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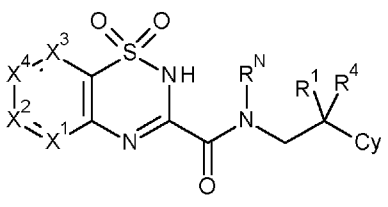
(54) Title: FUSED [1,2,4]THIADIAZINE DERIVATIVES WHICH ACT AS KAT INHIBITORS OF THE MYST FAMILY



(I)

(57) Abstract: A compound of formula (I): which inhibits the activity of one or more KATs of the MYST family, i.e., TIP60, KAT6B, MOZ, HBO1 and MOF.

FUSED [1,2,4]THIADIAZINE DERIVATIVES WHICH ACT AS KAT INHIBITORS OF THE MYST FAMILY

The present invention relates to compounds which act as Lysine Acetyl Transferase (KAT) inhibitors of the MYST family.

Background to the invention

The MYST family is the largest family of KATs and is named after the founding members in yeast and mammals: MOZ, Ybf2/ Sas3, Sas2 and TIP60 *(Dekker 2014)*. MYST proteins mediate many biological functions including gene regulation, DNA repair, cell-cycle regulation and development *(Avvakumov 2007; Voss 2009)*. The KAT proteins of the MYST family play key roles in post-translational modification of histones and thus have a profound effect on chromatin structure in the eukaryotic nucleus *(Avvakumov 2007)*. The family currently comprises five mammalian KATs: TIP60 (KAT5; HTATIP; MIM 601409), MOZ (KAT6A; MIM 601408; MYST3), MORF (KAT6b; QKF; MYST4), HBO (KAT8; HBO1; MYST2) and MOF (KAT8; MYST1) *(Voss 2009)*. These five members of the MYST family are present in humans and malfunction of MYST proteins is known to be associated with cancer *(Avvakumov 2007)*. The most frequently used names for members of the MYST family are:

Common name	**MYST name**	**Systematic name**
MOF	MYST1	KAT8
HBO	MYST2	KAT7
MOZ	MYST3	KAT6A
MORF	MYST4	KAT6B
TIP60		KAT5

<u>MYST functional domains</u>

MYST proteins function in multisubunit protein complexes including adaptors such as ING proteins that mediate DNA binding *(Avvakumov 2007)*. For instance, TIP60 is affiliated to the NuA4 multiprotein complex (which embraces more than 16 members) *(Zhang 2017)*. However, there have also been some reports of a helix-turn-helix DNA-binding motif within the structure of the MOZ protein itself *(Holbert 2007)*, which suggests the capacity to bind directly to DNA.

The acetyltransferase activity of MYST proteins is effected by the MYST domain (the catalytic domain). The MYST domain contains an acetyl-coenzyme A binding motif, which is structurally conserved with other HATs, and an unusual C_2HC-type zinc finger *(Voss 2009)*. The highly conserved MYST domain, including the acetyl-CoA binding motif and zinc finger, is considered to be the defining feature of this family of enzymes *(Avvakumov 2007)*.

Role of MYST proteins

Acetylation of histone residues is generally associated with transcriptional activation. However, in some instances, transcriptional repression has also been attributed to MYST proteins *(Voss 2009)*. The individual members of the MYST family are known to participate in a broad range of important biochemical interactions:

HBO1 positively regulates initiation of DNA replication *(Avvakumov 2007; Aggarwal 2004; Doyon 2006; Iizuka 2006)* via acetylation of histone substrates, which presumably leads to a more accessible chromatin conformation *(Avvakumov 2007, Iizuka 2006*). HBO1 is also known to play a role in the pathogenesis of breast cancer by promoting an enrichment of cancer stem-like cells *(Duong 2013)* and by destabilising the estrogen receptor α (ERα) through ubiquinitiation, which proceeds via the histone-acetylating activity of HBO1 *(Iizuka 2013)*. HBO1 has also been implicated in Acute myeloid leukaemia (AML) (*Shi 2015*).

TIP60 (KAT5) is the most studied member of the MYST family. TIP60 plays an important role not only in the regulation of transcription but also in the process of DNA damage repair, particularly in DNA double-strand breaks (DSB) *(Gil 2017)*. TIP60 can acetylate p53, ATM and c-Myc. TIP60 and MOF specifically acetylate lysine 120 (K120) of p53 upon DNA damage *(Avvakumov 2007)*. TIP60 has also been implicated in being important for regulatory T-cell (Treg) biology. FOXP3 is the master regulator in the development and function of Tregs and it has been shown that acetylation of FOXP3 by TIP60 is essential for FOXP3 activity (*Li 2007*, *Xiao 2014*). Underscoring this, conditional TIP60 deletion in mice leads to a scurfy-like fatal autoimmune disease, mimicking a phenotype seen in FOXP3 knock out mice (*Xiao 2014*). In cancer, Treg cells can facilitate tumour progression by suppressing adaptive immunity against the tumour.

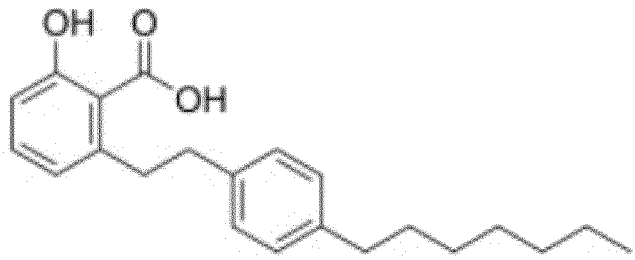
MOF ("males absent on the first") was originally identified as one of the components of the dosage compensation in Drosophila, and was classified as a member of the MYST family based on functional studies and sequence analysis *(Su 2016)*. The human ortholog

exhibits significant similarity to drosophila MOF; containing an acetyl-CoA-binding site, a chromodomain (which binds histones) and a C_2HC-type zinc finger *(Su 2016)*. MOF is a key enzyme for acetylating histone H4K16, and MOF-containing complexes are implicated in various essential cell functions with links to cancer *(Su 2016)*. Besides the global reduction of histone acetylation, depletion of MOF in mammalian cells can result in abnormal gene transcription, particularly causing abnormal expression of certain tumor suppressor genes or oncogenes, suggesting a critical role of MOF in tumorigenesis *(Su 2016)*. For example, KAT activity of MOF has been shown to be required to sustain MLL-AF9 leukemia and may be important for multiple AML subtypes (*Valerio 2017*).

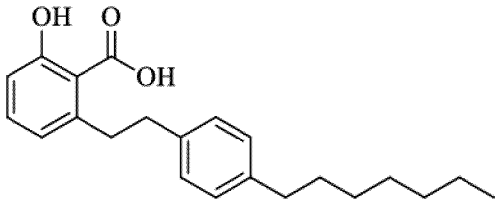
KAT6B (Querkopf) was first identified in a mutation screen for genes regulating the balance between proliferation and differentiation during embryonic development *(Thomas 2000)*. Mice homozygous for the KAT6B mutant allele have severe defects in cerebral cortex development resulting from a severe reduction in both proliferation and differentiation of specifically the cortical progenitor population during embryonic development. KAT6B is required for the maintenance of the adult neural stem cell population and is part of a system regulating differentiation of stem cells into neurons *(Merson 2006)*. KAT6B is also mutated in rare forms of leukaemia *(Vizmanos 2003)*.

The MOZ locus ranks as the 12th most commonly amplified region across all cancer types (*Zack 2013*). MOZ is within the 8p11-p12 amplicon, which is seen at frequencies around 10-15% in various cancers, especially breast and ovarian (*Turner-Ivey 2014*). MOZ was first identified as a fusion partner of the CREB-binding protein (CBP) during examination of a specific chromosomal translocation in acute myeloid leukaemia (AML) *(Avvakumov 2007; Borrow 1996)*. MOZ KAT activity is necessary for promoting the expression of MEIS1 and HOXa9, proteins that are typically seen overexpressed in some lymphomas and leukaemias. Increased survival of $MOZ^{+/-}$ heterozygote mice in the *E*μ-Myc transgenic model of B-cell lymphoma is seen, where loss of a single MOZ allele leads to a biologically relevant reduction in Meis1 and Hoxa9 levels in pre–B-cells (*Sheikh 2015*).

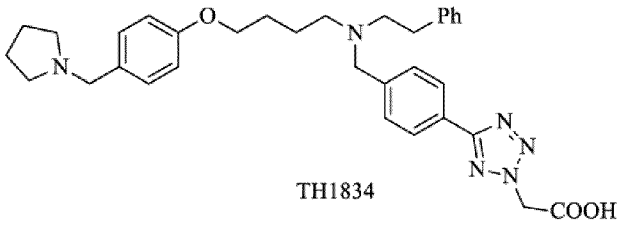
Inhibitors of some MYSTs are known. For example, the following Anacardic acid derivative is reported *(Ghizzoni 2012)* as inihibiting TIP60 (IC_{50} = 74μM) and MOF (IC_{50} = 47μM):



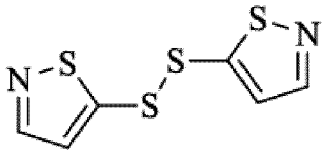
Other known inhibitors include (Zhang 2017):



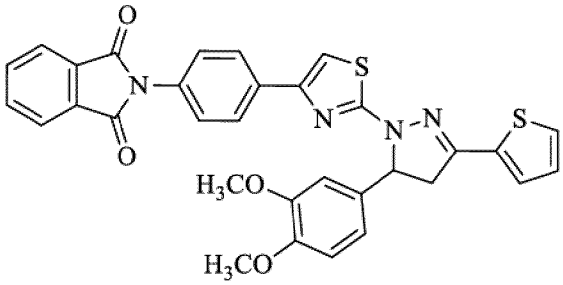
compound 20/MG149



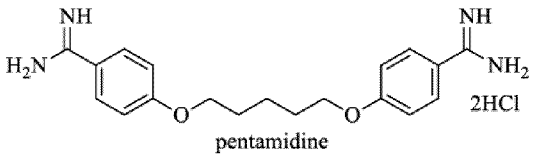
TH1834



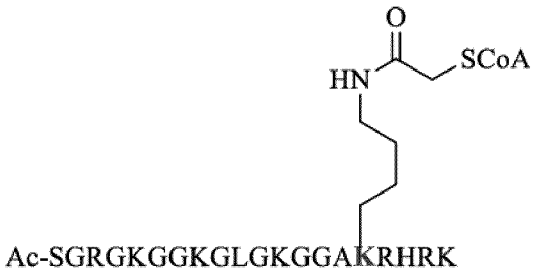
NU9056



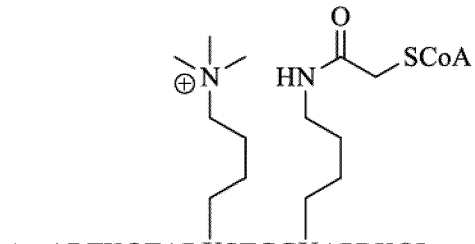
compound a



pentamidine



Ac-SGRGKGGKGLGKGGAKRHRK
H4K16CoA



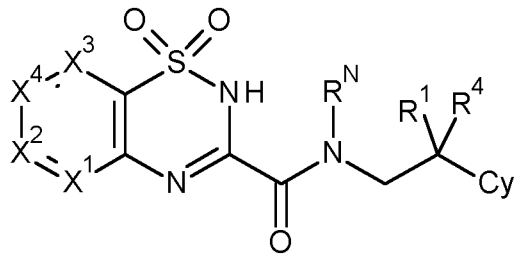
Ac-ARTKQTARKSTGGKAPRKQL
H3K9me3K14CoA

In light of the established role of KATs in general, and MYSTs in particular, in diseases such as cancer, a need exists for new inhibitors of these molecules.

Disclosure of the invention

The present invention provides compounds which inhibit the activity of one or more KATs of the MYST family, i.e., TIP60, KAT6B, MOZ, HBO1 and MOF.

A first aspect of the present invention provides a compound of formula I:



(I)

wherein:

R^N is H or Me;

X^4 is selected from CY and N;

X^1, X^2 and X^3 are each selected from CH and N, where none or one of X^1, X^2, X^3 and X^4 are N;

Y is selected from the group consisting of: H; halo; cyano; R^2, where R^2 is selected from CH_3, CH_2F, CHF_2 and CF_3; ethynyl; cyclopropyl; OR^3, where R^3 is selected from H, CH_3, CH_2F, CHF_2 and CF_3; $NR^{N1}R^{N2}$, where R^{N1} and R^{N2} are independently selected from H and CH_3; COQ^1, where Q^1 is selected from C_{1-4} alkyl, OH, OC_{1-4} alkyl and $NR^{N1}R^{N2}$; $NHSO_2Q^3$, where Q^3 is C_{1-3} alkyl; pyridyl; C_5 heteroaryl, which may be substituted by a group selected from C_{1-3} alkyl, which itself may be substituted by OH or $CONR^{N1}R^{N2}$; SO_2Me; C_{1-3} alkyl, substituted by NHZ, where Z is H, Me, SO_2Me, or COMe; C_{1-3} alkyl, substituted by OH;

Cy is selected from pyridyl, oxazolyl, cyclohexyl and optionally substituted phenyl, where the optional substituents are selected from the group consisting of: R^2; OR^5, where R^5 is selected from H, CH_3, CH_2F, CHF_2, CF_3 and cyclopropyl; benzyloxy; halo; cyano; amino; C_5 heteroaryl, optionally substituted by methyl, CH_2OH, CH_2OCH_3 or =O; phenyl; pyridyl, optionally substituted with methyl; COQ^5, where Q^5 is selected from OH, OCH_3 and $NR^{N1}R^{N2}$; and CH_2OQ^6, where Q^6 is H or Me;

R^1 is selected from the group consisting of: F; phenyl; pyridyl; C_5 heteroaryl, optionally substituted by methyl, CH_2OCH_3, CH_2CF_3, CHF_2, NH_2, or =O; C_9 heteroaryl; OH; OMe; OPh; COQ^4, where Q^4 is selected from OH, C_{1-3} alkyloxy, $NR^{N5}R^{N6}$, where R^{N5} is selected from H and Me, and R^{N5} is selected from C_{1-4} alkyl, which itself may be substituted by

CONHMe, or where R^{N5} and R^{N6} together with the N atom to which they are bound form a C_{4-6} N-containing heterocyclyl group, $(CH_2)_{n1}CONR^{N7}R^{N8}$, where n1 is 1 to 3, and R^{N7} and R^{N8} are independently selected from H and Me, and $O(CH_2)_{n2}CONR^{N9}R^{N10}$, where n2 is 1 or 3. And R^{N9} and R^{N10} are independently selected from H and Me; $(CH_2)_nOQ^7$, where n is 1 or 2 and Q^7 is H or Me; $NHCO_2Q^8$, where Q^8 is C_{1-3} alkyl; $OCONR^{N5}R^{N6}$;

R^4 is selected from H, F and methyl; or

R^1 and R^4 together with the carbon atom to which they are bound may form a C_{4-6} cycloalkyl; and

when Cy is cyclohexyl, pyridyl or substituted phenyl, R^1 may additionally be selected from H.

A second aspect of the present invention provides a compound of the first aspect for use in a method of therapy. The second aspect also provides a pharmaceutical composition comprising a compound of the first aspect and a pharmaceutically acceptable excipient.

A third aspect of the present invention provides a method of treatment of cancer, comprising administering to a patient in need of treatment, a compound of the first aspect of the invention or a pharmaceutical composition of the first aspect of the invention. The third aspect of the present invention also provides the use of a compound of the first aspect of the invention in the manufacture of a medicament for treating cancer, and a compound of the first aspect of the invention or pharmaceutical composition thereof for use in the treatment of cancer.

As described below, the compound of the first aspect may be administered simultaneously or sequentially with radiotherapy and/or chemotherapy in the treatment of cancer.

A third aspect of the present invention provides the synthesis of compounds of the first aspect of the invention, as decribed below.

Definitions

C_{5-9} heteroaryl: The term "C_{5-9} heteroaryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic structure having from 5 to 9 rings atoms, of which from 1 to 3 are ring heteroatoms. The term 'aromatic structure' is used to denote a single ring or fused ring systems having aromatic properties, and the term 'ring heteroatom' refers to a nitrogen, oxygen or sulphur atom.

In this context, the prefixes (e.g. C_{5-9}, C_5, etc.) denote the number of atoms making up the aromatic structure, or range of number of atoms making up the aromatic structure, whether carbon atoms or heteroatoms.

Examples of C_{5-9} heteroaryl structures include, but are not limited to, those derived from:
N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6); pyridone (C_6); indole (C_9);
O_1: furan (oxole) (C_5);
S_1: thiophene (thiole) (C_5);
N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);
N_2O_1: oxadiazole (furazan) (C_5);
N_1S_1: thiazole (C_5), isothiazole (C_5);
N_2S_1: thiadiazole (C_5)
N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);
benzimidazole (C_9)
N_3: triazole (C_5), triazine (C_6).

Halo: The term “halo” as used herein, refers to a group selected from fluoro, chloro, bromo and iodo.

Cyano: The term “cyano” as used herein, refers to a group -C≡N.

C_{1-4} alkyl: The term “C_{1-4} alkyl” as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated hydrocarbon compound having from 1 to 4 carbon atoms.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), and butyl (C_4).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), and n-butyl (C_4).

Examples of saturated branched alkyl groups include *iso*-propyl (C_3), *iso*-butyl (C_4), *sec*-butyl (C_4) and *tert*-butyl (C_4).

C_{4-6} heterocyclyl: The term "C_{4-6} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a monocyclic heterocyclic compound, which moiety has from 4 to 6 ring atoms; of which from 1 to 2 atoms are heteroatoms, chosen from oxygen or nitrogen.

In this context, the prefixes (e.g. C_{4-6}) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms.

Examples of C_{4-6} heterocyclyl groups include, but are not limited to, those derived from:
N_1: azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
N_2: diazetidine (C_4), imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
O_1: oxetane (C_4), tetrahydrofuran (C_5); oxane (C_6);
O_2: dioxetane (C_4), dioxolane (C_5); dioxane (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6).

Where the C_{4-6} heterocyclyl is defined as being "N-containing" this means one of the ring atoms is N, such that the group may be selected from:
N_1: azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
N_2: diazetidine (C_4), imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6).

Benzyloxy: -OCH_2-Phenyl.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in *Berge 1977*.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g. -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e. NH_4^+) and substituted ammonium ions (e.g. NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g. $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric,

glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, trifluoroacetic acid and valeric.

Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Solvates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g. active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

Isomers

Certain compounds of the invention may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

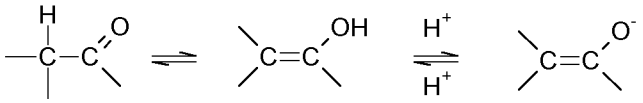
Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

In the present invention, the carbon atom to which R^1 and Cy are bound may be a stereochemical centre, i.e. when R^1 is not H and R^1 and Cy are different. The compounds of the present invention may be a racemic mixture, or may be in enantiomeric excess or substantially enantiomerically pure.

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference

to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g. C_{1-7} alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

Note that specifically included in the term “isomer” are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and

excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent. The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Inhibition

The compounds of the present invention inhibit the activity of one or more KATs of the MYST family, i.e., TIP60, KAT6B, MOZ, HBO1 and MOF.

The inhibitory activity of the compounds of the invention is likely to vary between the KATs of the MYST family.

The compounds of the present invention may selectively inhibit the activity of one or more KATs of the MYST family over other KATs of the MYST family, i.e. the inhibitory activity of the compound may be higher for one or more of the KATs of the MYST family over one or more of the other KATs of the MYST family.

Compounds of the present invention may (selectively) inhbit the activity of a single HAT of the MYST family. Thus, compounds of the present invention may inhibit the activity of TIP60, MORF, MOZ, HBO1 or MOF.

Compounds of the present invention may inhibit the activity of two KATs of the MYST family, for example TIP60 and HBO1.

Compounds of the present invention may inhibit the activity of three KATs of the MYST family, for example TIP60, HBO1 and MOF.

Compounds of the present invention may inhibit the activity of four KATs of the MYST family, for example TIP60, HBO1, MOF and MOZ.

Compounds of the present invention may inhibit the activity of all five KATs of the MYST family, thus the compounds may inhibit the acitvty of TIP60, KAT6B, MOZ, HBO1 and MOF.

Therapeutic Indications

Compounds disclosed herein may provide a therapeutic benefit in a number of disorders, in particular, in the treatment or prevention of cancers.

Cancer

Inhibitors of post-translational lysine acetylation mediated by KATs of the MYST family are considered to be promising anti-neoplastic agents and therefore may be useful therapeutic agents, e.g. for use in the treatment of cancer. Such agents may also be useful as therapeutic agents for the treatment of cancers which exhibit overexpression of MYST proteins.

A "cancer" may be any form of cancer. In particular, a cancer can comprise any one or more of the following: leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), non-Hodgkin's lymphoma, Hodgkin's disease, prostate cancer, lung cancer, melanoma, breast cancer, colon and rectal cancer, colon cancer, squamous cell carcinoma and gastric cancer.

Alternatively, the cancer may comprise adrenocortical cancer, anal cancer, bladder cancer, blood cancer, bone cancer, brain tumor, cancer of the female genital system, cancer of the male genital system, central nervous system lymphoma, cervical cancer, childhood rhabdomyosarcoma, childhood sarcoma, endometrial cancer, endometrial sarcoma,

esophageal cancer, eye cancer, gallbladder cancer, gastrointestinal tract cancer, hairy cell leukemia, head and neck cancer, hepatocellular cancer, hypopharyngeal cancer, Kaposi's sarcoma, kidney cancer, laryngeal cancer, liver cancer, malignant fibrous histiocytoma, malignant thymoma, mesothelioma, multiple myeloma, myeloma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, nervous system cancer, neuroblastoma, oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary tumor, plasma cell neoplasm, primary CNS lymphoma, rectal cancer, respiratory system, retinoblastoma, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, stomach cancer, testicular cancer, thyroid cancer, urinary system cancer, uterine sarcoma, vaginal cancer, vascular system, Waldenstrom's macroglobulinemia and/or Wilms' tumor.

Cancers may be of a particular type. Examples of types of cancer include lymphoma, melanoma, carcinoma (e.g. adenocarcinoma, hepatocellular carcinoma, medullary carcinoma, papillary carcinoma, squamous cell carcinoma), astrocytoma, glioma, medulloblastoma, myeloma, meningioma, neuroblastoma, sarcoma (e.g. angiosarcoma, chrondrosarcoma, osteosarcoma).

The cancer may be a MYST overexpressing cancer. The cancer may over-express MYST protein relative to non-cancerous tissue. In some cases, the cancer overproduces MYST mRNA relative to non-cancerous tissue. The overexpressed MYST protein or MYST mRNA may be any one KATs of the MYST family, i.e. any one of TIP60, KAT6B, MOZ, HBO1 and MOF. In some embodiments, the cancer may overexpress more than one KATs of the MYST family, e.g. two or more selected from the group consisting of TIP60, KAT6B, MOZ, HBO1 and MOF. The cancer may be a cancer that evades immune recognition, e.g. via tumor-associated Treg cells.

Alternatively or additionally, the cancer may be a bromodomain overexpressing cancer: The cancer cell may overexpress one or more bromodomain-containing proteins (herein referred to as “bromodomain proteins”) relative to non-cancerous tissue. It may overproduce one or more bromodomain mRNA as compared to non-cancerous tissue. In some cases, the level of bromodomain protein and/or mRNA in the cell is at a level approximately equivalent to that of a non-cancerous cell. The cancer may overexpress one or more bromodomain proteins selected from the group consisting of; a bromodomain protein (namely BRD2, BRD3, BRD4, BRD7, BRD8, BRD9 and BRDT), TAF1/TAF1L,

TFIID, SMARC2 (also called BRM) and SMARC4 (also called BRG1). For example, some colon cancers overexpress BRD8. Some acute myeloid leukemia cells overexpress BRD4.

Treg cells as a cancer target

Treg cells are immunosuppressive cells, which act to prevent autoimmunity in the healthy mammalian immune system. However, some cancers act to upregulate Treg activity to evade the host immune system. Infiltration of Tregs in many tumour types correlates with poor patient prognoses and Treg cell depletion in tumour models demonstrates increased anti-tumour immune responses *(Melero 2015)*. Tumour-associated Treg suppression of the host immune system has been reported in lung *(Joshi 2015), (Tso 2012)*, breast *(Gobert 2009; Yan 2011)*, prostate *(Miller 2006)* & pancreatic *(Wang X 2016)* cancers. FOXP3 is considered to be the master regulator of Treg differentiation, development and function of Treg cells.

Several studies have demonstrated that acetylation of FOXP3 plays a critical role in the stability of the FOXP3 protein and in regulating its ability to access DNA; and FOXP3 acetylation is mediated by KATs *(Dhuban 2017)*. Decreases in TIP60-mediated FOXP3 acetylation has been shown to attenuate Treg development, suggesting a further mechanism by which the inhibition of the acetylating activity of MYST proteins could be used to intervene in diseases such as cancer.

Combination therapies

The agents described herein may be useful in combination with other anti-cancer therapies. They may act synergistically with chemo- or radiotherapy, and/or with bromodomain targeted drugs. For example, the agents described herein may be useful in combination with a BET inhibitor. BET inhibitors reversibly bind the bromodomains of the BET proteins BRD2, BRD3, BRD4 and BRDT.

Inhibition of HAT proteins of the MYST family, to reduce the extent of lysine acetylation of histones (and other nuclear proteins described herein) will likely sensitize tumour cells to chemo- and radiotherapy by attenuating the process of DNA damage repair, e.g. the repair of DNA double-strand breaks (DSB), thus increasing the frequency of chemo- and radiotherapy induced cancer cell death. Therefore, it is likely that inhibition of HAT proteins of the MYST family would synergize well with low dose chemo- or radiotherapy.

Thus, in some cases, a MYST protein antagonist disclosed herein may be administered in conjunction with a radiotherapeutic or chemotherapeutic regime. It may be administered simultaneously or sequentially with radio and/or chemotherapy. Suitable chemotherapeutic agents and radiotherapy protocols will be readily appreciable to the skilled person. In particular, the compound described herein may be combined with low dose chemo or radio therapy. Appropriate dosages for "low dose" chemo or radio therapy will be readily appreciable to the skilled practitioner.

In particular, where the compounds of the present application are used to abrogate Treg suppression, these may be combined with with immune checkpoint inhibitors *(Melero 2015, Wang L 2016*). Furthermore, where compounds of the present invention which abrogate Treg suppression may be used in combination with radiotherapy, to reduce the depletion of Treg function in tumours (*Persa 2015, Jeong 2016*)

Methods of Treatment

The compounds of the present invention may be used in a method of therapy. Also provided is a method of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of the invention. The term "therapeutically effective amount" is an amount sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors.

As described above, the anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and docetaxel

(Taxotere) and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5*-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661 and and 4-((2,4-dichloro-5-methoxyphenyl)amino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline-3-carbonitrile (bosutinib, SKI-606; Cancer research (2003), 63(2), 375-81), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [HerceptinT], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by *Stern 2005*; such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763,

MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic and antilymphangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor A (VEGFA) antibody bevacizumab (AvastinT), the anti vascular endothelial cell growth factor A (VEGFA) antibody ranibizumab, the anti-VEGF aptamer pegaptanib, the anti vascular endothelial growth factor receptor 3 (VEGFR3) antibody IMC-3C5, the anti vascular endothelial cell growth factor C (VEGFC) antibody VGX-100, the anti vascular endothelial cell growth factor D (VEGFD) antibody VGX-200, the soluble form of the vascular endothelial growth factor receptor 3 (VEGFR3) VGX-300 and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (vandetanib; ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (cediranib; AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985), pazopanib (GW786034), axitinib (AG013736), sorafenib and sunitinib (SU11248; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies

Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intravitreal and intrasternal; by implant of a depot, for example, subcutaneously, intravitreal or intramuscularly. The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orang-utan, gibbon), or a human.

Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term “pharmaceutically acceptable” as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also

be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington’s Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid

diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/mL to about 10 µg/mL, for example from about 10 ng/ml to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the compound, and compositions comprising the compound, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition,

general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the active compound is in the range of about 100 ng to about 25 mg (more typically about 1 µg to about 10 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 100 mg, 3 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 150 mg, 2 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 200 mg, 2 times daily.

However in one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 50 or about 75 mg, 3 or 4 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 100 or about 125 mg, 2 times daily.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, regression of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Similarly, the term "prophylactically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired prophylactic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The Subject/Patient

The subject/patient may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus. In one preferred embodiment, the subject/patient is a human.

General synthesis methods

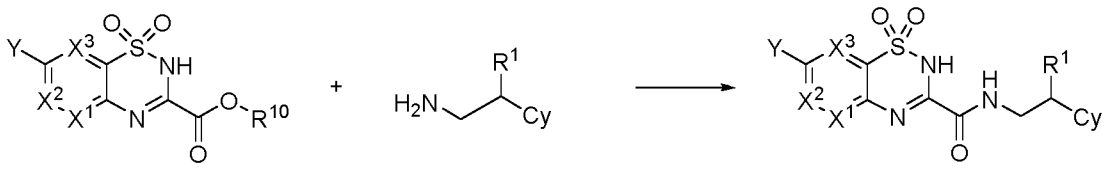
The compounds of the invention can be prepared employing the following general methods and using procedures described in detail in the examples. The reaction

conditions referred to are illustrative and non-limiting, for example one skilled in the art may use a diverse range of synthetic methods to synthesize the desired compounds such as but not limited to methods described in literature (for example but not limited to March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 7th Edition or Larock's Comprehensive Organic Transformations: Comprehensive Organic Transformations: A Guide to Functional Group Preparations).

Compounds of formula I, as described above, can be prepared by synthetic strategies outlined below, wherein the definitions above apply. The synthetic strategies could be applied to the use of racemic or single enantiomer starting materials.

General synthesis method 1

Scheme 1A illustrates the formation of the amide bond by coupling the relevant benzothiadiazinedioxide alkyl ester **G1** (R^{10} = alkyl) with primary amine **G2**. Methods to form such amides **G3** will be apparent to those skilled in the art, but include for example the use of microwave irradiation or conventional heating, either in a reagent-free fashion or with reagents such as NEt_3, DMAP or DIPEA and optionally with the use of a suitable solvent, e.g. ethanol or acetonitrile.

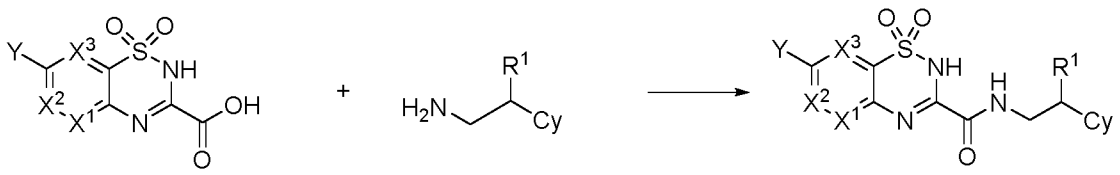


G1 G2 G3

Scheme 1A

General synthesis method 2

Scheme 2A illustrates the formation of the amide bond by coupling the relevant benzothiadiazinedioxide carboxylic acid **G4** to primary amine **G2**. Methods to form such amides **G3** will be apparent to those skilled in the art, but include for example, the use of reagents such as EDCI/DMAP, EDCI/HOBt, HATU, HBTU and T3P. Alternatively the acid can be activated prior to treatment with the primary amine **G2**. Such methods include, but are not limited to, acyl chloride formation from **G4** (e.g. $SOCl_2$, $POCl_3$, oxalyl chloride and DMF in an appropriate solvent), mixed anhydride formation from **G4** ($ClCO_2CH_3$ and Et_3N, *iso*-butylO_2CCl and Et_3N in an appropriate solvent, e.g. CH_2Cl_2 or MeCN) or acyl imidazolide formation (carbonyl diimidazole and DIPEA in an appropriate solvent).

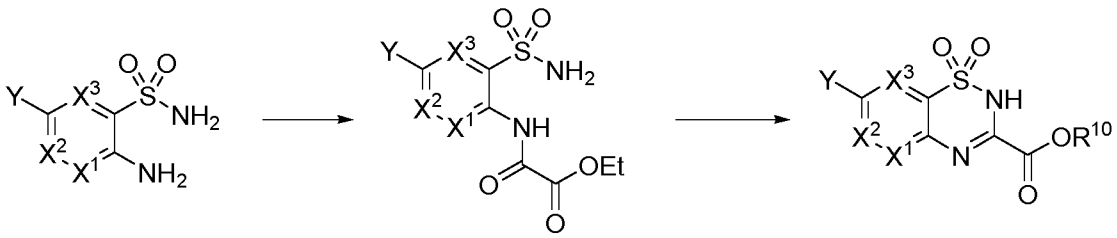


G4 G2 G3

Scheme 2A

General synthesis method 3

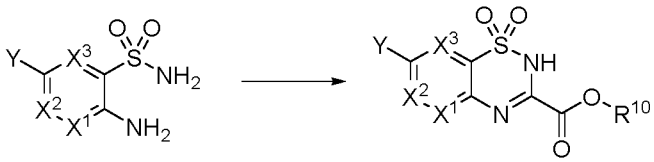
Scheme 3A illustrates the formation of the benzothiadiazinedioxide core G1 by acylation of the aminobenzenesulfonamide **G5** with ethyl 2-chloro-2-oxoacetate, followed by cyclization of **G6** with a base such as sodium hydride to form core **G1**.



G5 G6 G1(R^{10} = Et)

Scheme 3A

Alternatively **G5** can be treated with a reagent such as ethyl carbonocyanidate to form the bicyclic core **G1** directly (Scheme 4A).



G5 G1

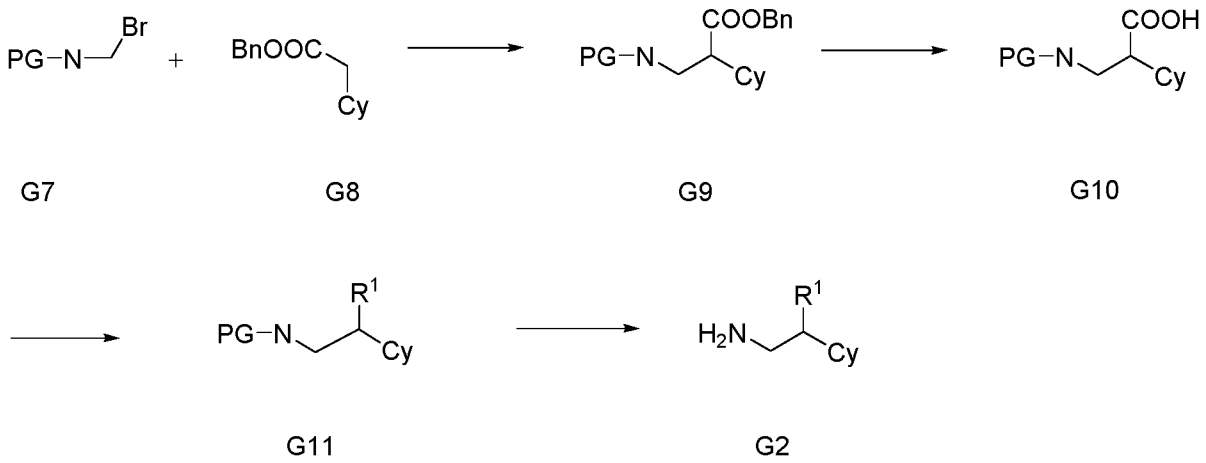
Scheme 4A

Formation of **G5** (Y = Cl, Br or I) can be achieved from **G5** (Y= H) using reagents such as *N*-chlorosuccinimide, Br_2 or ICl, which can then undergo cyclisation to give **G1** as shown in Scheme 3A or 4A.

General synthesis method 4

Scheme 5A illustrates the formation of primary amines **G2** from common intermediate **G10**. Preparation of versatile intermediate **G10** can be achieved through the alkylation of benzylacetate **G8** with an alkyl halide, e.g. **G7** (where PG is an appropriate protecting

group), using a strong base such as LiHMDS followed by the hydrogenation of ester **G9**. Alternative preparation of **G10** can be achieved through the *N*-protection of an appropriate beta amino acid. Carboxylic acid **G10** is a versatile intermediate that can be used to introduce a range of R^1 substituents. Formation of an oxazole can be achieved through activation to the acyl chloride and then treatment with 1,2,3-triazole in sulfolane. Likewise, treatment of the acyl chloride with a suitable hydrazide (e.g. formyl hydrazine), followed by Burgess reagent will furnish a 1,3,4-oxadiazole. The synthesis of other aromatic heterocycles from **G10** can be achieved by those skilled in the art, using methods described in *Hereocyclic Chemistry* (J.A. Joule and K. Mills, Blackwell Science). Carboxylic acid **G10** can be converted to amides using a suitable primary or secondary amine and an appropriate coupling agent (e.g. T3P, HATU, HBTU, EDCI, etc.). Curtius rearrangement can be achieved through treatment of carboxylic acid **G10** with an appropriate azido reagent, e.g. DPPA. The resulting isocyanate can be trapped with a suitable alcohol to give a carbamate. If a Boc-protected amine is introduced, the protecting group can be removed to furnish a primary amine, which itself could be further derivatised using methods known to those skilled in the art.

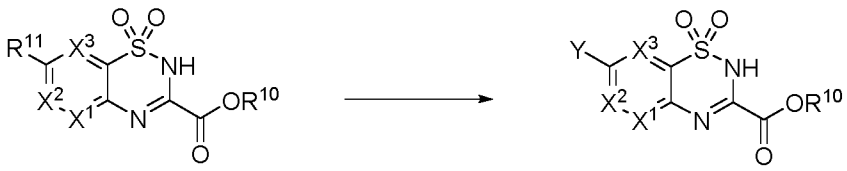


Scheme 5A

Deprotection of these materials **G11** yields primary amines **G2**, which can then be coupled following general synthesis methods 1 or 2. Conditions for the removal of the protecting group are dependent on the type of protecting group employed, and may include but are not limited to such methods as acid or base hydrolysis, transition metal catalysed cleavage and hydrogenation over transition metal catalysts. Other suitable protecting groups and removal methods will be known to those skilled in the art (for example *Greene's Protective Groups in Organic Synthesis, 4th Edition*). The use of such a protecting group could be relevant in the other Schemes described.

General synthesis method 5

Scheme 6A shows the conversion of intermediate G12 (where R^{10} is alkyl or H) and R^{11} is a halogen (e.g. I, Br or Cl) to **G1** with a range of substituents Y. Suzuki coupling from **G12** can be used to introduce heteroaromatic rings through the use of an appropriate boronic acid or boronate ester and an appropriate catalyst (e.g. Pd^{II} or Pd^{0}) optionally with a suitable ligand. Y=CN can be introduced through treatment of **G12** with a suitable source of cyanide using an appropriate catalyst and ligand. An ester can be introduced to Y using a carbonylation reaction, using carbon monoxide gas, a suitable alcohol (e.g. ethanol) and a suitable catalyst. The alkyl ester can be hydrolysed to give a carboxylic acid (e.g. using LiOH is a suitbale solvent) and then couple with a suitable amine to form an amide using a coupling reagent (e.g. T3P, HATU, HBTU etc). Intermediates **G1** can be converted to **G3**, for example by using general synthesis methods 1 or 2.

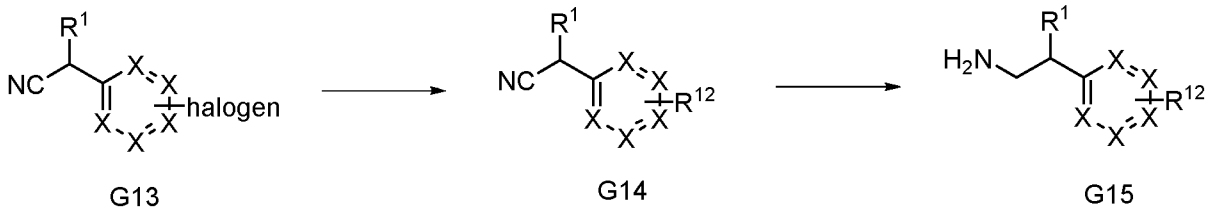


G12 G1

Scheme 6A

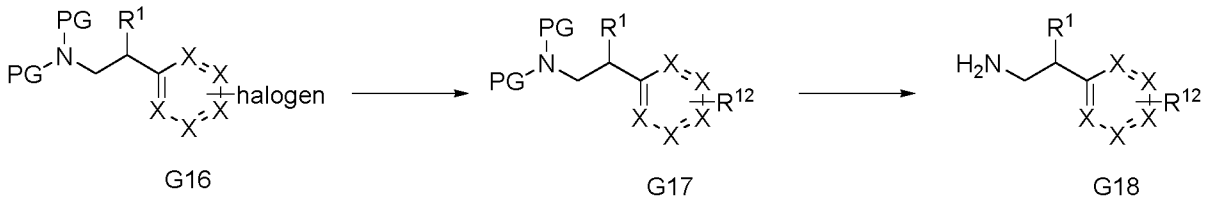
General synthesis method 6

Scheme 7A illustrates an alternative route for accessing primary amines (X=CH or N). The conversion of a suitable halophenyl or halopyridyl compound **G13** to **G14** can be achieved as shown in Scheme 7A. If the halogen in **G13** is iodo or bromo, an *N*-linked 5-membered aromatic heterocycle R^{12} can be introduced with the use of a suitable copper catalyst. Where R^{12} is a *C*-linked heterocycle, an appropriate boronic acid or boronate ester in combination with a suitable catalyst (e.g. Pd^{II} or Pd^{0}), can effect the formation of **G14**. Where the halogen is F or Cl, treatment of **G13** with a suitable nucleophile (e.g. an alcohol or 5-membered heterocycle, e.g. pyrazole or triazole), an S_NAr reaction could effect the formation of R^{12} = OR^3, or *N*-linked 5-membered aromatic heterocycle. Reduction of the nitrile group in **G14** with a suitable reducing agent, e.g. $LiAlH_4$ or BH_3 effects the formation of primary amine **G15**, which can be converted to **G3** using the general synthesis methods 1 or 2.



Scheme 7A

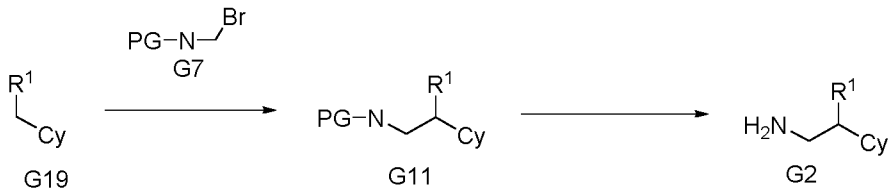
An alternative to the use of the nitrile shown in Scheme 7A, is shown in Scheme 8A, where PG is a suitable protecting group or a hydrogen atom. Such protecting groups include, but are not limited to, phthalimide, Boc, acetyl, CBZ, benzyl and dimethoxy benzyl. Halogen **G16** can be converted to **G17** using similar methods to those described for **G13** to **G14**. Deprotection of **G17** to give **G18** can be achieved using methods known to those skilled in the art.



Scheme 8A

General synthesis method 7

Scheme 8B illustrates an alternative route for accessing primary amine **G2**. Alkylation of structure **G19** can be achieved with an alkyl halide, e.g. **G7** (where PG is an appropriate protecting group), using an appropriate base such as but not limited to LiHMDS. Deprotection of **G11** yields primary amines **G2**, which may then be coupled following general synthesis methods 1 or 2.

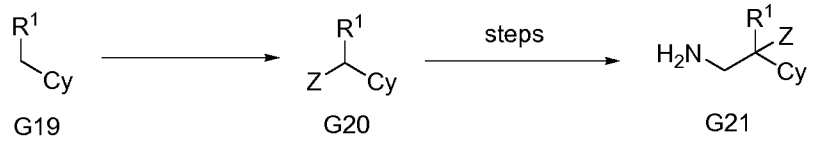


Scheme 8B

General synthesis method 8

Scheme 9A illustrates the introduction of substituent Z on the benzylic carbon in structure **G19** to form the corresponding structure **G20**. Substituent Z may be but is not limited to a halogen such as fluoro. For example, **G19** may be reacted with a suitable base such as for

example LiHMDS to form the corresponding carbanion which may be treated with a suitable source of F^+ such as but not limited to NFSI (*N*-fluorodibenzenesulfonimide).



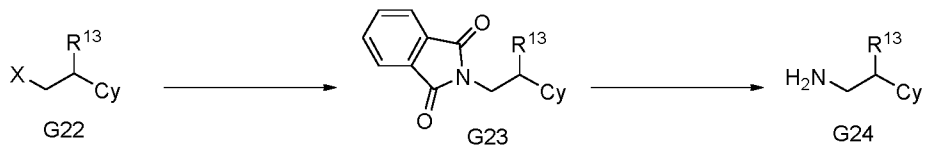
Scheme 9A

Subsequent alkylation and deprotection of **G20** described as described in general synthesis method 7 would give amine **G21**, which may then be coupled following general synthesis methods 1 or 2.

General synthesis method 9

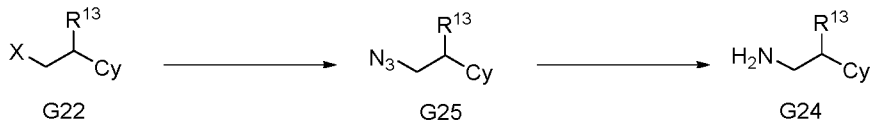
Scheme 10A and B illustrate the synthesis of a primary amine **G24** (where R^{13} represents a suitable substituent, including H) from starting material **G22** (where X = OH or halogen such as but not limited to Br or activated alcohol such as but not limited to mesylate), for example via intermediate **G23** in the Gabriel synthesis (Scheme 10A) or via the azide intermediate **G25** (Scheme 10B).

The formation of intermediate **G23** may be achieved via nucleophilic substitution or via the Mitsunobu reaction (when X = OH). Cleavage to give amine **G24** may be achieved by treating **G23** with for example hydrazine.



Scheme 10A

The azide **G25** may be achieved via for example nucleophilic substitution or Mitsunobu and then reduced to the primary amine by methods known to someone skilled in the art but may include the use of a metal catalyst in the presence of hydrogen or the use of triphenylphosphine (Staudinger reaction).

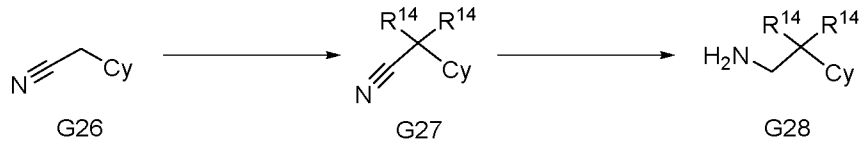


Scheme 10B

General synthesis method 10

Scheme 11A illustrates the formation of primary amine **G28** via alkylation of a nitrile such as **G26**. Groups R^{14} may be alkyl groups such as but not limited to methyl or ethyl and may connected to form for example a cyclopentyl or cyclohexyl moiety. Methods to form intermediate **G27** from **G26** may be known to someone skilled in the art and include the use of an appropriate base such as hydroxide or an alkoxide base to form an anion which is then reacted with for example an alkyl halide. If the two R14 groups form a cycle, the appropriate starting material may be a dihaloalkane such as for example 1,4-dibromobutane to form the cyclopentyl moiety.

Subsequent reduction of the nitrile in structure **G27** may be achieved via hydrogenation in the presence of a metal catalyst.



G26 G27 G28

Scheme 11A

Further Preferences

The following preferences may apply to all aspects of the invention as described above, or may relate to a single aspect. The preferences may be combined together in any combination.

R^N

In some embodiments, R^N is H.

In some embodiments, R^N is Me.

X^4

In some embodiments, X^4 is CY.

In some embodiments, X^4 is N.

X^1, X^2 and X^3

In some embodiments, none of X^1, X^2 and X^3 are N, i.e. they are all CH.

In some embodiments, none of X^1, X^2, X^3 and X^4 are N.

In some embodiments, X^1 is N.

In some embodiments, X^2 is N.

In some embodiments, X^3 is N.

Compounds where none of X^1, X^2, X^3 and X^4 are N may be preferred for compounds which inhibit TIP60.

Y

In some embodiments, Y is H.

In some emodiments, Y is halo. When Y is halo, it may be selected from I and F. In some of these embodiments, Y is F. In other of these embodiments, Y is I.

In some embodiments, Y is cyano (C≡N).

In some embodiments, Y is R^2. In some of these embodiments, R^2 is CH_3 (methyl). In other of these embodiments, R^2 is CH_2F. In other of these embodiments, R^2 is CHF_2. In other of these embodiments, R^2 is CF_3.
In certain embodiments, R^2 may be selected from from CH_3 and CF_3.

In some embodiments, Y is ethynyl (C≡CH).

In some embodiments, Y is cyclopropyl.

In some embodiments, Y is OR^3. In some of these embodiments, R^3 is H. In other of these embodiments, R^3 is CH_3 (methyl). In other of these embodiments, R^3 is CH_2F. In other of these embodiments, R^3 is CHF_2. In other of these embodiments, R^3 is CF_3.
In certain embodiments, R^3 may be selected from from H and CF_3.

In some embodiments, Y is $NR^{N1}R^{N2}$. In some of these embodiments, R^{N1} and R^{N2} are both H. In other of these embodiments, R^{N1} and R^{N2} are both Me. In other of these embodiments, R^{N1} is H and R^{N2} is Me.

In some embodiments, Y is COQ^1. In some of these embodiments, Q^1 is C_{1-4} alkyl, such as methyl. In other of these embodiments, Q^1 is OH. In other of these embodiments, Q^1 is OC_{1-4} alkyl, such as OMe. In other of these embodiments, Q^1 is $NR^{N1}R^{N2}$. In some of these particular embodiments, R^{N1} and R^{N2} are both H. In other of these particular embodiments, R^{N1} and R^{N2} are both Me. In other of these particular embodiments, R^{N1} is H and R^{N2} is Me.

In certain embodiments, Y is selected from COMe, CO_2H, CO_2Me, $CONH_2$, CONHMe and $CONMe_2$.

In some embodiments, Y is $NHSO_2Q^3$. In these embodiments, Q^3 is C_{1-3} alkyl, such as methyl.

In some embodiments, Y is pyridyl.

In some embodiments, Y is C_5 heteroaryl, which is optionally substituted. In some of these embodiments, the C_5 heteroaryl group may be selected from pyrrolyl, furanyl, thiolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl or triazolyl. The C_5 heteroaryl group may be selected from those containing a nitrogen ring atom. The C_5 heteroaryl group may be selected from those containing a nitrogen ring atom and a further ring heteroaom. The C_5 heteroaryl group may be selected from thiazolyl and pyrazolyl.
The substituent group may be selelcted from unsubstituted C_{1-3} alkyl, such as methyl, C_{1-3} alkyl substituted by OH, such as C_2H_4OH, and C_{1-3} alkyl substituted by $CONR^{N1}R^{N2}$, such as $CH_2CONHMe$.

In some embodiments, Y is SO_2Me.

In some embodiments, Y is C_{1-3} alkyl, substituted by NHZ, where Z is H, Me, SO_2Me, or COMe. In some of these embodiments, Z is H. In other of these embodiments, Z is Me. In other of these embodiments, Z is SO_2Me. In other of these embodiments, Z is COMe. In certain of these embodiments, Y is $CH(NH_2)CH_3$, $CH(NHCH_3)CH_3$, $CH(NHSO_2Me)CH_3$, or $CH(NHCOMe)CH_3$.

In some embodiments, Y is C_{1-3} alkyl, substituted by OH. In some of these embodiments, Y is $CH(OH)CH_3$.

Embodiments where Y is I or Br may be preferred for compounds which inhibit TIP60. Embodiments where Y is I may be further preferred for compounds which inhibit TIP60.

Embodiments where Y is selected from I, Br, CN, COQ^1 (where Q^1 is $NR^{N1}R^{N2}$) and C_5 heteroaryl may be preferred for compounds which inhibit MOZ. Embodiments where Y is

selected from CN, COQ^1 (where Q^1 is $NR^{N1}R^{N2}$) and C_5 heteroaryl may be further preferred for compounds which inhibit MOZ

Embodiments where Y is I or Br may be preferred for compounds which inhibit HBO1. Embodiments where Y is Br may be further preferred for compounds which inhibit HBO1.

R^1

In some embodiments (where Cy is pyridyl, cyclohexyl or substituted phenyl), R^1 is H. When Cy is cyclohexyl, in some embodiments R^1 may only be H if Y is present and is not H.

In some embodiments, R^1 is F.

In some embodiments, R^1 is phenyl.

In some embodiments, R^1 is pyridyl.

In some embodiments, R^1 is C_5 heteroaryl, optionally substituted by methyl, CH_2OCH_3, CH_2CF_3, CHF_2, NH_2, or =O. In some of these embodiments, R^1 is unsubstituted C_5 heteroaryl. In others of these embodiments, R^1 is C_5 heteroaryl substituted with methyl. In others of these embodiments, R^1 is C_5 heteroaryl substituted with CH_2OCH_3. In others of these embodiments, R^1 is C_5 heteroaryl substituted with CH_2CF_3. In others of these embodiments, R^1 is C_5 heteroaryl substituted with CHF_2. In others of these embodiments, R^1 is C_5 heteroaryl substituted with NH_2. In others of these embodiments, R^1 is C_5 heteroaryl substituted with =O.
In some of embodiments, the C_5 heteroaryl group may contain at least one nitrogen ring atom. In these embodiments, any other ring heteroatoms may be selected from nitrogen and oxygen. In certain embodiments, the C_5 heteroaryl group may be selected from pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl and triazolyl. In other certain embodiments, the C_5 heteroaryl group may be selected from pyrrolyl, oxazolyl, oxadiazolyl, pyrazolyl and triazolyl.

In some embodiments, R^1 is C_9 heteroaryl. In some of these embodiments, R^1 is indolyl.

In some embodiments, R^1 is OH.

In some embodiments, R^1 is OMe

In some embodiments, R^1 is OPh.

In some embodiments, R^1 is COQ^4, where Q^4 is selected from OH and C_{1-3} alkyloxy. In some of these embodiments, R^1 is CO_2H. In other of these embodiments, R^1 is CO_2Me. In other of these embodiments, R^1 is CO_2Et. In other of these embodiments, R^1 is $CO_2C(CH_3)_2$.

In some embodiments, R^1 is COQ^4, where Q^4 is $NR^{N5}R^{N6}$, where R^{N5} is selected from H and Me, and R^{N5} is selected from C_{1-4} alkyl, which itself may be substituted by CONHMe, or where R^{N5} and R^{N6} together with the N atom to which they are bound form a C_{4-6} N-containing heterocyclyl group. In some of these embodiments, R^1 is CO_2NH_2. In other of these embodiments, R^1 is CO_2NHMe. In other of these embodiments, R^1 is CO_2NMe_2. In other of these embodiments, R^1 is CO_2NHEt. In other of these embodiments, R^1 is CO_2piperidinyl.

In some embodiments, R^1 is COQ^4, where Q^4 is $(CH_2)_{n1}CONR^{N7}R^{N8}$, where n1 is 1 to 3, and R^{N7} and R^{N8} are independently selected from H and Me. In some of these embodiments, n1 is 1. In other of these embodiments, n1 is 2. In other of these embodiments, n1 is 3. In certain embodiments, R^1 is $C_3H_6CONHCH_3$.

In some embodiments, R^1 is COQ^4, where Q^4 is $O(CH_2)_{n2}CONR^{N9}R^{N10}$, where n2 is 1 or 2, and R^{N9} and R^{N10} are independently selected from H and Me. In some of these embodiments, n2 is 1. In other of these embodiments, n2 is 2. In certain embodiments, R^1 is $OC_2H_4CONHCH_3$.

In some embodiments, R^1 is $(CH_2)_nOQ^7$, where n is 1 or 2 and Q^7 is H or Me. In some of these embodiments R^1 is CH_2OH. In other of these embodiments, R^1 is $(CH_2)_2OH$. In other of these embodiments, R^1 is CH_2OMe. In other of these embodiments, R^1 is $(CH_2)_2OMe$.

In some embodiments, R^1 is $NHCO_2Q^8$, where Q^8 is C_{1-3} alkyl. In some of these embodiments, R^1 is $NHCO_2CH_3$. In other of these embodiments, R^1 is $NHCO_2C_2H_5$. In other of these embodiments, R^1 is $NHCO_2C(CH_3)_2$.

In some embodiments, R^1 is $OCONR^{N5}R^{N6}$. In some of these embodiments, R^{N5} and R^{N6} together with the N atom to which they are bound form a C_4 N-containing heterocyclyl group. In other of these embodiments, R^{N5} and R^{N6} are both Me.

R^4

In some embodiments, R^4 is H.

In some embodiments, R^4 is F.

In some embodiments, R^4 is methyl.

R^1 and R^4

When R^1 and R^4 together with the carbon atom to which they are bound may form a C_{4-6} cycloalkyl, they may form cylcobutyl, cylcopentyl or cylcohexyl.

In some of these embodiments, R^1 and R^4 together with the carbon atom to which they are bound form cylcobutyl.

In some of these embodiments, R^1 and R^4 together with the carbon atom to which they are bound form cylcopentyl.

In some of these embodiments, R^1 and R^4 together with the carbon atom to which they are bound form cylcohexyl.

Cy

In some embodiments, Cy is pyridyl.

In some embodiments, Cy is oxazolyl.

In some embodiments, Cy is cyclohexyl.

In some embodiments, Cy is unsubstituted phenyl.

In some embodiments, Cy is phenyl bearing a single substituent. The substituent may be in the 2-, 3- or 4- position. In some of these embodiments, the substituent is in the 2-position. In other of these embodiments, the substituent is in the 3- position. In other of these embodiments, the substituent is in the 4- position.

In some embodiments, the phenyl substituent is R^2. In some of these embodiments, R^2 is CH_3 (methyl). In other of these embodiments, R^2 is CH_2F. In other of these embodiments, R^2 is CHF_2. In other of these embodiments, R^2 is CF_3.

In certain embodiments, R^2 may be CF_3.

In some embodiments, the phenyl substituent is OR^5. In some of these embodiments, R^5 is H. In other of these embodiments, R^5 is CH_3 (methyl). In other of these embodiments, R^5 is CH_2F. In other of these embodiments, R^5 is CHF_2. In other of these embodiments, R^5 is CF_3. In other of these embodiments, R^5 is cyclopropyl.

In some embodiments, the phenyl substituent is benzyloxy.

In some embodiments, the phenyl substituent is halo. In some of these embodiments, the halo group is F. In others of these embodiments the halo group is Cl.

In some embodiments, the phenyl substituent is cyano.

In some embodiments, the phenyl substituent is amino (NH_2).

In some embodiments, the phenyl substituent is C_5 heteroaryl, optionally substituted by methyl, CH_2OH, CH_2OCH_3 or =O. In some of these embodiments, Cy is unsubstituted C_5 heteroaryl. In others of these embodiments, Cy is C_5 heteroaryl substituted with methyl. , In others of these embodiments, Cy is C_5 heteroaryl substituted with CH_2OH. In others of these embodiments, Cy is C_5 heteroaryl substituted with CH_2OCH_3. In others of these embodiments, Cy is C_5 heteroaryl substituted with =O.
In some of these embodiments, the C_5 heteroaryl group may contain at least one nitrogen ring atom. In these embodiments, any other ring heteroatoms may be selected from nitrogen and oxygen. In certain embodiments, the C_5 heteroaryl group may be selected from pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl and triazolyl. In other certain embodiments, the C_5 heteroaryl group may be selected from oxazolyl, pyrazolyl and triazolyl.

In some embodiments, the phenyl substituent is phenyl, i.e. Cy is biphenyl.

In some embodiments, the phenyl substituent is pyridyl, optionally substituted with methyl. In some of these embodiments, the phenyl substituent is unsubstituted pyridyl. In others of these embodiment, the phenyl substituent is pyridyl substituted by methyl.

In some embodiments, the phenyl substituent is COQ^5, where Q^5 is selected from OH, OCH_3 and $NR^{N1}R^{N2}$.

In some embodiments, Q^5 is OH.

In other embodiments, Q^5 is OCH_3.

In other embodiments, Q^5 is $NR^{N1}R^{N2}$. In some of these embodiments, R^{N1} and R^{N2} are both H. In other of these embodiments, R^{N1} and R^{N2} are both Me. In other of these embodiments, R^{N1} is H and R^{N2} is Me.

In some embodiments, the phenyl substituent is CH_2OQ^6, where Q^6 is H or Me. In some of these embodiments, the phenyl substituent is CH_2OH. In other of these embodiments, the phenyl substituent is CH_2OMe.

As discussed above, the compounds of the present invention have a stereochemical centre at the carbon atom to which R^1 and Cy are bound when R^1 is not H and R^1 and Cy are different. In some emodiments, these compounds are racemic. In other embodiments, these compounds are in enantiomeric excess. In other embdodiemts, these compounds are substantially enantiomerically pure/exist as a single enantiomer.

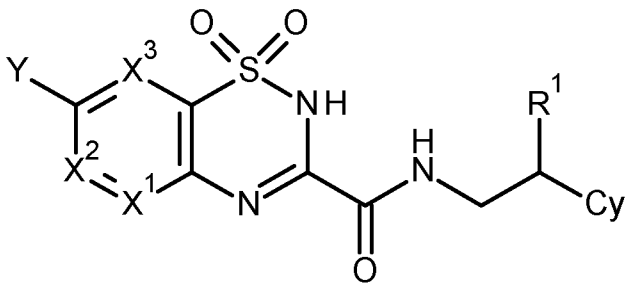
R^1 and Cy

In some embodiments, R^1 is H and Cy has a substituent in the 2- position, selected from $OCHF_2$ and a C_5 heteroaryl group selected from oxazolyl, pyrazolyl and triazolyl.

In some embodiments, R^1 is selected from oxazolyl, methyl-oxadiazolyl and pyrazolyl and Cy bears no substituent in the 2- position, i.e. Cy may be unsubstituted or bear a substituent in the 3- or 4- positions.

Compounds of particular interest include those of the examples.

In certain embodiments, the compounds of the invention are of formula Ia:



(Ia)

wherein:

X^1, X^2 and X^3 are each selected from CH and N, where none or one of X^1, X^2 and X^3 are N;
Y is selected from the group consisting of: H; halo; cyano; R^2, where R^2 is selected from CH_3, CH_2F, CHF_2 and CF_3; ethynyl; cyclopropyl; OR^3, where R^3 is selected from H, CH_3, CH_2F, CHF_2 and CF_3; $NR^{N1}R^{N2}$, where R^{N1} and R^{N2} are independently selected from H and CH_3; COQ^1, where Q^1 is selected from C_{1-4} alkyl, OH, OC_{1-4} alkyl and $NR^{N1}R^{N2}$; $NHSO_2Q^3$, where Q^3 is C_{1-3} alkyl; pyridyl; C_5 heteroaryl, which may be substituted by a group selected from C_{1-3} alkyl, which itself may be substituted by OH or $CONR^{N1}R^{N2}$;
Cy is selected from pyridyl and optionally substituted phenyl, where the optional substituents are selected from the group consisting of: R^2; O^{R3}; benzyloxy; halo; cyano; amino; C_5 heteroaryl, optionally substituted by methyl; pyridyl, optionally substituted with methyl; COQ^5, where Q^5 is selected from OH and $NR^{N1}R^{N2}$; and CH_2OQ^6, where Q^6 is H or Me;
R^1 is selected from the group consisting of: F; phenyl; pyridyl; C_5 heteroaryl, optionally substituted by methyl; C_9 heteroaryl; OH; OMe; OPh; COQ^4, where Q^4 is selected from OH, C_{1-3} alkyloxy, $NR^{N5}R^{N6}$, where R^{N5} is selected from H and Me, and R^{N5} is selected from C_{1-4} alkyl, which itself may be substituted by CONHMe, or where R^{N5} and R^{N6} together with the N atom to which they are bound form a C_{4-6} N-containing heterocyclyl group; $(CH_2)_nOH$, where n is 1 or 2; $NHCO_2Q^4$, where Q^4 is C_{1-3} alkyl; $OCONR^{N5}R^{N6}$; and
when Cy is pyridyl or substituted phenyl, R^1 may additionally be selected from H.

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), *n*-propyl (nPr), isopropyl (iPr), *n*-butyl (nBu), *tert*-butyl (tBu), phenyl (Ph), benzyl (Bn), methoxy (MeO), ethoxy (EtO), trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBDMS) and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), deuterated methanol (d_4-MeOD, methanol-d_4) ethanol (EtOH), isopropanol (*i*-PrOH), ether or diethyl ether (Et_2O), ethyl acetate (EtOAc), acetic acid (AcOH), acetonitrile (MeCN or ACN), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), dimethylsulfoxide (DMSO), deuterated chloroform ($CDCl_3$, chloroform-*d*), diethylamine (DEA), deuterated dimethylsulfoxide (d_6-DMSO, DMSO-d_6), *N*-ethyl-*N'-(*3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl, EDCI, EDCI·HCl), *meta*-chloroperoxybenzoic acid (mCPBA), 1,1'-bis(diphenylphosphino)ferrocene (dppf), *tert*-butyloxycarbonyl (Boc, BOC), 2-(trimethylsilyl)ethoxymethyl (SEM), triethylamine (Et_3N or TEA), 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 4-dimethylaminopyridine (DMAP), *N,N*-diisopropylethylamine (DIPEA or DIEA), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) ($PdCl_2$(dppf)), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$), tris(dibenzylideneacetone) dipalladium(0) ($Pd_2(dba)_3$), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), propylphosphonic anhydride (T3P), hexamethylphosphoramide (HMPA), 1,2-dichloroethane (DCE), benzyl (Bn) and 1-hydroxybenzotriazole (HOBt), petroleum ether (pet. ether), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), lithium bis(trimethylsilyl)amide (LHMDS or LiHMDS), acetylacetonate (acac), carbonyldiimidazole (CDI), methyl *tert*-butyl ether (MTBE), diisopropyl azodicarboxylate (DIAD), tetrabutylammonium fluoride (TBAF), methanesulfonyl chloride (MsCl).

In addition, TLC refers to thin layer chromatography.

Other abbreviations: overnight (o/n), retention time (rt, RT or R_t), minute(s) (min), hour(s) (h), room temperature (r.t., RT), concentrated (conc.), atmosphere (atm), aqueous (aq.), saturated (sat.), equivalent(s) (eq).

General Experimental Details

Unless otherwise stated the following generalisations apply. ^{1}H NMR spectra were recorded on a Bruker Ultrashield Plus (400 MHz) or a Bruker AVANCE (400 MHz). The multiplicity of a signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; br, broad; m, multiplet. All observed coupling constants, *J*, are reported in Hertz (Hz). Exchangeable protons are not always observed.

LCMS data was generated using either an Agilent 6100 Series Single Quad LCMS-A:, an Agilent 1260 Infinity Series UPLC/MS (LCMS-B) an Agilent 1200 Series Quad LCMS (LCMS-F) or Agilent 1200. Chlorine isotopes are reported as ^{35}Cl, Bromine isotopes are reported as either ^{79}Br or ^{81}Br or both ^{79}Br/^{81}Br.

LCMS Method A (LCMS-A):

Instrument: Agilent 6100 Series Single Quad LC/MS
Agilent 1200 Series HPLC
Pump: 1200 Series G1311A Quaternary pump
Autosampler: 1200 Series G1329A Thermostatted Autosampler
Detector: 1200 Series G1314B Variable Wavelength Detector

LC conditions:
Reverse Phase HPLC analysis
Column: Luna C8 (2) 5 µm 50 × 4.6 mm 100 Å
Column temperature: 30 °C
Injection Volume: 5 µL
Solvent A: Water 0.1 % Formic Acid
Solvent B: MeCN 0.1 % Formic Acid
Gradient: 5-100 % solvent B over 10 min
Detection: 254 nm or 214 nm

MS conditions:
Ion Source: Quadrupole

Ion Mode: Multimode-ES
Drying gas temp: 300 °C
Vaporizer temperature: 200 °C
Capillary voltage (V): 2000 (positive)
Capillary voltage (V): 4000 (negative)
Scan Range: 100-1000
Step size: 0.1 sec
Acquisition time: 10 min

LCMS Method B (LCMS-B):
Instrument: Agilent 1260 Infinity Series UPLC/MS
Pump: 1260 Infinity G1312B Binary pump
Autosampler: 1260 Infinity G1367E 1260 HiP ALS
Detector: 1290 Infinity G4212A 1290 DAD

LC conditions:
Reverse Phase HPLC analysis
Column: Poroshell 120 EC-C18 2.7 µm 50 × 3.0 mm
Column temperature: 35 °C
Injection Volume: 1 µL
Solvent A: Water 0.1 % Formic Acid
Solvent B: MeCN 0.1 % Formic Acid
Gradient: 5-100 % solvent B over 3.8 min
Detection: monitored at 254 nm and 214 nm

MS conditions:
Ion Source: Quadrupole
Ion Mode: API-ES
Drying gas temp: 350 °C
Capillary voltage (V): 3000 (positive)
Capillary voltage (V): 3000 (negative)
Scan Range: 100-1000
Step size: 0.1 sec
Acquisition time: 5 min

LCMS method C (LCMS-C):

LC model: Agilent 1200

(Pump type: Binary Pump, Detector type: DAD)

MS model: Agilent G6110A Quadrupole

LC conditions:

Column: Xbridge-C18, 2.5 μm, 2.1×30 mm

Column temperature: 30 °C

Acquisition of wavelength: 214 nm, 254 nm

Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH

MS conditions:

MS: Ion source: ES+ (or ES-) MS range: 50 - 900 m/z

Fragmentor: 60 Drying gas flow: 10 L/min

Nebulizer pressure: 35 psi Drying gas temperature: 350 °C

Vcap: 3.5 kV

Gradient Table :

Flow (mL/min)	T (min)	A (%)	B (%)
0.5	0.0	70	30
0.5	0.2	70	30
0.5	1.8	5	95
0.5	2.4	5	95
0.5	2.6	70	30
0.5	3.5	70	30

Sample preparation:

The sample was dissolved in methanol, the concentration about 0.11 - 1 mg/mL, then filtered through syringe filter with 0.22 μm. (Injection volume: 1 - 10μL)

LCMS method D (LCMS-D):

LC model: Agilent 1200

(Pump type: Binary Pump, Detector type: DAD)

MS model: Agilent G6110A Quadrupole

LCMS conditions:

LC: Column: Xbridge-C18, 2.5 µm, 2.1×30 mm
Column temperature: 30 °C
Acquisition of wavelength: 214 nm, 254 nm
Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH

MS conditions:
MS: Ion source: ES+ (or ES-) MS range: 50 - 900 m/z
Fragmentor: 60 Drying gas flow: 10 L/min
Nebulizer pressure: 35 psi Drying gas temperature: 350 °C
Vcap: 3.5 kV

Gradient Table :

Flow (mL/min)	T (min)	A (%)	B (%)
0.5	0.0	70	30
0.5	0.3	70	30
0.5	0.6	50	50
0.5	0.9	40	60
0.5	1.2	30	70
0.5	3.2	5	95
0.5	3.5	5	95
0.5	4.0	70	30
0.5	5.0	70	30

Sample preparation:
The sample was dissolved in methanol, the concentration about 0.11 - 1 mg/mL, then filtered through the syringe filter with 0.22 µm. (Injection volume: 1 - 10µL)

LCMS Method F (LCMS-F)
Instrument: Agilent 1200 series LC
Agilent 6120 Quadrupole Mass Detector
Agilent G1968D Active Splitter

LC conditions:
Reverse Phase HPLC analysis
Column: Agilent Eclipse XDB-C18 5µm 4.6 × 150mm

Injection loop volume: 900 µL
QPump Solvent A: Water plus 0.1% formic acid
QPump Solvent B: Acetonitrile plus 0.1% formic acid
QPump Gradient: 5-100% B over 10 min
Flow rate: 1 mL/min
Detection: 254nm

MS conditions:
Ion Source: Quadrupole
Ion Mode: ES
Vaporiser Temp: 200 °C
Gas Temp: 300 °C
Capillary voltage positive (V): 4000
Capillary voltage negative (V): 4000
Scan Range: 100-700 Amu
Acquisition time: 10min

Isocratic Pump (make-up flow):
Flow rate: 0.5 mL/min
Solvent: 50:50 water: acetonitrile plus 0.1% formic acid

LC-MS Method SYN-P-M (ES+)/SYN-N-M (ES-)
LC model: Agilent 1200; Pump type: Binary Pump, Detector type: DAD
MS model: Agilent G6110A Quadrupole

LC conditions
LC: Column: Xbridge-C18, 2.5 µm, 2.1×30 mm
Column temperature: 30 ℃
Acquisition of wavelength: 214 nm, 254 nm
Mobile phase: A: 0.07% HCOOH aqueous solution, B: MeOH
Run time: 5 min

MS conditions
Ion source: ES+ (or ES-) MS range: 50~900 *m/z*
Fragmentor: 60 Drying gas flow: 10 L/min
Nebulizer pressure: 35 psi Drying gas temperature: 350℃

Vcap: 3.5 kV

Gradient Table

Method Name（LCMS）	**Gradient**			
	Flow (ml/min)	T (min)	A (% yield)	B (% yield)
	0.5	0.0	70	30
	0.5	0.3	70	30
SYN-P-M (ES+)	0.5	0.6	50	50
or	0.5	0.9	40	60
SYN-N-M (ES-)	0.5	1.2	30	70
	0.5	3.2	5	95
	0.5	3.5	5	95
	0.5	4.0	70	30
	0.5	5.0	70	30

Sample preparation: The sample was dissolved in methanol, approximate concentration 0.11~1 mg/mL, then filtered through the syringes filter with 0.22 μm. (Injection volume: 1~10μL)

Preparative RP-HPLC:

Agilent 1260 Infinity HPLC system

UV detection at 210 nm and 254 nm

Gradient or isocratic elution through a Phenomenex Luna C8 (2) column 100 Å Axia (250 × 21.2 mm; particle size 5 μm)

Flow rate: 10 mL/min

Gradients are as specified in the individual examples.

Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminium-backed plates which were visualised using fluorescence quenching under UV light or a basic $KMnO_4$ dip or Ninhydrin dip.

Preparative thin-layer chromatography (preparative TLC or prep. TLC) was performed using Tklst (China), grand grade: (HPTLC): 8±2 μm>80 %; (TLC): 10-40 μm. Type: GF254. Compounds were visualised by UV (254 nm).

Flash chromatography was performed using a Biotage Isolera purification system using either Grace, SepaFlash® or RediSep® silica cartridges.

Column chromatography was performed using Tklst (China), grand grade, 100-200 meshes silica gel.

Microwave irradiation was achieved using a CEM Explorer SP Microwave Reactor.

Where necessary, anhydrous solvents were purchased from Sigma-Aldrich or dried using conventional methods.

Additional Cartridges used are as follows:

Phase Separator:

Manufacturer: Biotage

Product: ISOLUTE ® Phase Separator (3 mL unless otherwise stated)

SCX and SCX-2 cartridges:

Manufacturer: Biotage

Product: ISOLUTE ® SCX 1 g, (6 mL SPE Column unless otherwise stated)

Manufacturer: Biotage

Product: ISOLUTE ® SCX-2 1 g (6 mL Column)

Manufacturer: Silicycle

Product: SCX-2 500mg or 5g or 10g

Manufacturer: Agilent

Product: Bond Elut® SCX 10g

Sample extraction cartridge:

Manufacturer: Waters

Product: Oasis ® HLB 35 cc (6 g) LP extraction cartridge

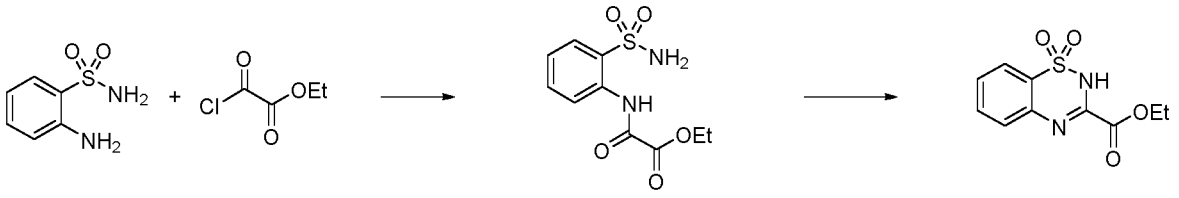
Si-amine cartridges:

Manufacturer: Agilent

Product: Bond Elut NH2 10g

Synthesis of intermediates

(i) Ethyl 2H-*benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2)*



I1 I2

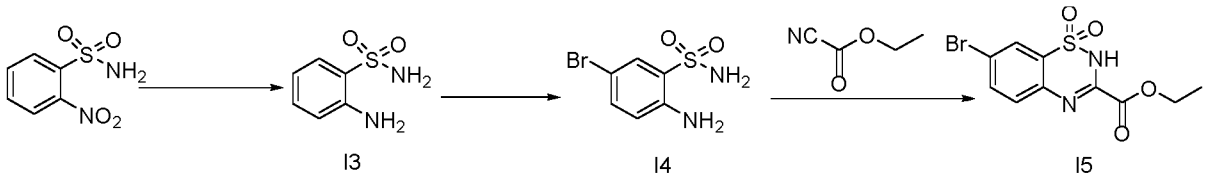
a) Ethyl 2-oxo-2-((2-sulfamoylphenyl)amino)acetate (I1)

To solution of 2-aminobenzenesulfonamide (10.000 g, 58.070 mmol) in THF (500 mL), at 0 °C, was added NEt_3 (8.50 mL, 60.973 mmol) followed by the dropwise addition of ethyl chlorooxoacetate (6.81 mL, 60.973 mmol) over 10 min. This was allowed to slowly warm to ambient temperature o/n. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo.* The resulting solid was slurried in warm EtOAc (50 mL), then filtered. The solid material was washed with a further portion of EtOAc (50 mL), then air dried to reveal ethyl 2-oxo-2-((2-sulfamoylphenyl)amino)acetate (12.399 g, 78 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 10.77 (s, 1H), 8.25 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.69 (s, 2H), 7.69 – 7.64 (m, 1H), 7.37 (ddd, *J* = 8.0, 7.4, 1.2 Hz, 1H), 4.32 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 1.33 (t, *J* = 7.1, 7.1 Hz, 3H). LC-MS (LCMS:B): rt 3.409 min; *m/z* 271.1 [M-H] (-ve); no corresponding product ions present in +ve mode.

b) Ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2)

To dry EtOH (200 mL), under a nitrogen atmosphere, was added NaH (60% dispersion in mineral oil, 1.463 g, 36.580 mmol) cautiously. This was allowed to stir for 15 min, upon which ethyl 2-oxo-2-(2-sulfamoylphenylamino)acetate (I1) (8.300 g, 30.483 mol) was added. This stirred for a further 3 h, upon which water (400 mL) was added and the pH adjusted to 3 using 2N aqueous HCl. The EtOH was removed *in vacuo*, and the precipitate filtered. The solid was washed with water, then air dried to reveal ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (5.575 g, 72 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 12.74 (s, 1H), 7.88 – 7.85 (m, 1H), 7.79 – 7.72 (m, 2H), 7.54 (ddd, *J* = 8.2, 6.3, 2.1 Hz, 1H), 4.40 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 1.36 (t, *J* = 7.1, 7.1 Hz, 3H). LC-MS (LCMS:B): rt 3.349 min; *m/z* 255.1 $[M+H]^+$.

(ii) Ethyl 7-bromo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5)



I3 I4 I5

a) 2-Aminobenzenesulfonamide (I3)

A mixture of 2-nitrobenzenesulfonamide (50 g, 245 mmol), zinc dust (81 g, 1.24 mol) and NH_4Cl (66 g, 1.24 mol) in EtOH (750 mL) and water (200 mL) was heated at 80 °C overnight then allowed to cool to r.t. The mixture was filtered and the solid was washed with DCM (20 mL). The filtrate was washed with brine, dried over sodium sulfate, filtered and concentrated to give the product (35 g, 82% yield) as a yellow solid. LCMS (ES-API): R_t 0.38 min; *m/z* 173.1 $[M+H]^+$.

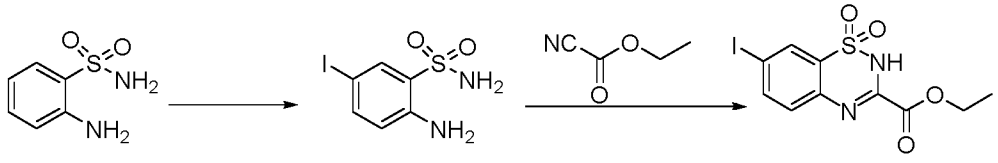
b) 2-Amino-5-bromobenzenesulfonamide (I4)

To a solution of 2-aminobenzenesulfonamide (I3) (20 g, 116 mmol) in CH_3COOH (200 mL) at r.t. was added a solution of Br_2 (10.9 g, 68 mmol) in CH_3COOH (200 mL) and the mixture was stirred at r.t. for 20 min then poured into ice-water (400 mL). The mixture was filtered and the solid was washed with water (100 mL). The combined filtrates were concentrated to give the product as a brown solid (17.2 g, 59% yield). LCMS (ES-API): R_t 1.11 min; *m/z* 250.9/252.9 $[M+H]^+$.

c) Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5)

To a solution of 2-amino-5-bromobenzenesulfonamide (I4) (10 g, 39.8 mmol) and ethyl carbonocyanidate (39.5 g, 398 mmol) in CH_3COOH (100 mL) at r.t. was added conc. HCl (10 mL) and the mixture was heated at 80 °C for 3 h then poured into ice-water (200 mL) and stirred for 1 h. The mixture was filtered and the solid was washed with water (100 mL). The combined filtrates were concentrated to give the product as a white solid (8 g, 60% yield). LCMS (ES-API): R_t 1.78 min; *m/z* 332.9/334.9 $[M+H]^+$.

(iii) Ethyl 7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7)



I3 I6 I7

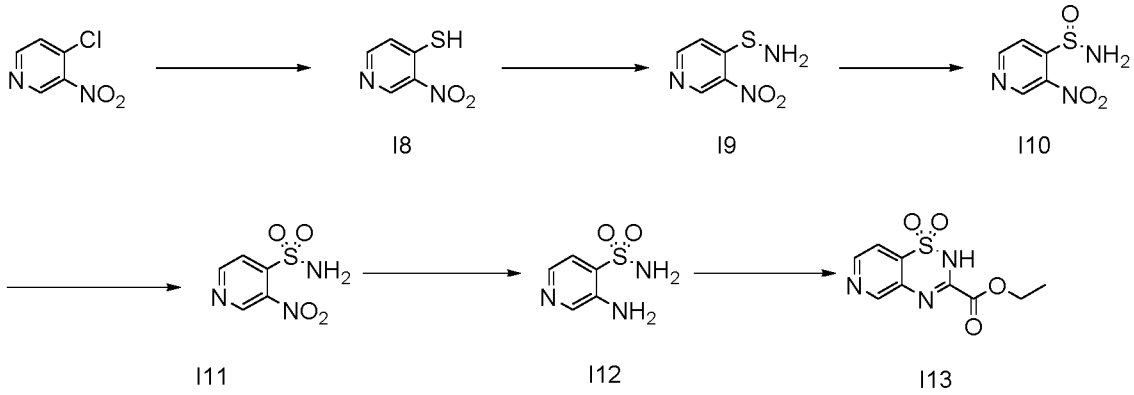
a) 2-Amino-5-iodobenzenesulfonamide (I6)

To a solution of 2-aminobenzenesulfonamide (I3) (3 g, 17.4 mmol) in $CHCl_3$ (150 mL) at -20°C was added a solution of ICl (1.98 g, 12.2 mmol) in $CHCl_3$ (150 mL) and the mixture was stirred at -20 °C for 30 min. The mixture was filtered and the solid was washed with $CHCl_3$ (50 mL) and 2 M aqueous $NaHCO_3$ (50 mL) then dried to give the product as a brown solid (3.3 g, 63% yield). LCMS (ES-API) R_t 1.34 min; *m/z* 298.9 $[M+H]^+$.

b) Ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7)

To a solution of 2-amino-5-iodobenzenesulfonamide (I6) (2 g, 6.7 mmol) and ethyl carbonocyanidate (6.5 g, 67 mmol) in CH_3COOH (40 mL) at r.t. was added conc. HCl (2 mL) and the mixture was heated at 80°C for 3 h then poured into ice-water (50 mL). The mixture was stirred for 1 h, filtered and the solid was washed with water (50 mL) then air dried to give the product as a brown solid (1.9 g, 75% yield). LCMS (ES-API) R_t 2.26 min; *m/z* 380.9 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.8 (brs, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 8.08 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.57 (d, *J* =8.8 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H).

*(iv) Ethyl 2*H*-pyrido[3,4-e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I13)*



a) 3-Nitropyridine-4-thiol (I8)

A mixture of 4-chloro-3-nitropyridine (15 g, 94.6 mmol) and $NaSH.H_2O$ (14 g, 189 mmol) in MeOH (100 mL) was stirred at r.t. for 10 min then heated at 60 °C for 10 min. The solvent was removed and the residue was dissolved in water and acidified to pH 6 with 1 M aqueous HCl. The resulting precipitate was collected by filtration, washed with water and air dried to give the product (10 g, 69% yield) as a yellow solid. LCMS (ES-API): R_t 0.31 min; *m/z* 43.0 $[M+H]^+$.

b) *S*-(3-Nitropyridin-4-yl)thiohydroxylamine (I9)

To a 28% solution of aqueous NaClO (300 mL) at -10 °C was added conc. NH_4OH (60 mL) dropwise with stirring. After 20 min, a solution of 3-nitropyridine-4-thiol (I8) (17 g, 0.11 mol)

in 2 M aqueous NaOH (60 mL) was added and stirring was continued for a further 1 h. The precipitate was collected by filtration and air dried to give the product (12 g, 67% yield) as a yellow solid. LCMS (ES-API): R_t 0.57 min; *m/z* 172.0 $[M+H]^+$.

c) 3-Nitropyridine-4-sulfinamide (I10)

To a mixture of *S*-(3-nitropyridin-4-yl)thiohydroxylamine (I9) (9.0 g, 52.6 mmol) in DCM (200 mL) at -5 °C was added m-CPBA (17 g, 78.9 mmol) in portions and the mixture was stirred at r.t. for 3 h. The mixture was concentrated and the residue was purified by column chromatography (EtOAc/Pet. Ether = 1:1) to give the product (2.5 g, 25% yield) as a yellow solid. LCMS (ES-API): R_t 0.35 min; *m/z* 187.9 $[M+H]^+$.

d) 3-Nitropyridine-4-sulfonamide (I11)

To a suspension of 3-nitropyridine-4-sulfinamide (I10) (2.0 g, 10.68 mmol) and water (1.92 g, 107 mmol) in ACN (60 mL) at 0 °C was added iodosylbenzene (2.59 g, 11.75 mmol) and the mixture was allowed to warm to r.t. and stirred for 2 h. The mixture was concentrated and the residue was purified by column chromatography (MeOH/DCM = 1:80) to give the product (1.75 g, 81% yield) as a yellow solid. LCMS (ES-API): R_t 0.36 min; *m/z* 203.9 $[M+H]^+$.

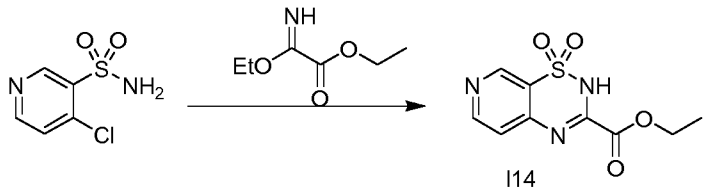
e) 3-Aminopyridine-4-sulfonamide (I12)

A mixture of 3-nitropyridine-4-sulfonamide (I11) (2.0 g, 9.89 mmol) and 10% Pd/C (200 mg) in EtOH (60 mL) was heated at 50 °C under 1 atm of H_2 for 16 h. The mixture was filtered through Celite® and the filtrate was concentrated to give the product (1.2 g, 70% yield) as a white solid. LCMS (ES-API): R_t 0.30; *m/z* 174.0 $[M+H]^+$.

f) Ethyl 2*H*-pyrido[3,4-*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I13)

A mixture of 3-aminopyridine-4-sulfonamide (I12) (500 mg, 2.89 mmol), ethyl 2-ethoxy-2-iminoacetate (629 mg, 4.34 mmol) and DBU (879 mg, 5.78 mmol) in EtOH (10 mL) was heated in a microwave at 135 °C for 30 min then allowed to cool to r.t.. The mixture was concentrated and the residue was dissolved in water, acidified to pH 2 with 1 M aqueous HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, concentrated and the residue was purified by preparative TLC (MeOH/DCM = 1:20) to give the product (50 mg, 7% yield) as a yellow solid. LCMS (ES-API): R_t 0.51 min; *m/z* 255.9 $[M+H]^+$. ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.2 (brs, 1H), 9.09 (s, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 7.88 (d, *J* =5.2 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

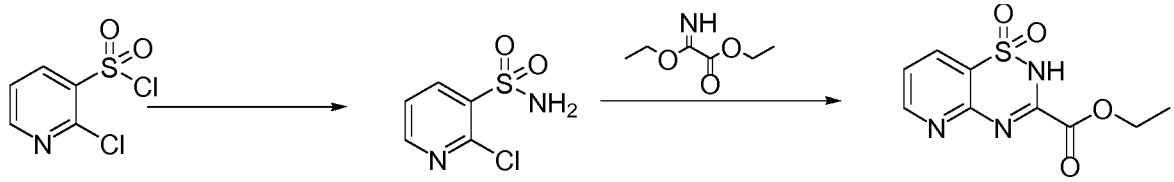
(v) Ethyl 2H-pyrido[4,3-e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I14)



I14

A mixture of 4-chloropyridine-3-sulfonamide (500 mg, 2.6 mmol), ethyl 2-ethoxy-2-iminoacetate (565 mg, 3.9 mmol) and DBU (790 mg, 5.2 mmol) in ethanol (10 mL) was heated in a sealed tube at 150 °C for 0.5 h then cooled to r.t.. The mixture was diluted with water (5 mL), adjusted to pH 5 with 1 M aqueous HCl and exacted with DCM (10 mL x 3). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by preparative TLC (MeOH/DCM = 1:20, v/v) to give the product as a yellow solid (100 mg, 15% yield). LCMS (ES-API) R_t 0.47 min; *m/z* 256 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO), 9.05 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J* = 5.6 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

(vi) Ethyl 2H-pyrido[2,3-e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I16)



I15 I16

a) 2-Chloropyridine-3-sulfonamide (I15)

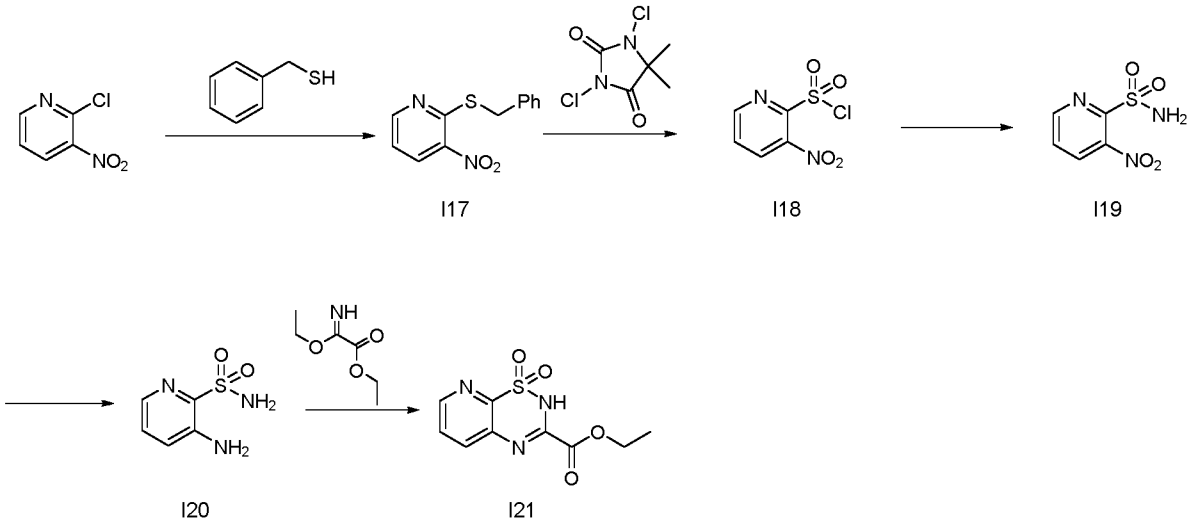
A solution of 2-chloropyridine-3-sulfonyl chloride (3 g, 14.1 mmol) in dioxane (50 mL) was added to a solution of conc. NH_4OH (50 mL) at 0 °C and the mixture was stirred at r.t. for 2 h then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography ($MeOH/CHCl_3$ = 0:100 – 1:10) to give the product as a yellow solid (2.4 g, 88% yield). LCMS (ES-API): R_t 1.79 min; *m/z* 193/195 $[M+H]^+$.

b) Ethyl 2*H*-pyrido[2,3-*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I16)

A mixture of 2-chloropyridine-3-sulfonamide (I15) (50 mg, 0.26 mmol), ethyl 2-ethoxy-2-iminoacetate (56 mg, 0.39 mmol) and DBU (79 mg, 0.52 mmol) in ethanol (5 mL) was heated in a sealed tube at 130 °C for 0.5 h then cooled to r.t.. The mixture was diluted with water (5 mL), adjusted to pH 5 with 1 M aqueous HCl and extracted with DCM (10 mL x 3).

The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative TLC (MeOH/DCM = 1:20) to give the product as a yellow solid (10 mg, 15% yield). LCMS (ES-API) R_t 0.51 min; *m/z* 256.1 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) 8.81 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

(vii) Ethyl 2H-pyrido[3,2-e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I21)



a) 2-(Benzylthio)-3-nitropyridine (I17)

A mixture of 2-chloro-3-nitropyridine (10 g, 63.1 mmol), phenylmethanethiol (8.6 g, 69.4 mmol) and K_2CO_3 (9.6 g, 69.4 mmol) in EtOH (300 mL) and water (60 mL) was stirred at r.t. overnight. Water was added with stirring and the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to give the product (10 g, 65% yield) as a yellow solid. LCMS (ES-API): R_t 2.96 min; *m/z* 247.0 $[M+H]^+$.

b) 3-Nitropyridine-2-sulfonyl chloride (I18)

To a mixture of 2-(benzylthio)-3-nitropyridine (I17) (6 g, 24.4 mmol) in water (24 mL), AcOH (12 mL) and DCM (84 mL) at r.t. was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (14. 4 g, 73.1 mmol). The mixture was stirred at r.t. for 16 h then poured into water and extracted with DCM. The organic extract was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to give the product (5 g), which was used directly in the next step without further purification.

c) 3-Nitropyridine-2-sulfonamide (I19)

A solution of 3-nitropyridine-2-sulfonyl chloride (I18) (5 g, 22.5 mmol) in DCM (100 mL) was added dropwise to a solution of conc. NH_4OH (100 mL) at 0 °C with stirring. The mixture was stirred for 30 min then concentrated and the residue was purified by column chromatography (MeOH/DCM = 1:30) to give the product (2.2 g, 44% for two steps) as a yellow solid. LCMS (ES-API): R_t 0.43 min; *m/z* 204.0 $[M+H]^+$.

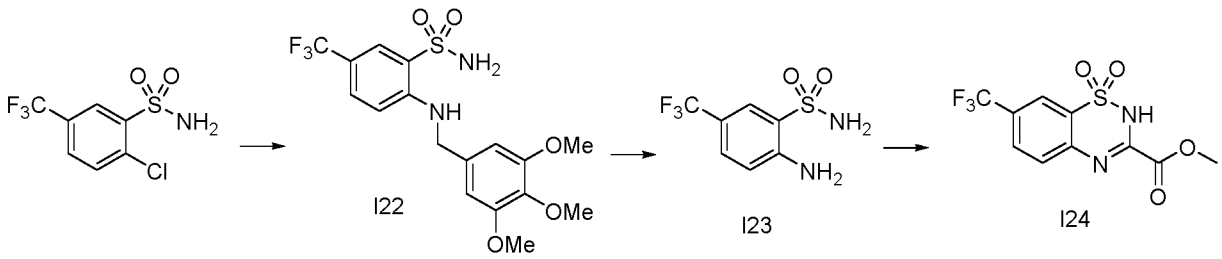
d) 3-Aminopyridine-2-sulfonamide (I20)

A mixture of 3-nitropyridine-2-sulfonamide (I19) (1.0 g, 4.92 mmol) and 10% Pd/C (100 mg) in EtOH (20 mL) was heated at 50 °C under 1 atm of H_2 for 16 h. The mixture was filtered through Celite and the filtrate was concentrated to give the product (0.7 g, 82% yield) as a yellow solid. LCMS (ES-API): R_t 0.28 min; *m/z* 174.0 $[M+H]^+$.

e) Ethyl 2*H*-pyrido[3,2-*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I21)

A mixture of 3-aminopyridine-2-sulfonamide (I20) (500 mg, 2.89 mmol), ethyl 2-ethoxy-2-iminoacetate (629 mg, 4.34 mmol) and DBU (879 mg, 5.78 mmol) in EtOH (10 mL) was heated at 125 °C in a microwave for 25 min then cooled to r.t.. The mixture was concentrated and the residue was diluted with water, acidified to pH 2 with 1 M aqueous HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (MeOH/DCM = 1:20) to give the desired product (120 mg, 16% yield) as a yellow solid. LCMS (ES-API): R_t 0.39 min; *m/z* 256.0 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.8 (brs, 1H), 8.70 (dd, *J* = 4.4 Hz, 1.2 Hz, 1H), 8.17 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

(viii) Methyl 7-(trifluoromethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I24)



a) 5-(Trifluoromethyl)-2-((3,4,5-trimethoxybenzyl)amino)benzenesulfonamide (I22)

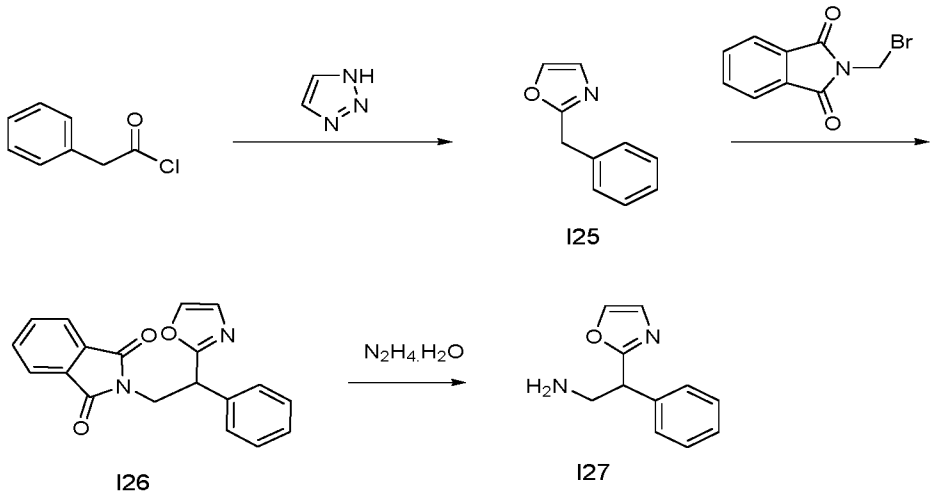
2-Chloro-5-(trifluoromethyl)benzenesulfonamide (1.34 g, 5.16 mmol) and 3,4,5-trimethoxybenzylamine (4.0 mL, 23 mmol) were heated at 130 °C overnight. The mixture was cooled and added to water (200 mL) with the aid of DMF (2 mL). The mixture was adjusted to pH 5 with acetic acid and sonicated. The mixture was filtered, the collected solid washed with water (2 x 50 mL) and air dried. Chromatography (40 g silica cartridge,

0-100% ethyl acetate/hexanes) gave the product as a solid (1.52 g, 70% yield). LCMS-A rt 5.93 min; *m/z* (negative ion) 419.1 [M-H]. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.88 (dd, J = 2.2, 0.9 Hz, 1H), 7.68 (s, 2H), 7.61 (dd, J = 8.9, 2.4 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.74 (s, 2H), 4.47 (d, J = 5.9 Hz, 2H), 3.73 (s, 6H), 3.62 (s, 3H).

b) 2-Amino-5-(trifluoromethyl)benzenesulfonamide (I23)
5-(Trifluoromethyl)-2-((3,4,5-trimethoxybenzyl)amino)benzenesulfonamide (I22) (1.878 g, 4.27 mmol) was dissolved in TFA (10 mL) and stirred at room temperature overnight. The mixture was concentrated *in vacuo*, the residue diluted with water (30 mL) and adjusted to pH 13 with 20% w/v aqueous sodium hydroxide. The mixture was filtered, the gummy precipitate washed with water (50 mL), and the precipitate transferred to a flask with ethanol. The mixture was concentrated in vacuo. Chromatography (40 g silica cartridge, 0-100% ethyl acetate/hexanes) gave the product as a yellow solid (766 mg, 75% yield). LCMS-A rt 5.31 min; *m/z* (negative ion) 239.0 [M-H]. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.83 – 7.78 (m, 1H), 7.56 – 7.50 (m, 1H), 7.45 (s, 2H), 6.93 (dd, J = 8.7, 0.9 Hz, 1H), 6.49 (s, 2H).

c) Methyl 7-(trifluoromethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I24)
Methyl 2,2,2-trimethoxyacetate (0.521 mL, 3.58 mmol), 2-amino-5-(trifluoromethyl)benzenesulfonamide (I23) (172 mg, 0.716 mmol), 4-methylbenzenesulfonic acid (0.025 g, 0.14 mmol) and methanol (0.5 mL) were heated in the microwave (120 °C/30 min). The mixture was cooled to room temperature and filtered to give the product as a white solid (52 mg). Additional product was recovered by chromatography of the filtrate (0-60% ethyl acetate/hexanes) (55 mg). Total product 107 mg, 47% yield. LCMS-B rt 3.13 min; *m/z* (negative ion) 306.8 [M-H]. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.21 – 8.19 (m, 1H), 8.12 (dd, J = 8.9, 2.1 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H). 19F NMR (376 MHz, DMSO-d6) δ -61.03.

(ix) 2-(Oxazol-2-yl)-2-phenylethanamine (I27)



a) 2-Benzyloxazole (I25)

To a solution of 1*H*-1,2,3-triazole (26.8 g, 388 mmol) in sulfolane (500 mL) at 0 °C was added 2-phenylacetyl chloride (50 g, 323 mmol) and K_2CO_3 (67 g, 485 mmol) and the mixture was stirred at r.t. for 20 min, then heated at 165 °C for 30 min. The mixture was cooled to r.t. and partitioned between water (3000 mL) and ether (500 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 1000 mL). The combined organic extracts were washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (Petroleum ether/EtOAc = 30:1—5:1) to give the desired product (25 g, 51% yield) as a yellow oil. LCMS (ES-API): R_t 2.78 min; *m/z* 160.1 $[M+H]^+$.

b) 2-(2-(Oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (I26)

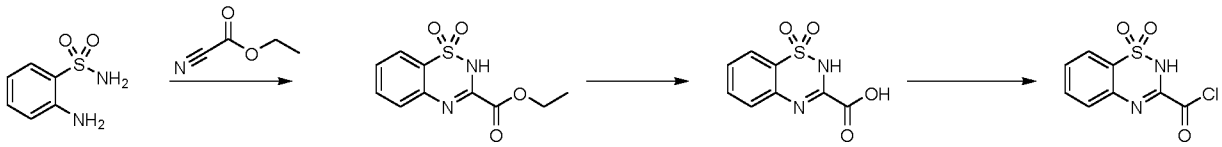
To a solution of 2-benzyloxazole (I25) (10 g, 62.8 mmol) in THF (350 mL) at -78 °C under nitrogen was added LHMDS (1 M solution in THF, 75.4 mL, 75.4 mmol) dropwise. A solution of 2-(bromomethyl)isoindoline-1,3-dione (18.1 g, 75.4 mmol) in THF (50 mL) was then added dropwise and the mixture allowed to warm slowly to r.t. and stirred overnight. The mixture was diluted with a saturated aqueous NH_4Cl solution (300 mL) and water (150 mL), then extracted with DCM (1000 mL x 3). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated and purified by column chromatography (Petroleum ether/EtOAc = 20:1—5:1) to give the desired product (5 g, 25% yield) as a white solid. LCMS (ES-API): R_t 2.62 min; *m/z* 319.1 $[M+H]^+$.

c) 2-(Oxazol-2-yl)-2-phenylethanamine (I27)

To a solution of 2-(2-(oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (I26) (4.2 g, 13.2 mmol) in ethanol (30 mL) was added hydrazine hydrate (2.7 g, 42.2 mmol) and the mixture

was heated at 80 °C under nitrogen for 3 h. The mixture was filtered and the solid was washed with ethanol (30 mL). The filtrate was concentrated under reduced pressure and the residue was partitioned between DCM (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to give the title product (1.4 g, 56% yield) as a yellow oil. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.99 (d, *J* = 0.6 Hz, 1H), 7.34-7.30 (m, 2H), 7.27 – 7.20 (m, 3H), 7.17 (s, 1H), 4.18 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.24-3.23 (m, 1H), 3.03-2.98 (m, 1H). LCMS (ES-API): R_t 2.23 min; *m/z* 189.1 $[M+H]^+$.

*(x) 2*H*-Benzo[e][1,2,4]thiadiazine-3-carbonyl chloride 1,1-dioxide (I30)*



I3 I2 I29 I30

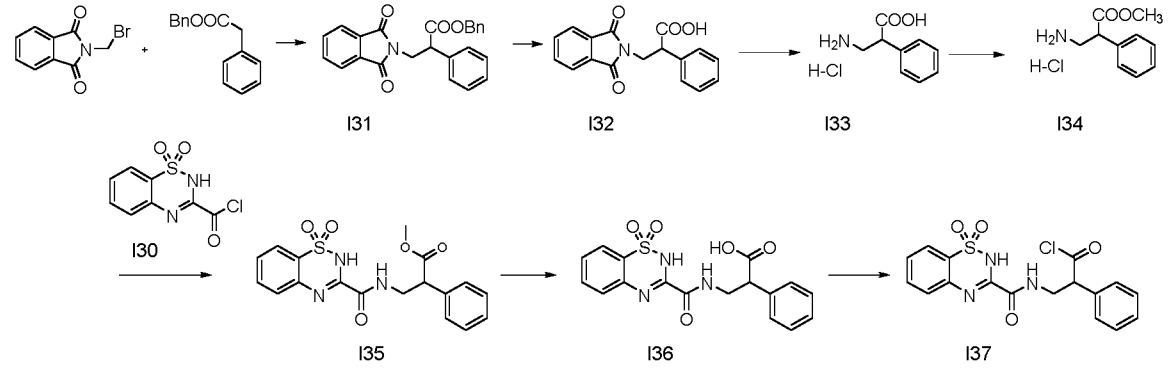
a) Ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2 – alternate synthesis)
A mixture of 2-aminobenzenesulfonamide (I3) (17 g, 98.22 mmol) and ethyl cyanoacetate (16 g, 197.4 mmol) in acetic acid (150 mL) and conc. HCl (15 mL) was heated at 80 °C under N_2 for 3 h. Most of the solvent was removed and then water (300 mL) was added. The resulting mixture was stirred at 0 °C for 2 h and the resulting precipitate was collected by filtration and washed with water. The solid was dissolved in EtOAc, washed with water and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 100:1-40:1) to give the desired product (7.2 g, 29% yield) as a white solid. LCMS (ES-API): R_t 0.66 min; *m/z* 255.0 $[M+H]^+$.

b) 2*H*-Benzo[*e*][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I29)
A mixture of ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (10 g, 39.3 mmol) in 2 M aqueous LiOH (50 mL) was stirred at r.t. for 3 h. The mixture was diluted with water (100 mL) and washed with EtOAc (x 2) then adjusted pH 1-2 and extracted with DCM (100 mL x 2). The organic layers were combined, washed with water, brine and dried over Na_2SO_4. The solvent was removed to give the desired product (6 g, 67% yield) as a light yellow solid. LCMS (ES-API): R_t 0.34 min; *m/z* 227.0 $[M+H]^+$.

c) 2*H*-Benzo[*e*][1,2,4]thiadiazine-3-carbonyl chloride 1,1-dioxide (I30)

A mixture of 2H-benzo[*e*][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I29) (2.5 g, 11.05 mmol) and $SOCl_2$ (20 mL) was heated at 85 °C for 2 h. The mixture was then concentrated to give the desired product which was used directly in the next step.

*(xi) 3-(1,1-Dioxido-2*H*-benzo[e][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoyl chloride (I37)*



a) Benzyl 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoate (I31)

To a solution of benzyl 2-phenylacetate (11.3 g, 50 mmol) in dry THF (100 mL) at -78 °C under nitrogen was added LiHMDS (2.5 M in THF, 40 mL, 100 mmol) dropwise over 25 min. A solution of 2-(bromomethyl)isoindoline-1,3-dione (14.4 g, 60 mmol) in THF (100 mL) was then added dropwise and the mixture was stirred at -78 °C for 2 h, then allowed to warm to r.t. and stirred overnight. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (DCM/MeOH = 100:0—100:1) to give the desired product (12.5 g, 65% yield) as a white solid. LCMS (ES-API): R_t 2.78 min; *m/z* 386.1 $[M+H]^+$.

b) 3-(1,3-Dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32)

A mixture of benzyl 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoate (I31) (8 g, 20.76 mmol) and 10% Pd/C (800 mg) in EtOAc (100 mL) and THF (100 mL) was heated at 45 °C under H_2 (1 atm) overnight. The mixture was filtered and the filtrate was concentrated to give the desired product (6 g, 98% yield) as a white solid. LCMS (ES-API): R_t 2.34 min; *m/z* 296.1 $[M+H]^+$.

c) 3-Amino-2-phenylpropanoic acid hydrochloride (I33)

To a solution of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (6 g, 20.3 mmol) in ethanol (200 mL) was added hydrazine hydrate (1.93 g, 39.6 mmol) and the mixture was heated at 80 °C for 1 h. The solvent was removed, water (200 mL) was added and the

mixture was again concentrated. The residue was diluted with water (200 mL) then adjusted to pH 2 with conc. HCl and stirred at r.t. for 30 min. The mixture filtered and the filtrate was concentrated to give the desired product (3.2 g, 95% yield) as a white solid. LCMS (ES-API): R_t 2.49 min; *m/z* 166.1 $[M+H]^+$.

d) Methyl 3-amino-2-phenylpropanoate hydrochloride (I34)

Thionyl chloride (2 mL) was added dropwise to methanol (20 mL) at 0 °C followed by 3-amino-2-phenylpropanoic acid hydrochloride (I33) (1.6 g, 9.69 mmol) and the mixture was heated at reflux for 3 h. The solvent was removed and the residue was washed with EtOAc and dried to give the desired product (1.2 g, 57 % yield) as a white solid, which was used directly in the next step.

e) Methyl 3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate (I35; 112)

To a solution of methyl 3-amino-2-phenylpropanoate hydrochloride (I34) (400 mg, 2.23 mmol) in THF (30 mL) at 0 °C under N_2 was added $NaHCO_3$ (1.87 g, 22.3 mmol) and the mixture was stirred for 15 min. 2*H*-Benzo[*e*][1,2,4]thiadiazine-3-carbonyl chloride 1,1-dioxide (I30) (1.09 g, 4.46 mmol) was then added and stirring was continued at r.t. for 30 min. TEA (2.25 g, 223 mmol) was then added and the mixture was stirred for 10 min. Additional 2H-benzo[*e*][1,2,4]thiadiazine-3-carbonyl chloride 1,1-dioxide (I30) (1.09 g, 4.46 mmol) was added and stirring was continued at r.t. for 30 min. The mixture was partitioned between EtOAc (200 mL) and water (200 mL), the layers were separated and the organic phase was washed with water, 1 M aqueous HCl, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep. TLC (DCM/MeOH = 50:1) to give the desired product (280 mg, 32% yield) as a light yellow solid. LCMS (ES-API): R_t 2.17 min; *m/z* 388.1 $[M+H]^+$.

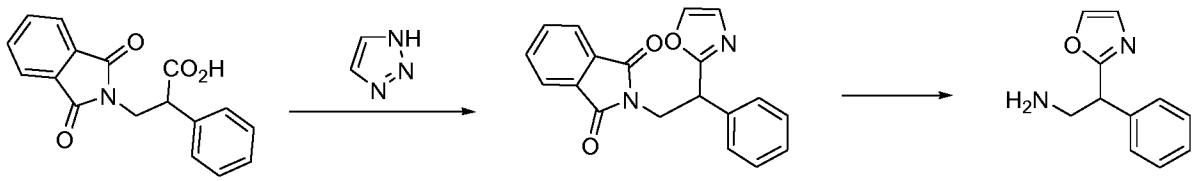
f) 3-(1,1-Dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoic acid (I36; 154)

To a solution of Methyl 3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate (I35; 112) (560 mg, 1.445 mmol) in DCM (20 mL) was added 2 M aqueous NaOH (20 mL) and the mixture was stirred at r.t. for 2 h. The layers were separated and the aqueous layer was washed with DCM (50 mL) then adjusted to pH 2 with 2 M aqueous HCl. The resulting precipitate was collected by filtration and dried to give the desired product (230 mg, 43% yield) as a white solid. LCMS (ES-API): R_t 2.47 min; *m/z* 374.1 $[M+H]^+$.

g) 3-(1,1-Dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoyl chloride (I37)

A solution of 3-(1,1-dioxido-2H-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoic acid (I36) (100 mg, 0.268 mmol) in thionyl chloride (10 mL) was heated at 90 °C for 3 h. The solvent was removed and the residue was used next step without further purification.

(ix) 2-(Oxazol-2-yl)-2-phenylethanamine (I27) – alternative preparation



I32 I26 I27

a) 2-(2-(Oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (I26)

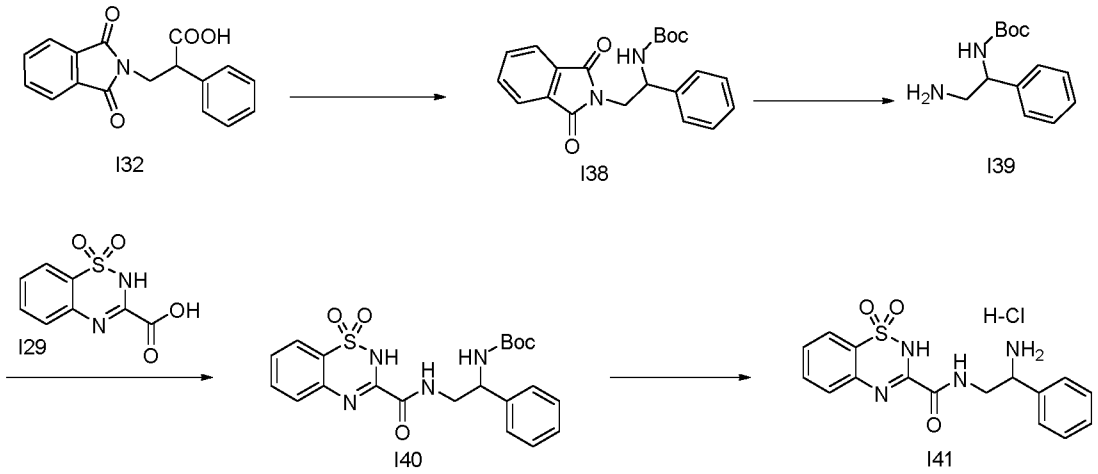
A mixture of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (3.00 g, 10.2 mmol) and thionyl chloride (10 mL) was stirred at 80 °C under an atmosphere of nitrogen for 3 h. The mixture was cooled to r.t. and excess thionyl chloride was evaporated *in vacuo*. The solid residue was dissolved in sulfolane (10 mL) before *1H-1*,2,3-triazole (0.83 mL, 14 mmol) and K_2CO_3 (2.81 g, 20.3 mmol) were added, and the mixture stirred at 150 °C under an atmosphere of nitrogen for 30 min. After returning to room temperature, water was added (40 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude solid was purified by column chromatography (Biotage Isolera, 80 g SiO_2 cartridge, 0-40% EtOAc in petroleum benzine 40-60 °C) to give the title compound as a white solid (5.37 g, ~60% purity, quantitative yield assumed for next step); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 – 8.00 (m, 1H), 7.81 (s, 4H), 7.31 – 7.21 (m, 5H), 7.19 – 7.13 (m, 1H), 4.76 – 4.67 (m, 1H), 4.31 – 4.17 (m, 2H); LCMS-B: rt 3.30 min; *m/z* 319.1 $[M+H]^+$.

b) 2-(Oxazol-2-yl)-2-phenylethan-1-amine (I27)

Hydrazine hydrate (50-60%, 2.53 mL, ~41 mmol) was added to a suspension of 2-(2-(oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (I26) (5.37 g, ~60% purity, 10.1 mmol) in EtOH (100 mL). The mixture was stirred at 80 °C for 3.5 h, cooled to room temperature and the volatiles removed *in vacuo*. The solid was suspended in aq. HCl (2 M, ~50 mL) and H_2O (~50 mL) and the precipitate removed by filtration. The aqueous filtrate was washed with DCM (3 × 75 mL) and then brought to pH ~14 with the addition of aq. NaOH (2 M).

The aqueous layer was extracted with DCM (3 × 75 mL), the organics combined, washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title compound as a colourless oil (0.951 g, 50% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.94 (m, 1H), 7.35 – 7.29 (m, 2H), 7.26 – 7.20 (m, 3H), 7.19 – 7.16 (m, 1H), 4.18 (dd, J = 8.4, 6.2 Hz, 1H), 3.24 (dd, J = 12.8, 8.4 Hz, 1H), 3.08 – 2.94 (m, 1H), exchangeable NH_2 protons not observed; LCMS-B: rt 0.98 min; *m/z* 189.1 $[M+H]^+$.

(xii) N-*(2-Amino-2-phenylethyl)-2*H-*benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I41)*



a) *tert*-Butyl (2-(1,3-dioxoisoindolin-2-yl)-1-phenylethyl)carbamate (I38)

A mixture of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (5 g, 16.9 mmol), DPPA (5.59 g, 20.3 mmol), Boc_2O (7.39 g, 33.9 mmol) and TEA (11.8 mL, 84.6 mmol) in t-BuOH (50 mL) and dioxane (80 mL) was heated at 100 °C overnight. The solvent was removed to give a residue which was purified by silica gel chromatography (Petroleum ether/EtOAc = 100:1-3:1) to give the desired product (4.5g, 73% yield) as a white solid. LCMS (ES-API): R_t 0.2.84 min; *m/z* 389.1 $[M+Na]^+$.

b) *tert*-Butyl (2-amino-1-phenylethyl)carbamate (I39)

To a solution of *tert*-butyl (2-(1,3-dioxoisoindolin-2-yl)-1-phenylethyl)carbamate (I38) (11 g, 30.0 mmol) in EtOH (400 mL) was added $NH_4.H_2O$ (4 mL, 60.0 mmol) and the mixture was heated at 80 °C for 2 h under N_2 atmosphere. The mixture was filtered and the solid was washed with more ethanol (2 mL). The combined filtrates were concentrated and purified by chromatography (DCM/MeOH = 50:1) to give the product (2.85 g, 40% yield) as a yellow oil. LCMS (ES-API): R_t 0.90 min; *m/z* 237.2 $[M+H]^+$.

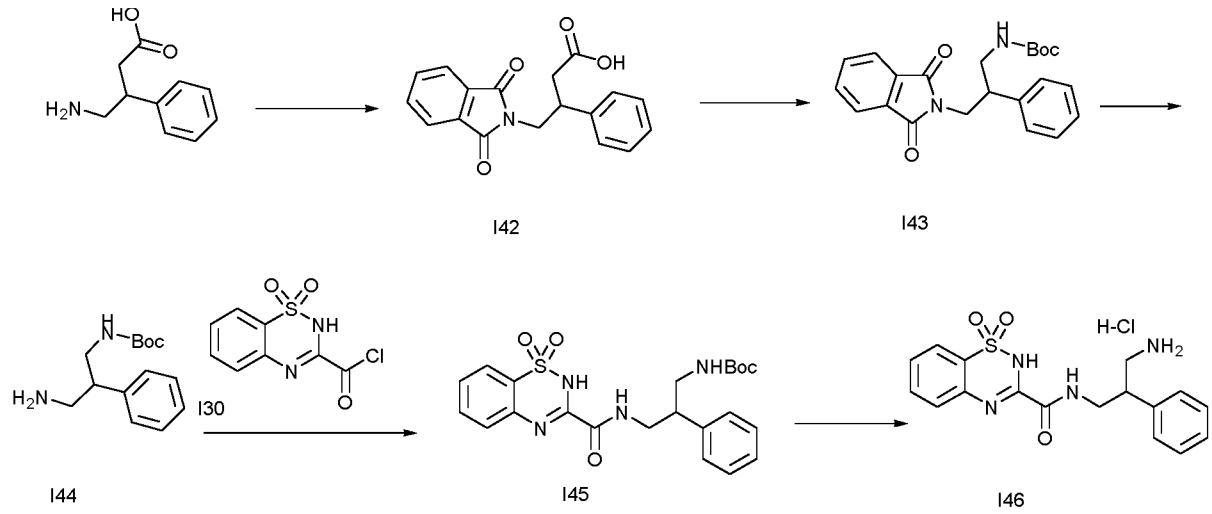
c) *tert*-Butyl (2-(1,1-dioxido-2H-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl)carbamate (I40)

To a solution of *tert*-butyl (2-amino-1-phenylethyl)carbamate (I39) (2.85 g, 12.0 mmol), 2H-benzo[e][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I29) (1.23 g, 5.0 mmol), EDCI (3.5 g, 18.1 mmol) and HOBT (2.45 g, 18.1 mmol) in DMF (50 mL) was added TEA (4.8 g, 48.2 mmol) and the mixture was stirred at r.t. overnight. The mixture was diluted with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (DCM/MeOH = 70:1) to give the product (0.73 g, 13% yield) as a yellow solid. LCMS (ES-API): R_t 2.54 min; *m/z* 445.1 $[M+H]^+$.

d) *N*-(2-Amino-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I41)

To a mixture of *tert*-butyl (2-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl)carbamate (I40) (600 mg, 1.35 mmol) in DCM (6 mL) was added 2 M HCl in EtOAc (18 mL) and the mixture was stirred at r.t. for 2 h. The mixture was concentrated to give the product (500 mg, 97% yield) as an off-white solid. LCMS (ES-API): R_t 0.60 min; *m/z* 345.1 $[M+H]^+$.

(xiii) N-*(3-Amino-2-phenylpropyl)-2*H-*benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I46)*



a) 4-(1,3-Dioxoisoindolin-2-yl)-3-phenylbutanoic acid (I42)

A solution of 4-amino-3-phenylbutanoic acid (2.6 g, 14.5 mmol) and phthalic anhydride (2.3 g, 15.2 mmol) in EtOH (50 mL) was heated at reflux for 3 h. The mixture was concentrated and the residue was purified by chromatography (DCM/MeOH = 100:1) to give the product (8.1 g, 62% yield) as an off-white solid. LCMS (ES-API): R_t 2.12 min; *m/z* 310.1 $[M+H]^+$.

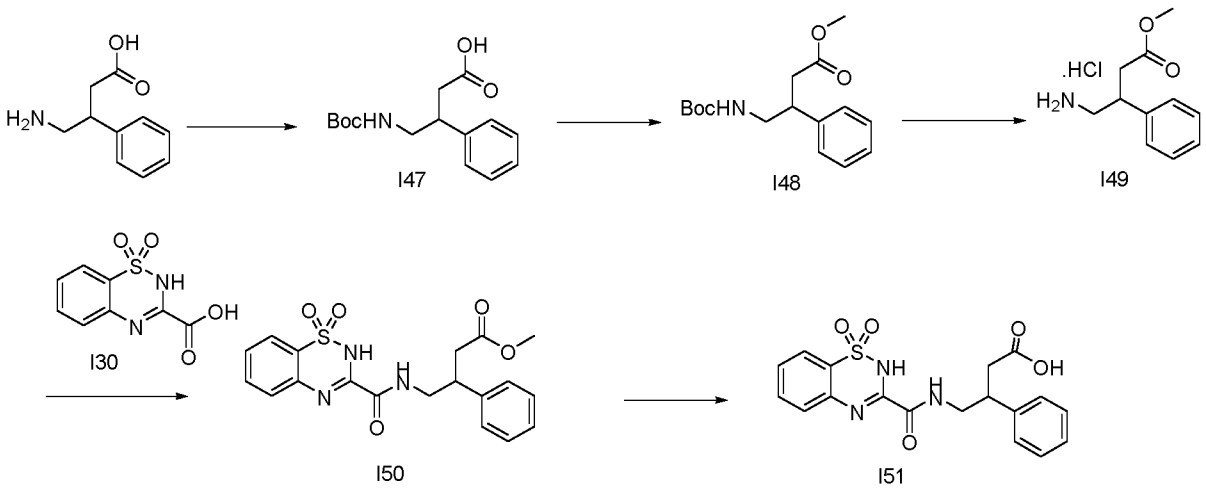
b) *tert*-Butyl (3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropyl)carbamate (I43)
A solution of 4-(1,3-dioxoisoindolin-2-yl)-3-phenylbutanoic acid (I42) (8.1 g, 26.2 mmol), DPPA (7.9 g, 28.8 mmol), Boc_2O (11.4 g, 52.4 mmol) and TEA (13.2 g, 130.9 mmol) in t-BuOH/dioxane (30 mL/80 mL) was heated at 100 °C overnight. The mixture was concentrated and the residue was dissolved in EtOAc (200 mL), washed with water (3 × 100 mL), dried over Na_2SO_4, filteredand concentrated. The residue was purified by chromatography (Petroleum ether/EtOAc = 10:1) to give the product (3.0 g, 30% yield) as a white solid. LCMS (ES-API): R_t 1.83 min; *m/z* 381.2 $[M+H]^+$.

c) *tert*-Butyl (3-amino-2-phenylpropyl) carbamate (I44)
To a solution of *tert*-butyl (3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropyl)carbamate (I43) (900 mg, 2.36 mmol) in EtOH (30 mL) was added $N_2H_4.H_2O$ (120 mg, 2.36 mmol) and the mixture was heated at 80 °C for 2 h. The mixture was filtered and the solid was washed with more ethanol (2 mL). The combined filtrates were concentrated and the residue was purified by chromatography (DCM/MeOH = 50:1) to give the product (300 mg, 51% yield) as yellow oil. LCMS (ES-API): R_t 0.83 min; *m/z* 251.2 $[M+H]^+$.

d) *tert*-Butyl (3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropyl)carbamate (I45)
To a solution of *tert*-butyl (3-amino-2-phenylpropyl)carbamate (I44) (250 mg, 1.0 mmol) in DCM (20 mL) was added $NaHCO_3$ (840 mg, 10.0 mmol) and the mixture was stirred at r.t. for 10 min. 2*H*-Benzo[*e*][1,2,4]thiadiazine-3-carbonyl chloride 1,1-dioxide (I30) (1.23 g, 5.0 mmol) was added and stirring was continued at r.t. for 1 h. The mixture was diluted with DCM (30 mL) and washed with water (2 × 50 mL), 1 M aqueous HCl (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the product (300 mg, 66% yield) as a light yellow solid. LCMS (ES-API): R_t 2.27 min; *m/z* 459.2 $[M+H]^+$.

e) *N*-(3-Amino-2-phenylpropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I46)
To a solution of *tert*-butyl (3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropyl)carbamate (I45) (300 mg, 0.65 mmol) in EtOAc (1 mL) was added 2 M HCl in EtOAc (3 mL) and the mixture was stirred at r.t. for 2 h. The mixture was concentrated to give the product (220 mg, 85% yield) as an off-white solid. LCMS (ES-API): R_t 0.57 min; *m/z* 359.1 $[M+H]^+$.

(xiv) 4-(1,1-Dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)-3-phenylbutanoic acid (I51)



a) 4-((*tert*-Butoxycarbonyl)amino)-3-phenylbutanoic acid (I47)

To a solution of 4-amino-3-phenylbutanoic acid (3.0 g, 16.7 mmol) in 1 M aqueous NaOH (35 mL) and t-BuOH (25 mL) at 0 °C was added $(Boc)_2O$ (3.65 g, 116.7 mmol) portion-wise and mixture was stirred at r.t. over the weekend. The mixture was washed with pentane (80 mL x 2) and extracted with ether (80 mL x 3). The combined ether extracts were dried over Na_2SO_4, filtered and concentrated to give the desired product (3.4 g, 73% yield) as a white solid. LCMS: R_t 2.43 min, *m/z* 302.1 $[M+Na]^+$

b) Methyl 4-((*tert*-butoxycarbonyl)amino)-3-phenylbutanoate (I48)

A mixture of 4-((*tert*-butoxycarbonyl)amino)-3-phenylbutanoic acid (I47) (2.793 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in THF (50 mL) was stirred at r.t. for 15 min. Methyl iodide (3.01 g, 20 mmol) was then added and stirring was continued at r.t. overnight. The mixture was diluted with DCM (500 mL), washed with water (x 2) and the organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/EtOAc = 100:1-30:1) to give the desired product (2.5 g, 85% yield) as a white solid. LCMS: R_t 2.16 min, *m/z* 316.2 $[M+Na]^+$

c) Methyl 4-amino-3-phenylbutanoate hydrochloride (I49)

A mixture of methyl 4-((tert-butoxycarbonyl)amino)-3-phenylbutanoate (I48) (2.5 g, 8.52 mmol) and 2 M HCl/EtOAc (100 mL) was stirred at r.t. for 3 h. The solvent was removed and the residue was washed with EtOAc to give the desired product (1.5 g, 91% yield) as a white solid, which was used directly in the next step.

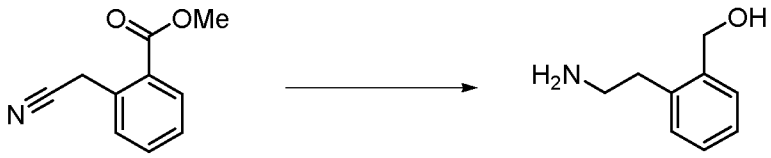
d) Methyl 4-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-3-phenylbutanoate (I50)

To a solution of methyl 4-amino-3-phenylbutanoate hydrochloride (I49) (1.5 g, 7.76 mmol) and 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I29) (2.63 g, 11.64 mmol) in DCM (100 mL) at r.t. was added triethylamine (3.14 g, 31.0 mmol) and HATU (4.43 g, 11.64 mmol) and the mixture was stirred at r.t. overnight. The solvent was removed and the residue was purified by silica gel chromatography (DCM/MeOH = 100:0-100:1) to give the desired product (1.2 g, 58% yield) as a white solid. LCMS: R_t min, *m/z* 402 $[M+H]^+$

e) 4-(1,1-Dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-3-phenylbutanoic acid (I51)

A mixture of methyl 4-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-3-phenylbutanoate (I50) (1.2 g, 3 mmol) in 2 M NaOH (100 mL) was stirred at r.t. for 3 h. The mixture was adjusted to pH 2-3 with conc. HCl and the resulting precipitate was collected by filtration, washed with twice with water and dried to give the desired product (600 mg, 52% yield) as a white solid. LCMS: R_t 2.16 min, *m/z* 388.1 $[M+H]^+$

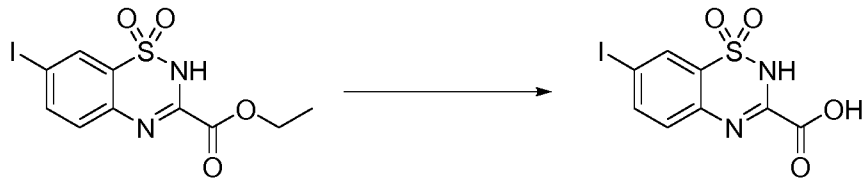
(xv) (2-(2-Aminoethyl)phenyl)methanol (I52)



I52

To a solution of methyl 2-(cyanomethyl)benzoate (3 g, 17.1 mmol) in THF (50 mL) was added a 1 M solution of BH_3·THF in THF (51.3 mL, 51.3 mmol) and the mixture was heated at 70 °C under N_2 for 16 h. After cooling to r.t., the mixture was adjusted to pH 5 with 1 M HCl, diluted with water (20 mL) and washed with EtOAc (30 mL x 3). The aqueous layer was adjusted to pH 9 with 1 M NaOH and then extracted with EtOAc (30 mL x 3). The combined organic extracts were concentrated to give the product (1.5 g, 57% yield) as a yellow oil. LCMS (ES-API): R_t 2.34 min; *m/z* 152.1 $[M+H]^+$.

(xvi) 7-Iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I53)



I7 I53

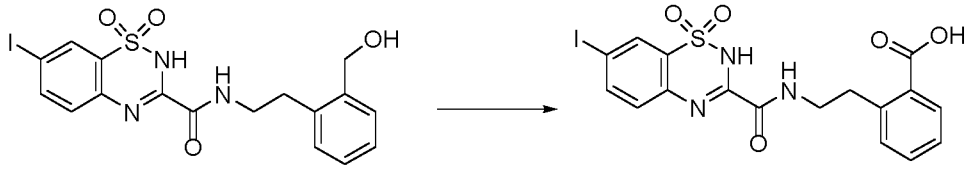
To a solution of ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (200 mg, 0.53 mmol) in THF (10 mL), MeOH (1 mL) and H_2O (0.1 mL) was added

$LiOH.H_2O$ (67 mg, 1.59 mmol) and the mixture was stirred at r.t. overnight. Most of the organic solvent was removed under reduced pressure and the aqueous residue was adjusted to pH 5 with 1 M aq HCl and extracted with DCM (10 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated to give the product (150 mg, 80% yield) as a yellow solid. LCMS (ES-API): R_t 1.0 min; *m/z* 353.1 $[M+H]^+$.

(xvii) N-*(2-(hydroxymethyl)phenethyl)-7-iodo-2*H-*benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (109)*

See below

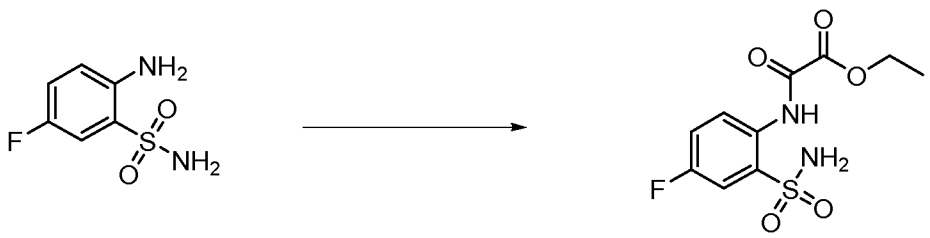
*(xviii) 2-(2-(7-Iodo-1,1-dioxido-2*H-*benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid (I55; 155)*



109 I55

To a solution of N-(2-(hydroxymethyl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (109) (200 mg, 0.4 mmol) in acetone (10 mL) at r.t. was added Jones reagent (10 mL) and the mixture was heated at 40 °C for 16 h then concentrated under reduced pressure. The residue was diluted with water (10 mL), the solid was collected by filtration, washed with diethyl ether (20 mL) and dried to give the product as a white solid (115 mg, 55% yield). ^1H NMR (400 MHz, d_6-DMSO) δ 12.8 (brs, 1H), 9.27 (m, 1H), 8.15 – 8.00 (m, 2H), 7.83 (m, 1H), 7.59 (d, *J* = 6.4 Hz, 1H), 7.46 (m, 1H), 7.37 – 7.24 (m, 2H), 3.55 (m, 2H), 3.22 (m, 2H). LCMS (ES-API) R_t 2.72 min; *m/z* 497.6 $[M-H]^-$.

(xix) Ethyl 2-((4-fluoro-2-sulfamoylphenyl)amino)-2-oxoacetate (I56)

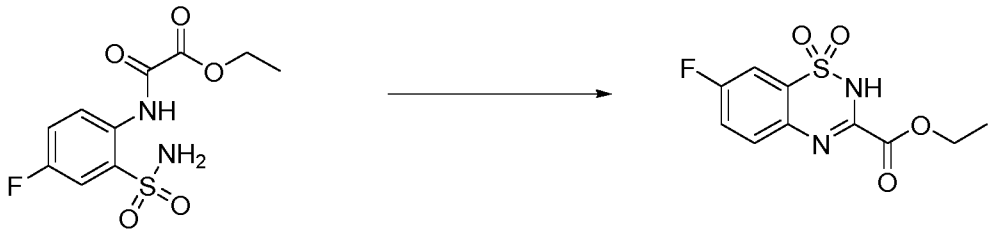


I56

To solution of 2-amino-5-fluorobenzenesulfonamide (0.200 g, 1.052 mmol) in THF (10 mL), at 0 °C, was added NEt_3 (0.154 mL, 1.104 mmol) followed by the dropwise addition of ethyl chlorooxoacetate (0.123 mL, 1.104 mmol) over 10 min. The mixture was allowed to slowly warm to ambient temperature for 48 h. The precipitate was removed by filtration and the

filtrate was concentrated *in vacuo* to give the product (0.320 g, 90% purity, 94% yield) as a white solid. LCMS-B: r.t. 3.059 min; *m/z* 289.0 $[M-H]^-$. ^1H NMR (400 MHz, *d*-DMSO) δ 10.63 (s, 1H), 8.25 (dd, *J* = 9.1, 4.9 Hz, 1H), 7.84 (s, 2H), 7.65 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.58 (ddd, *J* = 9.1, 8.0, 3.1 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

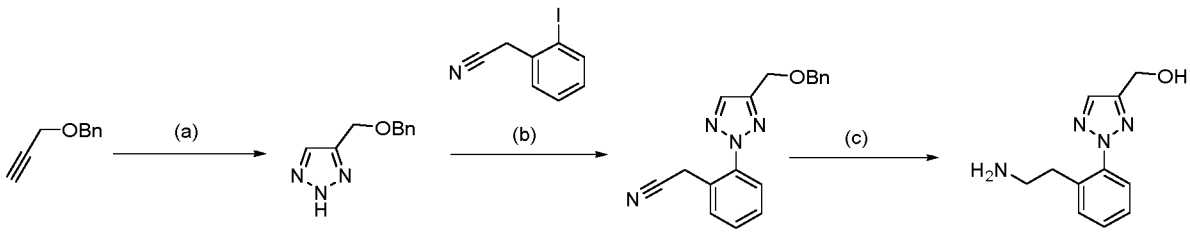
(xx) Ethyl 7-fluoro-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate (I57)



I56 I57

To solution of ethyl 2-((4-fluoro-2-sulfamoylphenyl)amino)-2-oxoacetate (I56) (0.320 g, 90% purity, 0.992 mmol) in dry EtOH (10 mL) under an atmosphere of nitrogen, was added NaH (60% dispersion in mineral oil, 0.079 g, 1.984 mmol) in portion. The reaction was then stirred at room temperature for 20 h. The reaction was quenched with water (10 mL) and acidified to pH 3 with 1M HCl. The EtOH was removed in vacuo and the precipitate was collected by filtration. The solid was washed with water then air dried to give the desired product ethyl 7-fluoro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (0.069 g, 26 % yield) as a white solid. LCMS-B: r.t. 3.409 min; *m/z* 271.0 $[M-H]^-$. ^1H NMR (400 MHz, *d*-DMSO) δ 7.85 (dd, *J* = 9.2, 4.6 Hz, 1H), 7.79 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.67 (td, *J* = 8.8, 2.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

(xxi) (2-(2-(2-Aminoethyl)phenyl)-2H-1,2,3-triazol-4-yl)methanol (I60)



I58 I59 I60

a) 4-((Benzyloxy)methyl)-2*H*-1,2,3-triazole I58

To a solution of ((prop-2-yn-1-yloxy)methyl)benzene (1.46 g, 10.0 mmol) in DMF (20 mL) and EtOH (2.5 mL) was added CuI (380 mg, 2 mmol) and azidotrimethylsilane (2.3 g, 20 mmol) and the mixture was heated at 130 °C under N_2 for 18 h. The mixture was diluted with water and extracted with EtOAc (200 mL). The combined organic extracts were washed with water (100 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet.

ether/EtOAc = 5/1) to give the title compound (900 mg, 50%) as a yellow oil. LCMS-D: R_t 1.42 min; *m/z* 190.1 $[M+H]^+$.

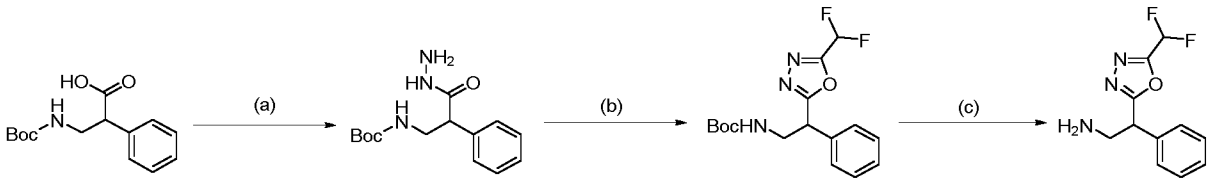
b) 2-(2-(4-((Benzyloxy)methyl)-2*H*-1,2,3-triazol-2-yl)phenyl)acetonitrile I59

A mixture of 4-((benzyloxy)methyl)-2*H*-1,2,3-triazole I58 (1.7 g, 9.0 mmol), 2-(2-iodophenyl)acetonitrile (3.0 g, 12.0 mmol), $Fe(acac)_3$ (1.1 g, 3.0 mmol), CuO (720 mg, 0.9 mmol) and Cs_2CO_3 (6.0 g, 18.0 mmol) in DMF (60 mL) was heated at 90 °C under N_2 for 30 h. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.4 g, 51%) as a yellow oil. LCMS-D: R_t 2.87 min; *m/z* 305.1 $[M+H]^+$.

c) (2-(2-(2-Aminoethyl)phenyl)-2*H*-1,2,3-triazol-4-yl)methanol I60

To a solution of 2-(2-(4-((benzyloxy)methyl)-2*H*-1,2,3-triazol-2-yl)phenyl)acetonitrile I59 (700 mg, 2.3 mmol) in MeOH (30 mL) was added 10% Pd/C (200 mg) and the mixture was stirred at RT under a H_2 atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 10/0 to 10/1) to give the title compound (300 mg, 60%) as a yellow oil. LCMS-D: R_t 0.33 min; *m/z* 219.1 $[M+H]^+$.

xxii) 2-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine trifluoroacetate (I63)



I61 I62 I63

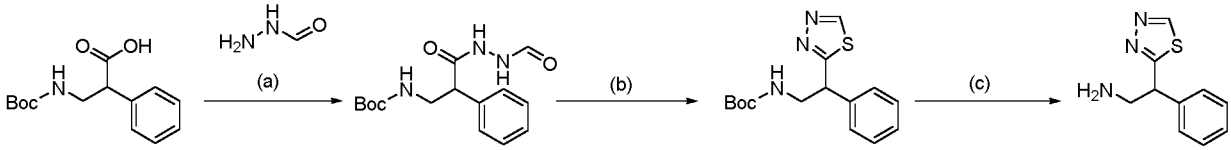
a) *tert*-Butyl (3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61

To a solution of 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid (2.65 g, 10.0 mmol) in dry THF (30 mL) was added CDI (1.93 g, 12.0 mmol) and the mixture was stirred at RT under N_2 for 90 min. Hydrazine monohydrate (1.5 g, 30.0 mmol) was then added and stirring was continued at RT for 18 h. The mixture was diluted with water and extracted with EtOAc (200 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (3.0 g, >100%) as a white solid, which was used in the next step without further purification. LCMS-D: R_t 2.29 min; *m/z* 302.0 $[M+Na]^+$.

b) *tert*-Butyl (2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I62
A mixture of *tert*-butyl (3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61 (240 mg, 0.86 mmol), trifluoroacetic anhydride (449 mg, 2.58 mmol) and imidazole (176 mg, 2.58 mmol) in DCM (10 mL) was heated at 50 °C under N_2 overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution and the mixture was extracted with DCM (50 mL × 3). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (170 mg, 58%) as a colorless oil. LCMS-D: R_t 2.69 min; *m/z* 362.0 $[M+Na]^+$.

c) 2-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine trifluoroacetate I63
To a solution of *tert*-butyl (2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I62 (60 mg, 0.18 mmol) in DCM (3 mL) was added TFA (1.0 mL) and the mixture was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to give the title compound (85 mg, >100%) as a yellow oil, which was used directly in the next step with further purification. LCMS-D: R_t 0.51 min; *m/z* 240.0 $[M+H]^+$.

xxiii) 2-Phenyl-2-(1,3,4-thiadiazol-2-yl)ethan-1-amine hydrochloride (I66)



a) *tert*-Butyl (3-(2-formylhydrazinyl)-3-oxo-2-phenylpropyl)carbamate I64
A mixture of 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid (2.0 g, 7.5 mmol), formic hydrazide (510 mg, 8.5 mmol), EDCI·HCl (2.1 g, 11.3 mmol), HOBt (2.0 g, 15.0 mmol) and Et_3N (2.3 g, 22.5 mmol) in DMF (30 mL) was stirred at RT overnight. The mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 30/1 to 10/1) to give the title compound (800 mg, 34%) as a yellow oil. LCMS-D: R_t 2.87 min; *m/z* 308.1 $[M+H]^+$.

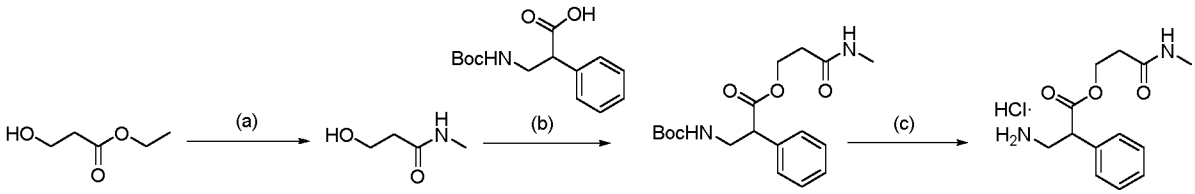
b) *tert*-Butyl (2-phenyl-2-(1,3,4-thiadiazol-2-yl)ethyl)carbamate I65
To a solution of *tert*-butyl (3-(2-formylhydrazinyl)-3-oxo-2-phenylpropyl)carbamate I64 (600 mg, 1.95 mmol) in THF (30 mL) was added Lawesson's reagent (2.4 g, 5.85 mmol) and the mixture was heated at 40 °C overnight. The mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 30/1) to give the title compound (200 mg, 34%) as a yellow oil. LCMS-D: R_t 0.71 min; *m/z* 306.1 $[M+H]^+$.

c) 2-Phenyl-2-(1,3,4-thiadiazol-2-yl)ethan-1-amine hydrochloride I66

To a solution of *tert*-butyl (2-phenyl-2-(1,3,4-thiadiazol-2-yl)ethyl)carbamate I65 (60 mg, 0.18 mmol) in DCM (10 mL) was added TFA (2.0 mL) and the mixture was stirred at RT overnight. 1 M aqueous HCl was added and the mixture was washed with EtOAc. The aqueous layer was concentrated under reduced pressure to give the title compound (260 mg, 98%) as a white solid. LCMS-CLCMS-C: R_t 0.62 min; *m/z* 206.1 $[M+H]^+$.

xxiv) 3-(Methylamino)-3-oxopropyl 3-amino-2-phenylpropanoate hydrochloride (I69)



I67 I68 I69

a) 3-Hydroxy-*N*-methylpropanamide I67

A mixture of ethyl 3-hydroxypropanoate (2.0 g, 16.9 mmol) and $MeNH_2$ (30% (v/v) solution in methanol, 45 mL) was heated at 85 °C for 36 h. The mixture was concentrated under reduced pressure to give the title compound (1.5 g, 88%) as an oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.28 (br s, 1H), 4.84 (br s, 1H), 3.82 (t, *J* = 5.8 Hz, 2H), 2.75 (d, *J* = 4.8 Hz, 3H), 2.42 (t, *J* = 5.8 Hz, 2H).

b) 3-(Methylamino)-3-oxopropyl 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoate I68

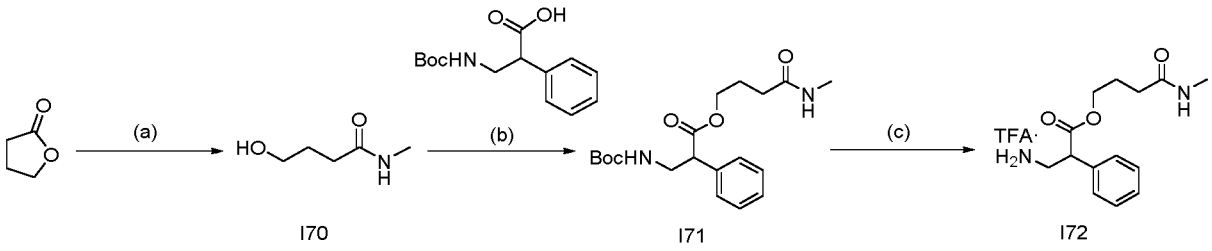
A mixture of 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid (500 mg, 1.8 mmol), 3-hydroxy-*N*-methylpropanamide I67 (1.1 g, 9.5 mmol), EDCI·HCl (542 mg, 2.83 mmol) and DMAP (350 mg, 1.8 mmol) in DCM (100 mL) was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the title compound (500 mg, 75%) as an oil. LCMS-D: R_t 2.13 min; *m/z* 251.3 $[M-Boc+2H]^+$.

c) 3-(Methylamino)-3-oxopropyl 3-amino-2-phenylpropanoate hydrochloride I69

To a solution of 3-(methylamino)-3-oxopropyl 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoate I68 (500 mg, 1.42 mmol) in DCM (30 mL) was added a 2 M solution of HCl in Et_2O (30 mL) and the mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue was recrystallised from water and

dried under reduced pressure to give the title compound (400 mg, 97%) as a white solid. LCMS-D: R_t 0.24 min; *m/z* 251.3 $[M+H]^+$.

xxv) 4-(Methylamino)-4-oxobutyl 3-amino-2-phenylpropanoate trifluoroacetate (I72)



I70 I71 I72

a) 4-Hydroxy-*N*-methylbutanamide I70

Dihydrofuran-2(3*H*)-one (334 mg, 4.0 mmol) was added to a 2 M solution of methylamine in THF (20.0 mL, 40.0 mmol) in a pressure tube at -78 °C. The flask was sealed and the mixture was stirred at RT overnight. The mixture was then concentrated under reduced pressure to give the title compound (350 mg, 75%) as a red solid. LCMS-CLCMS-C: R_t 0.33 min; *m/z* 118.1 $[M+H]^+$.

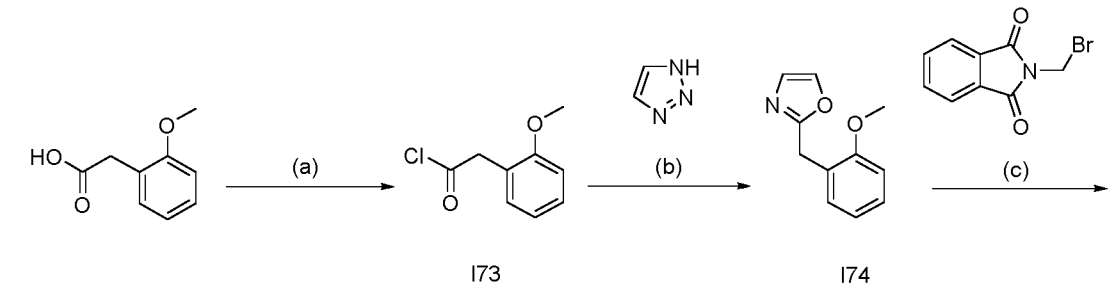
b) 4-(Methylamino)-4-oxobutyl 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoate I71

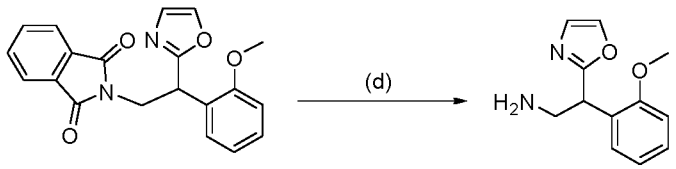
A mixture of 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid (500 mg, 1.88 mmol), 4-hydroxy-*N*-methylbutanamide I70 (331 mg, 2.83 mmol), EDCI·HCl (434 mg, 2.26 mmol) and DMAP (23 mg, 0.19 mmol) in DCM (20 mL) was stirred at RT overnight. The mixture was diluted with water (100 mL), extracted with DCM (60 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep. TLC (DCM/MeOH=300/1 to 100/1) to give the title compound (400 mg, 80%) as a yellow oil. LCMS-D: R_t 1.85 min; *m/z* 387.1 $[M+Na]^+$, 265.1 $[M-Boc+2H]^+$.

c) 4-(Methylamino)-4-oxobutyl 3-amino-2-phenylpropanoate trifluoroacetate I72

To a solution of 4-(methylamino)-4-oxobutyl 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoate I71 (220 mg, 0.55 mmol) in DCM (2 mL) was added TFA (1.0 mL) and the mixture was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to give the title compound (330 mg, >100%) as a yellow oil, which was used in the next step without further purification. LCMS-D: R_t 0.31 min; *m/z* 265.1 $[M+H]^+$ for the free base.

xxvi) 2-(2-Methoxyphenyl)-2-(oxazol-2-yl)ethan-1-amine (I76)





I75 I76

a) 2-(2-Methoxyphenyl)acetyl chloride I73

To a solution of 2-(2-methoxyphenyl)acetic acid (10 g, 60.2 mmol) in DCM (100 mL) was added oxalyl chloride (15 mL, 180.5 mmol) dropwise followed by DMF (3 drops) and the mixture was stirred at RT under N_2 for 2 h. The mixture was concentrated under reduced pressure to give the title compound (11 g, 100%) as a red oil. LCMS-D: R_t 2.28 min; *m/z* 181.0 $[M\text{-Cl+MeOH}]^+$.

b) 2-(2-Methoxybenzyl)oxazole I74

To a mixture of 1,2,3-triazole (5.4 g, 78.3 mmol) and K_2CO_3 (13.5 g, 97.8 mmol) in sulfolane (100 mL) at 0 °C was added 2-(2-methoxyphenyl)acetyl chloride I73 (12 g, 65.2 mmol) and the mixture was heated at 165 °C for 1 h. After cooling to RT, the mixture was diluted with water (500 mL) and extracted with Et_2O (500 mL × 3). The combined organic extracts were washed with water (500 mL × 3), brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 6/1) to give the title compound (8.0 g, 65%) as a yellow oil. LCMS-D: R_t 2.36 min; *m/z* 190.0 $[M+H]^+$, 212.0 $[M+Na]^+$.

c) 2-(2-(2-Methoxyphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I75

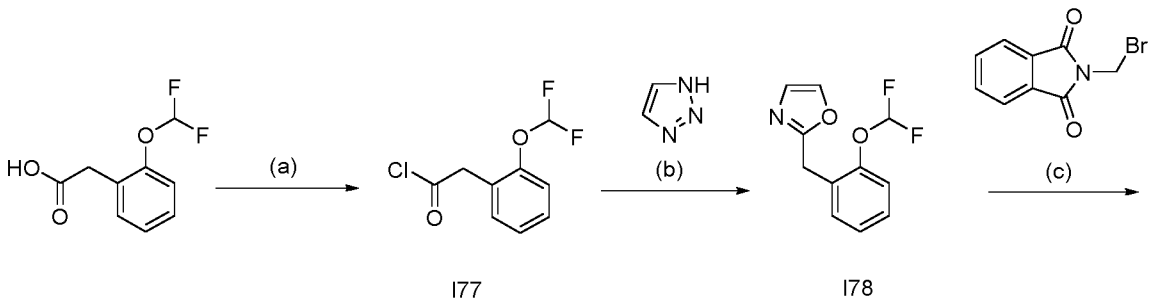
To a solution of 2-(2-methoxybenzyl)oxazole I74 (1.0 g, 5.3 mmol) in dry THF (20 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 6.4 mL, 6.4 mmol) dropwise. The mixture was stirred at -78 °C for 1 h, then added to a solution 2-(bromomethyl)isoindoline-1,3-dione (1.5 g, 6.34 mmol) in dry THF (20 mL) at -78 °C under N_2. The mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with a saturated

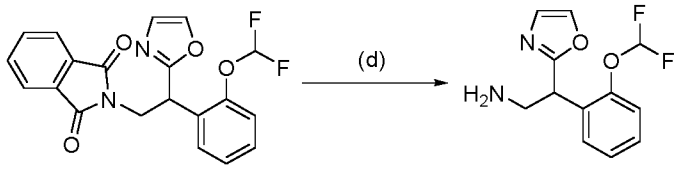
aqueous NH_4Cl solution and the mixture was extracted with DCM (200 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 6/1) to give the title compound (200 mg, 11%) as a green solid. LCMS-D: R_t 2.50 min; *m/z* 349.0 $[M+H]^+$.

d) 2-(2-Methoxyphenyl)-2-(oxazol-2-yl)ethan-1-amine I76

A suspension of 2-(2-(2-methoxyphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I75 (200 mg, 0.57 mmol) and hydrazine hydrate (86 mg, 1.72 mmol) in EtOH (10 mL) was heated at 80 °C under N_2 for 3 h. The mixture was filtered and the filter cake was washed with EtOH (2 mL). The filtrate was concentrated under reduced pressure to give the title compound (100 mg, 80%) as a yellow oil. LCMS-D: R_t 0.41 min; *m/z* 219.1 $[M+H]^+$.

xxvii) 2-(2-(Difluoromethoxy)phenyl)-2-(oxazol-2-yl)ethan-1-amine (I80)





a) 2-(2-Isopropoxyphenyl)acetyl chloride I77

To a solution of 2-(2-(difluoromethoxy)phenyl)acetic acid (2.0 g, 9.89 mmol) in DCM (20 mL) was added oxalyl chloride (3 mL, 29.67 mmol) dropwise followed by DMF (3 drops) and the mixture was stirred at RT for 3 h. The mixture was concentrated under reduced pressure to give the title compound (2.2 g, 100%) as a red oil. LCMS-D: R_t 2.02 min; *m/z* 239.0 $[M-Cl+MeO+Na]^+$

b) 2-(2-(Difluoromethoxy)benzyl)oxazole I78

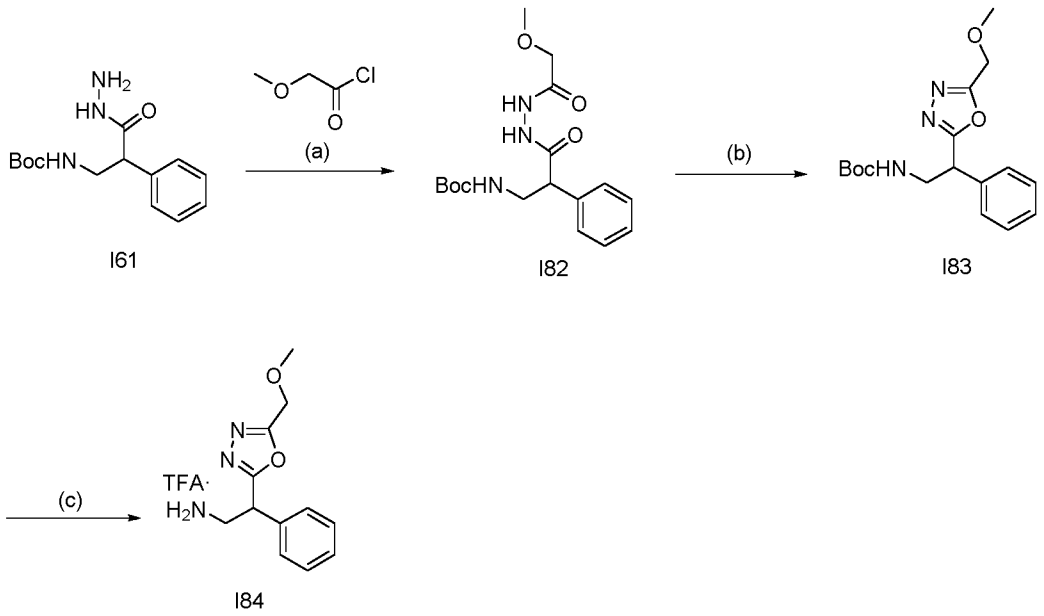
To a mixture of 1,2,3-triazole (1.0 g, 4.53 mmol) and K_2CO_3 (0.94 g, 6.80 mmol) in sulfolane (30 mL) at 0 °C was added 2-(2-isopropoxyphenyl)acetyl chloride I77 (1.0 g, 4.53

mmol) and the mixture was heated at 165 °C under N_2 for 1 h. After cooling to RT, the mixture was diluted with water (100 mL) and extracted with Et_2O (100 mL × 3). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 6/1) to give the title compound (800 mg, 78%) as a yellow oil. LCMS-D: R_t 1.74 min; *m/z* 226.0 $[M+H]^+$.

c) 2-(2-(2-(Difluoromethoxy)phenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I79
To a solution of 2-(2-(difluoromethoxy)benzyl)oxazole I78 (1.1 g, 4.88 mmol) in dry THF (30 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 6.0 mL, 6.0 mmol) dropwise. The mixture was stirred at -78 °C for 1 h, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (1.41 g, 5.86 mmol) in dry THF (20 mL) at -78 °C under N_2. The mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL) and the mixture was extracted with DCM (50 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 6/1) to give the title compound (360 mg, 19%) as a yellow solid. LCMS-D: R_t 2.21 min; *m/z* 385.0 $[M+H]^+$.

d) 2-(2-(Difluoromethoxy)phenyl)-2-(oxazol-2-yl)ethan-1-amine I80
A suspension of 2-(2-(2-(difluoromethoxy)phenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I79 (360 mg, 0.94 mmol) and hydrazine hydrate (0.15 mL, 2.81 mmol) in EtOH (20 mL) was heated at 80 °C under N_2 for 3 h. The mixture was filtered and the filter cake was washed with EtOH (2 mL). The filtrate was concentrated under reduced pressure to give the title compound (150 mg, 63%) as a yellow oil. LCMS-D: R_t 0.34 min; *m/z* 255.0 $[M+H]^+$

xxviii) 2-(5-(Methoxymethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine trifluoroacetate (I84)



a) *tert*-Butyl (3-(2-(2-methoxyacetyl)hydrazinyl)-3-oxo-2-phenylpropyl)carbamate I82

To a solution of *tert*-butyl (3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61 (515 mg, 1.84 mmol) in THF (50 mL) was added pyridine (292 mg, 3.69 mmol) and 2-methoxyacetyl chloride (240 mg, 2.21 mmol) and the mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted with DCM (100 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (230 mg, 36%) as a yellow oil. LCMS-CLCMS-C: R_t 1.60 min; *m/z* 352.0 $[M+H]^+$.

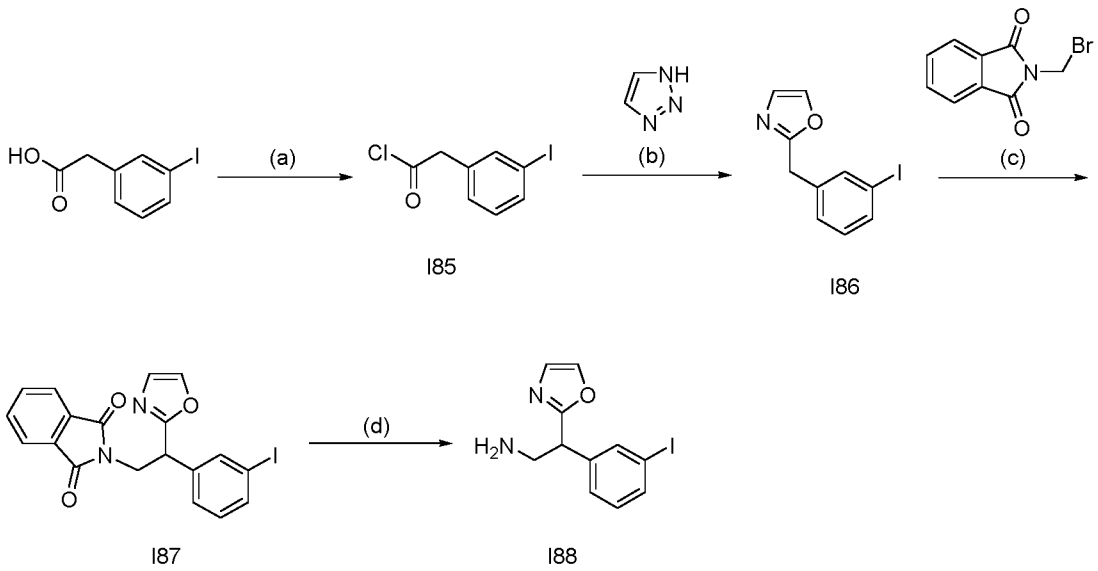
b) *tert*-Butyl (2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I83

To a solution of *tert*-butyl (3-(2-(2-methoxyacetyl)hydrazinyl)-3-oxo-2-phenylpropyl)carbamate I82 (30 mg, 0.085 mmol) in THF (2 mL) was added Burgess reagent (41 mg, 0.17 mmol) and the mixture was heated at 120 °C under microwave irradiation for 30 min. The procedure was repeated once on the same scale and once using *tert*-butyl (3-(2-(2-methoxyacetyl)hydrazinyl)-3-oxo-2-phenylpropyl)carbamate I82 (150 mg, 0.60 mmol) and Burgess reagent (711 mg, 2.98 mmol) in THF (3 mL). The three reaction mixtures were combined, diluted with water (50 mL) and extracted with DCM (50 mL ×3). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (70 mg, 27%) as a yellow oil. LCMS-D: R_t 1.96 min; *m/z* 356.0 $[M+Na]^+$.

c) 2-(5-(Methoxymethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine trifluoroacetate I84

A solution of *tert*-butyl (2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I83 (70 mg, 0.21 mmol) and TFA (2 mL) in DCM (1 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to give the title compound (60 mg, 82%) as a yellow oil, which was used in the next step without further purification. LCMS-C: R_t 0.87 min; *m/z* 233.9 $[M+H]^+$ for the free base.

xxix) 2-(3-Iodophenyl)-2-(oxazol-2-yl)ethan-1-amine (I88)



a) 2-(3-Iodophenyl)acetyl chloride I85

To a solution of 2-(3-iodophenyl)acetic acid (10.0 g, 38 mmol) in DCM (50 mL) was added oxalyl chloride (10.0 mL, 115 mmol) and DMF (1 mL) and the mixture was stirred at RT for 5 h. The mixture was concentrated under reduced pressure to give the title compound (10.0 g, 94%) as a yellow oil, which was used directly in the next step.

b) 2-(3-Iodobenzyl)oxazole I86

To a mixture of 1,2,3-triazole (3.0 g, 43.2 mmol) and K_2CO_3 (7.3 g, 53.0 mmol) in sulfolane (80 mL) was added a solution of 2-(3-iodophenyl)acetyl chloride I85 (10.0 g, 36.0 mmol) in sulfolane (20 mL) and the mixture was heated at 165 °C under N_2 for 1 h. After cooling to RT, the mixture was diluted with water and extracted with Et_2O. The combined organic extracts were concentrated under reduced pressure and the residue was purified by silica gel chromatography (Pet. ether/EtOAc = 50/1 to 20/1 to 10/1) to give the title compound (6.0 g, 58%) as a yellow oil. LCMS-C: R_t 2.13 min; *m/z* 285.9 $[M+H]^+$.

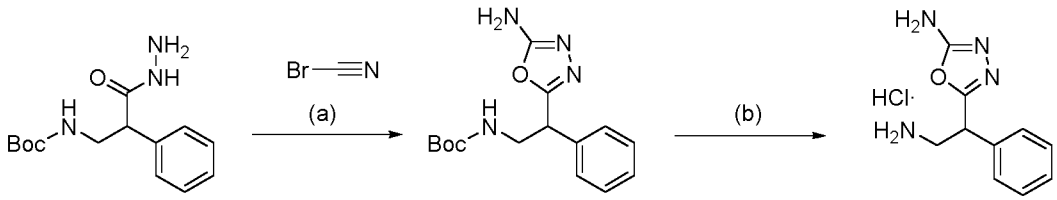
c) 2-(2-(3-Iodophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I87

To a solution of 2-(3-iodobenzyl)oxazole I86 (6.0 g, 21 mmol) in dry THF (100 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 25.0 mL, 25.0 mmol) dropwise and the mixture was stirred at -78 °C for 45 min. A solution of 2-(bromomethyl)isoindoline-1,3-dione (6.0 g, 25.0 mmol) in dry THF (60 mL) was then added dropwise at -78 °C and the mixture was allowed to warm to RT and stirred overnight. The mixture was diluted with water, extracted with EtOAc and the combined organic extracts were concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 30/1 to 10/1) to give the title compound (1.8 g, 19%) as a yellow oil. LCMS-C: R_t 2.33min; *m/z* 445.1 $[M+H]^+$.

d) 2-(3-Iodophenyl)-2-(oxazol-2-yl)ethan-1-amine I88

A suspension of 2-(2-(3-iodophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I87 (1.8 g, 4.0 mmol) and hydrazine monohydrate (600 mg, 12.0 mmol) in EtOH (30 mL) was heated at 80 °C under N_2 overnight. After cooling to RT, the mixture was diluted with water and extracted with DCM. The combined organic extracts were concentrated under reduced pressure to give the title compound (760 mg, 63%) as a yellow oil. LCMS-C: R_t 0.36 min; *m/z* 315.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.64 – 7.60 (m, 2H), 7.28 – 7.24 (m, 1H), 7.19 (s, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 4.22 – 4.16 (m, 1H), 3.25 – 3.18 (m, 1H), 3.04 – 2.98 (m, 1H).

xxx) 5-(2-Amino-1-phenylethyl)-1,3,4-oxadiazol-2-amine hydrochloride (I90)



I61 I89 I90

a) *tert*-Butyl(2-(5-amino-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I89

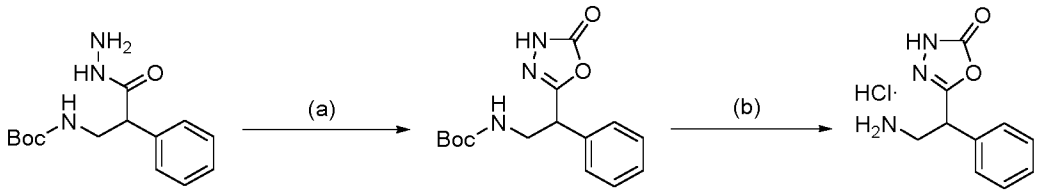
To a solution of *tert*-butyl(3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61 (130 mg, 0.5 mmol) in 1,4-dioxane (5 mL) was added a solution of $NaHCO_3$ (42 mg, 0.5 mmol) in water (1.5 mL) and a white suspension was formed. Bromoacetonitrile (53 mg, 0.5 mmol) was then added portion wise and the mixture was stirred at RT overnight. The reaction was scaled up accordingly using *tert*-butyl(3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate (1 mmol) and the reaction mixtures were combined, concentrated under reduced pressure to remove most of the 1,4-dioxane and the aqueous residue was extracted with EtOAc (100 mL). The organic extract was washed with a saturated aqueous $NaHCO_3$ solution, dried

over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (400 mg, 88%) as a white solid. LCMS-DLCMS-D: R_t 2.38 min, *m/z* 305.1 $[M+H]^+$.

b) 5-(2-Amino-1-phenylethyl)-1,3,4-oxadiazol-2-amine hydrochloride I90

A mixture of *tert*-butyl(2-(5-amino-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I89 (183 mg, 0.6 mmol) and a 2 M solution of HCl in 1,4-dioxane (10 mL) was stirred at RT under N_2 for 2 h. The mixture was then concentrated under reduced pressure to give the title compound (120 mg, 83%) as a white solid. LCMS-D: R_t 0.28 min, *m/z* 205.1 $[M+H]^+$.

xxxi) 5-(2-Amino-1-phenylethyl)-1,3,4-oxadiazol-2(3H)-one hydrochloride I92



I61 I91 I92

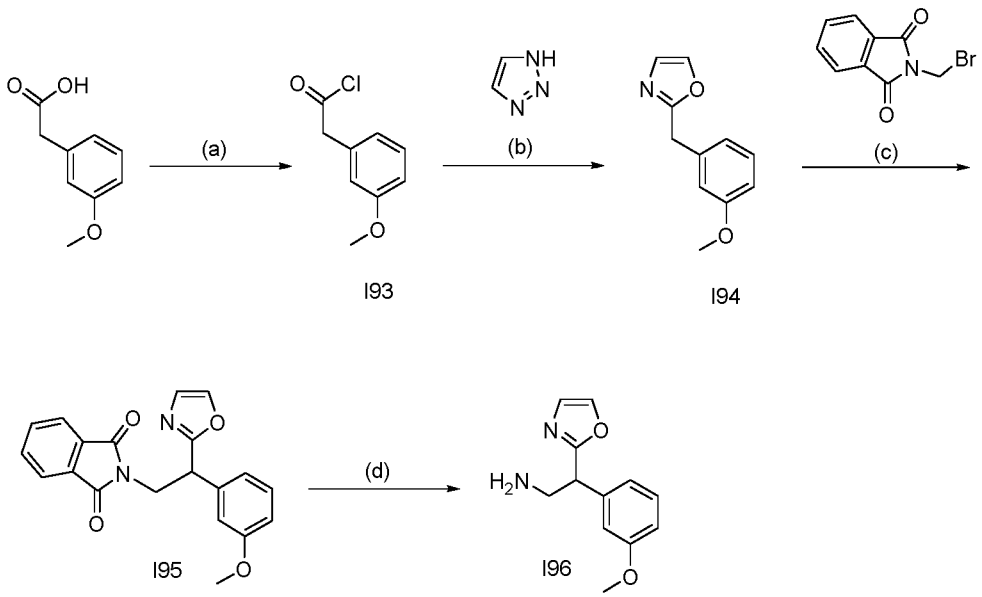
a) *tert*-Butyl (2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I91

To a solution of *tert*-butyl(3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61 (320 mg, 1.15 mmol) and DIPEA (297 mg, 2.3 mmol) in DCM (12 mL) at 0 °C under N_2 was added a solution of triphosgene (137 mg, 0.46 mmol) in DCM (8 mL) and the mixture was stirred for 15 min, then allowed to warm to RT and stirred overnight. The mixture was diluted with DCM (50 mL), washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (170 mg, 49%) as a white solid. LCMS-D: R_t 2.43 min, *m/z* 328.0 $[M+Na]^+$.

b) 5-(2-Amino-1-phenylethyl)-1,3,4-oxadiazol-2(3*H*)-one hydrochloride I92

A mixture of *tert*-butyl (2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-phenylethyl)carbamate I91 (110 mg, 0.36 mmol) and a 2 M solution of HCl in 1,4-dioxane (10 mL) was stirred at RT overnight. The mixture was then concentrated under reduced pressure to give the title compound (110 mg, >100%) as a white solid, which was used directly in the next step. LCMS-D: R_t 0.27 min, *m/z* 206.1 $[M+H]^+$.

xxxii) 2-(3-Methoxyphenyl)-2-(oxazol-2-yl)ethan-1-amine (I96)



a) 2-(3-Methoxyphenyl)acetyl chloride I93

To a solution of 2-(3-methoxyphenyl)acetic acid (10.0 g, 60.0 mmol) and DMF (3 drops) in DCM (100 mL) at 0 °C under N_2 was added oxalyl chloride (23.0 g, 180 mmol) and the mixture was stirred for 3 h. The solvent was removed under reduced pressure to give the title compound (11.0 g, 100%) as a yellow oil. LCMS-D: R_t 2.17 min, *m/z* 181.0 [M-Cl+MeO+H]$^+$.

b) 2-(3-Methoxybenzyl)oxazole I94

To a mixture of 1,2,3-triazole (5.00 g, 72.0 mmol) and K_2CO_3 (13.0 g, 90.0 mmol) in sulfolane (150 mL) at 0 °C was added 2-(3-methoxyphenyl)acetyl chloride I93 (11.0 g, 60.0 mmol) dropwise and the mixture was heated at 165 °C for 1 h. After cooling to RT, MTBE (400 mL) was added and the mixture was washed with water (500 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1) to give the title compound (5.2 g, 50%) as a yellow oil. LCMS-D: R_t 2.24 min, *m/z* 190.0 [M+H]$^+$.

c) 2-(2-(3-Methoxyphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I95

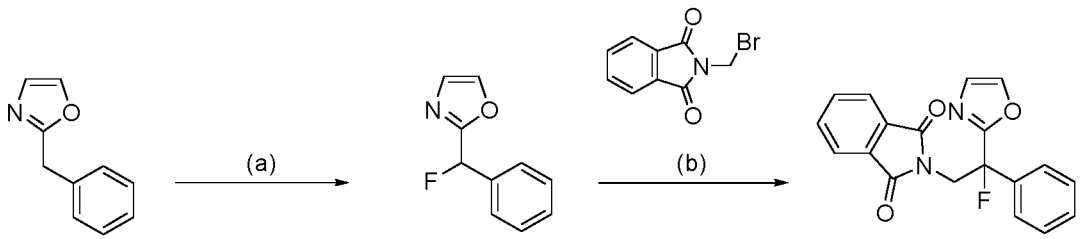
To a solution of 2-(3-methoxybenzyl)oxazole I94 (5.2 g, 27.5 mmol) in dry THF (80 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 33.0 mL, 33.0 mmol) dropwise. The mixture was stirred at -78 °C for 45 min, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (7.9 g, 33 mmol) in dry THF (120 mL) at -78 °C under N_2 and the mixture was stirred at -78 °C overnight. The solvent was removed under reduced pressure and the residue was diluted with DCM (200 mL), washed with a

saturated aqueous $NaHCO_3$ solution (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 4/1) to give the title compound (2.69 g, 28%) as a yellow solid. LCMS-D: R_t 2.58 min, *m/z* 349.1 $[M+H]^+$.

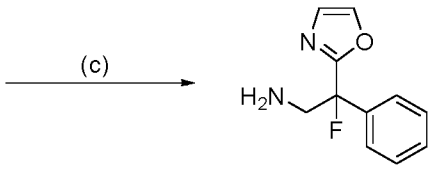
d) 2-(3-Methoxyphenyl)-2-(oxazol-2-yl)ethan-1-amine I96

A suspension of 2-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I95 (2.69 g, 7.70 mmol) and hydrazine monohydrate (1.20 g, 23.0 mmol) in EtOH (50 mL) was stirred at 80 °C under N_2 for 3 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give the title compound (1.4 g, 80%) as a yellow oil. LCMS-D: R_t 0.43 min, *m/z* 219.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.96 (m, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 6.87 – 6.74 (m, 3H), 4.16 (dd, *J* = 8.3, 6.2 Hz, 1H), 3.72 (s, 3H), 3.28 – 3.19 (m, 1H), 3.06 – 2.98 (m, 1H).

xxxiii) 2-Fluoro-2-(oxazol-2-yl)-2-phenylethanamine (I99)



I25 I97 I98



I99

a) 2-(Fluoro(phenyl)methyl)oxazole I97

To a solution of 2-benzyloxazole I25 (15.1 g, 95.0 mmol) in dry THF (150 mL) at -78 °C under N_2 was added *t*-BuLi (1.3 M solution in heptane, 81.0 mL, 105 mmol) dropwise. The mixture stirred at -78 °C for 45 min, then added to a solution of *N*-fluorobenzenesulfonimide (39.0 g, 124 mmol) in dry THF (100 mL) at -78 °C under N_2 and the mixture was stirred at -78 °C overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution (100 mL) and the mixture was extracted with EtOAc (300 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 28/1) to give the title compound (10.2 g,

63%) as a red oil. LCMS-D: R_t 1.25 min, *m/z* 178.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.55 – 7.41 (m, 5H), 7.32 (s, 1H), 6.84 (d, *J* = 24.0 Hz, 1H).

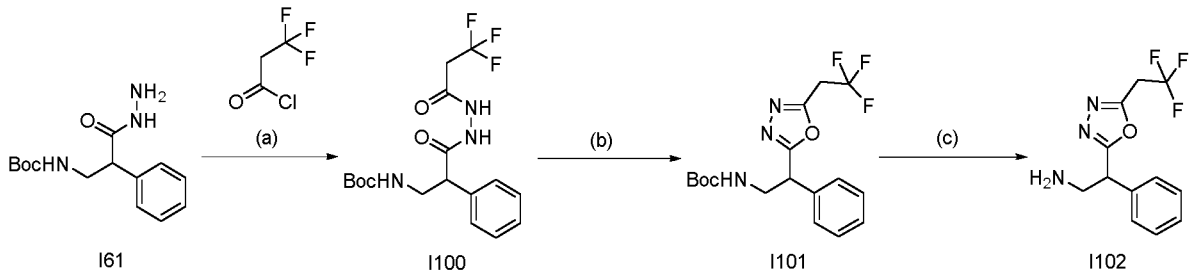
b) 2-(2-Fluoro-2-(oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione I98

To a solution of 2-(fluoro(phenyl)methyl)oxazole I97 (3.54 g, 20 mmol) in dry THF (30 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 24.0 mL, 24.0 mmol) dropwise. The mixture was stirred at -78 °C for 45 min, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (5.76 g, 24.0 mmol) in dry THF (60 mL) at -78 °C under N_2 and the mixture was stirred at -78 °C overnight. The mixture was diluted with water, extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 5/1) to give the title compound (520 mg, 8%) as a white solid. LCMS-D: R_t 2.12 min, *m/z* 337.0 $[M+H]^+$.

c) 2-Fluoro-2-(oxazol-2-yl)-2-phenylethanamine I99

A suspension of 2-(2-fluoro-2-(oxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione I98 (520 mg, 1.5 mmol) and hydrazine monohydrate (225 mg, 4.5 mmol) in EtOH (10 mL) was heated at 80 °C under N_2 for 3 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL), washed with water (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (250 mg, 80%) as a yellow oil. LCMS-D: R_t 0.28 min, *m/z* 207.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 – 8.16 (m, 1H), 7.48 – 7.26 (m, 6H), 3.58 – 3.44 (m, 1H), 3.39 – 3.25 (m, 1H).

xxxiv) 2-Phenyl-2-(5-(2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)ethanamine (I102)



I61 I100 I101 I102

a) *tert*-Butyl (3-oxo-2-phenyl-3-(2-(3,3,3-trifluoropropanoyl)hydrazinyl)propyl)carbamate I100

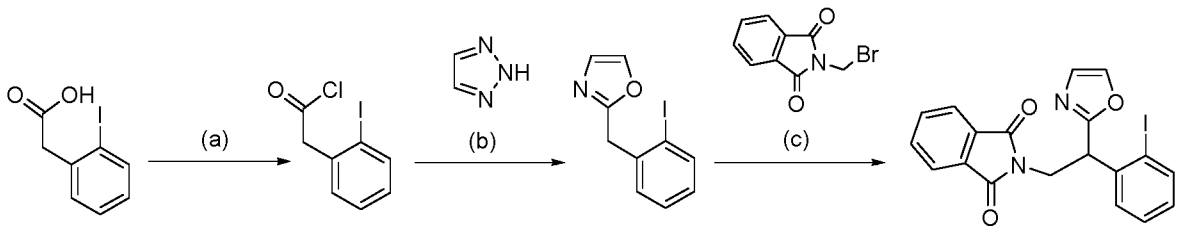
To a solution of *tert*-butyl (3-hydrazinyl-3-oxo-2-phenylpropyl)carbamate I61 (558 mg, 2.0 mmol) and pyridine (320 mg, 4.0 mmol) in dry THF (20 mL) at RT was added a solution of 3,3,3-trifluoropropanoyl chloride (580 mg, 4.0 mmol) in dry THF (5 mL) dropwise and the mixture was stirred for 2 h. The mixture was concentrated under reduced pressure and the

residue was diluted with EtOAc (50 mL), washed with 1 M aqueous HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (610 mg, 80%) as a white solid. LCMS-D: R_t 1.62 min, *m/z* 412.1 $[M+Na]^+$.

b) *tert*-Butyl (2-phenyl-2-(5-(2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate I101
A suspension of *tert*-butyl (3-oxo-2-phenyl-3-(2-(3,3,3-trifluoropropanoyl) hydrazinyl)propyl)carbamate I100 (312 mg, 0.8 mmol) and Burgess reagent (760 mg, 3.2 mmol) in dry THF (12 mL) was stirred at 160 °C in a sealed tube overnight. The mixture was diluted with DCM (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (50 mg, 17%) as a yellow solid. LCMS-D: R_t 2.30 min, *m/z* 372.1 $[M+H]^+$.

c) 2-Phenyl-2-(5-(2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)ethanamine I102
To a solution of *tert*-butyl (2-phenyl-2-(5-(2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl) ethyl)carbamate I101 (50 mg, 0.13 mmol) in DCM (10 mL) was added TFA (1 mL) and the mixture was stirred at RT overnight. The mixture was diluted with DCM (50 mL), washed with a saturated aqueous $NaHCO_3$ solution and concentrated under reduced pressure to give the title compound (20 mg, 60%) as a yellow solid. LCMS-D: R_t 0.25 min, *m/z* 272.0 $[M+H]^+$.

xxxv) 2-(2-Iodophenyl)-2-(oxazol-2-yl)ethanamine (I106)



a) 2-(2-Iodophenyl)acetyl chloride I103
To a solution of 2-(2-iodophenyl)acetic acid (15.7 g, 60 mmol) and DMF (3 drops) in DCM (100 mL) at 0 °C under N_2 was added oxalyl chloride (23 g, 180 mmol) dropwise and the mixture was stirred for 3 h. The mixture was concentrated under reduced pressure to give

the title compound (16.8 g, 100%) as a brown oil. LCMS-D: R_t 2.14 min, *m/z* 276.9 [M-Cl+MeO+H]$^+$.

b) 2-(2-Iodobenzyl)oxazole I104

To a mixture of 1,2,3-triazole (5.0 g, 72.0 mmol) and K_2CO_3 (13.0 g, 90.0 mmol) in sulfolane (200 mL) at 0 °C was added 2-(2-iodophenyl)acetyl chloride I103 (16.8 g, 60.0 mmol) and the mixture was heated at 165 °C for 45 min. After cooling to RT, the mixture was diluted with water, extracted with MTBE (500 mL × 3) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1) to give the title compound (9.5 g, 55%) as a yellow oil. LCMS-D: R_t 1.98 min, *m/z* 285.9 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J* = 1.0 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.12 (d, *J* = 0.9 Hz, 1H), 7.07 – 7.00 (m, 1H), 4.23 (s, 2H).

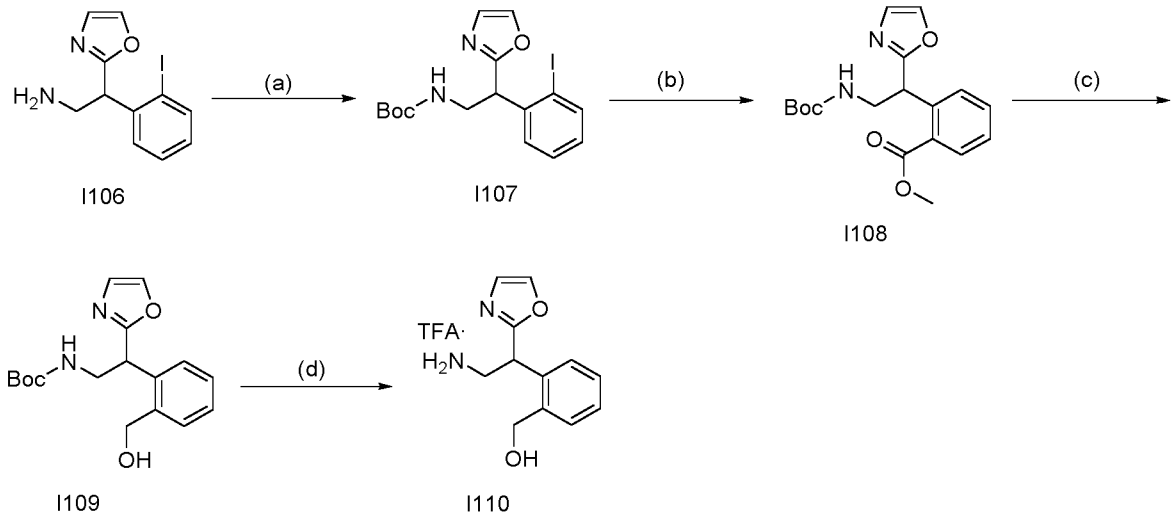
c) 2-(2-(2-Iodophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I105

To a solution of 2-(2-iodobenzyl)oxazole I104 (9.1 g, 32 mmol) in dry THF (100 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 38.4 mL, 38.4 mmol) dropwise. The mixture was stirred at -78 °C for 45 min, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (9.2 g, 38.4 mmol) in dry THF (150 mL) and the mixture was stirred at -78 °C under N_2 overnight. The mixture was diluted with water, extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 2/1) to give the title compound (4.6 g, 32%) as a yellow solid. LCMS-D: R_t 2.33 min, *m/z* 444.9 [M+H]$^+$.

d) 2-(2-Iodophenyl)-2-(oxazol-2-yl)ethanamine I106

A suspension of 2-(2-(2-iodophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I105 (4.6 g, 11.0 mmol) and hydrazine monohydrate (1.7 g, 33 mmol) in EtOH (120 mL) was heated at 80 °C under N_2 for 3 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (2.7 g, 79%) as an orange oil. LCMS-D: R_t 0.28 min, *m/z* 314.9 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, *J* = 1.0 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.21 (s, 1H), 7.11 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.05 – 6.98 (m, 1H), 4.52 – 4.44 (m, 1H), 3.25 – 3.15 (m, 1H), 3.05 – 2.97 (m, 1H).

xxxvi) (2-(2-Amino-1-(oxazol-2-yl)ethyl)phenyl)methanol trifluoroacetate salt (I110)



a) *tert*-Butyl (2-(2-iodophenyl)-2-(oxazol-2-yl)ethyl)carbamate I107

A suspension of 2-(2-iodophenyl)-2-(oxazol-2-yl)ethanamine I106 (628 mg, 2.0 mmol), Boc_2O (873 mg, 4.0 mmol) and Et_3N (606 mg, 6.0 mmol) in DCM (20 mL) was stirred at RT for 3 h. The mixture was diluted with water, extracted with DCM (100 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 4/1) to give the title compound (700 mg, 84%) as a yellow oil. LCMS-C: R_t 2.31 min, *m/z* 414.9 $[M+H]^+$.

b) Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-1-(oxazol-2-yl)ethyl)benzoate I108

A mixture of *tert*-butyl (2-(2-iodophenyl)-2-(oxazol-2-yl)ethyl)carbamate I107 (700 mg, 1.7 mmol), Pd(dppf)Cl_2·DCM (140 mg, 0.17 mmol), Et_3N (500 mg, 5 mmol) and MeOH (30 mL) was heated at 100 °C under a CO atmosphere (0.1 MPa) overnight. The mixture was diluted with water, extracted with DCM (100 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (460 mg, 77%) as a yellow oil. LCMS-C: R_t 2.19 min, *m/z* 347.0 $[M+H]^+$.

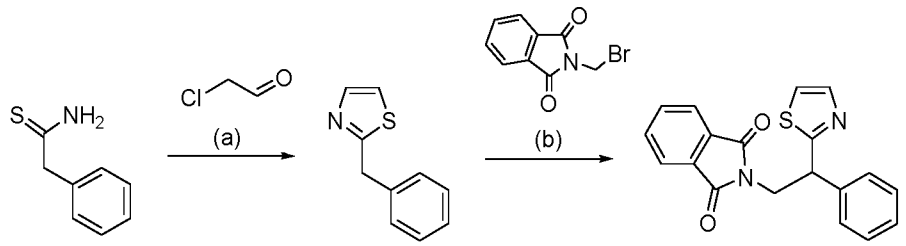
c) *tert*-Butyl(2-(2-(hydroxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)carbamate I109

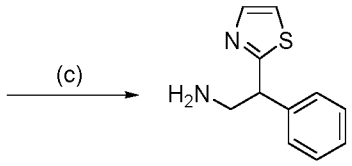
To a solution of methyl 2-(2-((*tert*-butoxycarbonyl)amino)-1-(oxazol-2-yl)ethyl) benzoate I108 (460 mg, 1.33 mmol) in dry THF (20 mL) was added $LiBH_4$ (2 M solution in THF, 1.33 mL, 2.66 mmol) and the mixture was stirred at RT for 2 h. The mixture was diluted with DCM (100 mL), washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (400 mg, 98%) as a yellow oil. LCMS-C: R_t 1.37 min, *m/z* 319.0 $[M+H]^+$.

d) (2-(2-Amino-1-(oxazol-2-yl)ethyl)phenyl)methanol trifluoroacetate salt I110

A solution of *tert*-butyl (2-(2-(hydroxymethyl)phenyl)-2-(oxazol-2-yl)ethyl) carbamate I109 (100 mg, 0.3 mmol) in TFA (1 mL) was stirred at RT for 2 h. The mixture was then concentrated under reduced pressure to give the title compound (66 mg, 67%) as a yellow oil. LCMS-C: R_t 0.38 min, *m/z* 219.0 $[M+H]^+$.

xxxvii) 2-Phenyl-2-(thiazol-2-yl)ethanamine (I113)





a) 2-Benzylthiazole I111

A suspension of 2-phenylethanethioamide (10.0 g, 66.0 mmol) and 2-chloroacetaldehyde (26.0 g, 132 mmol) in EtOH (150 mL) was heated at 100 °C under N_2 overnight. The mixture was diluted with EtOAc (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 10/1) to give the title compound (3.88 g, 33%) as a yellow oil. LCMS-C: R_t 1.52 min, *m/z* 176.0 $[M+H]^+$.

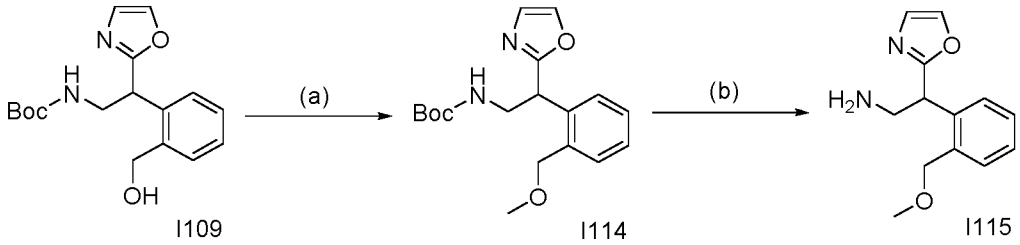
b) 2-(2-Phenyl-2-(thiazol-2-yl)ethyl)isoindoline-1,3-dione I112

To a solution of 2-benzylthiazole I111 (3.88 g, 22.1 mmol) in dry THF (60 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 26.5 mL, 26.5 mmol) dropwise. The mixture was stirred at -78 °C for 45 min, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (6.38 g, 26.5 mmol) in dry THF (60 mL) at -78 °C under N_2 and the mixture was stirred at -78 °C overnight. The mixture was diluted with EtOAc (300 mL), washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 2/1) to give the title compound (2.9 g, 39%) as a yellow solid. LCMS-C: R_t 2.23 min, *m/z* 335.0 $[M+H]^+$.

c) 2-Phenyl-2-(thiazol-2-yl)ethanamine I113

A suspension of 2-(2-phenyl-2-(thiazol-2-yl)ethyl)isoindoline-1,3-dione I112 (2.9 g, 8.68 mmol) and hydrazine monohydrate (1.3 g, 26.0 mmol) in EtOH (120 mL) was heated at 80 °C under N_2 overnight. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give the title compound (1.4 g, 80%) as a yellow oil. LCMS-C: R_t 0.33 min, 205.0 $[M+H]^+$.

xxxviii) 2-(2-(Methoxymethyl)phenyl)-2-(oxazol-2-yl)ethanamine trifluoroacetate (I115)



I109 I114 I115

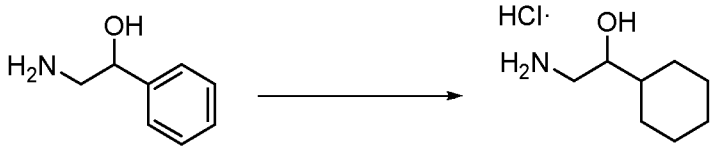
a) *tert*-Butyl(2-(2-(methoxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)carbamate I114

To a solution of *tert*-butyl (2-(2-(hydroxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)carbamate I109 (100 mg, 0.30 mmol) in CH_3CN (10 mL) was added Ag_2O (350 mg, 1.5 mmol) and CH_3I (426 mg, 3.0 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with DCM (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (40 mg, 40%) as a yellow oil. LCMS-C: R_t 2.28 min, *m/z* 333.1 $[M+H]^+$.

b) 2-(2-(Methoxymethyl)phenyl)-2-(oxazol-2-yl)ethanamine trifluoroacetate I115

A solution of *tert*-butyl(2-(2-(methoxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)carbamate I114 (40 mg, 0.12 mmol) in TFA (1 mL) was stirred at RT for 2 h. The mixture was then concentrated under reduced pressure to give the title compound (23 mg, 56%) as a yellow oil. LCMS-C: R_t 0.35 min, *m/z* 233.0 $[M+H]^+$.

xxxix) 2-Amino-1-cyclohexylethanol hydrochloride I116

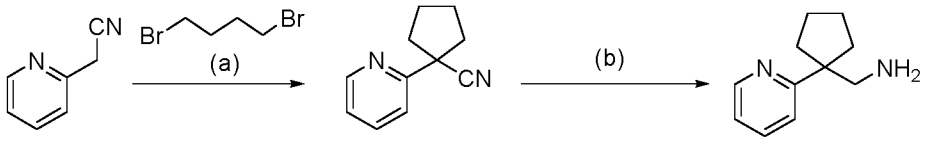


I116

To a solution of 2-amino-1-phenylethanol (274 mg, 2.0 mmol) in EtOH (20 mL) was added PtO_2 (45 mg, 0.2 mmol) and conc. aqueous HCl (1 mL) and the mixture was heated at 120 °C under a H_2 atmosphere (3 MPa) overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (57 mg, 16%) as a yellow

oil, which was used directly in the next step without further purification. LCMS-C: R_t 0.32 min, *m/z* 144.1 $[M+H]^+$.

xl) (1-(Pyridin-2-yl)cyclopentyl)methanamine I118



I117 I118

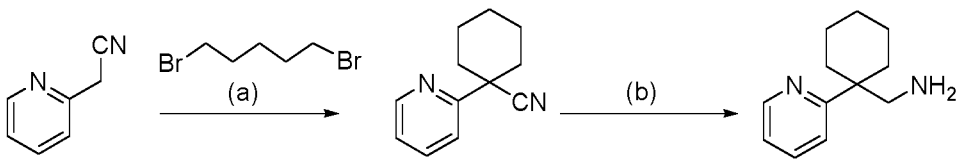
a) 1-(Pyridin-2-yl)cyclopentanecarbonitrile I117

To a solution of NaH (60% dispersion in mineral oil, 800 mg, 20 mmol) in DMSO (10 mL) at 15 °C under N_2 was added a solution of 2-(pyridin-2-yl)acetonitrile (1.18 g, 10 mmol) and 1,4-dibromobutane (2.16 g, 10 mmol) in Et_2O (10 mL) and DMSO (2 mL) dropwise over 1 h. The mixture was then allowed to warm to RT and stirred for 24 h. The reaction was carefully quenched by dropwise addition of isopropanol (5 mL) followed by water (10 mL). The mixture was stirred for 10 min, then extracted with EtOAc (200 mL) and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.72 g, 100%) as a brown oil. LCMS-C: R_t 1.11 min, *m/z* 173.0 $[M+H]^+$.

b) (1-(Pyridin-2-yl)cyclopentyl)methanamine I118

To a solution of 1-(pyridin-2-yl)cyclopentanecarbonitrile I117 (344 mg, 2 mmol) in THF (10 mL) was added $LiAlH_4$ (2.5 M solution in THF, 1.6 mL, 4 mmol) and the mixture was stirred at RT for 2 h. The mixture was diluted with water (5 mL), extracted with EtOAc (100 mL) and the organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (200 mg, 60%) as a yellow oil. LCMS-C: R_t 0.33 min, *m/z* 177.1 $[M+H]^+$.

xli) (1-(Pyridin-2-yl)cyclohexyl)methanamine (I120)



I119 I120

a) 1-(Pyridin-2-yl)cyclohexanecarbonitrile I119

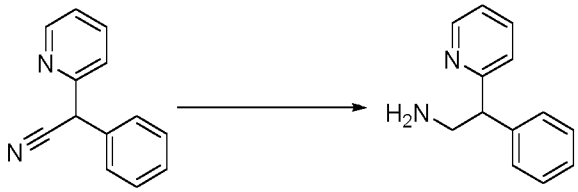
To a solution of NaH (60% dispersion in mineral oil, 800 mg, 20 mmol) in DMSO (10 mL) at 15 °C under N_2 was added a solution of 2-(pyridin-2-yl)acetonitrile (1.18 g, 10 mmol) and 1,5-dibromopentane (2.3 g, 10 mmol) in Et_2O (80 mL) and DMSO (2 mL) dropwise over 1

h. The mixture was allowed to warm to RT and stirred for 24 h. The reaction was carefully quenched by dropwise addition of isopropanol (5 mL) followed by water (10 mL). The mixture was stirred for 10 min, then extracted with EtOAc (200 mL) and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.86 g, 100%) as a brown oil. LCMS-C: R_t 1.87 min, *m/z* 187.0 $[M+H]^+$.

b) (1-(Pyridin-2-yl)cyclohexyl)methanamine I120

To a solution of 1-(pyridin-2-yl)cyclohexanecarbonitrile I119 (372 mg, 2 mmol) in THF (10 mL) was added $LiAlH_4$ (2.5 M solution in THF, 1.6 mL, 4 mmol) and the mixture was stirred at RT for 2 h. The mixture was diluted with water (5 mL), extracted with EtOAc (100 mL) and the organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (240 mg, 60%) as a yellow oil. LCMS-C: R_t 0.35 min, *m/z* 191.1 $[M+H]^+$.

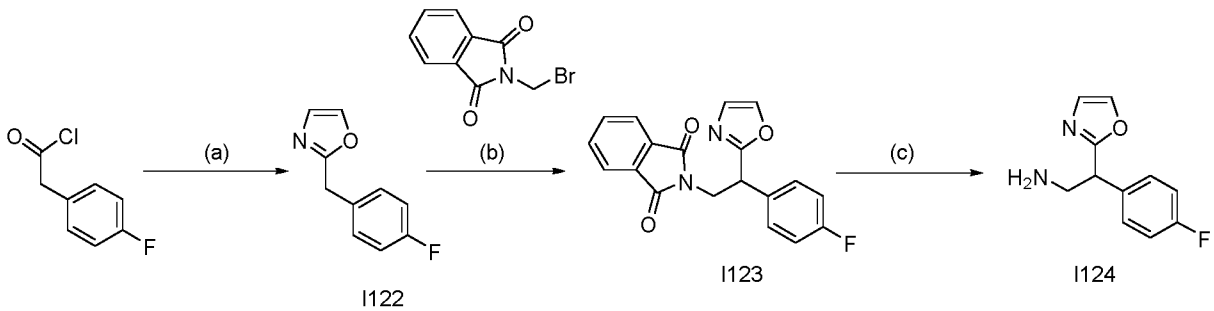
xlii) 2-Phenyl-2-(pyridin-2-yl)ethanamine (I121)



I121

A mixture of 2-phenyl-2-(pyridin-2-yl)acetonitrile (100 mg, 0.5 mmol) and Raney nickel (20 mg) in conc. aqueous NH_4OH (2 mL) was heated at 50 °C under a H_2 atmosphere overnight. The mixture was then filtered and the filtrate was partitioned between EtOAc and water. The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (50 mg, 49%). LCMS-C: R_t 0.36 min, *m/z* 199.1 $[M+H]^+$

xliii) 2-(4-Fluorophenyl)-2-(oxazol-2-yl)ethanamine I124



I122 I123 I124

a) 2-(4-Fluorobenzyl)oxazole I122

To a mixture of 1,2,3-triazole (10 g, 0.14 mol) and K_2CO_3 (25 g, 0.18 mmol) in sulfolane (300 mL) at 0 °C was added 2-(4-fluorophenyl)acetyl chloride (20 g, 0.12 mol) dropwise and the mixture was heated at 165 °C for 1 h. After cooling to RT, the mixture was diluted with MTBE (500 mL), washed with brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1) to give the title compound (10.5 g, 51%) as a red solid. LCMS-D: R_t 1.40 min; *m/z* 178.0 $[M+H]^+$.

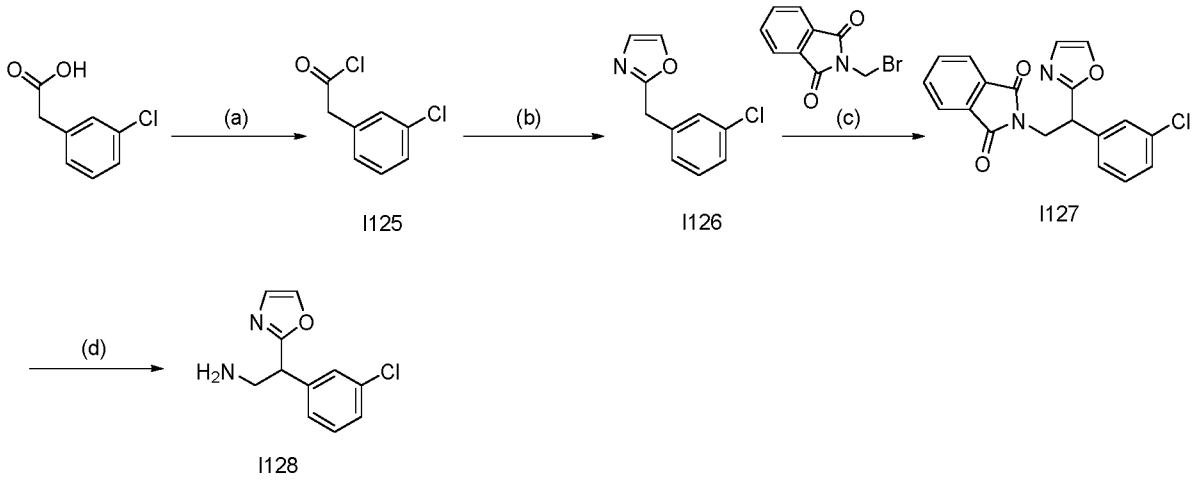
b) 2-(2-(4-Fluorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I123

To a solution of 2-(4-fluorobenzyl)oxazole I122 (10 g, 56 mmol) in THF (200 mL) at -78 °C under N_2 was LiHMDS (1 M solution in THF, 67.2 mL, 67.2 mmol) dropwise. The mixture was stirred for 45 min at -78 °C, then added dropwise to a solution of 2-(bromomethyl)isoindoline-1,3-dione (16.1 g, 67.2 mmol) in THF (200 mL) at -78 °C and the mixture was stirred at -78 °C overnight. The mixture was diluted with water, extracted with EtOAc (500 mL × 3) and the combined organic extracts were dried over Na_2SO, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 8/1 to 4/1) to give the title compound (3.0 g, 16%) as a white solid, which was used directly in the next step.

c) 2-(4-Fluorophenyl)-2-(oxazol-2-yl)ethanamine I124

A suspension of 2-(2-(4-fluorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I123 (1.0 g, 3.0 mmol) and hydrazine monohydrate (451 mg, 9.0 mmol) in EtOH (50 mL) was heated at 80 °C for 3 h. The mixture was filtered and the solid was washed with EtOH (50 mL). The filtrate was then concentrated under reduced pressure to give the title compound (532 mg, 87%) as a yellow oil. LCMS-C: R_t 0.29 min; *m/z* 207.0 $[M+H]^+$.

xliv) 2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethanamine (I128)



I125 I126 I127 I128

a) 2-(3-Chlorophenyl)acetyl chloride I125

To a solution of 2-(3-chlorophenyl)acetic acid (20.0 g, 0.12 mol) and DMF (0.2 mL) in DCM (100 mL) was added oxalyl chloride (45.7 g, 0.36 mol) dropwise and the mixture was stirred at RT for 1 h. The mixture was then concentrated under reduced pressure to give the title compound (10.0 g, 45%) as a red oil. LCMS-C: R_t 2.03 min; *m/z* 185.0 [M-Cl+MeO+H]$^+$.

b) 2-(3-Chlorobenzyl)oxazole I126

To a mixture of 1,2,3-triazole (8.8 g, 0.13 mol) and K_2CO_3 (23.5 g, 0.17 mol) in sulfolane (300 mL) at 0 °C was added 2-(3-chlorophenyl)acetyl chloride I125 (20.0 g, 0.11 mol) dropwise and the mixture was heated at 165 °C for 1 h. After cooling to RT, the mixture was diluted with MTBE (500 mL) and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 10/1) to give the title compound (10.7 g, 53%) as a yellow oil. LCMS-C: R_t 1.96min; *m/z* 194.0 [M+H]$^+$.

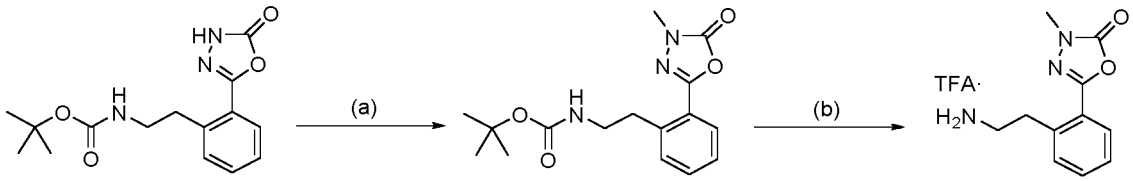
c) 2-(2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I127

To a solution of 2-(3-chlorobenzyl)oxazole I126 (10.0 g, 51.6 mmol) in dry THF (200 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 62.0 mL, 62.0 mmol). The mixture was stirred at -78 °C for 45 min, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (14.9 g, 62.0 mmol) in THF (200 mL) at -78 °C and the mixture was stirred at -78 °C overnight. The mixture was diluted with water and extracted with EtOAc (500 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 8/1 to 4/1) to give the title compound (6.8 g, 37%) as a white solid. LCMS-C: R_t 2.31 min; *m/z* 352.9 [M+H]$^+$.

d) 2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethanamine I128

A suspension of 2-(2-(3-chlorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I127 (1.0 g, 2.8 mmol) and hydrazine monohydrate (426 mg, 8.5 mmol) in EtOH (50 mL) was heated at 80 °C for 3 h. The mixture was then filtered and the solid was washed with EtOH (50 mL). The filtrate was concentrated under reduced pressure to give the title compound (0.56 g, 89%) as a yellow oil. LCMS-C: R_t 0.31 min; *m/z* 223.0 $[M+H]^+$.

xlv) 5-(2-(2-Aminoethyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one trifluoroacetate (I131)



I129 I130 I131

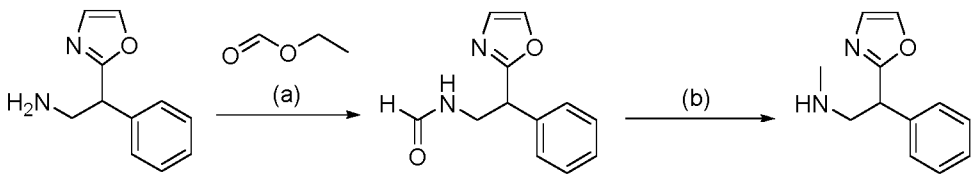
a) *tert*-Butyl 2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethylcarbamate I130

A mixture of *tert*-butyl 2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethylcarbamate I129 (see below) (200 mg, 0.66 mmol), K_2CO_3 (181 mg, 1.31 mmol) and CH_3I (186 mg, 1.31 mmol) in DMF (10 mL) was stirred at RT under N_2 overnight. Water was added and the mixture was extracted with EtOAc. The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (389 mg, >100%) as a yellow oil, which was used directly in the next step. LCMS-C: R_t 2.17 min; *m/z* 342.0 $[M+Na]^+$.

b) 5-(2-(2-Aminoethyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3*H*)-one trifluoroacetate I131

A mixture of *tert*-butyl 2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethylcarbamate I130 (389 mg, assumed 0.66 mmol) and TFA (5 mL) in DCM (10 mL) was stirred at RT under N_2 overnight. The mixture was concentrated under reduced pressure to give the title product (210 mg, 95%) as a yellow oil. LCMS-C: R_t 0.34 min; *m/z* 220.0 $[M+H]^+$.

xlvi) N-Methyl-2-(oxazol-2-yl)-2-phenylethan-1-amine (I133)



I27 I132 I133

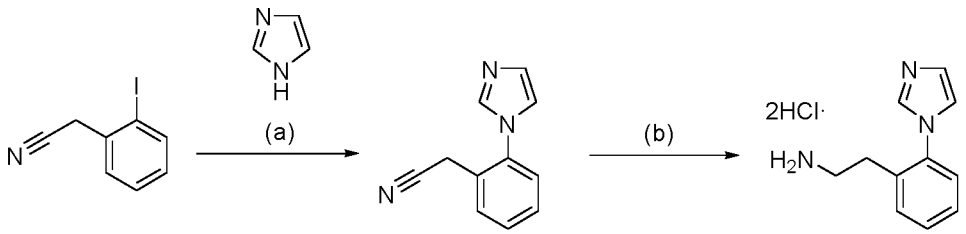
a) *N*-(2-(Oxazol-2-yl)-2-phenylethyl)formamide I132

A solution of 2-(oxazol-2-yl)-2-phenylethan-1-amine I27 (600 mg, 3.19 mmol) in ethyl formate (15 mL) was heated at 80 °C for 3 h. After cooling to RT, water (50 mL) was added and the mixture was extracted with DCM (50 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (500 mg, 72%), which was used directly in the next step without further purification. LCMS-D: R_t 0.46 min; *m/z* 217.1 $[M+H]^+$.

b) *N*-Methyl-2-(oxazol-2-yl)-2-phenylethan-1-amine I133

A mixture of *N*-(2-(oxazol-2-yl)-2-phenylethyl)formamide I132 (300 mg, 1.39 mmol) and BH_3·THF (1 M solution in THF, 6 mL, 6 mmol) was heated at 70 °C for 3 h, then allowed to cool to RT, adjusted to pH 5 with 10% aqueous HCl and stirred for 1 h. The mixture was washed with EtOAc (40 mL × 3) and the aqueous layer was then adjusted pH 9 with 1 M aqueous NaOH and extracted with EtOAc (40 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (130 mg, 46%) as a yellow oil. LCMS-D: R_t 0.32 min; *m/z* 203.1 $[M+H]^+$.

xlvii) 2-(2-(1H-Imidazol-1-yl)phenyl)ethan-1-amine dihydrochloride (I135)



I134 I135

a) 2-(2-(1*H*-Imidazol-1-yl)phenyl)acetonitrile I134

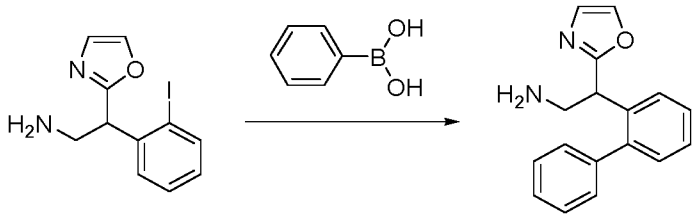
A mixture of 2-(2-iodophenyl)acetonitrile (600 mg, 2.47 mmol), 1*H*-imidazole (252 mg, 3.7 mmol), $Fe(acac)_3$ (262 mg, 0.741 mmol), Cs_2CO_3 (1.61 g, 4.94 mmol) and CuO (20 mg, 0.247 mmol) in DMF (15 mL) was heated at 90 °C under N_2 in a sealed tube for 30 h. The mixture was then filtered and the filtrate was diluted with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic extracts were concentrated under reduced pressure and the residue was purified by silica gel chromatography (DCM/MeOH = 15/1) to give the title compound (180 mg, 40%) as a yellow oil. LCMS-D: R_t 2.43 min, *m/z* 184.0 $[M+H]^+$.

b) 2-(2-(1*H*-Imidazol-1-yl)phenyl)ethan-1-amine dihydrochloride I135

To a solution of 2-(2-(1*H*-imidazol-1-yl)phenyl)acetonitrile I134 (90 mg, 0.49 mmol) in MeOH (5 mL) was added 10% Pd/C (50 mg) and conc. aqueous HCl (0.2 mL) and the

mixture was stirred at RT under a H_2 atmosphere overnight. The mixture was filtered and the filter cake rinsed with MeOH (3 mL × 2). The filtrate was concentrated under reduced pressure to give the title compound (80 mg, 63%) as a yellow oil. LCMS-D: R_t 0.89 min, *m/z* 188.0 $[M+H]^+$.

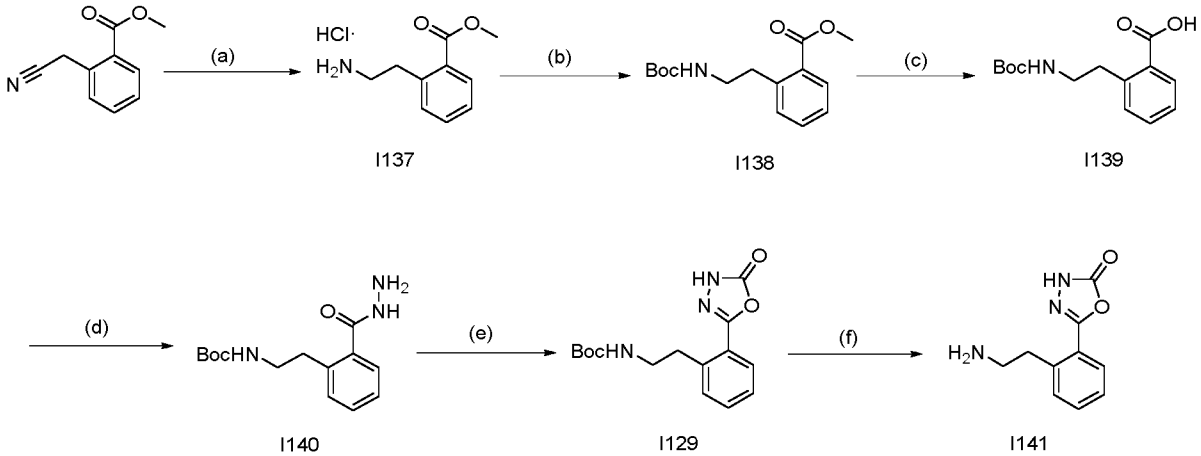
xlviii) 2-([1,1'-Biphenyl]-2-yl)-2-(oxazol-2-yl)ethanamine (I136)



I106 I136

To a solution of 2-(2-iodophenyl)-2-(oxazol-2-yl)ethanamine I106 (157 mg, 0.5 mmol) in DMF/H_2O (10 mL/2 mL) was added phenylboronic acid (122 mg, 1 mmol), $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) and Cs_2CO_3 (450 mg, 1.5 mmol) and the mixture was heated at 110 °C under N_2 overnight. The mixture was diluted with EtOAc (100 mL), washed with water (100 mL × 5) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (20 mg, 15%) as a yellow oil. LCMS-C: R_t 0.55 min, *m/z* 265.0 $[M+H]^+$.

xlix) 5-(2-(2-Aminoethyl)phenyl)-1,3,4-oxadiazol-2(3H)-one (I141)



I137 I138 I139

I140 I129 I141

a) Methyl 2-(2-aminoethyl) benzoate hydrochloride I137

To a solution of methyl 2-(cyanomethyl) benzoate (2.09 g, 11.9 mmol) in MeOH (30 mL) was added 10% Pd/C (1.05 g) and conc. aqueous HCl (5 mL) and the mixture was stirred at RT under a H_2 atmosphere overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was suspended in MeOH (5 mL) then diluted with Et_2O (100 mL). The solid was collected by filtration, washed with Et_2O and

dried under vacuum to give the title compound (1.25 g 58%) as a white solid. LCMS-D: R_t 0.31 min; *m/z* 180.1 $[M+H]^+$.

b) Methyl 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)benzoate I138

A solution of methyl 2-(2-aminoethyl) benzoate I137 (1.22 g 6.82 mmol), Boc_2O (2.23 g, 10.2 mmol) and Et_3N (2.07 g, 20.5 mmol) in DCM (30 mL) was stirred at RT under N_2 overnight. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.87 g, 98%) as a yellow oil. LCMS-D: R_t 2.27 min; *m/z* 180.1 $[M-Boc+2H]^+$.

c) 2-(2-((*tert*-Butoxycarbonyl)amino)ethyl)benzoic acid I139

To a solution of methyl 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)benzoate I138 (1.87 g, 6.72 mmol) in MeOH (18 mL) and water (5 mL) was added NaOH (1.34 g, 33.6 mmol) and the mixture was heated at 50 °C for 5 h. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was extracted with water. The combined aqueous layers were acidified to pH 2 with 1 M aqueous HCl and extracted with EtOAc. The organic extract was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (986 mg 55%) as a yellow solid. LCMS (ES-API): R_t 1.83 min; *m/z* 264.1 $[M-H]^-$.

d) *tert*-Butyl (2-(hydrazinecarbonyl) phenethyl)carbamate I140

To a solution of 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)benzoic acid I139 (980 mg, 3.70 mmol) in THF (15 mL) was added CDI (719 mg, 4.44 mmol) and the mixture was stirred at RT for 2 h. Hydrazine monohydrate (555 mg, 11.1 mmol) was then added and the mixture was stirred at RT for a further 5 h. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.00 g, 99%) as a colorless oil. LCMS-D: R_t 0.48 min; *m/z* 180.1 $[M-Boc+2H]^+$.

e) *tert*-Butyl (2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethyl)carbamate I129

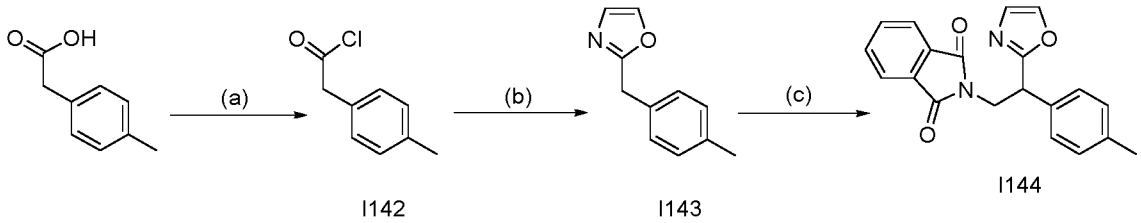
To a solution of *tert*-butyl (2-(hydrazinecarbonyl) phenethyl)carbamate I140 (1.00 g, 3.69 mmol) in THF (20 mL) was added CDI (1.79 g, 11.1 mmol) and the mixture was heated at reflux for 6 h. The solvent was removed under reduced pressure and the residue was diluted with water. The resulting precipitate was collected by filtration, washed with water

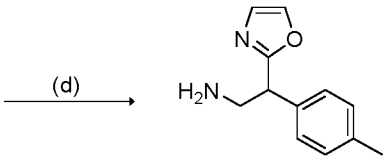
and dried under vacuum to give the title compound (900 mg, 80%) as a yellow oil. LCMS-D: R_t 1.91 min; *m/z* 206.0 $[M\text{-}Boc+2H]^+$.

f) 5-(2-(2-Aminoethyl)phenyl)-1,3,4-oxadiazol-2(3*H*)-one I141

A mixture of *tert*-butyl (2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethyl)carbamate I129 (850 mg, 2.79 mmol) and TFA (8 mL) in DCM (2 mL) was stirred at RT for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (DCM/MeOH = 50/1 to 30/1) to give the title compound (380 mg, 66%) as a white solid. LCMS-D: R_t 0.31 min; *m/z* 206.1 $[M+H]^+$.

l) 2-(Oxazol-2-yl)-2-(p-tolyl)ethan-1-amine (I145)





I145

a) 2-(*p*-Tolyl)acetyl chloride I142

To a solution of 2-(*p*-tolyl) acetic acid (12.7 g, 84.6 mmol) and DMF (0.2 mL) in DCM (100 mL) was added oxalyl chloride (32.2 g, 254 mmol) dropwise and the mixture was stirred at RT for 1 h. The mixture was then concentrated under reduced pressure to give the title compound (10.1 g, 71%), which was used directly in the next step. LCMS-C: R_t 2.00 min; *m/z* 165.0 $[M\text{-}Cl+MeO+H]^+$.

b) 2-(4-Methylbenzyl)oxazole I143

To a solution of 1,2,3-1*H*-triazole (4.9 g, 71.2 mmol) and K_2CO_3 (12.3 g, 88.9 mmol) in sulfolane (150 mL) at RT was added 2-(*p*-tolyl)acetyl chloride I142 (10.0 g, 59.3 mmol) dropwise and the mixture was heated at 165 °C under N_2 for 1 h. After cooling to RT, the mixture was diluted with water (200 mL) and extracted with diethyl ether (200 mL × 3). The combined organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel

chromatography (Pet. ether/EtOAc = 20/1 to 15/1) to give the title compound (7.2 g, 70%) as a burgundy colored oil. LCMS-C: R_t 1.77 min; *m/z* 174.0 $[M+H]^+$.

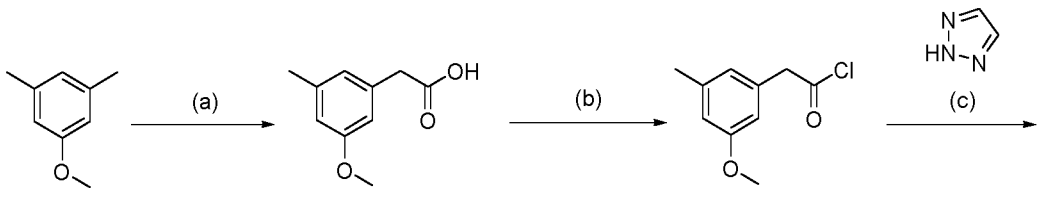
c) 2-(2-(Oxazol-2-yl)-2-(*p*-tolyl)ethyl)isoindoline-1,3-dione I144

To a solution of 2-(4-methylbenzyl)oxazole I143 (7.0 g, 40.5 mmol) in anhydrous THF (200 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 49.0 mL, 49.0 mmol) dropwise. The mixture was stirred at -78 °C for 1 h then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (11.7 g, 48.6 mmol) in anhydrous THF (100 mL) dropwise. The mixture was then allowed to warm to RT and stirred overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL) and the mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 5/1) to give the title compound (3.5 g, 26%) as a yellow oil. LCMS-C: R_t 2.22 min; *m/z* 333.0 $[M+H]^+$.

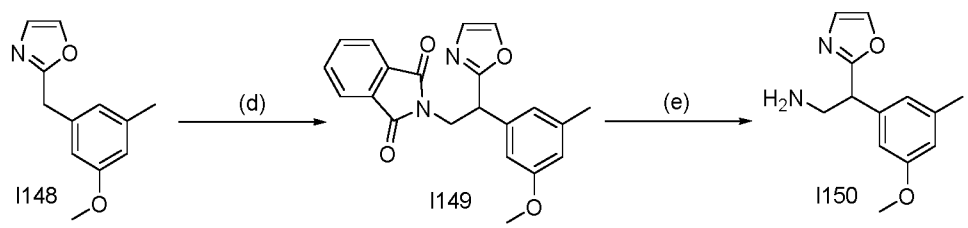
d) 2-(Oxazol-2-yl)-2-(*p*-tolyl)ethan-1-amine I145

A mixture of 2-(2-(oxazol-2-yl)-2-(*p*-tolyl)ethyl)isoindoline-1,3-dione I144 (3.5 g, 10.5 mmol) and hydrazine monohydrate (1.58 g, 31.6 mmol) in EtOH (120 mL) was heated at 80 °C for 3 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give the title compound (1.5 g, 70%) as a yellow oil. LCMS-C: R_t 0.38 min; *m/z* 203.0 $[M+H]^{+\cdot}$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, *J* = 0.8 Hz, 1H), 7.16 (d, *J* = 0.7 Hz, 1H), 7.14 – 7.08 (m, 4H), 4.13 (m, 1H), 3.21 (m, 1H), 2.98 (m, 1H), 2.26 (s, 3H).

li) 2-(3-Methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethan-1-amine (I150)



I146 I147



I148 I149 I150

a) 2-(3-Methoxy-5-methylphenyl)acetic acid I146

To a solution of 1-methoxy-3,5-dimethylbenzene (10.0 g, 73.4 mmol) in THF (400 mL) at -78 °C was added *n*-BuLi (2.5 M solution in hexane, 38.0 mL, 95.5 mmol) dropwise and the mixture was stirred for 15 min. *t*-BuOK (1 M solution in THF, 88.0 mL, 88.0 mmol) was then added dropwise followed by 2,2,6,6-tetramethylpiperidine (10.4 g, 73.4 mmol) and the mixture was stirred at -78 °C for 30 min. The reaction was quenched with excess dry ice and the mixture was allowed to RT. The solvent was removed under reduced pressure and the residue was diluted with Et_2O (500 mL × 4) and extracted with 2 M aqueous NaOH (3 × 50 mL). The combined aqueous layers were acidified to pH 1 with 2 M aqueous HCl, extracted with DCM and the organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (10.0 g, 75%) as a brown oil. LCMS-C: R_t 0.79 min; *m/z* 181.0 $[M+H]^+$.

b) 2-(3-Methoxy-5-methylphenyl)acetyl chloride I147

To a solution of 2-(3-methoxy-5-methylphenyl)acetic acid I146 (1.7 g, 9.5 mmol) in DCM (100 mL) was added oxalyl chloride (3.62 g, 28.5 mmol) dropwise and DMF (1 mL) and the mixture was stirred at RT for 3 h. The mixture was then concentrated under reduced pressure to give the title compound (1.63 g, 86%) as a red solid, which was used directly in the next step.

c) 2-(3-Methoxy-5-methylbenzyl)oxazole I148

To a solution of 1,2,3-1*H*-triazole (679 mg, 9.84 mmol) and K_2CO_3 (1.70 g, 12.3 mmol) in sulfolane (300 mL) at RT was added 2-(3-methoxy-5-methylphenyl)acetyl chloride I147 (1.63 g, 8.2 mmol) dropwise and the mixture was then heated at 165 °C for 1 h. The mixture was allowed to cool to RT, diluted with water and extracted with diethyl ether. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 15/1) to give the title compound (2.31 g, 54%) as a brown oil. LCMS-C: R_t 1.77 min; *m/z* 204.0 $[M+H]^+$.

d) 2-(2-(3-Methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I149

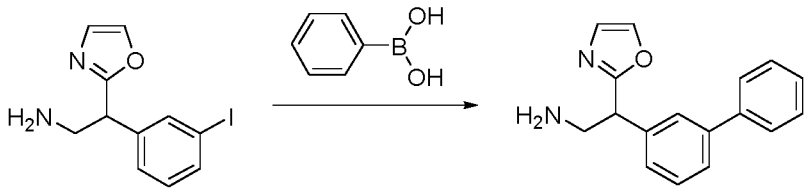
To a solution of 2-(3-methoxy-5-methylbenzyl)oxazole I148 (2.31 g, 11.4 mmol) in anhydrous THF (100 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 13.7 mL, 13.7 mmol) dropwise. The mixture was stirred at -78 °C for 1 h, then added to a solution of 2-(bromomethyl)isoindoline-1,3-dione (3.29 g, 13.7 mmol) in anhydrous THF

(100 mL) dropwise. The mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution and the mixture was diluted with water and extracted with DCM (500 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 20/1 to 5/1) to give the title compound (960 mg, 23%) as a yellow oil. LCMS-C: R_t 2.28 min; *m/z* 363.0 $[M+H]^{+.}$

e) 2-(3-Methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethan-1-amine I150

A mixture of 2-(2-(3-methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione I149 (960 mg, 2.65 mmol) and hydrazine monohydrate (397.5 mg, 7.95 mmol) in EtOH (150 mL) was heated at 80 °C for 3 h. The mixture was then concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc /Pet. ether = 50/1 to 2/1) to give the title compound (300 mg, 48%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.17 (s, 1H), 6.72 – 6.42 (m, 3H), 4.18 – 3.95 (m, 1H), 3.70 (s, 3H), 3.24 – 3.17 (m, 1H), 3.08 – 2.86 (m, 1H), 2.23 (s, 3H).

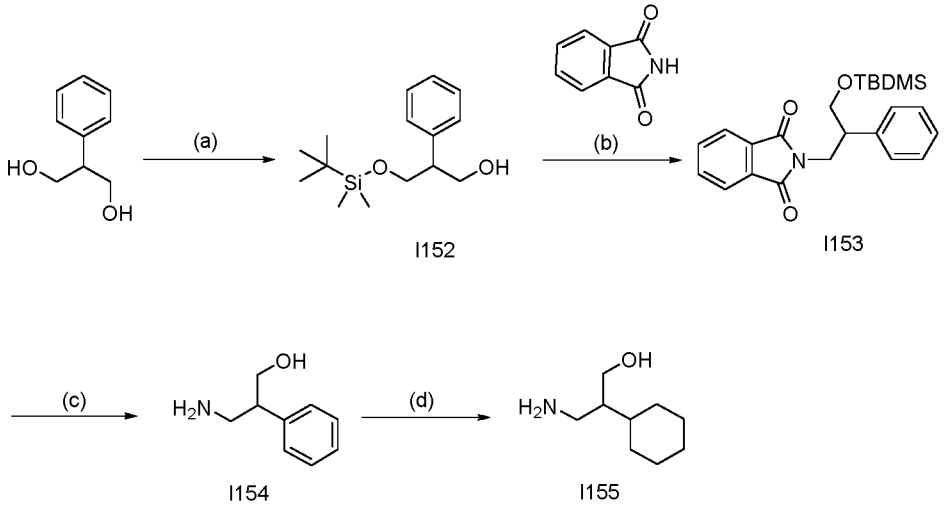
Iii) 2-([1,1'-Biphenyl]-3-yl)-2-(oxazol-2-yl)ethan-1-amine (I151)



I88 I151

To a solution of 2-(3-iodophenyl)-2-(oxazol-2-yl)ethan-1-amine I88 (100 mg, 0.32 mmol) in DMF (10 mL) and water (2 mL) was added phenylboronic acid (78 mg, 0.64 mmol), $Pd(PPh_3)_4$ (74 mg, 0.064 mmol) and Cs_2CO_3 (622 mg, 1.9 mmol) and the mixture was heated at 110 °C under N_2 overnight. The mixture was diluted with water, extracted with EtOAc and the organic extract was concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1, v/v) to give the title compound (30 mg, 35%) as a yellow solid. LCMS-C: R_t 0.55 min, *m/z* 265.1 $[M+H]^+$.

liii) 3-Amino-2-cyclohexylpropan-1-ol (I155)



a) 3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpropan-1-ol I152

To a solution of 2-phenylpropane-1,3-diol (5.0 g, 32.9 mmol), TBDMSCl (4.95 g, 32.9 mmol) and DMAP (40 mg, 0.329 mmol) in DCM (60 mL) at 0 °C under N_2 was added Et_3N (3.66 g, 36.2 mmol) and the mixture was stirred at RT for 12 h. The mixture was partitioned between water and DCM, the layers were separated and the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc = 30/1) to give the title compound (2.75 g, 32%) as a colorless oil. LCMS-C: R_t 2.69 min; *m/z* 267.1 $[M+H]^+$.

b) 2-(3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpropyl)isoindoline-1,3-dione I153

To an ice-cooled solution of 3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropan-1-ol I152 (1.4 g, 5.25 mmol), phthalimide (850 mg, 5.78 mmol) and PPh_3 (1.52 g, 5.78 mmol) in THF (20 mL) was added a solution of DIAD (1.17 g, 5.78 mmol) in THF (10 mL) dropwise and the mixture was stirred at RT overnight. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was concentrated under reduced pressure to give the title compound (1.2 g, 58%) as a yellow oil, which was used directly in the next step.

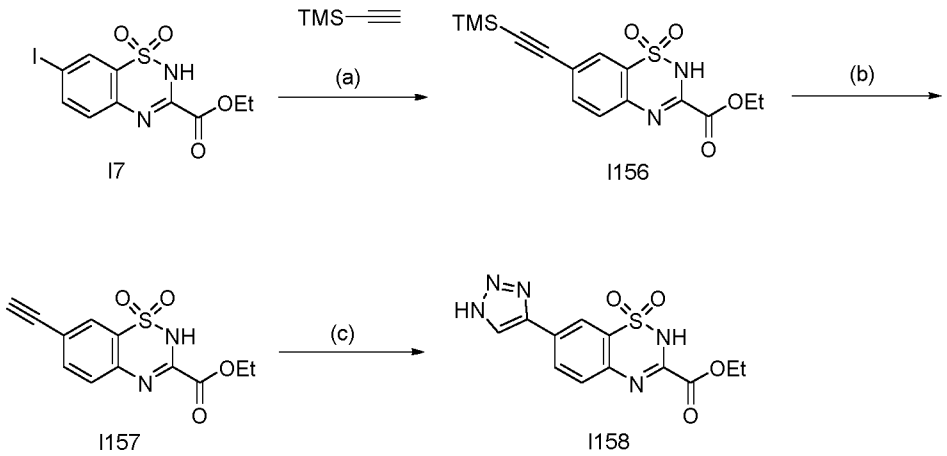
c) 3-Amino-2-phenylpropan-1-ol I154

A mixture of 2-(3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropyl)isoindoline-1,3-dione I153 (1.2 g, 3.03 mmol) and hydrazine monohydrate (445 mg, 9.09 mmol) in EtOH (50 mL) was heated at 80 °C for 3.5 h under N_2. The mixture was allowed to cool to RT, partitioned between water and EtOAc, the layers were separated and the organic layer was concentrated under reduced pressure to give the title compound (660 mg, 83%) as a colorless oil. LCMS-C: R_t 0.29 min; *m/z* 152.0 $[M+H]^+$.

d) 3-Amino-2-cyclohexylpropan-1-ol I155

A mixture of 3-amino-2-phenylpropan-1-ol I154 (100 mg, 0.66 mmol) and Pt_2O (10 mg) in AcOH (5 mL) was stirred at RT under a H_2 atmosphere for 72 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give the title compound (87 mg, 84%) as a colorless oil. LCMS (ES-API): R_t 0.27 min; *m/z* 158.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) 3.55 – 3.49 (m, 1H), 3.46 – 3.39 (m, 1H), 2.78 – 2.71 (m, 1H), 2.70 – 2.61 (m, 1H), 1.40 – 1.28 (m, 2H), 1.20 – 1.08 (m, 2H), 1.04 – 0.93 (m, 3H), 0.89 – 0.83 (m, 5H).

liv) Ethyl 7-(1H-1,2,3-triazol-4-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I158)



a) Ethyl 7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I156

To a mixture of ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (1.0 g, 2.63 mmol), CuI (25 mg, 0.13 mmol) and $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol) in Et_3N (20 mL) and DMF (50 mL) under N_2 was added ethynyltrimethylsilane (1.03 g, 0.1 mmol) and the mixture was stirred at 30 °C overnight. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH=100/1) to give the title compound (350 mg, 38%) as a black solid. LCMS (ES-API): R_t 2.43 min; *m/z* 351.0 $[M+H]^+$.

b) Ethyl 7-ethynyl-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I157

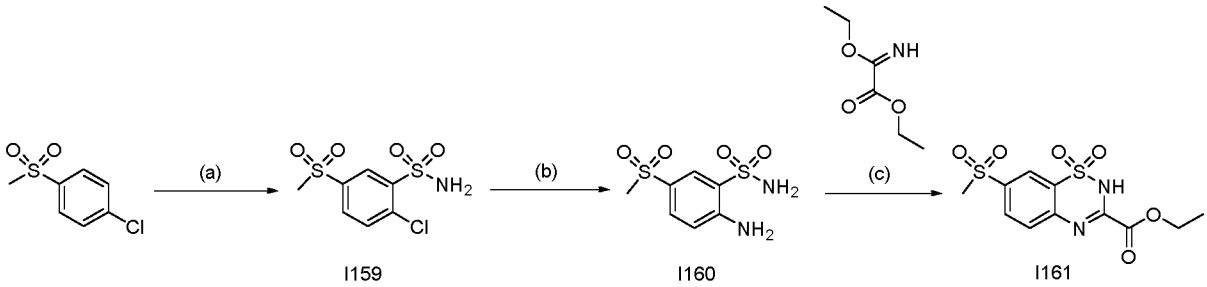
To a solution of ethyl 7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I156 (300 mg, 0.86 mmol) in THF (30 mL) was added TBAF (1 M solution in THF, 4.28 mL, 4.28 mmol) and the mixture was heated at 40 °C overnight. The mixture was

partitioned between water and EtOAc, the layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 100/1) to give the title compound (217 mg, 91%) as an orange solid. LCMS-C: R_t 2.58 min; *m/z* 279.0 $[M+H]^+$.

c) Ethyl 7-(1*H*-1,2,3-triazol-4-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I158

A mixture of ethyl 7-ethynyl-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I157 (180 mg, 0.65 mmol), azidotrimethylsilane (111.6 mg, 0.97 mmol) and CuI (37 mg, 0.19 mmol) in DMF (7 mL) and EtOH (1 mL) was heated at 120 °C overnight. The mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound (17 mg, 7%) as an orange oil. LCMS-C: R_t 0.45 min; *m/z* 321.9 $[M+H]^+$.

Iv) Ethyl 7-(methylsulfonyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I161)



I159 I160 I161

a) 2-Chloro-5-(methylsulfonyl)benzenesulfonamide I159

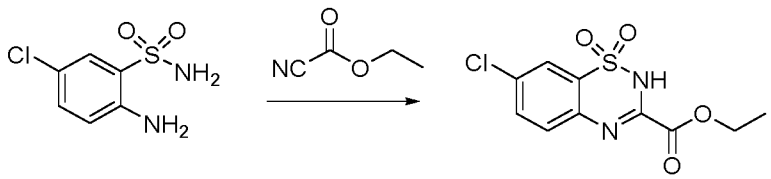
1-Chloro-4-(methylsulfonyl)benzene (10.0 g, 5.3 mmol) was slowly added to $ClSO_3H$ (63 mL) and the mixture was heated at 100 °C for 1 h. SO_2Cl_2 (3.8 mL) was then added and the mixture was heated at reflux for 2 h, then allowed to cooled to RT and poured into ice-water. The resulting precipitate was collected by filtration and washed with cold water. The solid was dissolved in aqueous NH_4OH solution (10% w/v, 375 mL) and the mixture was stirred at RT for 30 min. The mixture was concentrated under reduced pressure until precipitation occurred and the precipitate was collected by filtration and washed with water. The filter cake was dissolved in an aqueous NaOH solution (10% w/v, 50 mL) and the mixture was adjusted to pH 5 with 6 M aqueous HCl solution. The resulting precipitate was collected by filtration, washed with water and dried to give the title compound (2.0 g, 14%) as a white solid. LCMS-D: R_t 1.5 min, *m/z* 270.0 $[M+H]^+$.

b) 2-Amino-5-(methylsulfonyl)benzenesulfonamide I160

A solution of 2-chloro-5-(methylsulfonyl)benzenesulfonamide I159 (1.0 g, 3.7 mmol) in conc. aqueous NH_4OH (200 mL) was stirred at RT for 4 h. The mixture was concentrated under reduced pressure and the residue was adjusted to pH 5 with 6 M aqueous HCl. The resulting precipitate was collected by filtration, washed with water and dried to give the title compound (500 mg, 54%) as a white solid. LCMS-D: R_t 1.70 min, *m/z* 249.0 $[M-H]^-$.

c) Ethyl 7-(methylsulfonyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I161
To a solution of 2-amino-5-(methylsulfonyl)benzenesulfonamide I160 (240 mg, 0.96 mmol) and ethyl 2-ethoxy-2-iminoacetate (278 mg, 1.92 mmol) in EtOH (2 mL) was added Et_3N (291 mg, 2.88 mmol) and the mixture was heated at 120 °C under microwave irradiation for 2 h. The solvent was removed under reduced pressure and the residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (50 mg, 16%) as a white solid. LCMS-D: R_t 1.70 min, *m/z* 333.0 $[M+H]^+$.

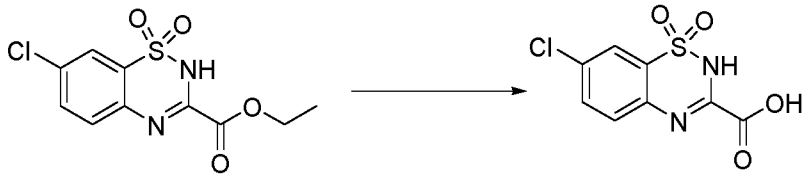
lvi) Ethyl 7-chloro-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I162)



I162

To a solution of 2-amino-5-chlorobenzenesulfonamide (1.0 g, 4.8 mmol) in AcOH (40 mL) was added ethyl carbonocyanidate (4.8 g, 48.0 mmol) and the mixture was stirred at RT under N_2 for 5 min. Concentrated aqueous HCl (1 mL) was then added and the mixture was heated at 85 °C for 4 h. The mixture was concentrated under reduced pressure to remove ~2/3 of the solvent and then diluted with water (20 mL). The resulting precipitate was collected by filtration and washed with water. The solid was diluted with DCM (60 mL), stirred for 1 h then filtered and the filter cake was rinsed with DCM. The combined filtrates were concentrated under reduced pressure to give the title compound (950 mg, 68%) as a grey solid. LCMS-D: R_t 1.05 min; *m/z* 288.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.9 (br s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.84 – 7.77 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

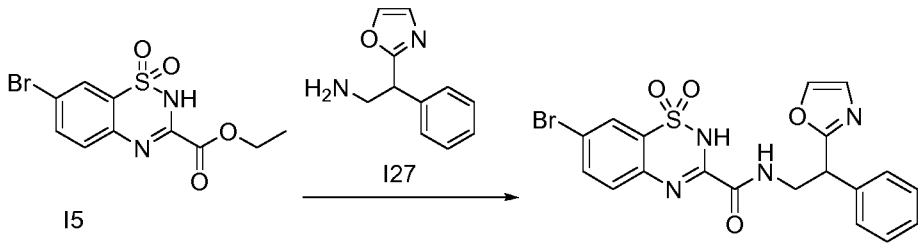
lviii) 7-Chloro-2H-benzo[e][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I163)



I162 I163

To a solution of ethyl 7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I162 (560 mg, 1.94 mmol) in MeOH (75 mL) and water (25 mL) at RT was added NaOH (388 mg, 9.7 mmol) and the mixture was stirred at RT for 4 h. Most of the MeOH was removed under reduced pressure and the aqueous residue was diluted with Et_2O (20 mL). The layers were separated and the organic phase was extracted with water (10 mL). The combined aqueous layers were adjusted to pH 2 with 1 M aqueous HCl and the resulting precipitate was collected by filtration and dried to give the title compound (300 mg, 59%) as a white solid. LCMS-C: R_t 0.39 min; *m/z* 258.9 $[M-H]^-$.

*Example 1: 7-Bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1)*



I5 I27 1

Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5) (1.06 g, 3.19 mmol) and 2-(oxazol-2-yl)-2-phenylethanamine (I27) (500 mg, 2.66 mmol) were dissolved in methanol (8 mL) and the mixture was heated in a sealed tube at 130 °C for 3h then cooled to r.t.. The mixture was filtered and the filter cake was washed with methanol (5 mL). The combined filtrates were concentrated to give the product (1.00 g, 39 % yield) as a white solid. LCMS (ES-API): R_t 2.62 min; *m/z* 475/477 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.8 (s, 1H), 9.30 (t, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.93 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.36-7.27 (m, 5H), 7.21 (s, 1H), 4.68 (t, *J* = 7.6 Hz, 1H), 4.05-3.85 (m, 2H).

Example 2: N-*(3-Hydroxy-2-phenylpropyl)*-2H-*benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (2)*

I36 2

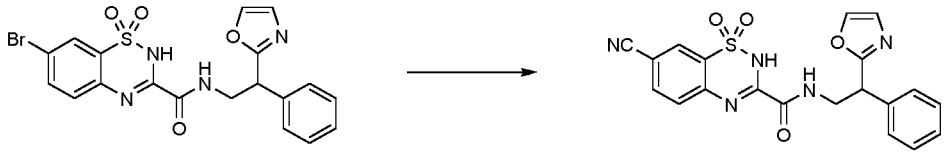
3-(1,1-Dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoic acid (I36) (50 mg, 0.129 mmol) was added into BH_3·THF (2 M in THF, 10 mL) at r.t. under nitrogen and the mixture was stirred at r.t. for 30 min. The solvent was removed under vacuum to give a residue which was purified by preparative TLC (DCM/MeOH = 20:1) to give the desired product (25 mg, 54% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.13 (t, *J* = 6.0 Hz, 1H), 7.85-7.79 (m, 2H), 7.74 – 7.72 (m, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.21 (m, 5H), 4.84 (t, *J* = 4.8 Hz, 1H), 3.60-3.58 (m, 4H), 3.17 – 3.10 (m, 1H); LCMS (ES-API): R_t 2.10 min, *m/z* 360.1 $[M+H]^+$

Example 3: N-*(4-Hydroxy-2-phenylbutyl)*-2H-*benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (3)*

I51 3

4-(1,1-Dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-3-phenylbutanoic acid (I51) (80 mg, 0.206 mmol) was added into BH_3·THF (2 M in THF, 40 mL) at r.t. under nitrogen and the mixture was stirred at r.t. for 3 h. The solvent was removed under vacuum to give a residue which was purified by preparative TLC (DCM/MeOH = 20:1) to give the desired product (40 mg, 52% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.17 (t, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.28 (m, 2H) , 7.23 – 7.18 (m, 3H), 4.49 (t, *J* = 4.8 Hz, 1H), 3.03-3.05 (m, 5H), 1.93-1.86 (m, 1H) , 1.73-1.62 (m, 1H); LCMS (ES-API): R_t 2.18 min, *m/z* 374.1 $[M+H]^+$

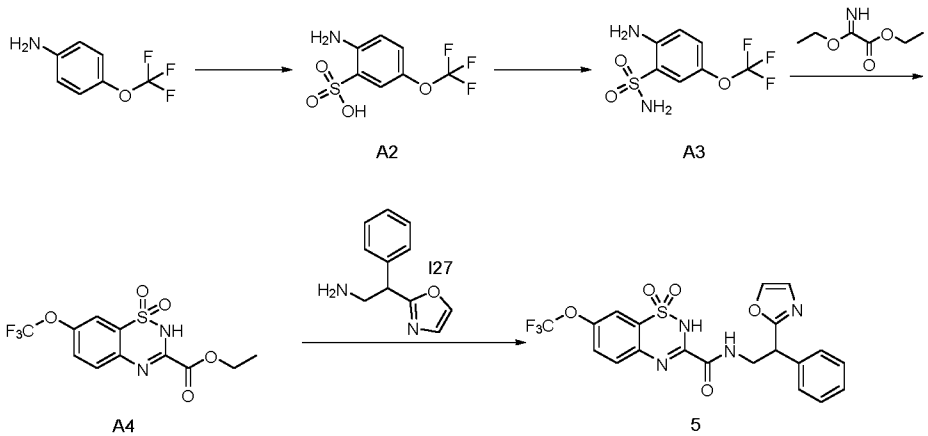
Example 4: 7-Isocyano-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (4)



1 4

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (50 mg, 0.105 mmol), $Zn(CN)_2$ (62 mg, 0.525 mmol), $Pd_2(dba)_3$ (19 mg, 0.021 mmol), Xantphos (18 mg, 0.0315 mmol) and Cs_2CO_3 (171 mg, 0.525 mmol) in DMF (3 mL) was heated at 160˚C in a microwave reactor for 30 min. The mixture was partitioned between dichloromethane and water and the aqueous layer was adjusted to pH 2-3 with aqueous HCl. The layers were separated and the aqueous phase was washed with water, brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by preparative TLC (DCM/MeOH = 50:1) to give the desired product (25 mg, 57% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.9 (s, 1H), 9.35 (t, *J* = 6.4 Hz, 1H), 8.48 (d, *J* = 1.6 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.05 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.36-7.27 (m, 5H) , 7.21 (s, 1H), 4.69 (t, *J* = 7.6 Hz, 1H), 4.05-3.98 (m, 1H), 3.91-3.85 (m, 1H); LCMS (ES-API): R_t 2.10 min, *m/z* 422.1 $[M+H]^+$

Example 5: N-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(trifluoromethoxy)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (5)



A2 A3 A4 5

a) 2-Amino-5-(trifluoromethoxy)benzenesulfonic acid (A2)

To a solution of 4-(trifluoromethoxy)aniline (20 g, 0.113 mol) in 1, 2, 4-trichlorobenzene (100 mL) at 100 °C was added H_2SO_4 dropwise (95%, 15.2 g). After addition, the mixture was heated at 210 °C for 3 h, cooled to r.t. and then basified with Na_2CO_3 (sat. aq.). The mixture was then washed with DCM and the aqueous layer was acidified to pH 2 with 1 M

HCl. The resulting precipitate was collected by filtration and dried to give the product (10 g, 34% yield) as an off-white solid. LCMS (ES-API): R_t 1.25 min; *m/z* 256.0 $[M-H]^-$.

b) 2-Amino-5-(trifluoromethoxy)benzenesulfonamide (A3)

To a solution of 2-amino-5-(trifluoromethoxy)benzenesulfonic acid (A2) (3.5 g, 13.61 mmol) in tetrahydrothiophene 1,1-dioxide (15 mL) at r.t. was added $POCl_3$ (6.26 g, 40.82 mmol) and the mixture was heated at 120 °C for 3 h. After cooling, the mixture was added dropwise to a solution of conc. NH_4OH (100 mL) at 0 °C and stirred for 30 min. The mixture was extracted with EtOAc, the organic layer was dried (Na_2SO_4), filtered, concentrated and purified by column chromatography (EtOAc/Pet. Ether = 1:1) to give the product (1.4 g, crude) which was used directly in the next step. LCMS (ES-API): R_t 2.06 min; *m/z* 257.0 $[M+H]^+$.

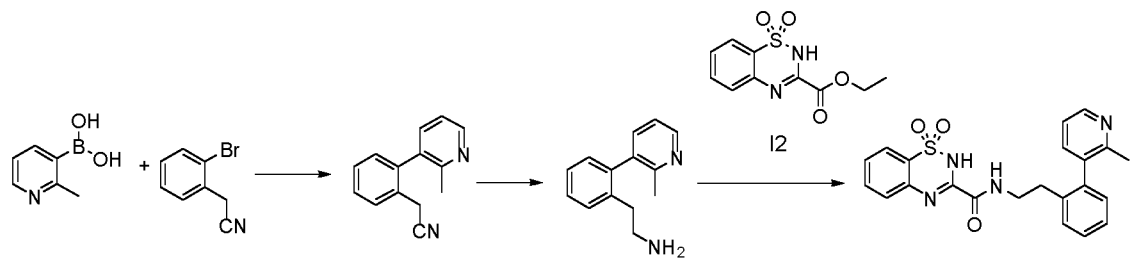
c) Ethyl 7-(trifluoromethoxy)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A4)

A mixture of 2-amino-5-(trifluoromethoxy)benzenesulfonamide (A3) (800 mg, 3.12 mmol), ethyl 2-ethoxy-2-iminoacetate (680 mg, 4.68 mmol) and TEA (631 mg, 6.24 mmol) in EtOH (20 mL) was heated at 85 °C for 8 h. The mixture was then poured into water and extracted with EtOAc. The organic layer was washed with 1 M HCl, dried (Na_2SO_4), filtered, concentrated and purified by column chromatography (EtOAc/Pet. Ether = 1:1) to give the product (200 mg, 19% yield) as a yellow solid. LCMS (ES-API): R_t 2.41 min; *m/z* 339.0 $[M+H]^+$.

d) *N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(trifluoromethoxy)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (5)

A mixture of ethyl 7-(trifluoromethoxy)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A4) (80 mg, 0.24 mmol) and 2-(oxazol-2-yl)-2-phenylethanamine (I27) (45 mg, 0.24 mmol) in EtOH (2 mL) was heated at 130 °C for 2 h. After cooling, the mixture was purified directly by preparative TLC (DCM/MeOH = 20:1) to give the product (75 mg, 66% yield) as a white solid. LCMS (ES-API): R_t 2.71 min; *m/z* 481.0 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.9 (s, 1H), 9.32 (t, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.86 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.36-7.26 (m, 5H), 7.21 (s, 1H), 4.68 (t, *J* = 7.6 Hz, 1H), 4.05-3.99 (m, 1H), 3.92-3.86 (m, 1H).

Example 6: N-(2-(2-Methylpyridin-3-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (6)



a) 2-(2-(2-Methylpyridin-3-yl)phenyl)acetonitrile (A5)

(2-Methylpyridin-3-yl)boronic acid (550 mg, 3.2 mmol), 2-(2-bromophenyl)acetonitrile (597 mg, 3.05 mmol), $Pd(PPh_3)_4$ (176 mg, 0.15 mmol) and K_2CO_3 (176 mg, 0.15 mmol) were dissolved in *i*PrOH (5 mL) and water (2 mL) and the mixture was heated at 80 °C under N_2 for 5h. The mixture was filtered and the solid was washed with DCM (20 mL). The filtrate was washed with brine, dried over sodium sulfate and concentrated. Column chromatography (DCM/MeOH = 100:0 – 20:1) gave the product (300 mg, 45% yield) as a yellow solid. LCMS (ES-API): R_t 0.44 min; *m/z* 209.1 $[M+H]^+$.

b) 2-(2-(2-Methylpyridin-3-yl)phenyl)ethanamine (A6)

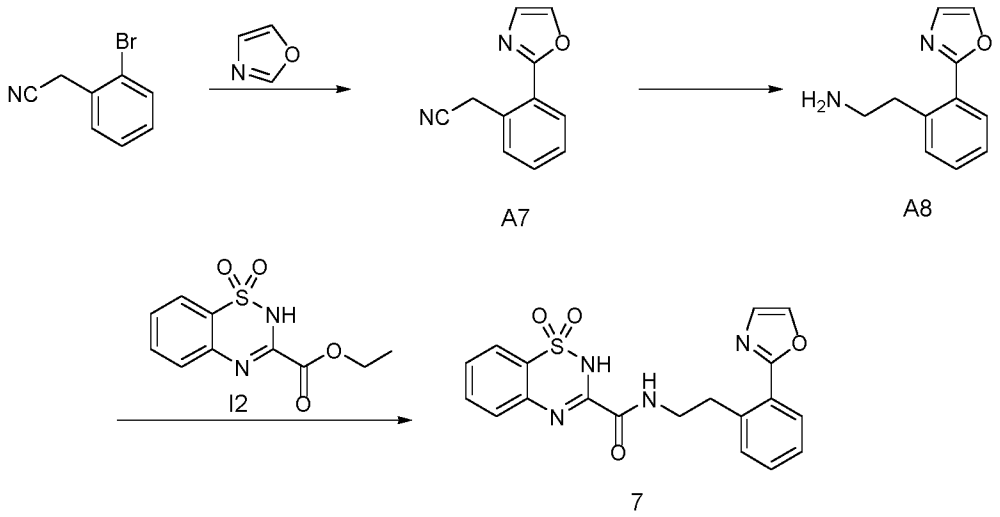
A mixture of 2-(2-(2-methylpyridin-3-yl)phenyl)acetonitrile (A5) (300 mg, 1.4 mmol), NaOH (173 mg, 4.3mmol) and Raney-Ni (100 mg) in THF (5 mL) and water (2 mL) was heated at 60 °C under H_2 for 5 h. The mixture was filtered and the solid was washed with DCM (20 mL). The filtrate was washed with brine, dried over sodium sulfate and concentrated to give the product (200 mg, 65% yield) as a white solid. LCMS (ES-API): R_t 0.29 min; *m/z* 213.1 $[M+H]^+$.

c) *N*-(2-(2-Methylpyridin-3-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (6)

A mixture of 2-(2-(2-Methylpyridin-3-yl)phenyl)ethanamine (A6) (35 mg, 0.17 mmol), ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (50 mg, 0.20 mmol) and triethylamine (0.2 mL) in methanol (3 mL) was heated in a sealed tube at 130 °C for 3h. The mixture was allowed to cool to r.t., adjusted to pH 5 with 1 M HCl and extracted with DCM (10 mL x 3). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give a residue which was purified by preparative TLC (MeOH/DCM = 1:20) to give the product (5 mg, 10% yield) as an off-white solid. LCMS (ES-API): R_t 1.63 min; *m/z* 421.1 $[M+H]^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.5 (s, 1H), 9.20 (t, *J* = 5.6 Hz, 1H), 8.46 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.85-7.79 (m, 2H), 7.74-7.70 (m,

1H), 7.54-7.50 (m, 2H), 7.41-7.29 (m, 3H), 7.24-7.21 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 3.32-3.27 (m, 2H), 2.27-2.65 (m, 1H), 2.58-2.52 (m, 1H), 2.20 (s, 3H).

Example 7: N-(2-(Oxazol-2-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide1,1-dioxide (7)



a) 2-(2-(Oxazol-2-yl)phenyl)acetonitrile (A7)

To a solution of oxazole (1.0 g, 10.2 mmol) in THF (30 mL) at -78°C was added n-BuLi (2.5 M in hexanes, 6.8 mL, 17.0 mmol) dropwise and the mixture was stirred at -78°C for 10 min. $ZnCl_2$ (4.17g, 30.6 mmol) was added and the mixture was allowed to warm to r.t.. $Pd(PPh_3)_4$ (577 mg, 0.5 mmol) and 2-(2-bromophenyl)acetonitrile (2.0 g, 14.3 mmol) were added and the mixture was heated at 60 °C overnight. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (40 mL) and then most of the THF was removed under reduced pressure. The aqueous mixture was extracted with EtOAc (50 mL × 3) and the combined extracts were dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc/Pet. ether = 1:10) to afford the desired product (120 mg, 7% yield) as yellow oil. LCMS (ES-API): R_t 2.20 min; *m/z* 185.1 $[M+H]^+$.

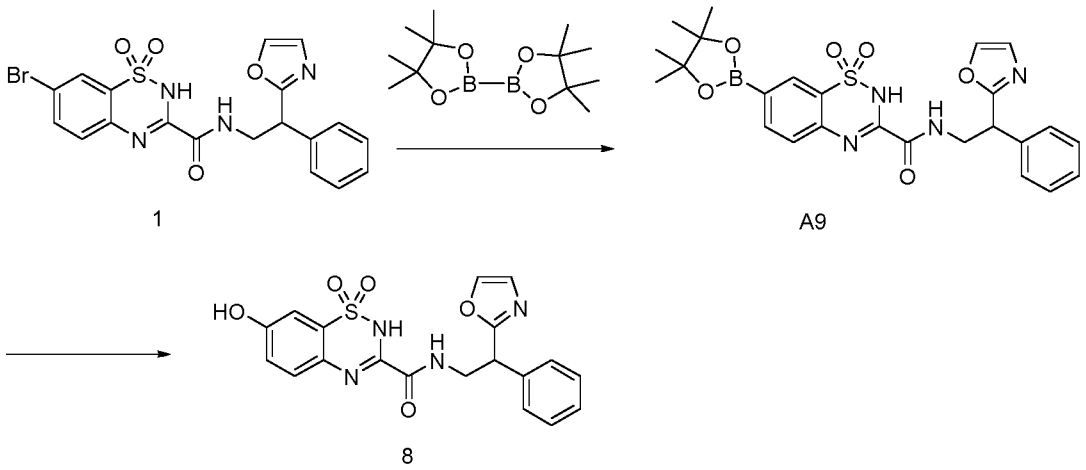
b) 2-(2-(Oxazol-2-yl)phenyl)ethanamine (A8)

To a solution of 2-(2-(oxazol-2-yl)phenyl)acetonitrile (A7) (120 mg, 0.65 mmol) in ethanol (3 mL) was added conc. NH_4OH (1 mL) and Raney Nickel (40 mg, 0.68 mmol) and the mixture was heated at 60 °C under a hydrogen (1 atm) overnight. More ethanol (5 mL) was added and the mixture was filtered. The filtrate was concentrated to afford the desired product (110 mg, 80% yield) as a white solid. LCMS (ES-API): R_t 2.25 min; *m/z* 189.1 $[M+H]^+$.

c) *N*-(2-(Oxazol-2-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide1,1-dioxide (7)

To a solution of 2-(2-(oxazol-2-yl)phenyl)ethanamine (A8) (110 mg, 0.58 mmol) in ethanol (3 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (150 mg, 0.58 mmol) and the mixture was heated at 120 °C for 2 h. The mixture was adjusted to ~pH 3 with 1 M HCl, diluted with water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, concentrated and the residue was purified by preparative TLC (DCM/EtOAc = 15:1) to give the desired product (40 mg, 18% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.38 (t, *J* = 5.8 Hz, 1H), 8.22 (s, 1H), 7.91-7.89 (m, 1H), 7.86-7.84 (m, 1H), 7.81-7.79 (m, 1H), 7.75-7.70 (m, 1H), 7.55-7.50 (m, 1H), 7.46-7.37 (m, 4H), 3.61-3.56 (m, 2H), 3.38-3.37 (m, 2H). LCMS (ES-API): R_t 2.49 min; *m/z* 397.0 $[M+H]^+$

Example 8: 7-Hydroxy-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (8)



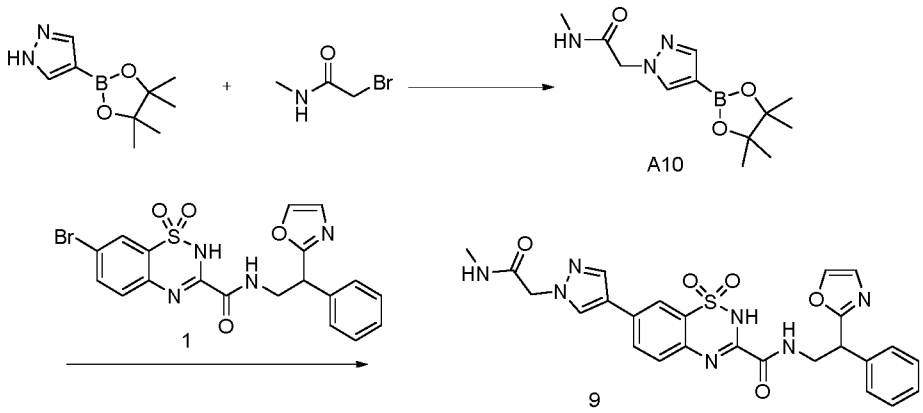
a) (*N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A9)

To a solution of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (400 mg, 0.84 mmol) and bis(pinacolato)diboron (427 mg, 1.68 mmol) in dioxane (20 mL) was added $Pd(dppf)_2Cl_2$ (69 mg, 0.084 mmol) and KOAc (248 mg, 2.52 mmol) and the mixture was heated at 90 °C under N_2 for 3 h. After cooling to r.t., the mixture was adjusted to pH 5 with 1 M HCl and filtered. The filter cake was washed with dioxane (5 mL) and the filtrate was washed with brine, dried over sodium sulfate and concentrated. The residue which was purified by preparative TLC (MeOH/DCM = 1:20) to give the product (80 mg, 18% yield) as a white solid. LCMS (ES-API): R_t 2.36 min; *m/z* 441 $[M+H]^+$ (boronic acid).

b) 7-Hydroxy-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (8)

To a solution of *N*-(2-(oxazol-2-yl)-2-phenylethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A9) (82 mg, 0.16 mmol) in THF (3 mL) and water (0.5 mL) was added NaOH (19 mg, 0.48 mmol) and H_2O_2 (27 mg, 0.79 mmol) and the mixture was stirred at r.t. for 3 h. The mixture was extracted with DCM (3 × 10 mL) and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give a residue which was purified by prep. TLC (MeOH/DCM = 1:20) to give the product (20 mg, 30% yield) as an off-white solid. LCMS (ES-API): R_t 2.28 min; *m/z* 413.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.34-7.24 (m, 5H), 7.18-7.11 (m, 3H), 4.61 (t, *J* = 8.0 Hz, 1H), 4.09-3.93 (m, 2H).

Example 9: 7-(1-(2-(Methylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (9)



a) *N*-Methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetamide (A10)

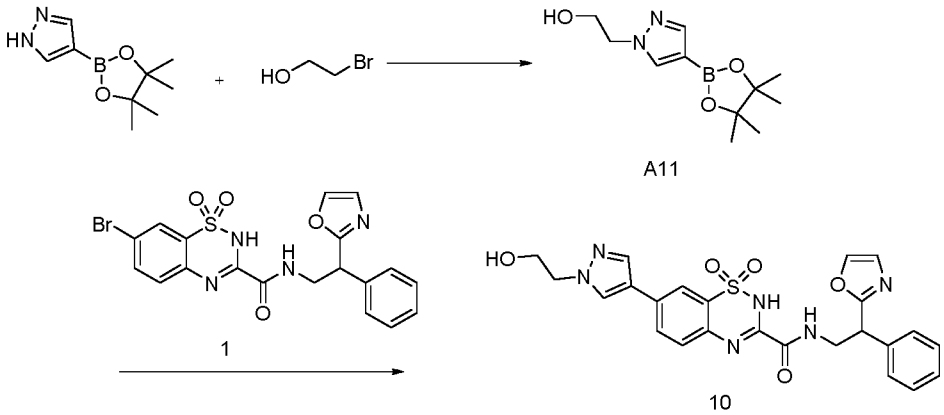
To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (200 mg, 1.03 mmol) in DMF (10 mL) was added 2-bromo-N-methylacetamide (172 mg, 1.13 mmol) and cesium carbonate (670 mg, 2.06 mmol) and the mixture was heated at 60 °C overnight. The mixture was filtered and the solid was washed with EtOAc. The filtrates were combined and the solvent was removed to give the desired product (160 mg, 59% yield) as a white solid. LCMS (ES-API): R_t 1.89min; *m/z* 266.1 $[M+H]^+$.

b) 7-(1-(2-(Methylamino)-2-oxoethyl)-1*H*-pyrazol-4-yl)-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (9)

To a solution of *N*-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetamide (A10) (70 mg, 0.25 mmol) and 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (100 mg, 0.21 mmol) in *i*-PrOH (3

mL) and toluene (1 mL) was added sodium carbonate (2 M in water, 0.32 mL, 0.63 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and the mixture was heated at 90 °C under a nitrogen atmosphere overnight. The solvent was removed and the residue was diluted with water and extracted with EtOAc. The organic extract was dried over sodium sulfate, concentrated and the residue was purified by preparative TLC (DCM/MeOH = 15:1) to give the desired product (100 mg, 89% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.22-9.19 (m,1H), 8.33 (s, 1H), 8.06-7.93 (m, 5H), 7.78-7.76 (m, 1H), 7.35-7.25 (m, 5H), 7.20 (s, 1H), 4.79 (s, 2H), 4.67 (m, 1H), 4.05-3.97 (m, 1H), 3.92-3.85 (m, 1H), 2.63 (d, J = 4.5 Hz, 3H). LCMS (ES-API): R_t 2.37 min, m/z 534.2 $[M+H]^+$

Example 10: 7-(1-(2-Hydroxyethyl)-1H-pyrazol-4-yl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (10)



a) 2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanol (A11)

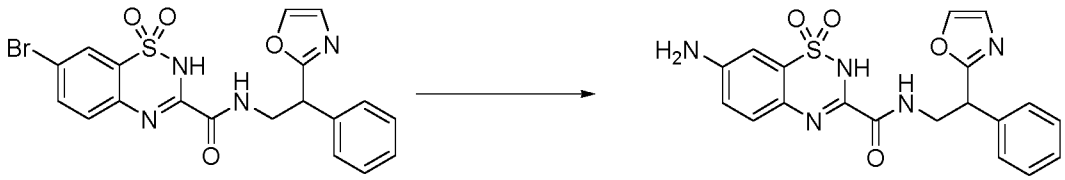
To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.58 mmol) in DMF (7 mL) was added 2-bromoethanol (645 mg, 5.16 mmol) and cesium carbonate (2.52 g, 7.74 mmol) and the mixture was heated at 85°C for 3 h. More cesium carbonate (2.52 g, 7.74 mmol) and 2-bromoethanol (645 mg, 5.16 mmol) were added and the mixture was again heated at 85°C overnight. The solvent was removed and the residue was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated to give the desired product (150 mg, 24% yield) as a yellow oil. LCMS (ES-API): R_t 2.0 min; m/z 239.1 $[M+H]^+$.

b) 7-(1-(2-Hydroxyethyl)-1H-pyrazol-4-yl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (10)

To a solution of 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanol (A11) (70 mg, 0.29 mmol) and 7-bromo-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (93 mg, 0.2 mmol) in dioxane (3

mL) was added K_2CO_3 (82 mg, 0.59 mmol) and $Pd(dppf)Cl_2$ (17 mg, 0.02 mmol) and the mixture heated at 130 °C in a sealed tube for 5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (20 mL x2). The combined organic extracts were dried over sodium sulfate, filtered and concentrated and the residue was purified by prep. TLC (DCM/MeOH = 15:1) to give the desired product (10 mg, 10% yield) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.19 (s, 1H), 8.33 (s, 1H), 8.03 (m, 2H), 7.99-7.90 (m, 2H), 7.74-7.72 (m, 1H), 7.36-7.32 (m, 2H), 7.29-7.27 (m, 3H), 7.21 (s, 1H), 4.93 (t, *J* = 5.2 Hz, 1H), 4.67 (m, 1H), 4.15 (t, *J* = 5.4 Hz, 2H), 4.05-3.97 (m, 1H), 3.94-3.86 (m, 1H), 3.79-3.75 (m, 2H).LCMS (ES-API): R_t 2.48 min, *m/z* 507.1 $[M+H]^+$

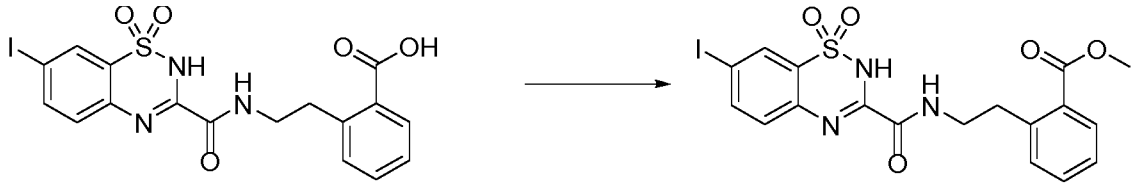
Example 11: 7-Amino-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (11)



1 11

To a solution of 7-bromo-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (80 mg, 0.17 mmol) and diphenylmethanimine (91.5 mg, 0.51 mmol) in dioxane (5 mL) was added $Pd_2(dba)_3$ (15.4 mg, 0.02 mmol), Xantphos (19.5 mg, 0.03 mmol) and Cs_2CO_3 (164.5 mg, 0.5 mmol) and the mixture was heated at 90 °C under N_2 for 3h. The mixture was filtered and the solid was washed with dioxane (5 mL). The filtrate was washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in dioxane (2 mL) and 1 M HCl (2 mL) was added. The mixture was stirred at r.t. for 1 h then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by preparative TLC (MeOH/DCM = 1:20) to give the product (10 mg, 10% yield) as a white solid. LCMS (ES-API): R_t 2.17 min; *m/z* 412.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.26-7.30 (m, 6H), 7.19 (s, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.02-6.99 (m, 1H), 4.63 (t, *J* = 7.2 Hz, 1H), 4.20-3.80 (m, 2H).

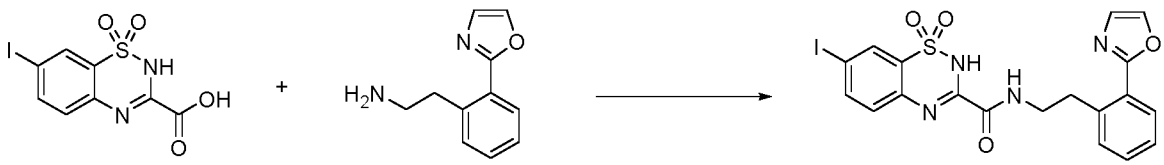
Example 12: Methyl 2-(2-(7-iodo-1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoate (12)



I55 12

To a solution of 2-(2-(7-iodo-1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid (I55) (20 mg, 0.06 mmol) in MeOH (5 mL) was added H_2SO_4 (1 drop) and the mixture was heated at 60 °C for 3 h. After cooling to r.t., the mixture was diluted with water (5 mL) and extracted with EtOAc (8 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the product (20 mg, 40% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.22 (t, *J* = 5.3 Hz, 1H), 8.09 – 8.02 (m, 2H), 7.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.37 – 7.31 (m, 2H), 3.84 (s, 3H), 3.55-3.49 (m, 2H), 3.16 (t, *J* = 7.0 Hz, 2H). LCMS (ES-API): R_t 2.84 min, *m/z* 513.7 $[M+H]^+$

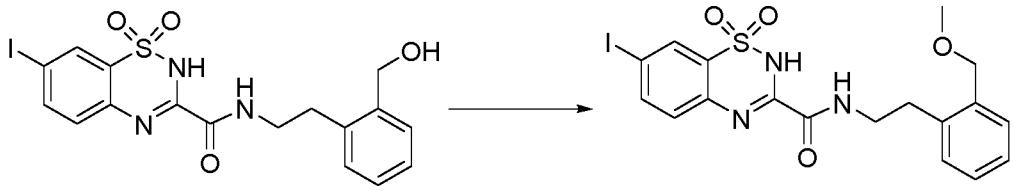
Example 13: 7-Iodo-N-(2-(oxazol-2-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (13)



I53 A8 13

To a solution of 7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylic acid 1,1-dioxide (I53) (26 mg, 0.14 mmol) and 2-amino-5-bromobenzenesulfonamide (A8) (50 mg, 0.14 mmol) in DCM (10 mL) was added EDCI (55 mg. 0.28mmol), HOBt (2 mg, 0.01 mmol) and DIPEA (72 mg, 0.56 mmol) and the mixture was stirred at r.t. overnight. A saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep. TLC (DCM/MeOH = 20:1) to give the product (3 mg, 4% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (s, 1H), 9.36 (brs, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.46-7.38 (m, 4H), 3.60-3.55 (m, 2H), 3.51-3.48 (m, 2H). LCMS (ES-API): R_t 2.8 min *m/z* 523.0 $[M+H]^+$.

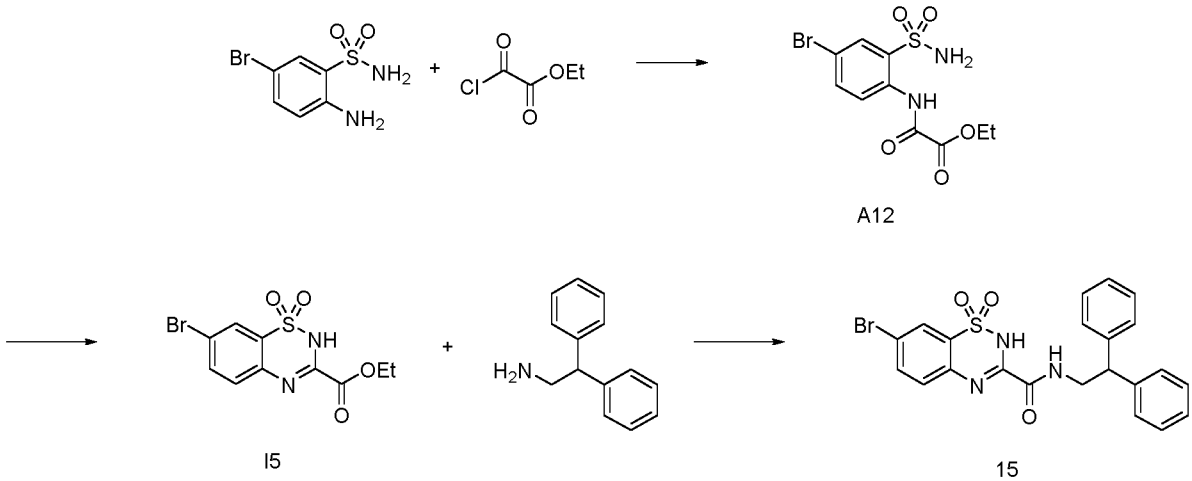
Example 14: 7-Iodo-N-(2-(methoxymethyl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (14)



109 14

To a solution of N-(2-(hydroxymethyl)phenethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (109) (60 mg, 0.12 mmol) in ACN (5 mL) was added Ag_2O (150 mg, 0.6 mmol) and CH_3I (180 mg, 1.2 mmol) and the mixture was heated at 50 °C under N_2 overnight. The solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by prep. TLC (CH_2Cl_2/MeOH = 20:1) to give the product (10 mg, 16% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.33 (m, 1H), 8.10 – 8.05 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.26 – 7.20 (m, 3H), 4.48 (s, 2H), 3.47 – 3.44 (m, 2H), 3.32 (s, 3H), 2.88 (t, *J* = 7.6 Hz, 2H). LCMS (ES-API): R_t 2.75 min; *m/z* 522.0 $[M+H]^+$.

Example 15: 7-Bromo-N-(2,2-diphenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15)



A12 I5 15

a) Ethyl 2-((4-bromo-2-sulfamoylphenyl)amino)-2-oxoacetate (A12)

A solution of 2-amino-5-bromobenzenesulfonamide (1.00 g, 3.98 mmol) in anhydrous THF (50 mL) under an atmosphere of nitrogen was cooled in an ice-salt bath. Triethylamine (0.58 mL, 4.2 mmol) was added, followed by the dropwise addition of ethyl chlorooxoacetate (0.47 mL, 4.2 mmol). The mixture was returned to room temperature and stirred for 48 h. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to give the product as a white solid (1.75 g, >100% yield). The crude material was used in the next step without further purification: LCMS-A r.t. 5.95 min; *m/z* 349.0 $[M-H]^-$.

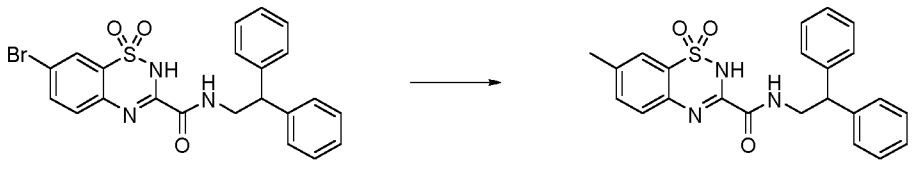
b) Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5 – alternate synthesis)

Sodium hydride (60% dispersion in mineral oil, 0.191 g, 4.78 mmol) was added to anhydrous EtOH (20 mL) under a nitrogen atmosphere and the mixture was stirred for 10 min. A slurry of ethyl 2-((4-bromo-2-sulfamoylphenyl)amino)-2-oxoacetate (A12) (1.399 g, 3.984 mmol) in anhydrous EtOH (20 mL) was then added and the mixture was stirred for 3 h at room temperature. Water (~50 mL) was added and the pH was adjusted to ~3 with aq. HCl (2 M). The mixture was concentrated *in vacuo* and the precipitate was isolated by filtration. The solid was washed with water and air dried to give the product as a white solid (0.651 g, 49% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.06 – 8.02 (m, 1H), 7.97 – 7.92 (m, 1H), 7.75 – 7.70 (m, 1H), 4.44 – 4.36 (m, 2H), 1.38 – 1.33 (m, 3H); LCMS-A r.t. 5.83 min; *m/z* 331/333 $[M-H]^-$.

c) 7-Bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15)

Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5) (500 mg, 1.50 mmol), 2,2-diphenylethan-1-amine (355 mg, 1.80 mmol) and absolute ethanol (5 mL) were heated in the microwave (100 °C/30 min). The mixture was cooled to room temperature, filtered, the collected solids washed with ethanol and air dried to give the product as a white solid (582 mg, 80% yield). LCMS-B rt: 3.52 min; *m/z* (negative ion) 483.7 [M-H]. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.24 (t, J = 5.9 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.9, 2.2 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.35 – 7.25 (m, 8H), 7.24 – 7.14 (m, 2H), 4.48 (t, J = 7.9 Hz, 1H), 3.92 (dd, J = 7.9, 5.9 Hz, 2H).

Example 16: N-(2,2-Diphenylethyl)-7-methyl-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (16)

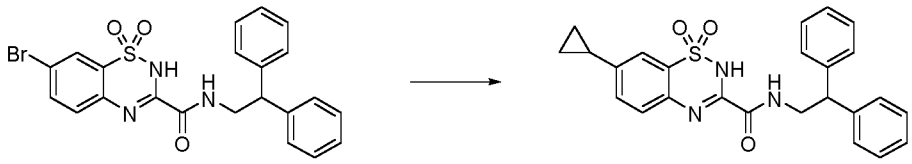


15 16

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.050 g, 0.103 mmol), methylboronic acid (0.012 g, 0.21 mmol) and K_2CO_3 (0.057 g, 0.41 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was bubbled with a stream of nitrogen for 10 min. Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 30 min. Additional methylboronic

acid (0.012 g, 0.21 mmol) and Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) were added, the mixture was bubbled with a stream of nitrogen for 10 min and then stirred in the microwave at 100 °C for 30 min. The volatiles were removed *in vacuo* before H_2O (5 mL) was added and the aqueous acidified with aq. HCl (2 M). The aqueous phase was extracted with DCM (3 × 15 mL), the organics were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.013 g, 30% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.21 (t, J = 5.9, 5.9 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.53 (dd, J = 8.6, 1.9 Hz, 1H), 7.35 – 7.26 (m, 8H), 7.23 – 7.16 (m, 2H), 4.49 (t, J = 7.9, 7.9 Hz, 1H), 3.92 (dd, J = 7.9, 5.9 Hz, 2H), 2.38 (s, 3H); LCMS-A rt 6.49 min; *m/z* 418.1 $[M-H]^-$.

Example 17: 7-Cyclopropyl-N-(2,2-diphenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (17)

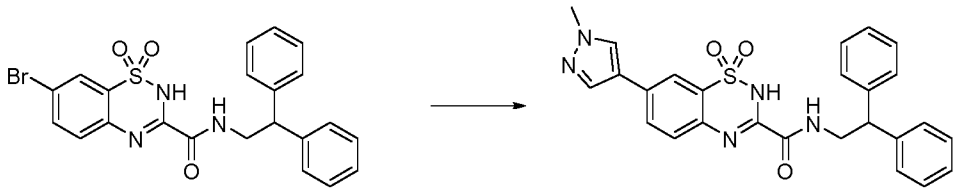


15 17

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.050 g, 0.103 mmol), cyclopropyl boronic acid (0.018 g, 0.21 mmol) and K_2CO_3 (0.057 g, 0.41 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was bubbled with a stream of nitrogen for 10 min. Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 60 min. Additional cyclopropyl boronic acid (0.018 g, 0.21 mmol) and Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) were added and the reaction mixture was bubbled with a stream of nitrogen for 10 min before heating in the microwave at 100 °C for 60 min. Further cyclopropyl boronic acid (0.036 g, 0.42 mmol) and Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) were added and the reaction mixture was bubbled with a stream of nitrogen for 10 min before heating in the microwave at 110 °C for 60 min. The volatiles were removed *in vacuo* before H_2O (5 mL) was added and the aqueous phase acidified with aq. HCl (2 M). The aqueous phase was extracted with DCM (3 × 15 mL), the organics combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.015 g, 33% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.25 – 9.13 (m, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.7, 2.1 Hz, 1H), 7.33 – 7.27 (m, 8H),

7.22 – 7.16 (m, 2H), 4.48 (t, J = 7.9, 7.9 Hz, 1H), 3.92 (dd, J = 7.9, 5.9 Hz, 2H), 2.14 – 2.03 (m, 1H), 1.08 – 0.94 (m, 2H), 0.79 – 0.68 (m, 2H); LCMS-B rt 3.45 min; *m/z* 446.1 $[M+H]^+$.

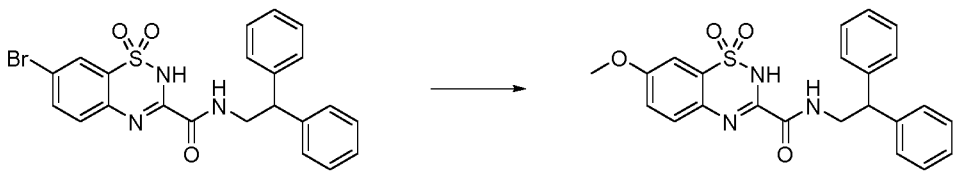
Example 18: N-(2,2-diphenylethyl)-7-(1-methyl-1H-pyrazol-4-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (18)



15 18

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.050 g, 0.10 mmol), 1-methylpyrazole-4-boronic acid, pinacol ester (0.043 g, 0.21 mmol) and K_2CO_3 (0.057 g, 0.41 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was bubbled with a stream of nitrogen for 10 min. Pd(dppf)Cl_2.DCM (0.008 g, 0.01 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 60 min. The volatiles were removed *in vacuo* before H_2O (5 mL) was added and the aqueous phase acidified with aq. HCl (2 M). The aqueous layer was extracted with DCM (3 × 15 mL), the organics combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.019 g, 38% yield): ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.61 (s, 1H), 9.20 (t, J = 6.0, 6.0 Hz, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.6, 2.1 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.34 – 7.27 (m, 8H), 7.22 – 7.17 (m, 2H), 4.49 (t, J = 7.9, 7.9 Hz, 1H), 3.93 (dd, J = 7.9, 5.9 Hz, 2H), 3.86 (s, 3H); LCMS-B rt 3.34 min; *m/z* 484.1 $[M-H]^-$.

Example 19: N-(2,2-diphenylethyl)-7-methoxy-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (19)

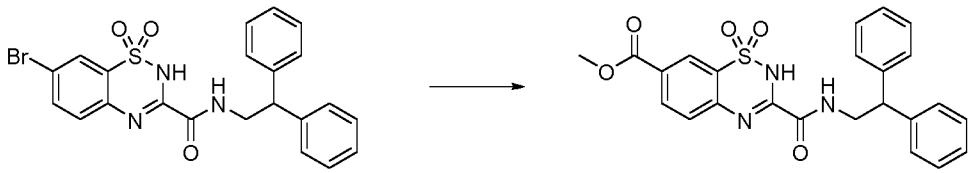


15 19

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.050 g, 0.10 mmol), Cs_2CO_3 (0.135 g, 0.413 mmol), 1,10-phenanthroline (0.007 g, 0.04 mmol) and CuI (0.008 g, 0.04 mmol) in MeOH (2 mL) was stirred under an atmosphere of nitrogen at 110 °C overnight. The reaction mixture was cooled to room temperature before sodium hydride (60% dispersion in mineral oil, 0.017 g, 0.41 mmol)

was added. The mixture was heated at 110 °C overnight under an atmosphere of nitrogen. The reaction mixture was returned to room temperature and additional sodium hydride (60% dispersion in mineral oil, 0.017 g, 0.41 mmol) and CuI (0.008 g, 0.04 mmol) were added. The mixture was heated at 120 °C under an atmosphere of nitrogen for 72 h. The mixture was cooled to room temperature, water (10 mL) and aq. HCl (2 M, 10 mL) were added and the aqueous was extracted with DCM (3 × 15 mL). The organics were combined, dried ($MgSO_4$), the solvent removed *in vacuo* and the solid purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.009 g, 20% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 9.20 (t, J = 6.0 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.37 – 7.28 (m, 9H), 7.25 – 7.17 (m, 3H), 4.49 (t, J = 7.9 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.84 (s, 3H); LCMS-B rt 3.35 min; *m/z* 436.1 $[M+H]^+$.

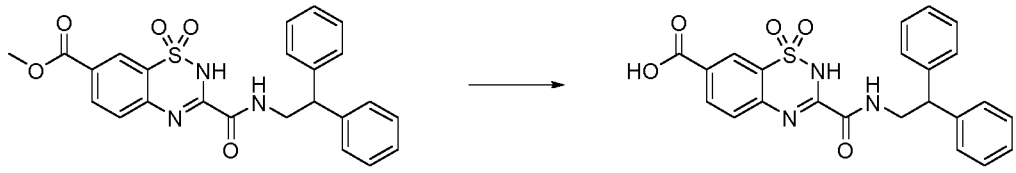
Example 20: Methyl 3-((2,2-diphenylethyl)carbamoyl)-2H-benzo[e][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide (20)



15 20

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.120 g, 0.248 mmol), $PdCl_2$(dppf).DCM (0.020 g, 0.025 mmol), triethylamine (0.14 mL, 0.99 mmol) and MeOH (3 mL) was loaded into a Schlenk tube under an atmosphere of nitrogen. The tube was flushed with carbon monoxide and the mixture was stirred overnight at 110 °C. Additional $PdCl_2$(dppf).DCM (0.020 g, 0.025 mmol) and triethylamine (1.0 mL, 7.2 mmol) were added and the mixture was stirred at 120 °C for 24 h under an atmosphere of carbon monoxide. The mixture was cooled to room temperature and the volatiles were removed *in vacuo*. Water (10 mL) and aq. HCl (2 M, 10 mL) were added and the aqueous was extracted with DCM (3 × 20 mL). The organics were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The resultant residue was purified by column chromatography (Biotage Isolera, 24 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product (~80% purity, 0.064 g, 45% yield) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.37 – 9.27 (m, 1H), 8.26 (d, J = 1.9 Hz, 1H), 8.24 – 8.19 (m, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.33 – 7.28 (m, 8H), 7.22 – 7.18 (m, 2H), 4.49 (t, J = 7.9 Hz, 1H), 3.96 – 3.90 (m, 2H), 3.89 (s, 3H); LCMS-B rt 3.39 min; *m/z* 464.1 $[M+H]^+$.

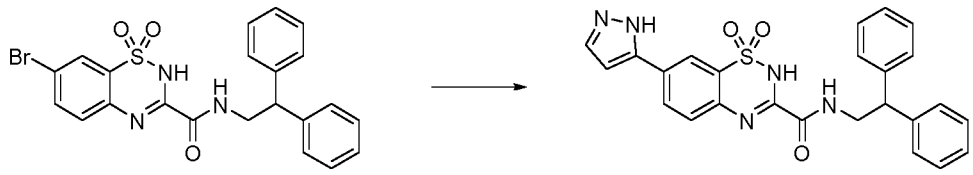
Example 21: 3-((2,2-Diphenylethyl)carbamoyl)-2H-benzo[e][1,2,4]thiadiazine-7-carboxylic acid 1,1-dioxide (21)



20 21

A mixture of methyl 3-((2,2-diphenylethyl)carbamoyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide (20) (~80% purity, 0.061 g, 0.11 mmol), $LiOH.H_2O$ (0.044 g, 1.1 mmol), THF (3.5 mL), MeOH (3.5 mL) and H_2O (0.75 mL) were stirred at room temperature overnight. The mixture was concentrated *in vacuo* before H_2O (5 mL) and aq. HCl (2 M, 5 mL) were added. The aqueous phase was extracted with EtOAc (3 × 20 mL), the organics were combined, washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the solid was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.016 g, 34% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 12.88 (s, 1H), 9.36 – 9.24 (m, 1H), 8.27 – 8.23 (m, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.35 – 7.27 (m, 8H), 7.23 – 7.16 (m, 2H), 4.49 (t, J = 7.9 Hz, 1H), 3.97 – 3.89 (m, 2H); LCMS-B rt 3.29 min; *m/z* 450.1 $[M+H]^+$.

Example 22: N-(2,2-diphenylethyl)-7-(1H-pyrazol-5-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (22)

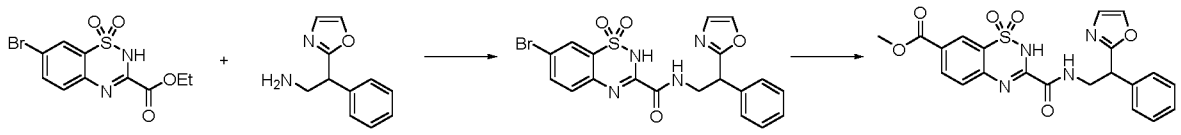


15 22

A mixture of 7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (0.040 g, 0.083 mmol), (1*H*-pyrazol-5-yl)boronic acid (0.018 g, 0.17 mmol), and K_2CO_3 (0.046 g, 0.33 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was bubbled with a stream of nitrogen for 5 min. $PdCl_2$(dppf).DCM (0.007 g, 0.008 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 60 min. The volatiles were removed *in vacuo*, H_2O (5 mL) was added and the pH of the aqueous was adjusted to ~3. The aqueous phase was extracted with DCM (3 × 10 mL), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The solid residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (~85% purity, 0.004 g, 9% yield): ^{1}H NMR

(400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 12.68 (s, 1H), 9.24 (t, J = 6.0 Hz, 1H), 8.22 – 8.12 (m, 2H), 7.88 – 7.77 (m, 2H), 7.36 – 7.26 (m, 8H), 7.24 – 7.15 (m, 2H), 6.92 – 6.82 (m, 1H), 4.50 (t, J = 7.9 Hz, 1H), 3.93 (dd, J = 7.9, 5.8 Hz, 2H); LCMS-B rt 3.31 min; *m/z* 472.1 $[M+H]^+$.

Example 23: Methyl 3-((2-(oxazol-2-yl)-2-phenylethyl)carbamoyl)-2H-benzo[e][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide (23)



I5 I27 1 23

a) 7-Bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) – further synthesis

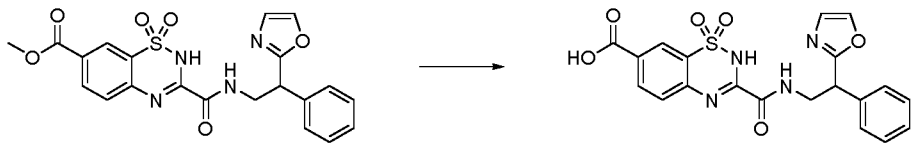
A mixture of ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5) (90% purity, 1.96 g, 5.31 mmol), 2-(oxazol-2-yl)-2-phenylethan-1-amine (I27) (0.951 g, 5.05 mmol) and EtOH (4 mL) was heated in the microwave at 100 °C for 60 min and then 110 °C for 30 min. To encourage consumption of starting material, the mixture was stirred in the microwave at 110 °C for a further 60 min and then 120 °C for 30 min. The white precipitate was isolated by vacuum filtration, washed with EtOH and air dried to give a mixture of the desired product and starting material. The solid was taken up in THF (10 mL), MeOH (1 mL) and H_2O (1 mL) and stirred with $LiOH.H_2O$ (0.300 g, 7.15 mmol) for 4 h at room temperature. The mixture was concentrated *in vacuo*, water (~50 mL) and aq. HCl (2 M, ~50 mL) were added and the mixture sonicated for 10 min. The white precipitate was isolated by vacuum filtration, washed with H_2O and air dried to give the product as a white solid (1.38 g, 57% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 – 12.63 (s, 1H), 9.36 – 9.24 (t, J = 5.9 Hz, 1H), 8.06 – 8.03 (m, 1H), 8.02 – 7.99 (d, J = 2.2 Hz, 1H), 7.96 – 7.91 (dd, J = 8.9, 2.2 Hz, 1H), 7.78 – 7.72 (d, J = 8.9 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 7.22 – 7.17 (m, 1H), 4.73 – 4.61 (t, J = 7.6 Hz, 1H), 4.08 – 3.95 (m, 1H), 3.93 – 3.81 (m, 1H); LCMS-A rt 6.33 min; *m/z* 475/477 $[M+H]^+$.

b) Methyl 3-((2-(oxazol-2-yl)-2-phenylethyl)carbamoyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide (23)

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (0.100 g, 0.210 mmol) and $Pd(dppf)Cl_2$.DCM (0.052 g, 0.063 mmol) in MeOH (2 mL) was bubbled with CO for 10 min. Triethylamine (2 mL) was added and the mixture was stirred at 120 °C under a balloon of CO for 16 h. Additional $Pd(dppf)Cl_2$.DCM (0.052 g, 0.063 mmol) was added and the mixture was stirred at 120 °C

under a balloon of CO for 4 h. The mixture was cooled to room temperature and concentrated *in vacuo*. Water (~15 mL) was added and the aqueous phase was brought to pH ~2 with aq. HCl (2 M). The aqueous layer was extracted with DCM (3 × 30 mL), the organics were combined, washed with brine, dried ($MgSO_4$), the solvent removed *in vacuo* and the residue purified by column chromatography (Biotage Isolera, 24 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as an orange solid (0.035 g, 37% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 9.36 – 9.29 (t, J = 6.2 Hz, 1H), 8.31 – 8.25 (d, J = 1.9 Hz, 1H), 8.25 – 8.19 (dd, J = 8.7, 1.9 Hz, 1H), 8.07 – 8.02 (d, J = 0.9 Hz, 1H), 7.93 – 7.86 (d, J = 8.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.25 (m, 3H), 7.22 – 7.18 (d, J = 0.9 Hz, 1H), 4.72 – 4.63 (t, J = 7.6 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.92 – 3.85 (m, 4H); LCMS-A rt 6.26 min; *m/z* 455.1 $[M+H]^+$.

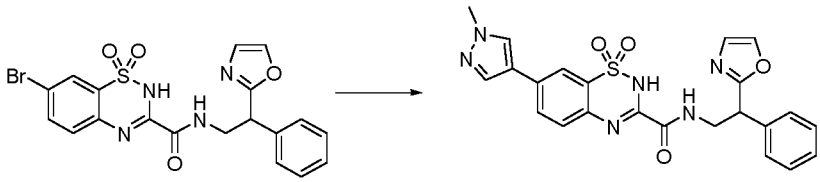
Example 24: 3-((2-(Oxazol-2-yl)-2-phenylethyl)carbamoyl)-2H-benzo[e][1,2,4]thiadiazine-7-carboxylic acid 1,1-dioxide (24)



23 24

A mixture of methyl 3-((2-(oxazol-2-yl)-2-phenylethyl)carbamoyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide (23) (0.060 g, 0.13 mmol), $LiOH.H_2O$ (0.028 g, 0.66 mmol), THF (3.5 mL), MeOH (3.5 mL) and H_2O (0.75 mL) was stirred at room temperature for 18 h. Additional $LiOH.H_2O$ (0.028 g, 0.66 mmol) was added and the mixture was stirred at room temperature for 4 h. Another portion of $LiOH.H_2O$ (0.028 g, 0.66 mmol) was added and the mixture was stirred at 40 °C for 1.5 h. The volatiles were removed *in vacuo*, H_2O (~20 mL) was added and the aqueous layer was washed with DCM (2 × 20 mL). The aqueous phase was adjusted to pH ~2 with aq. HCl (2 M) and then extracted with DCM (3 × 20 mL). The organics were combined, washed with brine, dried (Na_2SO_4), the solvent was removed *in vacuo* and the residue was purified by column chromatography (Biotage Isolera, 4 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C). The fraction containing the suspected product was purified by another round of column chromatography (Biotage Isolera, 4 g SiO_2 cartridge, 0-5% MeOH in DCM) to give the product as a white solid (0.007 g, 12% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 9.40 – 9.27 (t, J = 5.9 Hz, 1H), 8.30 – 8.24 (d, J = 1.8 Hz, 1H), 8.23 – 8.17 (dd, J = 8.9, 1.9 Hz, 1H), 8.08 – 8.01 (s, 1H), 7.93 – 7.83 (d, J = 8.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 7.24 – 7.15 (m, 1H), 4.75 – 4.59 (t, J = 7.5 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.94 – 3.82 (m, 1H), COOH not observed; LCMS-B RT 3.10 min; *m/z* 441.0 $[M+H]^+$.

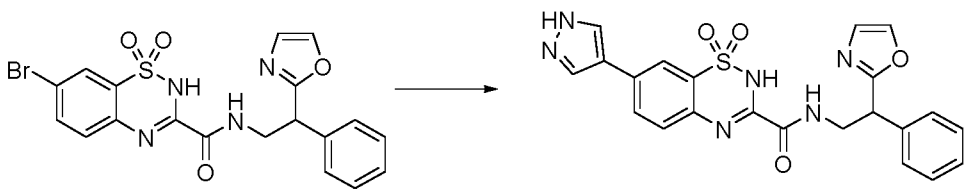
Example 25: 7-(1-Methyl-1H-pyrazol-4-yl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (25)



1 25

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (0.050 g, 0.11 mmol), 1-methyl-1*H*-pyrazole-4-boronic acid, pinacol ester (0.044 g, 0.21 mmol), Pd(dppf)Cl_2.DCM (0.009 g, 0.01 mmol), H_2O (0.5 mL) and dioxane (2 mL) were bubbled with a stream of nitrogen gas for 10 min. Potassium carbonate (0.058 g, 0.42 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 60 min. The mixture was returned to room temperature and the volatiles were removed *in vacuo*. Water (~10 mL) was added and the aqueous phase was adjusted to pH ~2 with aq. HCl (2 M) and then extracted with DCM (2 × 15 mL). The organics were combined, the solvent was removed *in vacuo* and the residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give a white solid. The solid was taken up in a minimum amount of DCM, cyclohexane was added and the suspension was sonicated for 5 min. The precipitate was isolated by filtration and air dried to give the product as a white solid (0.011 g, 22% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 9.36 – 9.15 (t, J = 5.9 Hz, 1H), 8.38 – 8.25 (s, 1H), 8.10 – 7.95 (m, 3H), 7.95 – 7.89 (m, 1H), 7.83 – 7.71 (d, J = 8.8 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 7.23 – 7.18 (s, 1H), 4.75 – 4.60 (t, J = 7.5 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.94 – 3.79 (m, 4H); LCMS-B RT 3.15 min; *m/z* 477.1 $[M+H]^+$.

Example 26: N-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(1H-pyrazol-4-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (26)

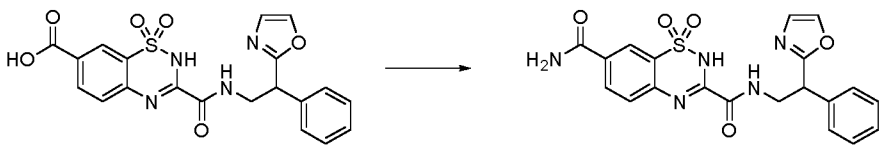


1 26

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (0.050 g, 0.11 mmol), pyrazole-4-boronic acid (HCl salt, 0.031 g, 0.21 mmol), Pd(dppf)Cl_2.DCM (0.009 g, 0.01 mmol), H_2O (0.5 mL) and dioxane (2 mL)

were bubbled with a stream of nitrogen gas for 10 min. Potassium carbonate (0.058 g, 0.42 mmol) was then added and the mixture was stirred in the microwave at 100 °C for 60 min. The mixture was returned to room temperature and the volatiles were removed *in vacuo*. Water (~10 mL) was added and the aqueous was adjusted to pH ~2 with aq. HCl (2 M) and then extracted with DCM (2 × 15 mL). The organics were combined, the solvent was removed *in vacuo* and the residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.010 g, 21% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 12.68 – 12.49 (s, 1H), 9.34 – 9.11 (m, 1H), 8.54 – 8.22 (s, 1H), 8.20 – 8.01 (m, 3H), 8.00 – 7.94 (dd, J = 8.6, 2.1 Hz, 1H), 7.83 – 7.71 (d, J = 8.6 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 7.23 – 7.17 (m, 1H), 4.72 – 4.63 (t, J = 7.5 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.94 – 3.83 (m, 1H); LCMS-A RT 5.49 min; *m/z* 463.2 $[M+H]^+$.

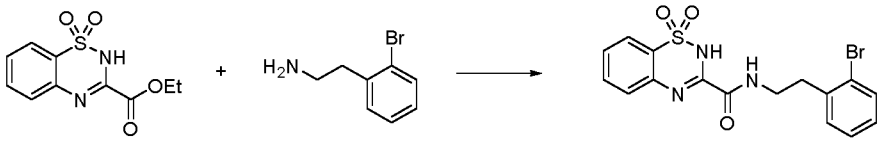
Example 27: N^3-(2-(Oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3,7-dicarboxamide 1,1-dioxide (27)



24 27

DIPEA (79 µL, 0.45 mmol) was added to a solution of 3-((2-(oxazol-2-yl)-2-phenylethyl)carbamoyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-7-carboxylic acid 1,1-dioxide (24) (0.040 g, 0.091 mmol) in THF (3 mL) and DMF (0.5 mL). HOBt (0.018 g, 0.14 mmol) and EDCI.HCl (0.026 g, 0.14 mmol) were then added followed by $(NH_4)_2CO_3$ (0.044 g, 0.45 mmol). The mixture was stirred for 48 h at room temperature before being concentrated *in vacuo*. Water (~15 mL) was added and the aqueous was brought to ~pH 2. The precipitate was isolated by filtration and air dried to give a brown solid. The solid was adsorbed onto silica and purified by column chromatography (Biotage Isolera, 4 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.003 g, 8% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 9.37 – 9.21 (m, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H), 8.17 (dd, J = 8.7, 2.0 Hz, 1H), 8.05 (d, J = 0.8 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.60 (s, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 7.21 (d, J = 0.9 Hz, 1H), 4.67 (t, J = 7.5 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.93 – 3.83 (m, 1H); LCMS-B RT 3.09 min; *m/z* 440.1 $[M+H]^+$.

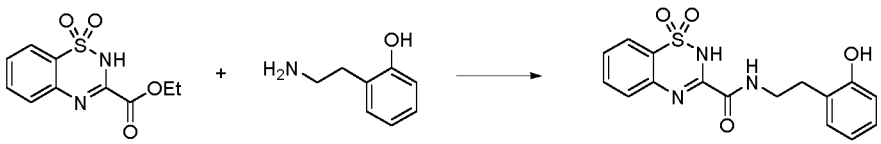
Example 28: N-(2-Bromophenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (28)



I2 28

A mixture of ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.050 g, 0.20 mmol) and 2-(2-bromophenyl)ethan-1-amine (40 µL, 0.28 mmol) in EtOH (0.2 mL) was heated in the microwave at 120 °C for 60 min. The mixture was returned to room temperature and the white precipitate was isolated by filtration, washed with EtOH and air dried to give the product as a white solid (0.057 g, 71% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 9.47 – 9.25 (t, J = 6.0 Hz, 1H), 7.88 – 7.83 (dd, J = 8.0, 1.4 Hz, 1H), 7.83 – 7.78 (m, 1H), 7.76 – 7.70 (m, 1H), 7.62 – 7.57 (m, 1H), 7.56 – 7.49 (m, 1H), 7.36 – 7.29 (m, 2H), 7.21 – 7.13 (m, 1H), 3.59 – 3.48 (m, 2H), 3.06 – 2.93 (t, J = 7.2 Hz, 2H); LCMS-B RT 3.28 min; *m/z* 408/410 $[M+H]^+$.

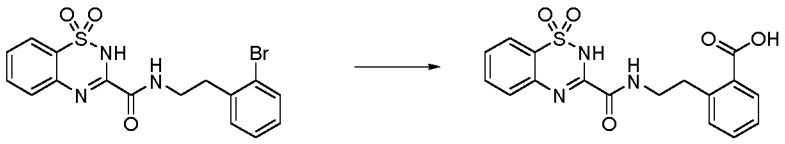
Example 29: N-(2-Hydroxyphenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (29)



I2 29

A mixture of ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.050 g, 0.20 mmol) and 2-(2-aminoethyl)phenol (0.038 g, 0.28 mmol) in EtOH (0.2 mL) was heated in the microwave at 120 °C for 60 min. The mixture was returned to room temperature and the white precipitate was isolated by filtration, washed with EtOH and air dried to give the product as a white solid (0.031 g, 46% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 9.38 (s, 1H), 9.21 (t, J = 5.9 Hz, 1H), 7.86 (dd, J = 8.0, 1.4 Hz, 1H), 7.81 (dd, J = 8.4, 1.2 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.56 – 7.48 (m, 1H), 7.10 – 6.97 (m, 2H), 6.79 (dd, J = 8.1, 1.2 Hz, 1H), 6.71 (td, J = 7.4, 1.2 Hz, 1H), 3.54 – 3.44 (m, 2H), 2.82 (t, J = 7.3 Hz, 2H); LCMS-A RT 6.07 min; *m/z* 344.1 $[M-H]^-$.

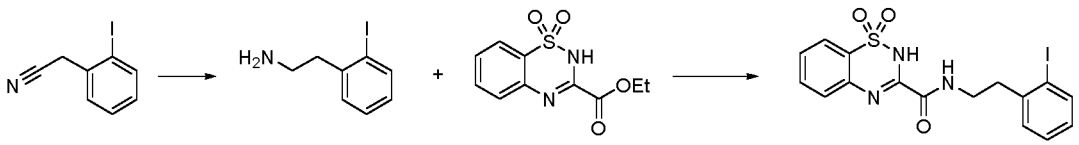
Example 30: 2-(2-(1,1-Dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid (30)



28 30

A solution of *N*-(2-bromophenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (28) (0.200 g, 0.490 mmol) in anhydrous THF (2 mL) was cooled to -78 °C under an atmosphere of nitrogen. A solution of *n*-butyllithium (1.6 M in hexanes, 0.64 mL, 1.0 mmol) was cautiously added and the mixture was stirred for 10 min at -78 °C. The mixture was then poured onto dry ice and returned to room temperature with stirring. Water was added (~10 mL) and the mixture was concentrated *in vacuo*. The aqueous was adjusted to pH ~2 with aq. HCl (2 M) and then extracted with DCM (2 × 15 mL). The organics were combined, washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The white solid was purified by column chromatography (Biotage Isolera, 24 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C then 0-25% MeOH in EtOAc) to give the product as a white solid (0.019 g, 10% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (t, J = 5.8 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.55 – 7.43 (m, 2H), 7.35 – 7.28 (m, 2H), 3.56 (q, J = 6.6 Hz, 2H), 3.22 (t, J = 7.0 Hz, 2H), CO_2H and SO_2NH not observed; LCMS-B RT 3.09 min; *m/z* 372.0 $[M-H]^-$.

Example 31: N-(2-Iodophenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (31)



A16 I2 31

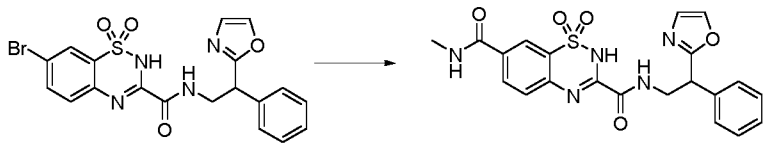
a) 2-(2-Iodophenyl)ethan-1-amine (A16)

A solution of 2-(2-iodophenyl)acetonitrile (1.00 g, 4.11 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen was treated with borane tetrahydrofuran complex solution (1.0 M in THF, 12.3 mL, 12.3 mmol). The mixture was stirred at reflux for 16 h, cooled to room temperature and excess borane reagent was quenched by the dropwise addition of water (until evolution of hydrogen ceased). MeOH (2.5 mL) and conc. H_2SO_4 (0.5 mL) was added and the mixture was stirred for 1 h at r.t.. The mixture was concentrated *in vacuo*, water (~10 mL) was added and the aqueous was adjusted to pH ~12 with aq. NaOH (2 M). The aqueous layer was extracted with EtOAc (3 × 30 mL), the organics were combined,

washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a colourless oil. Water (~20 mL) was added and the aqueous phase was adjusted to pH ~2 with aq. HCl (2 M). The aqueous layer was washed with DCM (3 × 30 mL) and then adjusted to pH ~12 with aq. NaOH (2 M). The aqueous layer was extracted with DCM (3 × 50 mL), the organics were combined, washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the product as a colourless oil (0.869 g, 85% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, J = 7.8, 1.2 Hz, 1H), 7.35 – 7.27 (m, 2H), 6.97 – 6.91 (m, 1H), 2.75 – 2.71 (m, 4H) exchangeable N*H* not observed; LCMS-B RT 2.77 min; *m/z* 248.0 $[M+H]^+$.

b) *N*-(2-Iodophenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (31)
A mixture of ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.250 g, 0.983 mmol) and A16 (0.340 g, 1.38 mmol) in EtOH (1 mL) was heated in the microwave at 120 °C for 60 min. The mixture was returned to room temperature and the white precipitate was isolated by filtration, washed with EtOH and air dried to give the title compound as a white solid (0.370 g, 83% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 9.36 (t, J = 5.8 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.80 (dd, J = 8.4, 1.2 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.56 – 7.49 (m, 1H), 7.37 – 7.28 (m, 2H), 7.01 – 6.94 (m, 1H), 3.55 – 3.46 (m, 2H), 2.98 (t, J = 7.3 Hz, 2H); LCMS-B RT 3.32 min; *m/z* 455.9 $[M+H]^+$.

Example 32: N^7-Methyl-N^3-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3,7-dicarboxamide 1,1-dioxide (32)

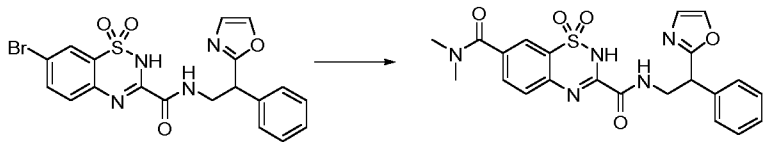


1 32

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (0.050 g, 0.11 mmol), methylamine hydrochloride (0.036 g, 0.53 mmol), $Pd(OAc)_2$ (0.002 g, 0.009 mmol) and xantphos (0.004 g, 0.007 mmol) in 1,4-dioxane (3 mL) and triethylamine (0.15 mL, 1.1 mmol) was bubbled with $CO_{(g)}$ for 10 min. The mixture was then refluxed under a balloon of CO for 16 h. Additional portions of methylamine hydrochloride (0.036 g, 0.53 mmol), $Pd(OAc)_2$ (0.002 g, 0.009 mmol), xantphos (0.004 g, 0.007 mmol) and triethylamine (0.15 mL, 1.1 mmol) were added and the mixture was stirred at reflux for a further 24 h under a balloon of CO. The mixture was returned to room temperature and then concentrated *in vacuo*. Water (~10 mL) was added to the residue and the pH was adjusted to ~2 with aq. HCl (2 M). The aqueous was extracted with EtOAc (3 × 15 mL), the organics were combined, washed with brine and

dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.014 g, 29% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 9.37 – 9.19 (m, 1H), 8.78 – 8.67 (m, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.13 (dd, J = 8.7, 2.0 Hz, 1H), 8.05 (d, J = 0.9 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 7.21 (d, J = 1.0 Hz, 1H), 4.67 (t, J = 7.5 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.93 – 3.83 (m, 1H), 2.80 (d, J = 4.5 Hz, 3H); LCMS-B RT 3.10 min; *m/z* 454.1 $[M+H]^+$.

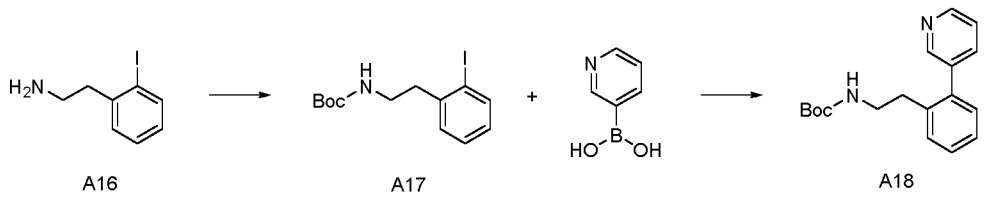
Example 33: N^7,N^7-Dimethyl-N^3-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3,7-dicarboxamide 1,1-dioxide (33)

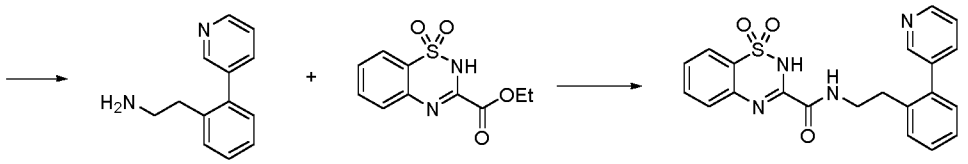


1 33

A mixture of 7-bromo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (1) (0.050 g, 0.11 mmol), dimethylamine hydrochloride (0.043 g, 0.53 mmol), $Pd(OAc)_2$ (0.002 g, 0.01 mmol) and xantphos (0.006 g, 0.01 mmol) in 1,4-dioxane (3 mL) and triethylamine (0.20 mL, 1.4 mmol) was bubbled with $CO_{(g)}$ for 10 min. The mixture was then refluxed under a balloon of CO for 16 h. Additional portions of dimethylamine hydrochloride (0.043 g, 0.53 mmol), $Pd(OAc)_2$ (0.002 g, 0.01 mmol), xantphos (0.006 g, 0.01 mmol) and triethylamine (0.20 mL, 1.4 mmol) were added and the mixture was stirred at reflux for a further 6 h under a balloon of CO. The mixture was returned to room temperature and stirred for 72 h. The mixture was concentrated *in vacuo*, water (~10 mL) was added and the pH was adjusted to ~2 with aq. HCl (2 M). The aqueous layer was extracted with EtOAc (3 × 15 mL), the organics were combined, washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.013 g, 26% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.44 – 9.09 (m, 1H), 8.05 (d, J = 0.9 Hz, 1H), 7.86 – 7.72 (m, 3H), 7.37 – 7.31 (m, 2H), 7.30 – 7.25 (m, 3H), 7.20 (d, J = 0.9 Hz, 1H), 4.67 (t, J = 7.5 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.93 – 3.83 (m, 1H), 2.95 (d, J = 25.7 Hz, 6H); LCMS-B RT 3.09 min; *m/z* 468.2 $[M+H]^+$.

Example 34: N-(2-(Pyridin-3-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (34)





a) *tert*-Butyl (2-iodophenethyl)carbamate (A17)

A mixture of 2-(2-iodophenyl)ethan-1-amine (A16) (0.432 g, 1.75 mmol), di-*tert*-butyl dicarbonate (0.458 g, 2.10 mmol), TEA (0.37 mL, 2.6 mmol) and DMAP (0.021 g, 0.18 mmol) in THF (5 mL) was stirred at room temperature for 16 h. Water (~10 mL) was added and the mixture concentrated *in vacuo*. The aqueous phase was adjusted to pH ~2 with aq. HCl (2 M) and then extracted with DCM (3 × 25 mL). The organics were combined, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography (Biotage Isolera, 24 g SiO_2 cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.506 g, 83% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (dd, J = 7.9, 1.3 Hz, 1H), 7.33 (td, J = 7.4, 1.3 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.00 – 6.90 (m, 2H), 3.20 – 3.08 (m, 2H), 2.83 – 2.75 (m, 2H), 1.36 (s, 9H); LCMS-B RT 3.50 min; *m/z* 370.0 $[M+Na]^+$, 291.9 $[M-t\text{-Bu}+2H]^+$.

b) *tert*-Butyl (2-(pyridin-3-yl)phenethyl)carbamate (A18)

A mixture of *tert*-butyl (2-iodophenethyl)carbamate (A17) (0.100 g, 0.288 mmol), pyridine-3-boronic acid (0.071 g, 0.58 mmol), K_2CO_3 (0.119 g, 0.864 mmol) and Pd(dppf)Cl_2·DCM (0.024 g, 0.029 mmol) in 1,4-dioxane (2 mL) and H_2O (0.5 mL) were stirred at reflux under an atmosphere of nitrogen for 3 h. The mixture was cooled to room temperature and then concentrated *in vacuo*. Water (~10 mL) and sat. aq. $NaHCO_3$ (~10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organics were combined, washed with brine, dried (Na_2SO_4), the volatiles evaporated in vacuo and the residue purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a colourless oil (0.063 g, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.9, 1.7 Hz, 1H), 8.57 (dd, J = 2.4, 0.9 Hz, 1H),

7.64 (dt, J = 7.7, 2.0 Hz, 1H), 7.41 – 7.27 (m, 4H), 7.21 (dt, J = 7.6, 1.0 Hz, 1H), 4.40 (s, 1H), 3.33 – 3.08 (m, 2H), 2.77 (t, J = 7.2 Hz, 2H), 1.39 (s, 9H): LCMS-B rt 3.05 min; *m/z* 299 $[M+H]^+$, 243 $[M-t\text{-}Bu+2H]^+$.

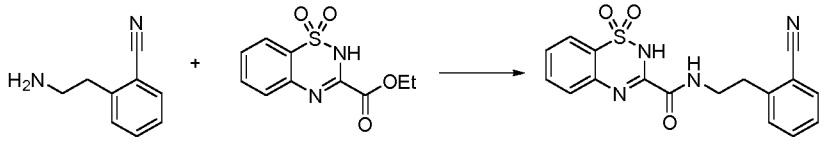
c) 2-(2-(Pyridin-3-yl)phenyl)ethan-1-amine (A19)

A solution of *tert*-butyl (2-(pyridin-3-yl)phenethyl)carbamate (A18) (0.063 g, 0.21 mmol) in DCM (5 mL) was treated with TFA (0.16 mL, 2.1 mmol) and the mixture was stirred at room temperature for 4 h. Another aliquot of TFA (0.16 mL, 2.1 mmol) was added and the mixture was stirred at room temperature for a further 1 hour. Water (~10 mL) was added, the aqueous phase was adjusted to pH ~12 with aq. NaOH (2 M) and then extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the product as a colourless oil (0.043 g, >95% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 – 8.52 (m, 2H), 7.64 (dt, J = 7.7, 2.0 Hz, 1H), 7.39 – 7.27 (m, 4H), 7.20 (dd, J = 7.4, 1.4 Hz, 1H), 2.87 – 2.73 (m, 6H); LCMS-B RT 0.50 min; *m/z* 199.1 $[M+H]^+$.

d) *N*-(2-(Pyridin-3-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (34)

A mixture of 2-(2-(pyridin-3-yl)phenyl)ethan-1-amine (A19) (0.043 g, 0.22 mmol), ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.050 g, 0.20 mmol) and EtOH (1.5 mL) was stirred in a sealed vessel at 110 °C for 1 hour and then at 120 °C for 2 h. The mixture was cooled to room temperature, the volatiles were removed *in vacuo* and the crude product purified by column chromatography (Biotage Isolera, 12 g SiO_2 cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the product as a white solid (0.016 g, 20% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 9.32 – 9.09 (m, 1H), 8.57 (dd, J = 4.8, 1.6 Hz, 1H), 8.55 – 8.53 (m, 1H), 7.84 (dd, J = 8.0, 1.4 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.75 – 7.69 (m, 1H), 7.55 – 7.48 (m, 1H), 7.45 – 7.38 (m, 3H), 7.35 – 7.29 (m, 1H), 7.25 – 7.18 (m, 1H), 3.39 – 3.34 (m, 2H), 2.84 (t, J = 7.4 Hz, 2H); LCMS-B rt 2.95 min; *m/z* 407.1 $[M+H]^+$.

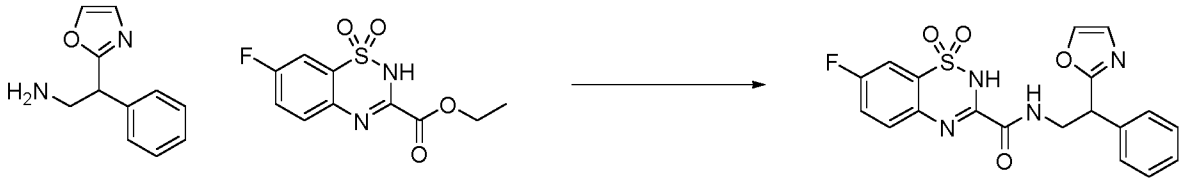
Example 35: N-(2-Cyanophenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (35)



I2 35

A mixture of ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.166 g, 0.655 mmol) and 2-(2-aminoethyl)benzonitrile (0.134 g, 0.917 mmol) in EtOH (1.5 mL) was heated in the microwave at 120 °C for 60 min. The mixture was returned to room temperature and the solvent removed *in vacuo*. The solid was taken up in DCM:MeOH (1:1 v/v) and loaded on to a Bond Elut SCX cartridge (10 g). The cartridge was eluted with DCM:MeOH (1:1 v/v, ~100 mL) and the filtrate was concentrated *in vacuo* to give the product as a white solid (0.118 g, 51% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 9.39 (t, J = 6.0 Hz, 1H), 7.88 – 7.77 (m, 3H), 7.76 – 7.70 (m, 1H), 7.64 (td, J = 7.9, 1.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 3.59 (q, J = 6.7 Hz, 2H), 3.10 (t, J = 6.9 Hz, 2H); LCMS-A RT 4.15 min; *m/z* 355.2 $[M+H]^+$.

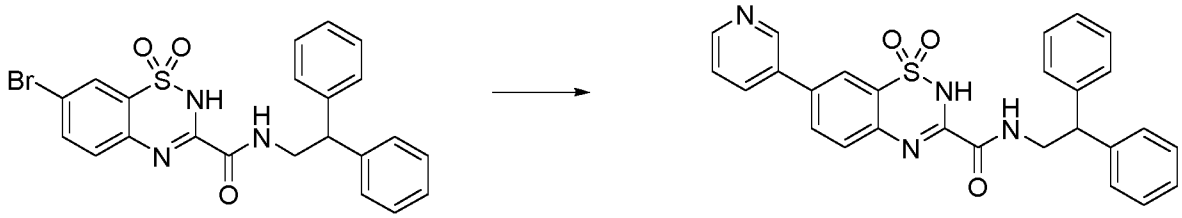
Example 36: 7-fluoro-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (36)



I27 I57 36

2-(Oxazol-2-yl)-2-phenylethan-1-amine (I27) (0.026 g, 0.138 mmol) and ethyl 7-fluoro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I57) (0.031 g, 80% purity, 0.092 mmol) were placed in a microwave vial. Dry EtOH (0.125 mL) was added and the reaction was subjected to microwave irradiation at 120 ° C for 1 hour. The reaction was allowed to cool to room temperature and the sides of the tube were continuously scratched with a spatula for about 2 min. The precipitated solid was collected by filtration, washed with EtOH (2 mL) and dried under high-vacuum to give the product (0.020, 53% yield) as an off-white solid. ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.28 – 9.17 (m, 1H), 8.04 (d, *J* = 0.9 Hz, 1H), 7.82 (dd, *J* = 9.8, 4.6 Hz, 2H), 7.72 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.63 (td, *J* = 8.9, 2.9 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.30 – 7.23 (m, 3H), 7.20 (d, *J* = 0.9 Hz, 1H), 4.66 (t, *J* = 7.5 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.91 – 3.83 (m, 1H). LCMS-B: RT 3.22 min; *m/z* 415.0 $[M+H]^+$.

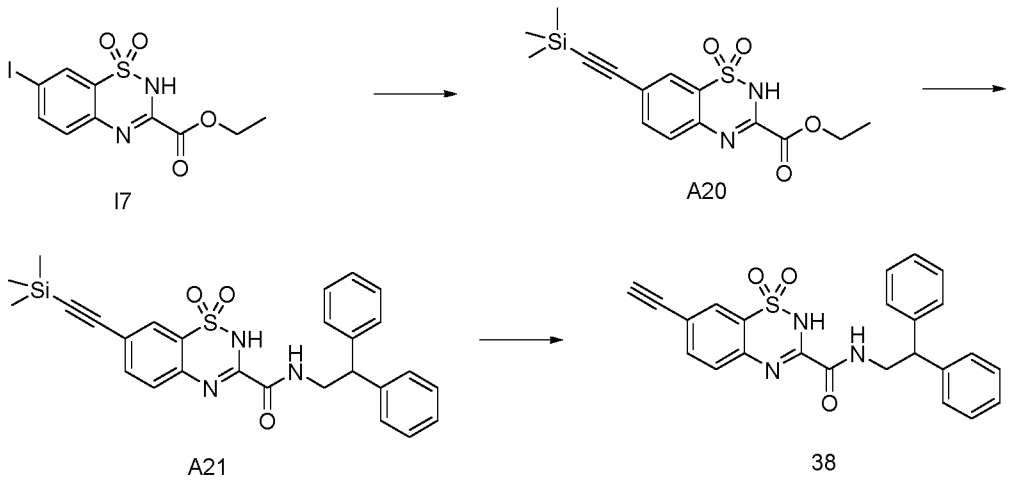
Example 37: N-(2,2-diphenylethyl)-7-(pyridin-3-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (37)



15 37

7-bromo-*N*-(2,2-diphenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (15) (50 mg, 0.10 mmol), pyridine 3-boronic acid (19 mg, 0.16 mmol), potassium carbonate (43 mg, 0.31 mmol) and PEPPSI-IPr (4 mg, 5 mol% yield) were loaded into a microwave tube and flushed with nitrogen. Absolute ethanol (1 mL) was added, the mixture degassed with a stream of nitrogen bubbles and heated in the microwave (80 °C for 30 min). The mixture was cooled to room temperature and then added to water (30 mL). The mixture was stirred and the pH adjusted to 3-4 with 30% w/v aq $NaHSO_4$. The precipitate was collected by centrifugation and dried azeotropically with ethanol. The mixture was slurried in 10% v/v MeOH/DCM (5 mL) and the solvent decanted. The remaining precipitate was purified by preparative TLC (100% ethyl acetate) to give the product (1 mg, 2% yield). LCMS-A: RT 5.60 min; *m/z* 481.1 $[M-H]^-$.

Example 38: N-(2,2-diphenylethyl)-7-ethynyl-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (38)



I7 A20

A21 38

a) Ethyl 7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A20)

Ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (190 mg, 0.50 mmol), copper(I) iodide (5 mg, 5 mol % yield), bis(triphenylphosphine)palladium(II) dichloride (18 mg, 5 mol % yield), triethylamine (filtered through neutral alumina, 2 mL) and

DMF (2 mL) were degassed with a stream of nitrogen bubbles. Trimethylsilylacetylene (0.214 mL, 1.5 mmol) was added and the mixture stirred at room temperature. After three days the mixture was poured into 0.5M aq HCl (60 mL) and extracted with DCM (3 × 30 mL). The pooled organic extracts were washed with brine (100 ml), dried over sodium sulfate and evaporated. Chromatography (12 g silica cartridge, 0-60% ethyl acetate/hexanes) gave the product as a pale yellow solid (101 mg, 58% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 9.48 (s, 1H), 8.07 (d, J = 1.7 Hz, 1H), 7.66 (dd, J = 8.5, 1.8 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 4.51 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H), 0.26 (s, 9H). LCMS-B: 3.49 min; *m/z* 348.8 $[M-H]^-$.

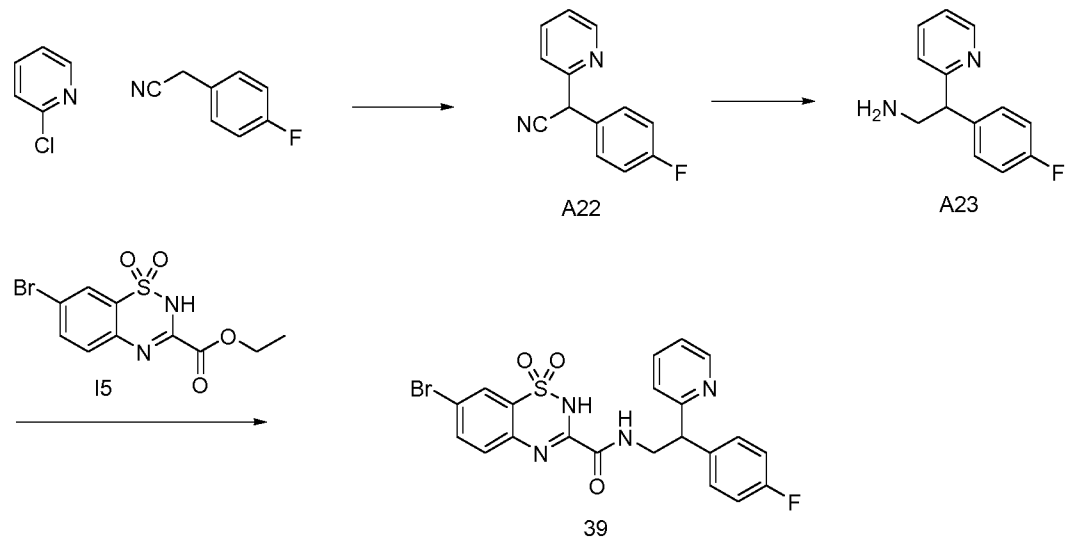
b) *N*-(2,2-diphenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A21)

Ethyl 7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A20) (25 mg, 0.071 mmol), 2,2-diphenylethan-1-amine (18 mg, 0.091 mmol) and absolute ethanol (1 mL) were heated in the microwave (100° for 1 h). The mixture was stood at room temperature for one hour and the resulting precipitate collected by filtration, washed with cold absolute ethanol (2 × 1 mL) and air dried to give the product as an off-white solid (8 mg, 22% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.24 (s, 1H), 7.84 – 7.78 (m, 1H), 7.75 (s, 2H), 7.35 – 7.25 (m, 9H), 7.25 – 7.15 (m, 2H), 4.48 (t, J = 7.9 Hz, 1H), 3.92 (dd, J = 7.8, 6.0 Hz, 2H), 0.24 (s, 9H). LCMS-A RT 6.76 min; *m/z* 500.1 $[M-H]^-$.

c) *N*-(2,2-diphenylethyl)-7-ethynyl-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (38)

N-(2,2-Diphenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A21) (7 mg, 0.012 mmol) was dissolved in 1:1 v/v MeOH:THF (1 mL) and a 1M aqueous solution of KOH (0.05 mL, 0.05 mmol) was added. After 30 min Dowex-50X8 H-form (200 mg) was added, the mixture filtered through a syringe filter and the resin washed with methanol (1 mL). The pooled filtrates were concentrated in vacuo, the residue rinsed with diethyl ether and dried in vacuo to give the product as a pale yellow solid (6 mg, quantitative yield). ^{1}H NMR (400 MHz, Acetone-d6) δ 8.60 – 8.53 (m, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.83 (dd, J = 8.6, 0.6 Hz, 1H), 7.79 (dd, J = 8.6, 1.8 Hz, 1H), 7.39 – 7.27 (m, 8H), 7.23 – 7.17 (m, 2H), 4.56 (t, J = 8.0 Hz, 1H), 4.15 – 4.07 (m, 2H), 3.88 (s, 1H), N*H* proton not observed. LCMS-B: RT 3.47 min; *m/z* 427.8 $[M-H]^-$.

Example 39: 7-bromo-N-(2-(4-fluorophenyl)-2-(pyridin-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (39)



a) 2-(4-fluorophenyl)-2-(pyridin-2-yl)acetonitrile (A22)

2-Chloropyridine (0.095 mL, 1.0 mmol) and 2-(4-fluorophenyl)acetonitrile (0.240 mL, 2.0 mmol) were dissolved in dry toluene (1 mL) and a 1.0M solution of NaHMDS in THF (2.0 mL, 2.0 mmol) was added. The mixture was stirred at room temperature overnight, filtered through a syringe filter and loaded onto a 12g silica column. Chromatography (0-50% ethyl acetate/hexanes) gave the product as an oil (118 mg, 56% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.60 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.46 – 7.36 (m, 3H), 7.29 – 7.22 (m, overlaps with $CHCl_3$), 7.11 – 7.01 (m, 2H), 5.29 (s, 1H). LCMS-A RT 4.02 min; *m/z* 213.1 $[M+H]^+$.

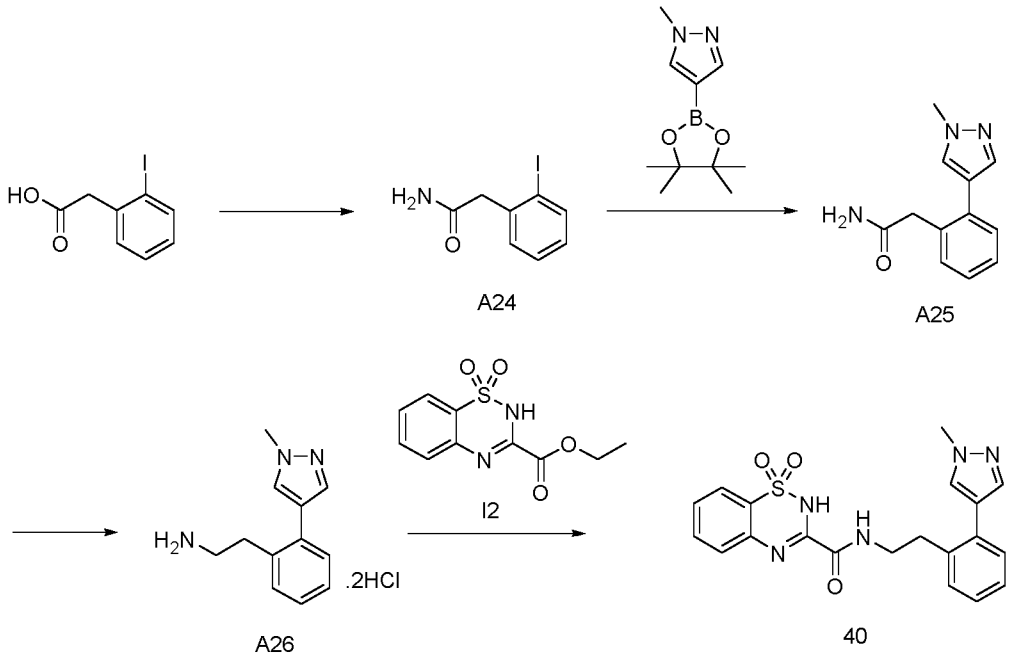
b) 2-(4-fluorophenyl)-2-(pyridin-2-yl)ethan-1-amine (A23)

2-(4-Fluorophenyl)-2-(pyridin-2-yl)acetonitrile (A22) (115 mg, 0.54 mmol) and cobalt(II) chloride (106 mg, 0.81 mmol) were dissolved in methanol (10 mL) and cooled to 0°C under nitrogen. Sodium borohydride (103 mg, 2.71 mmol) was added in one portion under strong nitrogen flow. The mixture was stirred at room temperature under nitrogen for 45 min. The mixture was quenched with 3M aq HCl (2 mL) and concentrated in vacuo. Water (10 mL) and ethyl acetate (10 mL) were added, the pH of the aqueous phase was adjusted to 13 with 20% w/v aq NaOH and the mixture filtered through Celite®. The separated aqueous phase was extracted with further ethyl acetate (2 × 10 mL), the pooled ethyl acetate phases dried over sodium sulfate and evaporated to give the product as a pale yellow syrup (26 mg, 22% yield). LCMS-A RT: 1.58 min; *m/z* (positive ion) 217.1 [M+H]

c) 7-bromo-*N*-(2-(4-fluorophenyl)-2-(pyridin-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (39)

Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I5) (33 mg, 0.10 mmol), 2-(4-fluorophenyl)-2-(pyridin-2-yl)ethan-1-amine (A23) (26 mg, 0.12 mmol) and ethanol (1 mL) were heated in the microwave at 100 °C for 30 min. The mixture was cooled to room temperature and filtered. The filtrate was purified by preparative TLC (60% ethyl acetate/hexanes) followed by recrystallization from acetonitrile to give the product as a white solid (10 mg, 19% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.23 (t, J = 6.0 Hz, 1H), 8.56 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.9, 2.2 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.25 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.15 – 7.05 (m, 2H), 4.60 (t, J = 7.5 Hz, 1H), 4.08 – 3.91 (m, 2H). LCMS-B RT 3.33 min; *m/z* 502.7 $[M+H]^+$.

Example 40: N-(2-(1-methyl-1H-pyrazol-4-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (40)



a) 2-(2-Iodophenyl)acetamide (A24)

2-Iodophenylacetic acid (2.62 g, 10.0 mmol), DCM (50 mL), oxalyl chloride (1.03 mL, 12.0 mmol) and DMF (0.05 mL) were stirred at room temperature. After one hour the mixture was concentrated in vacuo. The residue was dissolved in THF (50 mL) and a concentrated solution of aqueous ammonia (50 mL) added. The mixture was stirred for thirty min and concentrated in vacuo. The residue was slurried in water (100 mL), filtered, the collected solid washed with water (2 × 50 mL) and air dried to give the product as a tan solid (2.33 g,

89% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.90 – 7.86 (m, 1H), 7.40 – 7.33 (m, 2H), 7.03 – 6.96 (m, 1H), 5.42 (brs, 2H), 3.75 (s, 2H). LCMS-A RT 4.88 min; *m/z* 262.0 $[M+H]^+$.

b) 2-(2-(1-Methyl-1*H*-pyrazol-4-yl)phenyl)acetamide (A25)

2-(2-Iodophenyl)acetamide (A24) (261 mg, 1.00 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (312 mg, 1.50 mmol), cesium carbonate (977 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 5 mol% yield) and 1,4-dioxane (5 mL) were loaded into a microwave tube. The mixture was degassed with a stream of nitrogen bubbles and heated in the microwave (120 °C for 5 min). The mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and filtered through celite. The filtrate was concentrated in vacuo and separated by chromatography (12 g silica cartridge, 0-100% ethyl acetate/hexanes then 0-100% methanol/ethyl acetate) gave the product as a yellow oil (12 mg, 6% yield). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.75 – 7.72 (m, 1H), 7.58 (d, J = 0.8 Hz, 1H), 7.36 – 7.25 (m, 4H), 3.94 (s, 3H), 3.61 (s, 2H). LCMS-A RT 4.51 min; *m/z* 216.2 $[M+H]^+$.

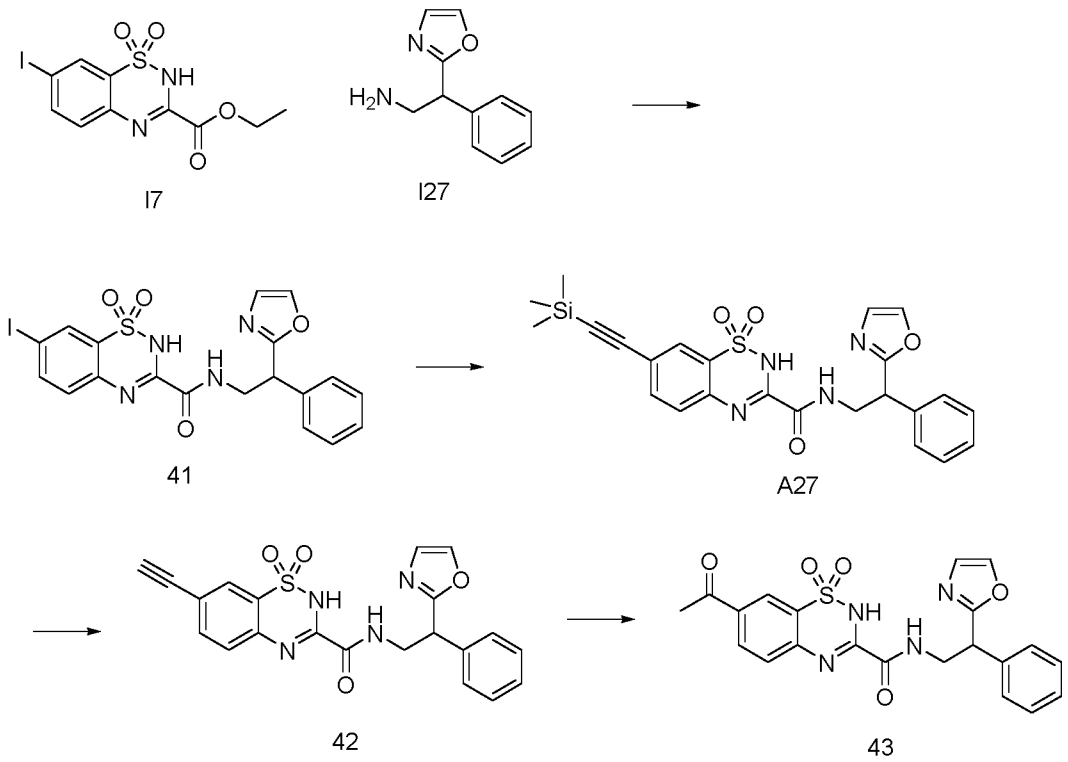
c) 2-(2-(1-Methyl-1*H*-pyrazol-4-yl)phenyl)ethan-1-amine bis(hydrochloride) (A26)

2-(2-(1-Methyl-1*H*-pyrazol-4-yl)phenyl)acetamide (A25) (12 mg, 0.056 mmol) and 1.0M borane in THF (0.50 mL, 0.50 mmol) were heated to 80 °C overnight. A 3M aq HCl solution (1 mL) was added and the mixture returned to 80 °C for thirty min then concentrated in vacuo. The residue was loaded onto a 0.5g SCX cartridge, washed with methanol (10 mL) and eluted with 7M ammonia in methanol (10 mL). The basic eluate was concentrated in vacuo, and the residue dissolved and concentrated twice from methanol. The residue was dissolved in 1,4-dioxane (0.5 mL) and 4.0M HCl/1,4-dioxane (0.5 mL) added. The mixture was concentrated in vacuo, the solid residue slurried in ether (2 mL), the ether decanted and the solid dried in vacuo to give the product as a white solid (18 mg). The material was carried forward without further purification. LCMS-B: RT 2.65 min; *m/z* 202.0 $[M+H]^+$ for the free base.

d) *N*-(2-(1-Methyl-1*H*-pyrazol-4-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (40)

Ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (12 mg, 0.047 mmol), 2-(2-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethan-1-amine bis(hydrochloride) (A26) (0.056 mmol at 100 % conversion), triethylamine (0.016 mL, 0.11 mmol) and ethanol (1 mL) were heated in the microwave (100 °C for 1 hour then 120 °C for 30 min). The mixture was separated by preparative TLC (100% ethyl acetate) to give the product as a white solid. LCMS-B RT 3.22 min; *m/z* 409.9 $[M+H]^+$; *m/z* 407.9 $[M-H]^-$.

Examples 41-43



a) 7-iodo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (41)

Ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (100 mg, 0.26 mmol), 2-(oxazol-2-yl)-2-phenylethan-1-amine (I27) (59 mg, 0.32 mmol) and ethanol (1 mL) were heated in the microwave (100 °C for 1h). The mixture was cooled to room temperature, the precipitate filtered and the collected solids washed with cold ethanol (3 × 1 mL) and air dried to give the product as a pink solid (67 mg). Further material (9 mg) was recovered by concentration of the combined filtrates and purification by chromatography (4g silica cartridge, 0-5% methanol/DCM). Total product: 74 mg, 54% yield. ^{1}H NMR (400 MHz, *d*-DMSO) δ 12.72 (br s, 1H), 9.32 – 9.20 (m, 1H), 8.12 – 7.99 (m, 3H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.24 (m, 5H), 7.20 (d, *J* = 0.9 Hz, 1H), 4.66 (t, *J* = 7.5 Hz, 1H), 4.05 – 3.94 (m, 1H), 3.91 – 3.81 (m, 1H). LCMS-B: rt 3.277 min; *m/z* 523.0 $[M+H]^+$.

b) *N*-(2-(oxazol-2-yl)-2-phenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A27)

7-iodo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (41) (72 mg, 0.14 mmol) was dissolved in NEt_3 (0.5 mL) and DMF (0.5 mL), CuI (1 mg, 5 mol% yield) and $Pd(PPh_3)_2Cl_2$ (5 mg, 5 mol% yield) were added and the mixture degassed with a stream of nitrogen bubbles. TMS-acetylene (0.057 mL, 0.41 mmol) was

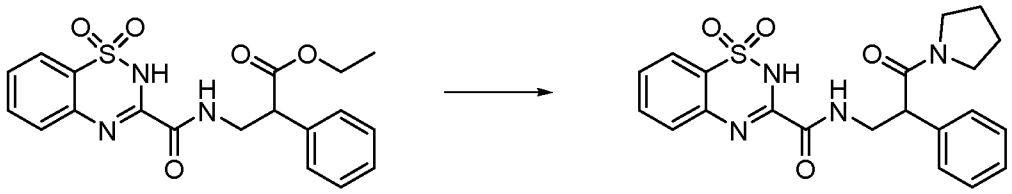
added and the mixture stirred overnight. The mixture was added to water (20 mL) and the pH adjusted to 5 with 3M HCl. The mixture was extracted with ethyl acetate (3 × 20 mL), the pooled ethyl acetate phases were washed with water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated in vacuo. Chromatography (4 g silica cartridge, 0-80% ethyl acetate/hexanes) gave the product as a pale yellow solid (27 mg, 40% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 9.86 (s, 1H), 8.38 (t, J = 6.5 Hz, 1H), 8.06 (d, J = 1.7 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.38 – 7.30 (m, 3H), 7.23 – 7.13 (m, 4H), 4.39 (t, J = 7.0 Hz, 1H), 4.08 (t, J = 6.7 Hz, 2H), 0.26 (s, 9H). LCMS-B RT 4.69 min; *m/z* 490.9 $[M-H]^-$.

c) 7-ethynyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (42)
N-(2-(oxazol-2-yl)-2-phenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A27) (26 mg, 0.053 mmol) was dissolved in 1:1 v/v THF: MeOH (4 mL) and 1.0M aq KOH (0.185 mL, 0.19 mmol) was added. The mixture was stirred for 45 min then Dowex 50X8 H^+-form (0.8 g) added. The mixture was filtered and the resin washed with methanol (5 mL). The pooled filtrates were concentrated in vacuo, the residue dried azeotropically by evaporation from ethanol (2 × 2 mL), rinsed with ether and dried in vacuo to give the product as a tan solid (17 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.30 (t, J = 5.9 Hz, 1H), 8.04 (d, J = 0.9 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.82 – 7.77 (m, 2H), 7.37 – 7.24 (m, 5H), 7.20 (d, J = 0.9 Hz, 1H), 4.67 (t, J = 7.6 Hz, 1H), 4.44 (s, 1H), 4.00 (ddd, J = 13.2, 7.6, 5.7 Hz, 1H), 3.92 – 3.83 (m, 1H). LCMS-A RT 5.63 min; *m/z* 421.1 $[M+H]^+$.

d) 7-acetyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (43)
Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (1.5 mg, 20 mol% yield), silver hexafluoroantimonate (0.8 mg, 20 mol% yield) and methanol (1 mL) were stirred at room temperature for two min. 7-ethynyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (42) (5.0 mg, 0.012 mmol) and milliQ water (0.5 mL) were added and the mixture stirred at 65°C overnight. The mixture was cooled to room temperature, diluted to 10 mL with methanol and mixed vigorously. Thiourea functionalised silica (SiliaMet thiourea, 1.1 mmol/g, 12 mg) was added and the mixture stirred vigorously at room temperature for one hour. The mixture was filtered through a syringe filter and the filtrate concentrated in vacuo. The residue was suspended in ethanol (20 mL) and again concentrated in vacuo. The residue was extracted with hot methanol (1 mL), the solvent was decanted and concentrated in vacuo. The residue was

dissolved in methanol (1 mL) and treated with thiol functionalised silica (SiliaMet thiol, 1.4 mmol/g, 10 mg) for thirty min. The mixture was filtered through a syringe filter and the filtrate concentrated in vacuo to give the product as a yellow solid (3.2 mg, 61% yield). LCMS-B: RT 3.17 min; *m/z* 438.8 $[M+H]^+$; *m/z* 436.8 $[M-H]^-$.

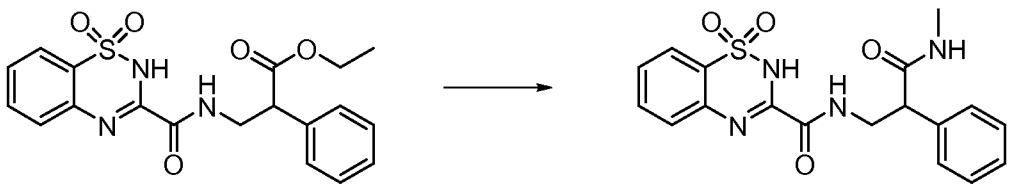
Example 44: N-(3-oxo-2-phenyl-3-(pyrrolidin-1-yl)propyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (44)



73 44

A suspension of ethyl 3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate (73) (0.025 g, 0.062 mmol) and pyrrolidine (0.010 mL, 0.125 mmol) in EtOH (0.1 mL) were irradiated in a microwave reactor at 100 °C for 30 min. The mixture was further treated with NEt_3 (0.017 mL, 0.125 mmol) and pyrrolidine (0.04 mL), then irradiated at 150 °C for 1 h. The crude material was loaded directly onto a column and purified by silica gel chromatography (Isolera Biotage 4 g, 0-100% EtOAc in petroleum benzine 40-60 °C, then 0-40% EtOAc in MeOH). The material was further purified by RP-HPLC (Grace Alltima, C8, 5 micron column, 250 mm × 22 mm ID, 30 – 100 % CH_3CN in water, 0.1 % TFA over 20 min) to give the product (0.003 g, 11% yield) as a white solid. LCMS-B: RT 3.465 min; *m/z* 427.2 $[M+H]^+$.

Example 45: N-(3-(methylamino)-3-oxo-2-phenylpropyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (45)

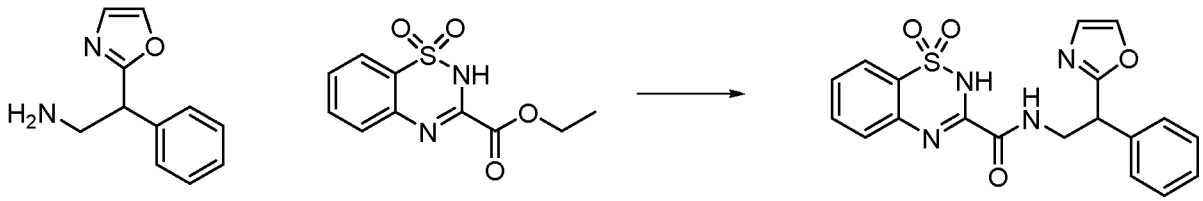


73 45

A suspension of ethyl 3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate (73) (0.025 g, 0.062 mmol), NEt_3 (0.017 mL, 0.125 mmol) and methylamine (0.016 mL, 0.125 mmol) in EtOH (0.1 mL) were irradiated in a microwave reactor at 150 °C for 30 min. The mixture was treated with additional equivalents of methylamine (0.016 mL, 0.125 mmol) and irradiated at 150 °C for a further 2 h. The

material was loaded directly onto a column and purified by RP-HPLC (Grace Alltima, C8, 5 micron column, 250 mm × 22 mm ID, 30 – 100 % CH_3CN in water, 0.1 % TFA over 20 min) to give the product (0.006 g, 25 % yield) as a white solid. ^{1}H NMR (400 MHz, MeOD): δ 7.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H), 7.60 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.53 (ddd, *J* = 8.3, 7.3, 1.1 Hz, 1H), 7.40 – 7.24 (m, 5H), 3.95 – 3.85 (m, 2H), 3.73 (td, *J* = 10.7, 9.3 Hz, 1H), 2.70 (s, 3H). LCMS-B RT 3.366 min; *m/z* 387.2 $[M+H]^+$.

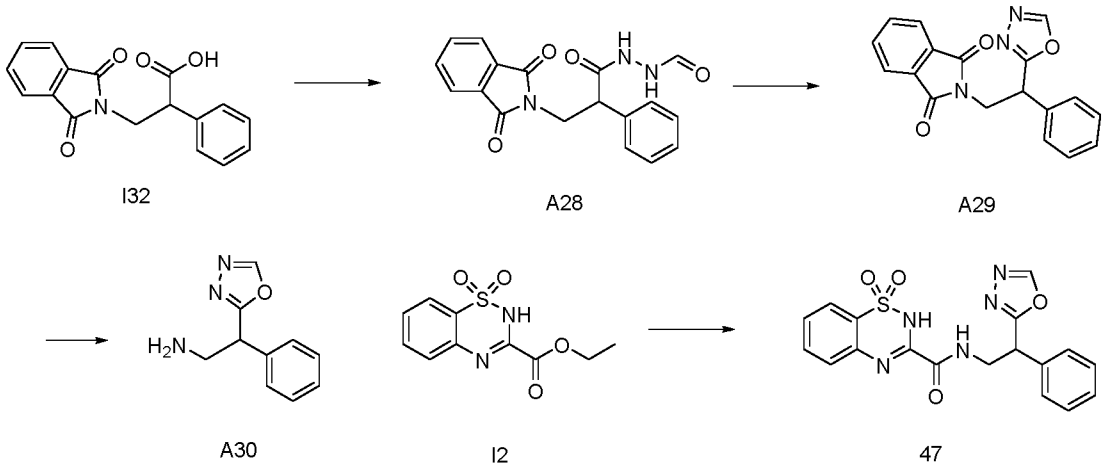
Example 46: N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (46)



I27 I2 46

To a suspension of the ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.063 g, 0.246 mmol) in EtOH (0.125 mL) was added 2-(oxazol-2-yl)-2-phenylethan-1-amine (I27) (0.051 g, 0.271 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction was cooled and the precipitate filtered. The solid was washed with EtOH (3 mL) and dried under vacuum to give the product (0.072 g, 74 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.62 (brs, 1H), 9.28 (t, *J* = 5.9 Hz, 1H), 8.05 (d, *J* = 0.8 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.55 – 7.49 (m, 1H), 7.36 – 7.30 (m, 2H), 7.30 – 7.24 (m, 3H), 7.20 (d, *J* = 0.8 Hz, 1H), 4.67 (t, *J* = 7.6 Hz, 1H), 4.00 (ddd, *J* = 13.2, 7.5, 5.7 Hz, 1H), 3.92 – 3.84 (m, 1H). LCMS-B: rt 3.495 min, *m/z* 397.2 $[M+H]^+$.

Example 47: N-(2-(1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (47)



a) 3-(1,3-dioxoisoindolin-2-yl)-*N'*-formyl-2-phenylpropanehydrazide (A28)

To a solution of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (0.250 g, 0.847 mmol), EDCI (0.194 g, 1.016 mmol) and formic hydrazine (0.051 g, 0.847 mmol) in DCM (10 mL) was added DMAP (0.124 g, 1.016 mmol). This was allowed to stir at r.t. for 17 h, upon which time the mixture was treated with 1M HCl (10 mL). The layers were separated and the organic portion concentrated *in vacuo* to give the product (0.464 g, >100% yield) as a white solid. The material was carried forward without further purification. LCMS:B: rt. 3.346 min, *m/z* 336.1 $[M-H]^-$.

b) 2-(2-(1,3,4-oxadiazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A29)

To a suspension of Burgess reagent (0.775 g, 3.253 mmol) in THF (4 mL) was added 3-(1,3-dioxoisoindolin-2-yl)-*N'*-formyl-2-phenylpropanehydrazide (28) (0.439 g, 1.301 mmol). This was irradiated in a microwave reactor at 140 °C for 15 min. Upon cooling, the mixture was loaded directly onto silica for purification. The crude material was purified by silica gel chromatography (Isolera Biotage 24g, 0-100% EtOAc in petroleum benzine 40-60 °C, then 0-40% MeOH in EtOAc). Product-containing fractions were combined and concentrated *in vacuo* to give the product (0.095 g, 23% yield) as a white solid. LCMS-B: rt. 3.558 min, *m/z* 320.2 $[M+H]^+$.

c) 2-(1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine (A30)

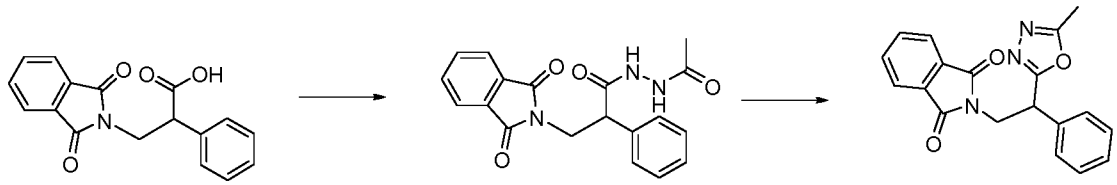
To a suspension of 2-(2-(1,3,4-oxadiazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A29) (0.045 g, 0.141 mmol) in EtOH (2 mL) was added hydrazine hydrate (50-60 %, 0.026 mL, 0.423-0.508 mmol). The solution was heated to 80 °C for 3h, upon which time it was cooled and the precipitate filtered. The precipitate was washed with a portion of cold EtOH (5 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo* to give the

product (0.030 g, >100% yield) as a yellow semi-solid. The material was carried forward without further purification. LCMS-B: rt. 3.411; no product ion detectable.

d) *N*-(2-(1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (47)

To a suspension of 2-(1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine (A30) (0.030 g, 0.111 mmol) in EtOH (0.5 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.020 g, 0.079 mmol). This was irradiated in a microwave reactor at 100 °C for 30 min. The solution was cooled and the EtOH evaporated. The residue was partitioned between EtOAc (3 mL) and 1M HCl (3 mL). The organic layer was separated and washed with a further portion of 1M HCl (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The material was purified by RP-HPLC (Grace Alltima, C8, 5 micron column, 250 mm × 22 mm ID, 30 – 100 % CH_3CN in water, 0.1 % TFA over 20 min) to give the product (0.003 g, 10% yield) as a white solid. LCMS-B: rt. 3.420 min, *m/z* 398.1 $[M+H]^+$.

Example 48: N-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (48)



a) *N'*-acetyl-3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanehydrazide (A31)

To a solution of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (0.500 g, 1.693 mmol), EDCI (0.387 g, 2.032 mmol) and formic hydrazine (0.125 g, 1.693 mmol) in DCM (20 mL) was added DMAP (0.248 g, 2.032 mmol). This was allowed to stir at r.t. for 17h, upon which time the mixture was treated with 1M HCl (20 mL). The layers were separated and the organic portion concentrated *in vacuo* to give the product (0.680 g, >100% yield) as a white solid. The material was carried forward without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ 10.15 (d, *J* = 2.0 Hz, 1H), 9.77 (d, *J* = 1.9 Hz, 1H), 7.81 – 7.78 (m, 4H), 7.33 – 7.28 (m, 2H), 7.27 – 7.16 (m, 3H), 4.25 (dd, *J* = 8.9, 7.1 Hz, 1H), 4.08 (dd, *J* = 13.7,

9.0 Hz, 1H), 3.96 (dd, *J* = 13.7, 7.2 Hz, 1H), 1.79 (s, 3H). LCMS-B: rt. 3.324, *m/z* 350.1 [M-H]$^-$.

b) 2-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A32)

To a suspension of Burgess reagent (1.153 g, 4.838 mmol) in THF (7 mL) was added *N'*-acetyl-3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanehydrazide (A31) (0.680 g, 1.935 mmol). This was irradiated in a microwave reactor at 140 °C for 15 min. Upon cooling, the crude material was loaded onto silica gel and purified by silica gel chromatography (Isolera Biotage, 40 g SiO_2 Cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C). The fractions containing the desired product were collected and concentrated *in vacuo* to yield the product (0.289 g, 45% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.87 – 7.79 (m, 4H), 7.35 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 4.76 (t, *J* = 8.0 Hz, 1H), 4.28 (dd, *J* = 13.9, 7.7 Hz, 1H), 4.21 (dd, *J* = 13.9, 8.3 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 2.43 (s, 3H). LCMS-B: rt. 3.588, *m/z* 334.2 [M+H]$^+$.

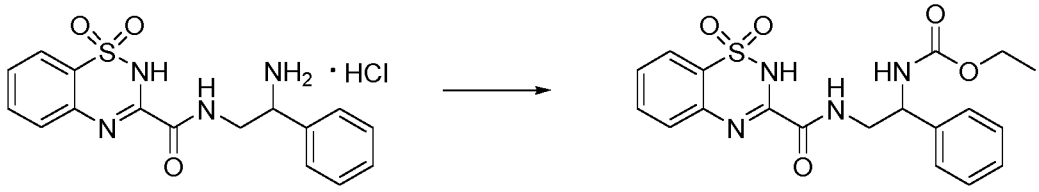
c) 2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine (A33)

To a suspension of 2-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A32) (0.285 g, 0.855 mmol) in EtOH (12 mL) was added hydrazine hydrate (50-60 %, 0.160 mL, 2.57-3.08 mmol). The solution was heated to 80 °C for 3h, upon which time it was cooled and the precipitate filtered. The precipitate was washed with a portion of cold EtOH (5 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo* to give the product (0.174 g, >100% yield) as a yellow oil. . The material was carried forward without further purification. LCMS-B: rt. 3.121; no product ion detectable.

d) *N*-(2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (48)

To a suspension of 2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-phenylethan-1-amine (A33) (0.100 g, 0.492 mmol) in EtOH (0.25 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.114 g, 0.447 mmol). This was irradiated in a microwave reactor at 100 °C for 30 min. The solution was cooled and the precipitate filtered. The resulting solid was washed with further portions of EtOH (3 x 3 mL) and dried to reveal the desired product (0.131 g, 71% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.60 (brs, 1H), 9.30 (brs, 1H), 7.86 – 7.80 (m, 1H), 7.73 (dt, *J* = 14.4, 7.7 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.42 – 7.29 (m, 5H), 4.72 (t, *J* = 7.5 Hz, 1H), 4.00 (ddd, *J* = 13.6, 8.0, 5.8 Hz, 1H), 3.87 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.44 (s, 3H). LCMS-B: rt. 3.408 min, *m/z* 412.2 [M+H]$^+$.

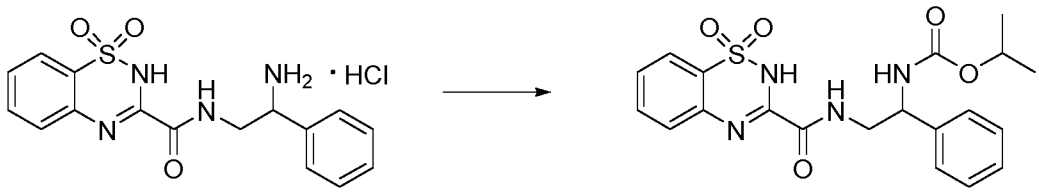
Example 49: Ethyl (2-(1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl)carbamate (49)



I41 49

To a suspension of *N*-(2-amino-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I41) (0.025 g, 0.066 mmol) in DCM (0.5 mL) was added NEt_3 (0.019 mL, 0.135 mmol), followed 10 min later by ethyl chloroformate (0.007 mL, 0.069 mmol) dropwise. This was allowed to stir at r.t. for 17 h upon which time the reaction was diluted with DCM (1 mL), washed with 1M HCl (1 mL), saturated Na_2CO_3 (1 mL), brine (1 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to reveal the product (0.022 g, 80% yield) as a white solid. LCMS-B: r.t. 3.474 min; *m/z* 417.2 $[M+H]^+$.

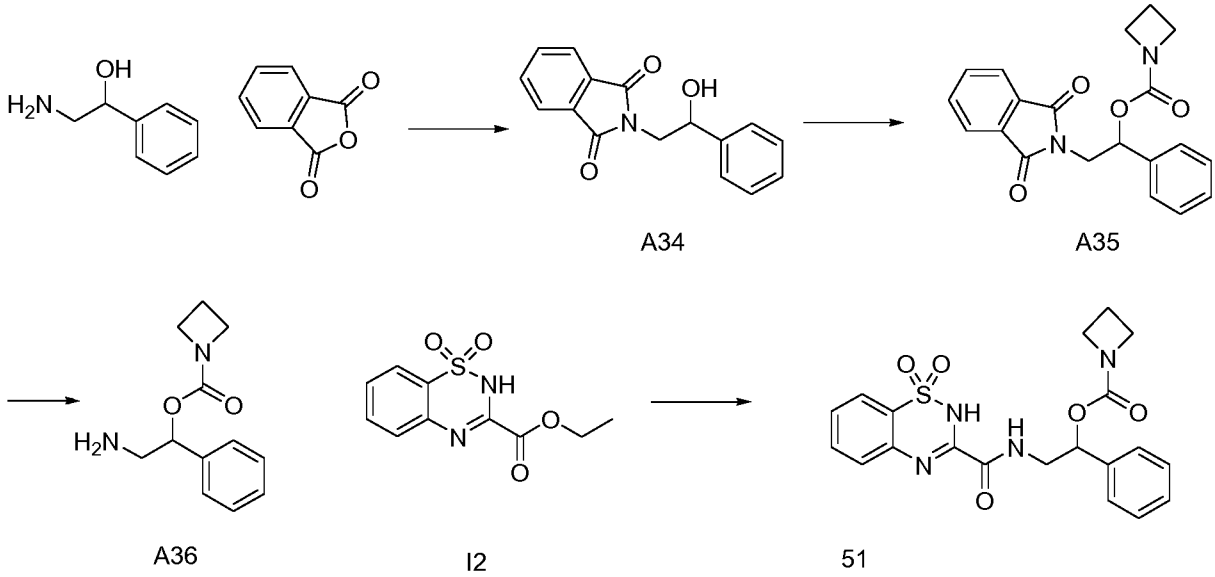
Example 50: Isopropyl (2-(1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl) carbamate (50)



I41 50

To a suspension of *N*-(2-amino-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I41) (0.020 g, 0.053 mmol) in DCM (0.5 mL) was added NEt_3 (0.015 mL, 0.111 mmol), followed 10 min later by a 1M solution of *iso*-propyl chloroformate (0.061 mL, 0.064) dropwise. This was allowed to stir at r.t. for 2 h upon which the reaction was diluted with DCM (1 mL) and washed with 1M HCl (1 mL), saturated Na_2CO_3 (1 mL), brine (1 mL) then dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by RP-HPLC (Grace Alltima, C8, 5 micron column, 250 mm × 22 mm ID, 30 – 100 % CH_3CN in water, 0.1 % TFA over 30 min) to give the product (0.002 g, 7% yield) as a white solid. LCMS-B: r.t. 3.519 min; *m/z* 429.2 $[M-H]^-$.

Example 51: 2-(1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl azetidine-1-carboxylate (51)



a) 2-(2-hydroxy-2-phenylethyl)isoindoline-1,3-dione (A34)

Phthalic anhydride (2.159 g, 14.579 mmol) and 2-amino-1-phenylethan-1-ol (2.000 g, 14.579 mmol) were combined in a microwave vessel and irradiated at 150 °C for 15 min. The resulting residue was dried under vacuum to reveal the desired product (3.600 g, 92% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.89 – 7.81 (m, 4H), 7.41 – 7.32 (m, 4H), 7.30 – 7.23 (m, 1H), 5.66 (brs, 1H), 4.93 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.77 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.64 (dd, *J* = 13.6, 4.8 Hz, 1H). LCMS-B: rt 3.567 min; *m/z* 266.1 $[M-H]^-$.

b) 2-(1,3-dioxoisoindolin-2-yl)-1-phenylethyl azetidine-1-carboxylate (A35)

To a solution of 2-(2-hydroxy-2-phenylethyl)isoindoline-1,3-dione (A34) (0.400 g, 1.497 mmol) in dry toluene (5 mL), under an atmosphere of N_2, was added CDI (0.291 g, 1.796 mmol). The mixture was allowed to stir at r.t. for 3h, upon which dry THF (2 mL) was added. The solution was stirred for a further hour, upon which azetidine·HCl (0.280 g, 2.993 mmol) was added. The mixture was left to stir overnight. EtOAc was added (10 mL) and the mixture was then washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo.* This crude material was purified by column chromatography (Isolera Biotage, 40 g SiO_2 Cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C), with the fractions containing the desired material combined and concentrated *in vacuo* to reveal the desired product (0.235 g, 45% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.00 – 7.77 (m, 4H), 7.50 – 7.24 (m, 5H), 5.82 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.03 – 3.92* (m, 2H), 4.05 – 3.88* (m, 1H), 3.81 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.76 – 3.58 (m, 2H), 2.23 – 2.04 (m, 2H). *overlapping peaks. LCMS-B: rt. 3.721; *m/z* 349.1 $[M-H]^-$

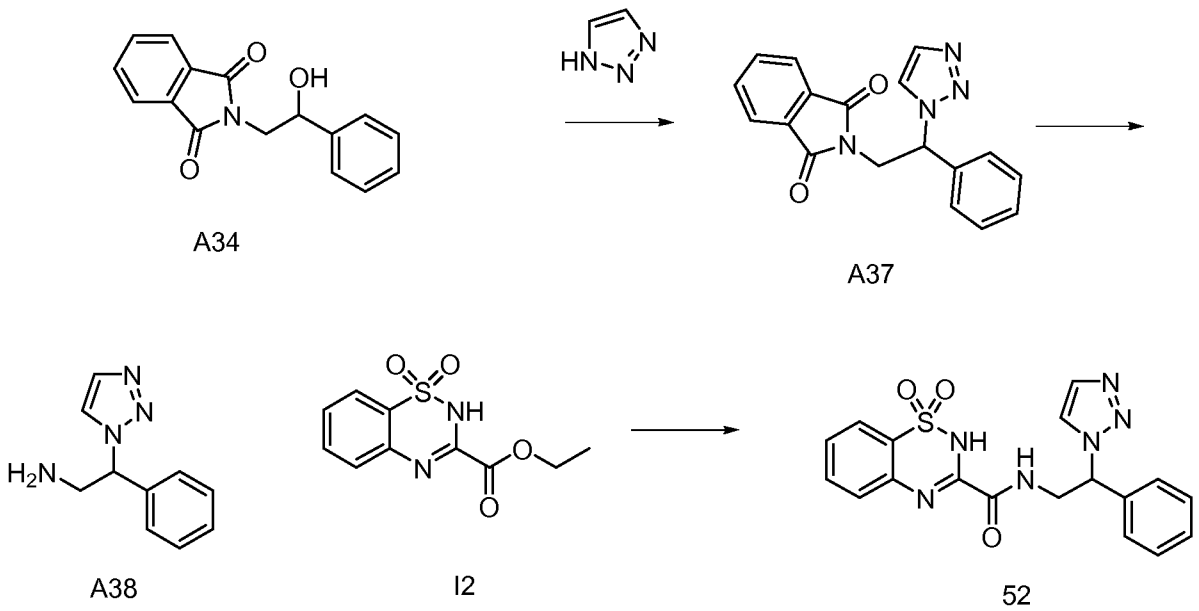
c) 2-amino-1-phenylethyl azetidine-1-carboxylate (A36)

To a suspension of 2-(1,3-dioxoisoindolin-2-yl)-1-phenylethyl azetidine-1-carboxylate (A35) (0.230 g, 0.656 mmol) in EtOH (12 mL) was added hydrazine hydrate (50-60 %, 0.123 mL, 1.97-2.36 mmol). The solution was heated to 80 °C for 3h, upon which time it was cooled and the precipitate filtered. The precipitate was washed with a portion of cold EtOH (5 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo* to reveal the product (0.122 g, 84% yield) as an oil. The material was carried forward without further purification. LCMS-B: rt. 3.079; no product ion detectable.

d) 2-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl azetidine-1-carboxylate (51)

To 2-amino-1-phenylethyl azetidine-1-carboxylate (A36) (0.050 g, 0.227 mmol) in EtOH (0.125 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.048 g, 0.189 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction was cooled and the solvent evaporated. The crude material was purified by silica gel chromatography (Isolera Biotage, 12 g SiO_2 Cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C). The fractions were combined and concentrated to dryness. The material was dissolved in a 1:1:1 mixture of THF: MeOH: 2M NaOH (3 mL) and allowed to stir overnight at r.t. The volatile solvents were removed and the aqueous layer was extracted with EtOAc (3 x 3 mL). This material was purified by column chromatography (Isolera Biotage, 12 g SiO_2 Cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C, then 0-40% MeOH in EtOAc). The fractions containing the desired product were combined and concentrated *in vacuo* to reveal the product (0.015 g, 19% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.69 (brs, 1H), 9.27 (brs, 1H), 7.88 – 7.65 (m, 3H), 7.55 – 7.47 (m, 1H), 7.45 – 7.27 (m, 5H), 5.80 (dd, J = 8.7, 4.0 Hz, 1H), 4.12 – 3.95* (m, 2H), 3.91 – 3.75* (m, 2H), 3.71 – 3.61* (m, 2H), 2.16 (p, J = 7.8, 7.8, 7.7, 7.7 Hz, 2H). *overlapping peaks. LCMS-B: rt. 3.521; *m/z* 427.1 $[M-H]^-$.

Example 52: N-(2-phenyl-2-(1H-1,2,3-triazol-1-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (52)



a) 2-(2-phenyl-2-(1*H*-1,2,3-triazol-1-yl)ethyl)isoindoline-1,3-dione (A37)
2-(2-Hydroxy-2-phenylethyl)isoindoline-1,3-dione (A34) (0.500 g, 1.871 mmol), 1,2,3-triazole (0.130 mL, 2.245 mmol) and triphenylphosphine (0.589 g, 2.245 mmol), under an atmosphere of nitrogen, were dissolved in THF (25 mL) and cooled to 0 °C. DIAD (0.422 mL, 2.245 mmol) was added dropwise over 10 min. The reaction was sealed, allowed to warm to r.t., then stirred overnight. Water (30 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage, 40 g, 0-100% EtOAc in petroleum benzine 40-60 °C) to yield the product (0.137 g, 23% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J* = 1.1 Hz, 1H), 7.86 – 7.81 (m, 4H), 7.70 (d, *J* = 1.0 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.43 – 7.33 (m, 3H), 6.20 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.60 (dd, *J* = 14.2, 9.2 Hz, 1H), 4.39 (dd, *J* = 14.2, 6.1 Hz, 1H).

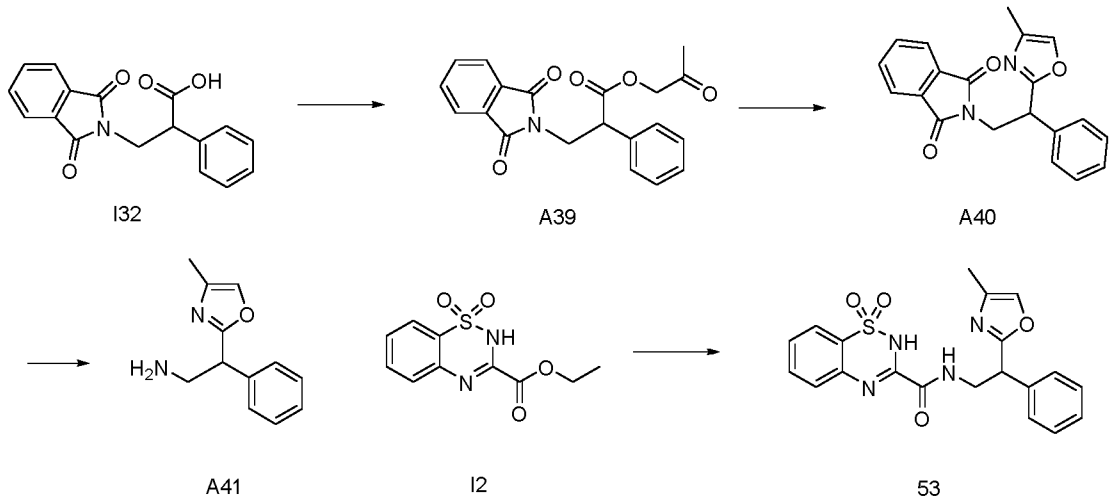
b) 2-phenyl-2-(1*H*-1,2,3-triazol-1-yl)ethan-1-amine (A38)
To a suspension of 2-(2-phenyl-2-(1*H*-1,2,3-triazol-1-yl)ethyl)isoindoline-1,3-dione (A37) (0.137 g, 0.430 mmol) in EtOH (12 mL) was added hydrazine hydrate (50-60 %, 0.080 mL, 1.29-1.55 mmol). The solution was heated to 80 °C for 3 h, upon which time it was cooled and the precipitate filtered. The precipitate was washed with a portion of cold EtOH (5 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo*. The material was suspended in cold EtOH (3 mL) and re-filtered. The filtrate was concentrated *in vacuo*

to reveal the product (0.060 g, 74% yield) as a yellow semi-solid. The material was carried forward without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, *J* = 1.0 Hz, 1H), 7.76 (d, *J* = 1.0 Hz, 1H), 7.39 – 7.27 (m, 5H), 5.69 (dd, *J* = 9.1, 5.4 Hz, 1H), 3.48 *partially obscured by solvent (dd, J = 13.5, 9.2 Hz, 2H), 3.26 *partially obscured by solvent (dd, *J* = 13.5, 5.4 Hz, 2H).

c) *N*-(2-phenyl-2-(1*H*-1,2,3-triazol-1-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (52)

To 2-phenyl-2-(1*H*-1,2,3-triazol-1-yl)ethan-1-amine (A38) (0.060 g, 0.319 mmol) in EtOH (0.125 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.068 g, 0.266 mmol). This was irradiated in a microwave reactor at 100 °C for 30 min. The solution was cooled, then concentrated *in vacuo*. The residue was taken up in EtOAc (2 mL) and the resulting precipitate filtered. The organic layer was washed with 1 M HCl (2 mL), water (2 mL), brine (2 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude solid was purified by silica gel chromatography (Isolera Biotage 12 g, 0-100% EtOAc in petroleum benzine 40-60 °C). Product-containing fractions were combined and concentrated *in vacuo* to give the product (0.025 g, 24% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.65 (s, 1H), 9.51 – 9.42 (m, 1H), 8.38 (d, *J* = 1.1 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.40 (d, *J* = 2.3 Hz, 2H), 7.38 – 7.33 (m, 1H), 6.16 (dd, *J* = 9.0, 5.6 Hz, 1H), 4.33 (ddd, *J* = 13.7, 9.0, 6.6 Hz, 1H), 4.06 (dt, *J* = 13.7, 5.5, 5.5 Hz, 1H). LCMS-B: rt. 3.408 min; *m/z* 397.1 $[M+H]^+$.

Example 53: N-(2-(4-methyloxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (53)



a) 2-oxopropyl 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoate (A39)
To a solution of 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoic acid (I32) (1.000 g, 3.38 mmol) in THF (5 mL), under an atmosphere of N_2, was added NEt_3 (0.566 mL, 4.06 mmol). The reaction mixture was allowed to stir for 10 min, upon which time it was cooled to 0 °C, and chloroacetone (0.419 mL, 5.08 mmol) was added slowly. The mixture was allowed to warm to r.t. and stirred overnight. The formed precipitate was removed by filtration and the filtrate concentrated *in vacuo* to reveal the product (1.062 g, 89% yield). LCMS-B: rt 3.290 min; no product ion detected.

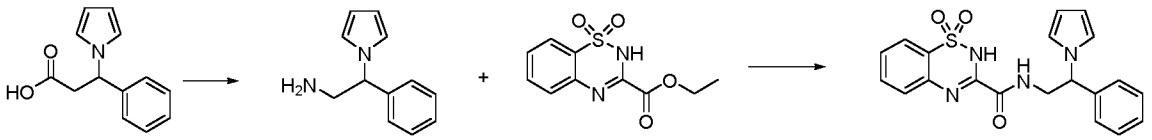
b) 2-(2-(4-methyloxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A40)
To a solution of 2-oxopropyl 3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanoate (A39) (1.062 g, 3.02 mmol) in THF (5 mL), under an atmosphere of nitrogen, was added $BF_3{\cdot}OEt_2$ (0.746 mL, 6.05 mmol) followed by acetamide (0.893 g, 15.1 mmol) The mixture was sealed then irradiated in a CEM microwave reactor at 150 °C for 2 h. The reaction mixture was cooled and the solid precipitate filtered. The solid was washed with EtOAc (10 mL) and the combined organics were concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage, 40 g Si Cartridge, 0-80% EtOAc in petroleum benzine 40-60 °C). Fractions containing suspected product, eluting at ~50 % EtOAc, were collected and concentrated *in vacuo*, to yield the product (0.060 g, 6% yield) as a white solid. LCMS-B: r.t. 3.345 min; *m/z* 333.1 $[M+H]^+$.

c) 2-(4-methyloxazol-2-yl)-2-phenylethan-1-amine (A41)
To a suspension of 2-(2-(4-methyloxazol-2-yl)-2-phenylethyl)isoindoline-1,3-dione (A40) (0.060 g, 0.18 mmol) in EtOH (4 mL) was added hydrazine hydrate (50-60 %, 0.034 mL, 0.55-0.65 mmol). The solution was heated at 80 °C for 17 h. A further portion of hydrazine hydrate (50-60 %, 0.034 mL, 0.55-0.65 mmol) was added and the solution allowed to stir for an additional 2 h, upon which time it was cooled and the resulting precipitate filtered. The precipitate was washed with a portion of cold EtOH (5 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo* to reveal the product (0.022 g, 60% yield). The crude material was carried forward without any further purification. LC-MS: (LCMS-B) r.t. 2.913 min, *m/z* 203.1 $[M+H]^+$.

d) *N*-(2-(4-methyloxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (53)
To 2-(4-methyloxazol-2-yl)-2-phenylethan-1-amine (A41) (0.022 g, 0.109 mmol) in EtOH (0.125 mL) was added ethyl 2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2)

(0.021 g, 0.084 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was cooled and EtOH removed *in vacuo*. The mixture was taken up in EtOAc (3 mL) and washed with 1 M HCl (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The material was further purified by silica gel chromatography (Isolera Biotage, 4 g, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the desired product (0.004 g, 12% yield) as a white solid. ^{1}H NMR (400 MHz, MeOD): δ 7.94 – 7.85 (m, 1H), 7.76 – 7.66 (m, 1H), 7.65 – 7.57 (m, 1H), 7.58 – 7.49 (m, 2H), 7.41 – 7.21 (m, 5H), 4.50 – 4.43 (m, 1H, partially overlapping with solvent), 4.10 – 4.00 (m, 1H), 4.00 – 3.90 (m, 1H), 2.16 (s, 3H), exchangeable N*H* protons not observed. LCMS-B: rt 3.194 min; *m/z* 411.1 $[M+H]^+$.

Example 54: N-(2-phenyl-2-(1H-pyrrol-1-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (54)



A42 I2 54

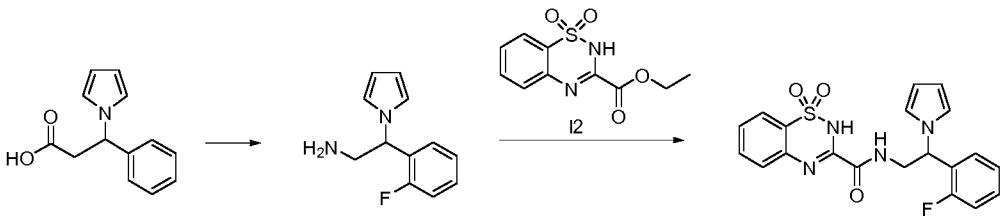
a) 2-phenyl-2-(1*H*-pyrrol-1-yl)ethan-1-amine (A42)

To a solution of 3-phenyl-3-(1H-pyrrol-1-yl)propanoic acid (0.300 g, 1.39 mmol) in toluene (6 mL) under an atmosphere of nitrogen was added triethylamine (0.389 mL, 2.79 mmol) and DPPA (0.603 mL, 2.79 mmol). The solution was heated to 80 °C, when the evolution of nitrogen began immediately. After 3 h at this temperature, the reaction mixture was cooled to r.t., a 2 M aq. NaOH solution (5 mL) was added and the mixture heated to 80 °C and left to stir overnight. Water (5 mL) was added and the reaction mixture was heated to 110 °C, then stirred for a further 17 h. The reaction mixture was concentrated *in vacuo* and the crude material taken up in minimal MeOH and loaded onto a 10 g SCX cartridge. The cartridge was washed with MeOH (90 mL), then stripped with a 1M solution of methanolic ammonia (90 mL). The ammonia washes were concentrated *in vacuo* to give the desired product (0.078 g, 30% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (m, 3H), 7.25 – 7.16 (m, 2H), 6.84 (t, *J* = 2.2 Hz, 2H), 6.27 (t, *J* = 2.1 Hz, 2H), 5.10 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.53 – 3.34 (m, 2H), exchangeable N*H* protons not observed. LCMS-B: rt. 0.766 min, product mass ion not present.

b) *N*-(2-phenyl-2-(1*H*-pyrrol-1-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (54)

To 2-phenyl-2-(1*H*-pyrrol-1-yl)ethan-1-amine (A42) (0.078 g, 0.42 mmol) in EtOH (0.125 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.071 g, 0.28 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was cooled and the resulting precipitate was filtered. The solid was washed with a portion of EtOH (2 mL) and then dried under vacuum to give the desired product (0.069 g, 63% yield) as a grey solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.92 – 12.40 (brs, 1H), 9.39 – 9.34 (dd, *J* = 6.6, 5.1 Hz, 1H), 7.88 – 7.79 (m, 2H), 7.76 – 7.68 (m, 1H), 7.57 – 7.47 (m, 1H), 7.39 – 7.21 (m, 5H), 6.95 – 6.90 (t, *J* = 2.1 Hz, 2H), 6.05 – 5.98 (t, *J* = 2.1 Hz, 2H), 5.64 – 5.55 (dd, *J* = 9.3, 5.7 Hz, 1H), 4.20 – 4.05 (ddd, *J* = 13.7, 9.4, 6.7 Hz, 1H), 4.00 – 3.84 (dt, *J* = 13.8, 5.5 Hz, 1H). LCMS-B: r.t. 3.305 min, *m/z* 395.1 $[M+H]^+$.

Example 55: N-(2-(2-fluorophenyl)-2-(1H-pyrrol-1-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (55)



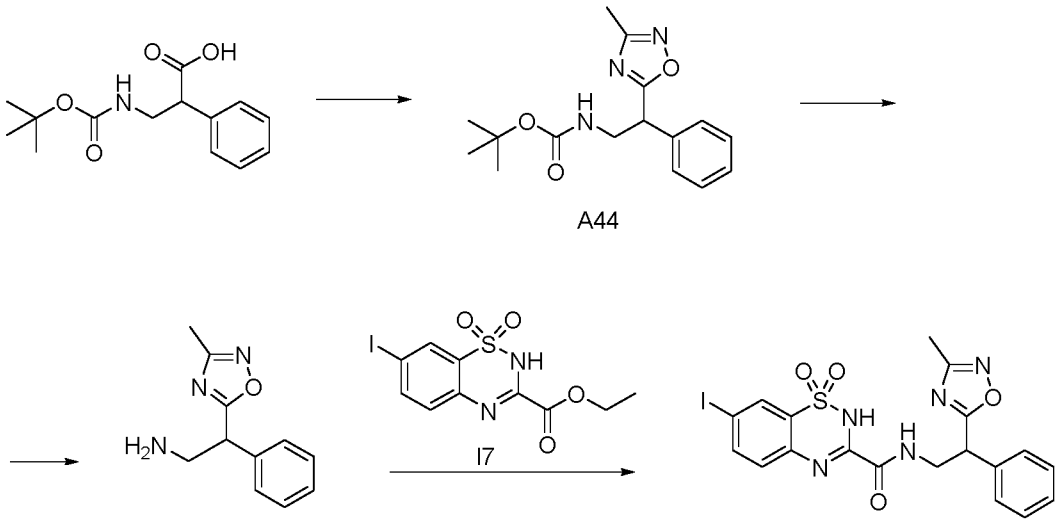
a) 2-(2-fluorophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-amine (A43)

To a solution of 3-phenyl-3-(1*H*-pyrrol-1-yl)propanoic acid (0.300 g, 1.29 mmol) in toluene (6 mL) under an atmosphere of nitrogen was added triethylamine (0.359 mL, 2.57 mmol) and DPPA (0.556 mL, 2.572 mmol). The solution was heated to 80 °C, whereby the evolution of nitrogen began immediately. After 3 h at this temperature, the reaction mixture was cooled to r.t., a 2 M aq. NaOH solution (5 mL) was added and the mixture heated to 80 °C and left to stir overnight. Water (5 mL) was added and the reaction mixture was heated to 110 °C, then stirred for a further 17 h. The reaction mixture was concentrated *in vacuo* and the crude material taken up in minimal MeOH and loaded onto a 10 g SCX cartridge. The cartridge was washed with MeOH (90 mL), then stripped with a solution of methanolic ammonia (90 mL). The ammonia washes were concentrated *in vacuo* to reveal the desired product (0.135 g, 51% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.10 (m, 1H), 7.01 – 6.87 (m, 3H), 6.73 (t, *J* = 2.1 Hz, 2H), 6.13 (t, *J* = 2.1 Hz, 2H), 5.28 (dd, *J* = 9.1, 5.4 Hz, 1H), 3.40 – 3.18 (m, 2H), exchangeable NH_2 protons not observed. LCMS-B: rt. 0.774 min, product mass ion not present.

b) *N*-(2-(2-fluorophenyl)-2-(1*H*-pyrrol-1-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (55)

To 2-(2-fluorophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-amine (A43) (0.135 g, 0.661 mmol) in EtOH (0.250 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I2) (0.112 g, 0.441 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction mixture was cooled and the resulting precipitate was filtered. The solid was washed with a portion of EtOH (2 mL) and then dried under vacuum to reveal the desired product (0.109 g, 60% yield) as a grey solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.92 – 12.28 (brs, 1H), 9.49 – 9.39 (t, *J* = 5.9 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.76 – 7.69 (m, 1H), 7.56 – 7.49 (m, 1H), 7.42 – 7.28 (m, 2H), 7.27 – 7.16 (m, 2H), 6.94 – 6.86 (t, *J* = 2.2 Hz, 2H), 6.04 – 5.99 (t, *J* = 2.1 Hz, 2H), 5.96 – 5.88 (dd, J = 9.0, 6.0 Hz, 1H), 4.20 – 4.05 (ddd, *J* = 13.6, 9.2, 6.6 Hz, 1H), 4.00 – 3.89 (dt, *J* = 13.7, 5.6 Hz, 1H). LCMS-B: r.t. 3.316 min, *m/z* 413.1 $[M+H]^+$.

Example 56: N-(2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (56)



a) *tert*-butyl (2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl)carbamate (A44)

To a solution of 3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid (1.00 g, 3.7 mmol) in DMF (10 mL), under an atmosphere of nitrogen, was added EDCI.HCl (0.723 g, 3.7 mmol) and HOBt (0.509 g, 3.769 mmol). After 10 min, *N*-hydroxyacetimidamide (0.279 g, 3.7 mmol) was added. The mixture was allowed to stir at r.t. for 2 h, upon which time the mixture was heated to 80 °C and allowed to stir for 17 h. The reaction mixture was quenched by pouring it into a sat. aq. Na_2CO_3 solution (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were washed with water (200

mL), brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by column chromatography (Isolera Biotage 40 g, 0-50% EtOAc in petroleum benzine 40-60 °C). Fractions containing the product were combined and concentrated *in vacuo* to reveal the product (0.475 g, 42% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.21 (m, 5H, partially obscured by solvent), 4.95 (s, 1H), 4.60 – 4.44 (m, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.42 (s, 9H). LCMS-F: r.t. 8.968 min, *m/z* 304.0 $[M+H]^+$, 204.0 $[M\text{-}Boc+H]^+$.

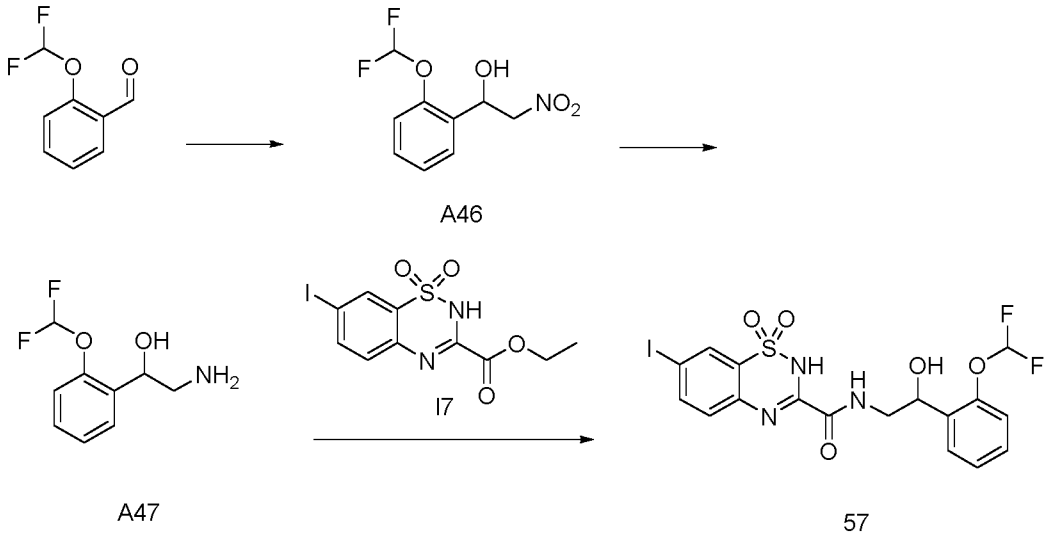
b) 2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethan-1-amine (A45)

To *tert*-butyl (2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl)carbamate (A44) (0.475 g, 1.57 mmol), in DCM (12.5 mL), was added TFA (1.25 mL). The mixture was stirred overnight at r.t. and then diluted with DCM (10 mL), and basified with 2 M NaOH (10 mL). The layers were separated and the aqueous layer washed with further portions of DCM (2 x 10 mL). The organics were combined, washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to reveal the product (0.299 g, 94% yield) as a clear oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.36 – 7.14 (m, 5H), 4.16 (dd, *J* = 7.8, 6.6 Hz, 1H), 3.35 (dd, *J* = 13.1, 7.7 Hz, 1H), 3.20 (dd, J = 13.1, 6.6 Hz, 1H), 2.31 (s, 3H), exchangeable NH_2 protons not observed.

c) *N*-(2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (56)

Ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (0.050 g, 0.13 mmol) and 2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethan-1-amine (A45) (0.032 g, 0.16 mmol) were suspended in EtOH (0.2 mL), then irradiated in a microwave reactor at 120 °C for 60 min. The mixture was allowed to cool and the precipitate filtered. The precipitate was washed with EtOH (2 mL). The filtrate was concentrated *in vacuo* then purified by column chromatography (Grace Biotage, 12 g SiO_2, 0-100 % EtOAc in petroleum benzines 40-60 °C). Fractions containing the desired product were combined and concentrated *in vacuo* to reveal the product (0.006 g, 9% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.73 (s, 1H), 9.40 (brs, 1H), 8.28 – 7.93 (m, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.41 – 7.27 (m, 5H), 4.83 (t, *J* = 7.5 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.89 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.33 (s, 3H). LC-MS (LCMS-B) r.t. 3.331 min; *m/z* 537.7 $[M+H]^+$.

Example 57: N-(2-(2-(difluoromethoxy)phenyl)-2-hydroxyethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (57)



a) 1-(2-(difluoromethoxy)phenyl)-2-nitroethan-1-ol (A46)

To a solution of 2-(difluoromethoxy)benzaldehyde (2.0 g, 11.7 mmol) in MeOH (25 mL) were added nitromethane (1.88 mL, 34.9 mmol) and sodium methoxide (0.75 g, 13.9 mmol). The solution was allowed to stir for 2 h, then quenched with the addition of 2 M HCl (10 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (30 mL x 2), dried (Na_2SO_4) and concentrated *in vacuo* to reveal the product (2.617 g, 97% yield) as an orange oil. The material was carried forward without any further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.32 – 7.20 (m, 1H), 7.14 (ddd, *J* = 8.2, 3.0, 1.1 Hz, 1H), 6.61 (t, *J* = 73.1 Hz, 1H), 5.76 (dd, *J* = 9.1, 3.0 Hz, 1H), 4.85 (dd, *J* = 7.0, 1.0 Hz, 1H), 4.67 – 4.48 (m, 2H).

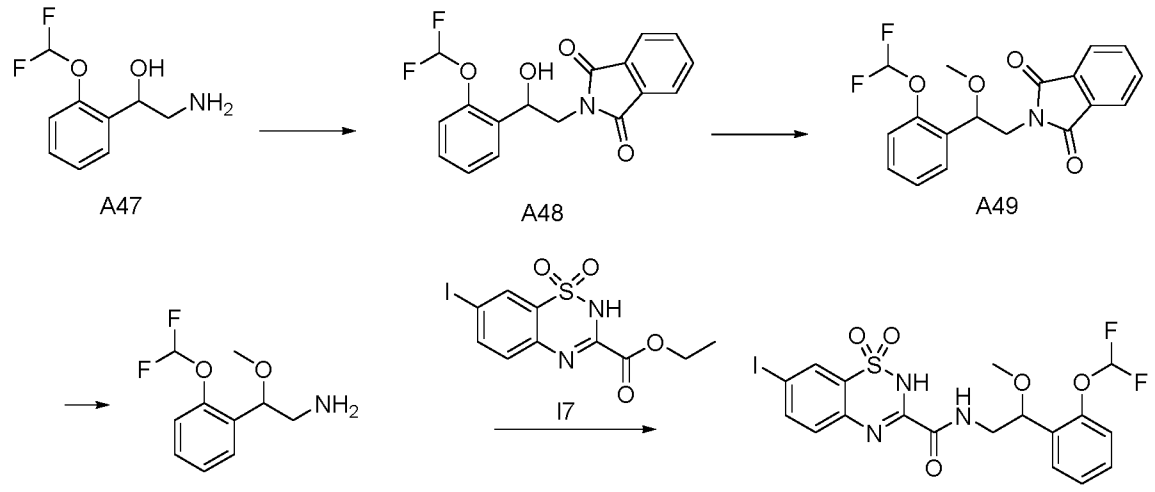
b) 2-amino-1-(2-(difluoromethoxy)phenyl)ethan-1-ol (A47)

1-(2-(Difluoromethoxy)phenyl)-2-nitroethan-1-ol (A46) (1.600 g, 6.862 mmol) and nickel (II) chloride hexahydrate (4.078 g, 17.16 mmol) were dissolved in dry methanol (50 mL) and stirred vigorously under nitrogen. The mixture was cooled to 0 °C and sodium borohydride (6.490 g, 171.5 mmol) was added in 0.5 g portions over 30 min (comment: exothermic, gas evolution). After 1 h, the mixture was quenched with the addition of 2 N HCl (20 mL). The reaction was then basified to ~pH 11 using sat. $NaHCO_3$ solution and the MeOH removed *in vacuo.* EtOAc (50 mL) was added and the layers separated. The aqueous was washed with further portions of EtOAc (3 x 50 mL). The organics were combined, washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to reveal the product (1.023 g, 73% yield) as an orange oil. The material was carried forward without any further purification. LCMS-A: r.t. 1.522 min, product mass ion not present.

c) *N*-(2-(2-(difluoromethoxy)phenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (57)

To 2-amino-1-(2-(difluoromethoxy)phenyl)ethan-1-ol (A47) (0.040 g, 0.20 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide, (I7) (0.050 g, 0.13 mmol). The mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was cooled and EtOH removed *in vacuo*. The reaction mixture was taken up in EtOAc (3 mL) and washed with 1 M HCl (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the product (0.046 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (brs, 1H), 9.15 – 8.95 (m, 1H), 8.13 – 8.02 (m, 2H), 7.65 – 7.55 (m, 2H), 7.37 – 7.31 (m, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17 (t, *J* = 73.7 Hz, 1H), 7.19 – 7.11 (m, 1H), 5.65 (d, *J* = 4.7 Hz, 1H), 5.14 (dt, *J* = 8.6, 4.4 Hz, 1H), 3.48 (dt, *J* = 13.0, 5.1 Hz, 1H), other CH_2 proton obscured by water signal as confirmed by 2D COSY. LCMS-B: r.t. 3.324 min; *m/z* 535.7 $[M-H]^-$.

Example 58: N-(2-(2-(difluoromethoxy)phenyl)-2-methoxyethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (58)



a) 2-(2-(2-(difluoromethoxy)phenyl)-2-hydroxyethyl)isoindoline-1,3-dione (A48)

2-Amino-1-(2-(difluoromethoxy)phenyl)ethan-1-ol (A47) (0.250 g, 1.23 mmol), phthalic anhydride (0.164 g, 1.1 mmol) and 3 Å molecular sieves were suspended in toluene (10 mL) and the solution heated to 110 °C. DMF (1 mL) was added to aid solubility and the reaction was left to stir overnight. The reaction mixture was cooled to r.t., poured into water (50 mL) and then extracted with EtOAc (50 mL). The organic layer was washed with a solution of 1 M HCl (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to reveal the product (0.245 g, 60% yield) as an orange oil. The material was carried forward

without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 – 7.79 (m, 4H), 7.62 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.29 – 7.23 (m, 1H), 7.15 (t, *J* = 74.1 Hz, 1H), 7.13 – 7.07 (m, 1H), 5.69 (d, J = 4.7 Hz, 1H), 5.25 (dt, *J* = 7.9, 5.0 Hz, 1H), 3.79 – 3.63 (m, 2H).

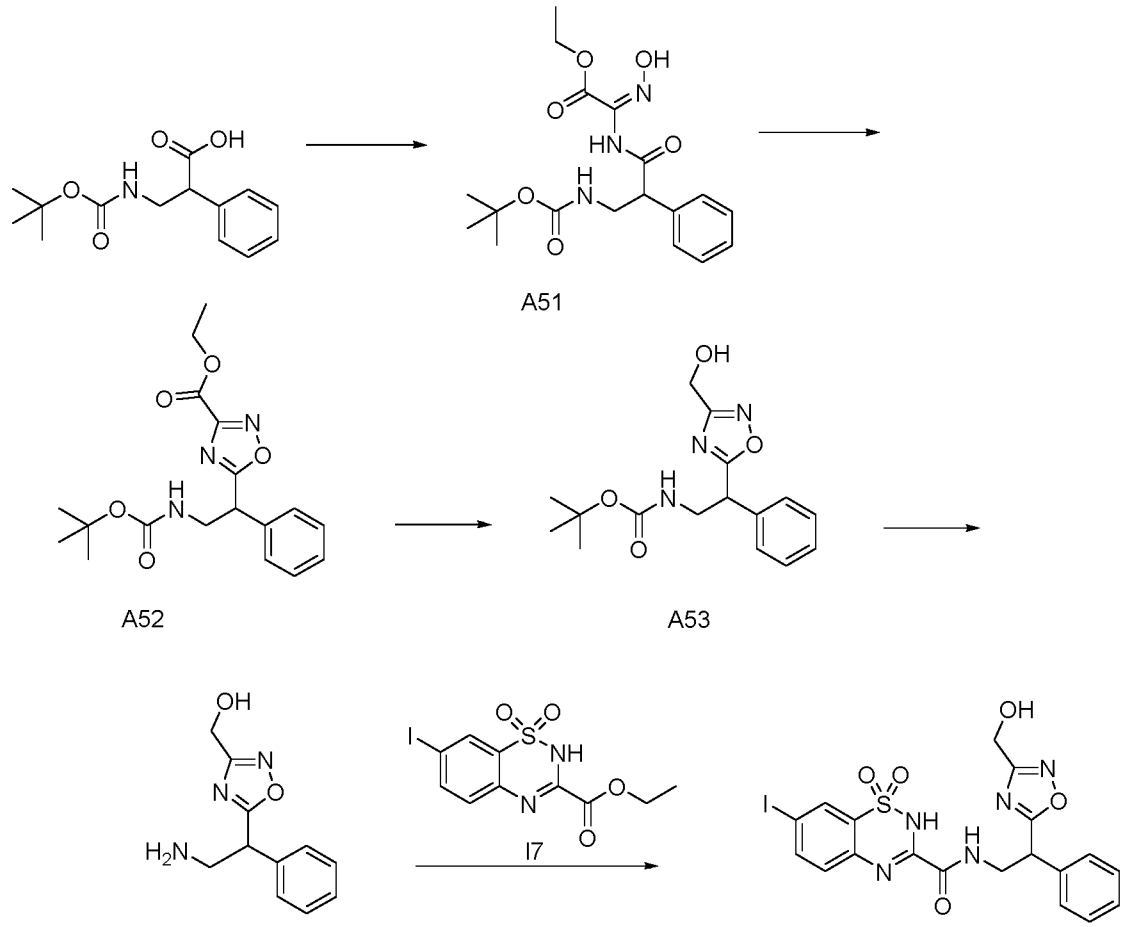
b) 2-(2-(2-(difluoromethoxy)phenyl)-2-methoxyethyl)isoindoline-1,3-dione (A49)
To a solution of 2-(2-(2-(difluoromethoxy)phenyl)-2-hydroxyethyl)isoindoline-1,3-dione (A48) (0.245 g, 0.735 mmol) in THF (5 mL) at 0 °C, under a nitrogen atmosphere, was added NaH (60% dispersion in mineral oil, 0.044 g, 1.1 mmol). The mixture was allowed to stir for 30 min at this temperature before methyl iodide (0.092 mL, 1.5 mmol) was added. After 30 min at 0 °C, the reaction mixture was allowed to warm to r.t. and stirred for 5 h. The reaction mixture was quenched by the addition of water (1 mL) and then the THF was removed *in vacuo*. The material was partitioned between EtOAc (10 mL) and aq. 1 M HCl (10 mL), then separated. The aqueous layer was further washed with EtOAc (2 x 10 mL). The organics were combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (Isolera Biotage, 12 g Si Cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C). Fractions containing suspected product were collected and concentrated *in vacuo* to yield ~70 % pure material (0.062 g, 24% yield). This impure material was used in the next step without further purification.

c) 2-(2-(difluoromethoxy)phenyl)-2-methoxyethan-1-amine (A50)
To a suspension of crude 2-(2-(2-(difluoromethoxy)phenyl)-2-methoxyethyl)isoindoline-1,3-dione (A49) (0.062 g, 0.179 mmol) in EtOH (3 mL) was added hydrazine hydrate (50-60%, 0.104 mL, 1.67-2.00 mmol). The solution was stirred at 80 °C overnight, cooled and the precipitate filtered. The precipitate was washed with a portion of cold EtOH (1 mL), and the combined EtOH fractions were pooled and concentrated *in vacuo.* The resulting solid was re-suspended in minimum cold EtOH, the solid filtered and the EtOH filtrate concentrated *in vacuo* to reveal the product (0.042 g, >100% yield). The material was carried forward without any further purification. LCMS-A: r.t. 1.678 min, no desired mass ion present.

d) *N*-(2-(2-(difluoromethoxy)phenyl)-2-methoxyethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (58)
To 2-(2-(difluoromethoxy)phenyl)-2-methoxyethan-1-amine (A50) (0.042 g, 0.193 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2*H*-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (0.037 g, 0.097 mmol). The mixture was subjected to microwave irradiation at 100 °C for 1 h. The reaction mixture was cooled and the precipitate filtered. The filtrate was

concentrated *in vacuo* to reveal a complex mixture of products. The crude material was loaded onto a column and purified by silica gel chromatography (Isolera Biotage 4 g Si cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C, then 0-40% MeOH in EtOAc). Product-containing fractions were combined and concentrated *in vacuo* to give the product (0.001 g, 0.5% yield over three steps) as a white solid. LCMS-B: rt. 3.768, *m/z* 549.7 $[M-H]^-$.

Example 59: N-(2-(3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl)-2-phenylethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (59)



a) Ethyl (2*E*)-2-[[3-(tert-butoxycarbonylamino)-2-phenyl-propanoyl]amino]-2-hydroxyimino-acetate (A51)

To 3-{[(*tert*-Butoxy)carbonyl]amino}-2-phenylpropanoic acid (1.0 g, 3.8 mmol), ethyl 2-(hydroxyamino)-2-imino-acetate (0.50 g, 3.8 mmol) and (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.4 g, 3.8 mmol) in acetonitrile (30 mL) was added N,N-diisopropylethylamine (0.66 mL, 3.8 mmol). This was allowed to stir at r.t. for 1 h, upon which time a white precipitate formed. The mixture was filtered and the

resulting solid was washed successively with EtOAc (20 mL), water (50 mL), ether (20 mL), then allowed to air dry to reveal the desired product (1.2 g, 80% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 – 7.25 (m, 5H), 7.03 (brs, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.08 (dd, J = 8.8, 6.6 Hz, 1H), 3.66 – 3.53 (m, 1H), 3.30 – 3.22* partially obscured by solvent (m, 1H), 1.35 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), exchangeable O*H* proton not observed. LCMS (LCMS-A) rt. 5.691 min; *m/z* 378.2 $[M-H]^-$.

b) Ethyl 5-[2-(*tert*-butoxycarbonylamino)-1-phenyl-ethyl]-1,2,4-oxadiazole-3-carboxylate (A52)

Ethyl (2E)-2-[[3-(*tert*-butoxycarbonylamino)-2-phenyl-propanoyl]amino]-2-hydroxyimino-acetate (A51) (0.85 g, 2.2 mmol) in DMF (5 mL) was heated to 120 °C and allowed to stir o/n. The reaction mixture was cooled and concentrated to dryness. The crude residue was loaded onto a silica gel cartridge and purified by column chromatography (Isolera, Grace 40 g Si cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) with the material eluting at ~30% EtOAc collected and concentrated *in vacuo* to reveal the desired product (430 mg, 53% yield) as a white solid. ^{1}H NMR: (400 MHz, Chloroform-d): δ 7.36 – 7.24 *partially obscured by solvent (m, 5H), 5.00 (br t, J = 6.4 Hz, 1H), 4.75 – 4.64 (m, 1H), 4.50 (q, J = 7.1 Hz, 2H), 3.89 – 3.72 (m, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H). LCMS-A: rt. 6.006 min; *m/z* 261.9 $[M+H\text{-}Boc]^+$.

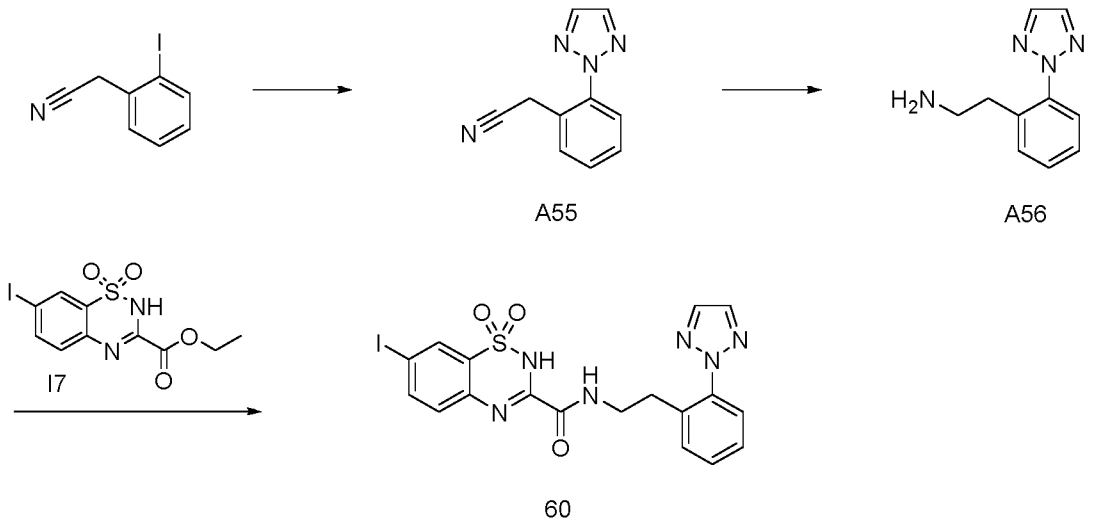
c) *tert*-Butyl N-[2-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]-2-phenyl-ethyl]carbamate (A53)

To a solution of ethyl 5-[2-(tert-butoxycarbonylamino)-1-phenyl-ethyl]-1,2,4-oxadiazole-3-carboxylate (A52) (0.27 g, 0.76 mmol) in EtOH (15 mL) and THF (3 mL), under an atmosphere of nitrogen, was added sodium borohydride (0.057 g, 1.5 mmol). The mixture was allowed to stir o/n at r.t. The reaction mixture was quenched with the addition of aq. 10% citric acid (15 mL). The EtOH and THF were removed *in vacuo* and EtOAc (15 mL) was added. The layers were separated and the aqueous layer further washed with EtOAc (15 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by column chromatography (Grace Biotage, 40 g Si cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) with the fraction eluting at ~50% EtOAc identified as the desired product. The fractions containing product were combined and concentrated *in vacuo* to reveal the desired product (202 mg, 83% yield) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.19*partially obscured by solvent (m, 5H), 5.16 (brt, J = 6.4 Hz, 1H), 4.76 (s, 2H), 4.63 – 4.47 (m, 1H), 3.86 – 3.69 (m, 2H), 3.66 (s, 1H), 1.39 (s, 9H). **LC-MS** (LCMS-A): rt. 5.520, *m/z* 219.9 $[M+H - Boc]^+$

d) [5-(2-amino-1-phenyl-ethyl)-1,2,4-oxadiazol-3-yl]methanol (A54)
tert-Butyl N-[2-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]-2-phenyl-ethyl]carbamate (A53) (0.20 g, 0.63 mmol) was dissolved in DCM (3 mL) and TFA (0.3 mL) was added. This was allowed to stir at r.t. for 2 h. Aqueous 1 M NaOH (1 mL) was added and the organic layer was separated, washed with brine (1 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the desired product (0.058 g, 42% yield) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.28 (m, 5H), 4.78 (s, 2H), 4.31 (dd, J = 7.6, 6.7 Hz, 1H), 3.47 (dd, J = 13.1, 7.7 Hz, 1H), 3.33 (dd, J = 13.1, 6.7 Hz, 1H), 1.78 (brs, 3H). LCMS-A:: rt 1.419 min; *m/z* 219.9 $[M+H]^+$.

e) *N*-(2-(3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl)-2-phenylethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine -3-carboxamide 1,1-dioxide (59)
To a solution of [5-(2-amino-1-phenyl-ethyl)-1,2,4-oxadiazol-3-yl]methanol (A54) 0.035 g, 0.16 mmol) in EtOH (0.125 mL) was added triethylamine (0.022 mL, 0.16 mmol). This was allowed to stir for 10 min, upon which ethyl 7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (0.050 g, 0.13 mmol) was added. The mixture was irradiated in a microwave reactor at 120 °C for 1 h. The ethanol was removed and the material taken up in EtOAc (3 mL). This was washed with 1 M HCl (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by column chromatography (Grace Biotage, 4 g Si cartridge, 0-100% EtOAc in petroleum benzine 40-60 °C) with the fraction eluting at ~80% EtOAc identified as the desired product. The fraction was concentrated *in vacuo* though not completely pure by ^{1}H NMR analysis. The resulting solid was washed with warm EtOAc (0.25 mL), warm DCM (0.25 mL), then air dried give the product (0.0025 g, 2.8% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.73 (brs, 1H), 9.31 (brs, 1H), 8.11 – 7.89 (m, 2H), 7.62 – 7.21 (m, 6H), 5.68 (t, J = 6.2 Hz, 1H), 4.86 (t, J = 7.6 Hz, 1H), 4.53 (d, J = 6.2 Hz, 2H), 3.90 (dt, J = 13.5, 6.7 Hz, 2H). LCMS-A:: rt 5.449 min; *m/z* 551.9 $[M-H]^-$.

Example 60: N-(2-(2H-1,2,3-triazol-2-yl)phenethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (60)



a) 2-[2-(triazol-2-yl)phenyl]acetonitrile (A55)

To iodophenylacetonitrile (0.57 mL, 4.1 mmol) in DMF (5 mL), under an atmosphere of nitrogen, was added successively, cesium carbonate (60 - 80 mesh, 2.7 g, 8.2 mmol), copper(I) iodide (0.078 g, 0.41 mmol), triazole (0.48 mL, 8.2 mmol) and dimethylethylenediamine (0.089 mL, 0.82 mmol). The mixture was irradiated in a microwave reactor for 40 min at 100 °C. The reaction mixture was cooled and poured into water (75 mL) and extracted with EtOAc (3 x 75 mL). The organics were combined and washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by column chromatography (Biotage Isolera, 120 g Si cartridge, 0-50% EtOAc in petroleum benzine 40-60 °C) with the material eluting at ~25% EtOAc identified as the desired material. The fractions containing the material were combined and concentrated *in vacuo* to give the product (0.10 g, 13% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.82 – 7.78 (m, 1H), 7.64 – 7.59 (m, 1H), 7.46 (pd, J = 7.4, 1.7 Hz, 2H), 4.08 (s, 2H).

b) 2-[2-(triazol-2-yl)phenyl]ethanamine (A56)

To 2-[2-(triazol-2-yl)phenyl]acetonitrile (A55) (0.10 g, 0.54 mmol) in THF (5 mL) was added borane-tetrahydrofuran complex (1.0 M solution in THF, 2.7 mL, 2.7 mmol) dropwise. The solution was heated to reflux and allowed to stir o/n. The reaction mixture was cooled and quenched slowly with water (5 mL). A 50% w/v aq. NaOH solution (2 mL) was added and the mixture was refluxed for 1 h. The reaction was cooled and the organics concentrated *in vacuo.* The remaining aqueous layer was washed with DCM (5 mL x 2). The organics were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was loaded onto an SCX cartridge (1 g) and the column was washed with

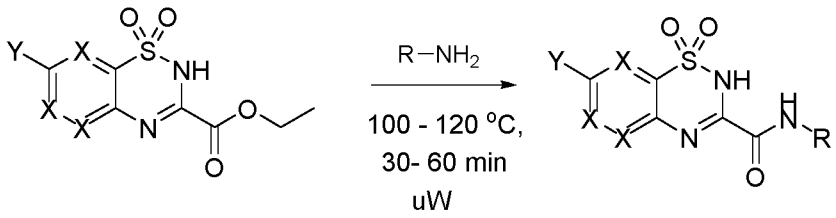
MeOH (10 mL), then a methanolic ammonia solution (10 mL). The methanolic ammonia washings were concentrated *in vacuo* leaving the product (0.074 g, 72% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.55 – 7.48 (m, 1H), 7.40 – 7.28 (m, 3H), 2.79 (s, 4H).

c) *N*-(2-(2*H*-1,2,3-triazol-2-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (60)

To 2-[2-(triazol-2-yl)phenyl]ethanamine (A56) (0.030 g, 0.16 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (I7) (0.050 g, 0.13 mmol). This was irradiated in a microwave reactor at 120 °C for 1 h. The reaction mixture was cooled and concentrated to dryness. The residue was taken up in EtOAc (1 mL) and washed with 1 M HCl (1 mL), brine (1 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was taken up in minimal warm EtOH (0.2 mL) and allowed to slowly cool. The resulting solid was collected and air dried to reveal the desired product *N*-(2-(2*H*-1,2,3-triazol-2-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (0.0070 g, 10% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.68 (s, 1H), 9.29 (t, J = 5.9 Hz, 1H), 8.09 (s, 2H), 8.12 – 8.03 (m, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.47 – 7.40 (m, 1H), 3.47 – 3.39* partially obscured by solvent (m, 2H), 2.91 (t, J = 7.2 Hz, 2H). LCMS-B: rt. 3.319 min; *m/z* 520.7 $[M-H]^-$.

General methods

METHOD A:



To a solution of the amine (1.2 eq.) in EtOH (0.8 M) was added the ester (1 eq.). This was irradiated in a microwave reactor for 30 min at 100 °C. The reaction mixture was cooled and the resulting precipitate filtered, washed with cold EtOH, then air dried to give the desired product.

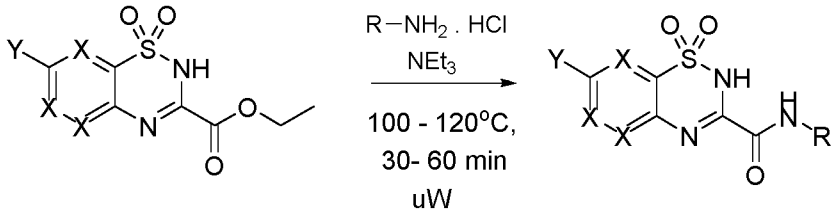
A-1: Reaction temperature increased to 120 °C; reaction time extended to 1 h

A-2: Reaction temperature increased to 120 °C; reaction time extended to 2 h

A-3: Additional EtOH wash of solid required to remove residual impurities

A-4: Column chromatography of isolated material required

METHOD B:



To a solution of the amine (1.2 eq.) in EtOH (0.8 M) was added triethylamine (1.2 eq.). After 10 min the ester (1 eq.) was added and the mixture was irradiated in a microwave reactor for 30 min at 100 °C. The reaction mixture was cooled and resulting precipitate filtered, washed with cold EtOH, then air dried to reveal the desired product.

B-1: Reaction time extended to 1 h

B-2: Reaction time extended to 1 h; column chromatography of isolated material required

B-3: Precipitated by cooling to 4 °C overnight

B-4: Reaction produced a mixture of two major products, separated by preparatory TLC in 2% MeOH/DCM

METHOD C:

To a solution of the amine (1.2 eq.) in EtOH (0.8 M) was added the ester (1 eq.). This was irradiated in a microwave reactor for 30 min at 100 °C. The reaction mixture was cooled and the solvent removed. The material was taken up in EtOAc and washed with 1 M HCl, brine, dried and concentrated *in vacuo* to reveal the desired product.

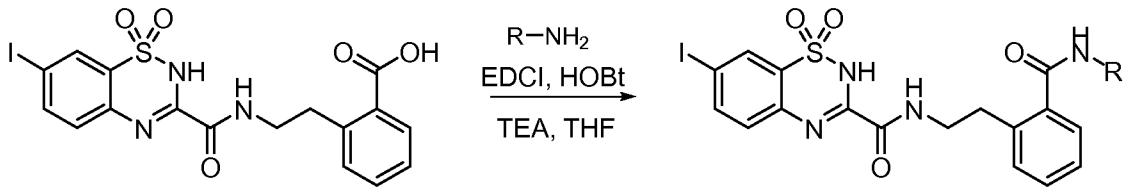
METHOD D:

To a solution of the amine (1.2 eq.) in EtOH (0.8 M) was added triethylamine (1.2eq.). After 10 min the ester (1 eq.) was added and the mixture was irradiated in a microwave reactor for 30 min at 100 °C. The reaction mixture was cooled and the solvent removed. The material was taken up in EtOAc and washed with 1 M HCl, brine, dried and concentrated *in vacuo* to reveal the desired product.

METHOD E:

To a solution of the ester (1 eq.) and amine (1.5 eq.) in EtOH (0.06 M) was added Et_3N (3 eq.) and the mixture heated at 120 °C in a sealed tube for 3 h. The mixture was concentrated under reduced pressure and the residue was recrystallized from MeOH (2 mL) to afford the desired product.

METHOD F:



I55

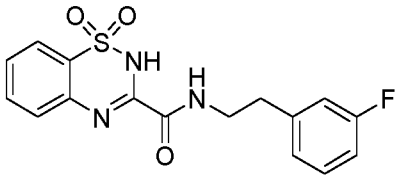
To a solution of the acid I55 (1 eq.), HOBt (1.5 eq.), EDCI.HCl (2 eq.) and triethylamine (3 eq.) in THF (0.02 M) was added the amine (1.5 eq.) and the mixture was stirred at r.t. for 16 h. Water (5 mL) was added and the mixture extracted with EtOAc (8 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (DCM/MeOH = 10:1) to give the desired product.

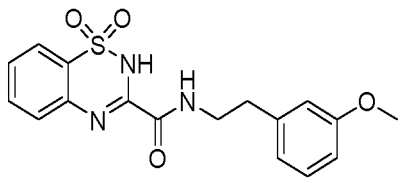
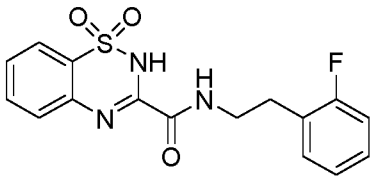
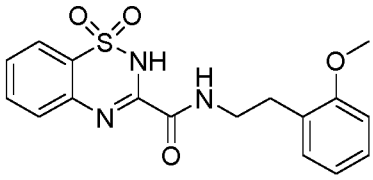
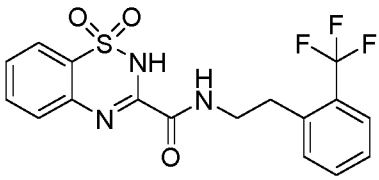
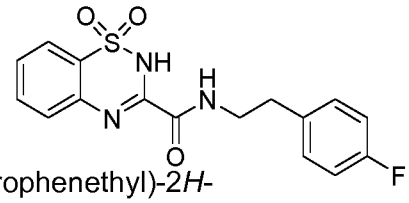
METHOD G:

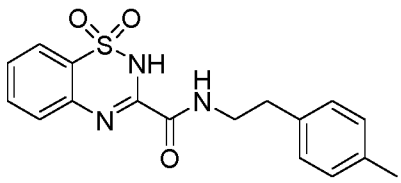
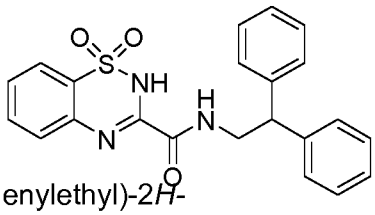
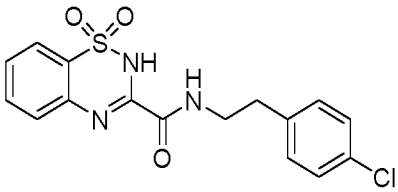
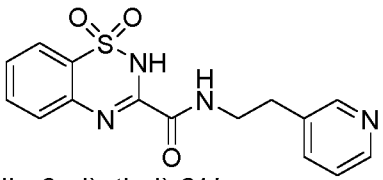
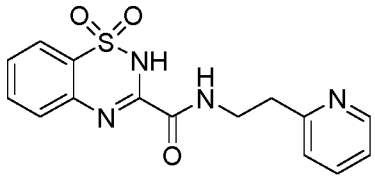
A suspension of the ester (1 eq.), amine (1 eq.) and Et_3N (2-4 eq.) in EtOH (0.8 M) was irradiated in the microwave at 150 °C for 30 min. Upon cooling, water (1 mL) and diethyl ether (5 mL) were added and the mixture sonicated for 10 min. The resulting precipitates were collected by filtration and air dried to yield the desired compounds.

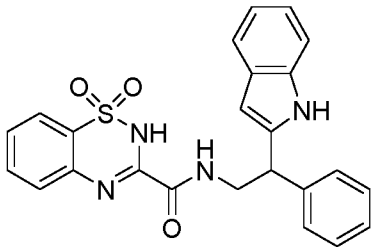
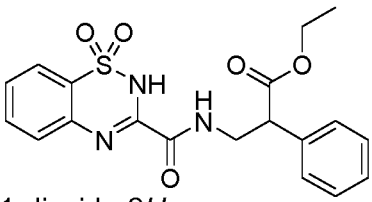
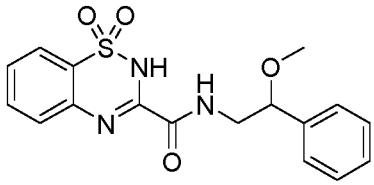
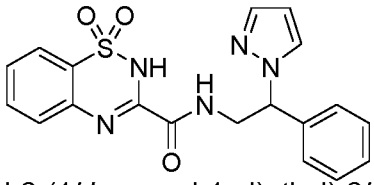
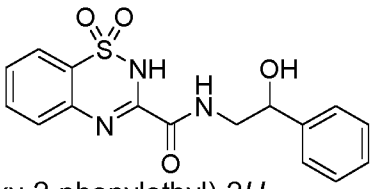
G-1: The precipitate was treated with LiOH-hydrate (217 mg) in THF: MeOH: water 10: 1: 0.5 at room temperature overnight and purified by column chromatography (0-100% EtOAc/hexanes, then 0-40% MeOH in EtOAc).

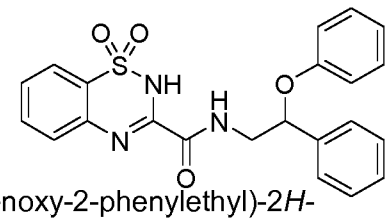
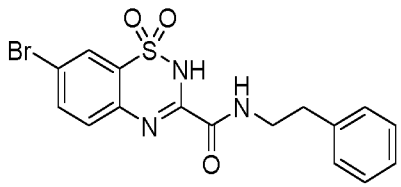
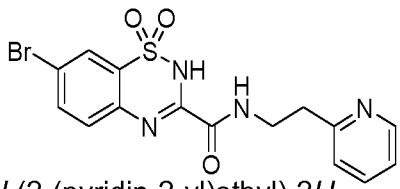
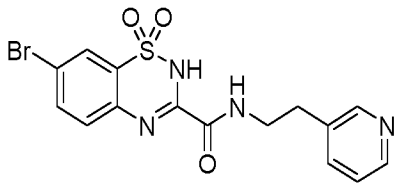
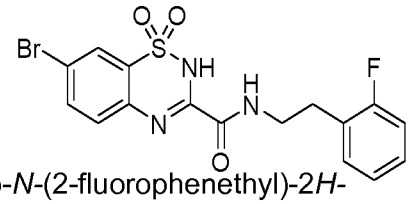
G-2: Heated at 100 °C for 30 min; precipitated by adding petroleum benzene

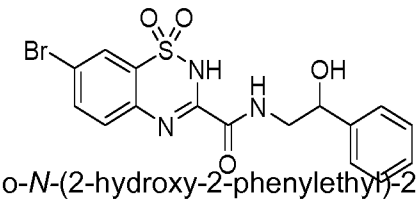
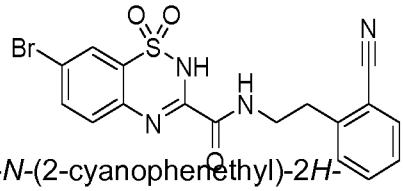
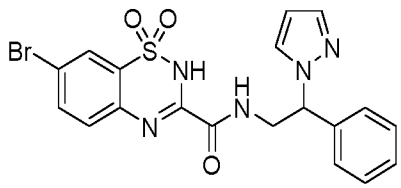
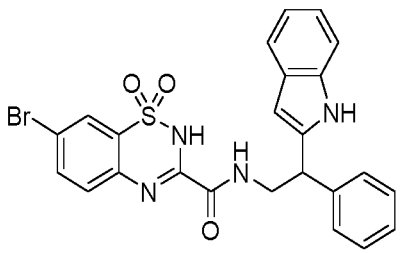
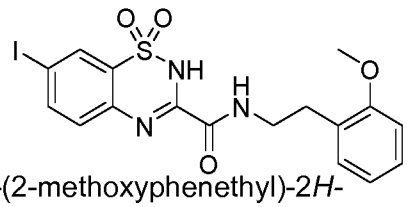
Example	Name & Structure	LCMS data	Method
61	 *N*-(3-fluorophenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LC-MS B: rt. 3.580 min, *m/z* 348.2 [M+H]+	A

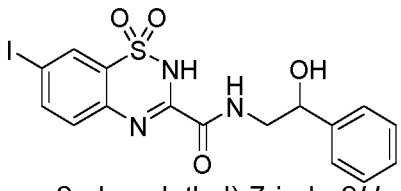
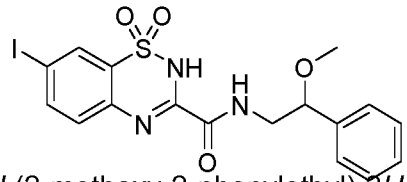
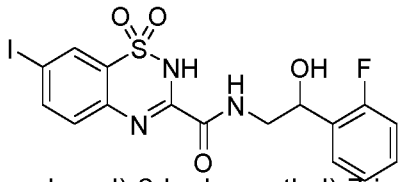
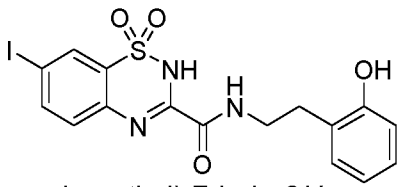
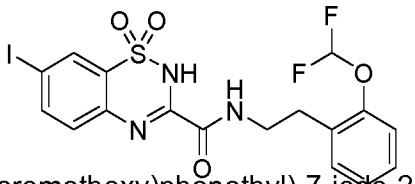
Example	Name & Structure	LCMS data	Method
62	 *N*-(3-methoxyphenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.556; *m/z* 360.2 [M+H]+	A
63	 *N*-(2-fluorophenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.575; *m/z* 348.1 [M+H]+	A
64	 *N*-(2-methoxyphenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.605; *m/z* 360.2 [M+H]+	A
65	 *N*-(2-(trifluoromethyl)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.682; *m/z* 396.1 [M-H]-	A
66	 *N*-(4-fluorophenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.573; *m/z* 348.1 [M+H]+	A

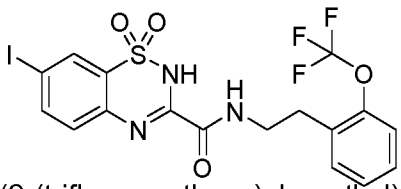
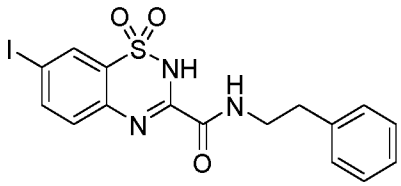
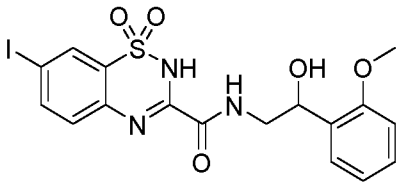
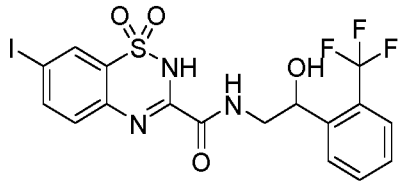
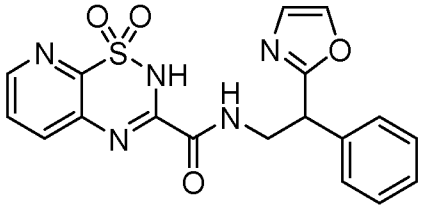
Example	Name & Structure	LCMS data	Method
67	 *N*-(4-methylphenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.637 min; *m/z* 344.2 [M+H]+	A
68	 *N*-(2,2-diphenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.709 min; *m/z* 406.2 [M+H]+	A
69	 *N*-(4-chlorophenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.709 min; *m/z* 362.2 [M-H]-	A
70	 *N*-(2-(pyridin-3-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.133 min; *m/z* 331.1 [M+H]+	A
71	 *N*-(2-(pyridin-2-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.139 min; *m/z* 331.1 [M+H]+	A

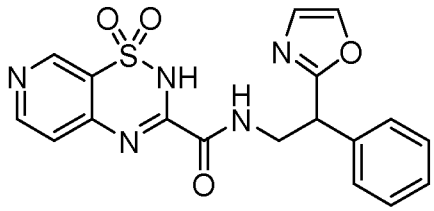
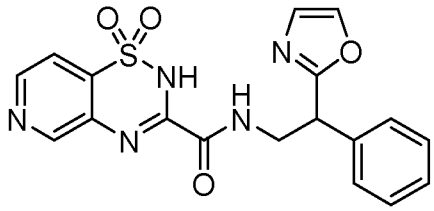
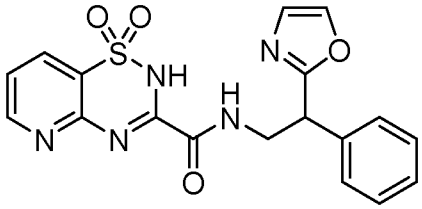
Example	Name & Structure	LCMS data	Method
72	 *N*-(2-(1*H*-indol-2-yl)-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.659 min; *m/z* 444.1 [M+H]+	A
73	 ethyl 3-(1,1-dioxido-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate	LCMS B: rt. 3.555 min, *m/z* 402.2 [M+H]+.	B
74	 *N*-(2-methoxy-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.525 min, *m/z* 358.1 [M-H]-.	A
75	 *N*-(2-phenyl-2-(1*H*-pyrazol-1-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt 3.489 min, *m/z* 396.2 [M+H].	C
76	 *N*-(2-hydroxy-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt 3.378 min, *m/z* 344.1 [M-H]-.	C

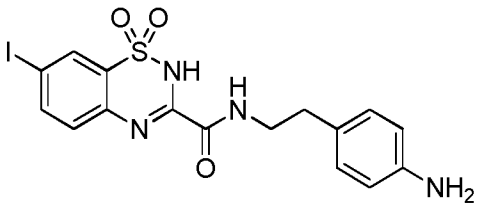
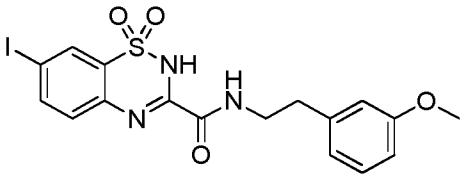
Example	Name & Structure	LCMS data	Method
77	 *N*-(2-phenoxy-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt 3.693 min, *m/z* 420.1 [M-H]-.	B
78	 7-bromo-*N*-phenethyl-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.320 min; *m/z* 408.0 [M]+.	A
79	 7-bromo-*N*-(2-(pyridin-2-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LC-MS B: rt. 2.791 min; *m/z* 408.8 [M+H]+	A-3
80	 7-bromo-*N*-(2-(pyridin-3-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 2.779 min; *m/z* 408.8 [M+H]+	A-3
81	 7-bromo-*N*-(2-fluorophenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.419 min; *m/z* 425.8 [M-H]-	A

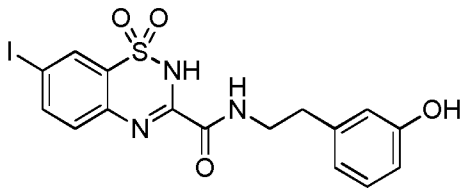
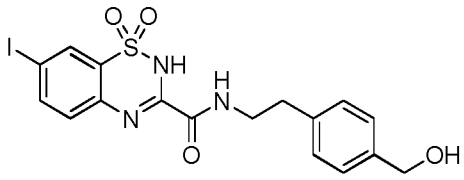
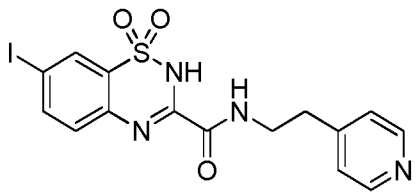
Example	Name & Structure	LCMS data	Method
82	 7-bromo-*N*-(2-hydroxy-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.245 min; *m/z* 421.7 [M-H]-	A
83	 7-bromo-*N*-(2-cyanophenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.342 min; *m/z* 433.8 [M+H]+	B
84	 7-bromo-*N*-(2-phenyl-2-(1*H*-pyrazol-1-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.338 min; *m/z* 473.8 [M+H]+	A
85	 *N*-(2-(1*H*-indol-2-yl)-2-phenylethyl)-7-bromo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.485 min; *m/z* 442.8 [M-Br]-	A
86	 7-iodo-*N*-(2-methoxyphenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.411 min; *m/z* 483.7 [M-H]-	A-1

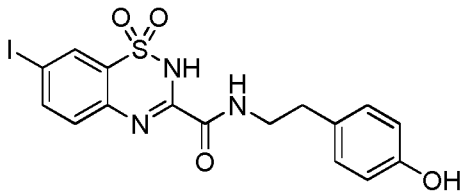
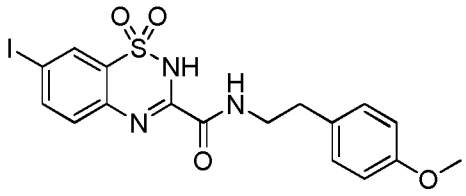
Example	Name & Structure	LCMS data	Method
87	 *N*-(2-hydroxy-2-phenylethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.217 min; *m/z* 469.7 [M-H]-	A-2
88	 7-iodo-*N*-(2-methoxy-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.380 min; *m/z* 483.7 [M-H]-	A-1
89	 *N*-(2-(2-fluorophenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.250 min; *m/z* 487.7 [M-H]-	A-2
90	 *N*-(2-hydroxyphenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.265 min; *m/z* 469.7 [M-H]-	B-1
91	 *N*-(2-(difluoromethoxy)phenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.403 min; *m/z* 519.7 [M-H]-	B-2

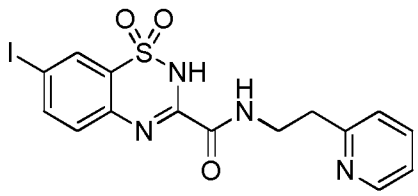
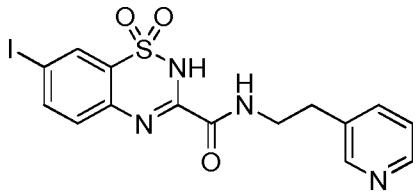
Example	Name & Structure	LCMS data	Method
92	 7-iodo-*N*-(2-(trifluoromethoxy)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.482 min; *m/z* 537.7 [M-H]-	B-1
93	 7-iodo-*N*-phenethyl-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.371 min; *m/z* 453.7 [M-H]- .	A-1
94	 *N*-(2-hydroxy-2-(2-methoxyphenyl)ethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.308 min; *m/z* 499.7 [M-H]- .	A-1
95	 *N*-(2-hydroxy-2-(2-(trifluoromethyl)phenyl)ethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.382 min; *m/z* 537.7 [M-H]- .	A-1
96	 *N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-pyrido[3,2-e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.137 min, *m/z* 398.1 $[M+H]^+$.	A-4

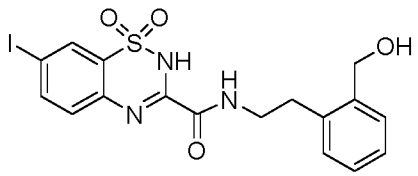
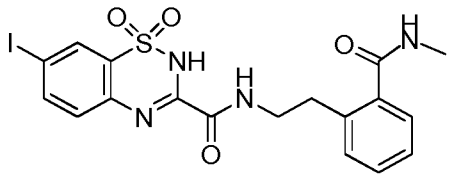
Example	Name & Structure	LCMS data	Method
97	 *N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-pyrido[4,3-e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LC-MS B: rt. 3.080 min; *m/z* 397.8 $[M+H]^+$.	A-1
98	 *N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-pyrido[3,4-e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS B: rt. 3.121 min, *m/z* 397.8 $[M+H]^+$.	A-1
99	 *N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-pyrido[2,3-e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-A: rt. 4.030 min; *m/z* 398.3 $[M+H]^+$.	A

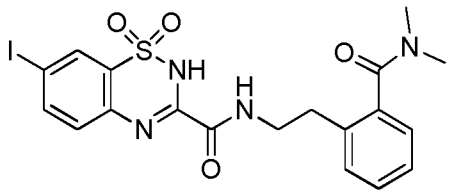
Example	Name and structure	LCMS data	^{1}HNMR data	Method
100	 *N*-(4-aminophenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.33 min, *m/z* 471.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 9.23 (t, *J* = 6.0 Hz, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.49 (d, *J* = 8.2 Hz, 2H), 3.38 (m, 2H), 2.66 (t, *J* = 7.6 Hz , 2H), exchangeable N*H* protons not observed.	E
101	 7-iodo-*N*-(3-methoxyphenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.83 min, *m/z* 486.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.28 (t, *J* = 6.0 Hz, 1H), 8.09 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.81 – 6.75 (m, 3H), 3.72 (s, 3H), 3.53 – 3.46 (m, 2H), 2.84 (t, *J* = 7.0 Hz, 2H).	E

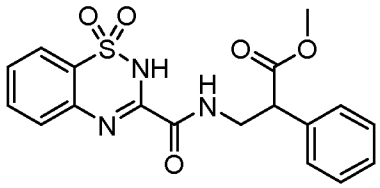
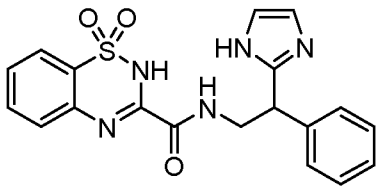
Example	Name and structure	LCMS data	^{1}HNMR data	Method
102	 *N*-(3-hydroxyphenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.67 min, *m/z* 472.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.8 (brs, 1H), 9.33-9.23 (m, 2H), 8.13 – 8.00 (m, 2H), 7.58 (m, 1H), 7.07 (m, 1H), 6.71 – 6.56 (m, 3H), 3.45 (m, 2H), 2.76 (m, 2H).	E
103	 *N*-(4-(hydroxymethyl)phenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.569 min, *m/z* 508.0 $[M+Na]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.27 (t, *J* = 5.5 Hz, 1H), 8.09 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 5.10 (t, *J* = 5.4 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 2H), 3.51-3.45 (m, 2H), 2.84 (t, *J* = 7.1 Hz, 2H).	E
104	 7-iodo-*N*-(2-(pyridin-4-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.106 min, *m/z* 456.9 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.32 (t, *J* = 5.7 Hz, 1H), 8.47 (brs, 2H), 8.13 – 8.02 (m, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.27 (brs, 2H), 3.60-3.48 (m, 2H), 2.89 (t, *J* = 6.9 Hz, 2H).	E

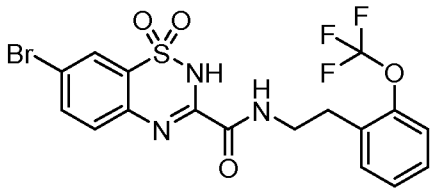
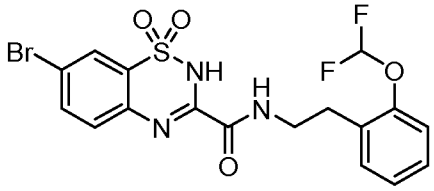
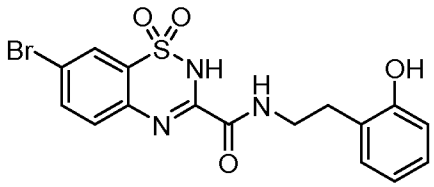
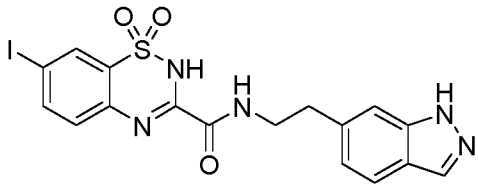
Example	Name and structure	LCMS data	^{1}HNMR data	Method
105	 *N*-(4-hydroxyphenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.966 min, *m/z* 472.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (s, 1H), 9.24 (t, *J* = 5.1 Hz, 1H), 9.18 (s, 1H), 8.14 – 8.03 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 8.2 Hz, 2H), 3.45 – 3.42 (m, 2H), 2.73 (t, *J* = 7.2 Hz, 2H).	E
106	 7-iodo-*N*-(4-methoxyphenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.744 min, *m/z* 486.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (s, 1H), 9.26 (t, *J* = 5.8 Hz, 1H), 8.13 – 8.03 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.71 (s, 3H), 3.48-334 (m, 2H), 2.79 (t, *J* = 7.3 Hz, 2H).	E

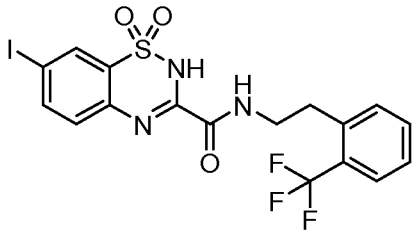
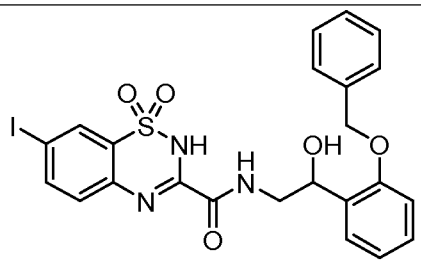
Example	Name and structure	LCMS data	^{1}HNMR data	Method
107	 7-iodo-*N*-(2-(pyridin-2-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.399 min, *m/z* 457.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.32 (t, *J* = 5.8 Hz, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 8.07 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.71 (td, *J* = 7.6, 2.0 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.66-3.61 (m, 2H), 3.02 (t, *J* = 7.3 Hz, 2H).	E
108	 7-iodo-*N*-(2-(pyridin-3-yl)ethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.272 min, *m/z* 457.0 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.32 (t, *J* = 5.7 Hz, 1H), 8.45 (s, 1H), 8.41 (d, *J* = 4.4 Hz, 1H), 8.09 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.32 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.55-3.50 (m, 2H), 2.89 (t, *J* = 6.9 Hz, 2H).	E

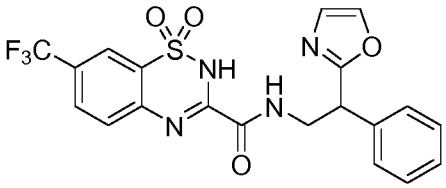
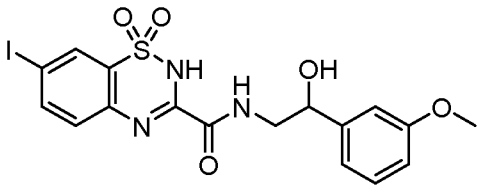
Example	Name and structure	LCMS data	^{1}HNMR data	Method
109	 *N*-(2-(hydroxymethyl)phenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.651 min, *m/z* 484.0 $[M]^-$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.34 (t, *J* = 5.8 Hz, 1H), 8.18 – 8.00 (m, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.35 (m , 1H), 7.22-7.17 (m, 3H), 5.10 (t, *J* = 5.2 Hz, 1H), 4.59 (d, *J* = 4.8 Hz, 2H), 3.47-3.33 (m, 2H), 2.93 – 2.80 (t, *J* = 7.8 Hz, 2H).	E
110	 7-iodo-*N*-(2-(methylcarbamoyl)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.46 min, *m/z* 512.7 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (brs, 1H), 9.34 (t, *J* = 4.8 Hz, 1H), 8.21 (m, 1H), 8.09 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.39 – 7.26 (m, 4H), 3.51 – 3.46 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 2.76 (d, *J* = 4.4 Hz, 3H).	F

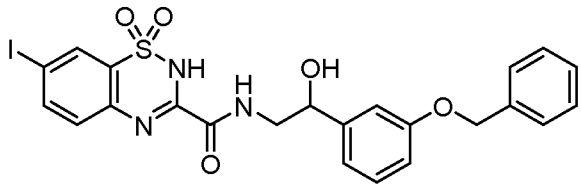
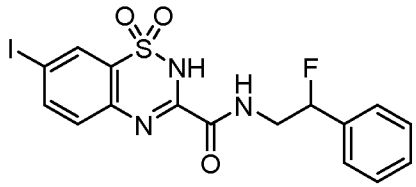
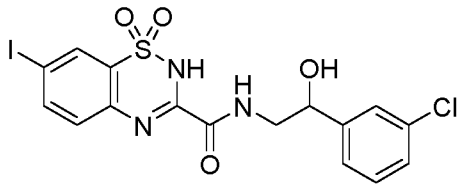
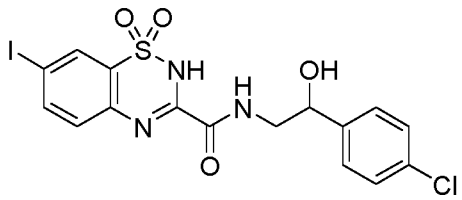
Example	Name and structure	LCMS data	^{1}HNMR data	Method
111	 *N*-(2-(dimethylcarbamoyl)phenethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.55 min, *m/z* 526.7 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 9.28 (t, *J* = 5.5 Hz, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 8.04 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 3.49 – 3.42 (m, 2H), 3.01 (s, 3H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.77 (s, 3H).	F

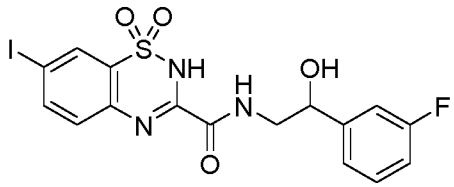
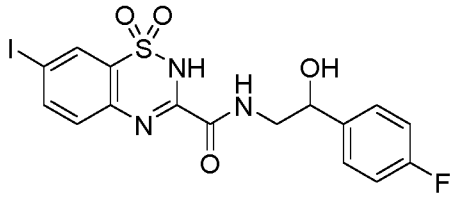
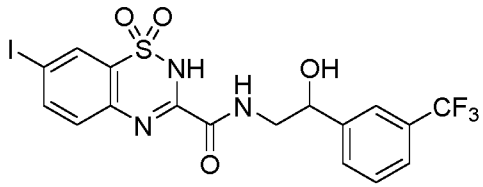
Example	Structure	LCMS	Method
112	 Methyl 3-(1,1-dioxido-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate	LCMS: r.t. 3.520 min; *m/z* 388.2 $M+H^+$.	G-1
113	 *N*-(2-(1*H*-imidazol-2-yl)-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS: r.t. 4.503 min; *m/z* = 396.2 $[M+H]^+$.	G-2

Example	Structure	LCMS	Method
114	 7-Bromo-*N*-(2-(trifluoromethoxy)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.51 min; *m/z* 489.8 $[M-H]^-$	B-3
115	 7-Bromo-*N*-(2-(difluoromethoxy)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.44 min; *m/z* 473.7 $[M-H]^-$	B-4
116	 7-Bromo-*N*-(2-hydroxyphenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.29 min; *m/z* 421.7 $[M-H]^-$	B-4
117	 *N*-(2-(1*H*-indazol-6-yl)ethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.36 min; 495.7 $[M+H]^+$	B-1

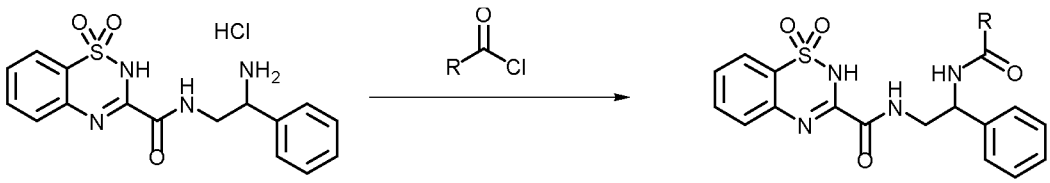
Example	Structure	LCMS	Method
118	 7-iodo-*N*-(2-(trifluoromethyl)phenethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.70 min; *m/z* 521.7 $[M-H]^-$	A-1
119	 *N*-(2-(2-(Benzyloxy)phenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.46 min; *m/z* 575.7 $[M-H]^-$	B-1

Example	Structure	LCMS	Method
120	 *N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(trifluoromethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.35 min; *m/z* 464.7 $[M+H]^+$	A-1
121	 *N*-(2-Hydroxy-2-(3-methoxyphenyl)ethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.21 min; *m/z* 499.7 $[M-H]^-$	B-1

Example	Structure	LCMS	Method
122	 *N*-(2-(3-(Benzyloxy)phenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.40 min; *m/z* 575.7 $[M-H]^-$	A-1
123	 *N*-(2-Fluoro-2-phenylethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.36 min; *m/z* 471.7 $[M-H]^-$	B-1
124	 *N*-(2-(3-Chlorophenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.30 min; *m/z* 503.7 $[M-H]^-$	B-1
125	 *N*-(2-(4-Chlorophenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.31 min; *m/z* 503.7 $[M-H]^-$	A-1

Example	Structure	LCMS	Method
126	 *N*-(2-(3-Fluorophenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.25 min; *m/z* 487.7 $[M-H]^-$	A-1
127	 *N*-(2-(4-Fluorophenyl)-2-hydroxyethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.24 min; *m/z* 487.7 $[M-H]^-$	A-1
128	 *N*-(2-Hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-7-iodo-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B rt 3.35 min; *m/z* 537.7 $[M-H]^-$	B-1

METHOD H:

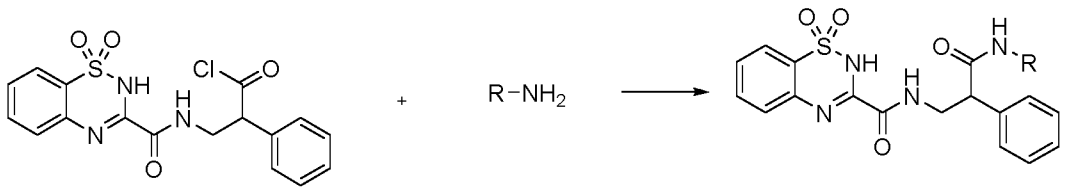


I41

To a mixture of *N*-(2-amino-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide hydrochloride (I41) (0.18 mmol) in DCM (3 mL) was added TEA (3 eq) and the acyl chloride (1.2 eq). The mixture was stirred at r.t. for 3 h under N_2 atmosphere. The mixture was diluted with DCM and washed with water (x 2), 1 M

HCl, brine, dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC (DCM/MeOH = 20:1) to give the desired product.

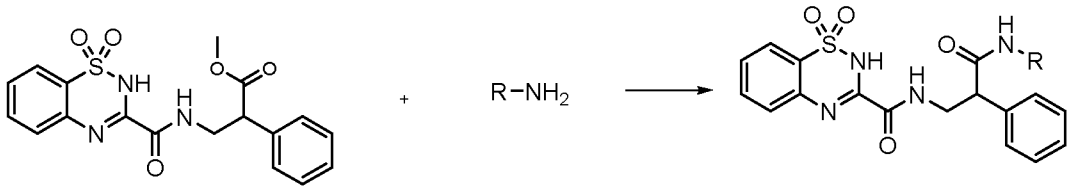
METHOD I:



I37

A solution of 3-(1,1-dioxido-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoyl chloride (I37) (0.13 mmol) and TEA (10 eq) in DCM (5 mL) was stirred at 0 °C under N_2 for 10 min. The amine (5 eq) was then added and the mixture was stirred at r.t. for 30 min. Water and 1 M HCl were added and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate, concentrated and the residue was purified by preparative TLC (DCM/MeOH = 20:1) to afford the desired product.

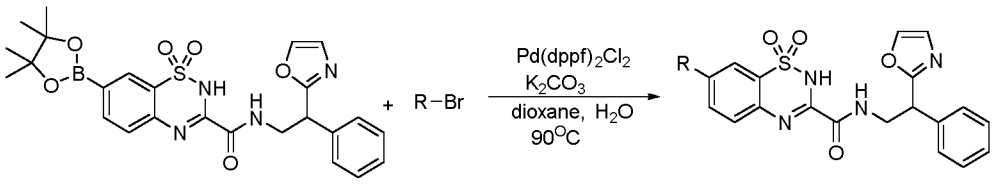
METHOD J:



I35

Methyl 3-(1,1-dioxido-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate (I35; 112) (0.18 mmol) was dissolved in the appropriate amine solution (5 mL) and the mixture was heated at 120 °C for 90 min in the microwave. The solvent was removed and the residue was purified by preparative TLC (DCM/MeOH = 20:1) to afford the desired product.

METHOD K:

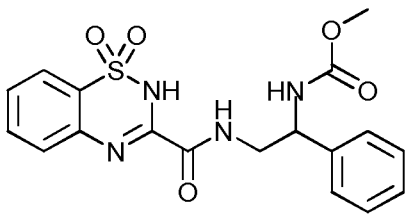
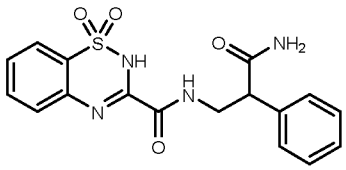


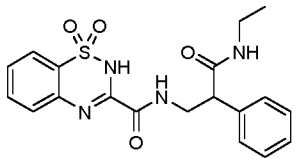
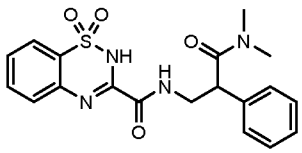
A9

A mixture of *N*-(2-(oxazol-2-yl)-2-phenylethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A9) (0.1 mmol), R-Br (4 eq), $Pd(dppf)_2Cl_2$ (0.1 eq), K_2CO_3 (4 eq) in dioxane (3 mL) and water (0.5 mL) was stirred under

N_2 at 90 °C for 3 h. The mixture was then allowed to cool to r.t. and extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give a residue which was purified by preparative TLC (DCM/MeOH = 20:1) to give the desired product.

5

Example	Name and structure	LCMS data	^{1}H NMR data	Method
129	 Methyl (2-(1,1-dioxido-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamido)-1-phenylethyl)carbamate	LCMS (ES-API): R_t 2.18 min, *m/z* 403.1 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.19 (m, 1H), 7.87-7.71 (m, 4H), 7.55-7.51 (m, 1H), 7.34-7.33 (m, 4H), 7.27-7.24 (m, 1H), 4.92–4.83 (m, 1H), 3.59-3.54 (m, 1H), 3.50 (s, 3H), 3.31-3.29 (m, 1H).	H
130	 *N*-(3-Amino-3-oxo-2-phenylpropyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.91 min, *m/z* 373.1 $[M+H]^+$	^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 9.06 (t, *J* = 6.0 Hz, 1H), 7.85-7.79 (m, 2H), 7.75-7.71 (m, 1H), 7.54-7.50 (m, 2H), 7.36-7.29 (m, 4H), 7.26-7.22 (m, 1H), 6.98 (s, 1H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.79-3.71 (m, 1H), 3.67-3.60 (m, 1H).	I

Example	Name and structure	LCMS data	^{1}H NMR data	Method
131	 *N*-(3-(Ethylamino)-3-oxo-2-phenylpropyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 1.03 min, *m/z* 401.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.23 (t, *J* = 6.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.61 (m, 1H), 7.48 (m, 1H), 7.39-7.33 (m, 3H), 7.30-7.28 (m, 3H), 5.37 (m, 1H), 4.00-3.93 (m, 1H), 3.87-3.80 (m, 1H), 3.68-3.64 (m, 1H), 3.32-3.24 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H).	J
132	 *N*-(3-(Dimethylamino)-3-oxo-2-phenylpropyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.29 min, *m/z* 401.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.27 (t, J = 6.0 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.61-7.57 (m, 1H), 7.48-7.44 (m, 1H), 7.37-7.28 (m, 6H), 4.02-3.99 (m, 1H), 3.92-3.85 (m, 1H), 3.83-3.76 (m, 1H), 2.98 (s, 3H), 2.79 (s, 3H).	I

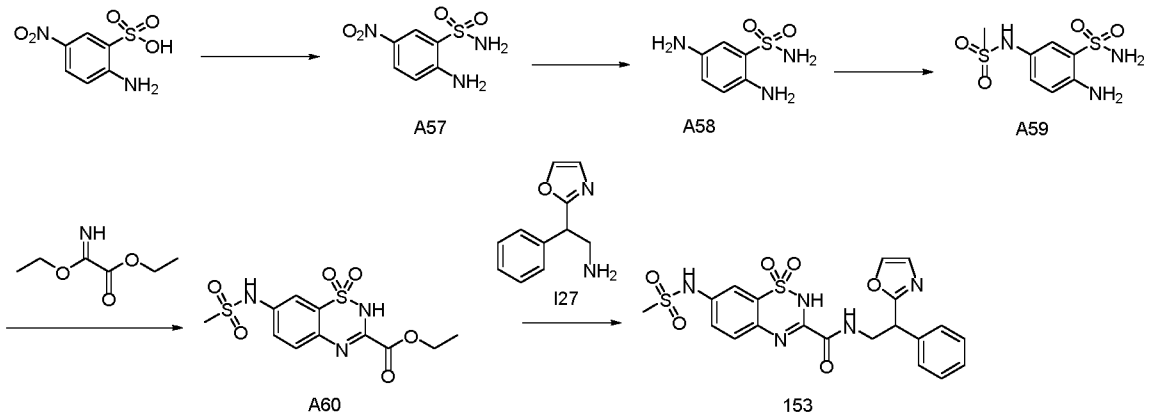
Chiral Separation

Some of the racemates produced above were separated using chiral columns as described below

Racemate	Enantiomer	SFC Purification Method	SFC data	LCMS data*
46	Enantiomer 1 – 136	Instrument: Waters SFC-80; Column: Lux C3 (250*30)mm, 5µ Mobile Phase: CO2: MeOH (70:30); Total flow: 60 ml/min Back Pressure: 100 bar; Wave length: 210 nm; Cycle time: 10 min	SFC: rt. 2.41 min	rt. 2.749 min; *m/z* 397.2 [M+H]+
	Enantiomer 2 – 137		SFC: rt 4.04 min	rt. 2.744 min; *m/z* 397.2 [M+H]+
1	Enantiomer 1 – 138	Instrument: Waters SFC-80; Column: Lux C3 (250*30)mm, 5µ Mobile Phase: CO2: MeOH (70:30); Total flow: 60 ml/min Back Pressure: 100 bar; Wave length: 210 nm; Cycle time: 10 min	SFC: rt 3.83 min	rt. 3.045 min; *m/z* 475.0 [M+H]+
	Enantiomer 2 – 139		SFC: rt 5.64 min	rt. 3.044 min; *m/z* 475.0 [M+H]+
48	Enantiomer 1 – 140	Instrument: Waters SFC-80; Column: YMC Amylose C (250*30)mm, 5µ Mobile Phase: CO2: MeOH (60:40); Total flow: 60 ml/min Back Pressure: 100 bar; Wave length: 210 nm; Cycle time: 10 min	SFC: rt 3.19 min	rt. 2.638 min; *m/z* 412.2 [M+H]+
	Enantiomer 2 – 141		SFC: rt 4.02 min	rt. 2.6220 min; *m/z* 412.2 [M+H]+
4	Enantiomer 1 – 142	Instrument: Waters SFC-80; Column: Chiralpak ADH (250*20)mm, 5µ Mobile Phase: CO2: MeOH (60:40); Total flow: 40 mL/min Back Pressure: 100 bar; Wave length: 210 nm ; Cycle time: 7 min	SFC: rt 3.88 min	n/a
	Enantiomer 2 – 143		SFC: rt 5.91 min	n/a

Racemate	Enantiomer	SFC Purification Method	SFC data	LCMS data*
36	Enantiomer 1 – 144	Instrument: Waters SFC-80; Column: Chiralpak ADH (250*20)mm, 5µ Mobile Phase: CO2: MeOH (60:40); Total flow: 40 mL/min Back Pressure: 100 bar; Wave length: 210 nm ; Cycle time: 7 min	SFC: rt 4.76 min	n/a
	Enantiomer 2 – 145		SFC: rt 6.17 min	n/a
41	Enantiomer 1 – 146	Instrument: Waters SFC-80; Column: Lux C3 (250*20)mm, 5µ Mobile Phase: CO2: MeOH (60:40); Total flow: 60 mL/min; Back Pressure: 100 bar; Wave length: 304 nm; Cycle time: 6 min	SFC: rt 2.22 min	n/a
	Enantiomer 2 – 147		SFC: rt 3.62 min	n/a
8	Enantiomer 1 - 148	Instrument: Waters SFC-80; Column: Lux A1 (250*30)mm, 5µ Mobile Phase: CO2: IPA (60:40); Total flow: 60 mL/min Back Pressure: 100 bar; Wave length: 312 nm; Cycle time: 5 min	SFC: rt 5.17 min	n/a
	Enantiomer 2 - 149		SFC: rt 6.84 min	n/a
94	Enantaiomer 1 - 150	Instrument: Waters SFC-80; Column: YMC Cellulose-SC (250*30)mm, 5µ Mobile Phase: CO2: MeOH (60:40); Total flow: 60 mL/min Back Pressure: 100 bar; Wave length: 304 nm; Cycle time: 6 min	SFC: rt 3.58 min	n/a
***LC-MS details:** Column: ZORBAX Extend C18 (50x4.6mm 5µ); MOBILE PHASE: A: 0.1% HCOOH IN WATER, B: METHANOL; FLOW RATE : 1.5mL/min				
113	Enantiomer 1 – 151	ChiralPak IA, 250 x 4.6 mm with 1:1 EtOH: hexane mobile phase.	rt 15.6 min	n/a
	Enantiomer 2 – 152		rt 20.5 min	n/a

Example 153: 7-(Methylsulfonamido)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (153)



a) 2-Amino-5-nitrobenzenesulfonamide (A57)

$POCl_3$ (6.86 mL, 82.2 mmol) was slowly added to a mixture of 2-amino-5-nitrobenzenesulfonic acid (3.00 g, 27.4 mmol) in sulfolane (20 mL) at r.t. and the mixture was heated at 120 °C for 3.5 h. The mixture was allowed to cool to r.t. then slowly poured into conc. NH_4OH (60 mL). The resulting precipitate was collected by filtration, washed with water (100 mL) and dried to give the product (1.90 g, 31 % yield) as a yellow solid. LCMS (ES-API): R_t 0.43 min; *m/z* 218.1 $[M+H]^+$.

b) 2,5-Diaminobenzenesulfonamide (A58)

To a solution of 2-amino-5-nitrobenzenesulfonamide (A57) (1.9 g, 8.7 mmol) in MeOH (20 mL) was added 10% Pd/C (190 mg) and the mixture was stirred at r.t. under H_2 (1 atm) for 16 h. The mixture was filtered and the filtrate was concentrated to give the product as a brown solid (1.3 g, 79 % yield). LCMS (ES-API): R_t 0.342 min; *m/z* 188.1 $[M+H]^+$.

c) 2-Amino-5-(methylsulfonamido)benzenesulfonamide (A59)

To a solution of 2,5-diaminobenzenesulfonamide (A58) (1.3 g, 0.69 mmol) in acetonitrile (20 mL) at r.t. was added pyridine (79 mg, 1.03 mmol) and MsCl (795 mg, 0.69 mmol) and the mixture was stirred at r.t. for 15 h. Diethyl ether (10 mL) was added and the resulting precipitate was collected by filtration and washed with diethyl ether (30 mL) to give the product as a yellow solid (1.4 g, 90 % yield). LCMS (ES-API): R_t 2.53 min; *m/z* 266.1 $[M+H]^+$.

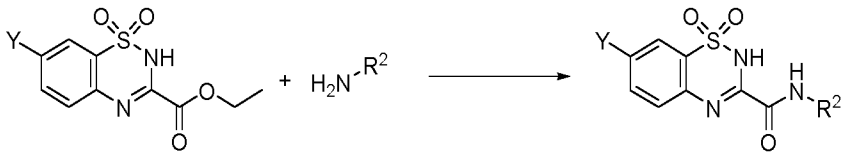
d) Ethyl 7-(methylsulfonamido)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A60)

To a solution of 2-amino-5-(methylsulfonamido)benzenesulfonamide (A59) (1.3 g, 4.9 mmol) in EtOH (20 mL) was added ethyl 2-ethoxy-2-iminoacetate (1.42 g, 9.8 mmol) and the mixture was heated at 100 °C for 15 h. After cooling to r.t., the precipitate was collected by filtration and washed with diethyl ether (20 mL) to give the product as a white solid (1.2 g, 70 % yield). LCMS (ES-API): R_t 0.584 min; *m/z* 347.8 $[M+H]^+$.

e) 7-(Methylsulfonamido)-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (153)

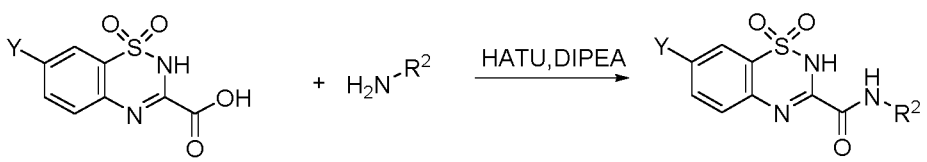
To a solution of ethyl 7-(methylsulfonamido)-2*H*-benzo*[e]*[1,2,4]thiadiazine-3-carboxylate 1,1-dioxide (A60) (85 mg, 0.24 mmol) in EtOH (3 mL) was added 2-(oxazol-2-yl)-2-phenylethanamine (I27) (51 mg, 0.27 mmol) and the mixture was heated at 100 °C for 15 h then allowed to cool to r.t.. The solvent was removed under reduced pressure and the residue was diluted with water (5 mL) and extracted with EtOAc (8 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by prep. TLC (DCM/MeOH = 10:1) to give the product as a white solid (20 mg, 17 % yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.7 (brs, 1H), 10.2 (brs, 1H), 9.26 (t, *J* = 5.8 Hz, 1H), 8.04 (d, *J* = 0.4 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.26 (m, 3H), 7.20 (d, *J* = 0.4 Hz, 1H), 4.67 (t, *J* = 7.6 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.92 – 3.84 (m, 1H), 3.05 (s, 3H). LCMS (ES-API): R_t 2.31 min; *m/z* 489.8 $[M+H]^+$.

General Method L



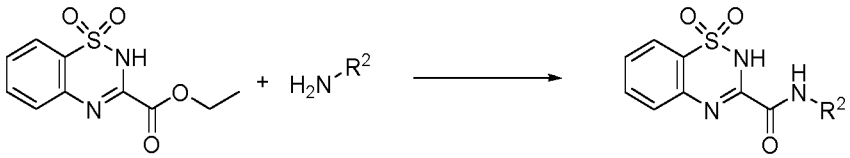
To a solution of the ester (x mmol) and amine (x mmol) in EtOH (x mL) was added Et_3N (3 equivalents) and the mixture was heated at 110 °C in a sealed tube overnight. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound.

General Method M



To a solution of the acid (x mmol), HATU (x mmol) and DIPEA (x mmol) in DMF (x mL) or MeCN (x mL) was added the amine (x mmol) and the mixture was stirred at RT overnight. Water was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound.

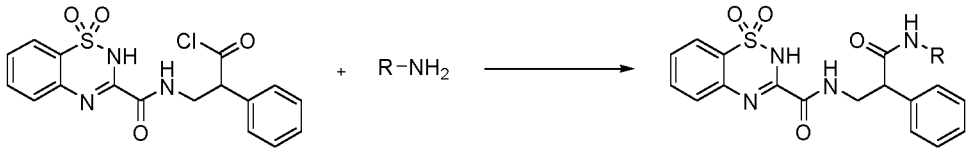
General Method N



I2

To a suspension of ethyl 4*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I2 (x mmol) in EtOH (0.125 mL) was added the amine (x mmol) and for some examples triethylamine (x mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. Method for isolation of product specified in Table L.

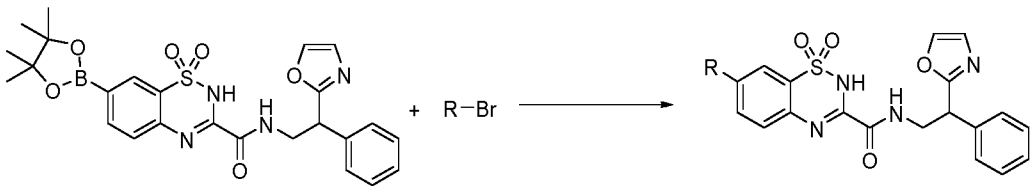
General Method O



I37

A solution of 3-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoyl chloride (I37) (0.13 mmol) and TEA (10 eq) in DCM (5 mL) was stirred at 0 °C under N_2 for 10 min. The amine (5 eq) was then added and the mixture was stirred at room temperature. for 30 min. Water and 1 M HCl were added and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate, concentrated and the residue was purified by preparative TLC (DCM/MeOH = 20:1) to afford the desired product.

General Method P

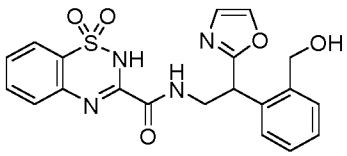
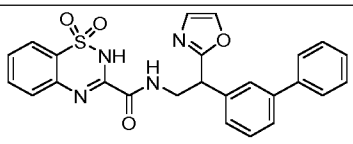


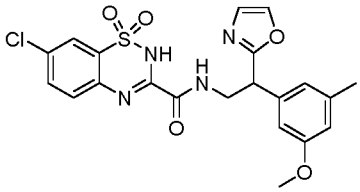
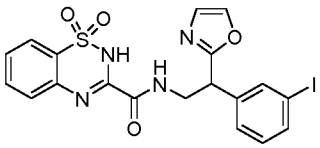
A9

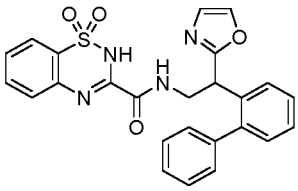
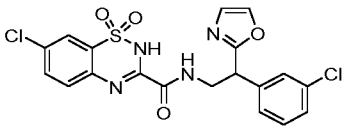
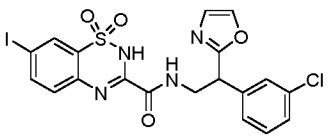
A mixture of *N*-(2-(oxazol-2-yl)-2-phenylethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide (A9) (0.1 mmol), R-Br (4 eq), $Pd(dppf)_2Cl_2$ (0.1 eq), K_2CO_3 (4 eq) in 1,4-dioxane (3 mL) and water (0.5 mL) was stirred under N_2 at 90 °C for 3 h. The mixture was then allowed to cool to room temperature and extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give a residue which was purified by preparative TLC (DCM/MeOH = 20:1) to give the desired product.

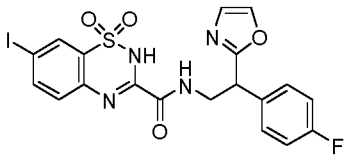
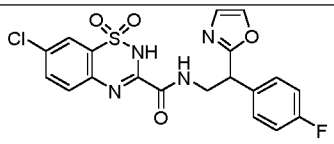
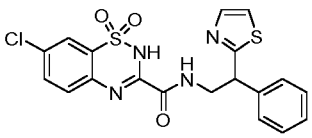
The following examples were prepared according to the procedures described in general methods L-P using the specified quantities of reagents.

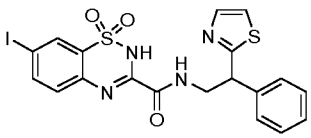
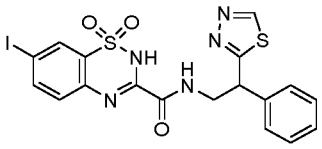
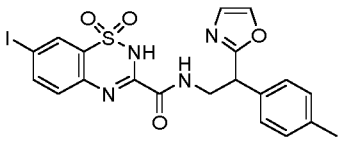
Table L

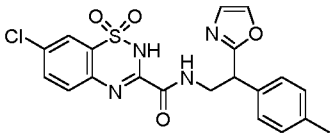
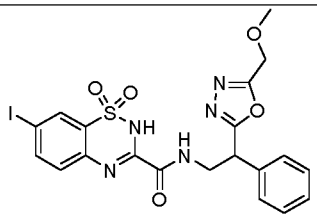
Example	Name and structure	Analytical data	Method	Notes
157	 *N*-(2-(2-(Hydroxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 0.78 min, *m/z* 427.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 12.4 (br s, 1H), 9.30 (t, *J* = 5.6 Hz, 1H), 8.01 (s, 1H), 7.85-7.79 (m, 2H), 7.74 (t, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.45-7.43 (m, 1H), 7.28-7.18 (m, 4H), 5.27 (t, *J* = 5.6 Hz, 1H), 4.96-4.94 (m, 1H), 4.70 (d, *J* = 5.2 Hz, 2H), 4.10-4.05 (m, 1H), 3.80-3.74 (m, 1H).	L	Ester I2 (0.18 mmol), amine I110 (0.15 mmol) EtOH (2 mL)
158	 *N*-(2-([1,1'-Biphenyl]-3-yl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.26 min, *m/z* 473.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (br s, 1H), 8.07 (s, 1H), 7.76 (br s, 1H), 7.59-7.42 (m, 6H), 7.41-7.23 (m, 8H), 4.74 (t, *J* = 7.2 Hz, 1H), 4.01-3.94 (m, 2H).	L	Ester I2 (0.12 mmol), amine I151 (0.12 mmol) EtOH (2 mL) Heated at 120 °C overnight

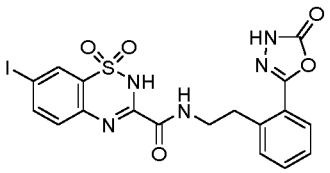
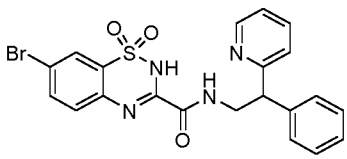
Example	Name and structure	Analytical data	Method	Notes
159	 7-Chloro-*N*-(2-(3-methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.31 min, *m/z* 474.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 8.94 (br s, 1H), 8.04 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.20 (s, 1H), 6.65-6.61 (m, 3H), 4.56 (t, *J* = 7.6 Hz, 1H), 3.96-3.78 (m, 2H), 3.69 (s, 3H), 2.23 (s, 3H).	L	Ester I162 (0.43 mmol), amine I150 (0.52 mmol) EtOH (3 mL) Reaction mixture was diluted with water and extracted with EtOAc. Organic extract was dried over Na_2SO_4 and concentrated to give the title compound.
160	 *N*-(2-(3-Iodophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.14 min, *m/z* 522.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.6 (br s, 1H), 9.33 (t, *J* = 5.6 Hz, 1H), 8.08 (s, 1H), 7.86-7.80 (m, 2H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.66-7.64 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.67 (t, *J* = 7.6 Hz, 1H), 4.01-3.96 (m, 1H), 3.89-3.82 (m, 1H).	L	Ester I2 (1.0 mmol), amine I162 (1.0 mmol) EtOH (8 mL) Heated at 120 °C for 3 h

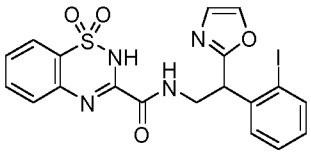
Example	Name and structure	Analytical data	Method	Notes
161	 *N*-(2-([1,1'-Biphenyl]-2-yl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.21 min, *m/z* 473.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (br s, 1H), 9.17 (t, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.39-7.29 (m, 8H), 7.21-7.18 (m, 2H), 4.74 (t, *J* = 7.2 Hz, 1H), 4.05-3.97 (m, 1H), 3.71-3.64 (m, 1H).	L	Ester I2 (0.12 mmol), amine I136 (0.10 mmol) EtOH (2 mL)
162	 7-Chloro-*N*-(2-(3-chlorophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.22 min, *m/z* 464.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.33 (t, *J* = 5.6 Hz, 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.84-7.79 (m, 2H), 7.38-7.33 (m, 3H), 7.25-7.22 (m, 2H), 4.70 (t, *J* = 7.2 Hz, 1H), 4.05-3.85 (m, 2H).	L	Ester I162 (0.28 mmol), amine I128 (0.33 mmol) EtOH (5 mL)
163	 *N*-(2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.23 min, *m/z* 556.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.14 (br s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.38-7.33 (m, 3H), 7.24-7.22 (m, 2H), 4.70 (t, *J* = 7.6 Hz, 1H), 4.01-3.92 (m, 1H), 3.90-3.83 (m, 1H).	L	Ester I7 (0.21 mmol), amine I128 (0.24 mmol) EtOH (5 mL)

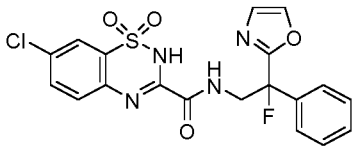
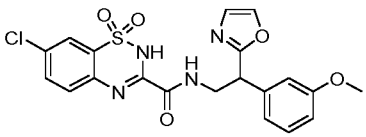
Example	Name and structure	Analytical data	Method	Notes
164	 *N*-(2-(4-Fluorophenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.20 min, *m/z* 540.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.16 (br s, 1H), 8.06-7.98 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.32-7.29 (m, 2H), 7.20-7.13 (m, 3H), 4.68 (t, *J* = 7.6 Hz, 1H), 3.98-3.91 (m, 1H), 3.87-3.80 (m, 1H).	L	Ester I7 (0.21 mmol), amine I124 (0.25 mmol) EtOH (5 mL)
165	 7-Chloro-*N*-(2-(4-fluorophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.13 min, *m/z* 448.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.13 (br s, 1H), 8.05 (s, 1H), 7.81 (s, 1H), 7.71 (s, 2H), 7.33-7.29 (m, 2H), 7.20-7.13 (m, 3H), 4.68 (t, *J* = 7.6 Hz, 1H), 3.98-3.92 (m, 1H), 3.87-3.81 (m, 1H).	L	Ester I162 (0.28 mmol), amine I124 (0.33 mmol) EtOH (5 mL)
166	 7-Chloro-*N*-(2-phenyl-2-(thiazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.19 min, *m/z* 446.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.32 (t, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.84-7.81 (m, 2H), 7.79 (d, *J* = 3.2 Hz, 1H), 7.63 (d, *J* = 3.2 Hz, 1H), 7.39-7.25 (m, 5H), 4.90 (t, *J* = 7.6 Hz, 1H), 4.11-4.04 (m, 1H), 4.02-3.95 (m, 1H).	L	Ester I162 (0.10 mmol), amine I113 (0.10 mmol) EtOH (2.5 mL)

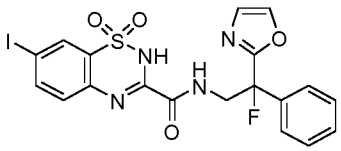
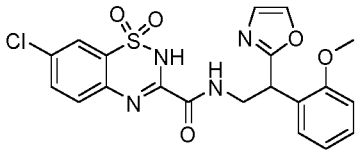
Example	Name and structure	Analytical data	Method	Notes
167	 7-Iodo-*N*-(2-phenyl-2-(thiazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.23 min, *m/z* 538.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.30 (t, *J* = 6.0 Hz, 1H), 8.08-8.04 (m, 2H), 7.79 (d, *J* = 3.2 Hz, 1H), 7.63 (d, *J* = 3.2 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.38-7.25 (m, 5H), 4.89 (t, *J* = 7.6 Hz, 1H), 4.10-4.03 (m, 1H), 4.01-3.94 (m, 1H).	L	Ester I7 (0.10 mmol), amine I113 (0.10 mmol) EtOH (2.5 mL)
168	 7-Iodo-*N*-(2-phenyl-2-(1,3,4-thiadiazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.04 min, *m/z* 539.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.54 (s, 1H), 9.36 (t, *J* = 5.2 Hz, 1H), 8.07-8.04 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.39-7.34 (m, 4H), 7.31-7.29 (m, 1H), 5.09 (t, *J* = 7.6 Hz, 1H), 4.17-4.10 (m, 1H), 4.04-3.97 (m, 1H).	L	Ester I7 (0.24 mmol), amine I66 (0.24 mmol) EtOH (3 mL)
169	 7-Iodo-*N*-(2-(oxazol-2-yl)-2-(*p*-tolyl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.24 min, *m/z* 536.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.27 (t, *J* = 4.4 Hz, 1H), 8.08-8.02 (m, 3H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.18-7.13 (m, 5H), 4.63 (t, *J* = 7.6 Hz, 1H), 4.01-3.93 (m, 1H), 3.88-3.81 (m, 1H), 2.24 (s, 3H).	L	Ester I7 (0.16 mmol), amine I145 (0.13 mmol) EtOH (3 mL)

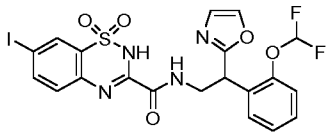
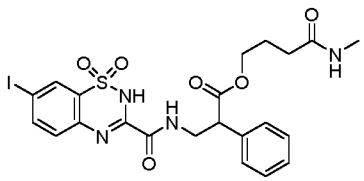
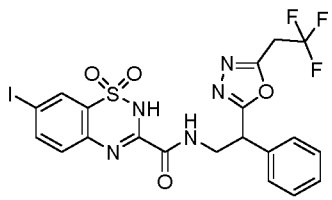
Example	Name and structure	Analytical data	Method	Notes
170	 7-Chloro-*N*-(2-(oxazol-2-yl)-2-(*p*-tolyl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.19 min, *m/z* 444.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.20 (br s, 1H), 8.03 (s, 1H), 7.86 (s, 1H), 7.77 (s, 2H), 7.18 (s, 1H), 7.16-7.11 (m, 4H), 4.63 (t, *J* = 7.6 Hz, 1H), 4.03-3.92 (m, 1H), 3.87-3.80 (m, 1H), 2.24 (s, 3H).	L	Ester I162 (0.34 mmol), amine I145 (0.17 mmol) EtOH (3 mL)
171	 7-Iodo-*N*-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.10 min, *m/z* 567.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.40 (t, *J* = 5.6 Hz, 1H), 8.09-8.04 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.39-7.29 (m, 5H), 4.80 (t, *J* = 7.6 Hz, 1H), 4.60 (s, 2H), 4.07-4.00 (m, 1H), 3.91-3.84 (m, 1H), 3.28 (s, 3H).	L	Ester I7 (0.13 mmol), amine I84 (0.13 mmol), Et_3N (1.29 mmol), EtOH (1 mL) Heated at 120 °C overnight

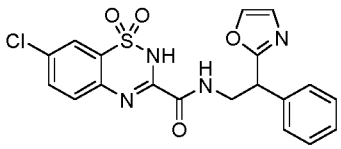
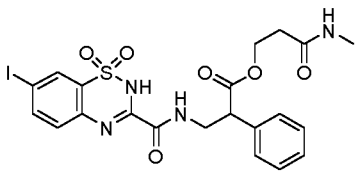
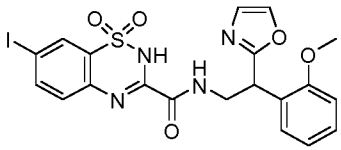
Example	Name and structure	Analytical data	Method	Notes
172	 7-Iodo-*N*-(2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.00 min, *m/z* 539.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58-8.55 (m, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.30-7.20 (m, 5H), 3.50-3.44 (m, 2H), 3.28-3.24 (m, 2H).	L	Ester I7 (0.161 mmol), amine I141 (0.146 mmol), MeOH (3 mL) used Diluted reaction mixture with EtOAc and washed with water. Organic layer was dried over Na_2SO_4 and concentrated to give the title compound.
173	 7-Bromo-*N*-(2-phenyl-2-(pyridin-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.00 min, *m/z* 485.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.25 (t, *J* = 5.6 Hz, 1H), 8.56 (d, *J* = 4.0 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.52-7.69 (m, 2H), 7.36-7.17 (m, 7H), 4.62 (t, *J* = 7.6 Hz, 1H), 4.04-4.01 (m, 2H).	L	Ester I5 (0.13 mmol), amine I121 (0.13 mmol) EtOH (2 mL)

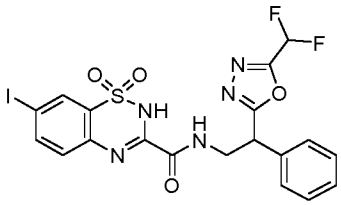
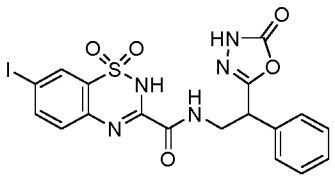
Example	Name and structure	Analytical data	Method	Notes
174	 *N*-(2-(2-Iodophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.05 min, *m/z* 522.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.41 (t, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 7.90-7.80 (m, 3H), 7.75 (t, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 5.01 (t, *J* = 7.6 Hz, 1H), 4.09-4.03 (m, 1H), 3.84-3.77 (m, 1H).	L	Ester I2 (0.30 mmol), amine I106 (0.30 mmol) EtOH (3 mL) Heated at 120 °C for 3 h Reaction mixture was concentrated, then diluted with EtOAc, washed with water. Organic layer was dried over Na_2SO_4 and concentrated. Crude product was triturated with hexanes to give the title compound.

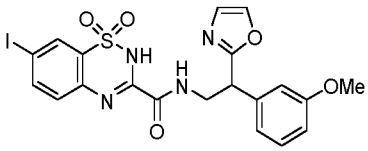
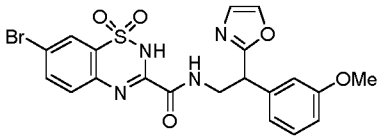
Example	Name and structure	Analytical data	Method	Notes
175	 7-Chloro-*N*-(2-fluoro-2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.16 min, *m/z* 448.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.6 (br s, 1H), 9.06 (t, *J* = 6.4 Hz, 1H), 8.24 (s, 1H), 7.91 (s, 1H), 7.79 (s, 2H), 7.48-7.32 (m, 6H), 4.38-4.30 (m, 2H).	L	Ester I162 (0.15 mmol), amine I99 (0.15 mmol) EtOH (2 mL) No Et_3N used Heated at 120 °C overnight A precipitate formed in the reaction. Collected by filtration to give title compound.
176	 7-Chloro-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.12 min, *m/z* 461.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.30 (t, *J* = 6.0 Hz, 1H), 8.04 (s, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.82-7.81(m, 2H), 7.26-7.20 (m, 2H), 6.85-6.80 (m, 3H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.03-3.91 (m, 1H), 3.90-3.85 (m, 1H), 3.71 (s, 3H).	L	Ester I162 (0.50 mmol), amine I96 (0.50 mmol) EtOH (4 mL) No Et_3N used Heated at 120 °C overnight A precipitate formed in the reaction. Collected by filtration to give title compound.

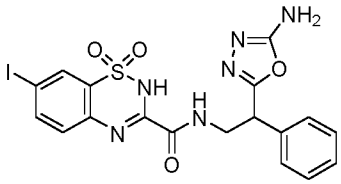
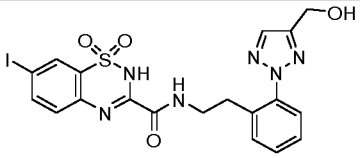
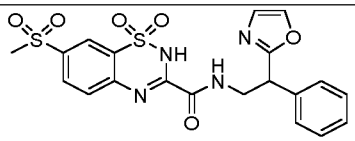
Example	Name and structure	Analytical data	Method	Notes
177	 *N*-(2-Fluoro-2-(oxazol-2-yl)-2-phenylethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.23 min, *m/z* 540.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.06 (t, *J* = 5.6 Hz, 1H), 8.24 (s, 1H), 8.10 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.42-7.37 (m, 6H), 4.38-4.32 (m, 2H).	L	Ester I7 (0.20 mmol), amine I99 (0.20 mmol) EtOH (2.5 mL) No Et_3N used Heated at 120 °C overnight A precipitate formed in the reaction. Collected by filtration to give title compound.
178	 7-Chloro-*N*-(2-(2-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.15 min, *m/z* 461.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.21 (t, *J* = 6.0 Hz, 1H), 8.00 (s, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.83-7.77 (m, 2H), 7.28-7.23 (m, 1H), 7.18 (s, 1H), 7.10 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 5.01 (t, *J* = 7.6 Hz, 1H), 4.03-3.96 (m, 1H), 3.82-3.75 (m, 1H), 3.32 (s, 3H).	L	Ester I162 (0.37 mmol), amine I76 (0.37 mmol) Et_3N (1.83 mmol) EtOH (2 mL) Heated at 120 °C for 3 h

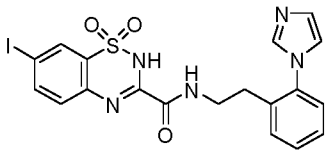
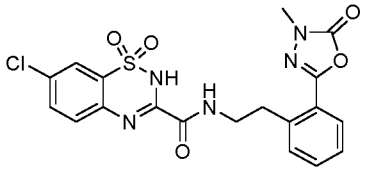
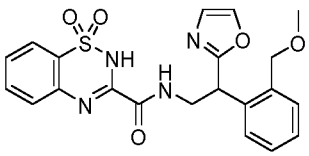
Example	Name and structure	Analytical data	Method	Notes
179	 *N*-(2-(2-(Difluoromethoxy)phenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.25 min, *m/z* 588.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.34 (t, *J* = 6.0 Hz, 1H), 8.11-8.04 (m, 2H), 8.02 (d, *J* = 0.9 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.40-7.34 (m, 2H), 7.27-7.17 (m, 3H), 7.15 (t, *J* = 73.6 Hz, 1H), 4.99 (t, *J* = 7.5 Hz, 1H), 4.09-4.02 (m, 1H), 3.85-3.79 (m, 1H).	L	Ester I7 (0.22 mmol), amine I80 (0.20 mmol) Et_3N (0.98 mmol) EtOH (2 mL) Heated at 120 °C for 3 h
180	 4-(Methylamino)-4-oxobutyl 3-(7-iodo-1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate	LCMS-C: R_t 1.98 min, *m/z* 598.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.24 (t, *J* = 5.6 Hz, 1H), 8.07-8.03 (m, 2H), 7.65 (d, *J* = 4.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.36-7.26 (m, 5H), 4.13 (t, *J* = 7.6 Hz, 1H), 4.04-3.96 (m, 2H), 3.90-3.83 (m, 1H), 3.66-3.59 (m, 1H), 2.52 (d, *J* = 4.4 Hz, 3H), 2.05 (t, *J* = 7.6 Hz, 2H), 1.76-1.68 (m, 2H).	L	Ester I7 (0.65 mmol), amine I72 (0.59 mmol) Et_3N (2.93 mmol) EtOH (2 mL) Heated at 120 °C for 3 h
181	 7-Iodo-*N*-(2-phenyl-2-(5-(2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.29 min, *m/z* 605.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.34 (br s, 1H), 8.07-8.03 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.39-7.31 (m, 5H), 4.81 (t, *J* = 7.6 Hz, 1H), 4.29 (q, *J* = 10.8 Hz, 2H), 4.06-3.99 (m, 1H), 3.91-3.86 (m, 1H).	L	Ester I7 (0.10 mmol), amine I102 (0.07 mmol) EtOH (2 mL) No Et_3N used Heated at 120 °C overnight Prep. TLC (DCM/MeOH=40/1)

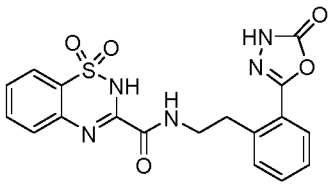
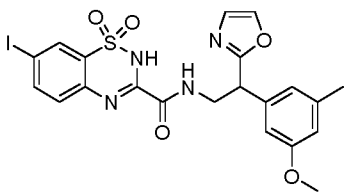
Example	Name and structure	Analytical data	Method	Notes
182	 7-Chloro-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.08 min, *m/z* 431.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.8 (br s, 1H), 9.32 (t, *J* = 6.0 Hz, 1H), 8.04 (d, *J* = 0.8 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.84-7.78 (m, 2H), 7.36-7.32 (m, 2H), 7.29-7.25 (m, 3H), 7.20 (d, *J* = 0.4 Hz, 1H), 4.69 (t, *J* = 7.6 Hz, 1H), 4.04-3.98 (m, 1H), 3.91-3.85 (m, 1H).	L	Ester I162 (0.35 mmol), amine I27 (0.53 mmol) EtOH (6 mL) Heated at 110 °C for 3 h
183	 3-(Methylamino)-3-oxopropyl 3-(7-iodo-1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)-2-phenylpropanoate	LCMS-C: R_t 1.92 min, *m/z* 584.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.7 (br s, 1H), 9.25 (t, *J* = 5.6 Hz, 1H), 8.09-8.05 (m, 2H), 7.79-7.74 (m, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.34-7.26 (m, 5H), 4.25 (t, *J* = 6.0 Hz, 2H), 4.11 (t, *J* = 7.6 Hz, 1H), 3.87-3.80 (m, 1H), 3.67-3.62 (m, 1H), 2.50 (3H overlap with solvent peak), 2.38 (t, *J* = 6.0 Hz, 2H).	M	Acid I53 (1.05 mmol), amine I69 (1.05 mmol) HATU (1.74 mmol); DIPEA (5.25 mmol); MeCN (45 mL)
184	 7-Iodo-*N*-(2-(2-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.22 min, *m/z* 552.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.7 (br s, 1H), 9.20 (t, *J* = 6.0 Hz, 1H), 8.08-8.04 (m, 2H), 7.99 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 7.18 (s, 1H), 7.10 (dd, 7.6, 1.6 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 5.01 (t, *J* = 7.6 Hz, 1H), 4.02-3.95 (m, 1H), 3.81-3.76 (m, 1H), 3.73 (s, 3H).	L	Ester I7 (0.25 mmol), amine I76 (0.23 mmol) Et_3N (1.15 mmol) EtOH (2 mL) Heated at 120 °C for 3 h Recrystallised from MeOH

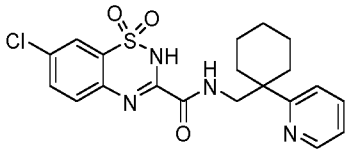
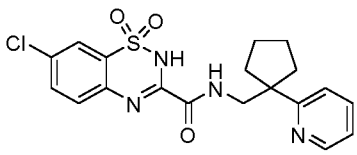
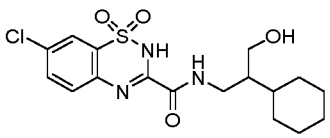
Example	Name and structure	Analytical data	Method	Notes
185	 *N*-(2-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.68 min, *m/z* 573.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.39 (t, *J* = 5.2 Hz, 1H), 8.07 (d, *J* = 1.9 Hz, 1H), 8.04 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.45-7.32 (m, 6H), 4.87 (t, *J* = 7.6 Hz, 1H), 4.10-4.03 (m, 1H), 3.92-3.86 (m, 1H).	M	Acid I53 (0.36 mmol), amine I63 (0.36 mmol) HATU (0.54 mmol) DIPEA (1.44 mmol) MeCN (5 mL) Purified by trituration with MeOH
186	 7-Iodo-*N*-(2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.50 min, *m/z* 539.8 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 12.3 (s, 1H), 9.40 (t, *J* = 6.0 Hz, 1H), 8.08-8.04 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.40-7.30 (m, 5H), 4.36 (t, *J* = 7.6 Hz, 1H), 3.97-3.90 (m, 1H), 3.75-3.66 (m, 1H).	M	Acid I53 (0.15 mmol), amine I92 (0.20 mmol) HATU (0.23 mmol) DIPEA (0.45 mmol) DMF (5 mL) Prep. TLC (DCM/MeOH=15/1)

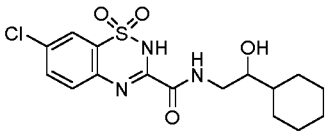
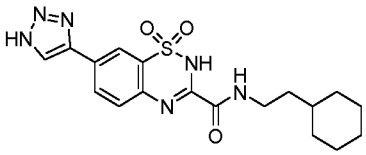
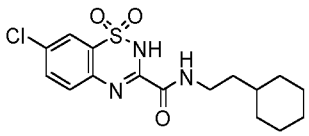
Example	Name and structure	Analytical data	Method	Notes
187	 7-Iodo-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.62 min, *m/z* 552.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.27 (t, *J* = 6.0 Hz, 1H), 8.08-8.04 (m, 3H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.26-7.20 (m, 2H), 6.85-6.80 (m, 3H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.00-3.94 (m, 1H), 3.91-3.84 (m, 1H), 3.71 (s, 3H).	L	Ester I7 (0.40 mmol), amine I96 (0.48 mmol) EtOH (5 mL) No Et_3N used Heated at 120 °C overnight A precipitate formed in the reaction. Collected by filtration to give title compound.
188	 7-Bromo-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.61 min, *m/z* 504.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.27 (t, *J* = 6.0 Hz, 1H), 8.04 (s, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.26-7.20 (m, 2H), 6.84-6.80 (m, 3H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.01-3.94 (m, 1H), 3.91-3.84 (m, 1H), 3.71 (s, 3H).	L	Ester I5 (0.30 mmol), amine I96 (0.36 mmol) EtOH (4 mL) No Et_3N used A precipitate formed in the reaction. Collected by filtration to give title compound.

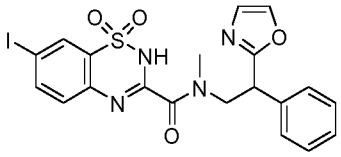
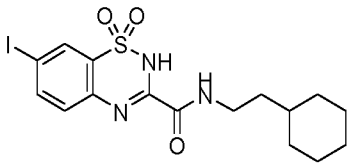
Example	Name and structure	Analytical data	Method	Notes
189	 *N*-(2-(5-Amino-1,3,4-oxadiazol-2-yl)-2-phenylethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.45 min, *m/z* 538.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.30 (t, *J* = 6.0 Hz, 1H), 8.08-8.04 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.37-7.27 (m, 5H), 6.94 (s, 2H), 4.53 (t, *J* = 7.6 Hz, 1H), 3.96-3.90 (m, 1H), 3.84-3.77 (m, 1H).	L	Ester I7 (0.20 mmol), amine I90 (0.24 mmol) EtOH (5 mL) Heated at 120 °C overnight Prep. TLC (DCM/MeOH=10/1)
190	 *N*-(2-(4-(Hydroxymethyl)-2*H*-1,2,3-triazol-2-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.57 min, *m/z* 553.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.30 (br s, 1H), 8.10-8.06 (m, 2H), 7.97 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 4H), 5.37 (br s, 1H), 4.65 (s, 2H), 3.47-3.46 (m, 2H), 2.93 (t, *J* = 6.4 Hz, 2H).	L	Ester I7 (1.0 mmol), amine I60 (0.92 mmol) EtOH (7 mL) Heated at 120 °C for 4 h
191	 7-(Methylsulfonyl)-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.29 min, *m/z* 473.0 $[M-H]^-$; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.42 (d, *J* = 5.6 Hz, 1H), 8.20 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.86-7.91 (m, 2H), 7.35-7.25 (m, 5H), 7.17 (s, 1H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.11-4.06 (m, 1H), 4.01-3.96 (m, 1H), 3.19 (s, 3H).	L	Ester I161 (0.15 mmol), amine I27 (0.30 mmol) EtOH (5 mL) Heated at 110 °C for 2 h

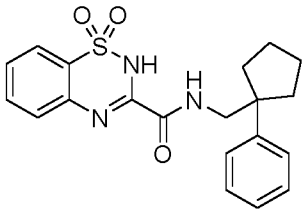
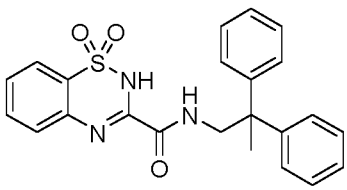
Example	Name and structure	Analytical data	Method	Notes
192	 *N*-(2-(1*H*-Imidazol-1-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-D: R_t 2.03 min, *m/z* 522.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.5 (br s, 1H), 9.22 (br s, 1H), 8.06-8.02 (m, 2H), 7.83 (s, 1H), 7.57-7.55 (m, 1H), 7.44-7.39 (m, 4H), 7.30 (br s, 1H), 7.09 (s, 1H), 3.50 (2H obscured by water peak), 2.73 (t, *J* = 6.8 Hz, 2H).	L	Ester I7 (0.26 mmol), amine I135 (0.214 mmol) EtOH (5 mL) Heated at 130 °C for 3 h
193	 7-Chloro-*N*-(2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.15 min, *m/z* 461.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.7 (br s, 1H), 9.29 (t, *J* = 5.6 Hz, 1H), 7.91 (s, 1H), 7.85-7.79 (m, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42-7.38 (m, 2H), 3.59-3.50 (m, 2H), 3.42 (s, 3H), 3.24 (t, *J* = 6.8 Hz, 2H).	M	Acid I163 (0.27 mmol), amine I131 (0.23 mmol) HATU (0.32 mmol) DIPEA (1.15 mmol) DMF (8 mL)
194	 *N*-(2-(2-(Methoxymethyl)phenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 1.85 min, *m/z* 441.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.6 (br s, 1H), 9.27 (t, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 0.9 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.74-7.70 (m, 1H), 7.52 (td, *J* = 7.7, 1.2 Hz, 1H), 7.37 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.20 (d, *J* = 0.9 Hz, 1H), 4.98 (t, *J* = 7.6 Hz, 1H), 4.61-4.53 (m, 2H), 4.12-4.01 (m, 1H), 3.83-3.77 (m, 1H), 3.32 (s, 3H).	L	Ester I2 (0.12 mmol), amine I115 (0.10 mmol) EtOH (2 mL)

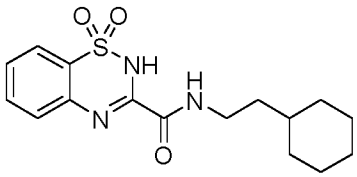
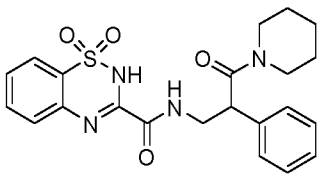
Example	Name and structure	Analytical data	Method	Notes
195	 *N*-(2-(5-Oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 1.08 min, *m/z* 413.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.6 (br s, 1H), 9.27 (t, *J* = 6.0 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 7.74-7.70 (m, 2H), 7.54-7.45 (m, 2H), 7.41-7.37 (m, 2H), 3.59-3.54 (m, 2H), 3.25 (t, *J* = 6.8 Hz, 2H).	M	Acid I29 (0.27 mmol), amine I141 (0.24 mmol) HATU (0.34 mmol) DIPEA (0.82 mmol) DMF (20 mL) Purified by prep. HPLC
196	 7-Iodo-*N*-(2-(3-methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.27 min, *m/z* 566.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.25-9.24 (m, 1H), 8.09-8.02 (m, 3H), 7.60-7.57 (m, 1H), 7.20 (d, *J* = 6.0 Hz, 1H), 6.65-6.62 (m, 3H), 4.63-4.55 (m, 1H), 4.00-3.92 (m, 1H), 3.88-3.82 (m, 1H), 3.69 (s, 1.5H), 3.68 (s, 1.5H), 2.23 (s, 1.5H), 2.21 (s, 1.5H).	L	Ester I7 (0.52 mmol), amine I150 (0.43 mmol) EtOH (3 mL) Reaction mixture was concentrated, the residue was diluted with water and extracted with EtOAc. Organic extract was washed with brine, dried over Na_2SO_4 and concentrated to give the title compound.

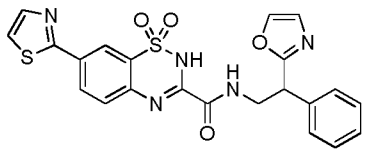
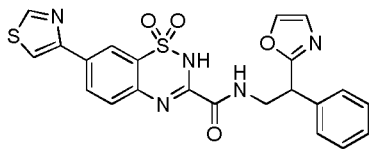
Example	Name and structure	Analytical data	Method	Notes
197	 7-Chloro-*N*-((1-(pyridin-2-yl)cyclohexyl)methyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 1.51 min, *m/z* 433.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.7 (br s, 1H), 8.81 (t, *J* = 6.4 Hz, 1H), 8.58 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.84-7.74 (m, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.26-2.23 (m, 2H), 1.59-1.54 (m, 4H), 1.42-1.34 (m, 2H), 1.25-1.22 (m, 2H).	L	Ester I162 (0.20 mmol), amine I120 (0.20 mmol) EtOH (3 mL)
198	 7-Chloro-*N*-((1-(pyridin-2-yl)cyclopentyl)methyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 0.77 min, *m/z* 418.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.8 (br s, 1H), 8.91 (t, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 4.0 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.84-7.73 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 3.60 (d, *J* = 6.4 Hz, 2H), 2.02-1.92 (m, 4H), 1.78-1.65 (m, 4H).	L	Ester I162 (0.20 mmol), amine I118 (0.30 mmol) EtOH (2.5 mL)
199	 7-Chloro-*N*-(2-cyclohexyl-3-hydroxypropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.17 min, *m/z* 400.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.8 (br s, 1H), 9.12 (t, *J* = 6.0 Hz, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.86-7.80 (m, 2H), 4.61 (t, *J* = 4.8 Hz, 1H), 3.51-3.34 (m, 4H), 3.27-3.20 (m, 1H), 1.69-1.54 (m, 7H), 1.24-1.11 (m, 4H).	L	Ester I162 (1.63 mmol), amine I155 (1.56 mmol) EtOH (20 mL) Heated at 110 °C for 3 h

Example	Name and structure	Analytical data	Method	Notes
200	 7-Chloro-*N*-(2-cyclohexyl-2-hydroxyethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.06 min, *m/z* 386.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 8.85 (t, *J* = 5.6 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.86-7.79 (m, 2H), 4.78 (d, *J* = 5.2 Hz, 1H), 3.46-3.40 (m, 2H), 3.23-3.16 (m, 1H), 1.80-1.58 (m, 5H), 1.17-0.88 (m, 6H).	L	Ester I162 (0.40 mmol), amine I116 (0.40 mmol) EtOH (3 mL)
201	 *N*-(2-Cyclohexylethyl)-7-(1*H*-1,2,3-triazol-4-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.18 min, *m/z* 403.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.3 (br s, 1H), 12.7 (br s, 1H), 9.20 (t, *J* = 6.0 Hz, 1H), 8.56 (br s, 1H), 8.29 (d, *J* = 1.2 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 3.31-3.26 (m, 2H), 2.06-1.96 (m, 2H), 1.74-1.58 (m, 5H), 1.46-1.40 (m, 2H), 1.18-1.10 (m, 2H), 0.92-0.84 (m, 2H).	L	Ester I158 (0.25 mmol), amine (0.25 mmol) EtOH (5 mL) Silica gel chromatography (DCM/MeOH=10/1)
202	 7-Chloro-*N*-(2-cyclohexylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.40 min, *m/z* 369.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (t, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 3.22-3.20 (m, 2H), 1.72-1.58 (m, 5H), 1.41-1.36 (m, 2H), 1.23-1.15 (m, 4H), 0.84-0.83 (m, 2H).	L	Ester I162 (0.35 mmol), amine (0.35 mmol) EtOH (5 mL)

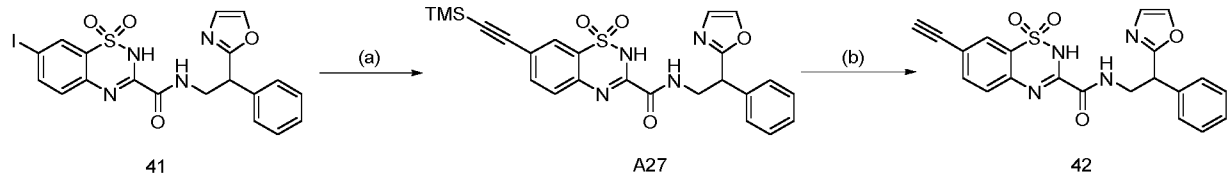
Example	Name and structure	Analytical data	Method	Notes
203	 7-Iodo-*N*-methyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 2.10 min, *m/z* 536.9 $[M+H]^+$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.8 (br s, 0.5H), 10.2 (br s, 0.5H), 8.23 (d, *J* = 1.8 Hz, 0.5H), 8.21 (d, *J* = 1.8 Hz, 0.5H), 7.86 (t, *J* = 1.6 Hz, 0.5H), 7.84 (t, *J* = 1.7 Hz, 0.5H), 7.66 (s, 0.5H), 7.58 (s, 0.5H), 7.38-7.29 (m, 3.5H), 7.24-7.14 (m, 2H), 7.06-7.04 (m, 1H), 6.92 (d, *J* = 8.6 Hz, 0.5H), 4.75-4.51 (m, 2H), 4.24-4.19 (m, 0.5H), 4.02-3.96 (m, 0.5H), 3.23 (s, 1.5H), 3.01 (s, 1.5H).	M	Acid I53 (0.54 mmol), amine I133 (0.49 mmol) HATU (0.74 mmol) DIPEA (1.48 mmol) DMF (7 mL)
204	 *N*-(2-Cyclohexylethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-C: R_t 3.12 min, *m/z* 461.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 9.20 (br s, 1H), 8.24-8.01 (m, 2H), 7.61 (s, 1H), 3.30-3.20 (m, 2H), 1.88-0.78 (m, 13H).	L	Ester I7 (0.39 mmol), amine (0.43 mmol) MeOH (10 mL) used Heated at 120 °C overnight Most of the solvent was removed and residue adjusted to pH 5 with 1 M aqueous HCl. Resulting precipitate was collected to give the title compound.

Example	Name and structure	Analytical data	Method	Notes
205	 *N*-((1-Phenylcyclopentyl)methyl)-4*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.772 min, *m/z* 384.2 $[M+H]^+$	N	Ester I2 (0.197 mmol), amine (0.197 mmol) Reaction was cooled and the solvent removed *in vacuo* to give the title compound.
206	 *N*-(2,2-Diphenylpropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.386 min, *m/z* 420.2 $[M+H]^+$	N	Ester I2 (0.197 mmol), amine (0.236 mmol) Reaction was cooled and the resulting precipitate was collected and washed with a portion of EtOH (2 mL) and dried under vacuum to give the title compound.

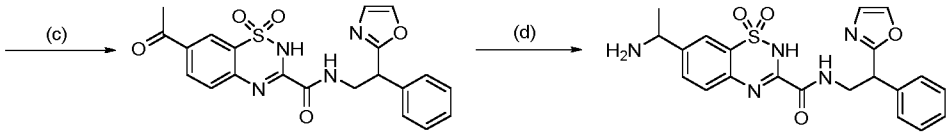
Example	Name and structure	Analytical data	Method	Notes
207	 *N*-(2-Cyclohexylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS-B: rt 3.717 min, *m/z* 336.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H), 9.20 (t, *J* = 5.9 Hz, 1H), 7.84 (ddd, *J* = 14.3, 8.2, 1.3 Hz, 2H), 7.73 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 3.32 – 3.25 (m, 2H), 1.73 (d, *J* = 12.5 Hz, 2H), 1.69 – 1.56 (m, 3H), 1.43 (q, *J* = 7.0, 7.0 Hz, 2H), 1.33 – 1.09 (m, 4H), 0.95 – 0.81 (m, 2H).	N	Ester I2 (0.098 mmol), amine (0.098 mmol), Et_3N (0.098 mmol) Reaction was cooled, precipitate was collected by filtration, washed with EtOH (2 mL) and then dried under vacuum to give the title compound.
133	 *N*-(3-Oxo-2-phenyl-3-(piperidin-1-yl)propyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.80 min, *m/z* 441.1 $[M+H]^+$; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.6 (s, 1H), 8.24 (t, *J* = 6.4 Hz, 1H), 7.97 (dd, *J* = 8.0. 1.2 Hz, 1H), 7.60 (m, 1H), 7.48 (m, 1H), 7.37-7.33 (m, 2H), 7.30-7.25 (m, 4H), 4.02-3.83 (m, 4H), 3.30-3.24 (m, 2H), 3.18-3.12 (m, 1H), 1.50-1.22 (m, 6H).	O	

Example	Name and structure	Analytical data	Method	Notes
134	 *N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(thiazol-2-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.58 min, *m/z* 480.1 $[M+H]^+$; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.9 (s, 1H), 9.18 (s, 1H), 8.26-8.21 (m, 2H), 8.05 (s, 1H), 7.98 (s, 1H), 7.87-7.81 (m, 2H), 7.35-7.21 (m, 6H), 4.68 (t, *J* = 6.8 Hz, 1H), 4.04-3.87 (m, 2H).	P	
135	 *N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(thiazol-4-yl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide	LCMS (ES-API): R_t 2.49 min, *m/z* 480.1 $[M+H]^+$; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.8 (s, 1H), 9.25 (s, 2H), 8.41 (s, 2H), 8.33 (d, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.35-7.28 (m, 5H), 7.21 (s, 1H), 4.68 (t, *J* = 6.8 Hz, 1H), 4.04-3.88 (m, 2H).	P	

Example 208: 7-(1-Aminoethyl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 208



41 A27 42



43 208

a) *N*-(2-(Oxazol-2-yl)-2-phenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A27

To a mixture of 7-iodo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 41 (880 mg, 1.7 mmol), $Pd(PPh_3)_2Cl_2$ (120 mg, 0.17 mmol) and CuI (32 mg, 0.17 mmol) in Et_3N (10 mL) and DMF (10 mL) under N_2 was added ethynyltrimethylsilane (700 mg, 6.8 mmol) and the mixture was stirred at RT under N_2 overnight. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (200 mL), washed with water (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.3 g, >100%) as a brown solid, which was used directly in the next step. LCMS-D: R_t 3.19 min, *m/z* 493.1 $[M+H]^+$.

b) 7-Ethynyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 42

To a solution of *N*-(2-(oxazol-2-yl)-2-phenylethyl)-7-((trimethylsilyl)ethynyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A27 (1.2 g, 2.4 mmol) in THF (20 mL) and MeOH (20 mL) was added a 1 M aqueous KOH solution (12.0 mL, 12.0 mmol) and the mixture was stirred at RT for 45 min. Dowex 50WX8 H^+ form (50 g) was added and stirring was continued for 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL) and concentrated under reduced pressure to give the title compound (800 mg, 80%) as a brown solid. LCMS-D: R_t 2.64 min, *m/z* 421.1 $[M+H]^+$.

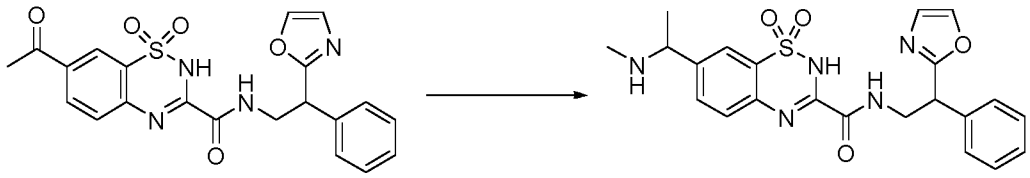
c) 7-Acetyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 43

A suspension of $AgSbF_6$ (69 mg, 0.2 mmol) and chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (124 mg, 0.2 mmol) in MeOH (12 mL) was stirred at RT for 2 min. 7-Ethynyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxmide 1,1-dioxide 42 (420 mg, 1.0 mmol) and water (6 mL) were then added and the mixture was heated at 65 °C overnight. The resulting precipitate was collected by filtration and dried to give the title compound (400 mg, 90%) as a brown solid, which was used in the next step without further purification. LCMS-D: Rt 1.77 min, *m/z* 439.1 $[M+H]^+$.

d) 7-(1-Aminoethyl)-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 208

To a solution of 7-acetyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 43 (219 mg, 0.5 mmol) in MeOH (5 mL) was added NH_4OAc (385 mg, 5 mmol) and $NaCNBH_3$ (32 mg, 0.5 mmol) and the mixture was heated at reflux for 18 h. The mixture was diluted with water, extracted with EtOAc (100 mL) and the organic layer was concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 10/1) to give the title compound (50 mg, 25%) as a yellow solid. LCMS-D: R_t 1.89 min, *m/z* 440.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.93 (s, 1H), 7.85 (s, 1H), 7.72 – 7.65 (m, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.36 – 7.24 (m, 5H), 7.17 (s, 1H), 4.65 – 4.61 (m, 1H), 4.54 (q, *J* = 6.7 Hz, 1H), 4.11 – 4.03 (m, 1H), 4.01 – 3.92 (m, 1H), 1.63 (d, *J* = 6.9 Hz, 3H).

Example 209: 7-(1-(Methylamino)ethyl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 209

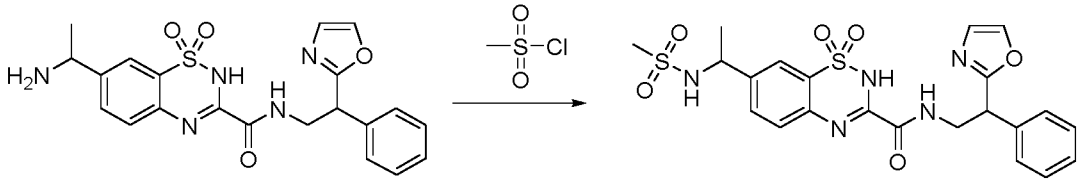


43 209

To a solution of 7-acetyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 43 (44 mg, 0.1 mmol) in MeOH (5 mL) was added CH_3NH_2 (2 M solution in THF, 0.5 mL, 1.0 mmol) and $NaBH_3CN$ (6.3 mg, 0.1 mmol). The flask was sealed and the mixture was heated at 66 °C overnight. The mixture was diluted with water, extracted with EtOAc and the organic extract was concentrated under reduced pressure.

The residue was purified by prep. TLC (DCM/MeOH = 10/1) to give the title compound (10 mg, 20%) as a yellow solid. LCMS-D: R_t 2.09 min, *m/z* 454.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.02 (s, 1H), 7.86 (s, 1H), 7.85 – 7.80 (m, 1H), 7.73 – 7.67 (m, 1H), 7.37 – 7.25 (m, 5H), 7.17 (s, 1H), 4.66 – 4.58 (m, 1H), 4.46 (q, *J* = 6.8 Hz, 1H), 4.12 – 4.04 (m, 1H), 4.02 – 3.93 (m, 1H), 2.60 (s, 3H), 1.69 (d, *J* = 6.9 Hz, 3H).

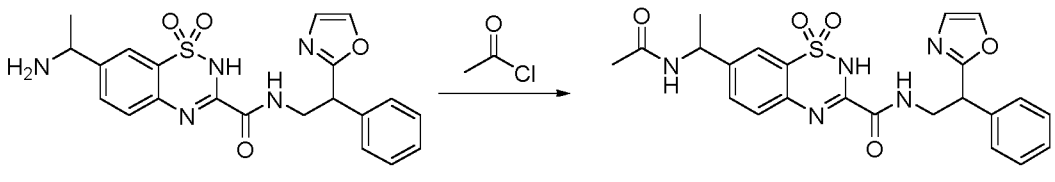
Example 210: 7-(1-(Methylsulfonamido)ethyl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 210



208 210

To a solution of 7-(1-aminoethyl)-*N*-(2-(oxazol-2-yl)-2-phenylethy l)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 208 (44 mg, 0.1 mmol) in pyridine (5 mL) at 0 °C was added MsCl (51 mg, 0.5 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with 1 M aqueous HCl (20 mL), extracted with EtOAc (100 mL) and the organic extract was washed with water (50 mL × 3) and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 10/1) to give the title compound (20 mg, 40%) as a yellow solid. LCMS-D: R_t 2.18 min, *m/z* 518.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 0.9 Hz, 1H), 7.73 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.36 – 7.24 (m, 5H), 7.17 (d, *J* = 0.9 Hz, 1H), 4.70 (q, *J* = 7.0 Hz, 1H), 4.62 (t, 7.6 Hz, 1H), 4.12 – 4.03 (m, 1H), 4.01 – 3.94 (m, 1H), 2.78 (s, 3H), 1.52 (d, *J* = 7.0 Hz, 3H).

Example 211: 7-(1-Acetamidoethyl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 211

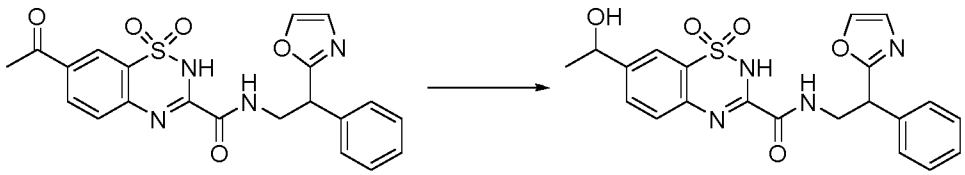


208 211

To a solution of 7-(1-aminoethyl)-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 208 (44 mg, 0.1 mmol) in pyridine (5 mL) at 0 °C was added acetyl chloride (78 mg, 1.0 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with 1 M aqueous HCl (20 mL), extracted with EtOAc

(100 mL) and the organic extract was washed with water (50 mL × 3) and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 10/1) to give the title compound (10 mg, 20%) as a white solid. LCMS-D: R_t 2.29 min, *m/z* 482.0 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.86 (s, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.31 (s, 5H), 7.17 (d, *J* = 0.8 Hz, 1H), 5.05 (q, *J* = 7.0 Hz, 1H), 4.62 (t, *J* = 7.6 Hz, 1H), 4.11 – 4.03 (m, 1H), 4.01 – 3.93 (m, 1H), 1.98 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H).

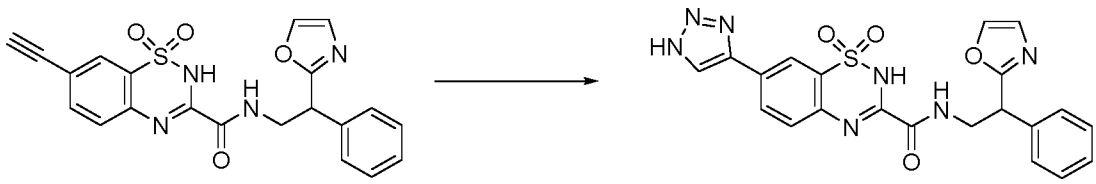
Example 212: 7-(1-Hydroxyethyl)-N-(2-(oxazol-2-yl)-2-phenylethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 212



43 212

To a solution of 7-acetyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 43 (44 mg, 0.1 mmol) in MeOH (5 mL) was added $NaBH_4$ (4.5 mg, 0.12 mmol) and the mixture was stirred at RT under N_2 for 1 h. The mixture was diluted with water, extracted with EtOAc and the organic extract was concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 10/1) to give the title compound (10 mg, 20%) as a yellow solid. LCMS-D: R_t 2.4 min, *m/z* 441.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.6 (s, 1H), 9.26 (t, *J* = 6.0 Hz, 1H), 8.04 (d, *J* = 0.9 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.69 – 7.64 (m, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 7.20 (d, *J* = 0.9 Hz, 1H), 5.44 (d, *J* = 4.4 Hz, 1H), 4.84 – 4.77 (m, 1H), 4.68 (t, *J* = 7.5 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.92 – 3.84 (m, 1H), 1.33 (d, *J* = 6.4 Hz, 3H).

Example 213: N-(2-(Oxazol-2-yl)-2-phenylethyl)-7-(1H-1,2,3-triazol-4-yl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 213

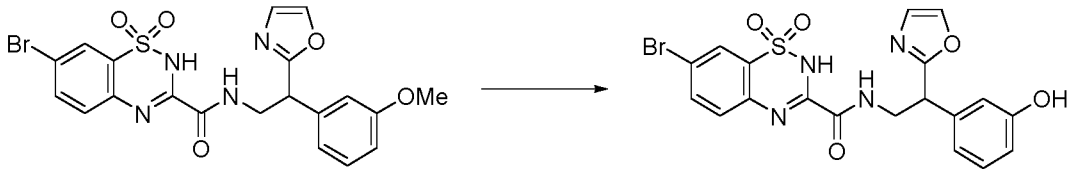


42 213

To a solution of 7-ethynyl-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 42 (52 mg, 0.12 mmol) in DMF (1 mL) and EtOH (0.25 mL) was added CuI (5 mg, 24 μmol) and azidotrimethylsilane (18 mg, 0.15 mmol) and the mixture

was stirred at 120 °C for 18 h in a sealed tube. The mixture was treated with 1 M aqueous HCl (1 mL), diluted with EtOAc (100 mL) and washed with water (50 mL × 3). The organic layer was concentrated under reduced pressure and the residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (20 mg, 40%) as a yellow solid. LCMS-D: R_t 2.4 min, *m/z* 464.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 15.5 – 15.2 (m, 1H), 12.7 (s, 1H), 9.28 (t, *J* = 6.0 Hz, 1H), 8.81 – 8.38 (m, 1H), 8.29 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 7.21 (s, 1H), 4.68 (t, *J* = 7.5 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.95 – 3.84 (m, 1H).

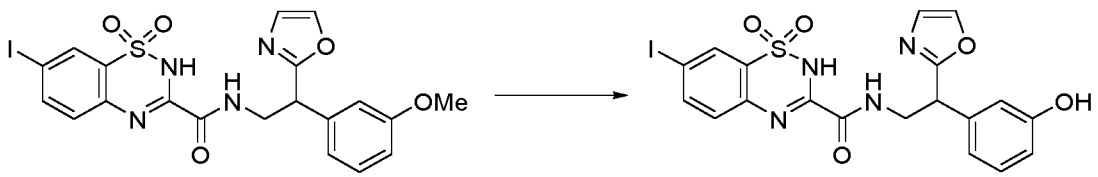
Example 214: 7-Bromo-N-(2-(3-hydroxyphenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 214



188 214

To a solution of 7-bromo-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 188 (101 mg, 0.2 mmol) in DCM (4 mL) at 0 °C was added BBr_3 (1 M solution in DCM, 0.4 mL, 0.4 mmol) and the mixture was stirred overnight. The mixture was diluted with DCM (50 mL), washed with a saturated aqueous $NaHCO_3$ solution and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (10 mg, 10 %) as a yellow solid. LCMS-D: R_t 2.41 min, *m/z* 490.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.44 (s, 1H), 9.27 (t, *J* = 5.9 Hz, 1H), 8.04 (d, *J* = 0.9 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.93 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 0.9 Hz, 1H), 7.15 – 7.08 (m, 1H), 6.71 – 6.62 (m, 3H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.02 – 3.93 (m, 1H), 3.86 – 3.77 (m, 1H).

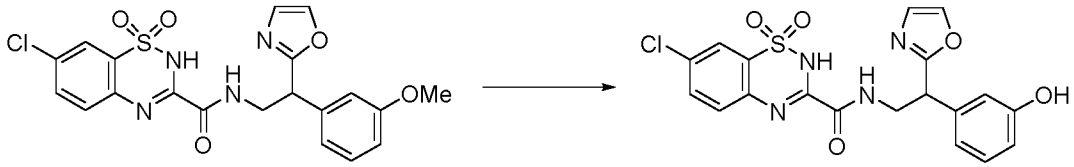
Example 215: N-(2-(3-Hydroxyphenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 215



187 215

To a solution of 7-iodo-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 187 (110 mg, 0.2 mmol) in DCM (10 mL) at 0 °C was added BBr_3 (1 M solution in DCM, 0.4 mL, 0.4 mmol) and the mixture was stirred overnight. The mixture was diluted with DCM (100 mL), washed with a saturated aqueous $NaHCO_3$ solution (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (20 mg, 20%) as a white solid. LCMS-D: R_t 2.44 min, *m/z* 538.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.45 (s, 1H), 9.21 (s, 1H), 8.09 – 8.01 (m, 3H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.19 (s, 1H), 7.15 – 7.07 (m, 1H), 6.72 – 6.61 (m, 3H), 4.56 (t, *J* = 7.5 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.85 – 3.76 (m, 1H).

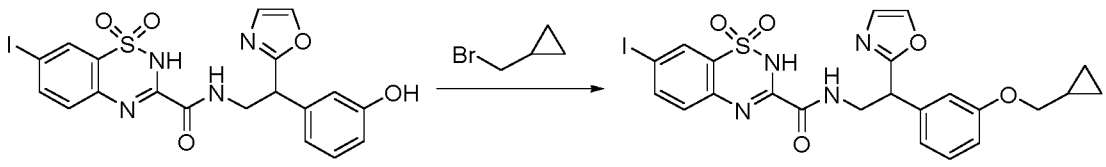
Example 216: 7-Chloro-N-(2-(3-hydroxyphenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 216



176 216

To a solution of 7-chloro-*N*-(2-(3-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 176 (60 mg, 0.13 mmol) in DCM (10 mL) at 0 °C was added BBr_3 (1 M solution in DCM, 0.4 mL, 0.4 mmol) and the reaction was stirred overnight. The mixture was diluted with DCM (100 mL), washed with water (× 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was rinsed with MeOH (2 mL) and dried to give the title compound (25 mg, 40%) as a grey solid. LCMS-C: R_t 2.30 min, *m/z* 446.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.45 (s, 1H), 9.29 (t, *J* = 5.9 Hz, 1H), 8.04 (s, 1H), 7.92 (s, 1H), 7.87 – 7.78 (m, 2H), 7.20 (s, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.72 – 6.62 (m, 3H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.88 – 3.75 (m, 1H).

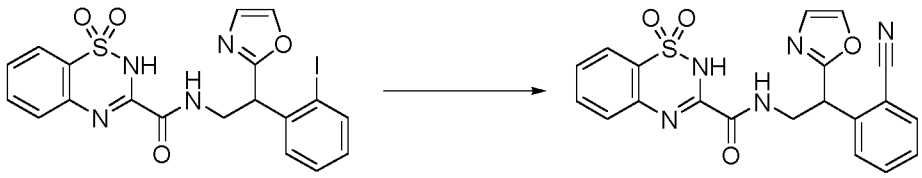
Example 217: N-(2-(3-(Cyclopropylmethoxy)phenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 217



215 217

To a solution of *N*-(2-(3-hydroxyphenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 215 (160 mg, 0.3 mmol) in CH_3CN (15 mL) was added Ag_2O (348 mg, 1.5 mmol) and (bromomethyl)cyclopropane (400 mg, 3.0 mmol) and the mixture was stirred at RT under N_2 overnight. The mixture was diluted with DCM (100 mL), washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (20 mg, 10%) as a yellow solid. LCMS-D: R_t 2.39 min, *m/z* 592.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.26 (t, *J* = 6.0 Hz, 1H), 8.11 – 8.01 (m, 3H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.83 – 6.76 (m, 3H), 4.61 (t, *J* = 7.5 Hz, 1H), 4.00 – 3.92 (m, 1H), 3.91 – 3.82 (m, 1H), 3.80 – 3.69 (m, 2H), 0.86 – 0.80 (m, 1H), 0.54 – 0.48 (m, 2H), 0.29 – 0.23 (m, 2H).

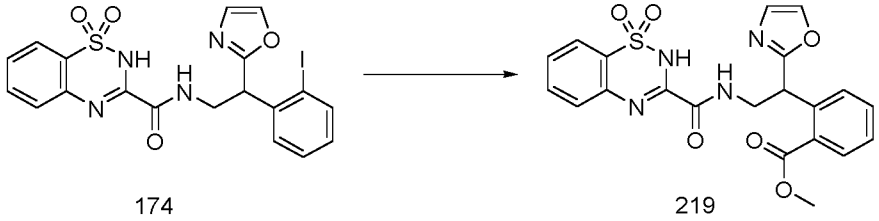
Example 218: N-(2-(2-Cyanophenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 218



174 218

To a solution of *N*-(2-(2-iodophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 174 (52 mg, 0.1 mmol) in DMF (2 mL) was added $Zn(CN)_2$ (24 mg, 0.2 mL) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and the mixture was bubbled with N_2 for 10 min. The flask was then sealed and the mixture was heated at 130 °C overnight. The mixture was diluted with EtOAc (50 mL), washed with water (50 mL × 3) and the organic layer was concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 40/1) to give the title compound (20 mg, 50%) as a white solid. LCMS-C: R_t 1.18 min, *m/z* 422.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.48 (t, *J* = 6.0 Hz, 1H), 8.09 (d, *J* = 0.9 Hz, 1H), 7.89 – 7.78 (m, 3H), 7.77 – 7.67 (m, 2H), 7.60 – 7.46 (m, 3H), 7.23 (s, 1H), 5.02 (t, *J* = 7.6 Hz, 1H), 4.21 – 4.10 (m, 1H), 4.03 – 3.92 (m, 1H).

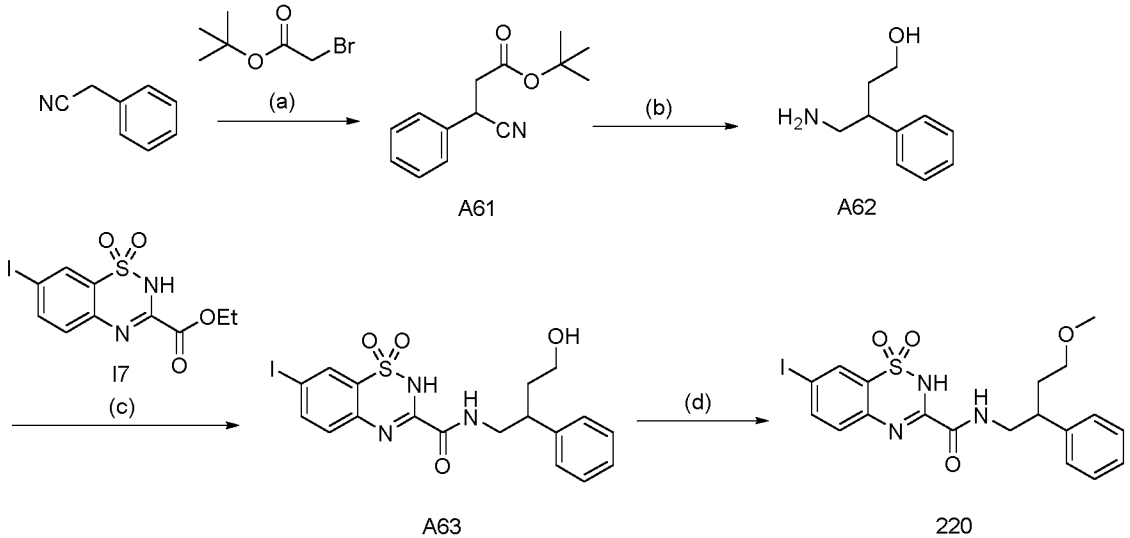
Example 219: Methyl 2-(2-(1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)-1-(oxazol-2-yl)ethyl)benzoate 219



174 219

To a solution of *N*-(2-(2-iodophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 174 (208 mg, 0.4 mmol) in MeOH (40 mL) in a high-pressure reaction vessel was added Et_3N (120 mg, 1.2 mL) and $Pd(dppf)Cl_2$ (32 mg, 0.04 mmol). The mixture was then heated at 100 °C under a CO atmosphere (0.2 MPa) overnight. The mixture was diluted with water, extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (55 mg, 32%) as a white solid. LCMS-C: R_t 1.77 min, *m/z* 455.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.6 (s, 1H), 9.21 (t, *J* = 6.0 Hz, 1H), 8.03 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.75 – 7.68 (m, 1H), 7.59 – 7.48 (m, 2H), 7.44 – 7.38 (m, 1H), 7.33 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21 (s, 1H), 5.49 (t, *J* = 7.3 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.91 – 3.81 (m, 1H), 3.80 (s, 3H).

Example 220: 7-Iodo-N-(4-methoxy-2-phenylbutyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 220



A61 A62

I7 A63 220

a) *tert*-Butyl 3-cyano-3-phenylpropanoate A61

To a solution of 2-phenylacetonitrile (2.34 g, 20 mmol) in dry THF (60 mL) at -78 °C under N_2 was added LiHMDS (1 M solution in THF, 24 mL, 24 mmol) dropwise. The mixture was stirred at -78 °C for 45 min then added to a solution of *tert*-butyl 2-bromoacetate (4.68 g, 24

mmol) in dry THF (60 mL) at -78 °C under N_2 and the mixture was stirred at -78 °C overnight. The mixture was diluted with water, extracted with EtOAc (300 mL) and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Pet. ether/EtOAc =20/1) to give the title compound (3.8 g, 80%) as a white solid. LCMS-C: R_t 2.30 min, *m/z* 232.0 $[M+H]^+$.

b) 4-Amino-3-phenylbutan-1-ol A62

To a solution of *tert*-butyl 3-cyano-3-phenylpropanoate A61 (231 mg, 1 mmol) in THF (10 mL) was added $LiAlH_4$ (1 M solution in THF, 2.0 mL, 2.0 mmol) and the mixture was stirred at RT for 2 h. The mixture was diluted with water, extracted with EtOAc (100 mL) and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (115 mg, 60%) as a yellow oil. LCMS -A (ES-API): R_t 0.322 min, *m/z* 166.1 $[M+H]^+$.

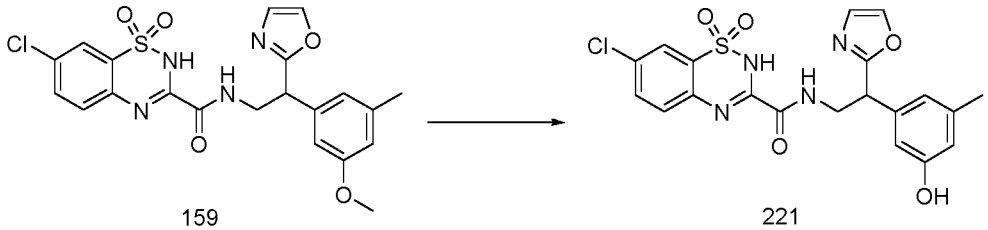
c) *N*-(4-Hydroxy-2-phenylbutyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A63

A suspension of 4-amino-3-phenylbutan-1-ol A62 (115 mg, 0.7 mmol), ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (266 mg, 0.7 mmol) and Et_3N (200 mg, 2 mmol) in EtOH (9 mL) was heated at 110 °C in a sealed tube overnight. The mixture was concentrated under reduced pressure and the residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (75 mg, 20%) as a yellow solid. LCMS-C: R_t 1.97 min, *m/z* 499.9 $[M+H]^+$.

d) 7-Iodo-*N*-(4-methoxy-2-phenylbutyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 220

To a solution of *N*-(4-hydroxy-2-phenylbutyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A63 (75 mg, 0.15 mmol) in CH_3CN (10 mL) was added Ag_2O (174 mg, 0.75 mmol) and iodomethane (213 mg, 1.5 mmol) and the mixture was stirred at RT under N_2 overnight. The mixture was concentrated under reduced pressure and the residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (45 mg, 60%) as a white solid. LCMS-C: R_t 2.27 min, *m/z* 513.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.20 (t, *J* = 6.0 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.20 – 3.15 (m, 1H), 3.14 (s, 3H), 3.12 – 3.05 (m, 2H), 2.02 – 1.90 (m, 1H), 1.79 – 1.66 (m, 1H).

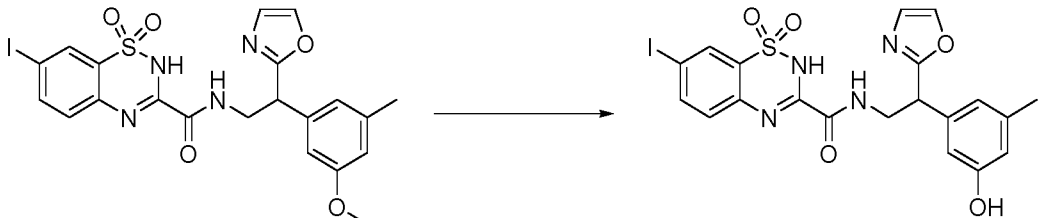
Example 221: 7-Chloro-N-(2-(3-hydroxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 221



159 221

To a solution of 7-chloro-*N*-(2-(3-methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 159 (50 mg, 0.11 mmol) in DCM (5 mL) was added BBr_3 (1 M solution in DCM, 0.33 mL, 0.33 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with water, extracted with diethyl ether and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. HPLC to give the title compound (7 mg, 15%) as a white solid. LCMS-C: R_t 1.97 min; *m/z* 460.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.32 (s, 1H), 9.24 (t, *J* = 5.9 Hz, 1H), 8.03 (s, 1H), 7.91 (d, *J* = 1.9 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.19 (s, 1H), 6.50 (s, 1H), 6.49 – 6.44 (m, 2H), 4.51 (t, *J* = 7.5 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.83 – 3.74 (m, 1H), 2.17 (s, 3H).

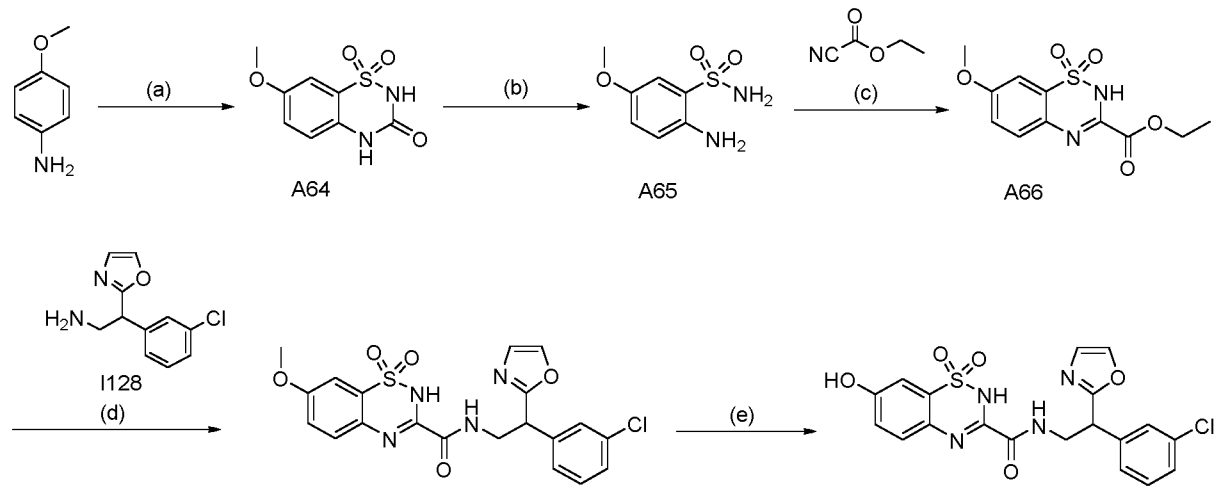
Example 222: N-(2-(3-Hydroxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 222



196 222

To a solution of 7-iodo-*N*-(2-(3-methoxy-5-methylphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 196 (50 mg, 0.09 mmol) in DCM (5 mL) was added BBr_3 (1 M solution in DCM, 0.27 mL, 0.27 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with water, extracted with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. HPLC to give the title compound (1 mg, 3%) as a white solid. LCMS-C: R_t 2.07 min; *m/z* 552.9 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.86 (d, *J* = 0.9 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 6.61 – 6.59 (m, 1H), 6.53 (dd, *J* = 10.2, 2.0 Hz, 2H), 4.51 – 4.46 (m, 1H), 4.07 – 3.99 (m, 1H), 3.96 – 3.89 (m, 1H), 2.24 (s, 3H).

Examples 223 and 224: N-(2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-methoxy-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 223 and N-(2-(3-chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-hydroxy-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 224



a) 7-Methoxy-2*H*-benzo[*e*][1,2,4]thiadiazin-3(4H)-one 1,1-dioxide A64

To a solution of sulfurisocyanatidic chloride (1.38 g, 9.76 mmol) in nitroethane (8 mL) at -40 °C was added a solution of 4-methoxyaniline (1.0 g, 8.13 mmol) in nitroethane (2 mL) dropwise and the mixture was stirred for 5 min. $AlCl_3$ (1.08 g, 8.13 mmol) was then added and the mixture was quickly heated to 110 °C and maintained at that temperature for 20 min. The mixture was then poured onto ice and the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to give the title compound (1.1 g, 60%) as a red solid. LCMS-C: R_t 0.32 min; *m/z* 228.9 $[M+H]^+$.

b) 2-Amino-5-methoxybenzenesulfonamide A65

A mixture of 7-methoxy-2*H*-benzo[*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxide A64 (600 mg, 2.63 mmol) and 50% (v/v) aqueous H_2SO_4 (20 mL) was heated at 130 °C until a homogeneous solution formed. The mixture was poured onto ice, neutralised and extracted with EtOAc. The organic extract was concentrated under reduced pressure to give the title compound (432 mg, 64%) as a red solid. LCMS-C: R_t 0.29 min; *m/z* 203.0 $[M+H]^+$.

c) Ethyl 7-methoxy-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide A66

A mixture of 2-amino-5-methoxybenzenesulfonamide A65 (432 mg, 2.14 mmol) and ethyl carbonocyanidate (2.12 g, 21.4 mmol) in AcOH (20 mL)/conc. aqueous HCl (0.5 mL) was heated at 85 °C for 4 h. Water was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give the title compound (150 mg, 23%) as a white solid. LCMS-C: R_t 0.51 min; *m/z* 284.9 $[M+H]^+$.

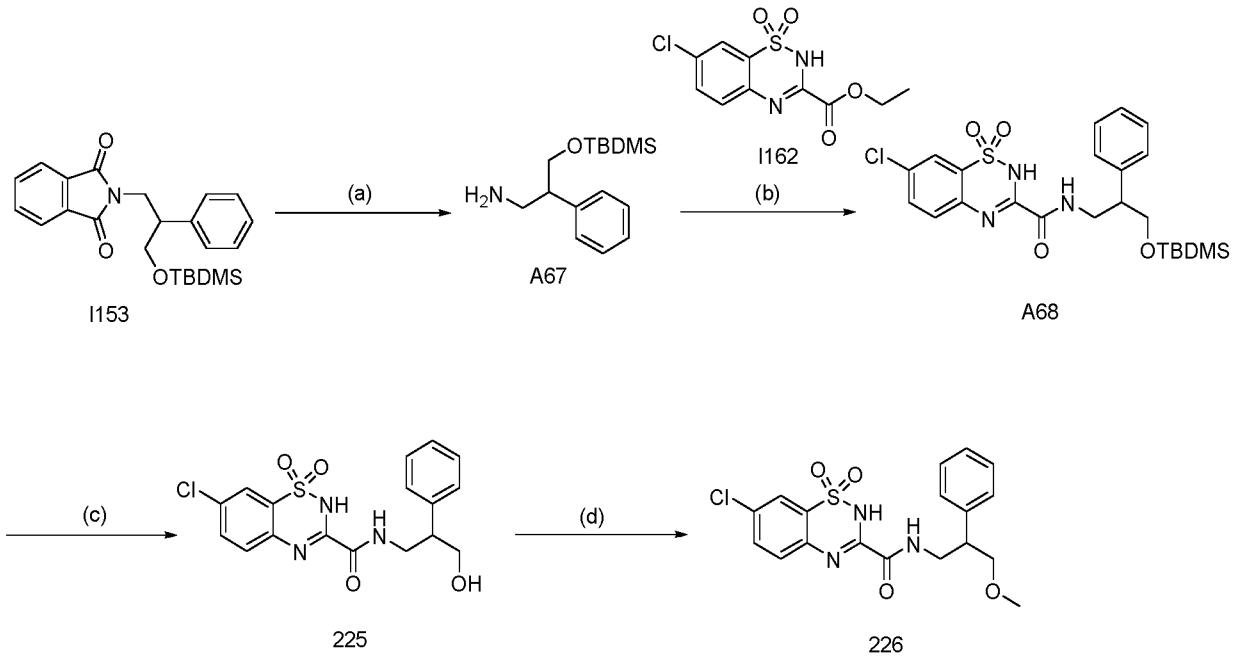
d) *N*-(2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-methoxy-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 223

A mixture of ethyl 7-methoxy-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide A66 (50 mg, 0.18 mmol), 2-(3-chlorophenyl)-2-(oxazol-2-yl)ethanamine I128 (49 mg, 0.22 mmol) and Et_3N (55 mg, 0.54 mmol) in MeOH (3 mL) was heated at 110 °C in a sealed tube for 3 h. The mixture was allowed to cool to RT, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (5.3 mg, 6%) as a white solid. LCMS-C: R_t 2.22 min; *m/z* 460.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.6 (s, 1H), 9.27 (t, *J* = 6.1 Hz, 1H), 8.07 (d, *J* = 0.9 Hz, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.28 – 7.21 (m, 3H), 4.69 (t, *J* = 7.5 Hz, 1H), 4.05 – 3.86 (m, 2H), 3.85 (s, 3H).

e) *N*-(2-(3-Chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-hydroxy-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 224

To a solution of *N*-(2-(3-chlorophenyl)-2-(oxazol-2-yl)ethyl)-7-methoxy-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 223 (15 mg, 0.03 mmol) in DCM (5 mL) was added BBr_3 (1 M solution in DCM, 1.5 mL, 1.5 mmol) and the mixture was stirred at RT for 48 h. The mixture was diluted with water (5 mL), extracted with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM /MeOH = 20/1) to give the title compound (3.1 mg, 23%) as a white solid. LCMS-C: R_t 1.98 min; *m/z* 446.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (s, 1H), 10.4 (s, 1H), 9.25 (t, *J* = 6.2 Hz, 1H), 8.07 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.29 – 7.20 (m, 2H), 7.19 – 7.12 (m, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 4.69 (t, *J* = 7.5 Hz, 1H), 4.03 – 3.84 (m, 2H).

Examples 225 and 226: 7-Chloro-N-(3-methoxy-2-phenylpropyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 225 and 7-chloro-N-(3-methoxy-2-phenylpropyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 226



a) 3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpropan-1-amine A67

A solution of 2-(3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropyl)isoindoline-1,3-dione I153 (1.0 g, 2.53 mmol) and hydrazine monohydrate (380 mg, 7.58 mmol) in EtOH (50 mL) was heated at 80 °C under N_2 for 3 h. The mixture was filtered and the filter cake was washed with EtOH. The filtrate was concentrated under reduced pressure to give the title compound (0.57 g, 85%) as a yellow oil. LCMS-C: R_t 2.85 min; *m/z* 265.8 $[M+H]^+$.

b) *N*-(3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpropyl)-7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A68

A solution of 3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropan-1-amine A67 (200 mg, 0.75 mmol), ethyl 7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I162 (261 mg, 0.90 mmol) and Et_3N (228 mg, 2.25 mmol) in ethanol (15 mL) was heated at 110 °C in a sealed tube for 24 h. The mixture was allowed to cool to RT, diluted with water and extracted with EtOAc. The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound (403 mg, >100%) as white solid, which was used in the next step without further purification. LCMS-C: R_t 2.74 min; *m/z* 508.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.14 (s, 1H), 7.89 (s, 1H), 7.86 – 7.75 (m, 2H), 7.36 – 7.18 (m, 5H), 3.82 – 3.69 (m, 2H), 3.69 – 3.53 (m, 2H), 3.25 – 3.15 (m, 1H), 0.80 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H).

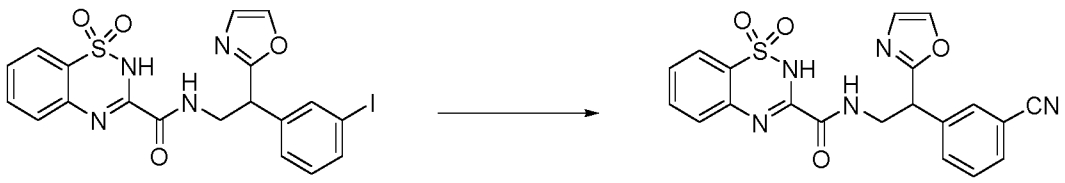
c) 7-Chloro-*N*-(3-hydroxy-2-phenylpropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 225

A mixture of *N*-(3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpropyl)-7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide A68 (383.6 mg, 0.755 mmol) and TBAF (1 M solution in THF, 3.78 mL, 3.78 mmol) in THF (15 mL) was stirred at RT overnight. The mixture was diluted with water, extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound (140 mg, 47%) as a white solid. LCMS-C: R_t 1.71 min; *m/z* 393.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.15 (t, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 2.1 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.34 – 7.17 (m, 5H), 4.81 (br s, 1H), 3.68 – 3.55 (m, 4H), 3.19 – 3.08 (m, 1H).

d) 7-Chloro-*N*-(3-methoxy-2-phenylpropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 226

A mixture of 7-chloro-*N*-(3-hydroxy-2-phenylpropyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 225 (90.0 mg, 0.23 mmol), Ag_2O (266 mg, 1.15 mmol) and iodomethane (326 mg, 2.3 mmol) in CH_3CN (10 mL) was stirred at RT for 4 days. The mixture was diluted with water, extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to give the title compound (8 mg, 9%) as a white solid. LCMS-C: R_t 2.20 min; *m/z* 407.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 9.14 (s, 1H), 7.89 (s, 1H), 7.79 (s, 2H), 7.42 – 7.13 (m, 5H), 3.67 – 3.46 (m, 4H), 3.30 – 3.26 (m, 1H), 3.23 (s, 3H).

Example 227: N-(2-(3-Cyanophenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 227

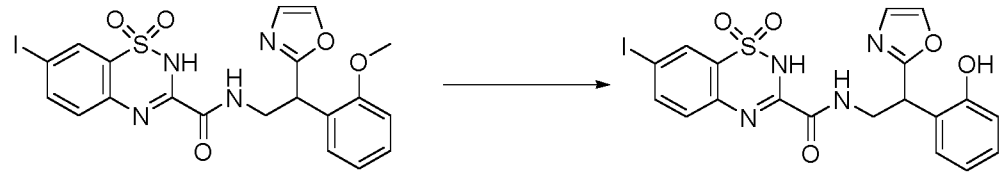


160 227

To a solution of *N*-(2-(3-iodophenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 160 (52 mg, 0.1 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and $Zn(CN)_2$ (24 mg, 0.2 mmol) and the mixture was heated at 120 °C overnight. The mixture was diluted with water, extracted with EtOAc and the combined

organic extracts were concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (20 mg, 47%) as a white solid. LCMS-C: R_t 1.28 min; *m/z* 421.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (br s, 1H), 7.99 – 7.75 (m, 3H), 7.75 – 7.53 (m, 4H), 7.53 – 7.40 (m, 2H), 7.29 – 7.21 (m, 1H), 4.82 – 4.59 (m, 1H), 4.31 – 3.78 (m, 2H).

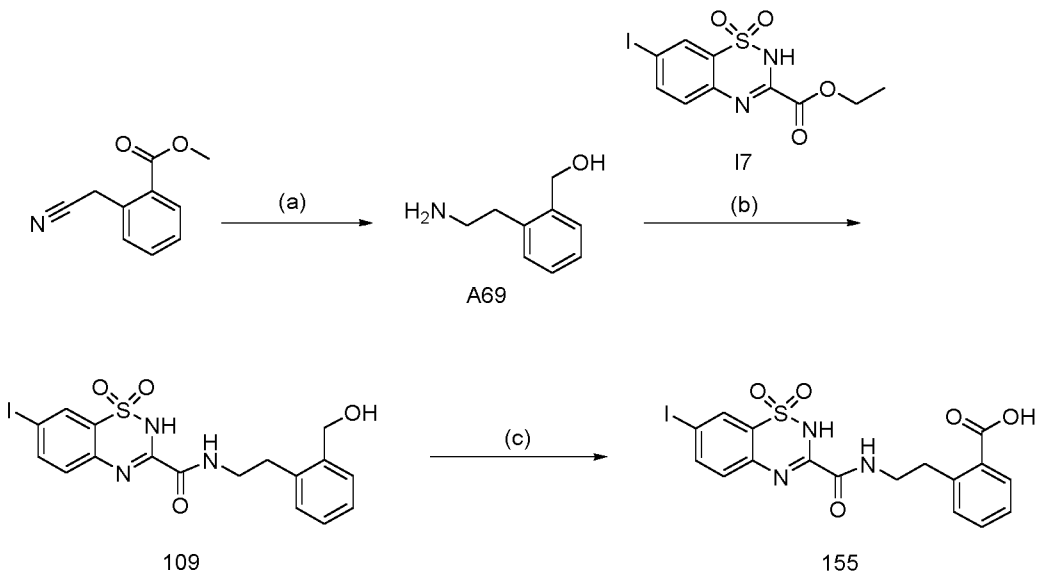
Example 228: N-(2-(2-Hydroxyphenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 228



184 228

To a solution of 7-iodo-*N*-(2-(2-methoxyphenyl)-2-(oxazol-2-yl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 184 (50 mg, 0.09 mmol) in DCM (5 mL) at 0 °C was added BBr_3 (1 M solution in DCM, 0.27 mL, 0.27 mmol) and the mixture was stirred at RT overnight. The reaction was quenched with brine (10 mL) and the mixture was diluted with water (20 mL) and extracted with DCM containing a small amount of MeOH (30 mL × 3). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (13 mg, 27%) as a white solid. LCMS-C: R_t 2.04 min; *m/z* 538.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 9.66 (s, 1H), 9.20 (t, *J* = 5.9 Hz, 1H), 8.11 – 8.03 (m, 2H), 7.99 (d, *J* = 0.9 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 0.8 Hz, 1H), 7.11 – 7.00 (m, 2H), 6.82 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.78 – 6.71 (m, 1H), 4.95 (t, *J* = 7.4 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.84 – 3.74 (m, 1H).

Example 155: 2-(2-(7-Iodo-1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid 155



a) (2-(2-Aminoethyl)phenyl)methanol A69

To a solution of methyl 2-(cyanomethyl)benzoate (3.0 g, 17.1 mmol) in THF (50 mL) was added BH_3·THF (1 M solution in THF, 51.0 mL, 51.0 mmol) and the mixture was heated at 70 °C under N_2 overnight. The mixture was adjusted to pH 5 with 1 M aqueous HCl, diluted with water (20 mL) and washed with EtOAc (30 mL × 3). The aqueous phase was adjusted to pH 9 with 1 M aqueous NaOH and extracted with EtOAc (30 mL × 3). The combined organic extracts were concentrated under reduced pressure to give the title compound (1.5 g, 57%) as a yellow oil. LCMS-C: R_t 0.39; *m/z* 152.1 $[M+H]^+$.

b) *N*-(2-(Hydroxymethyl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 109

The following procedure was performed three times: A solution of (2-(2-aminoethyl)phenyl)methanol A69 (300 mg, 1.98 mmol), ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (753 mg, 1.98 mmol) and Et_3N (600 mg, 7.84 mmol) in ethanol (10 mL) was heated at 150 °C in a sealed tube for 3 h. The mixture was allowed to cool to RT and concentrated under reduced pressure. The crude product of the three reactions were combined and purified by silica gel chromatography (DCM/MeOH = 100/1 to 20/1) to give the title compound (520 mg, 18%) as a white solid. LCMS-D: R_t 0.34 min; *m/z* 486.1 $[M+H]^+$.

c) 2-(2-(7-Iodo-1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid 155

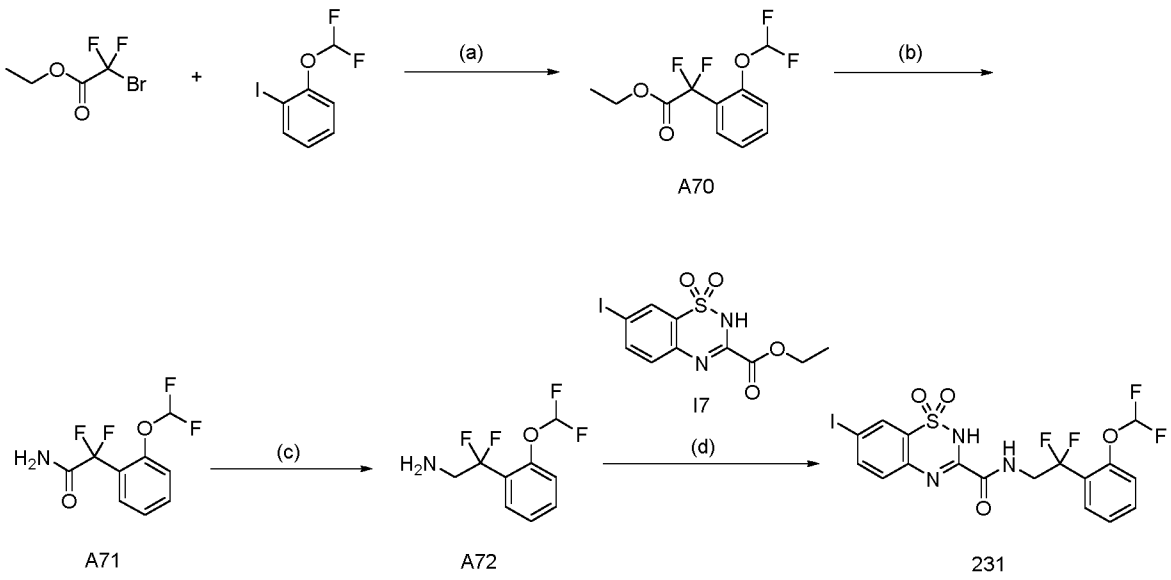
To a solution of *N*-(2-(hydroxymethyl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 109 (200 mg, 0.4 mmol) in acetone (10 mL) was added Jones reagent (10 mL) and the mixture was heated at 40 °C overnight. The mixture was concentrated under reduced pressure and the residue was diluted with water. The solids were collected by filtration and washed with diethyl ether to give the title compound (115 mg, 55%) as a white solid. LCMS-D: R_t 2.64 min; *m/z* 522.0 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 1H), 9.43 – 9.17 (m, 1H), 8.19 – 7.97 (m, 2H), 7.84 (t, *J* = 8.1 Hz, 1H), 7.69 – 7.17 (m, 4H), 3.60 – 3.48 (m, 2H), 3.26 – 3.19 (m, 2H).

Example 230: N-(2-Carbamoylphenethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 230

155 230

To a solution of 2-(2-(7-iodo-1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)ethyl)benzoic acid 155 (50 mg, 0.1 mmol), EDCI (23 mg, 0.12 mmol), DIPEA (39 mg, 0.3 mmol) and HOBt (16 mg, 0.12 mmol) in 1,4-dioxane (5 mL) was added NH_4Cl (11 mg, 0.2 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with water (15 mL), adjusted to pH 5 with 1 M aqueous HCl and extracted with EtOAc (50 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. TLC (DCM/MeOH = 20/1) to give the title compound (3 mg, 6%) as a grey solid. LCMS-D: R_t 2.11 min; *m/z* 499.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.6 (br s, 1H), 9.34 (br s, 1H), 8.08 – 7.98 (m, 2H), 7.79 (s, 1H), 7.57 – 7.49 (m, 1H), 7.43 (s, 1H), 7.41 – 7.29 (m, 3H), 7.29 – 7.22 (m, 1H), 3.55 – 3.50 (m, 2H), 3.01 (t, *J* = 7.2 Hz, 2H).

Example 231: N-(2-(2-(difluoromethoxy)phenyl)-2,2-difluoroethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 231



a) Ethyl 2-(2-(difluoromethoxy)phenyl)-2,2-difluoroacetate A70

To activate Cu powder: Copper powder was stirred vigorously with 1M aqueous HCl (10 mL) for 10 min at RT, then filtered. The process was sequentially repeated with water (10 mL), MeOH (10 mL) and acetone (10 mL). The final filtered material was dried under vacuum for 30 min then used immediately in the reaction.

DMSO (18.5 mL) was added to a nitrogen flushed flask containing activated copper (1.2 g, 19 mmol). 1-(Difluoromethoxy)-2-iodo-benzene (1.1 mL, 7.4 mmol) was added, followed by ethyl bromodifluoroacetate (0.95 mL, 7.4 mmol) and the reaction was heated to 60 °C and stirred overnight. The mixture was cooled and filtered through a pad of Celite® and the Celite® was washed with diethyl ether (100 mL). The green solution was washed with saturated aqueous NH_4Cl (100 mL × 2). The now orange organic layer was washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The material was purified by column chromatography (Grace Biotage 40 g SiO_2, 0-50% EtOAc in petroleum benzine 40-60 °C) to give the title compound (1.5 g, 77% yield) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.38 – 7.31 (m, 1H), 7.23 (dq, *J* = 8.3, 1.2 Hz, 1H), 6.44 (t, *J* = 73.3 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

b) 2-(2-(Difluoromethoxy)phenyl)-2,2-difluoroacetamide A71

7 M ammonia in MeOH (20 mL) was added to ethyl 2-(2-(difluoromethoxy)phenyl)-2,2-difluoroacetate A70 (1.5 g, 5.6 mmol) and the solution was stirred at RT for 1 h. The mixture was concentrated *in vacuo* to give the title compound (1.2 g, 90% yield) as an oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 – 7.48 (m, 1H), 7.41

– 7.29 (m, 1H), 7.29 – 7.15 (m, 1H), 6.56 (br s, 1H), 6.44 (t, *J* = 73.5 Hz, 1H), 6.11 (br s, 1H).

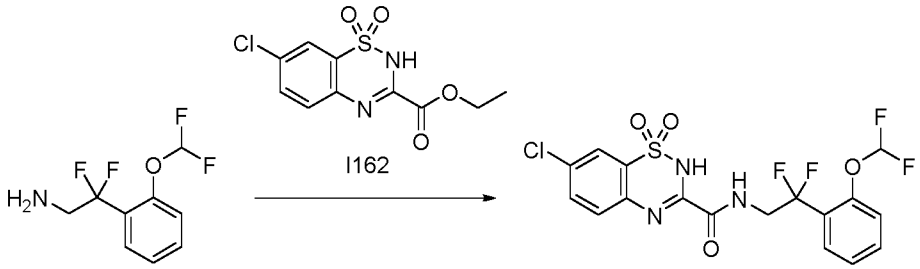
c) 2-(2-(Difluoromethoxy)phenyl)-2,2-difluoroethan-1-amine A72

To 2-(2-(Difluoromethoxy)phenyl)-2,2-difluoroacetamide A71 (1.2 g, 5.1 mmol) in THF (25 mL) at 0 °C was added borane-tetrahydrofuran complex 1.0 M solution in THF (2.4 mL, 2.4 mmol) dropwise. The solution was allowed to warm to RT and stirred overnight. The reaction was cooled to 0 °C and quenched with the slow addition of MeOH until gas evolution ceased (~25 mL). Conc. HCl was added (~20 mL) and the reaction allowed to stir for 1 h upon which time the mixture was concentrated to dryness. The crude material was loaded onto a Biotage SCX cartridge (2 × 10 g) and washed with MeOH (50 mL), then a methanolic ammonia solution (50 mL). The basic washings were concentrated *in vacuo* to give the title compound (0.14 g, 12% yield) as an orange oil. LCMS-B: rt 2.772 min; *m/z* 223.9 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.35 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 6.46 (t, *J* = 74.0 Hz, 1H), 3.33 (t, *J* = 15.1 Hz, 2H).

d) *N*-(2-(2-(Difluoromethoxy)phenyl)-2,2-difluoroethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 231

A suspension of 2-(2-(difluoromethoxy)phenyl)-2,2-difluoroethan-1-amine A72 (0.038 g, 0.17 mmol) and ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.050 g, 0.13 mmol) in EtOH (0.125 mL) was irradiated in a CEM microwave at 100 °C for 2 h. The reaction was cooled and the precipitate filtered, then washed with EtOH (2 mL). The filtrate was concentrated to dryness, then partitioned between EtOH (2 mL) and 1 M aqueous HCl (2 mL). The layers were separated and the organics washed with a further portion of 1 M aqueous HCl (2 mL), brine (2 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by column chromatography (Santai Sepa-Flash, 12 g SiO_2, 0-100% EtOAc in petroleum benzine 40-60 °C) with the material eluting at ~50% EtOAc collected and concentrated *in vacuo* to give the title compound (0.010 g, 14% yield) as a cream-colored solid. LCMS-B: rt 3.678 min; *m/z* 555.7 $[M-H]^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (br s, 1H), 9.47 (br s, 1H), 8.11 – 7.96 (m, 2H), 7.69 – 7.47 (m, 3H), 7.33 (t, *J* = 8.1 Hz, 2H), 7.26 (t, *J* = 73.3 Hz, 1H), 4.34 – 3.91 (m, 2H).

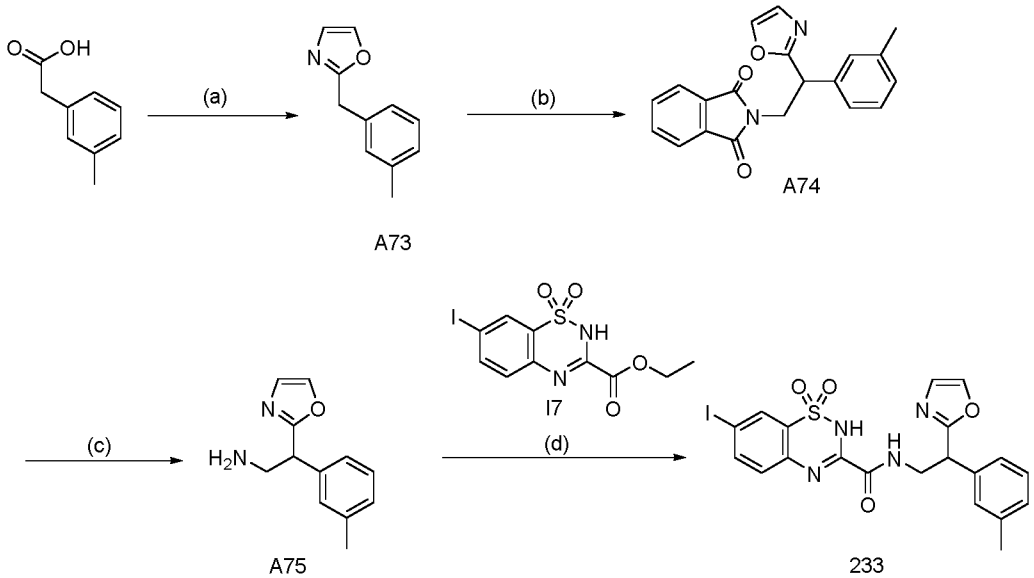
Example 232: 7-chloro-N-(2-(2-(difluoromethoxy)phenyl)-2,2-difluoroethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 232



A72 232

A suspension of 2-(2-(difluoromethoxy)phenyl)-2,2-difluoroethan-1-amine A72 (0.048 g, 0.22 mmol) and ethyl 7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I162 (0.048 g, 0.17 mmol) in EtOH (0.2 mL) was irradiated in a CEM microwave at 120 °C for 1 h. The crude material was purified by column chromatography (Santai Sepa-Flash, 12 g SiO_2, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.022 g, 28% yield) as a white solid. LCMS-B: rt 3.857 min; *m/z* 463.8 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 9.53 (br s, 1H), 7.92 (s, 1H), 7.81 (s, 2H), 7.68 – 7.49 (m, 2H), 7.33 (t, *J* = 8.1 Hz, 2H), 7.26 (t, *J* = 73.3 Hz, 1H), 4.10 (td, *J* = 14.2, 6.6 Hz, 2H).

Example 233: 7-iodo-N-(2-(oxazol-2-yl)-2-(m-tolyl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 233



a) 2-(3-Methylbenzyl)oxazole A73

m-Tolylacetic acid (5.0 g, 33 mmol) was dissolved in thionyl chloride (25 mL) and heated at 80 °C for 3 h. The remaining thionyl chloride was evaporated *in vacuo.* The residue was dissolved in sulfolane (10 mL), and to this was added 1*H*-1,2,3-Triazole (2.7 mL, 47 mmol) and K_2CO_3 (9.2 g, 67 mmol). The reaction was heated to 150 °C for 30 min, then cooled,

added to water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage 120 g SiO_2, 0-30% EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.58 g, 10% yield) as a clear oil. LCMS-B: rt 3.268 min, *m/z* 174.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 0.9 Hz, 1H), 7.22 (td, *J* = 7.6, 0.7 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.04 (d, *J* = 0.9 Hz, 1H), 4.09 (s, 2H), 2.33 (d, *J* = 0.7 Hz, 3H).

b) 2-(2-(Oxazol-2-yl)-2-(*m*-tolyl)ethyl)isoindoline-1,3-dione A74

To a solution of 2-(3-methylbenzyl)oxazole A73 (0.573 g, 3.31 mmol) in anhydrous THF (10 mL) at -78 °C under nitrogen was added lithium bis(trimethylsilyl)amide, 1.0 M solution in hexane (4.96 mL, 4.96 mmol) dropwise. A solution of *N*-(bromomethyl)phthalimide (1.19 g, 4.96 mmol) in anhydrous THF (8 mL) was then added dropwise and the mixture allowed to warm slowly to room temperature and stirred overnight. The mixture was diluted with a saturated aqueous NH_4Cl solution (50 mL) and water (25 mL), then extracted with DCM (50 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (Biotage, Grace 40 g SiO_2, 0-60 % EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.11 g, 10% yield) as a white solid. LCMS-A: rt 6.117 min; *m/z* 332.9 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.52 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.42 (d, *J* = 1.0 Hz, 1H), 7.05 – 6.96 (m, 3H), 6.92 – 6.82 (m, 2H), 4.61 (t, *J* = 8.1 Hz, 1H), 4.25 (dd, *J* = 13.7, 8.1 Hz, 1H), 4.16 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.12 (s, 3H).

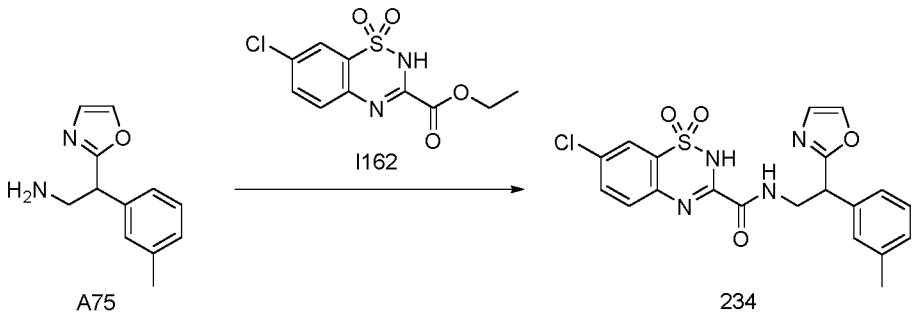
c) 2-(Oxazol-2-yl)-2-(*m*-tolyl)ethan-1-amine A75

To a suspension of 2-(2-(oxazol-2-yl)-2-(*m*-tolyl)ethyl)isoindoline-1,3-dione A74 (0.11 g, 0.34 mmol) in EtOH (3 mL), under an atmosphere of nitrogen, was added hydrazine hydrate (0.251 g, 5.01 mmol). This was heated to 80 °C and allowed to stir for 3 h, upon which time the reaction was cooled and the formed precipitate filtered. The solid was washed with cold EtOH (1 mL) and the combined filtrate concentrated *in vacuo.* The resulting solid was taken up in cold EtOH (1 mL) and filtered. The filtrate was concentrated *in vacuo.* The resulting semi-solid was once more taken up in cold EtOH (1 mL), the precipitate was filtered and the filtrate concentrated *in vacuo* to give the title compound (0.045 g, 66% yield) as a yellow oil. LCMS-B: rt 2.741 min; *m/z* 203.0 $[M+H]^+$.

d) 7-Iodo-*N*-(2-(oxazol-2-yl)-2-(*m*-tolyl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 233

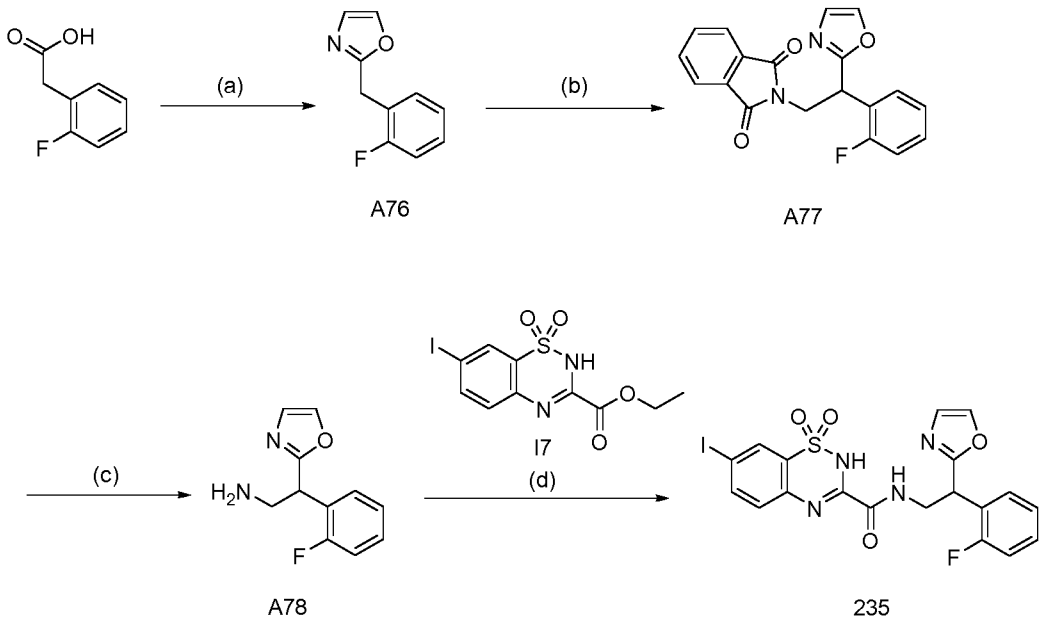
To a solution of 2-(oxazol-2-yl)-2-(*m*-tolyl)ethan-1-amine A75 (0.022 g, 0.11 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.034 g, 0.091 mmol). This was irradiated in a CEM microwave at 120 °C for 2 h. The reaction was cooled and the precipitate filtered. The solid was washed with EtOH (2 mL) and air dried to give title compound (0.020 g, 34% yield) as an off-white solid. LCMS-B: rt 3.565 min; *m/z* 536.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (br s, 1H), 9.17 (br s, 1H), 8.10 – 7.92 (m, 3H), 7.57 – 7.47 (m, 1H), 7.26 – 7.17 (m, 2H), 7.15 – 7.00 (m, 3H), 4.61 (t, *J* = 7.5 Hz, 1H), 3.99 (dt, *J* = 13.4, 6.8 Hz, 1H), 3.84 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.27 (s, 3H).

Example 234: 7-chloro-N-(2-(oxazol-2-yl)-2-(m-tolyl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 234



To a solution of 2-(oxazol-2-yl)-2-(*m*-tolyl)ethan-1-amine A75 (0.020 g, 0.099 mmol) in EtOH (0.125 mL) was added ethyl 7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I162 (0.024 g, 0.082 mmol). The reaction was irradiated in a CEM microwave at 120 °C for 1 h. The reaction was cooled and the precipitate filtered. The solid was washed with EtOH (2 mL) and air dried to give the title compound (0.020 g, 45% yield) as a white solid. LCMS-B: rt 3.616 min; *m/z* 444.7 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (br s, 1H), 9.23 (br s, 1H), 8.04 (d, *J* = 0.9 Hz, 1H), 7.89 (s, 1H), 7.86 – 7.66 (m, 2H), 7.29 – 7.16 (m, 2H), 7.15 – 6.95 (m, 3H), 4.62 (t, *J* = 7.5 Hz, 1H), 4.00 (dt, *J* = 13.3, 6.6 Hz, 1H), 3.85 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.27 (s, 3H).

Example 235: N-(2-(2-fluorophenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 235



a) 2-(2-Fluorobenzyl)oxazole A76

2-Fluorophenylacetic acid (3.0 g, 19 mmol) was dissolved in thionyl chloride (15 mL) and heated at 80 °C for 3 h. The remaining thionyl chloride was evaporated *in vacuo.* The residue was dissolved in sulfolane (10 mL), and to this was added 1*H*-1,2,3-triazole (1.6 mL, 27 mmol) and K_2CO_3 (5.4 g, 39 mmol). The reaction was heated to 150 °C for 30 min, then cooled, added to water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage 120 g SiO_2, 0-20% EtOAc in petroleum benzine 40-60 °C) to give the title compound (1.6 g, 47% yield) as a clear oil. LCMS-B: rt 3.322 min, *m/z* 178.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 0.9 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.15 – 7.02 (m, 3H), 4.17 (s, 2H).

b) 2-(2-(2-Fluorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione A77

To a solution of 2-(2-fluorobenzyl)oxazole A76 (1.63 g, 9.21 mmol) in anhydrous THF (30 mL) at -78 °C under nitrogen was added lithium bis(trimethylsilyl)amide, 1.0 M solution in hexane (13.8 mL, 13.8 mmol) dropwise. A solution of *N*-(bromomethyl)phthalimide (2.87 g, 12.0 mmol) in anhydrous THF (25 mL) was then added dropwise and the mixture allowed to warm slowly to RT and left to stir overnight. The mixture was diluted with a saturated aqueous NH_4Cl solution (100 mL) and water (50 mL), then extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (Isolera Biotage, Grace 120 g SiO_2, 0-60 % EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.91 g, 30% yield) as

a white solid. LCMS-B: rt 3.434 min; *m/z* 336.9 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H), 7.73 – 7.67 (m, 2H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.15 – 7.07 (m, 2H), 7.02 – 6.92 (m, 1H), 5.11 (dd, *J* = 8.8, 7.1 Hz, 1H), 4.50 – 4.33 (m, 2H). One aromatic proton obscured by solvent signal.

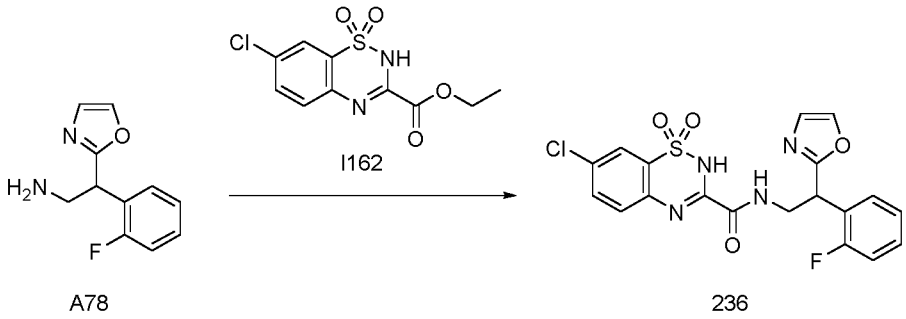
c) 2-(2-Fluorophenyl)-2-(oxazol-2-yl)ethan-1-amine A78

To a suspension of 2-(2-(2-fluorophenyl)-2-(oxazol-2-yl)ethyl)isoindoline-1,3-dione A77 (0.20 g, 0.59 mmol) in EtOH (6 mL), under an atmosphere of nitrogen, was added hydrazine hydrate (0.430 mL, 8.84 mmol). The reaction was heated to 80 °C and allowed to stir for 3 h, upon which time the reaction was cooled and the formed precipitate filtered. The solid was washed with cold EtOH (2 mL) and the combined filtrate concentrated *in vacuo.* The resulting solid was taken up in cold EtOH (1 mL) and filtered. The filtrate was concentrated *in vacuo.* The resulting semi-solid was once more taken up in cold EtOH (1 mL), the precipitate filtered and the filtrate concentrated *in vacuo* to give the title compound (0.11 g, 90% yield) as an orange oil. LCMS-B: rt 2.718 min; *m/z* 207.0 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 0.9 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.22 – 7.14 (m, 1H), 7.13 – 7.03 (m, 3H), 4.56 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.25 (dd, *J* = 12.9, 6.0 Hz, 1H).

d) *N*-(2-(2-Fluorophenyl)-2-(oxazol-2-yl)ethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 235

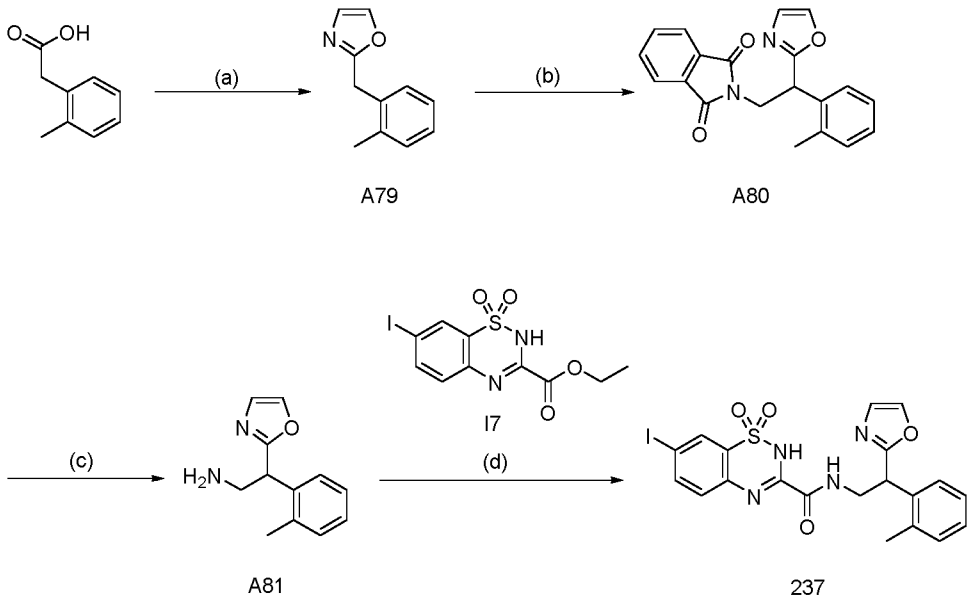
To a suspension of ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.040 g, 0.11 mmol) in EtOH (0.125 mL) was added 2-(2-fluorophenyl)-2-(oxazol-2-yl)ethan-1-amine A78 (0.026 g, 0.13 mmol). The reaction was irradiated in a CEM microwave at 120 °C for 3 h. The reaction was cooled and the precipitate filtered. The solid was washed with EtOH (2 mL) and air dried to give the title compound (0.020 g, 35% yield) as a white solid. LCMS-B: rt 3.591 min; *m/z* 540.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 9.38 (t, *J* = 6.0 Hz, 1H), 8.13 – 7.98 (m, 3H), 7.57 (dd, *J* = 19.2, 8.7 Hz, 2H), 7.35 (tdd, *J* = 8.5, 3.7, 1.5 Hz, 2H), 7.25 – 7.06 (m, 2H), 4.94 (t, *J* = 7.6 Hz, 1H), 4.06 (ddd, *J* = 12.9, 7.2, 5.7 Hz, 1H), 3.90 (ddd, *J* = 13.2, 8.1, 6.4 Hz, 1H).

Example 236: 7-chloro-N-(2-(2-fluorophenyl)-2-(oxazol-2-yl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 236



To a suspension of ethyl 7-chloro-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I162 (0.028 g, 0.097 mmol) in EtOH (0.125 mL) was added 2-(2-fluorophenyl)-2-(oxazol-2-yl)ethan-1-amine A78 (0.024 g, 0.12 mmol). The reaction was irradiated in a CEM microwave at 120 °C for 1 h. The reaction was cooled and the precipitate filtered. The solid was washed with EtOH (1 mL) and air dried to give the title compound (0.015 g, 29% yield) as a white solid. LCMS-B: rt 3.562 min; *m/z* 448.7 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (br s, 1H), 9.34 (br s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.90 (s, 1H), 7.80 (s, 2H), 7.35 (dddt, *J* = 9.3, 7.4, 3.7, 1.7 Hz, 2H), 7.26 – 7.12 (m, 3H), 4.94 (t, *J* = 7.5 Hz, 1H), 4.06 (dt, *J* = 13.0, 6.4 Hz, 1H), 3.91 (dt, *J* = 13.6, 7.1 Hz, 1H).

Example 237: 7-iodo-N-(2-(oxazol-2-yl)-2-(o-tolyl)ethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 237



a) 2-(2-Methylbenzyl)oxazole A79

2-(*o*-Tolyl)acetic acid (2.0 g, 13 mmol) was dissolved in thionyl chloride (10 mL) and heated at 80 °C for 3 h. The remaining thionyl chloride was evaporated *in vacuo.* The residue was dissolved in sulfolane (10 mL), and to this was added 1*H*-1,2,3-triazole (1.08 mL, 18.6

mmol) and K_2CO_3 (3.7 g, 27 mmol). The reaction was heated to 150 °C for 30 min, then cooled, added to water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage 120 g SiO_2, 0-60% EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.63 g, 27% yield) as a clear oil. LCMS-B: rt 3.185 min, *m/z* 174.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 0.9 Hz, 1H), 7.22 – 7.15 (m, 4H), 7.03 (d, *J* = 0.9 Hz, 1H), 4.12 (s, 2H), 2.34 (s, 3H).

b) 2-(2-(Oxazol-2-yl)-2-(*o*-tolyl)ethyl)isoindoline-1,3-dione A80

To a solution of 2-(2-methylbenzyl)oxazole A79 (0.62 g, 3.6 mmol) in anhydrous THF (10 mL) at -78 °C under nitrogen was added lithium bis(trimethylsilyl)amide, 1.0 M solution in hexane (4.68 mL, 4.68 mmol) dropwise. A solution of *N*-(bromomethyl)phthalimide (1.12 g, 4.68 mmol) in anhydrous THF (8 mL) was then added dropwise and the mixture allowed to warm slowly to room temperature and stirred overnight. The mixture was diluted with a saturated aqueous NH_4Cl solution (50 mL) and water (25 mL), then extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (Isolera Biotage, Grace 40 g SiO_2, 0-60 % EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.070 g, 5.9% yield) as a white solid. LCMS-B: rt 3.414 min; *m/z* 332.9 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.56 (d, *J* = 0.9 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.23 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 7.02 (d, *J* = 0.8 Hz, 1H), 5.09 (dd, *J* = 8.8, 7.1 Hz, 1H), 4.49 (dd, *J* = 13.7, 8.8 Hz, 1H), 4.25 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.42 (s, 3H).

c) 2-(Oxazol-2-yl)-2-(*o*-tolyl)ethan-1-amine A81

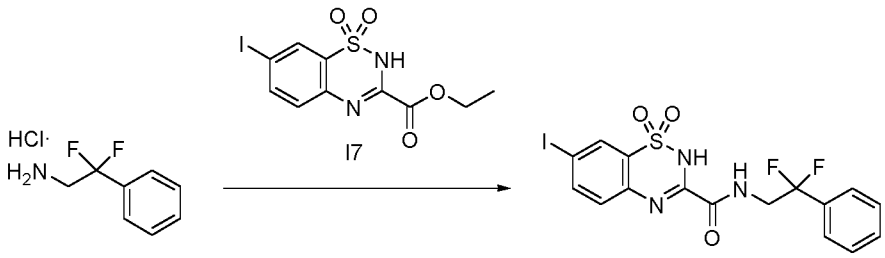
To a suspension of 2-(2-(oxazol-2-yl)-2-(*o*-tolyl)ethyl)isoindoline-1,3-dione A80 (0.067 g, 0.20 mmol) in EtOH (3 mL), under an atmosphere of nitrogen, was added hydrazine hydrate (0.150 g, 3.00 mmol). This was heated to 80 °C and allowed to stir for 3 h, upon which time the reaction was cooled and the formed precipitate filtered. The solid was washed with cold EtOH (1 mL) and the combined filtrates concentrated *in vacuo.* The resulting solid was taken up in cold EtOH (1 mL) and filtered. The filtrate was concentrated *in vacuo.* The resulting semi-solid was once more taken up in cold EtOH (1 mL), the precipitate filtered and the filtrate concentrated *in vacuo* to give the title compound (0.024 g, 59% yield) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 0.8 Hz, 1H),

7.23 – 7.17 (m, 1H), 7.18 – 7.13 (m, 2H), 7.12 – 7.07 (m, 2H), 4.45 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.46 (dd, *J* = 13.0, 8.4 Hz, 1H), 3.22 (dd, *J* = 13.0, 5.7 Hz, 1H), 2.44 (s, 3H).

d) 7-Iodo-*N*-(2-(oxazol-2-yl)-2-(*o*-tolyl)ethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 237

To a solution of 2-(oxazol-2-yl)-2-(*o*-tolyl)ethan-1-amine A81 (0.022 g, 0.11 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.034 g, 0.089 mmol). The reaction was irradiated in a CEM microwave at 120 °C for 1.5 h, then cooled and the precipitate filtered. The solid was washed with EtOH (2 mL) and air dried to give title compound (0.031 g, 54% yield) as a white solid. LCMS-B: rt 3.431 min; *m/z* 536.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 9.24 (br s, 1H), 8.15 – 7.91 (m, 3H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.27 – 7.10 (m, 5H), 4.91 (t, *J* = 7.5 Hz, 1H), 4.04 (dt, *J* = 14.0, 7.5 Hz, 1H), 3.78 (dt, *J* = 12.8, 6.1 Hz, 1H), 2.40 (s, 3H).

Example 238: N-(2,2-difluoro-2-phenylethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 238



238

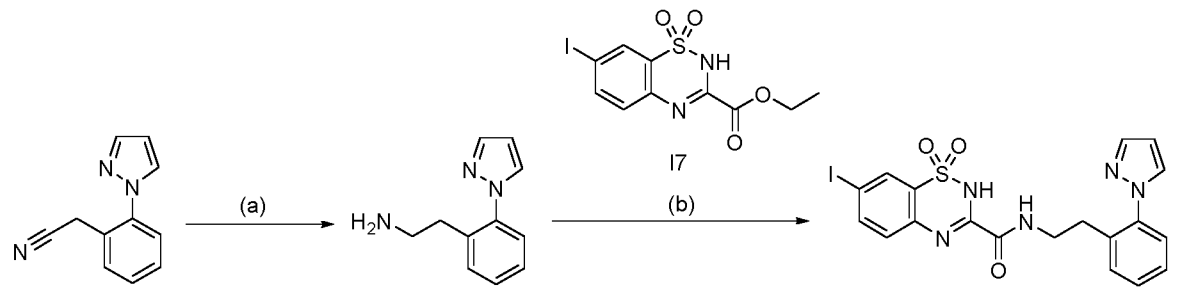
To 2,2-difluoro-2-phenyl-ethanamine hydrochloride (0.031 g, 0.16 mmol) in EtOH (0.125 mL), was added triethylamine (0.022 mL, 0.16 mmol). This was allowed to stir for 10 min at RT upon which time ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.050 g, 0.13 mmol) was added. The reaction was irradiated in a CEM microwave for 1.5 h at 120 °C, then cooled and the precipitate filtered. The solid was washed with cold EtOH (2 mL) and air dried to give the title compound (0.033 g, 51% yield) as a cream solid. LCMS-B: rt 3.344 min; *m/z* 489.7 $[M-H]^-$.

Example 239: 7-iodo-N-(2-(4-(methoxymethyl)-2H-1,2,3-triazol-2-yl)phenethyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 239

190 239

To a suspension of *N*-(2-(4-(hydroxymethyl)-2*H*-1,2,3-triazol-2-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 190 (0.050 g, 0.091 mmol) in acetonitrile (5 mL), under an atmosphere of nitrogen, was added silver(I)oxide (0.10 g, 0.45 mmol) and iodomethane (0.056 mL, 0.91 mmol). This was allowed to stir overnight at 50 °C. The reaction was cooled and filtered through a pad of Celite®. The Celite® was washed with a mixture of DCM/MeOH and the filtrate was concentrated *in vacuo.* The solid residue was washed with warm DCM/MeOH (5 mL/1 mL) and the remaining solid was dissolved in DCM/MeOH (20 mL/ 10 mL), 1.25 M HCl in methanol (4 mL) was added and the solution sonicated for 5 minutes. The cloudy solution was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to give the title compound (0.016 g, 31% yield) as a white solid. LCMS-B: rt 3.699 min; *m/z* 564.7 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 9.29 (t, *J* = 5.9 Hz, 1H), 8.12 – 8.06 (m, 2H), 8.05 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.57 – 7.37 (m, 4H), 4.58 (s, 2H), 3.46 (q, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). OCH_3 signal obscured by water. Presence confirmed via HMQC (3.33 ppm / 57.9 ppm).

Example 240: N-(2-(1H-pyrazol-1-yl)phenethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 240



A82 I7 240

a) 2-(2-(1*H*-pyrazol-1-yl)phenyl)ethan-1-amine A82

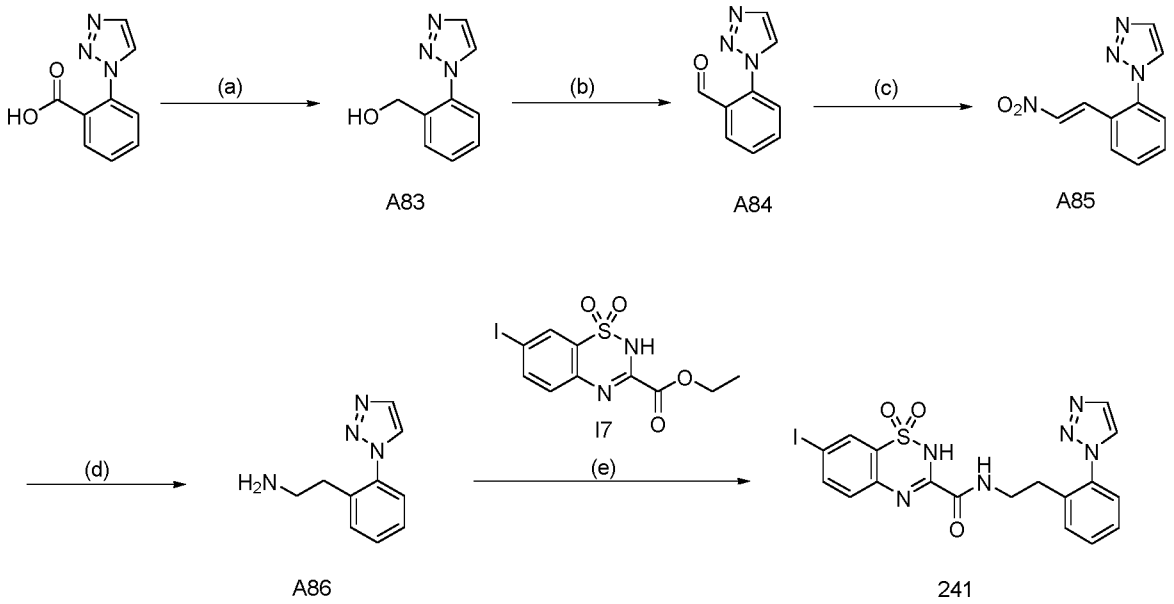
To 2-(2-pyrazol-1-ylphenyl)acetonitrile (0.13 g, 0.70 mmol) in THF (5 mL) was added borane-tetrahydrofuran complex 1.0 M solution in THF (3.5 mL, 3.5 mmol) dropwise. The solution was heated to reflux and allowed to stir overnight. The reaction was cooled and

quenched slowly with water (5 mL). A 50% w/v aq. NaOH solution (2 mL) was added and the mixture was refluxed for 1 h. The reaction was cooled and the organics concentrated *in vacuo.* The remaining aqueous layer was extracted with DCM (10 mL × 3), the organics were combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was loaded onto a Biotage SCX cartridge (5 g) and washed with MeOH (30 mL), then a methanolic ammonia solution (30 mL). The methanolic washings were concentrated *in vacuo* to give the title compound (0.12 g, 90% yield) as a yellow oil. LCMS-B: rt 0.930 min; *m/z* 188.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.61 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.32 – 7.29 (m, 2H), 6.44 (t, *J* = 2.1 Hz, 1H), 2.86 – 2.76 (m, 2H), 2.73 – 2.61 (m, 2H), 1.25 (br s, 2H).

b) *N*-(2-(1H-pyrazol-1-yl)phenethyl)-7-iodo-2H-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 240

To a solution of 2-(2-(1*H*-pyrazol-1-yl)phenyl)ethan-1-amine A82 (0.049 g, 0.26 mmol) in EtOH (0.2 mL) was added ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.050 g, 0.13 mmol). The reaction was irradiated in a microwave reactor at 120 °C for 1h, then cooled and the precipitate filtered. The solid was washed with EtOH (2 mL), then taken up in EtOAc (10 mL) and washed with 1M aqueous HCl (10 mL × 2) and brine. A precipitate formed from the organic layer and this solid was collected by filtration to give the title compound (0.0080 g, 12% yield) a pale grey solid. LCMS-B: rt 3.354min; *m/z* 521.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, 1H), 9.41 (m, 1H), 8.11 – 8.03 (m, 2H), 8.00 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.72 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.48 – 7.31 (m, 4H), 6.48 (t, *J* = 2.1 Hz, 1H), 3.45 – 3.36 (partially obscured by solvent, m, 2H), 2.83 (t, *J* = 7.1 Hz, 2H).

Example 241: N-(2-(1H-1,2,3-triazol-1-yl)phenethyl)-7-iodo-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 241



a) (2-(1*H*-1,2,3-Triazol-1-yl)phenyl)methanol A83

A solution of 2-(triazol-1-yl)benzoic acid (0.50 g, 2.6 mmol) in tetrahydrofuran (10 mL) (*note: required heat and sonication for complete dissolution*), under an atmosphere of nitrogen, was cooled to 0 °C. To this was added lithium aluminum hydride 1.0 M THF (3.96 mL, 3.96 mmol) dropwise over 15 min. After 10 min at this temperature, the reaction was allowed to warm to RT and stirred for a further 3 h. The reaction was cooled to 0 °C and cautiously added to 2M aqueous HCl (10 mL). The THF was removed *in vacuo* and the remaining aqueous phase extracted with DCM (10 mL × 3). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.37 g, 80% yield) as an amber oil. LCMS-A: rt 4.364 min; *m/z* 176.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 1.1 Hz, 1H), 7.89 (d, *J* = 1.1 Hz, 1H), 7.64 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.39 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.48 (s, 2H), 3.44 (br s, 1H).

b) 2-(1*H*-1,2,3-Triazol-1-yl)benzaldehyde A84

To a suspension of pyridinium chlorochromate (PCC) (0.91 g, 4.2 mmol) in DCM (6 mL), under an atmosphere of nitrogen, was added a solution of (2-(1*H*-1,2,3-triazol-1-yl)phenyl)methanol A83 (0.37 g, 2.1 mmol) in DCM (6 mL) dropwise. This was allowed to stir at RT for 1 h. Diethyl ether (10 mL) was added and the suspension filtered through a pad of Celite®. The pad was washed with diethyl ether (50 mL) and the filtrate concentrated *in vacuo.* The crude material was purified by column chromatography (Grace Biotage, 40 g SiO_2, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title

compound (0.18 g, 49% yield) as a white solid. LCMS-A: rt 4.369 min; *m/z* 174.0 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.89 (d, *J* = 0.7 Hz, 1H), 8.16 – 8.10 (m, 1H), 7.98 (d, *J* = 1.1 Hz, 1H), 7.94 (d, *J* = 1.2 Hz, 1H), 7.79 (td, *J* = 7.7, 1.6 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.53 (dd, *J* = 7.8, 0.8 Hz, 1H).

c) (*E*)-1-(2-(2-Nitrovinyl)phenyl)-1*H*-1,2,3-triazole A85

2-(1*H*-1,2,3-Triazol-1-yl)benzaldehyde A84 (0.16 g, 0.92 mmol), nitromethane (0.20 mL, 3.7 mmol) and ammonium acetate (0.036 g, 0.46 mmol) were added to glacial acetic acid (1 mL) and refluxed for 5 h. The reaction was cooled, poured into water (5 mL) and extracted with diethyl ether (3 × 5 mL). The organics were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was recrystallised from EtOH to give the title compound (0.075 g, 38% yield) as a white solid. LCMS-A: rt 5.082 min; *m/z* 216.9 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 1.1 Hz, 1H), 7.85 (d, *J* = 1.1 Hz, 1H), 7.81 (d, *J* = 13.6 Hz, 1H), 7.76 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 1H), 7.71 – 7.58 (m, 2H), 7.57 – 7.51 (m, 1H), 7.44 (d, *J* = 13.6 Hz, 1H).

d) 2-(2-(1*H*-1,2,3-Triazol-1-yl)phenyl)ethan-1-amine A86

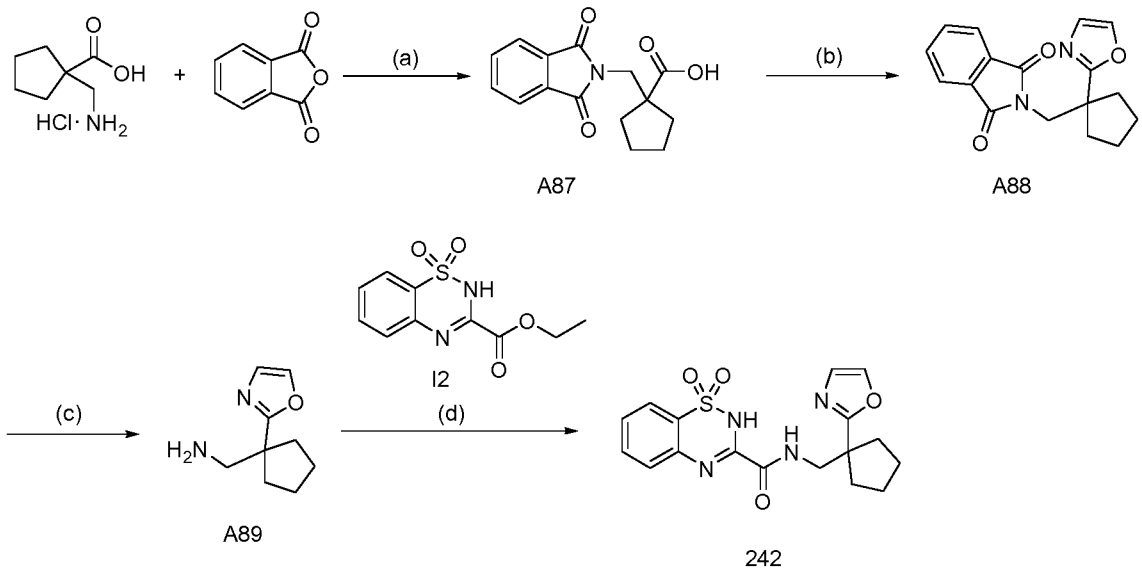
To (*E*)-1-(2-(2-Nitrovinyl)phenyl)-1*H*-1,2,3-triazole A85 (0.072 g, 0.33 mmol) in dry THF (2 mL) at 0 °C, under an atmosphere of nitrogen, was added lithium aluminum hydride 1.0 M THF (0.67 mL, 0.67 mmol) dropwise. This was allowed to warm to RT, then stirred for a further 3 h. The reaction was cooled to 0 °C and quenched with the slow addition of aqueous 1M NaOH (5 mL). Water (5 mL) and EtOAc (10 mL) were added and the layers separated. The aqueous was extracted with EtOAc (2x), the combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.043 g, 69% yield) as an oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.61 (m, 2H), 7.52 – 7.29 (m, 6H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.58 (td, *J* = 7.1, 2.4 Hz, 2H).

e) *N*-(2-(1*H*-1,2,3-triazol-1-yl)phenethyl)-7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 241

To 2-(2-(1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-amine A86 (0.043 g, 0.23 mmol) in EtOH (0.125 mL) was added ethyl 7-iodo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I7 (0.056 g, 0.15 mmol). The reaction was irradiated in a CEM microwave at 120 °C for 2 h, then concentrated to dryness and partitioned between 1M aqueous HCl (2 mL) and EtOAc (2 mL). The layers were separated and the organic layer concentrated *in vacuo.* The material was taken up in minimum EtOH and Et_2O was added dropwise until a precipitate formed. The precipitate was collected and the process repeated. This material was further

purified by column chromatography (Grace Biotage, 4 g SiO_2, 0-100% EtOAc in petroleum benzine 40-60 °C, then 0-40% EtOAc in MeOH) to give the title compound (0.0050 g, 4.2% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, 1H), 9.22 (br s, 1H), 8.43 (d, *J* = 1.1 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.94 (d, *J* = 1.0 Hz, 1H), 7.65 – 7.36 (m, 5H), 2.72 (t, *J* = 7.3 Hz, 2H). Two aliphatic protons obscured by the water signal.

Example 242: N-((1-(oxazol-2-yl)cyclopentyl)methyl)-2H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 242



a) 1-((1,3-Dioxoisoindolin-2-yl)methyl)cyclopentane-1-carboxylic acid A87

To 1-(aminomethyl)cyclopentane-1-carboxylic acid hydrochloride (0.500 g, 2.783 mmol) in 1,4-dioxane (8 mL) was added NEt_3 (1.164 mL, 8.350 mmol). This was allowed to stir for 10 min, upon which phthalic anhydride (0.495 g, 3.340 mmol) was added. The mixture was sealed and irradiated in a microwave reactor at 150 °C for 30 min. The precipitated salts were filtered and the filtrate concentrated *in vacuo.* The material was taken up in minimal MeOH and loaded onto a 10 g Agilent, Bond Elut NH_2 column. The column was washed with 3 volumes of MeOH (3 × 30 mL), then stripped with 1M HCl in 1,4-dioxane (100 mL). The HCl wash was concentrated *in vacuo* to give the title compound (0.560 g, 74 % yield) as a white solid. LCMS-B: rt 3.168 min; *m/z* 272.1 $[M-H]^-$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.34 (br s, 1H), 8.04 – 7.71 (m, 4H), 3.79 (s, 2H), 2.08 – 1.81 (m, 2H), 1.65 – 1.56 (m, 4H), 1.55 – 1.46 (m, 2H).

b) 2-((1-(Oxazol-2-yl)cyclopentyl)methyl)isoindoline-1,3-dione A88

1-((1,3-Dioxoisoindolin-2-yl)methyl)cyclopentane-1-carboxylic acid A87 (0.300 g, 1.098 mmol) was dissolved in thionyl chloride (2 mL) and heated at 80 °C for 3 h. The remaining thionyl chloride was evaporated *in vacuo.* The residue was dissolved in sulfolane (2 mL),

and to this was added 1,2,3-triazole (0.089 mL, 1.537 mmol) and K_2CO_3 (0.303 g, 2.196 mmol). The reaction was heated to 150 °C for 30 min, then cooled, added to water (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by silica gel chromatography (Isolera Biotage 40 g SiO_2, 0-100% EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.135 g, 42 % yield) as a white solid. LCMS-B: rt 3.285 min, *m/z* 297.1 $[M+H]^+$.

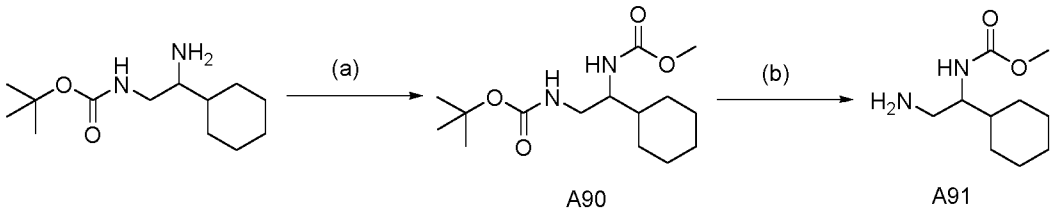
c) (1-(Oxazol-2-yl)cyclopentyl)methanamine A89

To a suspension of 2-((1-(oxazol-2-yl)cyclopentyl)methyl)isoindoline-1,3-dione A88 (0.135 g, 0.456 mmol) in EtOH (6 mL) was added hydrazine hydrate (0.057 mL, 1.822 mmol). The solution was heated at 80 °C for 3 h, an additional portion of hydrazine hydrate (0.057 mL) was added, and the reaction was allowed to stir for a further 2 h. The reaction was cooled and the precipitate filtered and washed with a portion of cold EtOH (5 mL). The combined EtOH fractions were allowed to stand at 0 °C overnight, the precipitate was removed by filtration and the filtrate was loaded directly onto a 5 g SCX cartridge (Agilent Bond Elut) and the cartridge was washed with MeOH (20 mL), the product was then eluted with a 10 % aq. NH_3 in MeOH solution (20 mL). The NH_3 washings were evaporated *in vacuo* give the title compound (0.049 g, 65 % yield) as an oil. LCMS-B: rt 1.534 min, *m/z* 167.1 $[M+H]^+$.

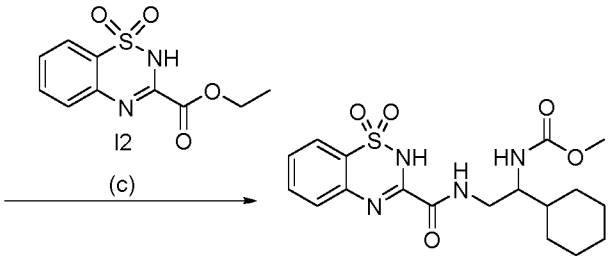
d) *N*-((1-(Oxazol-2-yl)cyclopentyl)methyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 242

To (1-(oxazol-2-yl)cyclopentyl)methanamine A89 (0.045 g, 0.270 mmol) in EtOH (0.250 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I2 (0.049 g, 0.193 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction was cooled and EtOH removed *in vacuo*. The residue was taken up in EtOAc (3 mL) and washed with 1M aqueous HCl (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.060 g, 84 % yield) as a white solid. LCMS-B: rt 3.162 min; *m/z* 375.1 $[M+H]^+$.

Example 243: methyl (1-cyclohexyl-2-(1,1-dioxido-2H-benzo[e][1,2,4]thiadiazine-3-carboxamido)ethyl)carbamate 243



A90 A91



I2

243

a) *tert*-Butyl methyl (1-cyclohexylethane-1,2-diyl)dicarbamate A90

To a solution of the *tert*-butyl (2-amino-2-cyclohexylethyl)carbamate (0.500 g, 2.063 mmol) in DCM (15 mL) was added NEt_3 (0.316 mL, 2.269 mmol). This was allowed to stir for 10 min upon which the reaction was cooled to 0 °C and methyl chloroformate (0.189 mL, 2.269 mmol) was added dropwise. The reaction slowly warmed to RT and was allowed to stir overnight. 1M aqueous HCl (15 mL) was added and the layers separated. The organics were washed with saturated aqusous Na_2CO_3 (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.450 g, 73 % yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.86 – 4.69 (m, 1H), 3.65 (s, 3H), 3.58 – 3.45 (m, 1H), 3.20 (m, 2H), 1.81 – 1.62 (m, 6H), 1.42 (s, 9H), 1.29 – 0.95 (m, 4H).

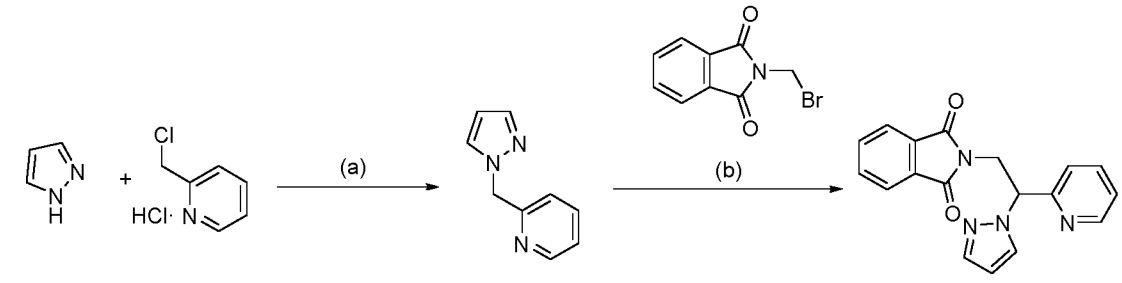
b) Methyl (2-amino-1-cyclohexylethyl)carbamate A91

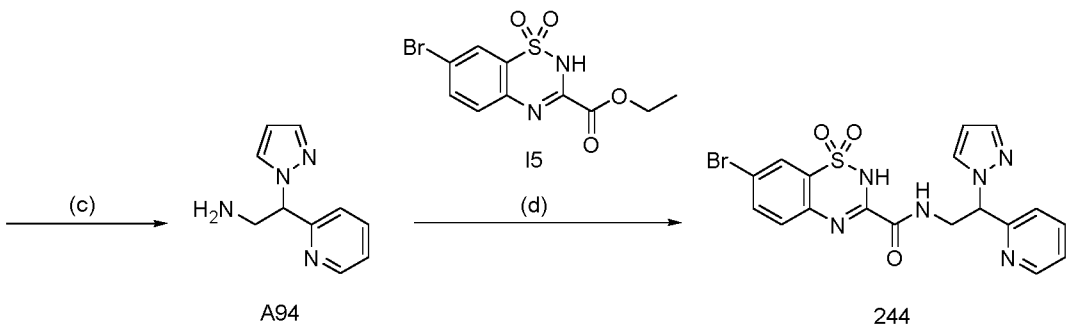
To a solution of *tert*-butyl methyl (1-cyclohexylethane-1,2-diyl)dicarbamate A90 (0.450 g, 1.498 mmol) in DCM (6 mL) was added TFA (0.6 mL). This was allowed to stir at RT for 2 h upon which time the reaction was concentrated *in vacuo* to give the crude product. A portion of the crude material (0.162 g) in MeOH (~1 mL) was gravity loaded onto a SCX cartridge (5 g). The cartridge was washed with 3 column volumes of MeOH, then 3 column volumes of a 10 % solution of NH_3 in MeOH. The methanolic ammonia washes were combined and concentrated *in vacuo* to give the title compound (0.059 g) as a clear oil which was used directly in the next step.

c) Methyl (1-cyclohexyl-2-(1,1-dioxido-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamido)ethyl)carbamate 243

To methyl (2-amino-1-cyclohexylethyl)carbamate A91 (0.059 g, 0.295 mmol) in EtOH (0.125 mL) was added ethyl 2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I2 (0.050 g, 0.197 mmol). The mixture was subjected to microwave irradiation at 100 °C for 30 min. The reaction was cooled and the solvent evaporated. The material was partitioned between 1M aqueous HCl (3 mL) and EtOAc (3 mL). The layers were separated and the organic phase was washed with brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.062 g, 77 % yield) as a white solid. LCMS-A: rt 6.007 min; *m/z* 407.2 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 9.03 (t, *J* = 5.8, 5.8 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.73 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 1H), 3.63 – 3.54 (m, 1H), 3.50 (s, 3H), 3.44 (dt, *J* = 13.0, 5.4, 5.4 Hz, 1H), 3.24 (dt, *J* = 13.7, 7.1, 7.1 Hz, 1H), 1.75 – 1.63 (m, 4H), 1.59 (d, *J* = 10.0 Hz, 1H), 1.46 – 1.33 (m, 1H), 1.26 – 1.06 (m, 3H), 1.06 – 0.89 (m, 2H).

Example 244: N-(2-(1H-pyrazol-1-yl)-2-(pyridin-2-yl)ethyl)-7-bromo-4H-benzo[e][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 244





a) 2-((1*H*-Pyrazol-1-yl)methyl)pyridine A92

To a solution of pyrazole (0.5 g, 7.35 mmol) in toluene (15 mL) was added 2-(chloromethyl)pyridine hydrochloride (1.44 g, 8.8 mmol), aqueous NaOH (40 % w/v, 10 mL) and 40% w/v aqueous tetrabutylammonium hydrogen sulphate (catalytic 12 drops). The reaction mixture was heated at reflux for 20 hours and then partitioned between water (50

mL) and diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*, and the crude product was purified by chromatography (24 g SiO_2 cartridge, 0-95 % EtOAc in petroleum benzine 40-60 °C) to give the title compound (1.24 g, 89% yield) as a colourless viscous oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 6.14 Hz, 2H), 7.60 (d, *J* = 1.80 Hz, 1H), 7.45 (d, *J* = 2.33 Hz, 1H), 7.03 (d, *J* = 6.15 Hz, 2H), 6.35 (t, *J* = 2.12 Hz, 1H), 5.36 (s, 2H). LCMS-B: R_t 0.587 min, *m/z* 160.1 $[M+H]^+$.

b) 2-(2-(1*H*-Pyrazol-1-yl)-2-(pyridin-2-yl)ethyl)isoindoline-1,3-dione A93

To a solution of 2-((1*H*-pyrazol-1-yl)methyl)pyridine A92 (0.412 g, 2.59 mmol) in anhydrous THF (10 mL) at -78 °C under nitrogen was added *N*-(bromomethyl)phthalimide (0.808 g, 3.36 mmol) dropwise. A solution of lithium bis(trimethylsilyl)amide, 1.0 M solution in hexane (3.36 mL, 3.36 mmol) in anhydrous THF (8 mL) was then added dropwise and the mixture allowed to warm slowly to room temperature and stirred overnight. The mixture was diluted with a saturated aqueous NH_4Cl solution (50 mL) and water (25 mL), then extracted with DCM (50 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography (0-100 % EtOAc in petroleum benzine 40-60 °C) to give the title compound (0.145 g, 18% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (s, 2H), 7.81 (dd, *J* = 3.07, 5.47 Hz, 2H), 7.72 (dd, *J* = 3.06, 5.50 Hz, 2H), 7.59 (d, *J* = 1.80 Hz, 1H), 7.51 (dd, J = 0.60, 2.43 Hz, 1H), 7.43 (d, *J* = 5.30 Hz, 2H), 6.27 (d, *J* = 2.04 Hz, 1H), 5.99 (dd, *J* = 6.38, 9.09 Hz, 1H), 4.63 (dd, *J* = 9.14, 14.04 Hz, 1H), 4.41 (dd, *J* = 6.40, 14.04 Hz, 1H). LCMS-A: R_t 4.60 min, *m/z* 318.9 $[M+H]^+$.

c) 2-(1*H*-Pyrazol-1-yl)-2-(pyridin-2-yl)ethan-1-amine A94

To a suspension of 2-(2-(1*H*-pyrazol-1-yl)-2-(pyridin-2-yl)ethyl)isoindoline-1,3-dione A93 (0.15 g, 0.46 mmol) in ethanol (30 mL) was added 64-65% v/v hydrazine hydrate (0.500 mL, 6.58 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was filtered and the solid was washed with ethanol. The filtrate was partitioned between DCM (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL × 3). The combined organic extracts were washed with brine, dried over magnesium sulphate and concentrated to give the title compound (0.0550 g, 64% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 2H), 7.63 (s, 1H), 7.48 (d, *J* = 2.46 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.34 (s, 1H), 5.36 – 5.28 (m, 1H), 3.70 (obscured by solvent), 3.44 – 3.22 (m, 1H).

d) *N*-(2-(1*H*-Pyrazol-1-yl)-2-(pyridin-2-yl)ethyl)-7-bromo-4*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide 244

Ethyl 7-bromo-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxylate 1,1-dioxide I5 (65 mg, 0.20 mmol), 2-(1*H*-pyrazol-1-yl)-2-(pyridin-2-yl)ethan-1-amine A94 (0.055 g, 0.29 mmol) and absolute ethanol (0.5 mL) were heated in the microwave at 100 °C for 30 minutes. The reaction mixture was heated in the microwave once more at 100 °C for 30 minutes, then cooled to room temperature and filtered. The filtrate was dried *in vacuo* then purified by chromatography (4 g SiO_2 cartridge, 0 - 100 % EtOAc in petroleum benzine 40-60 °C followed by 0 - 10 % MeOH in EtOAc) to give the title compound as an off-white solid (2.7 mg, 2% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.50 (d, *J* = 6.3 Hz, 2H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.64 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.32 (dd, *J* = 4.8, 1.5 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 1H), 5.87 (dd, *J* = 8.6, 5.4 Hz, 1H), 4.31 (dd, *J* = 13.9, 8.7 Hz, 1H), 4.14 (dd, *J* = 13.9, 5.4 Hz, 1H). LCMS R_t 2.99 min, *m/z* 476.7 $[M+H]^+$.

Assays

Acetyltransferase Biochemical Assay

Compounds may be tested for *in vitro* activity in the following assay:

To determine the inhibition of HAT enzymatic activity by test compounds, assay reactions were conducted in a volume of 8 µL in 384-well low volume assay plates. The reactions were performed in assay buffer (100 mM Tris-HCl, pH 7.8, 15 mM NaCl, 1 mM EDTA, 0.01% Tween-20, 1 mM Dithiothreitol, and 0.02% m/v chicken egg white albumin). Reactions were set up with 0.4 µM Acetyl coenzyme A (for all assays apart from KAT6A which was set up with 10 µM Acetyl coenzyme A), 100nM of full-length recombinant histone labelled by limited biotinylation (KAT6A, KAT6B, KAT7: H3.1, KAT5, KAT8: H4), 10/ 5/ 8/ 40/ 20 nM of KAT5/KAT6A/KAT6B/KAT7/KAT8 enzyme respectively, and an acetyl-lysine specific antibody (H3.1: Cell Signaling Technology, H4: Abcam). 11-point dilution series of the test compounds were prepared in DMSO; a volume of 100 nL was transferred using a pin tool into assay plates containing substrates, before adding enzyme to start the reaction. Positive (no compound) and negative (AcCoA omitted) control reactions were included on the same plates and received the same amount of DMSO as the compound treated wells. After adding all reagents, the plates were sealed with adhesive seals and incubated for 90 min at room temperature. An additional 4 µL of assay buffer containing AlphaScreen® Protein A acceptor beads and Streptavidin donor beads (PerkinElmer, Waltham, MA) to a final concentration of 8 µg/mL was then added. After incubation for 2 hours the plates were read using an EnVision 2103 multi label plate reader (PerkinElmer) in HTS AlphaScreen® mode. IC_{50} values were obtained from the raw

readings by calculating percent inhibition (%I) for each reaction relative to controls on the same plate (%I=(I-CN)/(CP-CN) where CN/ CP are the averages of the negative/ positive reactions, respectively), then fitting the %I data *vs*. compound concentration [I] to %I=(A+((B-A)/(1+((C/[I])^D)))) where A is the lower asymptote, B is the upper asymptote, C is the IC_{50} value, and D is the slope.

The results are shown in tables 1 to 5 below:

Table 1 (TIP60-KAT5)

Example	**IC50 (µM)**
1	0.286
2	>125
3	96.5
4	5.33
5	1.17
6	90.1
7	11.7
8	4.4
9	12.4
10	79.7
11	11.8
12	2.62
13	0.727
14	2.36
15	1.4
16	23.8
17	51
18	>125
19	33.2
20	29.5
22	72.4
23	3.73
24	7.16
25	6.89
26	1.66
27	1.29

Example	IC50 (μM)
28	63.5
29	>125
30	112
31	15.1
32	5.04
33	6.95
34	>125
35	>125
36	19.6
37	44
38	1.96
39	5.88
40	>125
41	0.0613
42	0.642
43	2.39
44	>125
45	109
46	9.71
49	>125
51	25.3
52	125
53	19.8
54	57.9
55	36.5
56	0.269
57	2.8
58	2.58
60	0.327
61	>125
62	>125
63	>125
64	92.1
65	85.4

Example	IC50 (μM)
66	>125
67	>125
68	14.5
69	>125
70	>125
73	10.1
74	>125
75	56.6
76	>125
77	87
78	16.7
79	87.8
80	>125
81	4.9
82	7.82
83	7.38
84	0.778
85	5.97
86	1.17
87	4.47
88	1.19
89	2.06
90	0.96
91	0.209
92	0.367
93	9.2
94	2.82
95	5.18
96	94.7
97	>125
98	>125
99	>125
100	40.5
101	>125

Example	IC50 (μM)
102	27.1
103	>125
104	>125
105	46.3
106	>125
107	20.8
108	77.7
109	3.42
110	75.6
111	16.6
112	18.5
113	>125
114	0.954
115	0.423
116	4.44
118	2.29
119	5.26
120	1.24
121	40.8
122	>125
123	5.01
124	24.6
125	>125
126	31.3
127	61.2
128	>125
129	>125
131	>125
133	>125
134	2.17
135	3.13
136	27.6
137	3.08
138	0.0952

Example	IC50 (μM)
139	1.3
142	4.27
143	13.8
144	1.65
145	18.9
146	0.0468
147	0.445
148	45.7
149	4.88
150	3.17
152	52.8
153	38.7
154	>125
206	36.8

Table 2 (MOZ-KAT6A)

Example	IC50 (μM)
1	0.0241
2	38.1
3	7.66
4	0.1
5	0.667
7	2.8
9	0.0421
10	0.0906
11	1.81
13	0.229
15	0.211
16	1.37
17	3.33
18	3.12
19	1.35
20	6.05
22	1.98

Example	IC50 (μM)
23	0.056
24	0.127
25	0.0512
26	0.0287
27	0.0195
28	4.42
29	28.6
31	8.23
32	0.0498
33	0.126
34	51.6
35	59.9
36	0.661
37	0.771
38	0.532
41	0.0179
43	0.243
44	125
45	35.2
46	0.324
49	7.67
51	4.82
52	36.1
53	0.273
54	8.87
55	5.66
56	0.0809
61	>125
62	>125
63	>125
64	102
65	53.9
66	>125
67	>125

Example	IC50 (μM)
68	3.81
69	>125
70	>125
74	67.5
75	1.72
76	>125
77	35.5
78	3.74
79	35.4
80	58.8
81	1.61
82	9.19
83	2.61
84	0.256
85	8.1
86	2.7
87	8.93
91	0.594
92	0.783
93	2.2
96	1.17
97	4
98	36.1
99	15.8
100	41.7
101	10.2
102	10.6
103	125
107	12
108	11.6
112	4.58
113	125
114	0.861
115	0.476

Example	IC50 (μM)
116	2.26
131	62.3
133	>125
134	0.149
135	0.168
136	8.03
137	0.107
139	0.464
142	0.0211
143	0.346
144	0.12
145	3.73
146	0.0259
147	0.645
148	5.39
149	0.102
152	47.5
154	>125
206	9.64

Table 3 (HBO-KAT7)

Example	IC50 (μM)
1	0.0638
4	2.56
5	2.04
7	11.9
8	1.2
9	20.1
11	2.53
12	5.87
13	0.981
14	1.78
24	0.141
25	1.93

Example	IC50 (μM)
26	1.48
28	15.7
29	84.4
30	125
31	5.84
32	4.64
33	6.78
34	60.3
35	31.6
36	0.538
38	0.154
39	0.192
40	9.45
41	0.0944
42	0.255
43	1.99
46	2.65
54	4.01
55	4.51
56	0.219
57	2.53
58	1.59
60	0.555
68	0.462
73	26.4
78	4.56
79	29.5
80	104
84	0.0836
86	1.33
87	12
88	0.659
89	3.37
90	0.915

Example	IC50 (μM)
91	0.339
92	0.675
93	9.59
94	3.8
95	4.22
96	3.17
97	49.4
98	68.6
99	9.16
100	112
101	>125
102	60.2
103	>125
104	>125
105	>125
106	>125
107	23.3
108	50.1
109	5.95
110	101
111	81.4
112	4.11
114	0.529
115	0.229
118	3.02
119	18.5
120	3.52
121	47
122	>125
123	1.72
124	18.7
125	>125
126	12.4
127	34.7

Example	IC50 (μM)
128	>125
129	>125
134	3.32
135	2.53
136	0.633
137	0.913
138	0.234
139	0.0615
142	6.57
143	1.75
146	0.16
147	0.167
153	3.41
173	0.051
174	7.49
175	0.162
176	0.207
177	0.064
178	0.571
206	7.17
216	0.063
217	1.74
233	0.038

Table 4 (MOF-KAT8)

Example	IC50 (μM)
1	14.6
4	28.8
5	27.7
7	>125
24	69.6
25	78.2
26	23.7
32	74.1

Example	IC50 (μM)
33	89.6
41	4.87
46	88.2
82	>125
84	33.3
86	39.4
87	114
88	47
91	12.1
92	21.8
114	>125
115	31.2
116	56.7
136	>125
137	100
138	8.07
139	19.1
142	56.7
143	30
146	4.19
147	26.1
162	4.20
163	9.78
164	29.6
165	43.1
167	6.48
168	3.39
169	5.14
170	3.75
171	41.7
172	5.13
173	39.1
174	>125
175	29.3

Example	IC50 (μM)
176	92.9
177	6.25
178	106
179	10.4
180	77.0
181	104
182	50.0
183	36.3
184	9.22
186	71.5
187	22.8
188	39.8
189	7.96
190	48.9
203	103
204	>125
208	24.1
212	40.8
213	3.54
214	7.058
215	8.74
216	64.3
217	22.5
218	>125
219	>125
228	6.52
233	6.13
234	57.3
235	6.59
236	20.2
237	6.35
238	41.4
239	>125
243	82.5

Example	IC50 (μM)
244	82.9

Table 5 (QKF-KAT6B)

Example	IC50 (μM)
18	0.268
46	0.122

Histone H3 Lysine 14 Acetylation Biomarker Assay

Compounds may be tested for their ability to inhibit acetylation of the histone H3K14 marker (which is HBO1 mediated) in the following assay:

The cell line U2OS was seeded at a density of 12,000 cells per well in 96 well optical quality tissue culture plates in RPMI medium and 10% foetal bovine serum, and allowed to adhere for 24 hours under standard culture conditions (37 degree Celsius, 5% CO_2). At the end of this period the cells were washed with serum free medium. Compound dilutions prepared in DMSO were added to the serum free medium, with negative control wells reserved for treatment with DMSO only and positive controls receiving a potent inhibitor compound (e.g. Example 36 in WO2016/198507) at 10 μM concentration. After incubation for 24 hours, the cells were fixed with 3.7% formaldehyde in PBS for 20 minutes at room temperature, washed with phosphate buffer saline containing 0.1%Tween 20 and blocked with Odyssey blocking buffer (LI-COR, Lincoln, NE) containing 0.1%TritonX100. Anti-H3K14ac specific antibody (Cell Signalling Technologies) in Odyssey blocking buffer containing 0.1%Tween 20 was added and incubated for 14 hours at 4 degree Celsius. After washing, a secondary antibody labelled with Alexa647 dye (LifeTechnologies) and Hoechst 33342 (1 μg/mL, SigmaAldrich) were added for 1 hour incubation. Plates were washed and read on a PerkinElmer Phenix high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the acetylation level was calculated from the Alexa647-related intensity in the same area. The resulting mean intensity per cell was directly converted to percent inhibition relative to controls on the same plate and the data fitted against a four-parameter logistic model to determine the 50% inhibitory concentration (IC_{50}).

The results are shown in table 6 below:

Example	IC50 (μM)
1	0.317
4	30

Example	IC50 (μM)
8	9.68
36	9.98
38	1.5
39	2.49
41	0.0861
46	8.16
56	0.65
60	1.61
84	0.765
91	0.615
92	1.39
93	30
101	30
115	1.06
136	7.89
137	2.45
138	0.145
139	0.263
142	17.5
143	14.6
146	0.429
147	0.193

H2A.Z Lysine 7 Acetylation Biomarker Assay

To discover a global TIP60/KAT5 cellular biomarker useful for monitoring PD responses of TIP60 inhibition *in vitro* and *in vivo*, various histone modifications were assessed for TIP60 dependence through genetic (TIP60 siRNA and CRISPR/Cas9) or TIP60 pharmacological inhibition. This analysis clearly identified acetylation of the histone variant H2A.Z at Lysine 7 (H2A.ZK7ac) as a global histone mark which is TIP60-dependent in both human and mouse cells. To a lesser extent, TIP60 also acetylated lysine 4 and 11 of H2A.Z.

Compounds may be tested for their ability to inhibit the histone H2A.Z Lysine 7 acetylation biomarker (which is TIP60 mediated) in the following assay:

The cell line U2OS was seeded at a density of 9,000 cells per well in 96 well optical quality tissue culture plates in RPMI medium and 10% foetal bovine serum, and allowed to adhere

for 24 hours under standard culture conditions (37 degree Celsius, 5% CO_2). At the end of this period the cells were washed with serum free medium. Compound dilutions prepared in DMSO were added to the serum free medium, with negative control wells reserved for treatment with DMSO only and positive controls receiving a potent inhibitor compound (e.g. Example 146) at 20 µM concentration. After incubation for 24 hours, the cells were fixed with 3.7% formaldehyde in PBS for 20 minutes at room temperature, washed with phosphate buffer saline containing 0.1% Tween 20 and blocked with Odyssey blocking buffer (LI-COR, Lincoln, NE) containing 0.1% TritonX100. Anti-H2A.Z K7ac specific antibody (Abcam) in Odyssey blocking buffer containing 0.1%Tween 20 was added and incubated for 14 hours at 4 degree Celsius. After washing, a secondary antibody labelled with Alexa647 dye (LifeTechnologies) and Hoechst 33342 (10 µM, SigmaAldrich) were added for 1 hour incubation. Plates were washed and read on a PerkinElmer Phenix high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the acetylation level was calculated from the Alexa647-related intensity in the same area. The resulting mean intensity per cell was directly converted to percent inhibition relative to controls on the same plate and the data fitted against a four-parameter logistic model to determine the 50% inhibitory concentration (IC_{50}).

The results are shown in table 7 below:

Example	IC50 (µM)
1	2.18
4	10
12	26.8
13	5.78
41	1
46	30
60	2.06
91	10
101	30
122	10
137	10
138	1.46
139	5.05
146	0.447
147	1.43

Further Assays

Protein Preparation

KAT5

Molecular Biology: A codon optimized DNA sequence (for expression in *Escherichia coli)* encoding amino acid residues 2 to 461 (Uniprot Q92993-2) of human KAT5 isoform was synthesised by GenScript USA Inc (Piscataway, New Jersey, USA). This was ligated into a modified pET43a *E. coli* expression vector designed to encode an N-terminal hexahistidine tag followed by a tobacco etch virus protease (TEV) cleavage site and by the KAT5 sequence. The resulting protein sequence is listed below.

MGHHHHHHGTENLYFQGSAEVGEIIEGCRLPVLRRNQDNEDEWPLAEILSVKDISGRKLF
YVHYIDFNKRLDEWVTHERLDLKKIQFPKKEAKTPTKNGLPGSRPGSPEREVKRKVEVVS
PATPVPSETAPASVFPQNGAARRAVAAQPGRKRKSNCLGTDEDSQDSSDGIPSAPRMTG
SLVSDRSHDDIVTRMKNIECIELGRHRLKPWYFSPYPQELTTLPVLYLCEFCLKYGRSLKC
LQRHLTKCDLRHPPGNEIYRKGTISFFEIDGRKNKSYSQNLCLLAKCFLDHKTLYYDTDPFL
FYVMTEYDCKGFHIVGYFSKEKESTEDYNVACILTLPPYQRRGYGKLLIEFSYELSKVEGK
TGTPEKPLSDLGLLSYRSYWSQTILEILMGLKSESGERPQITINEISEITSIKKEDVISTLQYL
NLINYYKGQYILTLSEDIVDGHERAMLKRLLRIDSKCLHFTPKDWSKRGKWAS*

Protein Expression: To produce recombinant KAT5 protein, expression plasmid was transformed into *E. coli* BL21 DE3 strain and grown with shaking at 37°C in 1 L volumes of Terrific broth (TB) supplemented with 100 µg/mL Ampicillin and 50 µM zinc until an OD600 of 0.8 was reached. Cultures were transferred to 18°C and protein expression induced by the addition of Isopropyl β-D-1-thiogalactopyranoside to a final concentration of 0.5 mM and the cultures shaken overnight for further 16 hours. Following expression, cell cultures were centrifuged at 5000 x g for 20 min and cell pellet stored frozen at -20°C.

Protein Purification: Protein purification was initiated by thawing the cell pellet (25 g wet weight) in Lysis buffer (50 mM Hepes pH 7.4, 500 mM NaCl, 5 mM imidazole, 5% [v/v] glycerol, 0.1% [w/v] CHAPS, 2 mM 2-mercaptoethanol, 3 mM $MgCl_2$, 0.5 mg/mL lysozyme, benzonase endonuclease [EMD Millipore], 1 mM PMSF, complete protease inhibitor tablets EDTA-free [Roche]) using a ratio of 6 mL of buffer per 1 g of cells. Cells were further lysed by sonication using a Misonix Liquid Processor (6 x 30 second pulses, amplitude 60 [70 watts]) and then centrifuged at 48,000 x g at 4°C. Supernatant (cell lysate) was mixed with

20 mL of Q-Sepharose FF resin (GE Healthcare) pre-equilibrated with Q buffer (20 mM Hepes pH 7.4, 1 M NaCl). The unbound fraction from Q-Sepharose FF was then incubated with 5 mL of cOmplete His-Tag Purification Resin (Roche), pre-equilibrated with IMAC Wash Buffer (20 mM hepes pH 7.4, 500 mM NaCl, 35 mM imidazole). The resin was washed with IMAC Wash Buffer, and bound KAT5 eluted with IMAC Elution buffer (20 mM hepes pH 7.4, 500 mM NaCl, 300 mM imidazole). IMAC-eluted protein was immediately desalted into Storage buffer (50 mM Na citrate pH 6.5, 500 mM NaCl, 5% [v/v] glycerol) using 2 x HiPrep 26/10 desalting columns (GE Healthcare) in series. Desalted protein was further purified by passing through a HiLoad 26/60 Superdex 75 column pre-equilibrated in Storage buffer. Finally, KAT5 protein was concentrated to 1.5 mg/mL using Amicon Ultra centrifugal filter unit (Utra-15 MWCO 10 kDa), flash-frozen in liquid nitrogen and stored in -70°C freezer.

KAT6A

Molecular Biology: The DNA sequence encoding amino acid residues 507 to 778 (Uniprot Q92794-1) of human KAT6A was amplified by PCR and was ligated into a modified pET *E. coli* expression vector designed to encode a NusA solubility tag followed by a hexahistidine tag and a tobacco etch virus protease (TEV) cleavage site and by the KAT6A sequence. The resulting protein sequence is listed below.

MNKEILAVVEAVSNEKALPREKIFEALESALATATKKKYEQEIDVRVQIDRKSGDFDTFRR
WLVVDEVTQPTKEITLEAARYEDESLNLGDYVEDQIESVTFDRITTQTAKQVIVQKVREAE
RAMVVDQFREHEGEIITGVVKKVNRDNISLDLGNNAEAVILREDMLPRENFRPGDRVRGV
LYSVRPEARGAQLFVTRSKPEMLIELFRIEVPEIGEEVIEIKAAARDPGSRAKIAVKTNDKRI
DPVGACVGMRGARVQAVSTELGGERIDIVLWDDNPAQFVINAMAPADVASIVVDEDKHT
MDIAVEAGNLAQAIGRNGQNVRLASQLSGWELNVMTVDDLQAKHQAEAHAAIDTFTKYLD
IDEDFATVLVEEGFSTLEELAYVPMKELLEIEGLDEPTVEALRERAKNALATIAQAQEESLG
DNKPADDLLNLEGVDRDLAFKLAARGVCTLEDLAEQGIDDLADIEGLTDEKAGALIMAARNI
CWFGDEATSGSGHHHHHHSAGENLYFQGAMGRCPSVIEFGKYEIHTWYSSPYPQEYSR
LPKLYLCEFCLKYMKSRTILQQHMKKCGWFHPPVNEIYRKNNISVFEVDGNVSTIYCQNLC
LLAKLFLDHKTLYYDVEPFLFYVLTQNDVKGCHLVGYFSKEKHCQQKYNVSCIMILPQYQR
KGYGRFLIDFSYLLSKREGQAGSPEKPLSDLGRLSYMAYWKSVILECLYHQNDKQISIKKL
SKLTGICPQDITSTLHHLRMLDFRSDQFVIIRREKLIQDHMAKLQLNLRPVDVDPECLRWTP
*

Protein Expression: To produce recombinant KAT6A protein, expression plasmid was transformed into *E. coli* BL21 DE3 strain and grown with shaking at 37°C in 1 L volumes of Terrific broth (TB) supplemented with 100 µg/mL Ampicillin until an OD600 of 0.8 was reached. Cultures were transferred to 18°C and protein expression induced by the addition of Isopropyl β-D-1-thiogalactopyranoside to a final concentration of 0.5 mM and the cultures shaken overnight for further 16 hours. Following expression, cell cultures were centrifuged at 5000 x g for 20 min and cell pellet stored frozen at -20°C.

Protein Purification: Protein purification was initiated by thawing the cell pellet (40 g wet weight) in Lysis buffer (25 mM Tris-HCl pH 7.8, 500 mM NaCl, 5 mM DTT, 0.01% [v/v] Triton-X 100, 5% [v/v] glycerol, 2 mM $MgCl_2$, 10 mM Imidazole, 0.5 mg/mL lysozyme, benzonase endonuclease [EMD Millipore], 1 mM PMSF, complete protease inhibitor tablets EDTA-free [Roche]) using a ratio of 5 mL of buffer per 1 g of cells. Cells were further lysed by 3 passes (at 15000 psi) through an ice cooled Avestin C5 cell crusher and then centrifuged at 48,000 x g at 4°C. Supernatant (cell lysate) was filtered through a 5 µm filter and applied onto 5 mL HiTrap IMAC Sepharose FF column (GE Healthcare) pre-equilibrated with IMAC wash buffer (25 mM Tris-HCl pH 7.8, 500 mM NaCl, 5 mM DTT, 0.01% [v/v] Triton-X 100, 5% [v/v] glycerol, 20 mM Imidazole) using a Profinia Affinity chromatography purification system (Bio-Rad). The IMAC column was then washed with IMAC Wash buffer and bound KAT6A protein eluted with IMAC Elution buffer (25 mM Tris-HCl pH 7.8, 500 mM NaCl, 5% [v/v] glycerol, 5 mM DTT, 250 mM Imidazole). IMAC-eluted protein was further purified by passing through a HiLoad 26/60 Superdex 200 column pre-equilibrated in Storage buffer (25 mM Tris-HCl pH 7.8, 500 mM NaCl, 5 mM DTT, 5% [v/v] glycerol). Finally, KAT6A protein was concentrated to ≤ 1 mg/mL using Amicon Ultra centrifugal filter unit (Utra-15 MWCO 10 kDa), flash-frozen in liquid nitrogen and stored in -70°C freezer.

KAT6B was obtained from SignalChem, catalog ID: K315-381BG

KAT7

Molecular Biology: A codon optimized DNA sequence encoding amino acid residues 325 to 611 (Uniprot O95251-1) of human KAT7 was synthesised by GenScript USA Inc (Piscataway, New Jersey, USA). This was ligated into a modified pET43a *E. coli*

expression vector designed to encode an N-terminal hexahistidine tag followed by a tobacco etch virus protease (TEV) cleavage site and by the KAT7 sequence. The resulting protein sequence is listed below.

MGHHHHHHGTENLYFQGSRLQGQITEGSNMIKTIAFGRYELDTWYHSPYPEEYARLGRL
YMCEFCLKYMKSQTILRRHMAKCVWKHPPGDEIYRKGSISVFEVDGKKNKIYCQNLCLLA
KLFLDHKTLYYDVEPFLFYVMTEADNTGCHLIGYFSKEKNSFLNYNVSCILTMPQYMRQGY
GKMLIDFSYLLSKVEEKVGSPERPLSDLGLISYRSYWKEVLLRYLHNFQGKEISIKEISQET
AVNPVDIVSTLQALQMLKYWKGKHLVLKRQDLIDEWIAKEAKRSNSNKTMDPSCLKWTPP
KGTAS

Protein Expression: To produce recombinant KAT7 protein, expression plasmid was transformed into *E. coli* BL21 DE3 RIL strain and grown with shaking at 37°C in 1 L volumes of Terrific broth (TB) supplemented with 100 µg/mL Ampicillin and 50 µM zinc until an OD600 of 0.8 was reached. Cultures were transferred to 18°C and protein expression induced by the addition of Isopropyl β-D-1-thiogalactopyranoside to a final concentration of 0.5 mM and the cultures shaken overnight for further 16 hours. Following expression, cell cultures were centrifuged at 5000 x g for 20 min and cell pellet stored frozen at -20°C.

Protein Purification: Protein purification was initiated by thawing the cell pellet (10 g wet weight) in Lysis buffer (50 mM Hepes pH 7.5, 300 mM NaCl, 5 mM DTT, 5 mM Imidazole, 0.05% [v/v] Brij 35, 10% [v/v] glycerol, 3 mM $MgCl_2$, 0.5 mg/mL lysozyme, benzonase endonuclease [EMD Millipore], 1 mM PMSF, complete protease inhibitor tablets EDTA-free [Roche]) using a ratio of 10 mL of buffer per 1 g of cells. Cells were further lysed by sonication using a Misonix Liquid Processor (6 x 30 second pulses, amplitude 60 [70 watts]) and then centrifuged at 48,000 x g at 4°C. Supernatant (cell lysate) was incubated with 1 mL of cOmplete His-Tag Purification Resin (Roche), pre-equilibrated with IMAC Wash Buffer 1 (25 mM Hepes pH 7.5, 800 mM NaCl, 5 mM imidazole, 10% [v/v] glycerol, 5 mM DTT, 0.01% [v/v] Brij 35, 50 mM arginine, 50 mM glutamic acid). The resin was sequentially washed with IMAC Wash buffer 1 and IMAC Wash buffer 2 (25 mM hepes pH 7.5, 300 mM NaCl, 20 mM imidazole, 10% [v/v] glycerol, 5 mM DTT, 0.01% [v/v] Brij 35, 50 mM arginine, 50 mM glutamic acid). Bound KAT7 protein was eluted with IMAC Elution buffer (25 mM hepes pH 7.5, 200 mM NaCl, 500 mM imidazole, 10% [v/v] glycerol, 5 mM DTT 0.01% [v/v] Brij 35, 50 mM arginine, 50 mM glutamic acid). The eluting protein was

collected directly into 4 volumes of Desalt Buffer (50 mM Na citrate pH 6.5, 200 mM NaCl, 0.01% [v/v] Brij 35, 10% [v/v] glycerol, 5 mM DTT) to bring the final imidazole concentration to 100 mM. IMAC-eluted protein was immediately desalted into Desalt buffer using 2 x HiPrep 26/10 desalting columns (GE Healthcare) in series. Desalted protein was further purified by passing through a HiLoad 26/60 Superdex 75 column pre-equilibrated in Storage Buffer (50 mM Na citrate pH 6.5, 200 mM NaCl, 10% [v/v] glycerol, 5 mM DTT). Finally, KAT7 protein was concentrated to 3.5 mg/mL using Amicon Ultra centrifugal filter unit (Utra-15 MWCO 10 kDa), flash-frozen in liquid nitrogen and stored in -70°C freezer.

KAT8

Molecular Biology: A codon optimized DNA sequence (for expression in *E. coli)* encoding amino acid residues 177 to 447 (Uniprot Q9H7Z6-1) of human KAT8 was synthesised by Thermo Fisher Scientific GENEART GmbH (Regensberg, Germany). This was ligated into pPROEX Hta *E. coli* expression vector designed to encode an N-terminal hexahistidine tag followed by a tobacco etch virus protease (TEV) cleavage site and by the KAT8 sequence. The resulting protein sequence is listed below.

MSYYHHHHHHDYDIPTTENLYFQGAKYVDKIHIGNYEIDAWYFSPFPEDYGKQPKLWLCE
YCLKYMKYEKSYRFHLGQCQWRQPPGKEIYRKSNISVYEVDGKDHKIYCQNLCLLAKLFL
DHKTLYFDVEPFVFYILTEVDRQGAHIVGYFSKEKESPDGNNVACILTLPPYQRRGYGKFLI
AFSYELSKLESTVGSPEKPLSDLGKLSYRSYWSWVLLEILRDFRGTLSIKDLSQMTSITQN
DIISTLQSLNMVKYWKGQHVICVTPKLVEEHLKSAQYKKPPITVDSVCLKWAP*

Protein Expression: To produce recombinant KAT8 protein, expression plasmid was transformed into *E. coli* BL21 DE3 strain and grown with shaking at 37°C in 1 L volumes of Terrific broth (TB) supplemented with 100 µg/mL Ampicillin until an OD600 of 0.8 was reached. Cultures were transferred to 18°C and protein expression induced by the addition of Isopropyl β-D-1-thiogalactopyranoside to a final concentration of 0.5 mM and the cultures shaken overnight for further 16 hours. Following expression, cell cultures were centrifuged at 5000 x g for 20 min and cell pellet stored frozen at -20°C.

Protein Purification: Protein purification was initiated by thawing the cell pellet (34 g wet weight) in Lysis buffer (20 mM Hepes pH 7.5, 500 mM NaCl, 5 mM Imidazole, 5% [v/v] glycerol, 0.01% [v/v] Triton-X 100, 5 mM 2-mercaptoethanol, 2 mM $MgCl_2$, 0.5 mg/mL

lysozyme, benzonase endonuclease [EMD Millipore], 1 mM PMSF, complete protease inhibitor tablets EDTA-free [Roche]) using a ratio of 3 mL of buffer per 1 g of cells. Cells were further lysed by 3 passes (at 15000 psi) through an ice cooled Avestin C5 cell crusher and then centrifuged at 48,000 x g at 4°C. Supernatant (cell lysate) was filtered through a 0.2 µm filter and applied onto 5 mL HiTrap IMAC Sepharose FF column (GE Healthcare) pre-equilibrated with IMAC wash buffer 1 (20 mM Hepes pH 7.5, 500 mM NaCl, 0.5 mM TCEP, 5 mM Imidazole) using a Profinia Affinity chromatography purification system (Bio-Rad). The IMAC column was then sequentially washed with IMAC Wash buffer 1 and IMAC Wash buffer 2 (20 mM Hepes pH 7.5, 500 mM NaCl, 0.5 mM TCEP, 10 mM Imidazole) and bound KAT8 protein eluted with IMAC Elution buffer (20 mM Hepes pH 7.5, 500 mM NaCl, 0.5 mM TCEP, 500 mM Imidazole). IMAC-eluted protein was further purified by passing through a HiLoad 26/60 Superdex 200 column pre-equilibrated in Storage buffer (20 mM Hepes pH 7.5, 500 mM NaCl, 1 mM TCEP). Finally, KAT8 protein was concentrated to ≤ 0.2 mg/mL using Amicon Ultra centrifugal filter unit (Utra-15 MWCO 10 kDa), flash-frozen in liquid nitrogen and stored in -70°C freezer.

Revised Acetyltransferase Biochemical Assay

To determine the inhibition of KAT enzymatic activity by test compounds, assay reactions were conducted in a volume of 8 µL in 384-well low volume assay plates. The reactions were performed in assay buffer (100 mM Tris-HCl, pH 7.8, 15 mM NaCl, 1 mM EDTA, 0.01% Tween-20, 1 mM Dithiothreitol, and 0.01% m/v chicken egg white albumin).

Reactions were set up with 1µM Acetyl coenzyme A, 100 nM offull-length recombinant histone labelled by limited biotinylation (KAT6A, KAT6B, KAT7: H3.1, KAT5, KAT8: H4), 10/ 5/ 8/ 40/ 20 nM of KAT5/KAT6A/KAT6B/KAT7/KAT8 enzyme respectively, and an acetyl-lysine specific antibody (H3.1: Cell Signaling Technology, H4: Abcam). 11-point dilution series of the test compounds were prepared in DMSO; a volume of 100 nLwas transferred using a pin tool into assay plates containing substrates, before adding enzyme to start the reaction. Positive (no compound, DMSO only) and negative (AcCoA omitted) control reactions were included on the same plates and received the same amount of DMSO as the compound treated wells. After adding all reagents, the plates were sealed with adhesive seals and incubated for 90 min at room temperature. An additional 4 µL of assay buffer containing AlphaScreen® Protein A acceptor beads and Streptavidin donor beads (PerkinElmer, Waltham, MA) to a final concentration of 8 µg/mL was thenadded. After incubation for 2 hours the plates were read using an EnVision 2103 multi label plate reader (PerkinElmer) in HTS AlphaScreen® mode.

IC_{50} values were obtained from the raw readings by calculating percent inhibition (%I) for each reaction relative to controls on the same plate (%I=(I-CN)/(CP-CN) where CN/ CP are the averages of the negative/ positive reactions, respectively), then fitting the %I data *vs.* compound concentration [I] to %I=(A+((B-A)/(1+((C/[I])^D)))) where A is the lower asymptote, B is the upper asymptote, C is the IC_{50} value, and D is the slope.

The results are shown in tables 8 to 12 below:

Table 8 (MOZ-KAT6A)

Example	**IC50 (µM)**
1	0.005
2	5.139
3	4.954
5	0.069
6	18.658
7	0.316
8	0.011
13	0.010
14	0.010
15	0.682
19	0.270
20	0.490
23	0.120
24	0.110
25	0.064
26	0.041
32	0.030
33	0.047
34	5.782
36	0.074
39	0.032
41	0.005
43	0.014
46	0.064
49	1.685

Example	IC50 (μM)
50	6.186
56	0.010
57	0.403
59	0.032
60	0.010
68	0.108
75	0.308
78	0.203
81	0.552
84	0.017
86	0.096
91	0.024
93	0.098
96	0.149
97	0.417
113	98.977
118	0.046
120	0.017
129	0.250
134	0.024
135	0.047
139	0.100
144	0.021
145	0.649
146	0.002
147	0.029
150	1.022
153	0.054
155	0.595
157	8.797
158	1.732
159	0.371
160	0.471
161	0.269

Example	IC50 (μM)
162	0.029
163	0.017
164	0.017
165	0.031
166	0.007
167	0.004
168	0.008
169	0.023
170	0.143
171	0.024
172	0.005
173	0.011
174	0.573
175	0.013
176	0.076
177	0.004
178	0.021
179	0.005
180	0.229
181	0.032
182	0.006
183	0.044
184	0.008
185	0.042
186	0.024
187	0.015
188	0.041
189	0.075
190	0.008
191	0.043
192	0.613
193	0.493
194	5.564
195	0.209

Example	IC50 (μM)
196	0.080
197	0.290
198	0.351
199	0.838
200	9.800
201	0.268
202	1.043
203	0.427
204	0.122
205	0.970
206	1.391
208	1.597
209	0.378
210	0.303
211	2.180
212	0.241
213	0.002
214	0.009
215	0.004
216	0.028
217	0.265
218	0.153
219	3.586
220	0.020
221	0.572
222	0.131
223	0.216
224	0.165
225	0.447
226	0.075
227	1.362
228	0.007
230	0.761
231	0.100

Example	IC50 (μM)
232	0.252
233	0.013
234	0.072
235	0.009
236	0.010
237	0.010
238	0.188
239	0.017
240	0.021
241	0.082
242	2.774
243	12.281
244	6.828

Table 9 (HBO-KAT7)

Example	IC50 (μM)
1	0.076
2	28.029
3	49.934
6	21.294
7	1.176
8	0.134
13	0.128
14	0.083
15	0.874
19	1.003
20	1.253
23	2.884
24	0.583
25	12.045
26	5.071
32	0.356
33	0.551
34	11.469

Example	IC50 (μM)
36	3.380
39	0.299
41	0.059
43	0.086
46	1.078
49	3.133
50	49.069
56	0.063
57	0.840
59	0.403
60	0.201
68	0.601
75	1.148
78	3.526
81	4.600
84	0.062
86	0.787
91	0.074
93	1.794
96	1.114
113	6.411
118	0.412
120	0.140
129	24.812
134	0.720
135	0.419
139	0.184
144	1.387
146	0.036
147	0.057
150	3.594
153	0.672
155	9.516
157	22.305

Example	IC50 (μM)
158	5.465
159	0.295
160	1.662
161	4.387
162	0.512
163	0.115
164	0.242
165	1.768
166	0.183
167	0.062
168	0.621
169	0.386
170	1.635
171	0.785
172	0.041
173	0.161
174	4.150
175	0.478
176	0.869
177	0.124
178	0.112
179	0.028
180	0.557
181	0.320
182	0.237
183	0.718
184	0.114
185	0.264
186	1.962
187	0.115
188	0.215
189	0.214
190	0.414
191	0.243

Example	IC50 (μM)
192	2.304
193	1.937
194	26.048
195	2.215
196	0.025
197	7.530
198	8.374
199	6.566
200	>125
201	56.499
202	>125
203	1.671
204	59.533
205	2.728
206	1.207
208	4.509
209	1.675
210	1.121
211	6.072
212	1.091
213	0.111
214	0.050
215	0.020
216	0.152
217	1.189
218	9.410
219	104.980
220	0.214
221	0.072
222	0.023
223	1.008
224	0.204
225	1.460
226	1.926

Example	IC50 (μM)
227	4.485
228	0.092
230	2.300
231	0.143
232	0.393
233	0.014
234	0.089
235	0.115
236	0.073
237	0.121
238	0.881
239	0.686
240	0.134
241	0.948
242	32.984
243	77.338
244	3.835

Table 10 (TIP60-KAT5)

Example	IC50 (μM)
1	0.068
2	60.736
3	99.577
5	0.493
6	>125
7	5.922
8	2.009
13	0.111
14	0.156
15	5.547
19	14.646
20	13.769
23	1.733
24	5.402

Example	IC50 (μM)
25	5.914
26	5.936
32	5.330
33	3.780
34	70.321
36	5.471
39	3.060
41	0.032
43	0.266
46	4.050
49	>125
50	>125
56	0.061
57	0.725
59	0.721
60	0.058
68	7.215
75	14.078
78	4.541
81	6.652
84	0.426
86	0.521
91	0.090
93	1.999
96	13.329
97	26.114
113	>125
118	0.208
120	0.224
129	58.315
134	0.648
135	0.646
139	0.707
144	1.061

Example	IC50 (μM)
145	7.455
146	0.013
147	0.132
150	1.375
153	3.374
155	2.685
157	>125
158	26.795
159	3.201
160	13.225
161	9.163
162	1.541
163	0.221
164	0.781
165	6.015
166	0.714
167	0.056
168	0.458
169	0.412
170	13.255
171	1.161
172	0.025
173	0.651
174	15.259
175	0.311
176	5.114
177	0.023
178	0.852
179	0.029
180	0.249
181	0.123
182	0.284
183	0.068
184	0.099

Example	IC50 (μM)
185	0.994
186	0.734
187	0.242
188	1.439
189	2.845
190	0.303
191	0.919
192	11.112
193	4.167
194	125.000
195	1.847
196	0.818
197	23.574
198	42.346
199	15.551
200	>125
201	43.711
202	>125
203	3.750
204	>125
205	30.020
206	13.658
208	13.297
209	8.447
210	10.867
211	24.658
212	4.003
213	0.193
214	0.070
215	0.025
216	0.506
217	1.458
218	16.764
219	>125

Example	IC50 (μM)
220	1.432
221	1.573
222	0.149
223	3.325
224	9.008
225	5.124
226	3.728
227	98.725
228	0.111
230	4.899
231	0.306
232	2.741
233	0.154
234	1.368
235	0.034
236	0.113
237	0.163
238	1.815
239	0.597
240	0.309
241	1.011
242	122.908
243	39.941
244	14.557

Table 11 (MOF-KAT8)

Example	IC50 (μM)
1	4.541
2	>125
3	12.168
7	81.608
8	10.526
13	36.448
14	37.823

Example	IC50 (μM)
19	>125
20	62.808
25	>125
26	39.893
32	>125
33	>125
41	9.785
43	71.630
46	99.430
56	1.303
57	11.346
59	26.833
60	23.981
68	16.547
75	>125
78	>125
84	77.003
86	42.366
91	21.080
93	>125
96	>125
113	>125
118	>125
120	41.456
129	>125
134	15.671
139	75.833
144	46.671
146	2.857
147	28.611
153	20.085
157	>125
158	30.651
159	16.307

Example	IC50 (μM)
160	4.889
161	22.952
162	34.488
163	14.704
164	34.379
165	>125
166	36.777
167	8.402
168	26.451
169	43.737
170	>125
171	>125
172	6.098
173	30.359
175	30.171
176	30.179
177	8.206
178	60.964
179	9.661
181	31.222
182	24.460
183	30.515
184	10.244
187	14.120
188	54.274
189	28.697
190	68.365
196	78.602
203	114.969
204	>125
213	15.171
214	20.058
215	5.724
216	58.551

Example	IC50 (μM)
218	>125
219	>125
220	26.838
225	>125
226	>125
227	>125
228	9.660
231	6.533
232	34.952
233	9.251
234	23.550
235	3.227
236	19.618
237	15.260
238	25.625
239	75.640
240	62.623

Table 12 (QKF-KAT6B)

Example	IC50 (μM)
1	0.060
8	0.210
14	0.058
25	0.610
26	0.120
32	0.155
36	0.724
41	0.028
46	0.589
60	0.039
91	0.350
93	1.782
113	>125
144	0.459

Example	IC50 (μM)
146	0.019
147	0.311
159	4.049
163	0.117
166	0.072
167	0.027
168	0.037
172	0.281
179	0.088
181	0.077
182	0.059
196	0.991
197	0.780
198	1.383
199	6.172
201	5.259
202	>125
203	3.313
204	>125
213	0.022
215	0.065
220	0.134
221	4.335
231	3.239
233	0.254
238	5.869

Histone H3 Lysine 14 Acetylation Biomarker Assay

Compounds may be tested for their ability to inhibit acetylation of the histone H3 Lysine 14 (which is HBO1 mediated) marker in the following assay:

The cell line U2OS was seeded at a density of 3,000 cells per well in 384-well optical quality tissue culture plates in RPMI medium supplemented with 10% foetal bovine serum and 10 mM Hepes. The cells were allowed to adhere for 24 hours under standard culture conditions (37 degree Celsius, 5% CO2). At the end of this period the cells were washed with serum free medium. Compound dilutions prepared in DMSO were added to the serum

free medium, with negative control wells reserved for treatment with DMSO only and 100% inhibition positive controls receiving a potent inhibitor compound (e.g. (*Z*)-4-fluoro-*N*-((3-hydroxyphenyl)sulfonyl)-5-methyl-[1,1'-biphenyl]-3-carbohydrazonic acid) at 10 µM concentration. After incubation for 24 hours, the cells were fixed with 4% formaldehyde in PBS for 15 minutes at room temperature, washed with phosphate buffer saline and blocked with blocking buffer containing 0.2% TritonX100 and 2% BSA. Anti-H3K14ac specific antibody (Cell Signalling Technologies) in blocking buffer was added and incubated overnight at 4 degree Celsius. After washing, a secondary antibody labelled with AlexaFluor 488 dye (ThermoFisher) and Hoechst 33342 (1 µg/mL, Life Technologies) were added for 2 hours incubation at room temperature. Plates were washed and read on a PerkinElmer Opera HCS high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the acetylation level was calculated from the AlexaFluor 488-related intensity in the same area. The resulting mean intensity per cell was converted to percent inhibition relative to controls on the same plate and the data fitted against a four-parameter logistic model to determine the 50% inhibitory concentration (IC50).

The results are shown in Table 13 below:

Table 13

Example	**IC50 (µM)**
162	6.52
163	0.892
164	2.08
166	0.611
167	0.349
168	6.44
169	1.30
171	10.4
172	2.87
175	1.84
176	4.43
177	1.03
179	0.219
181	35.3
182	0.488
186	>40.0

187	0.491
188	0.427
189	>20.0
190	4.95
193	31.2
196	0.095
201	>40.0
203	2.26
212	4.15
213	4.94
214	3.60
215	0.221
216	14.1
217	1.29
220	0.917
221	1.66
222	0.437
225	>40.0
226	24.4
228	3.25
231	3.88
233	3.20
237	0.498
238	13.7
239	19.2
240	3.32
244	>40.0

H2A.Z Lysine 7 Acetylation Biomarker Assay

Compounds may be tested for their ability to inhibit the histone H2A.Z Lysine 7 acetylation marker (which is TIP60 mediated) in the following assay:

The cell line U2OS was seeded at a density of 3,000 cells per well in 384-well optical quality tissue culture plates in RPMI medium supplemented with 10% foetal bovine serum and 10 mM Hepes. The cells were allowed to adhere for 24 hours under standard culture conditions (37 degree Celsius, 5% CO_2). At the end of this period the cells were washed

with serum free medium. Compound dilutions prepared in DMSO were added to the serum free medium, with negative control wells reserved for treatment with DMSO only and 100% inhibition positive controls receiving a potent inhibitor compound enantiomer 1 of 7-iodo-*N*-(2-(oxazol-2-yl)-2-phenylethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine-3-carboxamide 1,1-dioxide, which is compound 146, at 30 µM concentration. After incubation for 24 hours, the cells were fixed with 4% formaldehyde in PBS for 15 minutes at room temperature, washed with phosphate buffer saline and blocked with blocking buffer containing 0.2% TritonX100 and 2% BSA. Anti-H2A.ZK7ac specific antibody (Abcam) in blocking buffer was added and incubated overnight at 4 degree Celsius. After washing, a secondary antibody labelled with AlexaFluor 488 dye (ThermoFisher) and Hoechst 33342 (1 µg/mL, Life Technologies) were added for 2 hours incubation at room temperature. Plates were washed and read on a PerkinElmer Opera HCS high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the acetylation level was calculated from the AlexaFluor 488-related intensity in the same area. The resulting mean intensity per cell was converted to percent inhibition relative to controls on the same plate and the data fitted against a four-parameter logistic model to determine the 50% inhibitory concentration (IC_{50}).

The results are shown in Table 14 below:

Table 14

Example	IC50 (µM)
162	10.9
163	1.52
164	2.82
166	5.35
167	0.516
168	8.85
169	9.88
171	>40.0
172	2.09
175	11.9
176	15.4
177	1.18
178	20.5
179	1.10
180	37.5

181	>40.0
182	8.10
183	33.2
184	8.28
186	>40.0
187	5.46
189	>40.0
190	31.1
191	>40.0
193	>40.0
196	0.882
201	>40.0
203	>40.0
204	>40.0
213	29.5
214	8.78
215	4.44
216	15.9
217	32.1
220	7.81
221	6.87
222	1.28
225	>40.0
226	>40.0
228	5.71
231	4.52
233	1.99
234	6.15
235	1.08
236	7.85
237	3.41
240	11.21
241	>40.0

Histone H3 Lysine 23 Acetylation Biomarker Assay

Compounds may be tested for their ability to inhibit acetylation of the histone H3K23 marker, which is KAT6 mediated, in the following assay:

The cell line U2OS was seeded at a density of 9,000 cells per well in 96 well optical quality tissue culture plates in RPMI medium and 10% foetal bovine serum, and allowed to adhere for 24 hours under standard culture conditions (37 degree Celsius, 5% CO2). At the end of this period the medium was aspirated. Compound dilutions prepared in DMSO were added to medium, with negative control wells reserved for treatment with DMSO only and 100% inhibition positive controls receiving a potent inhibitor compound (e.g. cas 2055397-28-7, benzoic acid, 3-fluoro-5-(2-pyridinyl)-, 2-[(2-fluorophenyl)sulfonyl]hydrazide) (Baell, J., Nguyen, H.N., Leaver, D.J., Cleary, B.L., Lagiakos, H.R., Sheikh, B.N., Thomas. T.J., Aryl sulfonohydrazides, WO2016198507A1, 2016) at 10 µM concentration and 200 µL transferred to the cells. After incubation for 24 hours, the cells were fixed with 3.7% formaldehyde in PBS for 20 minutes at room temperature, washed (5 × 5 minutes) with phosphate buffer saline containing 0.1%Tween 20 and blocked with Odyssey blocking buffer (LI-COR, Lincoln, NE) containing 0.1%TritonX100. Anti-H3K23ac specific antibody (Abcam ab177275) in Odyssey blocking buffer containing 0.1%Tween 20 was added and incubated for 16 hours at 4 degree Celsius. After washing (as above), a secondary antibody labelled with Alexa647 dye (LifeTechnologies) and Hoechst 33342 (1 µg/mL, SigmaAldrich) were added for 1 hour incubation. Plates were washed as previously and read on a PerkinElmer Phenix high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the acetylation level was calculated from the Alexa647-related intensity in the same area. The resulting mean intensity per cell was directly converted to percent inhibition relative to controls on the same plate and the data fitted against a four-parameter logistic model to determine the 50% inhibitory concentration (IC50).

The results are shown in Table 15 below:

Table 15

Example	**IC50 (µM)**
1	0.064
8	5.865
14	1.063
25	3.822
26	1.078
32	>10
36	0.263

Example	IC50 (μM)
41	0.035
46	0.178
57	>10
60	1.418
91	7.687
93	>10
97	>10
113	>10
144	0.104
146	0.016
147	0.482
159	5.089
163	0.453
166	0.093
167	0.057
168	0.525
172	>10
175	0.154
177	0.195
179	0.112
181	>10
182	0.084
186	>10
193	9.078
196	1.009
197	3.040
198	5.198
199	10.000
201	>10
202	>10
203	>10
204	>10
213	0.116
215	0.953

Example	IC50 (μM)
220	0.540
221	>10
222	7.148
231	>10

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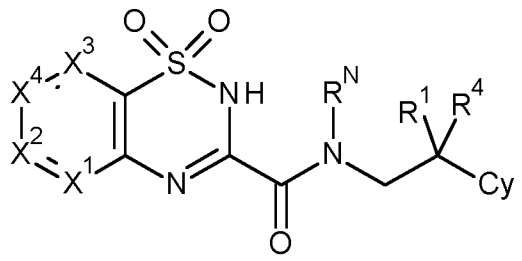
Claims

1. A compound of formula I:



(I)

wherein:

R^N is H or Me;

X^4 is selected from CY and N;

X^1, X^2 and X^3 are each selected from CH and N, where none or one of X^1, X^2, X^3 and X^4 are N;

Y is selected from the group consisting of: H; halo; cyano; R^2, where R^2 is selected from CH_3, CH_2F, CHF_2 and CF_3; ethynyl; cyclopropyl; OR^3, where R^3 is selected from H, CH_3, CH_2F, CHF_2 and CF_3; $NR^{N1}R^{N2}$, where R^{N1} and R^{N2} are independently selected from H and CH_3; COQ^1, where Q^1 is selected from C_{1-4} alkyl, OH, OC_{1-4} alkyl and $NR^{N1}R^{N2}$; $NHSO_2Q^3$, where Q^3 is C_{1-3} alkyl; pyridyl; C_5 heteroaryl, which may be substituted by a group selected from C_{1-3} alkyl, which itself may be substituted by OH or $CONR^{N1}R^{N2}$; SO_2Me; C_{1-3} alkyl, substituted by NHZ, where Z is H, Me, SO_2Me, or COMe; C_{1-3} alkyl, substituted by OH;

Cy is selected from pyridyl, oxazolyl, cyclohexyl and optionally substituted phenyl, where the optional substituents are selected from the group consisting of: R^2; OR^5, where R^5 is selected from H, CH_3, CH_2F, CHF_2, CF_3 and cyclopropyl; benzyloxy; halo; cyano; amino; C_5 heteroaryl, optionally substituted by methyl, CH_2OH, CH_2OCH_3 or =O; phenyl; pyridyl, optionally substituted with methyl; COQ^5, where Q^5 is selected from OH and $NR^{N1}R^{N2}$; and CH_2OQ^6, where Q^6 is H or Me;

R^1 is selected from the group consisting of: F; phenyl; pyridyl; C_5 heteroaryl, optionally substituted by methyl, CH_2OCH_3, CH_2CF_3, CHF_2, NH_2, or =O; C_9 heteroaryl; OH; OMe; OPh; COQ^4, where Q^4 is selected from OH, C_{1-3} alkyloxy, $NR^{N5}R^{N6}$, where R^{N5} is selected from H and Me, and R^{N5} is selected from C_{1-4} alkyl, which itself may be substituted by CONHMe, or where R^{N5} and R^{N6} together with the N atom to which they are bound form a C_{4-6} N-containing heterocyclyl group, $(CH_2)_{n1}CONR^{N7}R^{N8}$, where n1 is 1 to 3, and R^{N7} and R^{N8} are independently selected from H and Me, and $O(CH_2)_{n2}CONR^{N9}R^{N10}$, where n2 is 1 or 3. And R^{N9} and R^{N10} are independently selected from H and Me; $(CH_2)_n OQ^7$, where n is

1 or 2 and Q^7 is H or Me; $NHCO_2Q^8$, where Q^8 is C_{1-3} alkyl; $OCONR^{N5}R^{N6}$; R^4 is selected from H, F and methyl; or

R^1 and R^4 together with the carbon atom to which they are bound may form a C_{4-6} cycloalkyl; and

when Cy is pyridyl, cyclohexyl or substituted phenyl, R^1 may additional be selected from H.

2. A compound according to claim 1, wherein X^1, X^2 and X^3 are CH and X^4 is CY.

3. A compound according to claim 1, wherein:

(a) X^1 is N; or

(b) X^2 is N; or

(c) X^3 is N; or

(d) X^4 is N.

4. A compound according to any one of claims 1 to 3, wherein Y is H.

5. A compound according to any one of claims 1 to 3, wherein Y is halo.

6. A compound according to claim 5, wherein Y is selected from I and F.

7. A compound according to claim 6, wherein Y is I.

8. A compound according to claim 6, wherein Y is F.

9. A compound according to any one of claims 1 to 3, wherein Y is cyano.

10. A compound according to any one of claims 1 to 3, wherein Y is R^2.

11. A compound according to claim 10, wherein R^2 is CH_3.

12. A compound according to claim 10, wherein R^2 is CH_2F.

13. A compound according to claim 10, wherein R^2 is CHF_2.

14. A compound according to claim 10, wherein R^2 is CF_3.

15. A compound according to any one of claims 1 to 3, wherein Y is ethynyl.

16. A compound according to any one of claims 1 to 3, wherein Y is cyclopropyl.

17. A compound according to any one of claims 1 to 3, wherein Y is OR^3.

18. A compound according to claim 17, wherein R^3 is H.

19. A compound according to claim 17, wherein R^3 is CH_3.

20. A compound according to claim 17, wherein R^3 is CH_2F.

21. A compound according to claim 17, wherein R^3 is CHF_2.

22. A compound according to claim 17, wherein R^3 is CF_3.

23. A compound according to any one of claims 1 to 3, wherein Y is $NR^{N1}R^{N2}$.

24. A compound according to claim 23, wherein R^{N1} and R^{N2} are both H.

25. A compound according to claim 23, wherein R^{N1} and R^{N2} are both Me.

26. A compound according to claim 23, wherein R^{N1} is H and R^{N2} is Me.

27. A compound according to any one of claims 1 to 3, wherein Y is COQ^1.

28. A compound according to claim 27, wherein Q^1 is C_{1-4} alkyl.

29. A compound according to claim 27, wherein Q^1 is OH.

30. A compound according to claim 27, wherein Q^1 is OC_{1-4} alkyl.

31. A compound according to claim 27, wherein Q^1 is $NR^{N1}R^{N2}$.

32. A compound according to claim 32, wherein R^{N1} and R^{N2} are both H.

33. A compound according to claim 32, wherein R^{N1} and R^{N2} are both Me.

34. A compound according to claim 32, wherein R^{N1} is H and R^{N2} is Me.

35. A compound according to any one of claims 1 to 3, wherein Y is selected from COMe, CO_2H, CO_2Me, $CONH_2$, CONHMe and $CONMe_2$.

36. A compound according to any one of claims 1 to 3, wherein Y is $NHSO_2Q^3$.

37. A compound according to claim 36, wherein Q^3 is C_{1-3} alkyl.

38. A compound according to any one of claims 1 to 3, wherein Y is pyridyl.

39. A compound according to any one of claims 1 to 3, wherein Y is C_5 heteroaryl, which is optionally substituted.

40. A compound according to claim 39, wherein the C_5 heteroaryl group is selected from pyrrolyl, furanyl, thiolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl or triazolyl.

41. A compound according to claim 39, wherein the C_5 heteroaryl group is selected from those containing a nitrogen ring atom.

42. A compound according to claim 39, wherein the C_5 heteroaryl group is selected from those containing a nitrogen ring atom and a further ring heteroaom.

43. A compound according to claim 39, wherein the C_5 heteroaryl group is selected from thiazolyl and pyrazolyl.

44. A compound according to any one of claims 39 to 43, wherein the substituent group on the C_5 heteroaryl is selelcted from unsubstituted C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, and C_{1-3} alkyl substituted by $CONR^{N1}R^{N2}$.

45. A compound according to any one of claims 1 to 3, wherein Y is SO_2Me.

46. A compound according to any one of claims 1 to 3, wherein Y is C_{1-3} alkyl, substituted by NHZ, where Z is H, Me, SO_2Me, or COMe.

47. A compound according to claim 46, wherein Z is H.

48. A compound according to claim 46, wherein Z is Me.

49. A compound according to claim 46, wherein Z is SO_2Me.

50. A compound according to claim 46, wherein Z is COMe

51. A compound according to any one of claims 1 to 3, wherein Y is C_{1-3} alkyl, substituted by OH.

52. A compound according to claim 51, wherein Y is $CH(OH)CH_3$.

53. A compound according to any one of claims 1 to 52, wherein R^1 is H.

54. A compound according to any one of claims 1 to 52, wherein R^1 is F.

55. A compound according to any one of claims 1 to 52, wherein R^1 is phenyl.

56. A compound according to any one of claims 1 to 52, wherein R^1 is pyridyl.

57. A compound according to any one of claims 1 to 52, wherein R^1 is C_5 heteroaryl, optionally substituted by methyl, CH_2OCH_3, CH_2CF_3, CHF_2, NH_2, or =O.

58. A compound according to claim 57, wherein R^1 is unsubstituted C_5 heteroaryl.

59. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with methyl.

60. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with CH_2OCH_3.

61. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with CH_2CF_3.

62. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with CHF_2.

63. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with NH_2.

64. A compound according to claim 57, wherein R^1 is C_5 heteroaryl substituted with =O

65. A compound according to any one of claims 57 to 64, wherein the C_5 heteroaryl group contains at least one nitrogen ring atom.

66. A compound according to any one of claims 57 to 64, wherein the C_5 heteroaryl group is selected from pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl and triazolyl.

67. A compound according to any one of claims 57 to 64, wherein the C_5 heteroaryl group is selected from pyrrolyl, oxazolyl, oxadiazolyl, pyrazolyl and triazolyl.

68. A compound according to any one of claims 1 to 52, wherein R^1 is C_9 heteroaryl.

69. A compound according to claim 68, wherein R^1 is indolyl.

70. A compound according to any one of claims 1 to 52, wherein R^1 is OH.

71. A compound according to any one of claims 1 to 52, wherein R^1 is OMe

72. A compound according to any one of claims 1 to 52, wherein R^1 is OPh.

73. A compound according to any one of claims 1 to 52, wherein R^1 is COQ^4.

74. A compound according to claim 73, wherein R^1 is selected from:
(a) CO_2H;
(b) CO_2Me;

(c) CO_2Et; and

(d) $CO_2C(CH_3)_2$.

75. A compound according to claim 73, wherein Q^4 is $NR^{N5}R^{N6}$.

76. A compound according to claim 75, wherein R^1 is selected from:

(a) CO_2NH_2;

(b) CO_2NHMe;

(c) CO_2NMe_2;

(d) CO_2NHEt; and

(e) CO_2piperidinyl.

77. A compound according to claim 73, wherein Q^4 is $(CH_2)_{n1}CONR^{N7}R^{N8}$.

78. A compound according to claim 77, wherein R^1 is $C_3H_6CONHCH_3$.

79. A compound according to claim 73, wherein Q^4 is $O(CH_2)_{n2}CONR^{N9}R^{N10}$.

80. A compound according to claim 79, wherein R^1 is $OC_2H_4CONHCH_3$.

81. A compound according to any one of claims 1 to 52, wherein R^1 is $(CH_2)_nOQ^7$.

82. A compound according to claim 81, wherein R^1 is CH_2OH or $(CH_2)_2OH$.

83. A compound according to claim 81, wherein R^1 is CH_2OMe or $(CH_2)_2OMe$.

84. A compound according to any one of claims 1 to 52, wherein R^1 is $NHCO_2Q^8$, where Q^8 is C_{1-3} alkyl.

85. A compound according to claim 84, wherein R^1 is selected from :

(a) $NHCO_2CH_3$;

(b) $NHCO_2C_2H_5$; and

(c) $NHCO_2C(CH_3)_2$.

86. A compound according to any one of claims 1 to 52, wherein R^1 is $OCONR^{N5}R^{N6}$.

87. A compound according to claim 86, wherein:
(a) R^{N5} and R^{N6} together with the N atom to which they are bound form a C_4 N-containing heterocyclyl group; or
(b) R^{N5} and R^{N6} are both Me.

88. A compound according to any one of claims 1 to 87, wherein R^4 is H.

89. A compound according to any one of claims 1 to 87, wherein, R^4 is F.

90. A compound according to any one of claims 1 to 87, wherein R^4 is methyl.

91. A compound according to any one of claims 1 to 52, wherein R^1 and R^4 together with the carbon atom to which they are bound form a C_{4-6} cycloalkyl.

92. A compound according to claim 91, wherein the C_{4-6} cycloalkyl is cylcobutyl.

93. A compound according to claim 91, wherein the C_{4-6} cycloalkyl is cylcopentyl.

94. A compound according to claim 91, wherein the C_{4-6} cycloalkyl is cylcohexyl.

95. A compound according to any one of claims 1 to 94, wherein Cy is pyridyl.

96. A compound according to any one of claims 1 to 94, wherein Cy is oxazolyl.

97. A compound according to any one of claims 1 to 94, wherein Cy is cyclohexyl.

98. A compound according to any one of claims 1 to 84, wherein Cy is unsubstituted phenyl.

99. A compound according to any one of claims 1 to 94, wherein Cy is phenyl bearing a single substituent.

100. A compound according to claim 99, wherein the substituent is in the 2- position.

101. A compound according to claim 99, wherein the substituent is in the 3- position.

102. A compound according to claim 99, wherein the substituent is in the 4- position.

103. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is selected from:
a) CH_3;
b) CH_2F;
c) CHF_2; and
d) CF_3.

104. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is selected from:
a) OCH_3;
b) OCH_2F;
c) $OCHF_2$;
d) OCF_3; and
e) O-cyclopropyl.

105. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is benzyloxy.

106. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is halo.

107. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is cyano.

108. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is NH_2.

109. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is C_5 heteroaryl, optionally substituted by methyl, CH_2OH, CH_2OCH_3 or =O.

110. A compound according to claim 109, wherein the phenyl substituent is C_5 heteroaryl substituted by methyl.

111. A compound according to claim 109, wherein the phenyl substituent is C_5 heteroaryl substituted by CH_2OH.

112. A compound according to claim 109, wherein the phenyl substituent is C_5 heteroaryl substituted by CH_2OCH_3.

113. A compound according to claim 109, wherein the phenyl substituent is C_5 heteroaryl substituted by =O

114. A compound according to any one of claims 109 to 113, wherein the C_5 heteroaryl group contains at least one nitrogen ring atom.

115. A compound according to claim 114, wherin any other ring heteroatoms in the C_5 heteroaryl group are selected from nitrogen and oxygen.

116. A compound according to claim 115, wherein C_5 heteroaryl group is selected from pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl and triazolyl.

117. A compound according to claim 116, wherein the C_5 heteroaryl group is selected from oxazolyl, pyrazolyl and triazolyl.

118. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is phenyl.

119. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is pyridyl, optionally substituted with methyl.

120. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is CO_2H.

121. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is CO_2Me.

122. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is $CONR^{N1}R^{N2}$.

123. A compound according to claim 122, wherein:

a) R^{N1} and R^{N2} are both H; or

b) R^{N1} and R^{N2} are both Me; or

c) R^{N1} is H and R^{N2} is Me.

124. A compound according to any one of claims 99 to 102, wherein the phenyl substituent is:

a) CH_2OH; or

b) CH_2OMe.

125. A compound according to any one of claims 1 to 52, wherein R^1 is H and Cy has a substituent in the 2- position, selected from $OCHF_2$ and a C_5 heteroaryl group selected from oxazolyl, pyrazolyl and triazolyl.

126. A compound according to any one of claims 1 to 52, wherein R^1 is selected from oxazolyl, methyl-oxadiazolyl and pyrazolyl and Cy bears no substituent in the 2- position.

127. A compound according to any one of claims 1 to 126, wherein R^N is H.

128. A compound according to any one of claims 1 to 126, wherein R^N is Me.

129. A compound according to any one of claims 1 to 128 for use in a method of therapy.

130. A pharmaceutical composition comprising a compound according to any one of claims 1 to 128 and a pharmaceutically acceptable excipient.

131. A method of treatment of cancer, comprising administering to a patient in need of treatment, a compound according to any one of claims 1 to 128 or a pharmaceutical composition according to claim 130.

132. A method according to claim 131, wherein the compound is administered simultaneously or sequentially with radiotherapy and/or chemotherapy

133. The use of a compound according to any one of claims 1 to 128 in the manufacture of a medicament for treating cancer.

134. A compound according to any one of claims 1 to 128 or a pharmaceutical composition according to claim 130 for use in the treatment of cancer.

135. A compound or pharmaceutical composition according to claim 134, wherein the treatment is for simultaneous or sequential adminstration with radiotherapy and/or chemotherapy

136. A method of synthesis of a compound according to any one of claims 1 to 128.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/073431

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 C07D417/14 C07D513/04 C07D285/24 A61P35/00
A61K31/549 A61K31/542
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GREGORY J. WELLS ET AL: "1,2-Benzothiazine 1,1-Dioxide P 2 -P 3 Peptide Mimetic Aldehyde Calpain I Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 21, 1 October 2001 (2001-10-01), pages 3488-3503, XP055452021, ISSN: 0022-2623, DOI: 10.1021/jm010178b page 3491; compounds 31-32 -----	1-130
A	WO 98/21186 A1 (CEPHALON INC [US]) 22 May 1998 (1998-05-22) page 1, line 14 - line 17; claim 41 -----	1-130

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2018	03/12/2018

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/073431

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2016/198507 A1 (UNIV MONASH [AU]; THE WALTER AND ELIZA HALL INST OF MEDICAL RES [AU];) 15 December 2016 (2016-12-15) cited in the application claims 1,22	1-136
A	J. A. L. BROWN ET AL: "Targeting cancer using KAT inhibitors to mimic lethal knockouts", BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 44, no. 4, 15 August 2016 (2016-08-15), pages 979-986, XP055443651, GB ISSN: 0300-5127, DOI: 10.1042/BST20160081 table 1	1-136
A	EP 1 963 295 A1 (MERCK PATENT GMBH [DE]) 3 September 2008 (2008-09-03) claims 1,13	1-136

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Information on patent family members

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