 605 $(M+1)^+$

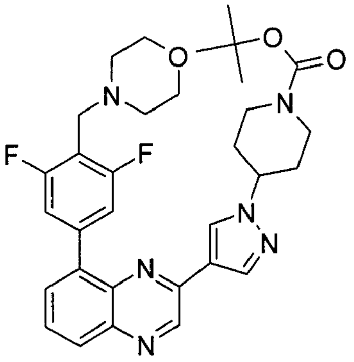
Example 135: (rac)-8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-3-ylmethyl-1H-pyrazol-4-yl)-quinoxaline



The title compound is obtained analogously to example 125 but using (rac)-3-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-ylmethyl}-piperidine-1-carboxylic acid tert-butyl ester (as obtained in example 134). R_t =0.685 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 505 $(M+1)^+$

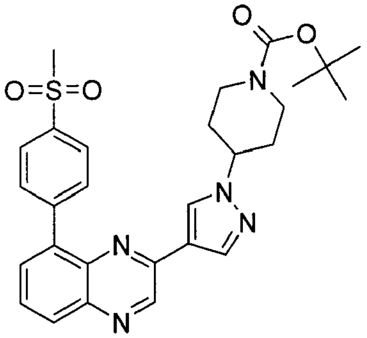
Using 4-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (as obtained in step 96.1) and the appropriate boronic acid or ester derivative the following Examples are prepared

Example 136: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



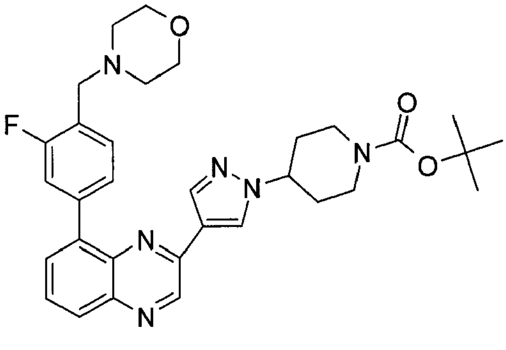
R_t =1.014 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 591 $(M+1)^+$

Example 137: 4-{4-[8-(4-Methanesulfonyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



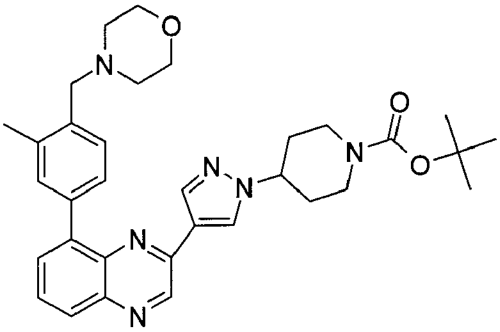
R_t =1.216 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 534 $(M+1)^+$

Example 138: 4-{4-[8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



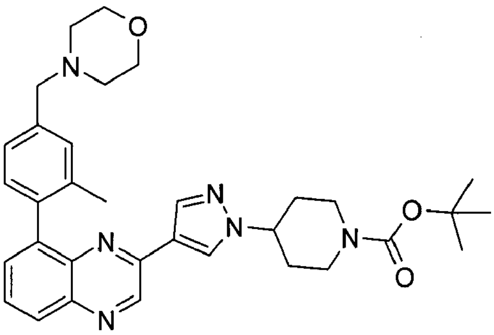
R_t =1.004 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 573 $(M+1)^+$

Example 139: 4-{4-[8-(3-Methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



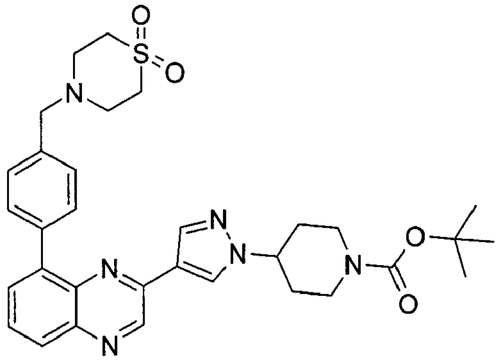
R_t =1.024 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 569 $(M+1)^+$

Example 140: 4-{4-[8-(2-Methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



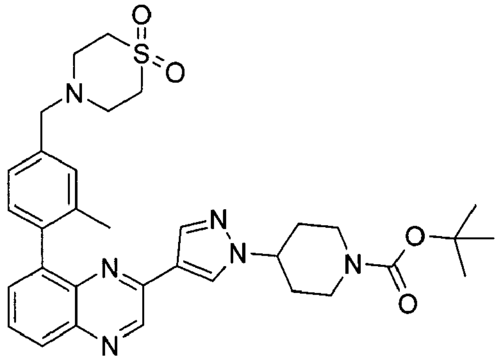
R_t =1.021 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 569 $(M+1)^+$

Example 141: 4-(4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



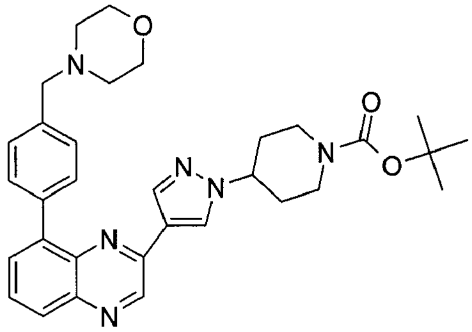
R_t =1.026 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 603 $(M+1)^+$

Example 142: 4-(4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-2-methyl-phenyl]-quinoxalin-2-yl}-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



R_t =1.044 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 617 $(M+1)^+$

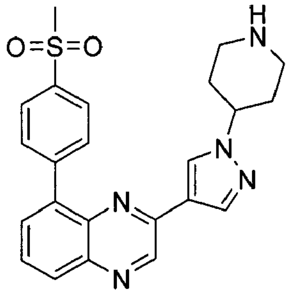
Example 143: 4-{4-[8-(4-Morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



R_t =0.994 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 555 $(M+1)^+$

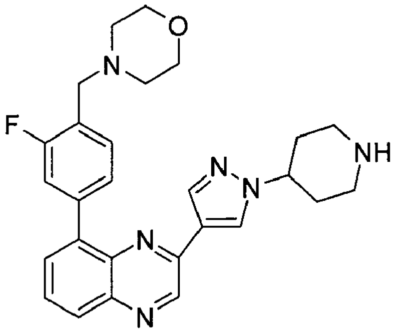
The following compounds are obtained analogously to example 125 but using the appropriate starting material from examples 137 to 143:

Example 144: 8-(4-Methanesulfonyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



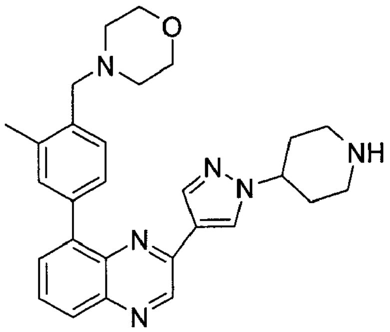
R_t =0.807 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 434 $(M+1)^+$

Example 145: 8-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



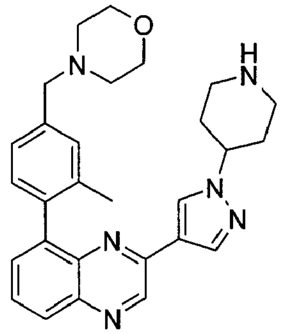
R_t =0.676 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 473 $(M+1)^+$

Example 146: 8-(3-Methyl-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



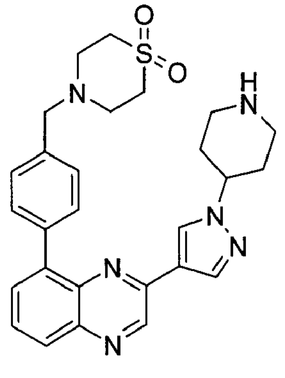
R_t =0.699 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 469 $(M+1)^+$

Example 147: 8-(2-Methyl-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



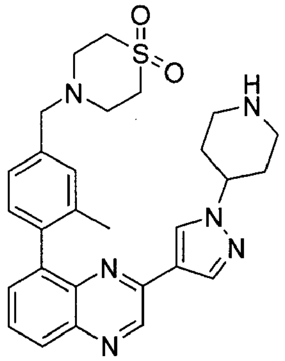
R_t =0.726 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 469 $(M+1)^+$

Example 148: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



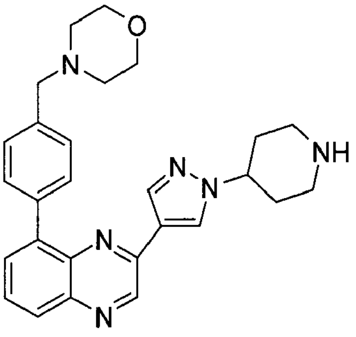
R_t =0.700 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 503 $(M+1)^+$

Example 149: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-2-methyl-phenyl]-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



R_t =0.724 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 517 $(M+1)^+$

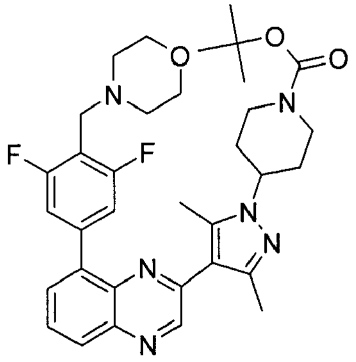
Example 150: 8-(4-Morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



R_t =0.670 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 455 $(M+1)^+$

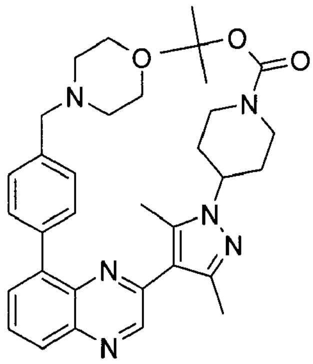
Using 4-[4-(8-Bromo-quinoxalin-2-yl)-3,5-dimethyl-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester [prepared analogously to step 96.1 but utilizing 4-[3,5-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester] and the appropriate boronic acid or ester derivative the following Examples are prepared

Example 151: 4-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-3,5-dimethyl-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



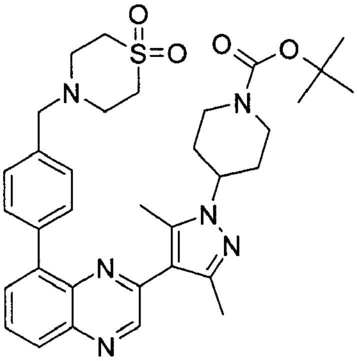
R_t =1.072 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 619 $(M+1)^+$

Example 152: 4-{3,5-Dimethyl-4-[8-(4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



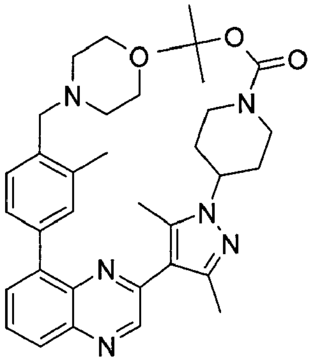
R_t =1.053 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 583 $(M+1)^+$

Example 153: 4-(4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-3,5-dimethyl-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



R_t =1.095 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 631 $(M+1)^+$

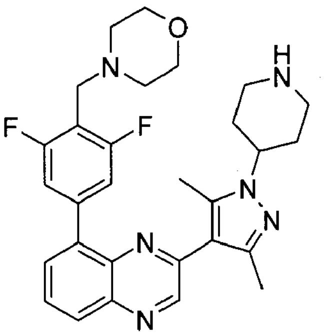
Example 154: 4-{3,5-Dimethyl-4-[8-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



R_t =1.083 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 597 $(M+1)^+$

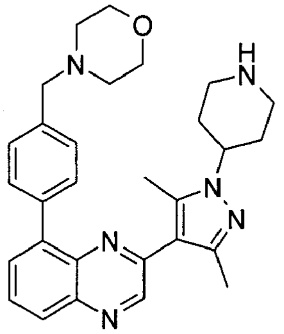
The following compounds are obtained analogously to example 125 but using the appropriate starting material from examples 151 to 154:

Example 155: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(3,5-dimethyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-quinoxaline



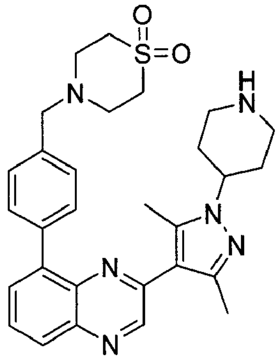
R_t =0.725 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 519 $(M+1)^+$

Example 156: 2-(3,5-Dimethyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-8-(4-morpholin-4-ylmethyl-phenyl)-quinoxaline



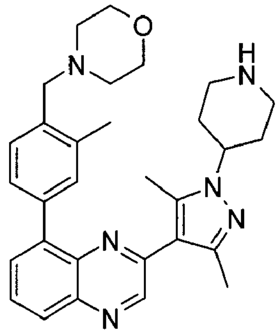
R_t =0.728 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 483 $(M+1)^+$

Example 157: 2-(3,5-Dimethyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-8-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxaline



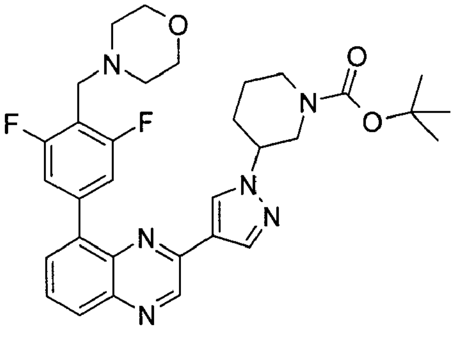
R_t =0.766 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 531 $(M+1)^+$

Example 158: 2-(3,5-Dimethyl-1-piperidin-4-yl-1H-pyrazol-4-yl)-8-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-quinoxaline



R_t =0.751 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 497 $(M+1)^+$

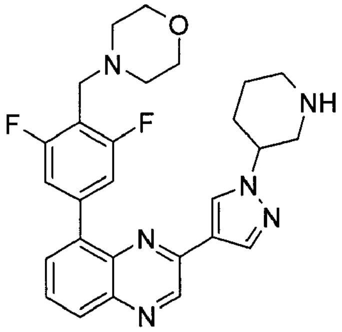
Example 159: (rac)-3-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared using the same synthetic methods as described in Example 1, but utilizing (rac)- 3-[4-(8-Bromo-quinoxalin-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester [prepared analogously to step 96.1 but utilizing (rac)-3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester, as obtained in preparation 103] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester.

R_t =1.046 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 591 $(M+1)^+$

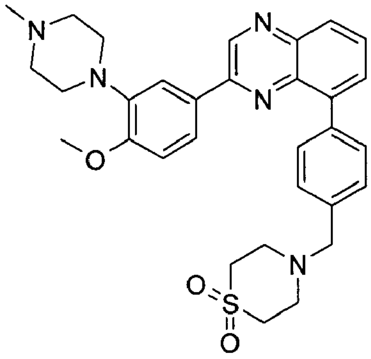
Example 160: (rac)-8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-(1-piperidin-3-yl-1H-pyrazol-4-yl)-quinoxaline



The title compound is obtained analogously to example 125 but using (rac)-3-{4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester (as obtained in example 159). R_t =0.697 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 491 $(M+1)^+$

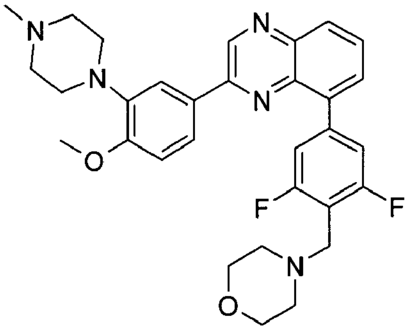
Using the same synthetic methods as described in Example 1, but utilizing 8-Bromo-2-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline [prepared analogously to step 1.5 but utilizing 1-[2-Methoxy-5-(4,4,5,5-tetramethyl -[1,3,2]dioxaborolan-2-yl)-phenyl]-4-methyl-piperazine in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 161: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-2-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



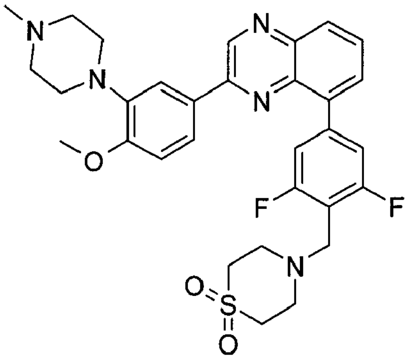
R_t = 4.81 min (HPLC conditions B); MS: 558 $(M+1)^+$

Example 162: 8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-2-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



R_t = 4.68 min (HPLC conditions B); MS: 546 $(M+1)^+$

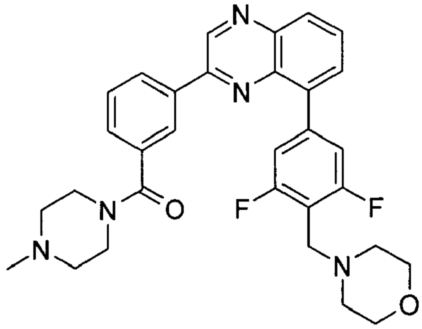
Example 163: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



R_t = 5.31 min (HPLC conditions B); MS: 594 $(M+1)^+$

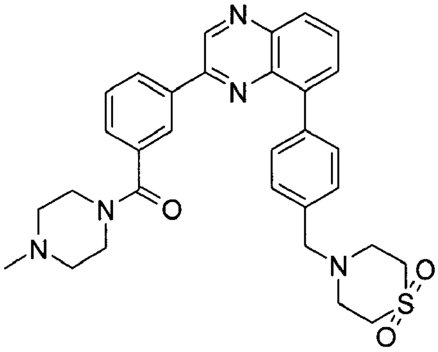
Using the same synthetic methods as described in Example 1, but utilizing [3-(8-Bromo-quinoxalin-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone [prepared analogously to step 1.5 but utilizing (4-Methyl-piperazin-1-yl)-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 164: {3-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



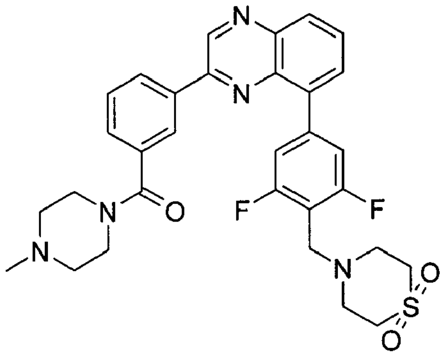
R_t = 0.55 min (HPLC conditions A); MS: 544 $(M+1)^+$

Example 165: (3-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-quinoxalin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone



R_t = 0.72 min (HPLC conditions A); MS: 556 $(M+1)^+$

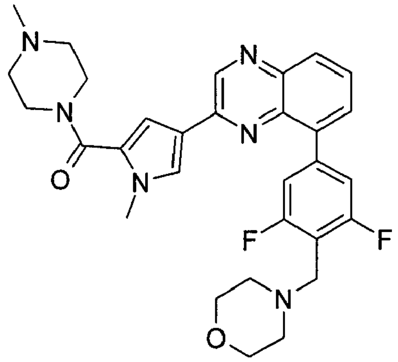
Example 166: (3-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone



R_t = 0.87 min (HPLC conditions A); MS: 592 $(M+1)^+$

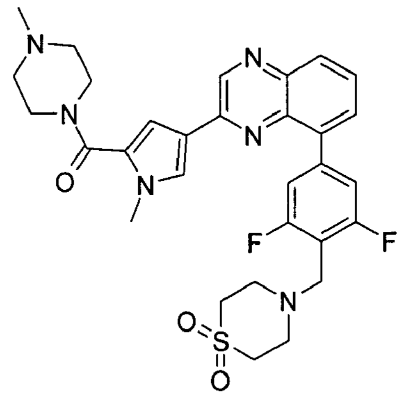
Using the same synthetic methods as described in Example 1, but utilizing [4-(8-Bromo-quinoxalin-2-yl)-1-methyl-1H-pyrrol-2-yl]-(4-methyl-piperazin-1-yl)-methanone [prepared analogously to step 1.5 but utilizing (4-Methyl-piperazin-1-yl)-[1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrol-2-yl]-methanone in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Examples

Example 167: {4-[8-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-quinoxalin-2-yl]-1-methyl-1H-pyrrol-2-yl}-(4-methyl-piperazin-1-yl)-methanone



R_t = 4.42 min (HPLC conditions B); MS: 547 $(M+1)^+$

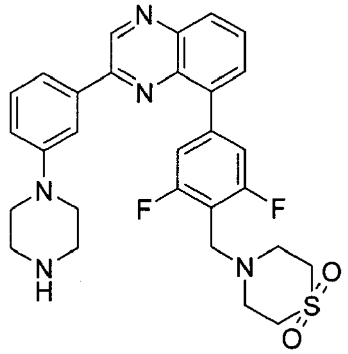
Example 168: (4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-1-methyl-1H-pyrrol-2-yl)-(4-methyl-piperazin-1-yl)-methanone



R_t = 4.98 min (HPLC conditions B); MS: 595 $(M+1)^+$

Using the same synthetic methods as described in Example 1, but utilizing 4-[3-(8-Bromo-quinoxalin-2-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl este [prepared analogously to step 1.5 but utilizing 4-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester in lieu of 3,4,5-trimethoxyphenylboronic acid] in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester derivative leads to the following Example

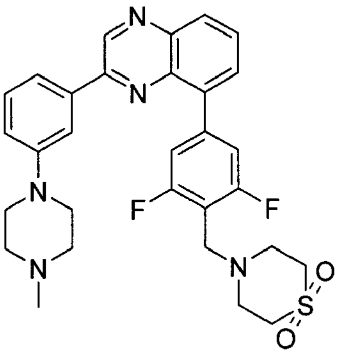
Example 169: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-(3-piperazin-1-yl-phenyl)-quinoxaline



The title compound is obtained after deprotection of 4-(3-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester with TFA in CH_2Cl_2 at RT.

R_t = 0.95 min (HPLC conditions A); MS: 550 $(M+1)^+$

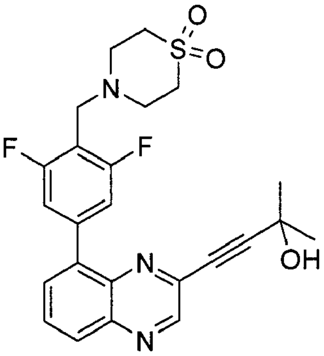
Example 170: 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-[3-(4-methyl-piperazin-1-yl)-phenyl]-quinoxaline



A solution of 8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-2-(3-piperazin-1-yl-phenyl)-quinoxaline (as obtained in example 169, 79 mg, 0.137 mmol) in MeOH (3 ml) and CH_2Cl_2 (1.5 ml) is treated with HCHO (41 µl, 0.550 mmol, 37% in H_2O/MeOH 9:1) and $NaBH_3CN$ (35 mg, 0.546 mmol) at RT for 2 h. The reaction mixture is concentrated under reduced pressure. The residue is purified by reverse phase prep-HPLC (Waters) to afford the title compound as a yellow solid.

R_t = 0.94 min (HPLC conditions A); MS: 564 $(M+1)^+$

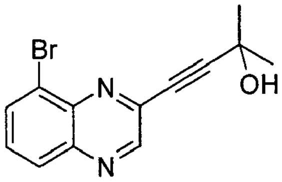
Example 171: 4-{8-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-quinoxalin-2-yl}-2-methyl-but-3-yn-2-ol



The title compound is prepared using the same synthetic methods as described in Example 1, but utilizing 4-(8-Bromo-quinoxalin-2-yl)-2-methyl-but-3-yn-2-ol (as obtained in step 171.1) in lieu of 8-Bromo-2-(3,4,5-trimethoxy-phenyl)-quinoxaline and the appropriate boronic acid or ester.

R_t =0.945 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 472 $(M+1)^+$

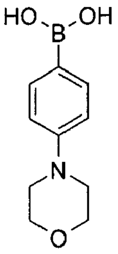
Step 171.1: 4-(8-Bromo-quinoxalin-2-yl)-2-methyl-but-3-yn-2-ol.

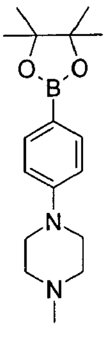


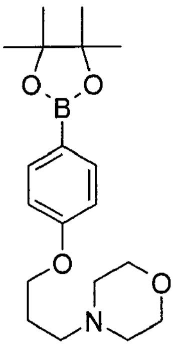
A microwave tube is charged with 200 mg (0.821 mmol) of 8-Bromo-2-chloro-quinoxaline, 159 µl (1.64 mmol) of 2-Methyl-but-3-yn-2-ol, 231 µl (1.64 mmol) of Et_3N, 6.26 mg (0.0329 mmol) of CuI and 11.8 mg (0.0164 mmol) of $Pd(PPh_3)_2Cl_2$. After several cycles of vacuum/ purge with argon, 5 ml of n-BuOH are added. The reaction mixture is then stirred at RT for 30 min. The reaction mixture is poured onto a solution of $NaHCO_3$ and diluted with EtOAc and the phases are separated. The organic phase is washed several times with de-ionized water and the aqueous layer re-extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and the filtrate is concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and purified by chromatography (silicagel, hexane: EtOAc = 1:1) to afford the title compound as a brown oil, R_t = 1.026 min (Acquity UPLC BEH C18, 2.1x50mm, 1.7 micron, detection 215nM, 0.1 min 2% CH_3CN in H_2O , 2% to 100% CH_3CN in H_2O in 1.5min, 0.4 min 100% CH_3CN + 0.1% TFA, flow rate 1.0ml/min); MS: 291 (M+1, $^{79}Br)^+$.

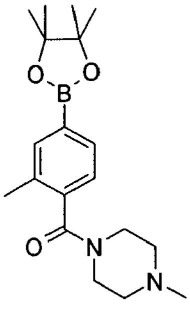
Example 172:

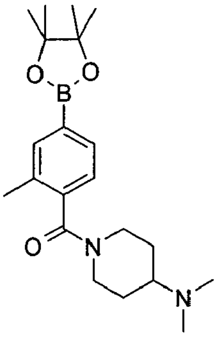
Further Example compounds can be obtained in accordance with the procedures described herein by substitution at the 2-position of 8-bromo-2-chloro-quinoxaline by one of the following boronic acid or ester derivatives:

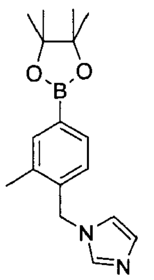


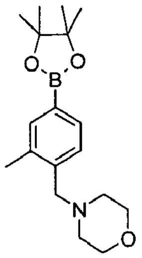


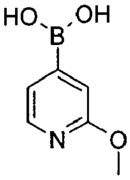


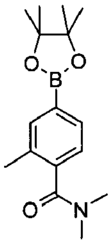


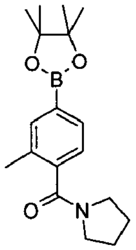


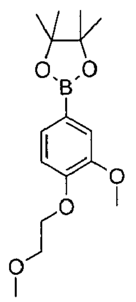


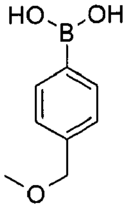


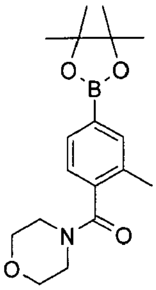


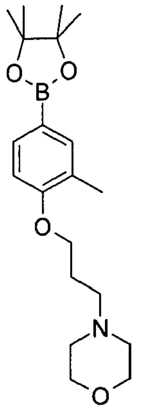


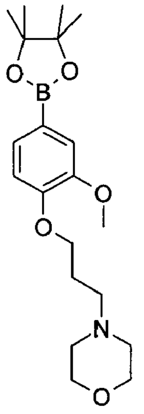


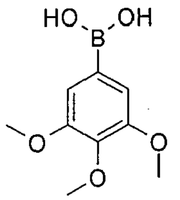


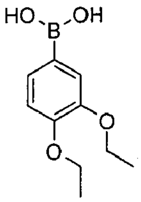


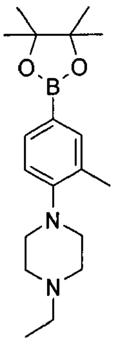


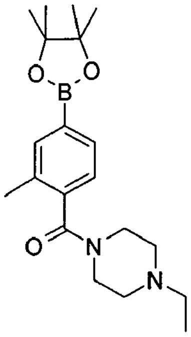


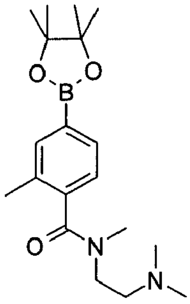


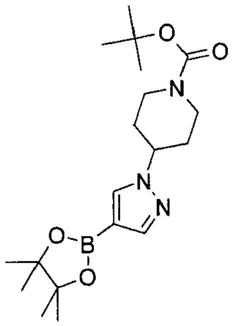


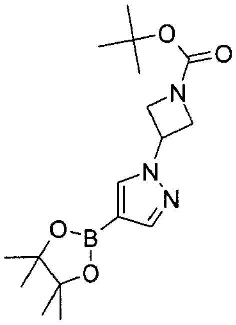


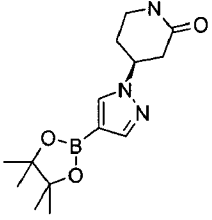


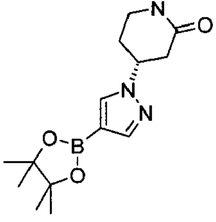


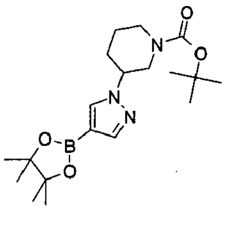


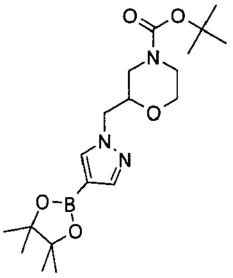
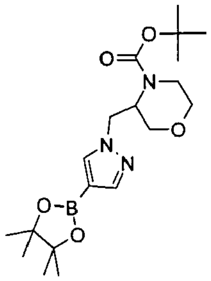
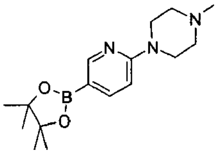
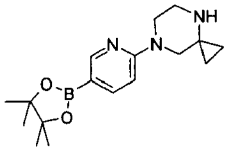
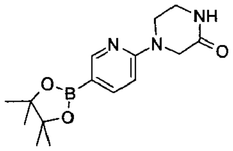
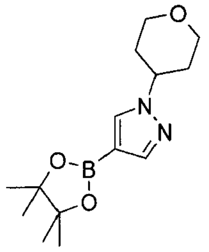
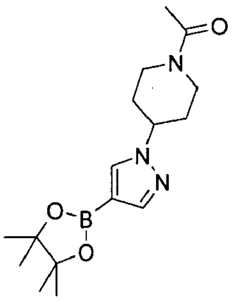
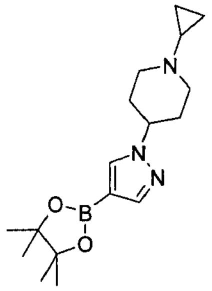
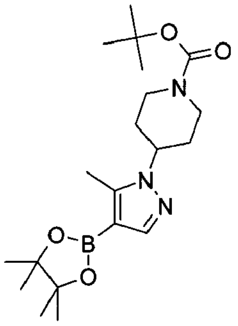
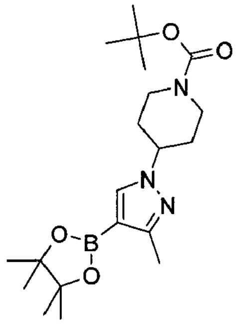
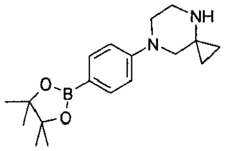
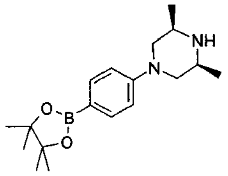
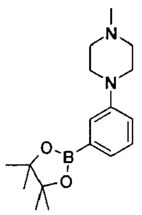
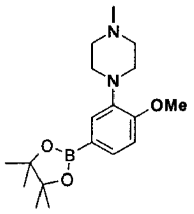
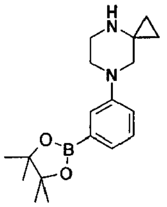




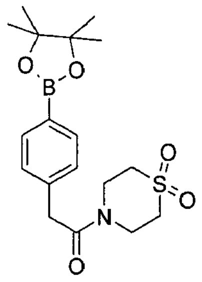
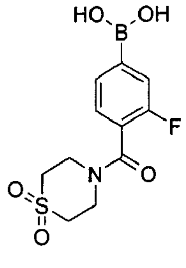
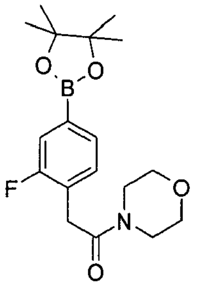
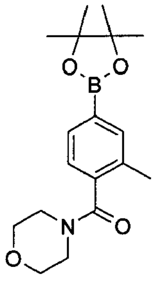
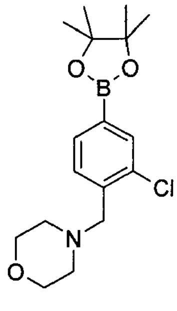


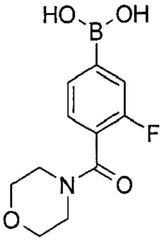
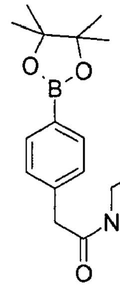
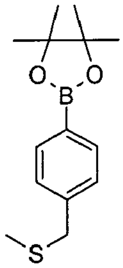
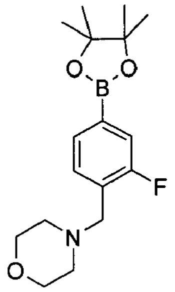
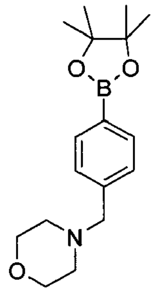
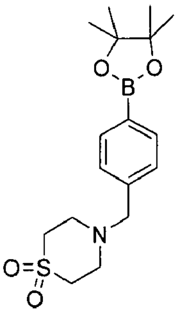
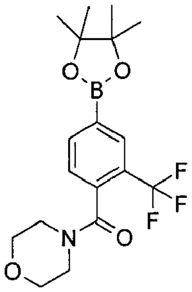
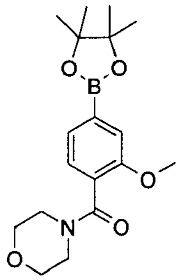
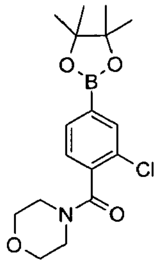
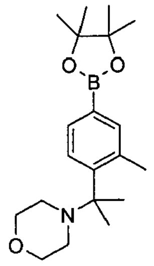
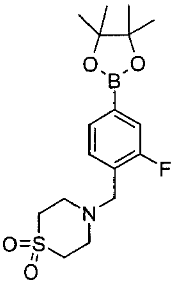
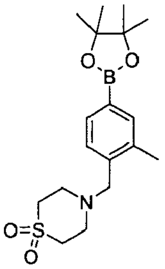
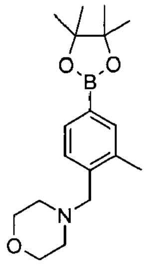
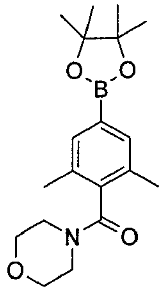
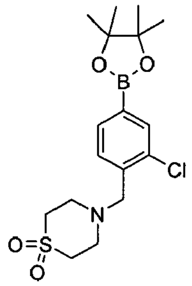
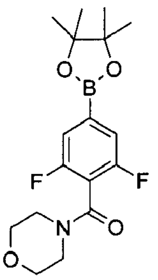
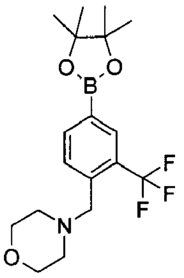
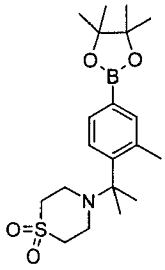
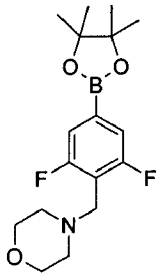
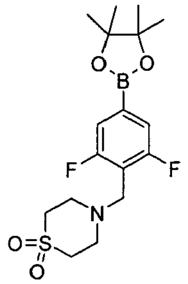
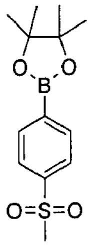
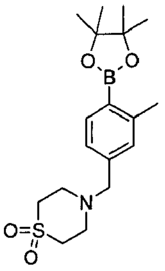
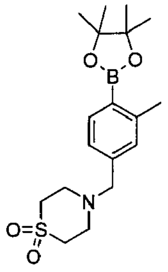
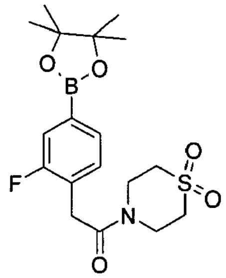
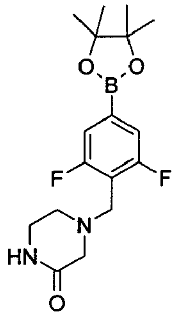




followed by substitution at the 8- position by one of the following boronic acid or ester derivatives:

Example 173: EPK JAK-family kinases profiling assays

The efficacy of the compounds of the invention as inhibitors of JAK-family kinases: JAK1-3 and TYK kinase activity can be demonstrated as follows:

All four kinases of the JAK- family kinases were used as purified recombinant GST-fusion proteins, containing the active kinase domains. GST-JAK1(866-1154), GST-JAK3(811-1124), and GST-TYK2(888-1187) were expressed and purified by affinity chromatography at the EPK biology unit. GST-JAK2(808-1132) was purchased from Invitrogen (Carlsbad, USA, #4288).

The kinase assays were based on the Caliper mobility shift assay using the LabChip 3000 systems. This technology is similar to capillary electrophoresis and uses charge driven separation of substrate and product in a microfluidic chip.

All kinase reactions were performed in 384 well microtiter plates in a total reaction volume of 18 µl. The assay plates were prepared with 0.1 µl per well of test compound in the appropriate test concentration, as described under the section "preparation of compound dilutions". The reactions were started by combining 9 µl of substrate mix (consisting of peptide and ATP) with 9 µl of kinase dilution. The reactions were incubated for 60 minutes at 30°C and stopped by adding 70 µl of stop buffer (100 mM Hepes, 5% DMSO, 0.1% Coating reagent, 10 mM EDTA, 0.015% Brij 35).

Fluorescently labeled synthetic peptides were used as substrates in all reactions. A peptide derived from the sequence of IRS-1 (IRS-1 peptide, FITC-Ahx-KKSRGDYMTMQIG-NH2 (SEQ ID NO: 1)) was used for JAK1 and TYK2 and a peptide named JAK3tide (FITC-GGEEEEYFELVKKKK-NH2 (SEQ ID NO: 2)) for JAK2 and JAK3. Specific assay conditions are described in Table1:

Table1: Assay conditions of individual kinase assays

Kinase	JAK1	JAK2	JAK3	TYK2
Buffer	50 mM Hepes pH 7.5, 0.02% Tween	50 mM Hepes pH 7.5, 0.02% Tween	50 mM Hepes pH 7.5, 0.02% Tween	50 mM Hepes pH 7.5, 0.02% Tween

Kinase	JAK1	JAK2	JAK3	TYK2
	20, 1 mM DTT, 0.02% BSA, 12 mM MgCl2	20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2	20, 1 mM DTT, 0.02% BSA, 1.5 mM $MgCl_2$	20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2
DMSO	0.6 %	0.6 %	0.6 %	0.6 %
Kinase conc.	50 nM	1.8 nM	6 nM	40 nM
Substrate peptide conc.	5 µM	2 µM	2 µM	5 µM
ATP conc.	40 µM	20 µM	80 µM	30 µM

The terminated reactions were transferred to the Caliper LabChip 3000 reader and the turnover of each reaction was measured by determining the substrate/product ratio.

Preparation of compound dilutions

Test compounds were dissolved in DMSO (10 mM) and transferred into 1.4mL flat bottom or V-shaped Matrix tubes carrying a unique 2D matrix chip by individual compound hubs. The numbers of these chips were distinctively linked to the individual compound identification numbers. The stock solutions were stored at –20°C if not used immediately. For the test procedure the vials were defrosted and identified by a scanner whereby a working sheet was generated that guided the subsequent working steps.

Compound dilutions were made in 96 well plates. This format enabled the assay of maximally 40 individual test compounds at 8 concentrations (single points) including 4 reference compounds. The dilution protocol included the production of pre-dilution plates, master plates and assay plates:

Pre-dilution plates: 96 polypropylene well plates were used as pre-dilution plates. A total of 4 pre-dilution plates were prepared including 10 test compounds each on the plate positions A1-A10, one standard compound at A11 and one DMSO control at A12. All dilution steps were done on a HamiltonSTAR robot.

Master plates: 100µL of individual compound dilutions including standard compound and controls of the 4 “pre-dilution plates” were transferred into a 384 “master plate” including the following concentrations 1'820, 564, 182, 54.6, 18.2, 5.46, 1.82 and 0.546μM, respectively in 90 % of DMSO.

Assay plates: Identical assay plates were then prepared by pipetting 100 nL each of compound dilutions of the master plates into 384-well "assay plates". In the following the compounds were mixed with 9μL of assays components plus 9μL enzyme corresponding to a 1:181 dilution steps enabling the final concentration of 10, 3.0, 1.0, 0.3, 0.1, 0.03, 0.01 and 0.003μM, respectively. The preparation of the master plates were handled by the Matrix PlateMate Plus robot and replication of assay plates by the HummingBird robot.

IC_{50} values in the range of from about 3nM to about 10μM, e.g. from about 3nM to about 5μM, can be found with compounds of the invention according to formula (I).

Exemplified compounds show inhibitory activities with respect to the JAK family kinases with IC_{50} values shown in Table 2.

On the basis of these studies, a compound of the invention may be used with therapeutic efficacy especially against disorders dependent on protein kinase, especially proliferative diseases mediated by JAK-family kinase activity.

Example 174: inhibition of the JAK/STAT pathway

The activity of the compounds of the invention as inhibitors of the JAK/STAT pathway can be demonstrated as follows:

The medium-throughput (96-well format), robust and reproducible cellular assay can be routinely used to assess the functional activation of Janus Kinases (JAKs), based on the nuclear translocation of their substrate, Signal Transducer and Activator of Transcription (STAT). Nuclear translocation can be monitored in HT1080 fibrosarcoma cells stably transfected with STAT1 fused to Green Fluorescence Protein (GFP). Stimulation with interferon-γ (IFN-γ) results in JAK1/JAK2-dependent nuclear translocation of STAT1-GFP that can be quantified using the Cellomics Cyto/NucTrans software package. This assay may be used to provide an assessment of the nuclear-cytoplasmic differential (NCD) of GFP-STAT1 using Hoechst dye to define the boundaries of the nucleus.

Cloning of STAT1 into pEGFP-N2:

STAT1 cDNA (GenBank Accession No. NM_007315) can be cloned in-frame with the Green Fluorescence Protein in pEGFP-N2 (Genebank Accession No. U57608, Clontech Cat. No. 6081-1) to obtain the final plasmid pEGFP-N2 STAT1 with an in/frame fusion of GFP at the carboxy-terminus of STAT1.

Generation of HT1080 Fibrosarcoma Cells stably expressing GFP-STAT1:
HT1080 fibrosarcoma cells may be obtained from ATCC (Cat. No. CCL-121) and can be cultured in alpha Modified Eagle Medium (Gibco Cat. No. 41061-029) with 10% FCS (Fetalclone II, Gibco, Cat. No. SH60066.03). Cells can be transfected with pEGFP-N2 STAT1 using Fugene 6 Transfection Reagent (Roche Diagnostics, Cat. No. 1 815 091) following the manufacturers protocol (3 μl of Fugene:1 μg of DNA). 24 hours after transfection the medium can be replaced and selected in 1 mg/ml Geneticin (Gibco, Cat. No. 1031-019).

Preparation of compound stocks:
Compounds can be dissolved in DMSO to a final stock concentration of 10 mM and stored as aliquots at 4 °C. Compounds may be pre-diluted in 100 % DMSO at 10 mM, 3 mM 1 mM, 0.3 mM, 0.1 mM, 0.03 mM, 0.01 mM and 0.003 mM. Subsequently, compounds may be diluted in medium and added in 50μl to the cells. The final compound concentrations tested may be 10 μM, 3 μM 1 μM, 0.3 μM, 0.1 μM, 0.03 μM, 0.01 μM and 0.003 μM and the final DMSO concentration can be 0.1 %.

Cellomics Analysis of Nuclear Translocation of STAT-1-GFP Cell stimulation and staining for Cellomics Analysis:
HT1080 fibrosarcoma cells may be cultured in alpha Modified Eagle Medium (Gibco Cat. No. 41061-029) with 10% FCS (Fetalclone II, Gibco, Cat. No. SH60066.03), and 400 μg/ml G418 (Gibco, Cat. No. 10131-027).
HT1080 STAT1-GFP cells may be plated at a density of 10,000 cells per well in clear-bottom black 96-well Packard View-Plates™ (Cat. No. 6005182). 16-24 hours later, the cells can be treated for 2 hours with 100 ng/ml IFN-γ (R&D Systems Cat. No. 285-IF), washed twice in pre-warmed PBS and fixed in 200 μl of pre-warmed fixation solution (PBS, 3.7% Formaldehyde (Sigma, Cat. No. F-1635)) for 10 minutes. The plates may be washed twice in 200 μl PBS and incubated, protected from light, in 100 μl of DNA-staining solution (PBS, 0.5 μg/ml Hoechst-33342 (Sigma, Cat. No. B-2261)) for 1 minute. The plates may then be

washed once in PBS, and 200 μl PBS finally added per well. The plates, being finally covered with a black adhesive, may be either read directly or stored at 4°C for later imaging. Where appropriate, the compounds may be added 30 min before stimulation with IFN-γ.

STAT1-GFP nuclear translocation measurement by Cellomics automated fluorescence microcopy imaging and analysis:

The plates can be read on a Cellomics® ArrayscanII automated fluorescence microscope plate reader equipped with a Mercury-Xenon white light illumination source and a Zeiss Axiovert inverted microscope, using the XF100 dichroic/emission filter cube and matching excitation filters, 10x magnification, and a 0.3 numerical aperture objective. Image acquisition and analysis can be performed using a customized protocol based on the 'NuclearTranslocation' Bioapplication (for details, see Appendices). For each well, multiple images (fields) can be acquired until a minimum of 1000 cells are counted using two 2 channels: Channel 1 (Hoechst) = focus + nuclear mask, Channel 2 (GFP) = signal quantification in mask areas as outlined below.

Nuclei may be first identified based on the Hoechst staining and a mask generated for each nucleus that then serves as a template to generate a circle (eroded inwards by 1 pixel) and a 3 pixel-wide collar-like ring (off-set outwards by 1 pixel), in which the nuclear and cytoplasmic intensity of GFP, respectively, are quantified in the corresponding channel. High content analysis yields numerous measurements per cell and the GPF intensity differential between the nuclear and the cytoplasmic masks may be chosen as a measure of sub-cellular GFP-STAT1 relocation. The resulting values may be averaged for all cells in the well to return a single measurement plus standard deviation.

To generate IC_{50} values, the nuclear-cytoplasmic GFP-STAT1 differential of untreated cells may be used as a baseline and the following equation used to determine the percentage increase in nuclear translocation:

Percentage = 100 * (NCD Compound pre-treated INF-γ-stimulated - NCD Untreated)/(NCD DMSO-pretreated IFN-γ stimulated – NCD Untreated).

Table 2: JAK1-3 and TYK kinase inhibitory activities and JAK/STAT pathway inhibitory activities

Ex n°	JAK1 IC$_{50}$ [umol l^{-1}]	JAK2 IC$_{50}$ [umol l^{-1}]	JAK3 IC$_{50}$ [umol l^{-1}]	TYK2 IC$_{50}$ [umol l^{-1}]	STAT1translo IC$_{50}$ [umol l^{-1}]
1	N.D.	0.082	4.4	N.D.	N.D.
2	N.D.	0.12	5.4	N.D.	N.D.
3	N.D.	0.085	9.4	N.D.	10.802
4	N.D.	0.22	> 10	N.D.	N.D.
5	N.D.	0.11	> 10	N.D.	N.D.
6	N.D.	0.067	4.5	N.D.	5.366
7	N.D.	0.095	8.422	N.D.	N.D.
8	N.D.	0.11	> 10	N.D.	N.D.
9	N.D.	0.17	> 10	N.D.	N.D.
10	N.D.	0.093	> 10	N.D.	N.D.
11	0.039	0.0090	0.81	0.26	0.7025
12	0.18	0.0525	> 10	N.D.	N.D.
13	0.027	0.0051	0.33	0.235	0.47
14	N.D.	0.08	4.3	N.D.	5.095
15	N.D.	0.081	> 10	N.D.	N.D.
16	N.D.	0.019	1.5	N.D.	N.D.
17	N.D.	0.013	1.3	N.D.	1.345
18	0.23	0.038	2.3	N.D.	0.3395
19	0.059	0.018	0.8	N.D.	1.84
20	0.16	0.024	1.2	N.D.	5.775
21	1.8	0.21	5.2	N.D.	> 10
22	N.D.	0.073	> 10	N.D.	8.195
23	N.D.	0.2	> 10	N.D.	N.D.
25	N.D.	0.042	> 10	N.D.	> 10
26	N.D.	0.022	0.7	N.D.	0.7725
27	N.D.	0.034	1.7	N.D.	0.198
28	N.D.	0.012	> 10	N.D.	2.18
29	N.D.	0.1	> 10	N.D.	11.35
30	N.D.	0.011	1.5	N.D.	3.805
31	N.D.	0.0073	1.1	N.D.	3.515
32	0.57	0.084	2.7	N.D.	7.788
33	N.D.	0.032	3.1	N.D.	9.885

34	0.027	0.0041	0.49	0.088	0.338
35	0.094	0.0119	1.863	0.52	1.72
36	0.041	0.017	0.94	N.D.	3.86
37	0.068	0.014	0.78	N.D.	3.075
38	N.D.	0.023	4.2	N.D.	N.D.
39	N.D.	0.19	> 10	N.D.	N.D.
40	0.0784	0.0073	0.627	0.29	0.160
41	0.13	0.0063	0.64	N.D.	0.3455
42	0.715	0.018	2.15	1.45	0.857
43	0.42	0.027	0.87	0.715	1.127
44	0.15	0.00655	0.405	0.24	0.049
45	0.19	0.03	2.2	N.D.	2.4015
46	0.11	0.02	1.6	N.D.	2.8155
47	N.D.	0.038	> 10	N.D.	
48	0.0099	< 0.003	0.077	N.D.	0.15
49	0.26	0.038	4.4	N.D.	1.225
50	0.038	0.00705	> 10	1.6	1.65
51	0.12	0.0315	> 10	> 10	2.045
52	0.0975	0.032	1.1	0.985	2.95
53	0.012	< 0.003	0.215	0.0935	0.15
54	0.017	< 0.003	0.065	N.D.	0.14
55	1.7	0.09	4.2	N.D.	3.144
56	0.15	0.012	0.57	N.D.	0.471
57	0.08	< 0.003	0.17	N.D.	0.163
58	0.09	0.011	0.32	N.D.	0.2205
59	0.52	0.02	1.95	N.D.	0.635
60	1.6	0.11	3.8	N.D.	4.75
61	0.165	0.015	1.4	N.D.	0.235
62	0.0445	0.0057	0.33	N.D.	0.082
63	0.37	0.0775	4.3	1.45	0.9865
64	0.068	0.00495	0.29	0.165	0.0465
65	0.24	0.0155	0.86	N.D.	2.185
66	0.14	0.00605	0.25	N.D.	1
67	0.0965	< 0.003	0.405	N.D.	0.475
68	2.3	0.109	6.85	N.D.	4.89
69	0.075	0.0067	0.89	N.D.	0.53
70	0.36	0.0305	1.75	1.35	0.5635

71	0.16	0.0081	0.79	0.51	2.4795
72	0.11	0.0057	0.67	N.D.	1.115
73	0.19	0.028	0.37	N.D.	> 10
74	0.31	0.025	1.3	N.D.	2.6095
75	0.41	0.034	1.7	N.D.	> 10
76	0.69	0.0595	4.1	N.D.	5.99
77	N.D.	0.13	9.8	N.D.	
78	N.D.	0.15	> 10	N.D.	9.69
79	N.D.	0.52	> 10	N.D.	
80	3.8	0.075	4.55	N.D.	1.549
81	1.15	0.0165	0.78	N.D.	0.389
82	0.49	0.014	1.25	N.D.	0.9455
83	0.0335	0.00625	0.89	0.27	2.08
84	0.0585	0.0055	0.975	0.27	1.46
85	0.0125	0.00325	0.22	0.115	0.24
86	0.00665	< 0.003	0.11	0.038	0.093
87	0.225	0.0335	3.5	0.72	1.32
88	0.027	0.00655	0.84	0.113	0.7
89	0.135	0.034	3.95	0.45	1.336
92	1.385	0.043	4.9	3.65	2.135
93	0.185	0.022	1.25	0.67	3.01
94	0.455	0.027	2.15	0.985	1.53
95	0.018	< 0.003	0.0735	0.04	0.105
96	0.053	< 0.003	0.26	0.0505	0.0355
97	0.72	0.0195	9.15	0.51	0.495
98	0.3898	0.011	5.4	0.5434	0.2025
99	0.87	0.022	4.85	0.805	1.36
100	1.4	0.13	N.D.	1.2	12.6
101	0.575	0.014	1.025	1.45	N.D.
102	1.216	0.074	5.333	2.7275	0.0315
103	1.15	0.0305	3.6	1.2	0.824
104	0.052	< 0.003	0.39	0.13	0.42
105	0.81	0.032	1.8	0.985	0.895
106	0.365	0.082	0.195	1.9725	0.2015
107	1.35	0.0955	9.8	2.95	2.4665
108	0.254	0.0245	2.4	0.417	0.15
109	0.15	0.024	N.D.	0.36	3.065

110	5.55	0.575	> 10	9.3	1.588
111	0.92	0.1045	9.3	1.7	1.232
112	5.35	0.32	> 10	> 10	13.6
113	0.615	0.0285	3.3	1.15	1.935
114	0.25	0.0115	1.65	0.345	6.385
115	0.0725	0.0093	1.6	0.48	1.44
116	0.243	0.008	2.9	0.437	N.D.
117	0.0765	< 0.003	1.035	0.125	0.06
118	0.47	0.025	> 10	0.955	0.36
119	0.25	0.00985	6.4	0.28	0.34
120	0.13	0.013	N.D.	0.35	1.73
121	0.2	0.0038	N.D.	0.23	N.D.
122	0.475	0.00935	3.25	0.54	N.D.
123	0.135	0.005	1.95	0.17	0.18
125	0.31	<0.003	N.D.	0.21	0.369
127	0.066	<0.003	N.D.	0.038	0.086
128	0.13	<0.003	N.D.	0.16	0.196
129	0.078	<0.003	N.D.	0.096	0.162
130	0.15	0.0034	N.D.	0.2	0.163
131	0.05	<0.003	N.D.	0.033	0.09
133	0.55	0.0054	N.D.	0.75	0.84
135	0.24	0.0061	N.D.	0.51	1.35
136	0.29	0.0046	N.D.	0.26	0.532
144	0.96	0.025	N.D.	0.97	7.655
145	0.25	0.01	N.D.	0.3	0.685
146	0.84	0.0092	N.D	0.57	3.39
147	1.5	0.097	N.D	1	N.D.
148	0.073	0.0034	N.D	0.11	0.73
149	0.65	0.051	N.D	0.9	9.56
150	0.83	0.03	N.D	0.83	4.275
155	3.4	0.063	N.D	7.6	N.D
156	>10	0.95	N.D	>10	N.D
157	3.6	0.14	N.D	6.4	N.D
158	>10	0.65	N.D	>10	N.D
160	0.36	0.0064	N.D	0.4	N.D
161	0.11	<0.003	N.D	0.48	N.D
162	0.069	0.0057	N.D	0.36	N.D

163	0.077	<0.003	N.D	0.088	N.D
164	0.3	0.05	N.D	2	N.D
165	0.16	0.074	N.D	1.2	N.D
166	0.07	0.011	N.D	0.27	N.D
167	0.053	0.0081	N.D	0.18	N.D
168	0.016	<0.003	N.D	0.03	N.D
169	0.017	<0.003	N.D	0.026	N.D
170	0.021	0.004	N.D	0.14	0.296
171	0.44	0.07	N.D	2	N.D

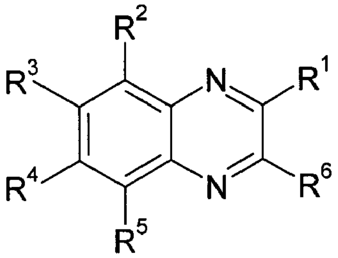
N.D. = not determined.

Example 175: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows: 250 g pulverized active ingredient is suspended in 2L Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^2 is aryl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^8;

R^3, R^4 and R^5 are each independently hydrogen or R^9;

R^6 is hydrogen; and

R^7, R^8 and R^9 are each independently selected from organic and inorganic substituents;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound of formula (I) as defined in claim 1, wherein R^1 is substituted with at least one R^7 and R^2 is substituted with at least one R^8.

3. A compound of formula (I) as defined in claim 1 or claim 2, wherein R^2 is aryl.

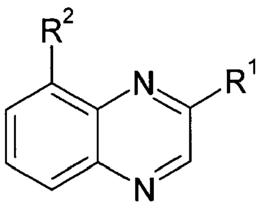
4. A compound of formula (I) as defined in claim 3, wherein R^2 is phenyl.

5. A compound of formula (I) as defined in any one of claims 1 to 4, wherein R^1 is heterocyclyl.

6. A compound of formula (I) as defined in claim 5, wherein R^1 is pyridinyl or pyrazolyl.

7. A compound of formula (I) as defined in any one of claims 1 to 6, wherein R^3 is H.

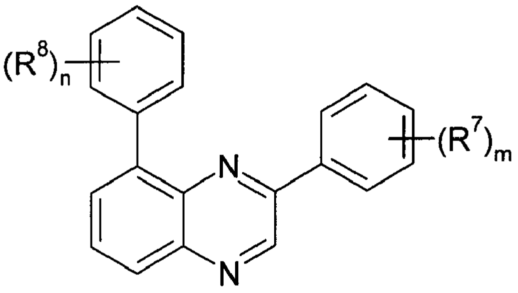
8. A compound of formula (I) as defined in any one of claims 1 to 7, wherein the compound is of the formula (II):



(II)

or a pharmaceutically acceptable salt or prodrug thereof.

9. A compound of formula (I) as defined in claim 8, wherein the compound is of the formula (IV):



(IV)

wherein m and n are each independently 1, 2, 3, 4 or 5;
or a pharmaceutically acceptable salt or prodrug thereof.

10. Use of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the treatment, prevention or delay or progression of a proliferative or immunological disease

11. Use according to claim 10, wherein the disease is a proliferative disease selected from tumor diseases, leukaemias, polycythemia vera, essential thrombocythemia and myelofibrosis with myeloid metaplasia.

12. Use according to claim 10, wherein the disease is an immunological disease selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes.

13. A compound of formula (I) as defined in claims 1 to 9, or a pharmaceutically acceptable salt or prodrug thereof, for therapeutic use.

14. A pharmaceutical formulation comprising a compound of formula (I) as defined in claims 1 to 9, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier or excipient.

15. A formulation according to claim 14, further comprising one or more antiproliferative, cytostatic or cytotoxic compounds.

16. A method of treating, preventing or delaying progression of a proliferative or immunological disease in a patient, comprising administering a therapeutically effective amount of a quinoxaline compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or prodrug thereof.