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(54) Title: [1,2,4]TRIAZOLO[4,3-A]QUINOXALINES AS DUAL PDE2/PDE10 INHIBITORS

(57) Abstract: The present invention relates to novel compounds as dual PDE2/PDE10 inhibitors. Separate aspects of the invention are directed to pharmaceutical compositions comprising said compounds and uses thereof.



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[1,2,4]TRIAZOLO[4,3-A]QUINOXALINES AS DUAL PDE2/PDE10 INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to novel therapeutic agents for the treatment of neurological and psychiatric disorders. Separate aspects of the invention are directed to pharmaceutical compositions comprising said compounds and uses thereof.

BACKGROUND ART

10 Phosphodiesterases (PDEs) are a family of enzymes which are subdivided into 11 distinct families according to structural and functional properties. PDEs metabolically inactivate widely occurring intracellular second messengers, cAMP and cGMP. On the basis of substrate specificity, the PDE families can be divided into three groups: the cAMP-specific PDEs, which include PDE4, 7 and 8; the cGMP-selective enzymes PDE5, 6 and 9; and the dual-substrate PDEs, PDE1, 2 and 3, as well as PDE10 and 11.

15 Phosphodiesterase 2A (PDE2A) is a dual substrate enzyme with higher affinity for cGMP although it may metabolize either cAMP or cGMP depending on the tissue. Although expressed in the periphery, the highest expression levels of PDE2A are in the brain. An immunohistochemical study demonstrates a consistent pattern of PDE2A expression in the brain across mammalian species including humans (Stephenson, et al. J. Histochem. Cytochem. 2009, 57, 933). PDE2 expression is shown to be prominent
20 in regions associated with cognitive function and mood control, including the cortex, striatum, hippocampus, amygdala and the habenula.

The selective PDE2A inhibitor, Bay 60-7550, preferentially increases cGMP in primary neuronal cultures and hippocampal slices. Bay 60-7550 also increases long term potentiation (LTP) induction in rat hippocampal slices. Consistent with its biochemical and electrophysiological effects, Bay 60-7550
25 was found to be active in novel object and social recognition tasks (Boess, et al. Neuropharmacology 2004, 47, 1081). Recent studies indicate that PDE2A inhibition may also efficacy in the treatment of anxiety states (Masood, et al. J. Pharmacol. Exp. Ther. 2009, 331, 699). Induction of oxidative stress in mice by depletion of central glutathione levels with buthionine sulfoximine (BSO) results in an increase in a number of anxiety-like behaviours assessed by open field time and the elevated plus maze assays.
30 These effects were reversed by treatment with Bay 60-7550.

Phosphodiesterase 10A (PDE10A) is another dual-specificity enzyme that is expressed in the neurons in the striatum, n. accumbens and in the olfactory tubercle (Seeger, et al. Brain Research, 2003, 985, 113-126) as well as the thalamus, hippocampus, frontal cortex and olfactory tubercle (Menniti, et al., William Harvey Research Conference, Porto, December, 2001). These brain regions are believed to
35 participate in the pathomechanism of schizophrenia (Lapiz, et al. Neurosci. Behav. Physiol. 2003, 33,

13) so that the location of the enzyme indicates a predominate role of PDE10A in psychosis and other disorders such as Parkinson's Disease, Huntington's Disease, addiction and depression.

Focusing on the dopaminergic input on the medium spiny neurons, PDE10A inhibitors by up-regulating cAMP and cGMP levels act as D1 agonists and D2 antagonists because the activation of Gs-protein coupled dopamine D1 receptor increases intracellular cAMP, whereas the activation of the Gi-protein coupled dopamine D2 receptor decreases intracellular cAMP levels through inhibition of adenylyl cyclase activity. Elevated intracellular cAMP levels mediated by D1 receptor signalling seems to modulate a series of neuronal processes responsible for working memory in the prefrontal cortex (Sawaguchi, Parkinsonism Relat. Disord. 2000, 7, 9), and it is reported that D1 receptor activation may improve working memory deficits in schizophrenic patients (Castner, et al., Science 2000, 287, 2020).

These findings indicate that the dual inhibition of PDE2A and PDE10A can be a mechanism to exploit for the treatment of certain neurological and psychiatric disorders. Several manuscripts and patent applications relating to the discovery and pharmacology of dual PDE2A/PDE10A inhibitors have been disclosed.

Janssen announced the synthesis, preliminary evaluation and structure-activity relationship of a series of 1-aryl-4-methyl[1,2,4]triazolo[4,3-a]quinoxalines as dual PDE2/PDE10 inhibitors (Vanhoof, et al. Bioorg. Med. Chem. Lett. 2013, 23, 785-90). Additional compounds were published in WO 2013/000924. It is noted that the compounds in these disclosures are substituted with a single moiety in position 7 of the [1,2,4]triazolo[4,3-a]quinoxaline core.

WO 2012/104293 relates to (1,2,4)triazolo[4,3-a]quinoxaline derivatives which are inhibitors of PDE2 and/or PDE10, useful in treating central nervous system diseases. It is noted that the compounds of examples 1-106 are optionally substituted with only one moiety at either of positions 4-7 of the [1,2,4]triazolo[4,3-a]quinoxaline core.

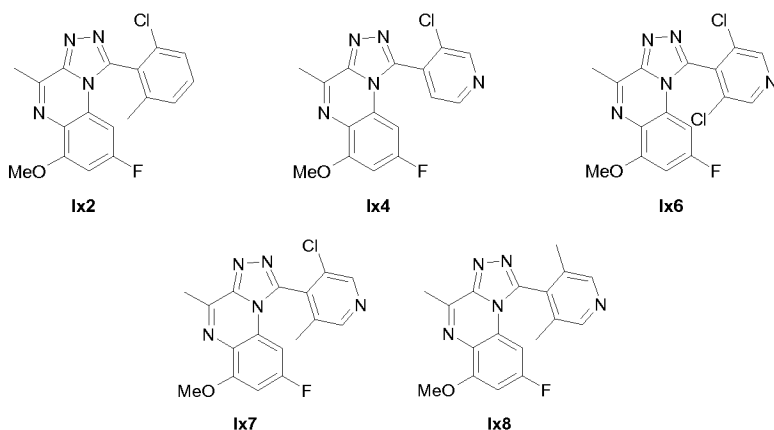
For use in humans, the PDE2/PDE10 inhibitor must have an appropriate safety profile and an issue to address is the potential genotoxicity of a drug. The study of DNA damage at the chromosome level is an essential part of genetic toxicology because chromosomal mutation is an important event in carcinogenesis. The micronucleus (MN) assay has emerged as one of a preferred method for assessing chromosome damage because it enables both chromosome loss and chromosome breakage to be measured reliably. A positive result in the MN assay indicates that it carries a risk of mutagenesis and a compound would likely be abandoned for further development.

Several compounds in WO 2012/104293 and the Vanhoof, et al. manuscript were synthesized and tested positive in the MN assay; thus, those compounds are not considered suitable drug candidates. Based on the data generated in the MN assay, no structure activity relationship is inherent to accessing whether a compound may be genotoxic. The unpredictability in accessing the safety matter by examining the structure activity relationship frustrates drug development.

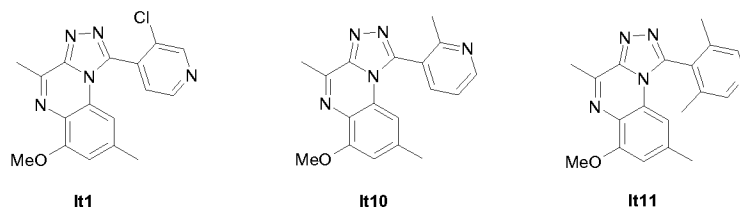
Surprisingly, the instant compounds were found to be negative in the micronucleus test which addresses the genotoxicity issue. This micronucleus result enables the compound to advance further as a potential drug candidate. Accordingly, the present invention relates to novel compounds as dual PDE2/PDE10 inhibitors with an improved safety profile. Further aspects relate to their preparation, to their medical use and to medicaments comprising them.

SUMMARY OF THE INVENTION

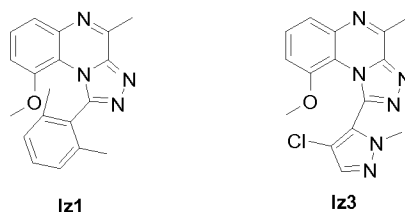
An objective of the present invention is to provide therapeutic agents which inhibit PDE2A and PDE10A and have an improved safety profile. One aspect of the invention relates to compounds of formulas Ix2, Ix4, Ix6, Ix7 and Ix8.



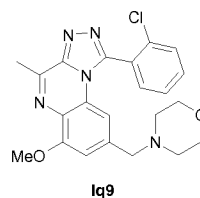
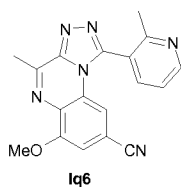
A second aspect of invention relates to compounds of formulas It1, It10 and It11.



A third aspect of the invention is directed to compounds of formula Iz1 and Iz3.



A fourth aspect of the invention relates to compound of formula Iq6 and Iq9.



In separate embodiments, the compound is selected from one of formula Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 and Iq9.

- 5 The present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 or Iq9 and a pharmaceutically acceptable carrier.

- 10 Methods of treating a subject suffering from anxiety, a cognitive disorder or schizophrenia comprising administering a therapeutically effective amount of a compound of formula Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 or Iq9 is provided.

- 15 The present invention further provides uses of a compound of formula Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 or Iq9 in the manufacture of a medicament for treating anxiety, a cognitive disorder or schizophrenia.

Another aspect of the present invention provides a compound of formula Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 or Iq9 for use in treating anxiety, a cognitive disorder or schizophrenia.

- 20 Yet another aspect provides a method of treating anxiety, a cognitive disorder or schizophrenia comprising administering a therapeutically effective amount of the compound of the invention as combination therapy together with at least one neuroleptic agent.

25 DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery of the compounds of formulas I Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 and Iq9 are dual inhibitors of PDE2A/PDE10A and tested negative in the micronucleus assay, and as such, carry an improved safety profile.

30 **Definitions**

As used herein, the phrase “effective amount” when applied to a compound of the invention, is intended to denote an amount sufficient to cause an intended biological effect. The phrase “therapeutically effective amount” when applied to a compound of the invention is intended to denote an amount of the compound that is sufficient to ameliorate, palliate, stabilize, reverse, slow or delay the

progression of a disorder or disease state, or of a symptom of the disorder or disease. In an embodiment, the method of the present invention provides for administration of combinations of compounds. In such instances, the “effective amount” is the amount of the combination sufficient to cause the intended biological effect.

- 5 The term “treatment” or “treating” as used herein means ameliorating or reversing the progress or severity of a disease or disorder, or ameliorating or reversing one or more symptoms or side effects of such disease or disorder. “Treatment” or “treating”, as used herein, also means to inhibit or block, as in retard, arrest, restrain, impede or obstruct, the progress of a system, condition or state of a disease or disorder. For purposes of this invention, “treatment” or “treating” further means an approach for
- 10 obtaining beneficial or desired clinical results, where “beneficial or desired clinical results” include, without limitation, alleviation of a symptom, diminishment of the extent of a disorder or disease, stabilized (i.e., not worsening) disease or disorder state, delay or slowing of a disease or disorder state, amelioration or palliation of a disease or disorder state, and remission of a disease or disorder.

15 **Pharmaceutically Acceptable Salts**

- The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the
- 20 like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-
- 25 toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines (for example, 8-bromotheophylline and the like). Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in S. M. Berge, et al., J. Pharm. Sci., 1977, 66, 2.

Pharmaceutical compositions

- 30 The present invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound and a pharmaceutically acceptable carrier. The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of one of the specific compounds disclosed in the Experimental Section and a pharmaceutically acceptable carrier.
- 35 The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions

according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

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Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, the compositions may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art. Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs. Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use.

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Oral dosages may be administered in one or more dosages, typically, one to three dosages per day. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art. The formulations may also be presented in a unit dosage form by methods known to those skilled in the art. For illustrative purposes, a unit dosage form for oral administration may contain from about 0.01 to about 1000 mg, from about 0.05 to about 500 mg, or from about 0.5 to about 200 mg.

20

Therapeutic Methods and Uses

Methods of treating a subject suffering from anxiety, a cognitive disorder or schizophrenia comprising administering a therapeutically effective amount of a compound of the invention are provided in this invention. The present invention provides uses in the manufacture of a medicament for treating an anxiety disorder, a cognitive disorder or schizophrenia. Another aspect provides a compound for use in treating an anxiety disorder, a cognitive disorder or schizophrenia.

25

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The present invention provides a method of treating an anxiety disorder is selected from anxiety; panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; and generalized anxiety disorder.

35

The present invention further provides a method of treating a subject suffering from a cognition disorder comprising administering to the subject a therapeutically effective amount of a compound of the invention. Examples of cognition disorders that can be treated according to the present invention include, but are not limited to, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia

associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; and age-related cognitive decline.

5 This invention also provides a method of treating a movement disorder comprising administering to the subject a therapeutically effective amount of a compound of the invention. Examples of movement disorders that can be treated according to the present invention include, but are not limited to, Huntington's disease and dyskinesia associated with dopamine agonist therapy. Further provided is a method of treating a movement disorder selected from Parkinson's disease and restless leg syndrome.

10 The present invention provides a method of treating schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type;
15 and personality disorder of the schizoid type; and wherein the drug addiction is an alcohol, amphetamine, cocaine, or opiate addiction.

The compounds of the invention or pharmaceutically acceptable salts thereof may be administered in combination with at least one neuroleptic agent to provide improved treatment of psychiatric disorders
20 such as schizophrenia. The combinations, uses and methods of treatment of the invention may also provide advantages in treatment of patients who fail to respond adequately or who are resistant to other known treatments.

The present invention thus provides a method of treating a mammal suffering from a psychiatric
25 disorder, such as schizophrenia, which method comprises administering to the mammal a therapeutically effective amount of a compound of the invention as combination therapy together with at least one neuroleptic agent.

The present invention thus provides a method of treating a mammal suffering from anxiety, a cognitive
30 disorder or schizophrenia, which method comprises administering to the mammal a therapeutically effective amount of a compound of the invention as combination therapy together with at least one neuroleptic agent.

The term "neuroleptic agent" as used herein refers to drugs, which have the effect on cognition and
35 behaviour of antipsychotic agent drugs that reduce confusion, delusions, hallucinations, and psychomotor agitation in patients with psychoses. Also known as major tranquilizers and antipsychotic drugs, neuroleptic agents include, but are not limited to: typical antipsychotic drugs, including phenothiazines, further divided into the aliphatics, piperidines, and piperazines, thioxanthenes (e.g.,

cisordinol), butyrophenones (e.g., haloperidol), dibenzoxazepines (e.g., loxapine), dihydroindolones (e.g., molindone), diphenylbutylpiperidines (e.g., pimozide), and atypical antipsychotic drugs, including benzisoxazoles (e.g., risperidone), sertindole, olanzapine, quetiapine, osanetant and ziprasidone.

5

EXPERIMENTAL SECTION

The compounds of formulas Ix2, Ix4, Ix6, Ix7, Ix8, It1, It10, It11, Iz1, Iz3, Iq6 and Iq9 can be prepared by the methods outlined in the following schemes and in the examples. In the methods below, it is possible to make use of variants or modifications, which are themselves known to chemists skilled in the art or could be apparent to the person of ordinary skill in this art.

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Abbreviations & chemicals used.

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AcOH = acetic acid (e.g. Sigma-Aldrich 320099). Acetonitrile (e.g. Aldrich 271004). Activated charcoal (e.g. Sigma-Aldrich 161551). 3-Amino-3-methyl-1-butyne (e.g. Aldrich 687189). 2-Amino-pyridine (e.g. 62090). 2-Amino-3-nitrophenol (e.g. Sigma-Aldrich 29,700-3). APPI = atmospheric pressure photo ionization. Aq = aqueous. 37% aq HCl (e.g. Sigma-Aldrich 320331). 1,2-benzenediamine (e.g. Aldrich P23938). Benzoyl chloride (e.g. Sigma-Aldrich 259950). Brine = saturated aq solution of sodium chloride (e.g. Aldrich S7653). 4-Bromo-1-fluoro-2-nitro-benzene (e.g. Aldrich 680931). 4-Bromo-2-fluoro-1-nitro-benzene (e.g. Aldrich 680931). 4-Bromo-2-methoxy-6-nitro-phenylamine (e.g. Fchgroup FCH1363540, PBMR RBK_057306, Princeton PBMR099062, or Specbio DSA39417). 3-Bromo-2-nitro-phenylamine (e.g. BBB-SCI 3B-19030 or CombiBlocks AN-1330 or Apollo OR2214). Butanoic acid chloride (e.g. Sigma-Aldrich 236349). Butyryl chloride (e.g. Aldrich 236349). Cesium carbonate (e.g. Aldrich 441902). Chloramine-T = N-Chloro-4-toluenesulfonamide sodium salt (e.g. Sigma-Aldrich 402869 for the trihydrate). (4-Chloro-benzene-1,2-diamine (e.g. Aldrich 108871). 2-Chlorobenzhydrazide (e.g. Aldrich 259993). 2-Chlorobenzoyl chloride (e.g. Aldrich 103918). 2-Chloro-3-ethyl-quinoxaline (e.g. Apollo OR25841 or Maybridge 13-31). 2-Chloro-6-fluorobenzaldehyde (e.g. Aldrich 141240). 3-Chloro-isonicotinic acid (e.g. Aldrich 633410). 2-Chloro-6-methylbenzaldehyde (e.g. Aldrich 680133). 2-Chloro-6-methyl-benzoyl chloride (e.g. Fluorochem 38160 or Betapharm 15-47106). 2-Chloro-3-methoxyquinoxaline (e.g. BBB-SCI 3B-16097/3B3-015501 or Anichem T14691). 3-Chloro-5-methyl-pyridine-4-carbaldehyde (e.g. Abbypharma AP-30-8237, Fchgroup FCH1190517, HE-chemical 62694). 4-Chloro-3-nitroanisole (e.g. Aldrich 116289). 4-Chloro-3-nitrotoluene (e.g. Aldrich 213055). (4-Chloro-phenyl)-acetyl chloride (e.g. Aldrich 638951). 3-Chloro-pyridine-4-carbaldehyde (e.g. Sigma-Aldrich 63,674-6). Chloroform (e.g. Sigma-Aldrich 650498). Concentrated aq nitric acid (e.g. Sigma-Aldrich 438073). Copper(I) bromide-dimethyl sulfide complex (e.g. Aldrich 230502). Cuprous monochloride (e.g. Sigma-Aldrich 224332). DCM = methylene chloride / dichloromethane (e.g. Aldrich 270997). 2,3-Dichlorobenzoyl

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- chloride (e.g. ABCR L09506 or BBB-SCI 3B4-0231). 2,6-Dichlorobenzoyl chloride (e.g. Fluka 35423). 1,2-Dichloroethane (e.g. Sigma-Aldrich 284505). 3,5-Dichloro-4-pyridinecarboxaldehyde (e.g. Aldrich 572470). Dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (e.g. Sigma-Aldrich 63,806-4). Diethyl amine (e.g. Sigma-Aldrich 471216). Diethyl ether (e.g. Sigma-Aldrich 346136). 1,3-
- 5 Difluoro-2-nitrobenzene (e.g. Aldrich 382957). 2-Difluoromethoxy-benzoic acid (e.g. Aldrich CDS004515). 2,6-Dimethylbenzaldehyde (e.g. Aldrich 515159). 1,2-Dimethylbenzene (e.g. Sigma-Aldrich 95662). 4,5-Dimethyl-2-nitro-phenylamine (e.g. Sigma-Aldrich D17,220-0). 2,4-Dimethyl-2H-pyrazole-3-carbaldehyde (e.g. Chembridge 4028990, Matrix 034098). DIPEA = di-iso-propyl ethyl amine (e.g. Aldrich 387649). DMSO = dimethyl sulfoxide (e.g. Sigma D4540). 1,4-Dioxane (e.g.
- 10 Sigma-Aldrich 296309). DPPF = 1,1'-bis(diphenylphosphino)ferrocene (e.g. Aldrich 177261). ELS = evaporative light scattering. Ethanol (e.g. Sigma-Aldrich 459844). (2-Ethenyl)tri-n-butyltin (e.g. Sigma-Aldrich 27,143-8). Ethyl pyruvate (e.g. Fluka 15960). EtOAc = ethyl acetate (e.g. Fluka 34972). Fe(acac)₃ = tris(acetylacetonato) iron(III) (e.g. Fluka 44920). 3-Fluoro-4-nitroanisole (e.g. BBB-SCI 3B3-013992 or ABCR AB229166). 4-Fluoro-benzene-1,2-diamine (e.g. Aldrich 653586). h = hour(s).
- 15 Heptanes (e.g. Sigma-Aldrich 730491). HPLC = high performance liquid chromatography. Hydrazine hydrate (e.g. Sigma-Aldrich 225819). 30% aq hydrogen peroxide (e.g. Sigma-Aldrich H3410). Iron powder (e.g. Aldrich 12310). Isobutyryl chloride (e.g. Aldrich 139122). K₂CO₃ (e.g. Sigma-Aldrich 209619). KI (e.g. Sigma-Aldrich 60400). LC = liquid chromatography. LC/MS = liquid chromatography / mass spectrometry. 2M = 2 molar solution (similarly 8M = 8 molar solution etc).
- 20 Methanol (e.g. Sigma-Aldrich 34860). 2-Methylbenzaldehyde (e.g. Aldrich 117552). 3-Methylbenzene-1,2-diamine (e.g. Aldrich 272361). 4-methyl-benzene-1,2-diamine (e.g. Aldrich 339938). 3-Methyl-isonicotinic acid (e.g. Matrix 020640 or Fluorochem 040096). 2-Methyl-nicotinic acid (e.g. Aldrich 325228). Methyl-prop-2-ynyl-amine (e.g. Sigma-Aldrich 68897). 2-Methyl-pyridine-3-carbaldehyde (e.g. Sigma-Aldrich 741183). Methyl vanillate (e.g. Sigma-Aldrich 138126). 2-Methoxy-
- 25 6-nitro-phenylamine (e.g. BBB-SCI 3B3-069963 or Synchem inc. SC-24920). 4-Methoxybenzhydrazide (e.g. Aldrich 558346). 4-Methoxy-benzoic acid chloride (e.g. Aldrich A88476). 3-Methyl-benzene-1,2-diamine (e.g. Sigma-Aldrich 45923). MgSO₄ (e.g. Sigma-Aldrich 246972). min = minutes. MnO₂ (e.g. Aldrich 377201). MTBE = methyl tert-butyl ether (e.g. Sigma-Aldrich 306975). MW = microwave. MW conditions = reactions performed in sealed tubes using a
- 30 Biotage Initiator instrument or a CEM Explorer-48 instrument. Na₂CO₃ (e.g. Sigma-Aldrich S7795). NaHCO₃ (e.g. Sigma-Aldrich S6014). NaIO₄ (e.g. Sigma-Aldrich 311448). NaOH (e.g. Sigma-Aldrich S5881). NaNO₂ (e.g. Sigma-Aldrich 237213). Na₂SO₄ (e.g. Sigma-Aldrich 238597). N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (e.g. Sigma-Aldrich E6383). NH₄Cl (e.g. Aldrich 254134). NMO = N-methylmorpholine N-oxide (e.g. Aldrich 224286). N-(tert-
- 35 Butoxycarbonyl)propargylamine (e.g. Aldrich 687146). OsO₄ in tert-butyl alcohol (e.g. Sigma-Aldrich 208868). Oxalic acid bis-hydrate (e.g. Sigma-Aldrich 35294). 2-Oxo-propanoic acid methyl ester (e.g. Aldrich 371173). 5% Palladium on charcoal (e.g. Aldrich 75991). 10% Palladium on charcoal (e.g.

- Aldrich 75990). Palladium(II)acetate (e.g. Aldrich 205869). PDA = photo diode array. Pd₂dba₃ = tris(dibenzylidene)dipalladium(0) (e.g. Aldrich 328774). Pd(DPPF)Cl₂ = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (e.g. Aldrich 697230). Pd(DPPF)Cl₂-DCM = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride-dichloromethane complex (e.g. Aldrich 379670). Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium(0) (e.g. Fluka 87645). Pd(P(tert-butyl)₃) (e.g. Sigma-Aldrich 676578). 5% Platinum on charcoal (e.g. Aldrich 80982). p-Nitrobenzenesulfonyl chloride (e.g. Aldrich 272248). PtO₄ (e.g. Aldrich 206032). Pentane (e.g. Sigma-Aldrich 236705). PhI(OAc)₂ = iodobenzene diacetate (e.g. Fluka 31490). PhPOCl₂ = phenylphosphonic dichloride (e.g. Aldrich 389560). POCl₃ = phosphoryl chloride (e.g. Aldrich 262099). 2-Propanol (e.g. Sigma-Aldrich 34959). Potassium (morpholin-4-yl)methyltrifluoroborate (e.g. Matrix 048488). Potassium (piperidin-1-yl) methyltrifluoroborate (e.g. Combi-blocks TB0016, Frontier P10328, Boron-mol BM751). Potassium (pyrrolidin-1-yl)methyltrifluoroborate (e.g. Fluorochem 47012, Boron-mol BM736). Potassium 1-methyl-4-trifluoroboratomethylpiperazine (e.g. Fontier P10315, Combi-blocks P10315). Potassium dimethylaminomethyl trifluoroborate (e.g. Combi-blocks TB-0024, Frontier P10369). Potassium N-cyclohexyl-N-methyl-aminomethyltrifluoroborate (e.g. Sigma-Aldrich 710911). Potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (e.g. Frontier P10963, Anichem T18141). Propargyl alcohol (e.g. Aldrich P50803). Propargyl(dimethylamine) (e.g. Sigma-Aldrich 38330). PyBroP = benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (e.g. Fluka 12809). Pyridine (e.g. Sigma P3776). Racemic alanine (e.g. Sigma A7502). RT = retention time. Sat = saturated. SFC = supercritical fluid chromatography. Sodium ethoxide in ethanol (e.g. Sigma-Aldrich 230553). 96% Sulphuric acid (e.g. Sigma-Aldrich 320501). T = time. Tetrahydro-pyran-4-carbonyl chloride (e.g. BBB-SCI 3B3-077297 or Maybridge CC29902CB). TBAI = tetra-n-butyl ammonium iodide (e.g. Sigma-Aldrich 39,690-7). tert-Butyl alcohol (e.g. (Sigma-Aldrich 471712). Tetramethyltin (e.g. Sigma-Aldrich 48,139-4). TFA = trifluoroacetic acid (e.g. Sigma-Aldrich 302031). THF = tetrahydrofuran (e.g. Sigma-Aldrich 401757). THP = tetrahydropyranyl. 2.0M trimethylaluminum in toluene (e.g. Aldrich 198048). (Trimethylsilyl)acetylene (e.g. Aldrich 218170). Zinc (e.g. Fluka 96454, Sigma-Aldrich 31653, Aldrich 2099889. Zinc cyanide (e.g. Aldrich 256498).

Analytical LC-MS data were obtained using one of the following methods:

- LC/MS Method 131: LC/MS were run on a Sciex API150EX equipped with APPI-source operating in positive ion mode. The HPLC consisted of Shimadzu LC10-ADvp LC pumps, SPD-M20A PDA detector (operating at 254 nm) and SCL-10A system controller. Autosampler was Gilson 215, Column oven was a Jones Chromatography 7990R and ELS detector was a Sedere Sedex 85. LC-conditions: The column was a Waters Symmetry C-18, 4.6 x 30 mm, 3.5 microm operating at 60 °C with 3.0 mL/min of a binary gradient consisting of water + 0.05 % TFA (A) and methanol + 0.05 % TFA. Gradient: 0.01 min: 17% B; 0.27 min 28% B; 0.53 min 39% B; 0.80 min 50% B; 1.07 min 59% B;

1.34 min 68% B; 1.60 min 78% B; 1.87 min 86% B; 2.14 min 93% B; 2.38 min 100% B; 2.40 min 17% B; 2.80 min 7% B; Total run time: 2.8 min.

5 LC/MS Method 132: same hardware as LC/MS method 131. LC-conditions: The column was a Waters Symmetry C-18, 4.6 x 30 mm, 3.5 microm operating at 60 °C with 2.5 mL/min of a binary gradient consisting of water + 0.05 % TFA (A) and methanol + 0.05 % TFA. Gradient: 0.01 min 5% B; 2.38 min 100% B; 2.40 min 5% B; 2.80 min 5% B. Total run time: 2.8 min.

10 LC/MS Method 350: LC/MS were run on a Sciex API300 equipped with APPI source operating in positive ion mode. The UPLC consisted of Waters Aquity including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nM) and ELS detector. LC-conditions: The column was a Waters Aquity UPLC BEH C-18, 2.1 x 50 mm, 1.7 microm operating at 60 °C with 1.2 mL/min of a binary gradient consisting of water + 0.05 % TFA (A) and 95 % acetonitrile containing 5 % water + 0.03 % TFA. Gradient: 0.00 min 10.0% B; 1.00 min 100.0% B; 1.01 min 10.0% B; 1.15 min 10.0% B. Total run time 1.15 min.

20 Method 550: LC-MS were run on Waters Aquity UPLC-MS consisting of Waters Aquity including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nM), ELS detector, and TQ-MS equipped with APPI-source operating in positive ion mode. LC-conditions: The column was Acquity UPLC BEH C18 1.7µm ; 2.1x50mm operating at 60°C with 1.2 ml/min of a binary gradient consisting of water + 0.05 % trifluoroacetic acid (A) and acetonitrile + 5% water + 0.05 % trifluoroacetic acid. Gradient: 0.00 min 10% B; 1.00 min 100% B; 1.01 min 10% B ; 1.15 min 10% B. Total run time: 1.15 min

Methods WXE-AB01 and WXE-AB10 and WXF-CD05

Equipment	Agilent 1100 LCMS system with ELS Detector [method WXF-CD05 Agilent 1200 LCMS system with ELS	
	Pump	G1311A
	Degasser	G1379A
	Well-plate Autosampler	G1367A
	Column Oven	G1316A
	DAD	G1315B
	MSD	G1946C or G1956A
	ELSD	Alltech ELSD 800
Column	YMC ODS-AQ (WVF-CD05: Waters XBridge ShieldRP18,2)	
	Particle size	5 micrometer
	Pore size	12 nm
	Dimension	50 * 2.0 mm ID [method WXF-
Injection volume	2 microL	

Column temperature	50°C	
Flow	0.8 mL/min	
Mobile phases	A	0.1% TFA in water (WXF-CD05 0.05% ammonia in water)
	B	0.05% TFA in acetonitrile (WXF-
	Total run time	4.5 min
	Gradient	linear
UV Detection	Wavelength	254 nm
ELSD Detection	Temperature:	50°C
	Gas Pressure:	3.2 bar
	Time	Gradient
WXE-AB01	0 min	99% A 1%B
	3.4 min	100% B
	4 min	100% B
	4.01 min	99% A 1% B
	4.5 min	99% A 1%B
WXE-AB10	0 min	90% A 10% B
	3.4 min	100% B
	4 min	100% B
	4.5 min	90% A 10% B
WXF-CD05	0 min	85% A 15% B
	3.4 min	100% B
	4 min	100% B
	4.01 min	85 % A 15% B
	4.5 min	85% A 15% B

Unless stated otherwise, preparative LC/MS was performed using either of the following methods.

- Prep LC-MS method 1: The prep station was based on a Sciex API150EX equipped with APPI source operating in positive ion mode. The LC system consisted of Gilson 333 and 334 pumps, Gilson
- 5 UV/VIS 155 detector Gilson GX 281 autosampler/fraction collector, and water bath for column and solvent heating. MS was controlled by Analyst (Sciex) and LC by Trilution (Gilson).

- LC-conditions (polar methods, generic description). The column was a Waters Atlantis Prep dC18, 5 microm, 10 x 100 mm (19 x 50 for large scale) operating at 40 °C with 15-40mL/min of a binary
- 10 gradient consisting of water + 0.05 % TFA (A) and methanol + 0.05 % TFA (B). Gradient: 0.00min 5 or 10% B; 1.20 min 5 or 10% B; 4.00 min 100% B; 4.70 min 100% B; 4.75 min 5 or 10% B; 5.20 min 5 or 10% B. Total runtime 8.0 min. Injection volume 0-200 microL. Injection into mobile phase B – time from injection to application on column/mixture with mobile phase A: 1.7 min (prior to T=0 minute in gradient program).

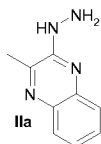
LC-conditions (normal methods, generic description). The column was a Waters Symmetry Prep C18, 5 microm, 10 x 100 mm (19 x 50/100 for large scale) operating at 40 °C with 15-40 mL/min of a binary gradient consisting of water + 0.05 % TFA (A) and methanol + 0.05 % TFA (B). Gradient: 0.00 min 10%B, 1.20 min 10%B, 4.00 min 100% B, 4.70 min 100% B, 4.75 min 10%B, 5.20 min 10% B. Total runtime 8.0 min. Injection volume 0-200 microL. Injection into mobile phase B – time from injection to application on column/mixture with mobile phase A: 0.7 minute (prior to T=0 minute in gradient program).

Prep LC-MS method 2: The prep station consisted of the following Waters components: SQ 3100 with APPI source working in positive ion mode, Binary Gradient Module 2545, HPLC Pumps 515 (x2), Sample Manager 2767, Photodiode Array Detector 2998, and System Fluidics Organizer SFO.

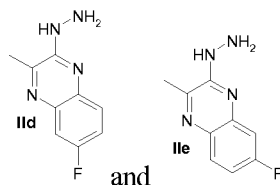
LC-conditions

The column was a Waters Symmetry Prep C18, 10 microm, 30 x 100 mm operating at 40 °C with 90 mL/min of a binary gradient consisting of water + 0.1 % TFA (A) and methanol + 0.1 % TFA (B). Gradient: 0.00 min 20% B; 1.20 min 20%B, 5.00 min 100% B, 5.40 min 100%B, 5.50 min 20% B. Total runtime 6.5 min. Injection volume 0-400 microL. Injection into mobile phase B – time from injection to application on column/mixture with mobile phase A: 1.2 minute (from T=0).

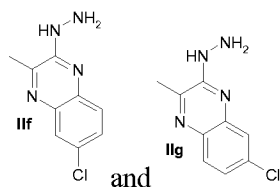
20 PREPARATION OF INTERMEDIATES



INTERMEDIATE: (3-Methyl-quinoxalin-2-yl)-hydrazine (IIa). 2-Oxo-propanoic acid methyl ester (9.0 mL) was added to a solution of 1,2-benzenediamine (10.8 g) in methanol (80 mL). The resulting suspension was refluxed for 10 min before it was cooled to ambient temperature. The precipitated solid was filtered off and dried to afford 3-methyl-1H-quinoxalin-2-one (15.3 g) sufficiently pure for the next step. 1.60 g of this material was dissolved in phosphoryl chloride (10 mL) and heated under MW conditions at 130 °C for 0.5h. The volatiles were removed in vacuo, and the residue was treated with ice/water to quench excess phosphoryl chloride. Diethyl ether and brine were added and the organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 2-chloro-3-methyl-quinoxaline (1.7 g) sufficiently pure for the next step. This material was dissolved in ethanol (150 mL) and hydrazine hydrate (2.43 mL) was added. The mixture was refluxed for 1.5h. The volatiles were removed in vacuo, and the residual solid was washed with water, filtered off and dried to afford IIa (1.2 g) sufficiently pure for the next step.

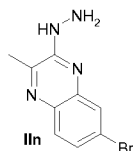


INTERMEDIATE: (6-Fluoro-3-methyl-quinoxalin-2-yl)-hydrazine (IIId) and (7-fluoro-3-methyl-quinoxalin-2-yl)-hydrazine (IIe). Ethyl pyruvate (8.69 mL) was added to a solution of 4-fluorobenzene-1,2-diamine (9.91 g) in methanol (150 mL). The resulting suspension was refluxed for 10 min and cooled to ambient temperature. The solid was filtered off, washed with diethyl ether, and dried to afford an approximate 3:2 or 2:3 mixture of 6-fluoro-3-methyl-1H-quinoxalin-2-one and 7-fluoro-3-methyl-1H-quinoxalin-2-one (7.3 g in total). 356 mg of this mixture was dissolved in acetonitrile (4 mL) and phosphoryl chloride (373 microL) was added. The resulting mixture was heated at 125 °C for 0.5h under MW conditions. The volatiles were removed in vacuo. The residue was partitioned between DCM and 5% aq NaHCO₃. The organic layer was dried over Na₂SO₄, filtered through a short silica plug, and concentrated in vacuo to afford an approximate 4:3 or 3:4 mixture of 2-chloro-6-fluoro-3-methyl-quinoxaline and 3-chloro-6-fluoro-2-methyl-quinoxaline (366 mg in total). 710 mg of this mixture prepared in a similar manner was dissolved in ethanol (10 mL) and hydrazine hydrate (1.05 mL) was added. The mixture was heated at 130 °C for 0.5h under MW conditions. The volatiles were removed in vacuo. The residue was triturated with 2% aq ammonia. The solid was filtered off and dried to afford an approximate 4:5 or 5:4 mixture of IIId and IIe (0.66 g in total) sufficiently pure for the next step.

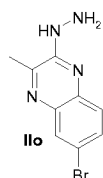


INTERMEDIATE: (6-Chloro-3-methyl-quinoxalin-2-yl)-hydrazine (IIIf) and (7-Chloro-3-methyl-quinoxalin-2-yl)-hydrazine (IIg). Ethyl pyruvate (12.2 mL) was added to a solution of 4-chlorobenzene-1,2-diamine (14.2 g) in methanol (150 mL). The resulting suspension was refluxed for 10 min. After cooling to ambient temperature the solid was filtered, washed with ether and dried. This material was an approximate 1:1 mixture of 6-chloro-3-methyl-1H-quinoxalin-2-one and 7-chloro-3-methyl-1H-quinoxalin-2-one (13 g in total). 1.17 g of this mixture was dissolved in acetonitrile (4 mL) and heated with phosphoryl chloride (1.12 mL) under MW conditions at 125 °C for 0.5h. The volatiles were removed in vacuo. The residue was partitioned between DCM and 5% aq NaHCO₃. The organic layer was dried over Na₂SO₄, filtered through a short silica plug, and concentrated in vacuo to afford an approximate 1:1 mixture of the two regioisomers 2,6-dichloro-3-methyl-quinoxaline and 3,6-dichloro-2-methyl-quinoxaline (1 g in total). A larger portion (5.0 g) prepared in a similar manner was dissolved in ethanol (100 mL) and refluxed with hydrazine hydrate (6.85 mL) for 3h. The volatiles were removed

in vacuo. The residue was triturated with 2% aq ammonia (25 mL). The solid was filtered off and dried to afford an approximate 1:1 mixture of II f and II g (3.90 g in total) sufficiently pure for the next step.

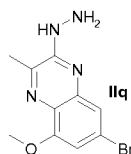


INTERMEDIATE: (7-Bromo-3-methyl-quinoxalin-2-yl)-hydrazine (II n). A mixture of 4-bromo-1-fluoro-2-nitro-benzene (99 g), racemic alanine (120 g), and Cs₂CO₃ (440 g) were refluxed for 5h in a mixture of in ethanol (1.2 L) and water (400 mL). After cooling to ambient temperature the mixture was diluted with water (600 mL) and acidified to pH 3. The solid was filtered off and dried to afford 2-(4-bromo-2-nitro-phenylamino)-propionic acid (110 g) as yellow solid. A portion of this material (10 g) was dissolved in AcOH (35 mL), and iron powder (5.8 g) was added. The mixture was stirred at 90 °C for 2h, cooled to ambient temperature, and filtered. Most of the volatiles in the filtrate were removed in vacuo. The remaining slurry was diluted in DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 7-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (6.4 g) as a yellow solid. A larger portion of this material prepared in a similar manner (45 g) was mixed with water (180 mL) and 30% aq hydrogen peroxide (140 mL). The mixture was stirred at 60 °C for 6h, cooled and the solid was filtered off, washed with water, and dried to afford 7-bromo-3-methyl-1H-quinoxalin-2-one (36 g) as a yellow solid. A portion of this material (12 g) was stirred in PhPOCl₂ (80 mL) at 150 °C for 4h. After cooling to ambient temperature, water was added and pH was adjusted to 7 with aqueous ammonia. The precipitated solid was filtered off, washed with water, and dried to afford 6-bromo-3-chloro-2-methyl-quinoxaline (8.0 g) as a yellow solid. A larger portion of this material prepared in a similar manner (16 g) was dissolved in ethanol (250 mL). Hydrazine hydrate (160 mL) was added, and the mixture was refluxed for 3h, cooled to ambient temperature, and most of the volatiles were removed in vacuo. The residue was suspended in water, the solid was filtered off, washed with water, and dried to afford II n (13 g) as a yellow solid sufficiently pure for the next step.



INTERMEDIATE: (6-Bromo-3-methyl-quinoxalin-2-yl)-hydrazine (II o). 4-Bromo-2-fluoro-1-nitro-benzene (40 g), racemic alanine (16.2 g), and K₂CO₃ (30 g) were refluxed overnight in a mixture of in ethanol (200 mL) and water (200 mL). After cooling to ambient temperature, the mixture was diluted with water, and acidified with 1M aq HCl. The precipitated solid was collected and dried to afford 2-(5-bromo-2-nitro-phenylamino)-propionic acid (41 g). A larger portion of this material prepared in a similar manner (60 g) was dissolved in methanol (250 mL) and treated with SOCl₂ (30 mL, added drop-wise). The reaction mixture was stirred at ambient temperature overnight. The volatiles were

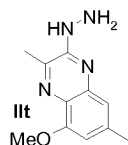
removed in vacuo. The residue was partitioned between EtOAc and aq NaHCO₃. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo to afford (5-bromo-2-nitro-phenylamino)-propionic acid methyl ester (60 g). This material was dissolved in AcOH (400 mL), iron powder (55 g) was added, and the mixture was refluxed for 4h. After cooling to ambient temperature, the solid was filtered off and the filtrate was concentrated in vacuo. The residue was partitioned between EtOAc and sat. aq NaHCO₃. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica (eluent: heptanes → EtOAc) to afford 6-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (47.7 g) as a pale yellow solid. A portion of this material (10 g) was dissolved in THF (150 mL), and the solution was cooled on an ice/water bath. MnO₂ (19.3 g) was added. The resulting mixture was stirred at ambient temperature overnight. EtOAc (100 mL) was added to the mixture. The solid was filtered off. The filtrate was concentrated in vacuo to afford 6-bromo-3-methyl-1H-quinoxalin-2-one (8.8 g). A larger portion of this material prepared in a similar manner (10 g) was stirred in PhPOCl₂ (80 mL) at 150°C for 3h. After cooling to ambient temperature, water was added and pH was adjusted to 7 with aqueous ammonia. The precipitated solid was filtered off, washed with water and dried to afford 6-bromo-2-chloro-3-methyl-quinoxaline (6.67 g). A larger portion of this material prepared in a similar manner (14 g) was dissolved in ethanol (250 mL) and hydrazine hydrate (180 mL) was added. The mixture was refluxed for 3h, cooled to ambient temperature, and most of the volatiles were removed in vacuo. The residue was diluted with water, and solid was filtered off, washed with water, and dried to afford IIo (11.2 g) as a yellow solid sufficiently pure for the next step.



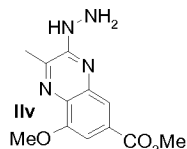
INTERMEDIATE (7-Bromo-5-methoxy-3-methyl-quinoxalin-2-yl)-hydrazine (IIq).

2-Amino-3-nitrophenol (25 g) and NaOH (25.0 g) were dissolved in a mixture of THF (500 mL) and water (200 mL). TBAI (2.5 g) and methyl iodide (21.2 mL) were added. The mixture was stirred overnight at ambient temperature. Most of the THF was removed in vacuo. The residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to afford 2-methoxy-6-nitro-phenyl amine (29.4 g). 22 g of this material and NaOAc (17.8 g) were mixed in acetic acid (300 mL) at ambient temperature. Bromine (6.9 mL) in acetic acid (5 mL) was added drop-wise over 15 min. The precipitated solid was filtered off, washed with water and heptanes, and dried to afford 4-bromo-2-methoxy-6-nitro-phenylamine (25.5 g). 2.47 g of this material dissolved in DCM (100 mL). DMAP (1.22 g) and Boc₂O (2.62 g) were added, and the mixture was overnight at ambient temperature. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes → EtOAc). Fractions containing the desired material were pooled and most of the EtOAc was removed in vacuo. The residual solution was diluted with heptanes, and the resulting mixture was allowed to stand at ambient temperature overnight. The

precipitated solid was filtered off and dried to afford (4-bromo-2-methoxy-6-nitro-phenyl)-iminocarbonicacid-bis-(tert-butyl ester) (3.94 g). A larger portion of this material (25.6 g) prepared in a similar manner was dissolved in ethanol (700 mL). 5% Platinum on charcoal (4.0 g) was added, and the mixture was treated with hydrogen gas (1 bar) for 45 min using a Parr shaker instrument. The catalyst was filtered off. The filtrate was concentrated in vacuo. The residual solid was suspended in heptanes, filtered, and dried to afford 6-amino-4-bromo-2-methoxy-phenyl)-iminocarbonicacid-bis (tert-butyl ester) (22.0 g). This material was dissolved in DCM (250 mL) and treated with TFA (5 mL) overnight at ambient temperature. The volatiles were removed in vacuo. The residue was partitioned between EtOAc and 2M aq NaOH (until pH was 9). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes → EtOAc) to afford the mono-protected material (ca 11 g). This material was dissolved in a mixture of DCM (100 mL) and TFA (50 mL) and stirred overnight at ambient temperature. The volatiles were removed in vacuo. The residue was partitioned between EtOAc and 2M NaOH (until pH 9). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo to afford 5-bromo-3-methoxy-benzene-1,2-diamine (3.63 g). This material was dissolved in methanol (200 mL). 2-Oxo-propanoic acid methyl ester (2.0 g) was added, and the mixture was stirred overnight at ambient temperature. The precipitated 7-bromo-5-methoxy-3-methyl-1H-quinoxalin-2-one was filtered off. The filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes → EtOAc) to afford more 7-bromo-5-methoxy-3-methyl-1H-quinoxalin-2-one as the first eluting isomer followed by 6-bromo-8-methoxy-3-methyl-1H-quinoxalin-2-one as the second eluting isomer. The two crops of 7-bromo-5-methoxy-3-methyl-1H-quinoxalin-2-one were mixed and washed with a little acetone to afford 7-bromo-5-methoxy-3-methyl-1H-quinoxalin-2-one (1.7 g) sufficiently pure for the next step. The fractions containing the second eluting isomer were pooled and concentrated in vacuo; the residual solid was washed with a little acetone to afford 6-bromo-8-methoxy-3-methyl-1H-quinoxalin-2-one (0.61 g) sufficiently pure for the next step. The structure of the isomers were elucidated by identifying the nitrogen carrying a proton by 2D ¹⁵N-¹H HSQC and comparing with the shift of the nitrogen having long range correlation to an aromatic proton in 2D ¹⁵N-¹H HMBC. 7-Bromo-5-methoxy-3-methyl-1H-quinoxalin-2-one (1.7 g) was refluxed in phosphoryl chloride (23 mL) for 2h. The volatiles were removed in vacuo. The residue was partitioned between DCM and ice/water. The mixture was basified with 2M aq Na₂CO₃. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo to afford 7-bromo-2-chloro-5-methoxy-3-methyl-quinoxaline (0.61 g). This material was dissolved in ethanol (38 mL). Hydrazine hydrate (3 mL) was added and the mixture was refluxed for 2h. The volatiles were removed in vacuo. The residual solid was suspended in water, filtered off, washed with heptanes, and dried to afford IIq (0.58 g) sufficiently pure for the next step.

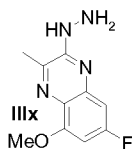


INTERMEDIATE: (5-Methoxy-3,7-dimethyl-quinoxalin-2-yl)-hydrazine (IIIt). 4-bromo-2-methoxy-6-nitro-phenylamine (11.0 g) was dissolved in ethanol (400 mL) and treated portion-wise with iron powder (12.5 g). Concentrated hydrochloric acid (20 mL) was added drop-wise, before the mixture was refluxed for 3h. After cooling, the mixture was filtered, and the pH of the filtrate was adjusted to 10 with NaHCO₃. The product was extracted into DCM, and the organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 10:1) to afford 5-bromo-3-methoxy-benzene-1,2-diamine (9 g). This procedure was repeated to produce more material. 18.0 g of the compound was dissolved in methanol (200 mL). 2-Oxo-propionic acid methyl ester (16.9 g) was added, and the mixture was stirred at room temperature overnight. The precipitate was filtered off and dried to afford 21.4 g of a mixture of 5-bromo-3,7-dimethyl-1H-quinoxalin-2-one and 8-bromo-3,6-dimethyl-1H-quinoxalin-2-one (these can be separated by chromatography on silica gel using pentane/EtOAc 1:0 to 0:1 as the eluent; this was not done in the preparation of IIIt). 14 g of this material was dissolved in DMF (140 mL) and tetramethyltin (14 g) and Pd(PPh₃)₄ (3 g) were added. The mixture was heated to 140 °C for 4h, cooled, poured into water, extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 3:1) to afford a mixture of 5-methoxy-3,7-dimethyl-1H-quinoxalin-2-one and 8-methoxy-3,6-dimethyl-1H-quinoxalin-2-one (6.7 g). This material was refluxed in phosphoryl chloride (20 mL) for 3h, before the volatiles were removed in vacuo. The residue was poured onto ice/water and pH was adjusted to 10 with NaHCO₃. The products were extracted into DCM, and the extract was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 5:1) to afford a mixture of the two regioisomeric products. This mixture was purified by chromatography on silica gel (eluent: pentane:EtOAc 20:1) to afford 2-chloro-5-methoxy-3,7-dimethyl-quinoxaline (2.2 g). This material was dissolved in ethanol (20 mL) and hydrazine-monohydrate (10 mL) was added and the mixture was refluxed overnight. Most of the volatiles were removed in vacuo, and the precipitated solid was collected, washed with water, and dried to afford IIIt (1.37 g).



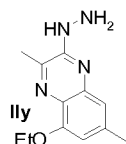
INTERMEDIATE: 3-Hydrazino-8-methoxy-2-methyl-quinoxaline-6-carboxylic acid methyl ester (IIv). A solution of methyl vanillate (25.4 g) in acetic acid (100 mL) was cooled on an ice/water bath. A mixture of concentrated aq nitric acid (10.2 mL) and acetic acid (52 mL) was added drop-wise over 1h,

before the ice/water bath was removed and the mixture was allowed to warm to ambient temperature over 4h. The precipitated solid was filtered off, washed with water, heptanes, and diethyl ether before it was dried to afford methyl 4-hydroxy-3-methoxy-5-nitrobenzenecarboxylate (21.8 g). This material was dissolved in DMF (200 mL) and the solution was cooled to -20 °C. Oxalyl chloride (23.7 mL) was added drop-wise over 10 min, and the mixture was stirred at 80 °C for 3h. The mixture was cooled to ambient temperature and poured onto ice/water and stirred overnight. The precipitated solid was filtered off and dissolved in DCM. This solution was washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was dissolved in EtOAc and washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The solid residue was recrystallized from methanol to afford methyl 4-chloro-3-methoxy-5-nitrobenzenecarboxylate (16.8 g). 16.3 g of this material was dissolved in dimethyl sulfoxide (250 mL), and racemic alanine (13 g) and potassium carbonate (9.2 g) were added. The mixture was stirred at 90 °C for 6h before it was cooled to ambient temperature and partitioned between water and EtOAc and acidified with dilute aq HCl. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to afford 4-(1-carboxy-ethylamino)-3-methoxy-5-nitro-benzoic acid methyl ester (19.8 g). 522 mg of this material was dissolved in methanol (25 mL) and treated with hydrogen gas (3 bar) in the presence of 10% palladium on charcoal for 40 min. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue and 10% palladium on charcoal (50 mg) were refluxed in xylenes (15 mL) overnight. The crude mixture was cooled to room temperature, diluted with THF (150 mL) and filtered through Celite. The filtrate was concentrated in vacuo, before it was refluxed in phosphoryl chloride (25 mL) for 0.5h. The volatiles were removed in vacuo, and the residue was partitioned between DCM and ice/water. The mixture was basified with potassium carbonate. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 0:1) to afford 3-chloro-8-methoxy-2-methyl-quinoxaline-6-carboxylic acid methyl ester (90 mg). This procedure was repeated to produce more material. 790 mg of the compound was dissolved in ethanol (50 mL), and hydrazine-monohydrate (0.19 mL) was added before the mixture was stirred at 60 °C for 4.5h where more hydrazine-monohydrate (0.065 mL) was added and stirring was continued at 60 °C for 1h. Approximately half of the solvent was removed in vacuo, and the residual solution was stored at 5 °C overnight. The precipitated solid was filtered off, washed with water and heptanes before it was dried to afford IIv (507 mg).



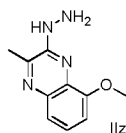
INTERMEDIATE: (7-Fluoro-5-methoxy-3-methyl-quinoxalin-2-yl)-hydrazine (IIIx). To a solution of 3,5-difluoroanisole (16 g) in DCM (150 mL), concentrated aq nitric acid (40 mL) was slowly added under ice-cooling with stirring during 1h. The resulting mixture was stirred at 0 °C for 3h before it was

partitioned between DCM and water. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was recrystallized from pentane:EtOAc (5:1) to afford 1,5-difluoro-3-methoxy-2-nitro-benzene (17.2 g). 5 g of this material and 25% aq ammonia (40 mL) in THF (20 mL) was stirred at 95 °C in a sealed tube for 18h. The resulting mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a solid, which was purified by chromatography on silica gel (eluent: pentane:EtOAc 50:1) to afford 5-fluoro-3-methoxy-2-nitro-phenylamine (2.32 g). This procedure was repeated to produce more material. 7.2 g of the compound and 5% Pd/C (0.70 g) in ethanol (100 mL) was hydrogenated at room temperature for 5h. The catalyst was filtered off using celite, and the filtrate was concentrated to afford 5-fluoro-3-methoxy-benzene-1,2-diamine (6.0 g). This material and methyl 2-oxopropanoate (4.71 g) in ethanol (180 mL) was stirred at room temperature for 4h. The solid was filtered off and dried to afford a mixture of 7-fluoro-5-methoxy-3-methyl-1H-quinoxalin-2-one and 6-fluoro-8-methoxy-3-methyl-1H-quinoxalin-2-one (5.5 g). This mixture was dissolved in phosphoryl chloride (50 mL) and stirred at 110 °C for 3.5h before the volatiles were removed in vacuo. The residue was partitioned between EtOAc and ice/water. The organic layer was concentrated in vacuo. The residue was purified by chromatography on gel silica (eluent pentane:EtOAc 50:1 to 10:1) to afford 2-chloro-7-fluoro-5-methoxy-3-methyl-quinoxaline (3.15 g). 3.0 g of this material was mixed with ethanol (30 mL) and treated with hydrazine-monohydrate (30 mL) at 80 °C for 2h. After cooling to ambient temperature, the precipitated solid was filtered, washed with ethanol and MTBE and dried to afford IIIx (3.0 g).



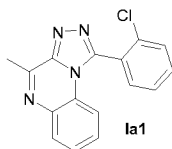
INTERMEDIATE: (5-Ethoxy-3,7-dimethyl-quinoxalin-2-yl)-hydrazine (IIy). A mixture of 5-bromo-3,7-dimethyl-1H-quinoxalin-2-one (3.5 g), CuCl (0.27 g) and 2-aminopyridine (0.26 g) were stirred in ethanol (10 mL) at room temperature for 5 min, before 25% sodium ethoxide in ethanol (50 mL) was added drop-wise. The mixture was refluxed for 40 h, before it was concentrated in vacuo. The residue was diluted with water and pH was adjusted to 4 with aq HCl. The precipitated solid was filtered off, washed with water, and dried to afford 5-ethoxy-3,7-dimethyl-1H-quinoxalin-2-one (2.5 g). This procedure was repeated to produce more material. 3.8 g of the compound was refluxed in phosphoryl chloride (15 mL) 2h, before the volatiles were removed in vacuo. The residue was poured onto ice/water, and pH was adjusted to 10 with NaOH. The product was extracted into DCM. The organic extract was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 10:1) to afford 2-chloro-5-ethoxy-3,7-dimethyl-quinoxaline (3.2 g). This material 3.2 g was dissolved in ethanol (20 mL), and hydrazine-monohydrate (15 mL) was added. The mixture was refluxed overnight, cooled, and concentrated in vacuo to remove

most of ethanol. The precipitated solid was filtered off, washed with water, and dried to afford IIy (1.6 g).

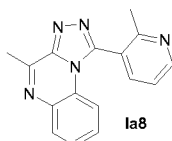


INTERMEDIATE 3-Hydrazinyl-5-methoxy-2-methylquinoxaline (IIz). To a solution of 3-fluoro-2-nitroanisole (5 g) in DMSO (60 mL) were added racemic alanine (5.8 g,) and K₂CO₃ (4.0 g). The reaction mixture was heated at 90 °C for 3h and then at 110 °C for 20h. The reaction mixture was then cooled to ambient temperature. The crude mixture was poured onto 100 mL ice and the acidified with 37% aq HCl. EtOAc was added, and the organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was dissolved in a mixture of THF (20 mL), ethanol (100 mL), and 2M aq sulfuric acid (7 mL). A stream of argon was bubbled through the mixture for 5 min after which 10% palladium on charcoal (600 mg) was added and mixture was treated with hydrogen gas (3 bar) for 23h using a Parr shaker. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was partitioned between DCM and a 1:1 mixture of sat. aq K₂CO₃ and water. The aq layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to afford 8-methoxy-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (4.9 g) as a black oil. This material was dissolved in 1,3-xylene (200 mL). 10% palladium on charcoal (600 mg) was added and the mixture was refluxed for 12h. The reaction was allowed to cool to ambient temperature and THF (200 mL) was added. The mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo to afford 8-methoxy-3-methyl-1H-quinoxalin-2-one (3.91 g). This material was added to ice-cold phosphoryl chloride (60 mL). The reaction was then heated at 100 °C for 140 min. After cooling to ambient temperature the volatiles were removed in vacuo. The residue was diluted with DCM (100 mL) and poured carefully onto ice (150 mL). The pH was adjusted to neutral using K₂CO₃. The aq layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica (eluent: heptanes → EtOAc) to afford 3-chloro-5-methoxy-2-methyl-quinoxaline (2.8 g). This material was added to a mixture of ethanol (90 mL) and hydrazine hydrate (3.3 mL) and refluxed for 25h before it was cooled to ambient temperature. The volatiles were removed in vacuo. The resulting solid was washed with water and heptanes and dried to afford IIz (2.7 g) sufficiently pure for next step.

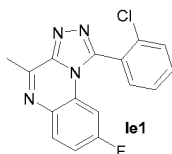
EXEMPLIFIED COMPOUNDS



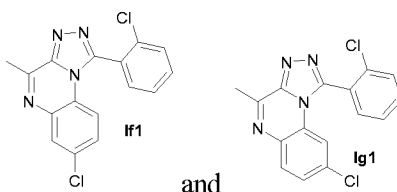
Example Ia1 1-(2-Chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. Ia (250 mg) and 2-chlorobenzoyl chloride (220 microL) were mixed in acetonitrile (3 mL) and heated at 150 °C for 0.5h. The crude mixture was concentrated in vacuo. The residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. 200 mg of the residue was purified by preparative LC/MS to afford example Ia1 (90 mg). LC/MS (method 350): RT(PDA) 0.61 min; PDA / ELS-purities 93.1% / 100%; mass observed 295.3.



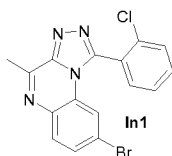
Example Ia8 4-Methyl-1-(2-methyl-pyridin-3-yl)-[1,2,4]triazolo[4,3-a]quinoxaline. 2-Methylnicotinic acid (103 mg), Ia (125 mg), acetonitrile (3 mL), and phosphoryl chloride (67 microL) were added to a MW vial. The mixture was heated at 140 °C for 0.5h under MW conditions. The precipitated solid was filtered off and dissolved in hot methanol, and the black oily gum was decanted off. The solution was treated with activated charcoal, filtered, and concentrated in vacuo to afford example Ia8 (87 mg) as a beige semisolid. LC/MS (method 131): RT(PDA) 0.83 min; PDA / ELS-purities 91.1% / 100%; mass observed 276.2.



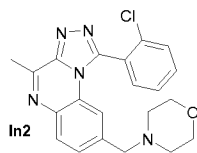
Example Ia1 1-(2-chloro-phenyl)-8-fluoro-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. 2-Chlorobenzoyl chloride (1.34 mL) was added to an approximate 4:5 or 5:4 mixture of IId and Ile (1.0 g in total) dissolved in a mixture of pyridine (0.85 mL) and acetonitrile (10 mL). The mixture was stirred at ambient temperature for 1h. Phosphoryl chloride (0.98 mL) was added, and the mixture was heated at 135 °C for 0.5h under MW conditions. The volatiles were removed in vacuo. The residue was triturated with 5% aq ammonia. The precipitated solid was filtered off and dried to afford an approximate 1:1 mixture of 1-(2-chloro-phenyl)-7-fluoro-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline and 1-(2-chloro-phenyl)-8-fluoro-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline (2.40 gram in total). 75 mg of this mixture was purified by preparative SFC to afford example Ia1 (25 mg) as the second eluting isomer using a Berger Multigram II system fitted with a Princeton SFC CN 6A 5u (250 x 21.2 mm) column operating at 50 mL/min at 35 °C and 100 bar back-pressure using stacked injections. The eluent was CO₂ (90 %) and 2-propanol + 0.1 % diethylamine (30%). Example Ia1: RT(PDA) 1.52 min; PDA / ELS-purities 99.1% / 99.7%; mass observed 313.0.



Example If1 7-Chloro-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline and example Ig1 8-chloro-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. 2-Chlorobenzoyl chloride (1.34 mL) was added to an approximate 1:1 mixture of If and Ig (2.20 g) dissolved in a mixture of pyridine (0.85 mL) and acetonitrile (100 mL). The resulting mixture was stirred at ambient temperature for 2h. The volatiles were removed in vacuo. The residue was triturated with water and the solid (3.6 g after drying) was filtered and dried. This material was suspended in acetonitrile (12 mL) and treated with phosphoryl chloride (0.98 mL) at 135 °C for 0.5h under MW conditions. The volatiles were removed in vacuo. The residue was dissolved in EtOAc (100 mL) and treated with activated charcoal. The mixture was filtered and the filtrate was concentrated in vacuo to afford an approximate 1:1 mixture of 7-chloro-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline and 8-chloro-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline (2.2 g in total). 100 mg of this material was subjected to preparative LC/MS purification. The second eluting isomer was example If1 (9 mg) and the first eluting isomer was example Ig1 (11 mg). LC/MS (method 131) for example If1: RT(PDA) 1.74 min; PDA / ELS-purities 99.4% / 100%; mass observed 329.2. LC/MS (method 131) for example Ig1: RT(PDA) 1.66 min; PDA / ELS-purities 100% / 100%; mass observed 329.1.

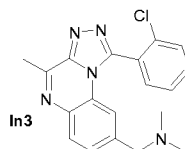


Example In1 8-Bromo-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. A solution of In (18 g) in 1,4-dioxane (370 mL) was mixed with 2-chloro benzoyl chloride (12.4 g) and phosphoryl chloride (10 mL). The mixture was stirred at 80 °C for 2h, cooled to ambient temperature. The mixture was poured into ice-water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica (eluent: pentane/EtOAc 10:1 → 1:1) to give example In1 (8.7 g) as a white solid. LC/MS (method 131): RT(PDA) 1.70 min; PDA/ELS purities 96.3% / 100.0%; mass observed 374.7.



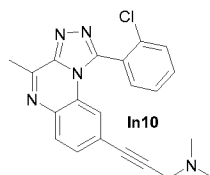
Example In2 1-(2-Chloro-phenyl)-4-methyl-8-morpholin-4-ylmethyl-[1,2,4]triazolo[4,3-a]quinoxaline. Cesium carbonate (0.13 g), palladium(II)acetate (3.0 mg), dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (13 mg) and potassium (morpholin-4-yl)methyltrifluoroborate (30 mg) were added to a flask followed by THF (3 mL), water (1 mL), and example In1 (50 mg). The mixture was stirred at 80 °C for 1 day before the crude mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent:

heptanes:(EtOAc:Et₃N:MeOH 8:2:1) 1:0 to 0:1) to afford example In2 (33 mg). LC/MS (method 131): RT(PDA) 0.70 min; PDA/ELS purities 89.7% / 100.0%; mass observed 393.9.



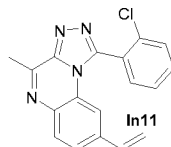
Example In3 [1-(2-Chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-8-ylmethyl]-

- 5 dimethyl-amine. Prepared as described for example In2 from potassium dimethylaminomethyl trifluoroborate (24 mg) and example In1 (50 mg) to afford example In3 (7 mg). LC/MS (method 131): RT(PDA) 0.69 min; PDA/ELS purities 92.2% / 100.0%; mass observed 352.3.

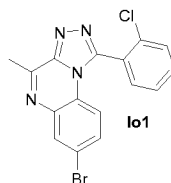


Example In10 {3-[1-(2-Chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-8-yl]-prop-2-

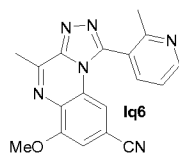
- 10 ynyl}-dimethyl-amine. Example In1 (100 mg), copper(I) bromide-dimethyl sulfide complex (11 mg) and Pd(PPh₃)₄ (31 mg) mixed in triethylamine (4 mL). Propargyl(dimethylamine) (33 mg) was added and the reaction was stirred overnight at 70 °C. After cooling to ambient temperature, the crude mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 0:1) to afford example In10 (67 mg). LC/MS (method 131): RT(PDA) 0.88 min; PDA/ELS purities 96.6% / 100.0%; mass observed 377.0.



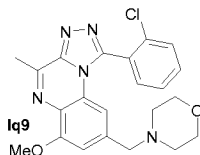
Example In11 1-(2-Chloro-phenyl)-4-methyl-8-vinyl-[1,2,4]triazolo[4,3-a]quinoxaline. Example In1 (200 mg), Pd(PPh₃)₄ (62 mg) and (2-ethenyl)tri-n-butyltin (0.19 mL) were mixed in DMF (10 mL) and the mixture was stirred at 100 °C for 6h. The crude mixture was cooled, and partitioned between water and EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 0:1) to afford example In11 (122 mg). LC/MS (method 131): RT(PDA) 1.59 min; PDA/ELS purities 93.4% / 100.0%; mass observed 320.8.



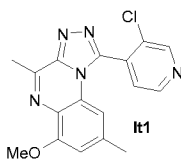
- Example Io1 7-Bromo-1-(2-chloro-phenyl)-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. A solution of Io (7 g) in anhydrous 1,4-dioxane (300 mL) was mixed with 2-chloro benzoyl chloride (4.84 g) in the presence of phosphoryl chloride (35 mL). The mixture was stirred at 80 °C for 2h. After cooling to ambient temperature the reaction mixture was poured into ice-water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica (eluent: pentane/EtOAc 10:1 → 1:1) to afford example Io1 (3.74 g). LC/MS (method 131): RT(PDA) 1.73 min; PDA/ELS purities 94% / 100%; mass observed 374.8.



- Example Iq6 6-Methoxy-4-methyl-1-(2-methyl-pyridin-3-yl)-[1,2,4]triazolo[4,3-a]quinoxaline-8-carbonitrile. A mixture of Ioq (700 mg) and 2-methyl-pyridine-3-carbaldehyde (449 mg) in DCM (60 mL) was refluxed for 3h, before PhI(OAc)₂ (1.03 g) was added, and the mixture was refluxed for 3h. The volatiles were removed in vacuo, and the residue was purified by column chromatography on gel silica (eluent: pentane:EtOAc 1:2) to afford 8-bromo-6-methoxy-4-methyl-1-(2-methyl-pyridin-3-yl)-[1,2,4]triazolo[4,3-a]quinoxaline (900 mg). 400 mg of this material was mixed with zinc cyanide (144 mg), Pd(t-Bu₃P)₂ (106.3 mg), and cesium carbonate (1.07 g) in DMF (10 mL). The mixture was stirred at 100 °C for 1.2h under MW conditions. The volatiles were removed, and the residue was purified by chromatography on silica gel (eluent: EtOAc) to afford example Iq6 (63.5 mg). LC/MS (method WXE-AB01): RT(PDA) 1.59 min; PDA/ELS purities 97% / 100%; mass observed 331.1.

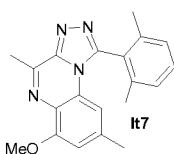


- Example Iq9 1-(2-Chloro-phenyl)-6-methoxy-4-methyl-8-morpholin-4-ylmethyl-[1,2,4]triazolo[4,3-a]quinoxaline. Prepared as described for example In2 from potassium (morpholin-4-yl)methyltrifluoroborate (41 mg) and example Iq1 (50 mg) to afford example Iq9 (11 mg). LC/MS (method 131): RT(PDA) 0.68 min; PDA/ELS purities 93.5% / 100.0%; mass observed 423.8.

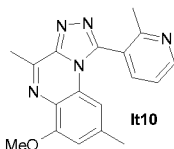


- Example It1 1-(3-Chloro-pyridyl-4-yl)-6-methoxy-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline. Ioq (700 mg) and 3-chloro-pyridine-4-carbaldehyde (523 mg) were refluxed in DCM (5 mL) for 3h before PhI(OAc)₂ (1.03 g) was added, and the mixture was refluxed for 3h. The volatiles were removed in vacuo, and the residue was purified by column chromatography on gel silica (eluent: pentane:EtOAc 10:1) to afford 8-bromo-1-(3-chloro-pyridin-4-yl)-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-

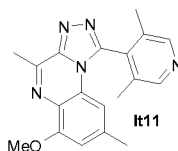
a]quinoxaline (900 mg). 160 mg of this material was dissolved in THF (16 mL). Cesium carbonate (399 mg), potassium methyltrifluoroborate (77 mg), and water (1.42 mL) were added followed by [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane complex (81 mg). The flask was capped and stirred at 75 °C for 1 day. The mixture was cooled on an ice/water bath, diluted with EtOAc (40 mL), and filtered through a short Celite plug and eluted with EtOAc. The filtrate was partitioned between water and EtOAc. The organic layer was washed brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was mixed with THF (16 mL), cesium carbonate (399 mg), potassium methyltrifluoroborate (77 mg), water (1.42 mL), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane complex (81 mg). The flask was capped and stirred at 75 °C for 2 days and worked up as described above. The crude product was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 0:1) to afford a material that was dissolved in EtOAc and stirred at 0 °C to precipitate a solid that was collected and dried to afford example It1 (38 mg). LC/MS (method 131): RT(PDA) 0.93 min; PDA/ELS purities 82.3% / 100%; mass observed 340.1.



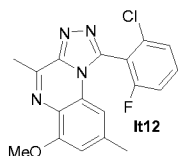
Example It7 1-(2,6-Dimethyl-phenyl)-6-methoxy-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline. A solution of IIq (99 mg) and 2,6-dimethylbenzaldehyde (49.4 mg) in DCM (5 mL) was heated at 75 °C for 0.5h under MW conditions before PhI(OAc)₂ (130 mg) was added. The mixture was heated at 75 °C for 40 min under MW conditions, before the volatiles were removed in vacuo. The obtained residue was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 1:9) to afford 8-bromo-1-(2,6-dimethyl-phenyl)-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline (110 mg). Example It7 was prepared as described for example It1 starting from 8-bromo-1-(2,6-dimethyl-phenyl)-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline (105 mg) to afford example It7 (35 mg). LC/MS (method 131): RT(PDA) 1.07 min; PDA/ELS purities 86.7% / 99.5%; mass observed 333.3.



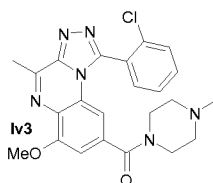
Example It10 1-(2-methyl-pyridin-3-yl)-6-methoxy-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline. Itt (266 mg) was dissolved in DCM (15 mL) and 2-methyl-pyridine-3-carbaldehyde (436 mg) was added. The mixture was refluxed for 2.5h, before (bisocetoxy)iodobenzene (964 mg) was added, and the mixture was stirred at room temperature for 2h. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 1:0 to 0:1) to afford example It10 (379 mg). LC/MS (method WXF-CD05): RT(PDA) 1.62 min; PDA/ELS purities 98.9% / 98.9%; mass observed 320.2.



Example It11 1-(3,5-Dimethyl-pyridin-4-yl)-6-methoxy-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline. 8-Bromo-1-(3,5-dichloro-pyridin-4-yl)-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline (200 mg) was dissolved in DMF (2.0 mL). 4Å molecular sieves (20 mg) were added, followed by tetramethyltin (82 microL) and Pd(PPh₃)₄ (8.0 mg). The mixture was heated at 150 °C under MW conditions for 3h. More tetramethyltin (76.0 microL) was added, and the mixture was heated at 150 °C for 1.5h. Heptanes (5 mL) added and the biphasic was stirred vigorously before the upper layer was pipetted off (repeated with three times). The residual DMF layer was partitioned between EtOAc and water. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent; heptanes:EtOAc 1:0 to 0:1) to afford crude example It11 (10 mg). This material was further purified by preparative LC/MS. The resulting material was partitioned between EtOAc, sat. NaHCO₃, and water. The aq. layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to afford example It11 (8 mg). LC/MS (method 550): RT(PDA) 0.4 min; PDA purity 76%; mass observed 334.3.

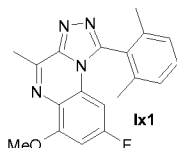


Example It12 1-(2-Chloro-6-fluoro-phenyl)-6-methoxy-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline. A solution of IIt (400 mg) and 2-chloro-6-fluorobenzaldehyde (319 mg) in DCM refluxed for 2.5h, before PhI(OAc)₂ (885 mg) was added and the resulting mixture was stirred at room temperature for 3h. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 1:0 to 0:1) to afford example It12 (329 mg). LC/MS (method WXE-AB10): RT(PDA) 2.05 min; PDA/ELS purities 96.7%/100%; mass observed 357.1.



Example Iv3 [1-(2-Chloro-phenyl)-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-8-yl]-(4-methyl-piperazin-1-yl)-methanone. 1-methyl-piperazine (44 microL) was dissolved in DCM (1 mL). 2.0 M of trimethylaluminum in toluene (0.2 mL) was added, and the mixture was stirred at room temperature for 10 min before a solution of Iiv (100 mg) in DCM (1 mL) was added drop-wise. The mixture was heated at 120 °C for 35 min under MW conditions, before it was poured into 0.5M aq HCl.

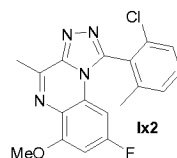
The product was extracted into DCM, and the organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: heptanes:EtOAc 1:0 to 0:1) to afford example Iv3 (60 mg). LC/MS (method 550): RT(PDA) 0.42 min; PDA/ELS purities 99.1% / 100.0%; mass observed 450.8.



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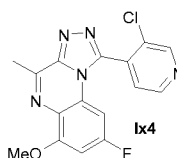
Example Ix1 1-(2,6-Dimethyl-phenyl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. IIIx (150 mg) in DCM (5 mL) was reacted with 2,6-dimethylbenzaldehyde (181 mg) at 30 °C for 2h, and the resulting mixture was used for next step without further purification. To this solution was added $\text{PhI}(\text{OAc})_2$ (435 mg), and the mixture was stirred at 30 °C for 3h. The volatiles were removed in vacuo. The residue was purified by chromatography on gel silica (eluent: pentane:EtOAc 5:1) to afford example Ix1 (109 mg). LC/MS (method WXE-AB10): RT(PDA) 2.12 min; PDA/ELS purities 99.4% / 100%; mass observed 337.2.

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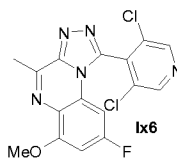
Example Ix2 1-(2-Chloro-6-methyl-phenyl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. Prepared as described for example Ix1 starting from IIIx (150 mg) and 2-chloro-6-methyl-benzaldehyde (209 mg) to afford example Ix2 (103 mg). LC/MS (method WXE-AB10): RT(PDA) 2.11 min; PDA/ELS purities 99.1% / 100%; mass observed 357.1.

15



Example Ix4 1-(3-Chloro-pyridin-4-yl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. Prepared as described for example Ix1 starting from IIIx (250 mg) and 3-chloro-pyridine-4-carbaldehyde (319 mg) to afford example Ix4 (62 mg) after preparative TLC instead of chromatography on silica gel. LC/MS (method WXE-AB01): RT(PDA) 1.95 min; PDA/ELS purities 98.0% / 99.6%; mass observed 344.1.

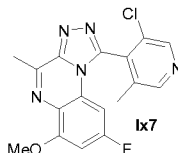
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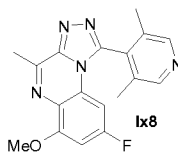
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Example Ix6 1-(3,5-Bischloro-pyridin-4-yl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. To a solution of DIPEA (1.64 g) in THF (5 mL) was added n-BuLi (6.74 mL, 2.4 M) during 3 min at -70 °C. After stirring for 20 min at -70 °C, a solution of 3,5-dichloropyridine (2.00 g) in

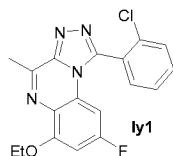
THF was added during 10 min. After stirring for 20 min at -70 °C, DMF (1.92 g) was added. The mixture was stirred for another 0.5h at -70 °C before it was quenched with aq NH₄Cl and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 20:1) to afford 3,5-dichloro-pyridine-4-carbaldehyde (1.8 g). Example Ix6 was prepared as described for example Ix1 starting from IIIx (200 mg) and 3,5-dichloro-pyridine-4-carbaldehyde (316 mg) to afford example Ix6 (62 mg) after preparative TLC instead of chromatography on silica gel. LC/MS (method WXE-AB01): RT(PDA) 2.32 min; PDA/ELS purities 96.6% / 100%; mass observed 378.0.



- 10 Example Ix7 1-(3-Chloro-5-methyl-pyridin-4-yl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. Prepared as described for example Ix1 starting from IIIx (200 mg) and 3-chloro-5-methyl-pyridine-4-carbaldehyde (168 mg) to afford example Ix7 (320 mg). LC/MS (method WXE-AB01): RT(PDA) 2.01 min; PDA/ELS purities 99.7% / 100%; mass observed 358.1.

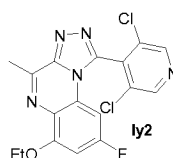


- 15 Example Ix8 1-(3,5-Bismethyl-pyridin-4-yl)-8-fluoro-6-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. A mixture of 3,5-dimethyl-isonicotinic acid ethyl ester (0.50 g; for the preparation of this material see G. Attardo, S. Tripathy, PCT Int. Appl., 2010132999, 25 Nov 2010) and sodium hydroxide (123 mg) in ethanol (5 mL) and water (1 mL) was refluxed for 5h. Most of the volatiles were removed in vacuo. The pH of the residue was adjusted to ca 4, and the solid was filtered off and washed with DCM/MeOH 50:1. The filtrate was concentrated in vacuo to afford 3,5-dimethyl-isonicotinic acid (402 mg). A mixture of 34 mg of this material and IIIx (50 mg) were treated with PyBroP (110 mg) and DIPEA (0.08 mL) in DMF (2 mL) at room temperature for 18h. The volatiles were removed in vacuo. The residue was partitioned between EtOAc and water. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford 3-chloro-5-methyl-isonicotinic acid N'-(7-fluoro-5-methoxy-3-methyl-quinoxalin-2-yl)-hydrazide (60 mg). This material was dissolved in a mixture of 1,4-dioxane (1 mL) was phosphoryl chloride (0.5 mL), and the mixture was stirred at 80 °C for 1h. The volatiles were removed in vacuo. The residue was partitioned between DCM and water. The organic layer was washed with sat aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (eluent pentane:EtOAc 1:1) to afford example Ix8 (17.2 mg). LC/MS (method WXE-AB01): RT(PDA) 1.86 min; PDA/ELS purities 100% / 100%; mass observed 338.1.

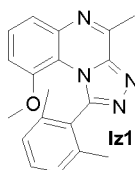


Example Iy1 1-(2-Chloro-phenyl)-8-fluoro-6-ethoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline.

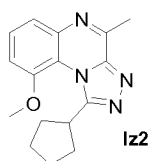
- Ily (200 mg) in DCM (15 mL) was reacted with 2-chlorobenzaldehyde (127 mg) at 40 °C for 1.5h, before the volatiles were removed in vacuo. The residue was dissolved in DCM (20 mL) and
 5 PhI(OAc)₂ (42 mg) was added, and the mixture was stirred at room temperature for 2.5h. The volatiles were removed in vacuo. The residue was purified by chromatography on gel silica (eluent: pentane:EtOAc 5:1) to afford example Iy1 (154 mg). LC/MS (method WXE-AB10): RT(PDA) 2.2 min; PDA/ELS purities 97.5% / 100%; mass observed 353.1.



- 10 Example Iy2 1-(3,5-Bischloro-pyridin-4-yl)-8-fluoro-6-ethoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. Prepared as described for Iy1 from Ily (100 mg) and 3,5-dichloro-pyridine-4-carbaldehyde (70 mg) to afford example Iy2 (120 mg). LC/MS (method WXE-AB10): RT(PDA) 2.11 min; PDA/ELS purities 98.1% / 100%; mass observed 388.1.

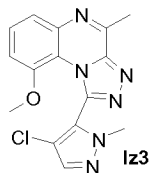


- 15 Example Iz1 1-(2,6-Dimethylphenyl)-9-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. 2,6-Dimethylbenzaldehyde (136 mg) and Ilz (206 mg) were mixed in DCM (5 mL) and heated briefly to reflux before the mixture was allowed to stir overnight at ambient temperature before PhI(OAc)₂ (325 mg) was added. The mixture for stirred for 3h at ambient temperature. The crude reaction mixture was purified by chromatography on silica (eluent: heptanes:EtOAc 1:0 to 0:1) to afford example Iz1 (236 mg). LC/MS (method 131): RT(PDA)=1.52 min; PDA / ELS-purities 95.3% / 100%; mass observed
 20 319.0.

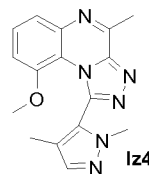


- Example Iz2 1-Cyclopentyl-9-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. To a
 suspension of Ilz (68 mg) in acetonitrile (1.65 mL) was added cyclopentanecarboxylic acid (30 mg) and
 25 phosphoryl chloride (51 mg). The mixture was heated at 140 °C for 25 min under MW conditions. The supernatant of the resulting suspension was decanted off and concentrated in vacuo. The residue was

purified by chromatography on silica gel (eluent: EtOAc/heptanes 1:9→3:7) to afford example Iz2 (13 mg). LC/MS (method 131): RT(PDA)=1.54 min; PDA / ELS-purities 94.4% / 100%; mass observed 283.4.



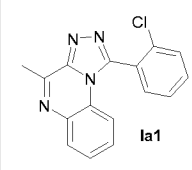
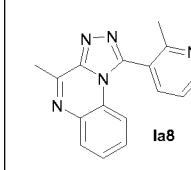
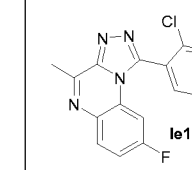
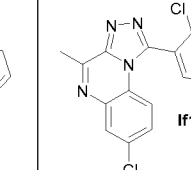
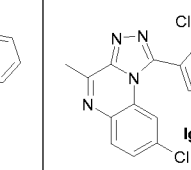
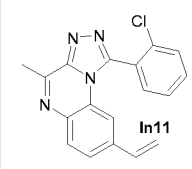
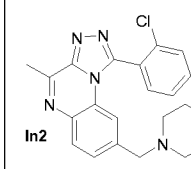
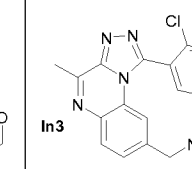
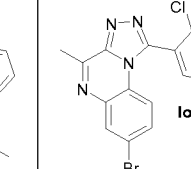
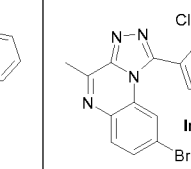
- 5 Example Iz3 1-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-9-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. To a solution of IIz (300mg) in dioxane (10mL) was added 4-chloro-2-methyl-2H-pyrazole-3-carbonyl chloride (263 mg; for a reference on this material see: H. Yoshida, K. Oomori, K. Fuse From Jpn. Kokai Tokkyo Koho (1996), JP 08012652 A 19960116. After stirring for 5 min at ambient temperature phosphoryl chloride (0.3 mL) was added and the mixture was refluxed for 3h.
- 10 After cooling to room temperature the crude mixture was poured onto ice/water, and pH was adjusted to 12 with NaHCO₃. EtOAc was added, and the organic layer was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 1:1) to afford example Iz3 (265 mg). LC/MS (method 131): RT(PDA)=1.32 min; PDA/ELS-purities 85.7% / 100%; mass observed 329.3.



- 15 Example Iz4 1-(2,4-Dimethyl-2H-pyrazol-3-yl)-9-methoxy-4-methyl-[1,2,4]triazolo[4,3-a]quinoxaline. To a solution of 2,4-dimethyl-2H-pyrazole-3-carboxylic acid (500 mg, for a reference for the preparation of this compound see: IR Baldwin, KD Down, P Faulder, S Gaines, JN Hamblin, J Le, CJ Luniss, J Nigel, TJ Ritchie, E John, JK Simpson, CAP Smethurst WO 2009147188) and IIz
- 20 (343 mg) in a mixture of DMF (10 mL) and DIPEA (632 mg) was added BOP (1.2 g). The mixture was stirred at room temperature overnight before water was added and the product was extracted in EtOAc. The organic layer was washed with water and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 2:1) to afford 2,4-dimethyl-2H-pyrazole-3-carboxylic acid N'-(8-methoxy-3-methyl-quinoxalin-2-yl)-hydrazide (680 mg). This material was
- 25 dissolved in dioxane (20 mL). Phosphoryl chloride (0.5 mL) was added and the mixture was refluxed for 3h. After cooling to ambient temperature the crude mixture was poured onto ice/water and pH was adjusted to 12 with NaHCO₃. The product was extracted into EtOAc, and the organic layer was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: pentane:EtOAc 1:1) to afford example Iz4 (70.2 mg). LC/MS (method 131): RT(PDA)=1.07 min;
- 30 PDA/ELS-purities 89.9% / 100%; mass observed 309.3.

The compounds of formulas Ia1, Ia8, Ia1, If1, Ig1, In11, In2, In3, Io1 and In1 are described in Table 1. These compounds can be prepared according to procedures in WO 2012/104293 and WO 2013/000924.

Table 1: WO 2012/104293 and WO 2013/000924

 Ia1	 Ia8	 Ia1	 If1	 Ig1
 In11	 In2	 In3	 Io1	 In1

5

PDE in-vitro assays

The inhibitory activities of the compound of the invention were determined in connection with the following methods:

10 PDE10A enzyme

Active PDE10A enzyme is prepared in a number of ways for use in PDE assays (Loughney, K. et al. Gene 1999, 234, 109-117; Fujishige, K. et al. Eur J Biochem. 1999, 266, 1118-1127 and Soderling, S. et al. Proc. Natl. Acad. Sci. 1999, 96, 7071-7076). PDE10A can be expressed as full-length proteins or as truncated proteins, as long as they express the catalytic domain. PDE10A can be prepared in
 15 different cell types, for example insect cells or E. coli. An example of a method to obtain catalytically active PDE10A is as follows: The catalytic domain of human PDE10A (amino acids 440-779 from the sequence with accession number NP 006652) is amplified from total human brain total RNA by standard RT-PCR and is cloned into the BamH1 and Xho1 sites of the pET28a vector (Novagen). Expression in coli is performed according to standard protocols. Briefly, the expression plasmids are
 20 transformed into the BL21(DE3) E. coli strain, and 50 mL cultures inoculated with the cells allowed to grow to an OD600 of 0.4-0.6 before protein expression is induced with 0.5mM IPTG. Following induction, the cells are incubated overnight at room temperature, after which the cells are collected by centrifugation. Cells expressing PDE10A are resuspended in 12 mL (50 mM TRIS-HCl-pH8.0, 1 mM MgCl₂ and protease inhibitors). The cells are lysed by sonication, and after all cells are lysed,
 25 TritonX100 is added according to Novagen protocols. PDE10A is partially purified on Q sepharose and the most active fractions were pooled.

PDE10A inhibition assay

A typical PDE10A assay was performed as follows: the assay was performed in 60 microL samples containing a fixed amount of the PDE2A enzyme (sufficient to convert 20–25% of the cyclic nucleotide

substrate), a buffer (50 mM HEPES pH 7.6; 10 mM MgCl₂; 0.02% Tween20), 10 nM tritium labelled cAMP and varying amounts of inhibitors. Reactions were initiated by addition of the cyclic nucleotide substrate, and reactions were allowed to proceed for 1 h at room temperature before being terminated through mixing with 20 microL (0.2 mg) yttrium silicate SPA beads (Amersham). The beads were
5 allowed to settle for 1 h in the dark before the plates were counted in a Wallac 1450 Microbeta counter. The measured signals were converted to activity relative to an uninhibited control (100%) and IC₅₀ values were calculated using XIFit (model 205, IDBS).

PDE2A enzyme

- 10 Likewise, active human PDE2A enzyme (ATCC68585) is prepared in a number of ways for use in PDE assays and procedures are well known to those skilled in the art.

PDE2A inhibition assay

- A typical PDE2A assay was performed as follows: the assay was performed in 60 microL samples containing a fixed amount of the PDE2A enzyme (sufficient to convert 20–25% of the cyclic nucleotide
15 substrate), a buffer (50 mM HEPES pH 7.6; 10 mM MgCl₂; 0.02% Tween20), 0.1 mg/ml BSA, 15 nM tritium labelled cAMP and varying amounts of inhibitors. Reactions were initiated by addition of the cyclic nucleotide substrate, and reactions were allowed to proceed for 1 h at room temperature before being terminated through mixing with 20 microL (0.2 mg) yttrium silicate SPA beads (Amersham). The beads were allowed to settle for 1 h in the dark before the plates were counted in a Wallac 1450
20 Microbeta counter. The measured signals were converted to activity relative to an uninhibited control (100%) and IC₅₀ values were calculated using XIFit (model 205, IDBS).

- Each of the exemplified compounds of the invention were tested in the assays above and were found to possess IC₅₀ values of less than about 2000 nM at PDE10A and/or PDE2A. The claimed compounds of
25 the invention were found to possess IC₅₀ values of less than about 200 nM at PDE10A and/or PDE2A.

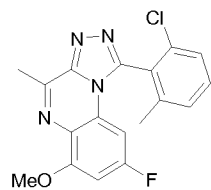
- The compounds of the invention were tested in an in vitro micronucleus assay, which is a genotoxicity assay that is routinely used in the drug discovery process as a method to test drug candidates for clastogenic and aneugenic potential. The assay protocol used herein is described in the literature (S.L.
30 Avlasevich, S.M. Bryce, S.E. Cairns, S.D. Dertinger Environmental and Molecular Mutagenesis 2006, 47, 56-66).

Data obtained for exemplified compounds of the invention are listed in the table below.

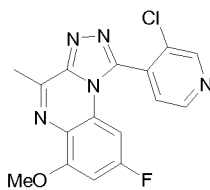
Example	PDE10A IC ₅₀	PDE2A IC ₅₀	Prior art	Micronucleus test outcome
Ia1	560	55	WO 2013/000924	positive
Ia8	1600	450	WO 2012/104293	negative
Ie1	180	23	WO 2012/104293	positive
If1	390	65	WO 2012/104293	negative
Ig1	110	7.5	WO 2012/104293	negative
In1	140	6.2	WO 2013/000924	negative
In10	19	1	-	positive
In11	57	2.3	WO 2013/000924	negative
In2	36	5.2	WO 2013/000924	negative
In3	300	49	WO 2013/000924	positive
Io1	870	130	WO 2013/000924	negative
Iq6	97	560	-	negative
Iq9	1.4	5.3	-	negative
It1	12	36	-	negative
It7	1.7	23	-	positive
It10	3.7	83	-	negative
It11	6.3	70	-	negative
It12	0.37	1.7	-	positive
It7	1.7	23	-	positive
Iv3	1.4	3.8	-	positive?
Ix1	25	100	-	positive
Ix2	11	27	-	negative
Ix4	23	83	-	negative
Ix6	9.3	51	-	negative
Ix7	20	92	-	negative
Ix8	45	820	-	negative
Iy1	19	42	-	positive
Iy2	18	120	-	positive
Iz1	190	540	-	negative
Iz2	86	69	-	positive
Iz3	67	34	-	negative
Iz4	31	8.3	-	positive

CLAIMS

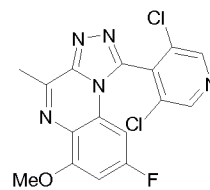
1. A compound selected from the group consisting of the compound of formulas Ix2, Ix4, Ix6, Ix7 and Ix8:



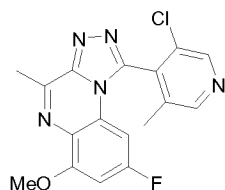
Ix2



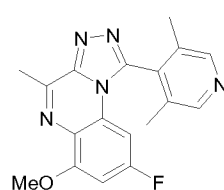
Ix4



Ix6

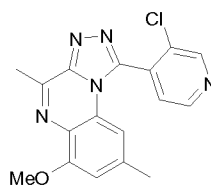


Ix7

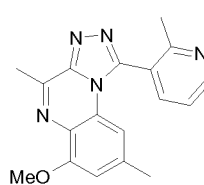


Ix8

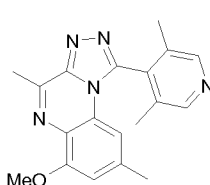
2. A compound selected from the group consisting of the compound of It1, It10 and It11:



It1

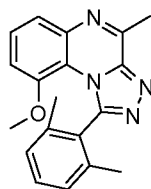


It10

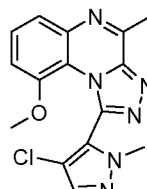


It11

3. A compound of formula Iz1 or Iz3:

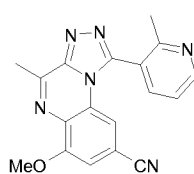


Iz1

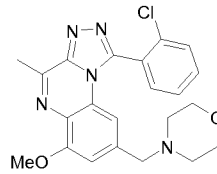


Iz3

4. A compound of formula Iq6 or Iq9:



Iq6



Iq9

5. A pharmaceutical composition comprising a therapeutically effective amount of the compound of anyone of claims 1-4 and a pharmaceutically acceptable carrier.
6. A method of treating a subject suffering from anxiety, a cognitive disorder or schizophrenia comprising administering a therapeutically effective amount of a compound of anyone of claims 1-4.

7. Use of the compound of anyone of claims 1-4 in the manufacture of a medicament for treating anxiety, a cognitive disorder or schizophrenia.
8. A compound of anyone of claims 1-4 for use in treating anxiety, a cognitive disorder or schizophrenia.
9. A method of treating anxiety, a cognitive disorder or schizophrenia comprising administering a therapeutically effective amount of the compound of anyone of claims 1-4 as combination therapy together with at least one neuroleptic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/054645

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A31P25/00 A61K31/4985
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/000924 A1 (JANSSEN PHARMACEUTICA NV [BE]; ANDRES-GIL JOSE IGNACIO [ES]; ROMBOUTS) 3 January 2013 (2013-01-03) cited in the application compound B5	1-9
A	----- WO 2012/104293 A1 (BOEHRINGER INGELHEIM INT [DE]; LANKAU HANS-JOACHIM [DE]; LANGEN BARBAR) 9 August 2012 (2012-08-09) cited in the application compounds 73-75	1-9
X,P	----- WO 2013/034755 A1 (LUNDBECK & CO AS H [DK]; JOERGENSEN MORTEN [DK]; BRUUN ANNE TECHAU [DK]) 14 March 2013 (2013-03-14) compounds Iq1, Ic1, Ic2 ----- -/--	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 2014

Date of mailing of the international search report

15/05/2014

Name and mailing address of the ISA/

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Authorized officer

Bareyt, Sébastien

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/054645

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2013/034758 A1 (LUNDBECK & CO AS H [DK]; JOERGENSEN MORTEN [DK]; BRUUN ANNE TECHAU [DK] 14 March 2013 (2013-03-14) compound Ia4 -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/054645

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9

related to all compounds

1.1. claims: 1, 2, 4(completely); 5-9(partially)

related to the compounds Ix2, Ix4, Ix6-7, It1, It10, It11
Iq6 and Iq9.

1.2. claims: 3(completely); 5-9(partially)

related to the compounds Iz1 and Iz3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/054645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013000924 A1	03-01-2013	AU 2012277912 A1 CA 2838645 A1 CN 103619846 A EA 201490165 A1 EP 2723744 A1 WO 2013000924 A1	19-12-2013 03-01-2013 05-03-2014 30-04-2014 30-04-2014 03-01-2013
WO 2012104293 A1	09-08-2012	AR 085099 A1 AU 2012213471 A1 CA 2824929 A1 CN 103459395 A CO 6811848 A2 EA 201300871 A1 EP 2670754 A1 JP 2014503576 A KR 20140019342 A MA 34844 B1 SG 192210 A1 TW 201245198 A US 2012302564 A1 UY 33888 A WO 2012104293 A1	11-09-2013 04-07-2013 09-08-2012 18-12-2013 16-12-2013 30-01-2014 11-12-2013 13-02-2014 14-02-2014 02-01-2014 30-09-2013 16-11-2012 29-11-2012 31-08-2012 09-08-2012
WO 2013034755 A1	14-03-2013	NONE	
WO 2013034758 A1	14-03-2013	NONE	