NOVEL COMPOUNDS

Field of the invention

The present invention relates to compounds and their use in treating or preventing various proliferative diseases, and to related compositions, methods and intermediate compounds.

Background of the invention

Inflammation, autoimmunity, fibrosis and in addition cancer share numerous underlying disease mechanisms, in particular aberrant cell proliferation and in some situations shared pathology. Autoimmunity is best described as adherent recognition of self-antigens that lead to tissue destruction by lymphocytes of the T-cell and B-cell lineage, rheumatoid arthritis (RA) being a typical example. Inflammation, while encompassing these mechanisms can also be primarily driven by innate immunity through metabolic imbalances or repeated injury and irritation, an example being non-alcoholic steatohepatitis (NASH): initiated and sustained by accumulating lipids in the liver and potentially microfauna from the gastro-intestinal system. All these mechanisms can also lead to organ sclerosis, scarring and fibrosis through the activation and proliferation of fibroblasts, although in some instances fibrosis can occur without obvious evidence of inflammation or autoimmunity: an example being idiopathic pulmonary fibrosis (IPF). These exemplified diseases highlight that our current knowledge of mechanistic progression in pathologies of the immune system is poor and as a result clinical unmet need for patients remains high. In the case of cancer our understanding of disease progression is significantly more advanced with many genetic mutations identified that lead to loss of cell cycle regulation and uncontrolled proliferation the primary hallmarks of oncological diseases. Unmet clinical need in cancer also remains high however due to the number and diversity of mutations present that make targeted therapy challenging.

In many of these diseases, compounds that primarily target excessive cell proliferation via metabolic processes are a mainstay of therapeutic intervention. Example drugs include methotrexate (MTX) and fluorouracil (5-FU) that are used to treat both cancer and autoimmune diseases such as RA via supressing proliferation of the cancer cells and T and B cells in the case of autoimmunity. MTX and 5-FU target enzymes on the one-carbon (1C) metabolism pathway which involves the transfer of single carbon units between molecules used for redox balance and the biosynthesis of methyl donors, purines and thymidylates. The 1C metabolism is significantly upregulated in rapidly dividing cells including lymphocytes and numerous cancer cells. (Ducker

and Rabinowitz, 2017; Yang and Vousden, 2016). Despite being in clinical use for decades for the treatment of cancer and auto-immune diseases (Grem JL. 2000; Chan ESL. & Cronstein BN. 2010) and demonstrating significant disease modifying efficacy, side effects such as anemia, vomiting, diarrhoea, parathesis, lethargy and joint pain limit effectiveness of these drugs. MTX is a strong suppressor of the 1C cycle acting as an inhibitor of dihydrofolate reductase (DHRF), blocking the conversion of folate to tetrahydrofolate. This drives efficacy but at the cost of numerous side effects as previously described.

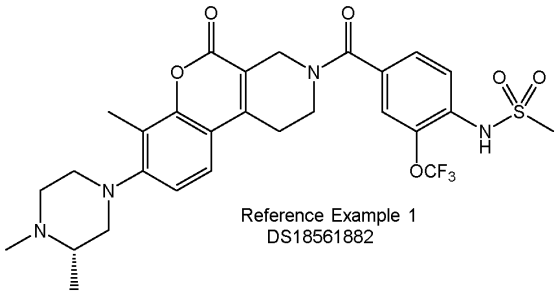
Targeting 1C metabolism in a more specific and disease relevant context is likely to maintain therapeutic benefit but reduce the side effect burden associated with current 1C targeted medication (Cuthbertson CR. *et al.*, 2021). Since the inception of MTX and 5-FU, the understanding of the enzymes involved in 1C metabolism has greatly improved and it is recognised that more selective and focused modulation of 1C metabolism could lead to more effective therapies, with an improved risk to benefit profile. Enzymes of interest for selective targeting of 1C targeting include cytoplasmic methylene tetrahydrofolate dehydrogenase 1 (MTHFD1) and mitochondrial methylene tetrahydrofolate dehydrogenase 2 (MTHFD2).

In the cytoplasm the trifunctional enzyme MTHFD1 converts 5,10-methylenetetrahydrofolate (5,10 me-tetrahydrofolate) into formate. MTHFD1 dehydrogenase/cyclohydrolase domain (D/C-d) first converts 5,10 me-tetrahydrofolate to 10-formyl tetrahydrofolate via oxidation mediated by NADP. In a second ATP driven reaction, MTHFD1 synthetase domain (S-d) converts 10-formyl tetrahydrofolate to formate (Kurniawan H. *et al.*, 2021).

In the mitochondria the dehydrogenase and cyclohydrolase functionality are carried out by MTHFD2 with preference for oxidization mediated by nicotinamide adenine dinucleotide (NAD).

It is recognised that MTHFD1 cytoplasmic 1C metabolism is required largely for homeostatic function whereas mitochondrial MTHFD2 flux supports highly proliferating cells and disease progression in several inflammation states, autoimmune diseases, and cancers. MTHFD2 expression is increased in diseases where rapid cell division is also present, most notably in inflammation and cancer; in addition, other key enzymes in the mitochondrial 1C pathway are also increased (Eich ML. *et al.*, 2019; Adewale F. *et al.*, 2017; Lee D. *et al.*, 2017; Nilsson R. *et al.*, 2014). Thus, the use of inhibitors of MTHFD2 that selective target the 1C pathway in cells driving disease could lead to new therapies with an enhanced safety prolife in comparison to MTX and 5-FU.

RNA-seq analysis from immune cells in peripheral blood showed that MTHFD2 was consistently overexpressed across multiple inflammatory conditions including ulcerative colitis, Crohn's disease, Celiac disease, systemic lupus erythematosus (SLE), psoriatic arthritis, multiple sclerosis (MS), Sjogren's syndrome and RA (Aune TM. et al., 2017). Furthermore, activated $CD4^+$ T-cells showed a significant increase in MTHFD2 mRNA after activation, with protein expression peaking at 48 hours. In particular the $CD4^+$ T-cell subsets Th17 and Th1 that are strongly associated with inflammatory diseases had the highest expression of MTHFD2.



Reference Example 1
DS18561882

Moreover, treatment with an MTHFD2 inhibitor DS18561882 (disclosed by Daiichi Sankyo in US2019/0284198 as Example 5, herein referred to as "Reference Example 1") greatly decreased the number of Th1 and Th17 cells differentiated *in vitro* from $CD4^+$ T-cells and expression of the respective Th1 and Th17 cytokines. IFNγ and IL-17 were also significantly reduced (Kawai J., 2019). DS18561882 treatment also increased immune-suppressive Treg cells, suggesting that inhibition of MTHFD2 can also deviate the immune response from pro-inflammatory to anti-inflammatory affects. Further assessment *in vivo* demonstrated that DS18561882 could reduce ear-swelling in a murine keyhole limpet hemocyanin (KLH) contact sensitization model ((Sugiura A. *et al.*, 2022) However, as shown hereinbelow, Reference Example 1, has activity on certain receptors not involved in the 1C pathway. This may ultimately lead to off-target effects, which may limit the development of such molecules into medications.

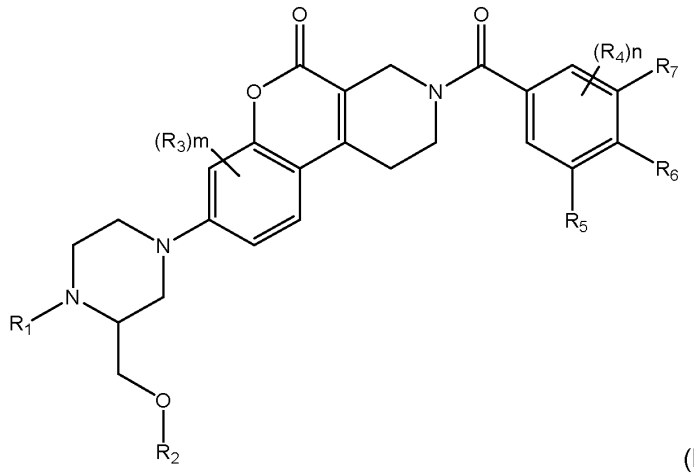
Further validation for therapeutic targeting the MTHFD2 in the context of autoimmune disease was demonstrated in a murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS). The disease was induced and from day 4 to day 26 the mice were treated with the oral dual MTHFD1 D/C-d and MTHDF2 inhibitor LY345899 (Gustafsson R. *et al.*, 2017); treatment led to significantly reduced disease severity and cumulative clinical score compared to vehicle with reduced immune cell infiltrate into the spinal cord also noted. Given these observations, it is possible that dual MTHFD1 D/C-d and MTHFD2 inhibitors may be more effective in certain indications than inhibitors targeting MTHFD2 alone. Dual MTHFD1 D/C-d and MTHFD2 inhibitors may present a different risk benefit profile and lead to new therapies with an enhanced safety prolife in comparison to MTX and 5-FU.

Both DS18561882 and LY345899 were well tolerated at the therapeutic doses used [Sugiura A. *et al.*, 2022]. Further validation for MTHFD2 as suitable target in inflammation was demonstrated in a murine model of heart transplantation. T-cell specific ablation of MTHFD2 in the host protected the allografted heart from vascular occlusion and fibrosis and significantly increased survival of the grafted mice [Li Y. *et al.*, 2023].

There remains a need to identify and develop new compounds possessing enhanced properties compared to existing MTHFD2 inhibitors, for example that the compounds are more suitable drug candidates. The inventors have now developed compounds which, as well as being potent MTHFD2 and MTHFD1 D/C-d inhibitors, or selective MTHFD2 inhibitors over MTHFD1 D/C-d, also avoid the problem of off-target effects compared with other compounds of the prior art.

Summary of the invention

The present invention provides a compound of formula (I):



(I):

wherein:

R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

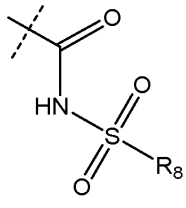
R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2;

and R_5, R_6 and R_7 are defined as follows:

(a) R_6 is  and R_7 is absent;

R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

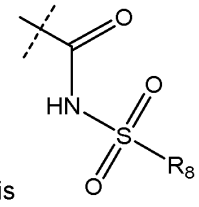
R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or:

(b) R_7 is  : and

(i) R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10}

cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(ii) R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(iii) R_5 and R_6 join to form a 4-8 membered heterocyclic ring;

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein:

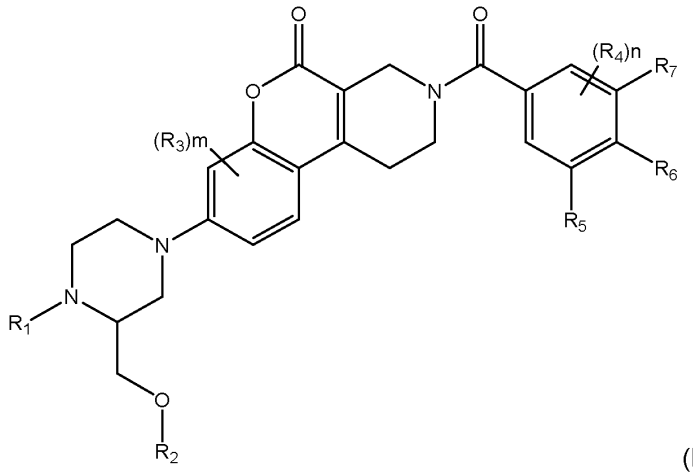
R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

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



(I)

wherein:

R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

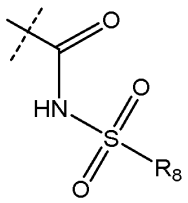
R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2;

and R_5, R_6 and R_7 are defined as follows:

(a) R_6 is  and R_7 is absent;

R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

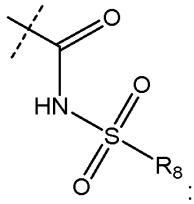
R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or:

(b) R_7 is  : and

(i) R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(ii) R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(iii) R_5 and R_6 join to form a 4-8 membered heterocyclic ring;

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein:

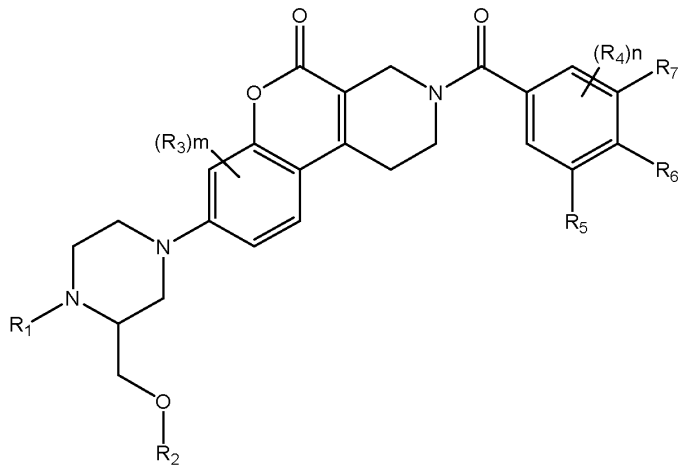
R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

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



(I):

wherein:

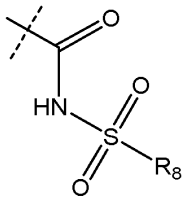
R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

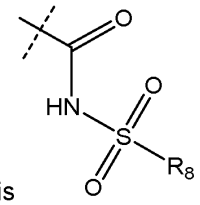
R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

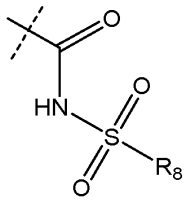
R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and 4-7 membered heterocycloalkyl;

R_6 is  and R_7 is absent; or

R_7 is  ;

wherein:

when R_6 is  and R_7 is absent:

R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

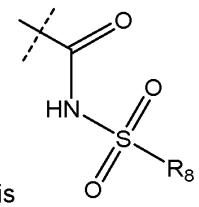
R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

or:

when R_7 is  :

R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 and R_6 join to form a 4-8 membered heterocyclic ring; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2;

or a pharmaceutically acceptable salt and/or solvate thereof.

Detailed description of the invention

Compounds of formula (I)

Embodiments and preferences set out herein with respect to the compound of formula (I) apply

equally to the pharmaceutical composition, compound or pharmaceutically acceptable salt and/or solvate thereof for use, pharmaceutical composition for use, use and method aspects of the invention, as well as intermediates used in the synthesis of the compounds of formula (I). These also apply equally well, where appropriate, to compounds of formula (IA), (IB), (IC), (IC-1) and (ID).

The term "alkyl" (e.g. C_{1-4} alkyl or C_{1-3} alkyl) as used herein refers to a straight or branched fully saturated hydrocarbon group having the specified number of carbon atoms. The term encompasses methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. The term "alkyl" also encompasses "alkylene" which is a bifunctional straight or branched fully saturated hydrocarbon group having a specified number of carbon atoms. Example "alkylene" groups include methylene, ethylene, n-propylene and n-butylene.

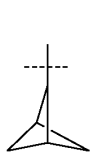
The term "halo" as used herein refers to fluoro, chloro, bromo and iodo. Particular examples of halo are fluorine and chlorine, especially fluorine.

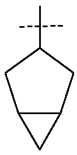
The term "alkoxy" (e.g. C_{1-3} alkoxy) as used herein refers to an alkyl group (e.g. C_{1-3} alkyl) as defined above, singularly bonded via an oxygen atom. The term encompasses methoxy, ethoxy, 1-propoxy and 2-propoxy.

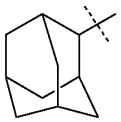
The term "haloalkyl" (e.g. C_{1-3} haloalkyl) as used herein refers to a straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms and at least one halogen atom, such as fluoro or chloro, especially fluoro. An example of haloalkyl is CF_3.

The term "haloalkoxy" (e.g. C_{1-3} haloalkoxy) as used herein refers to a haloalkyl group (e.g. C_{1-3} haloalkyl), as defined above, singularly bonded via an oxygen atom. Examples of haloalkoxy groups include OCF_3, $OCHF_2$ and OCH_2CF_3.

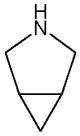
The term "cycloalkyl" (e.g. C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or OC_{3-10} cycloalkyl) as used herein refers to a fully saturated cyclic hydrocarbon group having the specified number of carbon atoms. The term encompasses cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl, as well as bridged and fused systems such as bicyclo[1.1.1]pentyl, bicyclo[3.1.0]hexyl and 2-adamantanyl:

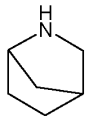

bicyclo[1.1.1]pentyl

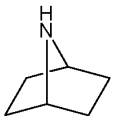

bicyclo[3.1.0]hexyl

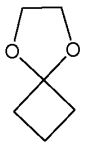

2-adamantanyl

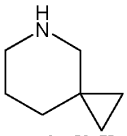
The term "heterocycloalkyl" (e.g. 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, 4-7 membered heterocycloalkyl or 5-7 membered heterocycloalkyl) as used herein refers to a non-aromatic cyclic group having the specified number of ring atoms, at least one of which is a heteroatom selected from N, O, S and B such as N or O, e.g. N. The term "heterocycloalkyl" is interchangeable with "heterocyclic ring". Heterocyclic groups can typically be substituted by one or more (e.g. one or two) oxo groups. Suitably, thietanyl is substituted by one or two oxo groups. The term encompasses oxetanyl, thietanyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, tetrahydropyranyl, piperazinyl, morpholinyl, thiomorpholinyl, azepanyl and oxepanyl, as well as bridged, fused and spirocyclic ring systems such as 5,8-dioxaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexyl, 2-azabicyclo(2.2.1)heptyl, 7-azanorbornanyl and 5-azaspiro[2.5]octyl:


3-azabicyclo[3.1.0]hexyl

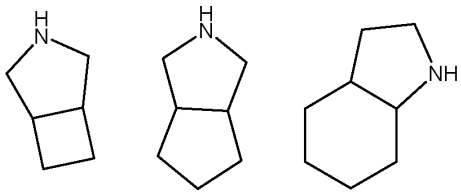

2-azabicyclo(2.2.1)heptyl


7-azanorbornanyl

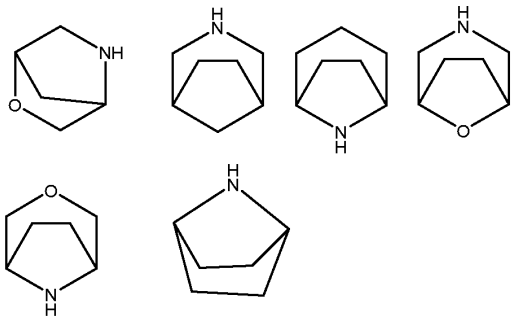

5,8-dioxaspiro[3.4]octanyl


5-azaspiro[2.5]octyl

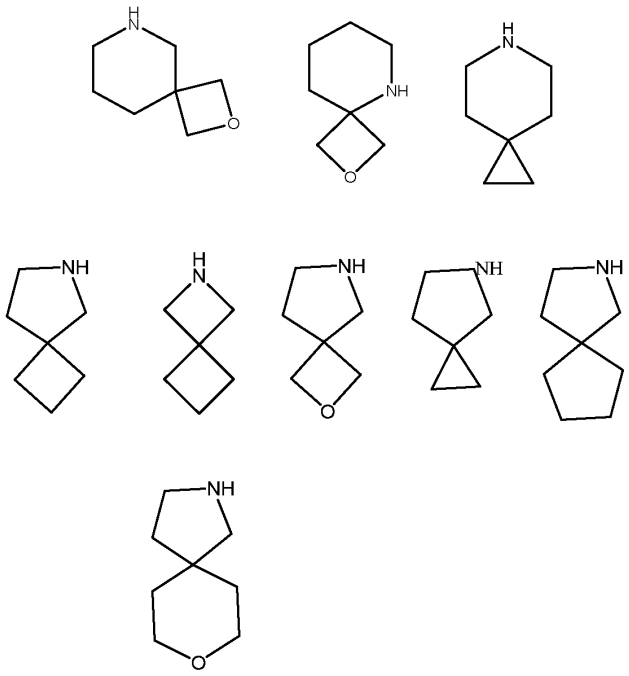
Further examples of fused ring systems include the following:



Further examples of bridged ring systems include the following:



Further examples of spiro ring systems include the following:



Most suitable heterocycloalkyl groups contain one N atom and no other heteroatoms or contain one N atom and one O atom.

Such groups may be joined to the compound of formula (I) *via* the NH atom (in which case the H atom is replaced by a group joined to the heterocycloalkyl group) or *via* an available carbon atom, meaning that the carbon atom must have at least one C-H bond, and the H is replaced by a group joined to the heterocycloalkyl group.

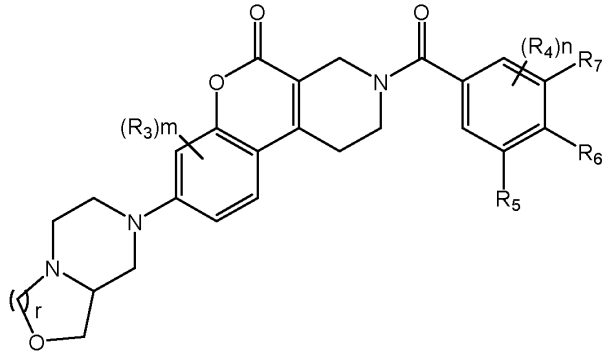
In some suitable compounds of formula (I), R_1 is C_{1-4} alkyl, such as methyl. In other suitable compounds of formula (I), R_1 is C_{3-5} cycloalkyl, such as cyclopropyl.

Most suitably, R_1 is methyl or cyclopropyl.

In some suitable compounds of formula (I), R_2 is C_{1-4} alkyl, such as methyl.

Alternatively, in some suitable compounds of formula (I), R_1 and R_2 join to form a 5-7 membered heterocycloalkyl, such as a 6 membered heterocycloalkyl.

In such compounds of formula (I), the following structure may form:

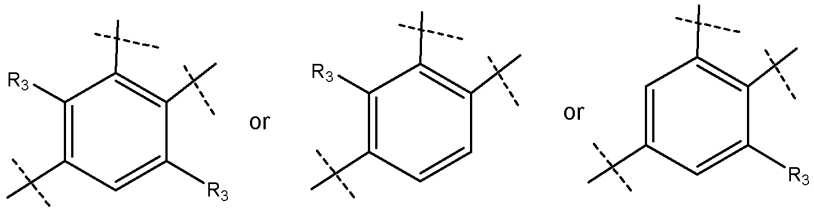


wherein r is 1, 2 or 3, most suitably 2.

In some suitable compounds of formula (I), R_3 is C_{1-3} alkyl, such as methyl. In other suitable compounds of formula (I), R_3 is halo, such as chloro.

Most suitably, R_3 is methyl or chloro.

In some suitable compounds of formula (I), when m is 1 or 2, R_3 is attached in the following positions:



wherein  represents the point of connection to the remainder of the compound of formula (I).

In some suitable compounds of formula (I), m is 0. In other suitable compounds of formula (I), m is 1. In other suitable compounds of formula (I), m is 2.

Most suitably, m is 1 or 2.

In some suitable compounds of formula (I), R_3 is methyl and m is 2. In some suitable compounds of formula (I), R_3 is selected from methyl and halo (e.g. chloro) and m is 2 e.g. one occurrence is methyl and the other occurrence is methyl or halo (e.g. chloro).

In some suitable compounds of formula (I), R_1 is C_{1-4} alkyl, such as methyl, R_2 is C_{1-4} alkyl, such as methyl and R_3 is C_{1-4} alkyl, such as methyl.

In some suitable compounds of formula (I), R_4 is C_{1-3} alkyl, such as methyl. In other suitable compounds of formula (I), R_4 is halo, such as fluoro or chloro e.g. fluoro. In other suitable compounds of formula (I), R_4 is C_{1-3} haloalkyl, such as trifluoromethyl. In other suitable compounds of formula (I), R_4 is C_{1-3} alkoxy, such as methoxy. In other suitable compounds of formula (I), R_4 is C_{1-3} haloalkoxy. In other suitable compounds of formula (I), R_4 is 4-7 membered heterocycloalkyl, such as pyrrolidinyl. In other suitable compounds of formula (I), R_4 is $NR_{4a}R_{4b}$.

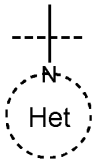
In some suitable compounds of formula (I), R_{4a} is H. In other suitable compounds of formula (I), R_{4a} is C_{1-3} alkyl, such as methyl.

In some suitable compounds of formula (I), R_{4b} is H. In other more suitable compounds of formula (I), R_{4b} is C_{1-3} alkyl, such as is methyl.

Most suitably, R_4 is fluoro.

In some suitable compounds of formula (I), R_1 is C_{1-4} alkyl, such as methyl, R_2 is C_{1-4} alkyl, such as methyl, R_3 is C_{1-4} alkyl, such as methyl and R_4 is halo, such as fluoro.

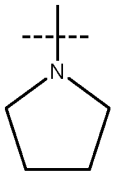
In some compounds of formula (I), R_4 is a 4-7 membered heterocycloalkyl group wherein the group is attached via a nitrogen atom, i.e.



wherein 

is the 4-7 membered heterocycloalkyl group and ------ indicates the join to the remainder of the compound of formula (I).

For example, and when the 4-7 membered heterocycloalkyl group is pyrrolidinyl, the pyrrolidinyl group is attached via the nitrogen atom, and is referred to as 1-pyrrolidinyl:



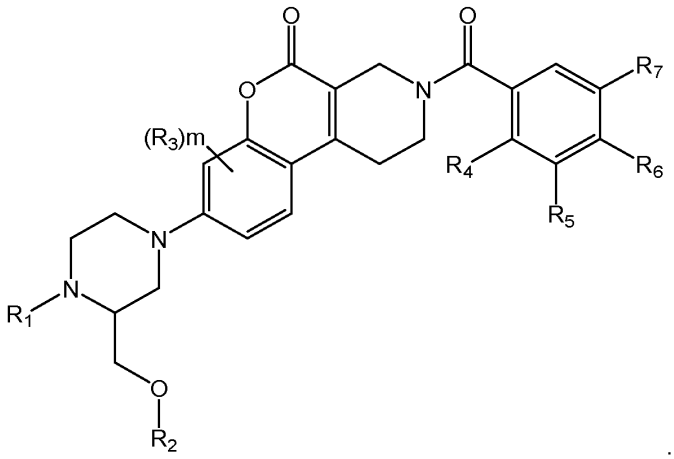
1-pyrrolidinyl

wherein ------ indicates the join to the remainder of the compound of formula (I).

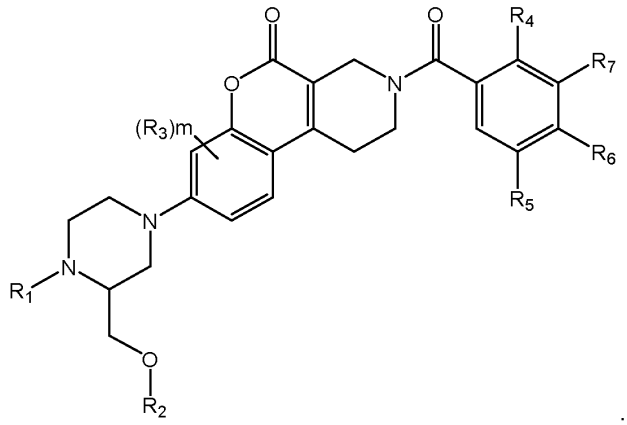
In some suitable compounds of formula (I), n is 0. In other suitable compounds of formula (I), n is 1. In other suitable compounds of formula (I), n is 2.

Most suitably, n is 0 or 1.

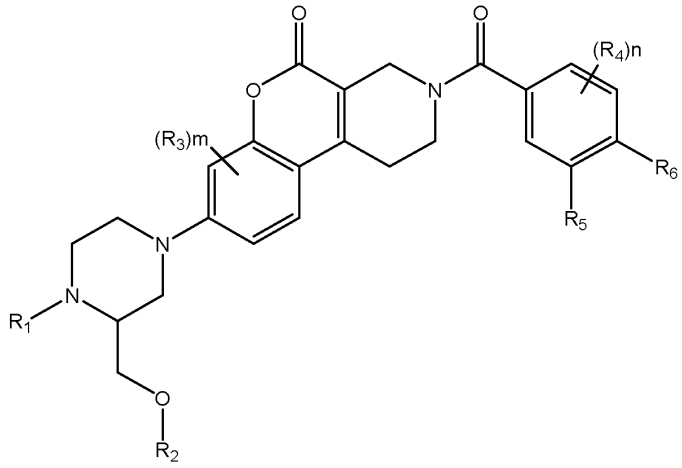
In some suitable compounds of formula (I), and when n is 1, R_4 is attached to the phenyl ring in the following position:



In other suitable compounds of formula (I), and when n is 1, R_4 is attached to the phenyl ring in the following position:



As stated above, in some suitable compounds of formula (I), R_7 is absent such that the following structure forms:

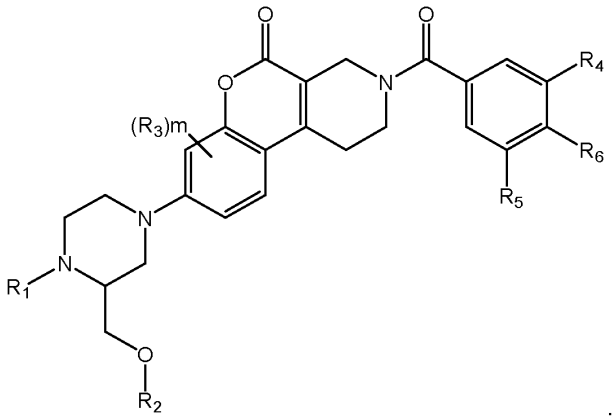


wherein all other variables are defined above.

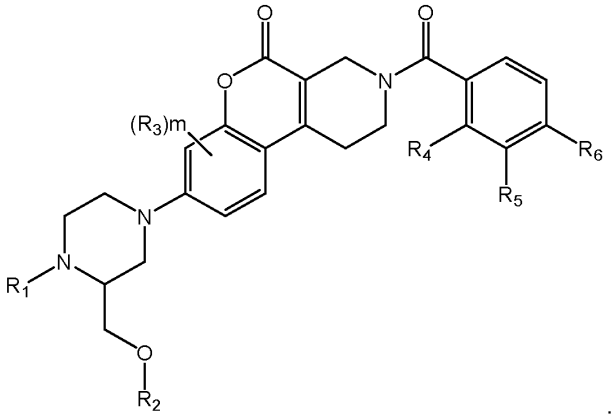
In such suitable compounds, R_4 may be present in any unsubstituted position on the phenyl ring. By "unsubstituted position" it is meant any position where there is a C-H bond. The substituent R_4 replaces the H atom, thus forming a C-R_4 bond as shown below.

As such, in some suitable compounds of formula (I), R_7 being absent means a hydrogen atom is present in position R_7. In other suitable compounds of formula (I), and when R_7 is absent, R_4 may be in the position of R_7, as shown below.

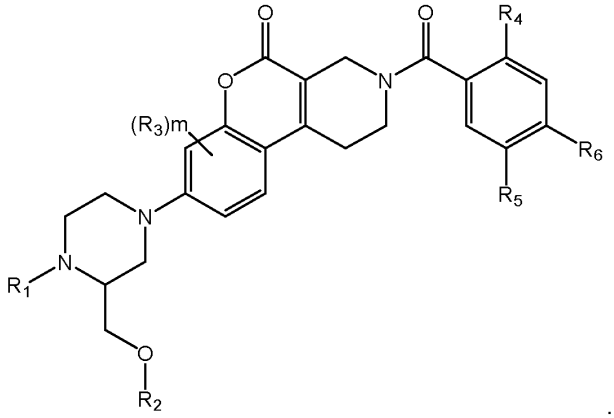
Thus, in some suitable compounds of formula (I) wherein R_7 is absent and when n is 1, R_4 is attached to the phenyl ring in the following position:



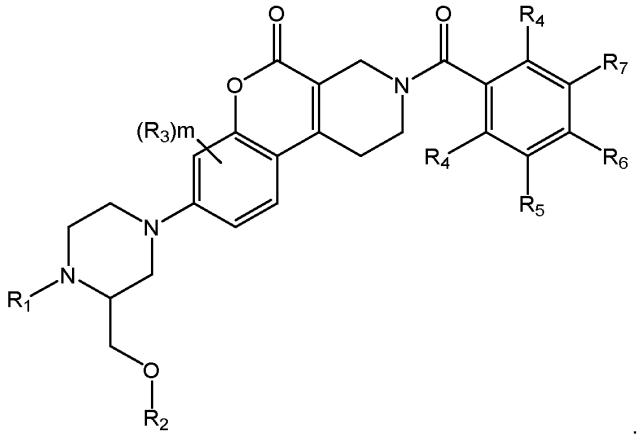
In some suitable compounds of formula (I) wherein R_7 is absent and when n is 1, R_4 is attached to the phenyl ring in the following position:



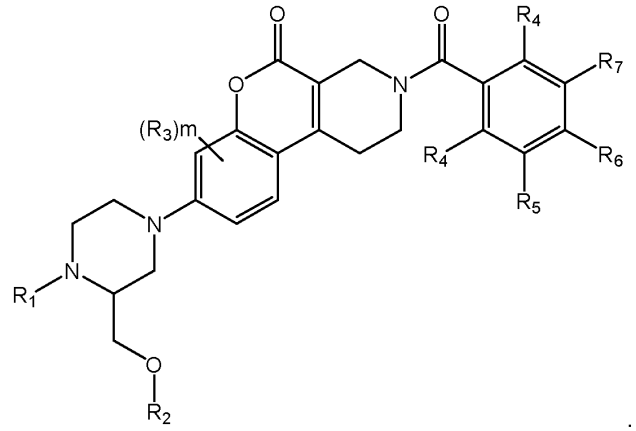
In some suitable compounds of formula (I) wherein R_7 is absent and when n is 1, R_4 is attached to the phenyl ring in the following position:



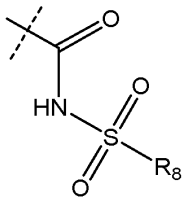
In some suitable compounds of formula (I), and when n is 2, R_4 is attached to the phenyl ring in the following position, wherein both R_4 are identical:



In some suitable compounds of formula (I), and when n is 2, R_4 is attached to the phenyl ring in the following position, wherein both R_4 are non-identical:



Option (a)

In some compounds of formula (I), R_6 is  and R_7 is absent.

In such compounds, R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7

membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some such compounds, R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some such compounds, R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some suitable compounds of formula (I), R_5 is H. In other suitable compounds of formula (I), R_5 is halo, such as chloro. In other suitable compounds of formula (I), R_5 is C_{1-3}alkyl, such as methyl or ethyl. In other suitable compounds of formula (I), R_5 is C_{1-3} alkoxy, such as methoxy or ethoxy, e.g. methoxy. In other suitable compounds of formula (I), R_5 is C_{1-3} haloalkoxy. In other suitable compounds of formula (I), R_5 is SC_{1-3} alkyl. In other suitable compounds of formula (I),

R_5 is SC_{1-3} haloalkyl. In other suitable compounds of formula (I), R_5 is OC_{3-10} cycloalkyl, such as cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, bicyclo[3.1.0]hexyloxy and 2-adamantanyloxy. In other suitable compounds of formula (I), R_5 is 4-7 membered heterocycloalkyl, such as pyrrolidinyl, piperidinyl, 3-azabicyclo[3.1.0]hexyl, 2-azabicyclo(2.2.1)heptyl and 7-azanorbornanyl. In other suitable compounds of formula (I), R_5 is $NR_{5b}R_{5c}$.

Most suitably, R_5 is C_{1-3} alkoxy, such as methoxy or ethoxy, e.g. methoxy, or OC_{3-10} cycloalkyl, such as cyclobutyloxy or cyclopentyloxy.

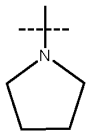
In some compounds of formula (I), R_5 is a 4-7 membered heterocycloalkyl group wherein the group is attached via a nitrogen atom, i.e.



wherein 

is the 4-7 membered heterocycloalkyl group and ------ indicates the join to the remainder of the compound of formula (I).

For example, and when the 4-7 membered heterocycloalkyl group is pyrrolidinyl, the pyrrolidinyl group is attached via the nitrogen atom, and is referred to as 1-pyrrolidinyl:



1-pyrrolidinyl

wherein ------ indicates the join to the remainder of the compound of formula (I).

In some such suitable compounds of formula (I), and when R_5 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_5 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_5 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{5a}. In other suitable compounds of formula (I), and when R_5 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{5a}.

In some such suitable compounds of formula (I), R_{5a} is halo, such as fluoro. In other suitable compounds of formula (I), R_{5a} is C_{1-3} alkyl, such as methyl.

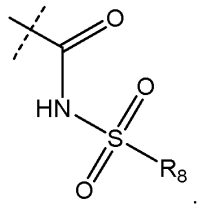
In some such suitable compounds of formula (I), R_5 is substituted by one R_{5a} group, such as methyl. In other suitable compounds of formula (I), R_5 is substituted by two R_{5a} groups, such as methyl and fluoro. In other suitable compounds of formula (I), R_5 is substituted by three R_{5a} groups. In other suitable compounds of formula (I), R_5 is substituted by two R_{5a} groups which are attached to the same carbon atom and join to form a C_{3-6} cycloalkyl ring, such as a C_3 cycloalkyl ring.

In some such suitable compounds of formula (I), R_{5b} is H. In other suitable compounds of formula (I), R_{5b} is C_{1-3} alkyl, such as methyl.

In some such suitable compounds of formula (I), R_{5c} is C_{1-3} alkyl, such as methyl or isopropyl. In other suitable compounds of formula (I), R_{5c} is C_{3-6} cycloalkyl, such as cyclopropyl.

Most suitably, R_{5b} and R_{5c} are both methyl. Most suitably, R_5 is $NR_{5b}R_{5c}$ and R_{5b} and R_{5c} are both methyl.

Option (b)

In some alternative compounds of formula (I), R_7 is 

.

Option (b)(i)

In some such compounds, R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some such compounds, R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

For example, R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

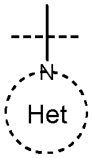
R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some such suitable compounds of formula (I), R_5 is H. In other suitable compounds of formula (I), R_5 is halo. In other suitable compounds of formula (I), R_5 is C_{1-3}alkyl, such as methyl or ethyl. In some other suitable compounds of formula (I), R_5 is C_{1-3} alkoxy. In other suitable compounds of formula (I), R_5 is C_{1-3} haloalkoxy. In some other suitable compounds of formula (I), R_5 is SC_{1-3} alkyl. In other suitable compounds of formula (I), R_5 is SC_{1-3} haloalkyl. In other suitable compounds of formula (I), R_5 is OC_{3-10} cycloalkyl, such as cyclobutyloxy. In other suitable compounds of formula (I), R_5 is 4-7 membered heterocycloalkyl. In some other suitable compounds of formula (I), R_5 is $NR_{5b}R_{5c}$.

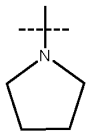
In some such compounds of formula (I), R_5 is a 4-7 membered heterocycloalkyl group wherein the group is attached via a nitrogen atom, i.e.



wherein 

is the 4-7 membered heterocycloalkyl group and ------ indicates the join to the remainder of the compound of formula (I).

For example, and when the 4-7 membered heterocycloalkyl group is pyrrolidinyl, the pyrrolidinyl group is attached via the nitrogen atom, and is referred to as 1-pyrrolidinyl:



1-pyrrolidinyl

wherein ------ indicates the join to the remainder of the compound of formula (I).

In some such suitable compounds of formula (I), and when R_5 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_5 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_5 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{5a}. In other suitable compounds of formula (I), and when R_5 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{5a}.

In some such suitable compounds of formula (I), R_{5a} is halo. In other suitable compounds of formula (I), R_{5a} is C_{1-3} alkyl.

In some suitable compounds of formula (I), R_5 is substituted by two R_{5a} groups which are attached to the same carbon atom and join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring.

In some such suitable compounds of formula (I), R_{5b} is H. In other suitable compounds of formula (I), R_{5b} is C_{1-3} alkyl.

In some such suitable compounds of formula (I), R_{5c} is C_{1-3} alkyl. In other suitable compounds of formula (I), R_{5c} is C_{3-6} cycloalkyl.

Option (b)(ii)

Alternatively, in some such compounds, R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some such compounds, R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

For example, R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

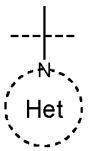
R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

In some suitable compounds of formula (I), R_6 is H. In other suitable compounds of formula (I), R_6 is halo. In other suitable compounds of formula (I), R_6 is C_{1-3}alkyl, such as methyl or ethyl. In other suitable compounds of formula (I), R_6 is C_{1-3} alkoxy. In other suitable compounds of formula (I), R_6 is C_{1-3} haloalkoxy. In other suitable compounds of formula (I), R_6 is SC_{1-3} alkyl. In other suitable compounds of formula (I), R_6 is SC_{1-3} haloalkyl. In other suitable compounds of formula (I), R_6 is OC_{3-10} cycloalkyl, such as cyclobutyloxy. In other suitable compounds of formula (I), R_6 is 4-7 membered heterocycloalkyl. In other suitable compounds of formula (I), R_6 is $NR_{6b}R_{6c}$.

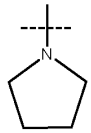
In some compounds of formula (I), R_6 is a 4-7 membered heterocycloalkyl group wherein the group is attached via a nitrogen atom, i.e.



wherein 

is the 4-7 membered heterocycloalkyl group and ------ indicates the join to the remainder of the compound of formula (I).

For example, and when the 4-7 membered heterocycloalkyl group is pyrrolidinyl, the pyrrolidinyl group is attached via the nitrogen atom, and is referred to as 1-pyrrolidinyl:



1-pyrrolidinyl

wherein ------ indicates the join to the remainder of the compound of formula (I).

In some suitable compounds of formula (I), and when R_6 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_6 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_6 is OC_{3-10} cycloalkyl, the OC_{3-10} cycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{6a}. In other suitable compounds of formula (I), and when R_6 is 4-7 membered heterocycloalkyl, the 4-7 membered heterocycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{6a}.

In some suitable compounds of formula (I), R_{6a} is halo. In other suitable compounds of formula (I), R_{6a} is C_{1-3} alkyl.

In some suitable compounds of formula (I), R_6 is substituted by two R_{6a} groups which are attached to the same carbon atom and join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring.

In some suitable compounds of formula (I), R_{6b} is H. In other suitable compounds of formula (I), R_{6b} is C_{1-3} alkyl.

In some suitable compounds of formula (I), R_{6c} is C_{1-3} alkyl. In other suitable compounds of

formula (I), R_{6c} is C_{3-6} cycloalkyl.

Option (b)(iii)

Alternatively, in some such compounds R_5 and R_6 join to form a 4-8 membered heterocyclic ring, such as a 5,8-dioxaspiro[3.4]octanyl ring.

R_8 group

In some suitable compounds of formula (I), R_8 is C_{3-6} cycloalkyl, such as cyclopropyl. In other suitable compounds of formula (I), R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl, such as pyrrolidinyl (e.g. pyrrolidin-1-yl), piperidinyl (e.g. piperidin-1-yl), 7-azanorbornanyl, 3-azabicyclo[3.1.0]hexyl (e.g. 3-azabicyclo[3.1.0]hexan-3-yl) , 6-azaspiro[2.5]octyl (e.g. 6-azaspiro[2.5]octan-6-yl) and 3-oxa-6-azabicyclo[3.2.1]octyl (e.g. 3-oxa-8-azabicyclo[3.2.1]octan-8-yl), suitably pyrrolidinyl (e.g. pyrrolidin-1-yl). Further examples include 7-azabicyclo[2.2.1]heptan-7-yl, (3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl, octahydro-2*H*-isoindol-2-yl, 2-azaspiro[3.3]heptan-2-yl, (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl), 2-azabicyclo[2.2.1]heptan-2-yl) and 8-azabicyclo[3.2.1]octan-8-yl.

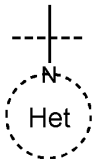
In other suitable compounds of formula (I), R_8 is $NR_{8b}R_{8c}$.

In some suitable compounds of formula (I), R_{8b} is H. In other suitable compounds of formula (I), R_{8b} is C_{1-3} alkyl, such as methyl. In other suitable compounds of formula (I) R_{8b} is C_{3-6} cycloalkyl, such as cyclopropyl or cyclopentyl.

In some suitable compounds of formula (I), R_{8c} is H. In other suitable compounds of formula (I), R_{8c} is C_{1-3} alkyl, such as methyl. In other suitable compounds of formula (I) R_{8c} is C_{3-6} cycloalkyl such as cyclopropyl or cyclopentyl.

For example, R_8 is $N(C_{1-3}$ alkyl$)_2$, such as $N(CH_3)_2$ or $N(CH_3)(CH(CH_3)_2)$. Alternatively, R_8 is N(cyclopropyl)$_2$, NMe(cyclopropyl) or NMe(cyclopentyl).

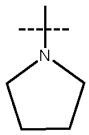
In some compounds of formula (I), R_8 is a 4-8 membered heterocycloalkyl group wherein the group is attached via a nitrogen atom, i.e.



wherein 

is the 4-10 (e.g. 4-8) membered heterocycloalkyl group and ------ indicates the join to the remainder of the compound of formula (I).

For example, and when the 4-10 (e.g. 4-8) membered heterocycloalkyl group is pyrrolidinyl, the pyrrolidinyl group is attached via the nitrogen atom, and is referred to as 1-pyrrolidinyl:



1-pyrrolidinyl

wherein ------ indicates the join to the remainder of the compound of formula (I).

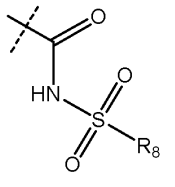
Examples of substituted heterocycloalkyl groups that R_8 may represent include (3-CF_3)-pyrroldin-1-yl, (2-CH_2OMe)- pyrroldin-1-yl, (2-CH_2OCH_2Me)- pyrroldin-1-yl, (4-CF_3)-piperidin-1-yl, (3-OMe)-piperidin-1-yl, (3-OMe)-pyrrolidin-1-yl, (2-CF_3)-pyrroldin-1-yl, (4-OMe)-piperidin-1-yl, (3-diF)-piperidin-1-yl, (3-diF)-pyrrolidin-1-yl, (3-diMe)-pyrrolidin-1-yl, (2,5-diMe)-pyrrolidin-1-yl, (4-F)-piperidin-1-yl, and (3-F)-pyrrolidin-1-yl.

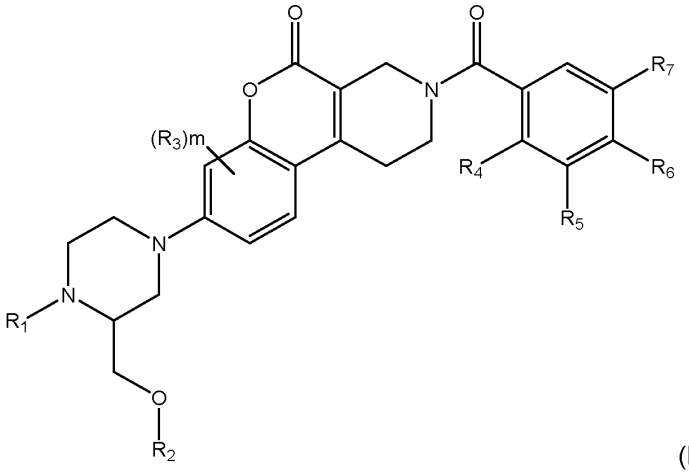
In some suitable compounds of formula (I), and when R_8 is C_{3-6} cycloalkyl, the C_{3-6} cycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl, the 4-10 (e.g. 4-8) membered heterocycloalkyl is unsubstituted. In other suitable compounds of formula (I), and when R_8 is C_{3-6} cycloalkyl, the C_{3-6} cycloalkyl is substituted by one or more (such as one, two or three, e.g. one) R_{8a}. For example, R_8 represents 1-methyl-cyclopropyl. In other suitable compounds of formula (I), and when R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl, the 4-10 (e.g. 4-8)_ membered heterocycloalkyl is substituted by one or more (such as one, two or three, e.g. one or two e.g. one) R_{8a}.

In some suitable compounds of formula (I), R_{8a} is C_{1-3} alkyl, such as methyl. In other suitable compounds of formula (I), R_{8a} is C_{1-3} alkyl substituted by OH such as -CH_2OH. In other suitable compounds of formula (I), R_{8a} is C_{1-2} alkyl substituted by OC_{1-2} alkyl such as -CH_2OMe or CH_2OCH_2Me. In other suitable compounds of formula (I), R_{8a} is C_{1-3} alkoxy such as OMe. In other suitable compounds of formula (I), R_{8a} is halo such as F. In other suitable compounds of

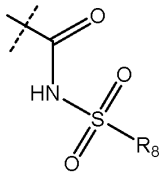
formula (I), R_{8a} is C_{1-3} haloalkyl such as CF_3.

In some suitable compounds of formula (I), R_8 is substituted by two R_{8a} groups, such as two methyl groups.

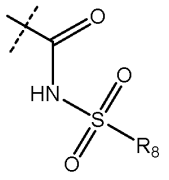
In some suitable compounds of formula (I), R_1 and R_2 are methyl, m is 1 or 2, R_3 is selected from methyl and halo (e.g. chloro) such as is methyl, n is 1 and R_4 is fluoro, R_5 is OC_{3-10} cycloalkyl, such as cyclobutyloxy, R_6 is  , R_7 is absent and R_8 is 4-8 membered heterocycloalkyl such as 1-pyrrolidinyl. In such compounds of formula (I), suitably R_4 is attached ortho to R_5 i.e. compounds of formula (IA) defined below:



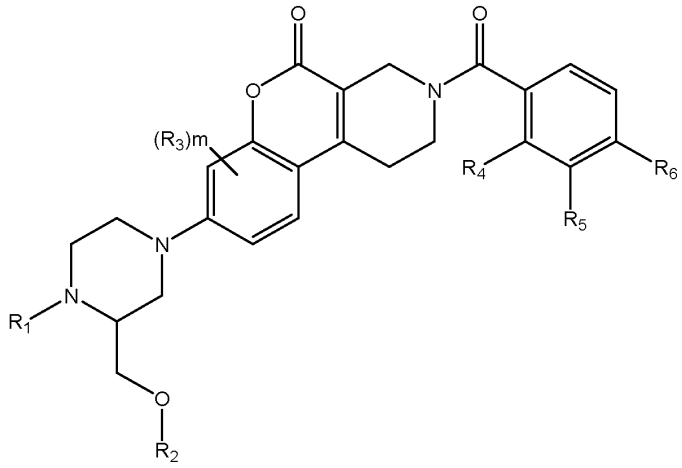
(IA)

wherein R_1 and R_2 are methyl, m is 1 or 2, R_3 is selected from methyl and halo (e.g. chloro) (for example m is 1 or 2 and R_3 is methyl), R_4 is fluoro, R_5 is OC_{3-10} cycloalkyl, such as cyclobutyloxy, R_6 is  , R_7 is absent i.e. hydrogen and R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl such as 1-pyrrolidinyl. When m is 2 for example one occurrence of R_3 is methyl and the other occurrence is methyl or halo (e.g. chloro).

In other suitable compounds of formula (I), R_1 and R_2 are methyl, m is 1 or 2, R_3 is methyl, n is 1 and R_4 is fluoro, R_5 is C_{1-3} alkoxy, such as methoxy and ethoxy, or $NR_{5b}R_{5c}$, wherein R_{5b} and R_{5c}



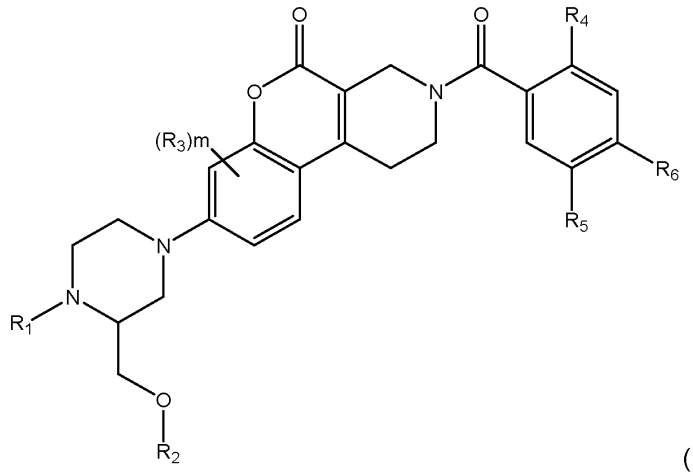
are each independently C_{1-3} alkyl, such as methyl, R_6 is , R_7 is absent and R_8 is 4-8 membered heterocycloalkyl or C_{3-6} cycloalkyl which is substituted by one R_{8a} wherein R_{8a} is C_{1-3} alkyl. In such suitable compounds of formula (I), and when R_5 is C_{1-3} alkoxy, such as methoxy or ethoxy, suitably, R_4 is attached ortho to R_5 i.e. i.e. compounds of formula (IB) defined below:



(IB)

wherein R_1 and R_2 are methyl, m is 1 or 2, R_3 is selected from methyl and halo (e.g. chloro) (for example m is 1 or 2 and R_3 is methyl), n is 1, R_4 is fluoro, R_5 is C_{1-3} alkoxy, such as methoxy and ethoxy, or $NR_{5b}R_{5c}$, wherein R_{5b} and R_{5c} are each independently C_{1-3} alkyl, such as methyl, R_6 is -C(=O)NHSO$_2$R$_8$ and R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl or C_{3-6} cycloalkyl which is substituted by one R_{8a} wherein R_{8a} is C_{1-3} alkyl and R_5 is C_{1-3} alkoxy, such as methoxy or ethoxy. When m is 2 for example one occurrence of R_3 is methyl and the other occurrence is methyl or halo (e.g. chloro).

In other such suitable compounds of formula (I), and when R_5 is methoxy, ethoxy, cyclopropyloxy or $NR_{5b}R_{5c}$ (for example, R_5 is $NR_{5b}R_{5c}$ (such as NMe_2)), suitably, R_4 is attached para to R_5 i.e. i.e. compounds of formula (IC) defined below:



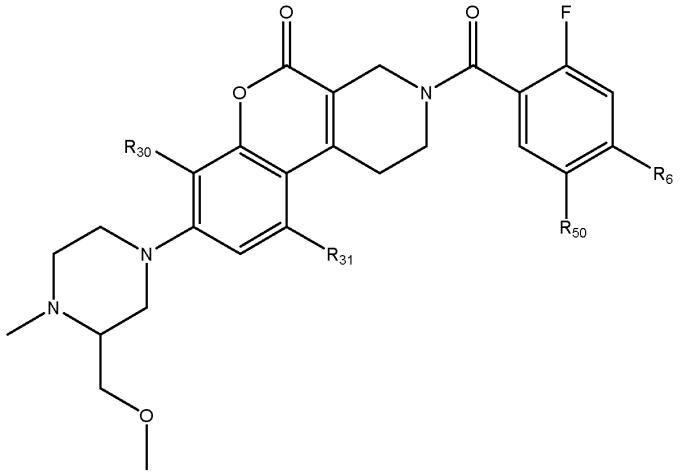
(IC)

wherein R_1, R_2, R_3, m, R_4 and R_6 are as defined elsewhere herein and R_5 is methoxy, ethoxy, cyclopropyloxy or $NR_{5b}R_{5c}$ (such as NMe_2).

In compounds of formula (IC) suitably:

R_1 is methyl, R_2 is methyl, m is 1 or 2 and more suitably 2, R_3 is selected from methyl and halo (e.g. chloro), R_4 is fluoro, R_5 is methoxy, ethoxy, cyclopropyloxy or $NR_{5b}R_{5c}$ in which R_{5b} and R_{5c} are each methyl, R_6 is $-C(=O)NHSO_2R_8$ and R_8 is R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl containing one nitrogen atom and wherein the R_8 groups is connected to the remainder of the molecule via said nitrogen atom. When m is 2 for example one occurrence of R_3 is methyl and the other occurrence is methyl or halo (e.g. chloro).

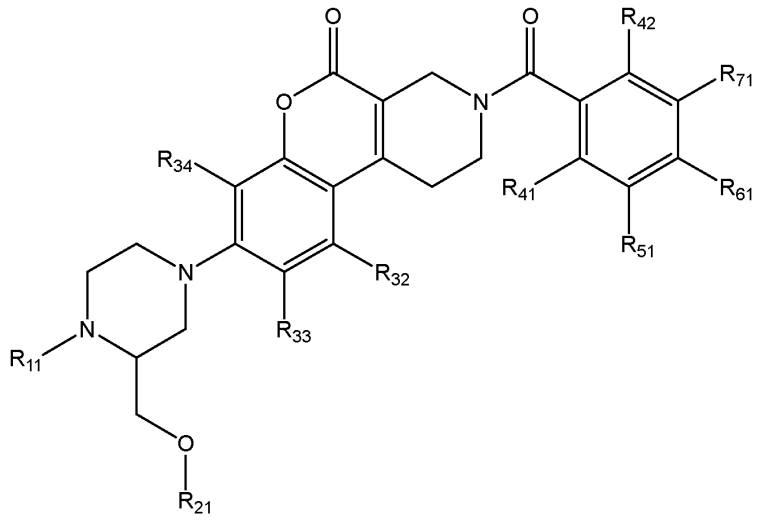
Some suitable compounds of formula (IC) are compounds of formula (IC-1)



(IC-1)

wherein R_{50} is methoxy, ethoxy, cyclopropyloxy or NMe_2, R_6 is $-C(=O)NHSO_2R_8$ and R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl containing one nitrogen atom and optionally one oxygen atom and wherein the R_8 groups is connected to the remainder of the molecule via said nitrogen atom and wherein said 4-10 (e.g. 4-8) membered heterocycloalkyl may optionally be substituted by one or two R_{8a} groups and wherein R_{30} and R_{31} are independently selected from methyl and halo (e.g. chloro) and for example R_{30} is methyl and R_{31} is methyl or halo (e.g. chloro). Suitably in compounds of formula (IC-1), R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl containing one nitrogen atom and no other heteroatoms. For example, in compounds of formula (IC-1), the 4-10 (e.g. 4-8) membered heterocycloalkyl group is not substituted by an R_{8a} group. In one embodiment R_{50} is methoxy. In one embodiment R_{50} is ethoxy. In one embodiment R_{50} is cyclopropyloxy. In one embodiment R_{50} is NMe_2.

The invention also provides compounds of formula (ID):



(ID)

wherein:

R_{11} is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_{21} is C_{1-4} alkyl; or

R_{11} and R_{21} join to form a 5-7 membered heterocycloalkyl;

R_{32}, R_{33} and R_{34} are independently selected from the group consisting of H, C_{1-3} alkyl and halo provided that at least one of R_{32}, R_{33} and R_{34} is H;

R_{41} and R_{42} are independently selected from H, C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

provided that at least one of R_{41}, R_{42} and R_{71} is H;

R_{51}, R_{61} and R_{71} are independently selected from the group consisting of -C(=O)NHSO$_2$R$_8$, H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, N$R_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or R_{51} and R_{61} join to form a 4-8 membered heterocyclic ring;

provided that one and only one of R_{51}, R_{61} and R_{71} is -C(=O)NHSO$_2$R$_8$,

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, N$R_{8b}R_{8c}$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

Compounds of formula (ID) are of use according to the invention as provided for compounds of formula (I).

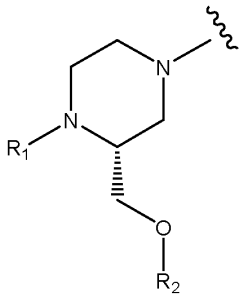
In compounds of formula (ID), for example, R_{61} is -C(=O)NHSO$_2$R$_8$.

In compounds of formula (ID), for example, R_{71} is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, N$R_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl.

In compounds of formula (ID), for example, R_{41}, R_{42} and R_{71} are independently selected from H, and halo (such as F or Cl). In an embodiment R_{41} is H, R_{42} is H and R_{71} is H. In an embodiment R_{41} is halo e.g. Cl or F, R_{42} is H and R_{71} is H. In an embodiment R_{41} is H, R_{42} is halo e.g. Cl or F (especially F) and R_{71} is H. In an embodiment R_{41} is H, R_{42} is H and R_{71} is halo e.g. Cl or F. In compounds of formula (ID), suitably R_{33} is H In compounds of formula (ID), for example, R_{32} and

R_{34} are independently selected from methyl and halo (e.g. chloro) and, for example, R_{34} is methyl and R_{32} is methyl or halo (e.g. chloro).

In compounds of formula (I), (IA), (IB), (IC) and (IC-1), and correspondingly for compounds of formula (ID), suitably the stereochemistry around the piperazine ring is as follows:



Suitably, the compound of formula (I) is selected from the group consisting of any one of Examples 1 to 180, or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of any one of Examples 1 to 270 e.g. 181-270, or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of any one of Examples 1 to 331 e.g. 271-331, or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of:
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
and
2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of:
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide; and
(*R*)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of:
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;
2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide; and
2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

Suitably, the compound of formula (I) is selected from the group consisting of:
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-(methoxy-d_3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-ethoxy-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*-cyclopropyl-*N*-methylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide; and
(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

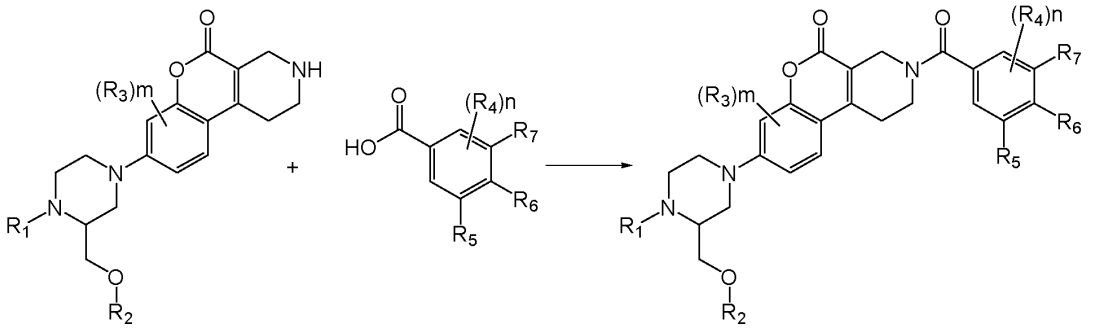
Suitably, the compound of formula (I) is selected from the group consisting of:
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide ;
(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

The invention provides each of the aforesaid example compounds (i.e. Examples 1-331) and pharmaceutically acceptable salts and/or solvates thereof in all stereoisomeric forms (such as, for example, in the (S) form instead of the (R) form as indicated above, referring to the stereocentre involving the attachment of the $-CH_2OR_2$ moiety to the piperazine ring) including all

mixtures of stereoisomeric forms, such as racemic mixtures.

Compounds of formula (I) may be synthesised as shown in the scheme below and as shown in the Examples section. For each scheme, variables are as defined above unless otherwise stated.

Scheme 1: Synthesis of compounds of formula (I)

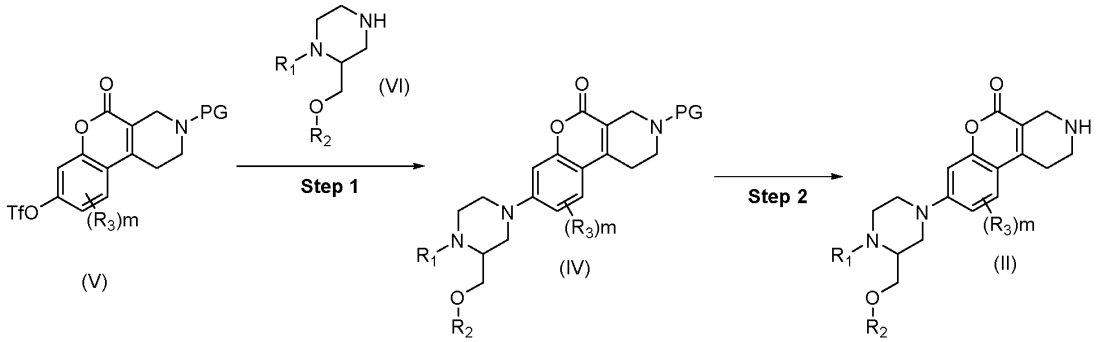


(II) (III) (I)

Compounds of formula (I) may be prepared by coupling amine intermediate (II) with carboxylic acid (III) using coupling agents (such as EDCI and HOBt) in the presence of an organic base (such as TEA) in a solvent (such as DCM).

Compounds of formula (II) and formula (III) may be synthesised for example as set out in the Example section below, or according to the following Schemes.

Scheme 2: Synthesis of compounds of formula (II)



(V) (VI) (IV) (II)

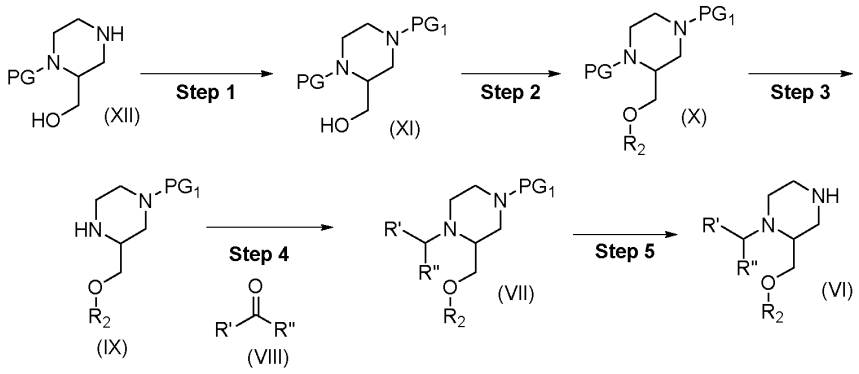
wherein R_1, R_2, R_3 and m are defined elsewhere herein and PG is a nitrogen protecting group. Compounds of formula (V) may be prepared according to literature (such as the Daiichi Sankyo patent application disclosed above).

Step 1: Compounds of formula (V) are reacted with compounds of formula (VI) under palladium-

catalysed reaction conditions to form compounds of formula (IV).

Step 2: The nitrogen protecting group is removed under standard deprotection conditions which are known to the person skilled in the art, to give compounds of formula (II). For example, if PG is Boc, this group may be removed under acidic conditions such as HCl in 1,4-dioxane, amongst other known methods such as those described herein.

Scheme 3: Synthesis of compounds of formula (VI)



wherein R_2 is defined elsewhere herein, -CH(R')(R'') corresponds to R^1, and PG and PG_1 are orthogonal nitrogen protecting groups.

Step 1: Compounds of formula (XII) are reacted with PG_1-X (wherein X is a leaving group such as halo e.g. chloro) to give compounds of formula (XI).

Step 2: Compounds of formula (XI) are reacted with alkyl halide R_2-X_1 wherein X_1 is a leaving group such as bromo, iodo or tosyl, to give compounds of formula (X).

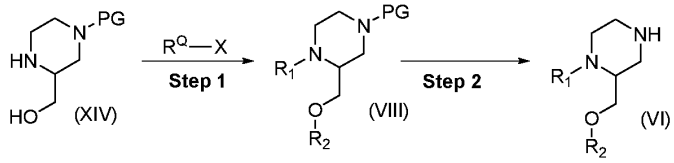
Step 3: PG is removed from compounds of formula (X) under standard deprotection conditions which are known to the person skilled in the art, to give compounds of formula (IX). For example, if PG is Boc, this group may be removed under acidic conditions such as TFA in DCM, amongst other known methods such as those described herein.

Step 4: Compounds of formula (IX) undergo a reductive amination with compounds of formula (VIII) under standard reductive amination conditions (such as $NaBH(OAc)_3$ in acetonitrile and water) to give compounds of formula (VII). Since -CH(R')(R'') corresponds to R^1, R' and R'' may independently be H or C_{1-3} alkyl, or join to form a C_{3-5} cycloalkyl ring.

Step 5: PG_1 is removed from compounds of formula (VII) under standard deprotection

conditions which are known to the person skilled in the art, to give compounds of formula (VI). For example, if PG_1 is Cbz, this group may be removed under hydrogenation conditions such as Pd/C, H_2 in MeOH, amongst other known methods.

Scheme 4: Alternative synthesis of compounds of formula (VI)

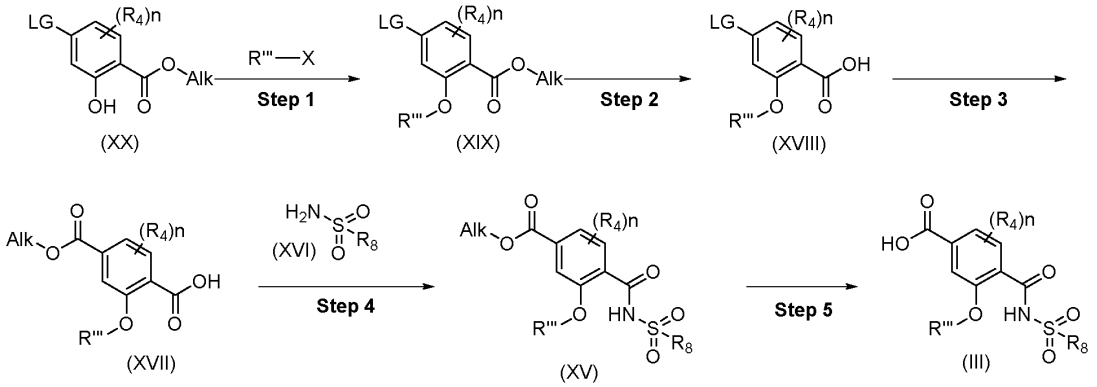


wherein R^Q is R_1 and R_2, PG is a nitrogen protecting group and X is a leaving group such as bromo, iodo or tosyl. This route may be used when R_1 is the same as R_2.

Step 1: Compounds of formula (XIV) are reacted with R^Q-X wherein $R^Q = R_1 = R_2$ under basic conditions such as NaH/THF or N-methyl-2-pyrrolidone, to give compounds of formula (VIII).

Step 2: The nitrogen protecting group is removed under standard deprotection conditions which are known to the person skilled in the art, to give compounds of formula (VI). For example, if PG is Boc, this group may be removed under acidic conditions such as HCl in 1,4-dioxane or EtOAc, amongst other known methods such as those described herein.

Scheme 5: Method A for preparing compounds of formula (III) when R_5 is OR''' and R_7 is absent



wherein R_4, n and R_8 are defined elsewhere herein, R''' is C_{1-3} alkyl, C_{1-3} haloalkyl or C_{3-10} cycloalkyl, Alk is C_{1-4}alkyl, LG is a leaving group such as halo e.g. bromo and X is halo or OH.

Step 1: Compounds of formula (XX) are reacted with R'''-X under S_N2 reaction conditions (X is halo such as chloro or bromo) in the presence of a base such as Cs_2CO_3 in DMA or Mitsunobu reaction conditions (X is OH) in the presence of DIAD, PPh_3, in a solvent such as THF to give

compounds of formula (XIX).

Step 2: The alkyl ester in compounds of formula (XIX) is hydrolysed under basic conditions (such as LiOH in MeOH/H_2O) to give carboxylic acids of formula (XVIII).

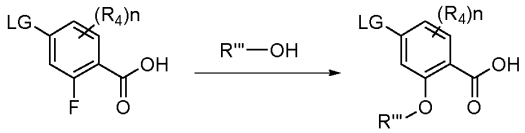
Step 3: Compounds of formula (XVIII) are carbonylated under palladium catalysed conditions to give compounds of formula (XVII) e.g. Pd catalyst, a base such as TEA, CO, an alcohol e.g. EtOH and DMA.

Step 4: Compounds of formula (XVII) are coupled with compounds of formula (XVI) under standard coupling conditions (such as EDCI, DMAP and DCM, or other conditions disclosed herein) to give compounds of formula (XV).

Step 5: Hydrolysis of the alkyl ester in compounds of formula (XV), for example under basic conditions e.g. LiOH in MeOH/H_2O, provides compounds of formula (III).

For Method A, it is also possible to swap Steps 3 and 4.

Scheme 6: Alternative synthesis of compounds of formula (XVIII) when R_5 is OR'''

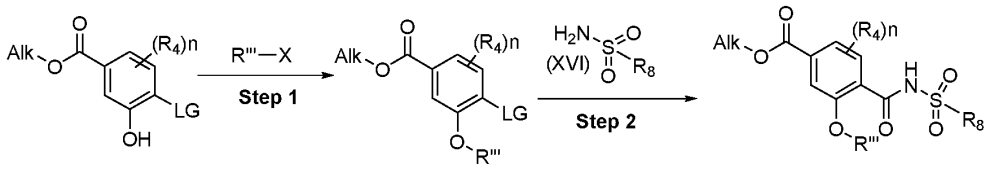


(XXI) (XVIII)

wherein R_4 and n are defined elsewhere herein, R''' is C_{1-3} alkyl, C_{1-3} haloalkyl or C_{3-10} cycloalkyl and LG is a leaving group such as halo e.g. bromo.

Compounds of formula (XXI) are reacted with R'''-OH under basic conditions (e.g. NaH in DMF) to give compounds of formula (XVIII).

Scheme 7: Method B for preparing compounds of formula (III) when R_5 is OR''' and R_8 is a N-linked group such as $N(C_{1-3}$ alkyl$)_2$ or a N-linked 4-8 membered heterocycloalkyl and R_7 is absent



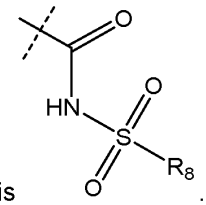
(XXIII) (XXII) (XV)

wherein R_4 and n are defined elsewhere herein, R''' is C_{1-3} alkyl, C_{1-3} haloalkyl or C_{3-10} cycloalkyl, Alk is C_{1-4}alkyl, LG is a leaving group such as halo e.g. bromo and X is halo or OH.

Step 1: Compounds of formula (XXIII) are reacted with R'''-X under S_N2 reaction conditions (X is halo such as chloro or bromo) in the presence of a base such as Cs_2CO_3 in DMA or Mitsunobu reaction conditions (X is OH) in the presence of DIAD, PPh_3, in a solvent such as THF to give compounds of formula (XXII).

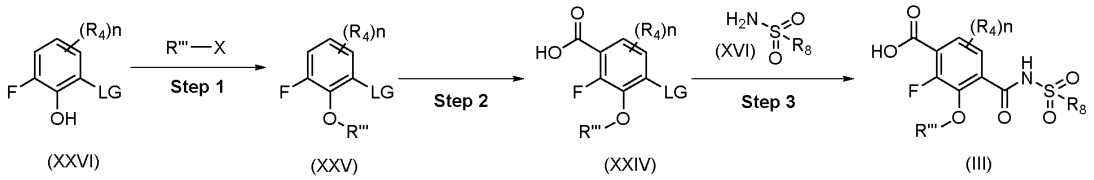
Step 2: Compounds of formula (XXII) are reacted with compounds of formula (XVI) under palladium catalysed reaction conditions (such as Herrmann's palladacycle, $[(tBu)_3PH]BF_4$, $Mo(CO)_6$, DBU and 1,4-dioxane) to give compounds of formula (XV).

Compounds of formula (XV) can be converted to compounds of formula (III) using methods disclosed herein.

It is possible to hydrolyse the alkyl ester in compounds of formula (XXII) before performing Step 2. This route can also be used to synthesis compounds of formula (III) which are precursors to compounds of formula (I) wherein R_5 is H, R_6 is -OR''' and R_7 is 

.

Scheme 8: Method C for preparing compounds of formula (III) wherein at least one R_4 is fluoro, R_5 is OR''', R_7 is absent and R_8 is a N-linked group such as $N(C_{1-3}$ alkyl$)_2$ or a N-linked 4-8 membered heterocycloalkyl



(XXVI) (XXV) (XXIV) (III)

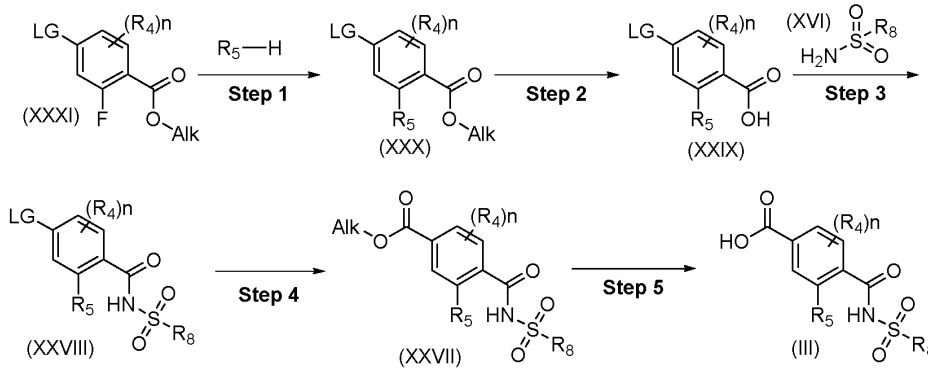
wherein R_4 and n are defined elsewhere herein, R''' is C_{1-3} alkyl, C_{1-3} haloalkyl or C_{3-10} cycloalkyl, Alk is C_{1-4}alkyl, LG is a leaving group such as halo e.g. bromo and X is halo or OH.

Step 1: Compounds of formula (XXVI) are reacted with R'''-X under S_N2 reaction conditions (X is halo such as chloro or bromo) in the presence of a base such as Cs_2CO_3 in DMA or Mitsunobu reaction conditions (X is OH) in the presence of DIAD, PPh_3, in a solvent such as THF to give compounds of formula (XXV).

Step 2: Compounds of formula (XXV) can be carbonylated using a strong base such as LDA, CO_2 in THF to give compounds of formula (XXIV).

Step 3: Compounds of formula (XXIV) are reacted with compounds of formula (XVI) under palladium catalysed reaction conditions (such as Herrmann's palladacycle, $[(tBu)_3PH]BF_4$, $Mo(CO)_6$, DBU and 1,4-dioxane) to give compounds of formula (III).

Scheme 9: Method D for preparing compounds of formula (III) when R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl and R_7 is absent



wherein R_4, R_8, n are defined elsewhere herein, R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl, Alk is C_{1-4}alkyl, LG is a leaving group such as halo e.g. bromo and X is halo or OH.

Step 1: Compounds of formula (XXXI) are reacted with R_5-H under basic conditions such as K_2CO_3 and KI in DMSO, to give compounds of formula (XXX).

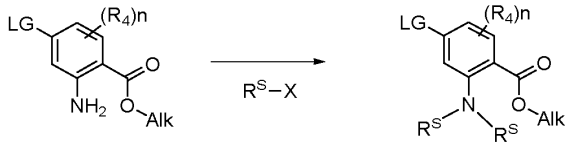
Step 2: The alkyl ester in compounds of formula (XXX) is hydrolysed, for example under basic conditions e.g. LiOH, MeOH/THF/H_2O, to give compounds of formula (XXIX).

Step 3: Compounds of formula (XXIX) are coupled with compounds of formula (XVI) under conditions such as HATU, DIPEA, NaH in DMF, or other conditions disclosed herein to give compounds of formula (XXVIII).

Step 4: Compounds of formula (XXVIII) can be carbonylated under palladium catalysed reaction conditions (such as Pd catalyst, KOAc, CO and an alcohol such as EtOH) to give compounds of formula (XXVII).

Step 5: The alkyl ester in compounds of formula (XXVIII) is hydrolysed, for example under basic conditions e.g. LiOH, MeOH/THF/H_2O, to give compounds of formula (III).

Scheme 10: Alternative synthesis of (XXX) when R_5 is $NR_{5b}R_{5c}$ and R_{5b} and R_{5c} are the same

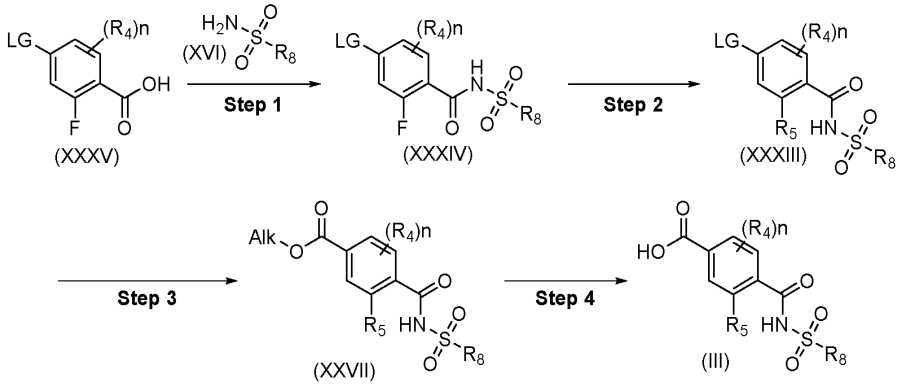


(XXXII) (XXX)

wherein R_4 and n are defined elsewhere herein, R^S = R_{5b} = R_{5c}, Alk is $C_{1\text{-}4}$alkyl, LG is a leaving group such as halo e.g. bromo and X is halo, such as chloro or bromo.

Compounds of formula (XXXII) are reacted with R^S-X under basic conditions (such as NaH in DMF) to give compounds of formula (XXX).

Scheme 11: Method E for preparing compounds of formula (III) when R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl and R_7 is absent



wherein R_4, R_8, n are defined elsewhere herein, R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl, Alk is C_{1-4}alkyl and LG is a leaving group such as halo e.g. bromo.

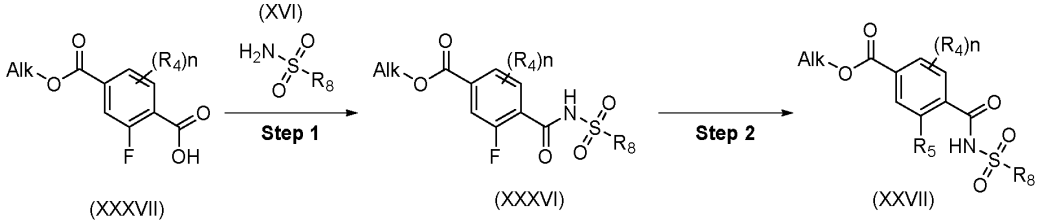
Step 1: Compounds of formula (XXXV) are coupled with compounds of formula (XVI) under coupling conditions such as HATU, DIPEA, NaH in DMF, or other conditions disclosed herein to give compounds of formula (XXXIV).

Step 2: Compounds of formula (XXXIV) are reacted with R_5-H under basic conditions such as K_2CO_3 and KI in DMSO (or other conditions disclosed herein), to give compounds of formula (XXXIII).

Step 3: Compounds of formula (XXXIII) can be carbonylated under palladium catalysed reaction conditions (such as Pd catalyst, KOAc, CO and an alcohol such as EtOH) to give compounds of formula (XXVII).

Step 4: The alkyl ester in compounds of formula (XXVII) is hydrolysed, for example under basic conditions e.g. LiOH, MeOH/THF/H_2O, to give compounds of formula (III).

Scheme 12: Method F for preparing compounds of formula (III) when R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl and R_7 is absent



(XXXVII) (XXXVI) (XXVII)

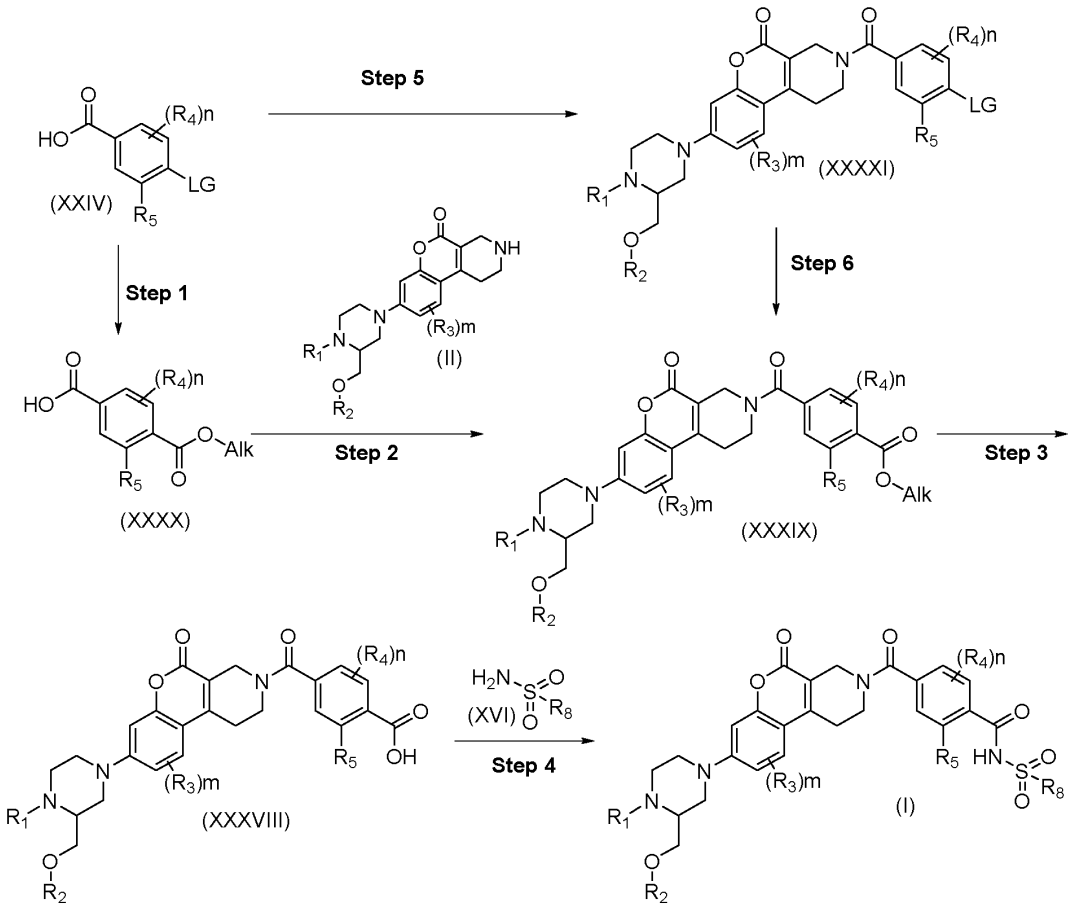
wherein R_4, R_8, n are defined elsewhere herein, R_5 is an N-linked group such as $NR_{5b}R_{5c}$ or an N-linked 4-7 membered heterocycloalkyl and Alk is C_{1-4}alkyl.

Step 1: Compounds of formula (XXXVII) are coupled with compounds of formula (XVI) under coupling conditions such as HATU, DIPEA, NaH in DMF, or other conditions disclosed herein to give compounds of formula (XXXVI).

Step 2: Compounds of formula (XXXVI) are reacted with R_5-H under basic conditions such as DIPEA in DMSO or other conditions disclosed herein, to give compounds of formula (XXVII). Compounds of formula (XXVII) can be converted to compounds of formula (III) as described herein.

Compounds of formula (III) and related intermediates in which R_7 is not absent may be prepared by adaptation of Schemes 5, 7, 8, 9, 11 and 12 which is within the knowledge of a skilled person.

Scheme 13: Alternative synthesis of compounds of formula (I) in which R_7 is absent



wherein R_1, R_2, R_3, R_4, R_5, R_8, n and m are defined elsewhere herein, Alk is C_{1-4}alkyl and LG is a leaving group such as halo e.g. bromo.

Step 1: Compounds of formula (XXIV) can be carbonylated under palladium catalysed reaction conditions (such as Pd catalyst, TEA, CO, an alcohol such as EtOH and DMA) to give compounds of formula (XXXX).

Step 2: Compounds of formula (XXXX) are coupled with compounds of formula (II) under standard coupling conditions (such as EDCI, HOBt, DIPEA and DCM, or other conditions disclosed herein) to give compounds of formula (XXXIX).

Step 3: The alkyl ester in compounds of formula (XXXIX) is hydrolysed, for example under basic conditions e.g. LiOH, MeOH/THF/H_2O, to give compounds of formula (XXXVIII).

Step 4: Compounds of formula (XXXVIII) are coupled with compounds of formula (XVI) under

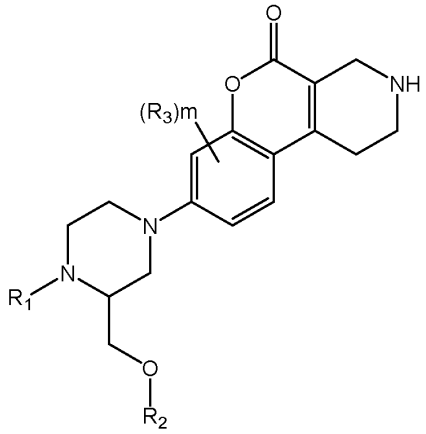
standard coupling conditions (such as EDCI, DMAP and DCM, or other conditions disclosed herein) to give compounds of formula (I).

Alternatively, **Steps 5 and 6** can be used to convert compounds of formula (XXIV) to (XXXIX). **Step 5** is a coupling reaction as in Steps 2 in Scheme 13, and **Step 6** is a carbonylation as is Step 1 in Scheme 13.

Compounds of formula (I) in which R_7 is not absent may be prepared by adaptation of Scheme 13 which is within the knowledge of a skilled person.

The invention provides novel intermediates as an aspect of the invention.

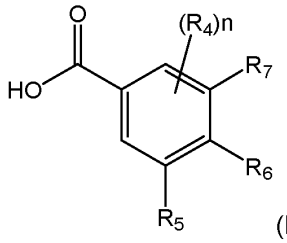
Thus, the invention provides a compound of formula (II):



(II)

or a salt and/or solvate thereof;
wherein R_1, R_2, R_3 and m are as defined elsewhere herein.

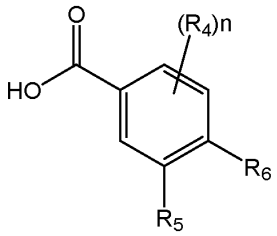
The invention also provides a compound of formula (III):



(III)

or a salt and/or solvate thereof;
wherein R_4, R_5, R_6, R_7 and n are as defined elsewhere herein. In particular, R_5 may be an O-linked group such as C_{1-3} alkoxy, C_{1-3} haloalkoxy or OC_{3-10} cycloalkyl, or an N-linked group such as $NR_{5b}R_{5c}$ or N-linked 4-7 membered heterocycloalkyl.

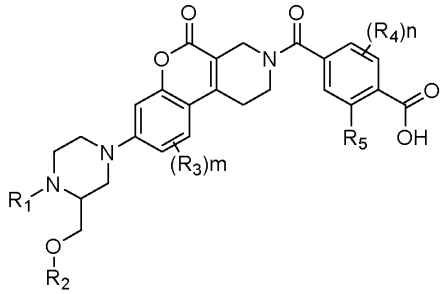
In some suitable compounds of formula (III), the compound of formula (III) has the following structure:



or a salt and/or solvate thereof;

wherein R_4, R_5, R_6 and n are as defined elsewhere herein. In particular, R_5 may be an O-linked group such as C_{1-3} alkoxy, C_{1-3} haloalkoxy or OC_{3-10} cycloalkyl, or an N-linked group such as $NR_{5b}R_{5c}$ or N-linked 4-7 membered heterocycloalkyl.

The invention also provides a compound of formula (XXXVIII):

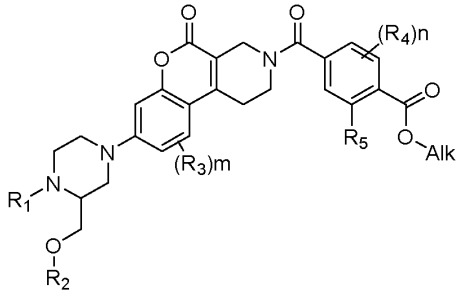


(XXXVIII)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined elsewhere herein.

The invention also provides a compound of formula (XXXIX):

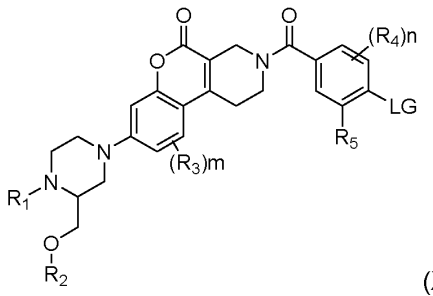


(XXXIX)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined elsewhere herein, and Alk is C_{1-4}alkyl.

The invention also provides a compound of formula (XXXXI):



(XXXXI)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined elsewhere herein, and LG is a leaving group such as halo e.g. bromo.

It will be appreciated that for use in therapy the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include acid addition salts, suitably salts of compounds of the invention comprising a basic group such as an amino group, formed with inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid. Also included are salts formed with organic acids, e.g., succinic acid, maleic acid, acetic acid, fumaric acid, citric acid, tartaric acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid and 1,5-naphthalenedisulfonic acid. Other salts, e.g., oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention, as are basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts.

Pharmaceutically acceptable salts may also be formed with organic bases such as basic amines, e.g., with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine, benzathine or lysine.

In one embodiment there is provided a compound of formula (I) in the form of a salt, such as a pharmaceutically acceptable salt. Alternatively, there is provided a compound of formula (I). When the compound contains a basic group as well as the free acid it may be zwitterionic.

Suitably, the compound of formula (I) is not in the form of a salt, e.g., is not in the form of a pharmaceutically acceptable salt.

Suitably, where the compound of formula (I) is in the form of a salt, the pharmaceutically acceptable salt is a basic addition salt such as a carboxylate salt formed with a group 1 metal (e.g., a sodium or potassium salt), a group 2 metal (e.g., a magnesium or calcium salt) or an

ammonium salt of a basic amine (e.g., an NH_4^+ salt), such as a sodium salt.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g., as the hydrate. This invention includes within its scope stoichiometric solvates (e.g., hydrates) as well as compounds containing variable amounts of solvent (e.g., water). Suitably, the compound of formula (I) is not a solvate.

The invention extends to a pharmaceutically acceptable derivative thereof, such as a pharmaceutically acceptable prodrug of compounds of formula (I). Typical prodrugs of compounds of formula (I) which comprise a carboxylic acid include ester (e.g. C_{1-6} alkyl e.g. C_{1-4} alkyl ester) derivatives thereof. Thus, in one embodiment, the compound of formula (I) is provided as a pharmaceutically acceptable prodrug. In another embodiment, the compound of formula (I) is not provided as a pharmaceutically acceptable prodrug.

It is to be understood that the present invention encompasses all isomers of compounds of formula (I) including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). In particular, the invention extends to all tautomeric forms of the compounds of formula (I). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The present invention also includes all isotopic forms of the compounds provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom may naturally exists as a mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or> 99% by number of the atoms of that atomic number (the latter embodiment referred to as an “isotopically enriched variant for”). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that

which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

An unnatural variant isotopic form of a compound may thus contain one or more artificial or uncommon isotopes such as deuterium (^{2}H or D), carbon-11 (^{11}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-15 (^{15}N), oxygen-15 (^{15}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), phosphorus-32 (^{32}P), sulphur-35 (^{35}S), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), fluorine-18 (^{18}F) iodine-123 (^{123}I), iodine-125 (^{125}I) in one or more atoms or may contain an increased proportion of said isotopes as compared with the proportion that predominates in nature in one or more atoms.

Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Unnatural variant isotopic forms which incorporate deuterium i.e. ^{2}H or D may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Further, unnatural variant isotopic forms may be prepared which incorporate positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in positron emission topography (PET) studies for examining substrate receptor occupancy.

In one embodiment, the compounds of formula (I) are provided in a natural isotopic form. In one embodiment, the compounds of formula (I) are provided in an unnatural variant isotopic form. In a specific embodiment, the unnatural variant isotopic form is a form in which deuterium (i.e. ^{2}H or D) is incorporated where hydrogen is specified in the chemical structure in one or more atoms of a compound of formula (I). In one embodiment, the atoms of the compounds of formula (I) are in an isotopic form which is not radioactive. In one embodiment, one or more atoms of the compounds of formula (I) are in an isotopic form which is radioactive. Suitably radioactive isotopes are stable isotopes. Suitably the unnatural variant isotopic form is a pharmaceutically acceptable form.

In one embodiment, a compound of formula (I) is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound of formula (I) is provided whereby two or more atoms exist in an unnatural variant isotopic form.

Unnatural isotopic variant forms can generally be prepared by conventional techniques known to those skilled in the art or by processes described herein e.g. processes analogous to those described in the accompanying Examples for preparing natural isotopic forms. Thus, unnatural isotopic variant forms could be prepared by using appropriate isotopically variant (or labelled) reagents in place of the normal reagents employed in the Examples. Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the purer forms used in the pharmaceutical compositions.

Therapeutic indications

Targeting MTHFD2 and optionally additionally MTHFD1 D/C-d with specific inhibitors presents a novel and exciting approach to regulate the 1C pathway in autoimmunity, inflammation and cancer with potential for an enhanced safety profile in comparison to clinically validated agents like MTX that block 1C metabolism more broadly. Inhibiting selectively MTHFD2 represents a particularly attractive option for autoimmunity with the potential to target very specifically the activated lymphocytes that orchestrate inflammation and tissue damage.

Compounds of formula (I) are of use in therapy, particularly for treating or preventing proliferative diseases such as inflammatory, autoimmune or fibrotic diseases, and cancer. Biological Example 1 shows that the compounds of the invention have inhibitory activity against MTHFD2. Certain examples show comparable inhibitory activity against MTHFD2 and MTHFD1 D/C-d therefore certain compounds of formula (I) are expected to have utility in the treatment of diseases where targeting both MTHFD2 and MTHFD1 D/C-d would be beneficial. By comparable activity, this means that the selectivity for targeting MTHFD2 over targeting MTHFD1 D/C-d is less than 3 fold (e.g. as shown by ratio values in Table 1), i.e. the IC_{50} for MTHFD1 D/C-d is less than 3 fold greater than the IC_{50} for MTHFD2. Certain other examples are selective (e.g. 3 to 30 fold selective or >30 fold selective) for MTHFD2 over MTHFD1 D/C-d (e.g. as shown by ratio values in Table 1 i.e. the IC_{50} value for MTHFD1 D/C-d is 3 times or more the IC_{50} value for MTHFD2) and therefore certain compounds of formula (I) are expected to have utility in the treatment of diseases where targeting MTHFD2 over MTHFD1 D/C-d would be beneficial. Certain other examples are selective (e.g. 30 to 600 fold selective) for MTHFD2 over MTHFD1 D/C-d (e.g. as shown by ratio values in Table 1 i.e. the IC_{50} value for MTHFD1 D/C-d is 30 times or more the IC_{50} value for

MTHFD2) and therefore certain compounds of formula (I) are expected to have utility in the treatment of diseases where targeting MTHFD2 over MTHFD1 D/C-d would be beneficial. Reference to targeting MTHFD1 throughout is interchangeable with targeting MTHFD1 D/C-d. Biological Example 2 shows that certain examples do not possess off-target effects against the α4β2 nicotinic receptor, unlike Reference Example 1 as shown in Table 2. Therefore compounds of formula (I) are expected to be more suitable for drug development compared with Reference Example 1.

Thus, in a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use as a medicament.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating or preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of a medicament for treating or preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of a medicament for treating a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of

a medicament for preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

In a further aspect, the present invention provides a method of treating or preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In a further aspect, the present invention provides a method of treating a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In a further aspect, the present invention provides a method of preventing a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In any one of the above embodiments, the disease is an inflammatory, autoimmune or fibrotic disease. Alternatively, the disease is cancer.

Suitably, the compounds of formula (I) that show comparable inhibitory activity against MTHFD2 and MTHFD1 D/C-d are for use in treating or preventing an inflammatory, autoimmune or fibrotic disease.

Suitably, the compounds of formula (I) that show comparable inhibitory activity against MTHFD2 and MTHFD1 D/C-d are for use in treating or preventing cancer.

Suitably, the compounds of formula (I) that are selective (e.g. 3 to 30 fold selective or >30 fold selective) for MTHFD2 over MTHFD1 D/C-d are for use in treating or preventing an inflammatory, autoimmune or fibrotic disease.

Suitably, the compounds of formula (I) that are selective (e.g. 3 to 30 fold selective or >30 fold selective) for MTHFD2 over MTHFD1 D/C-d are for use in treating or preventing cancer.

Suitably, the inflammatory, autoimmune or fibrotic disease is selected from the group consisting

of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, myasthenia gravis (MG), Crohn's disease, multiple sclerosis, sarcoidosis, ulcerative colitis, Celiac's disease, systemic lupus erythematosus (SLE), Sjogren's syndrome, asthma, atopic dermatitis, vitiligo, systemic sclerosis (SSC), graft versus host disease (GvHD), Type 1 diabetes, Hidradenitis suppurativa, idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD) and non-alcoholic steatohepatitis (NASH).

The following diseases may be treated using methotrexate, which as stated in the introduction, target enzymes on the one-carbon (1C) metabolism pathway, and has known utility in the treatment of autoimmune diseases (Koźmiński P. et al., 2020; Kerschbaumer A. et al., 2019; Ferrara G. *et al.*, 2018; Gotterer L. *et al.,* 2016; Díaz-Manera J. *et al.*, 2012; Chantam W. 2010; Smolen JS. *et al.*, 2010; Mahr AD. *et al.*, 2007; Baughman RP. *et al.*1999). Since the compounds of the invention are expected to work in a similar yet superior way to methotrexate, it is expected that compounds of formula (I) will have utility in the treatment of the same diseases listed below.

Thus, suitably, the inflammatory, autoimmune or fibrotic disease is selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, myasthenia gravis (MG), Crohn's disease, multiple sclerosis and sarcoidosis.

The following diseases are linked to the overexpression of MTHFD2 (Aune TM. *et al.*, 2017; Sugiura A. *et al.*, 2022), and thus inhibition of MTHFD2 using the compounds of formula (I) represents a strategy for treating the diseases listed below.

Suitably, the inflammatory, autoimmune or fibrotic disease is selected from the group consisting of ulcerative colitis, Celiac's disease, systemic lupus erythematosus (SLE) and Sjogren's syndrome.

The following diseases are linked to T-cell differentiation which as stated in the introduction, $CD4^+$ T-cell subsets Th17 and Th1 that are strongly associated with inflammatory diseases had the highest expression of MTHFD2 (Sun L. *et al.*, 2023; Witte K. *et al.*, 2023; Gaydosik AM. *et al.*, 2021; Karl F. *et al.*, 2021; Raphael I. *et al.*, 2020; Sabat R. *et al.*, 2019). Known MTHFD2 inhibitor DS18561882 greatly decreased the number of Th1 and Th17 cells differentiated *in vitro* from $CD4^+$ T-cells and expression of the respective Th1 and Th17 cytokines. Thus inhibiting MTHFD2 with the compounds of formula (I) which are superior to DS18561882, as shown in the biological example section, represents a strategy for treating the diseases listed below.

Suitably, the inflammatory, autoimmune or fibrotic disease is selected from the group consisting of asthma, atopic dermatitis, vitiligo, systemic sclerosis (SSC), graft versus host disease (GvHD), Type 1 diabetes and Hidradenitis suppurativa.

The following diseases are linked to fibrosis which shares a number of underlying disease mechanisms with inflammation and autoimmunity (Yanjie G. *et al.*, 2023; Hamanaka RB., *et al.*, 2022; Hiroshi F. *et al.*, 2021). Thus the compounds of formula (I) are expected to have utility in the treatment of the following diseases.

Suitably, the inflammatory, autoimmune or fibrotic disease is selected from the group consisting of idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD) and non-alcoholic steatohepatitis (NASH).

The following diseases may be treated using methotrexate, which as stated in the introduction, target enzymes on the one-carbon (1C) metabolism pathway, and has known utility in the treatment of cancer, in particular those listed below (Gong F. *et al.*, 2019; De Wilde V. *et al.*, 2016; Bergner N. *et al.*, 2012; Zhu JJ. *et al.*, 2009; Abrão R. *et al.*, 2008; Fahey JB. 2007; Meyers PA. *et al.*, 2005; Batchelor TT. *et al.*, 2003; Khan RB. *et al.*, 2002; Krailo M. *et al.*, 1987; Rizzoli V. *et al.*, 1985; Canello GP., *et al.*, 1981; Nilsson R. *et al.*, 2014). Since the compounds of the invention are expected to work in a similar yet superior way to methotrexate, it is expected that compounds of formula (I) will have utility in the treatment of the same diseases listed below. Furthermore, it is known that MTHFD2 knockdown in tumour cell lines is associated with an anti-proliferative effect (Zhu Z., *et al.*, 2020). Therefore inhibitors of MTHFD2, such as the compounds of formula (I), are expected to have utility in the treatment of cancer.

Suitably, the cancer is selected from the group consisting of acute lymphoblastic leukaemia (ALL), primary central nervous system lymphoma (PCNSL), lymphoma, mycosis fungoides, refectory non-Hodgkin lymphoma (NHL), head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), bladder cancer, lymphoma, breast cancer, osteoscarcoma, gestational trophoblastic neoplasia (GTN), acute myeloid leukaemia (AML), hepatocellular carcinoma, renal cell carcinoma, colorectal cancer, lung cancer, glioma, ovarian cancer, melanoma, and solid tumours such as cervical, uterine, testicular, stomach, prostate and pancreatic tumours.

Suitably, the cancer is selected from the group consisting of acute lymphoblastic leukaemia (ALL), primary central nervous system lymphoma (PCNSL), lymphoma, mycosis fungoides, refectory non-Hodgkin lymphoma (NHL) and acute myeloid leukaemia (AML).

References providing links between the diseases and MTHFD2 and/or MTHFD1 (D/C-d) are provided in the reference section and above.

Administration

The compound of formula (I) is usually administered as a pharmaceutical composition. Thus, in one embodiment, is provided a pharmaceutical composition comprising a compound of formula (I) and one or more pharmaceutically acceptable diluents or carriers. The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use as a medicament.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating or preventing a disease selected from the group consisting of inflammatory diseases, autoimmune diseases and cancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating a disease selected from the group consisting of inflammatory diseases, autoimmune diseases and cancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in preventing a disease selected from the group consisting of inflammatory diseases, autoimmune diseases and cancer.

The compound of formula (I) may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal, intrathecal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compound of formula (I) may be administered topically to the target organ e.g. topically to the eye, lung, nose or skin. Hence the invention provides a pharmaceutical composition comprising a compound of formula (I) optionally in combination with one or more topically acceptable diluents or carriers.

A compound of formula (I) which is active when given orally can be formulated as a liquid or solid, e.g. as a syrup, suspension, emulsion, tablet, capsule or lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound of formula (I) in a suitable liquid carrier(s). Suitably the carrier is non-aqueous e.g. polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the compound of formula (I) in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Aerosol dosage forms can also take the form of pump-atomisers.

Topical administration to the lung may be achieved by use of an aerosol formulation. Aerosol formulations typically comprise the active ingredient suspended or dissolved in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC).

Topical administration to the lung may also be achieved by use of a non-pressurised formulation such as an aqueous solution or suspension. These may be administered by means of a nebuliser e.g. one that can be hand-held and portable or for home or hospital use (i.e. non-portable). The formulation may comprise excipients such as water, buffers, tonicity adjusting agents, pH adjusting agents, surfactants and co-solvents.

Topical administration to the lung may also be achieved by use of a dry-powder formulation. The formulation will typically contain a topically acceptable diluent such as lactose, glucose or mannitol (preferably lactose).

The compound of the invention may also be administered rectally, for example in the form of suppositories or enemas, which include aqueous or oily solutions as well as suspensions and emulsions and foams. Such compositions are prepared following standard procedures, well known by those skilled in the art. For example, suppositories can be prepared by mixing the active ingredient with a conventional suppository base such as cocoa butter or other glycerides. In this case, the drug is mixed with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of the compound of the present invention will be about 0.0001 to less than 4.0% (w/w).

Preferably, for topical ocular administration, the compositions administered according to the present invention will be formulated as solutions, suspensions, emulsions and other dosage forms.

The compositions administered according to the present invention may also include various other ingredients, including, but not limited to, tonicity agents, buffers, surfactants, stabilizing polymer, preservatives, co-solvents and viscosity building agents. Suitable pharmaceutical compositions of the present invention include a compound of the invention formulated with a tonicity agent and

a buffer. The pharmaceutical compositions of the present invention may further optionally include a surfactant and/or a palliative agent and/or a stabilizing polymer.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, simple sugars such as dextrose, fructose, galactose, and/or simply polyols such as the sugar alcohols mannitol, sorbitol, xylitol, lactitol, isomaltitol, maltitol, and hydrogenated starch hydrolysates may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150-450 mOsm, preferably 250-350 mOsm and most preferably at approximately 290 mOsm). In general, the tonicity agents of the invention will be present in the range of 2 to 4% w/w. Preferred tonicity agents of the invention include the simple sugars or the sugar alcohols, such as D-mannitol.

An appropriate buffer system (e.g. sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably however, the buffer will be chosen to maintain a target pH within the range of pH 5 to 8, and more preferably to a target pH of pH 5 to 7.

Surfactants may optionally be employed to deliver higher concentrations of compound of the present invention. The surfactants function to solubilise the compound and stabilise colloid dispersion, such as micellar solution, microemulsion, emulsion and suspension. Examples of surfactants which may optionally be used include polysorbate, poloxamer, polyosyl 40 stearate, polyoxyl castor oil, tyloxapol, Triton, and sorbitan monolaurate. Preferred surfactants to be employed in the invention have a hydrophile/lipophile/balance “HLB” in the range of 12.4 to 13.2 and are acceptable for ophthalmic use, such as Triton™ X-114 and tyloxapol.

Additional agents that may be added to the ophthalmic compositions of compounds of the present invention are demulcents which function as a stabilising polymer. The stabilizing polymer should be an ionic/charged example with precedence for topical ocular use, more specifically, a polymer that carries negative charge on its surface that can exhibit a zeta-potential of (–)10–50 mV for physical stability and capable of making a dispersion in water (i.e. water soluble). A preferred stabilising polymer of the invention would be polyelectrolyte, or polyelectrolytes if more than one,

from the family of cross-linked polyacrylates, such as carbomers and Pemulen®, specifically Carbomer 974p (polyacrylic acid), at 0.1–0.5% w/w.

Other compounds may also be added to the ophthalmic compositions of the compound of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edentate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the compound of formula (I) is formulated with a carrier such as sugar and acacia, tragacanth, or gelatine and glycerine.

Compositions suitable for transdermal administration include ointments, gels and patches.

The composition may contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the compound of formula (I), depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05 mg to 1000mg, for example from 1.0 mg to 500 mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg of the compound of formula (I), depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100mg to 400 mg of the carrier, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide, suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 500 mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

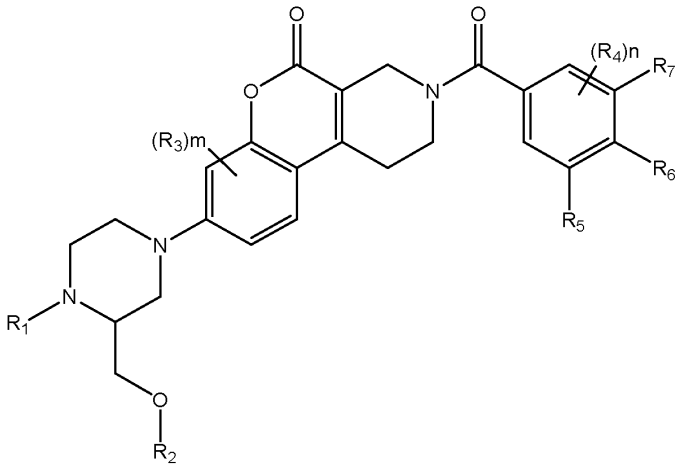
In one embodiment of the invention, the compound of formula (I) is used in combination with a further therapeutic agent or agents. When the compound of formula (I) is used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route. Alternatively, the compounds may be administered separately.

Compounds of formula (I) may display, or may be expected to have, one or more of the following desirable properties:

- inhibitory activity against MTHFD1 and MTHFD2;
- selective inhibitory activity against MTHFD2 over MTHFD1;
- no off-target effects such as against the α4β2 nicotinic receptor;
- improved suitability as a potential drug candidate;
- improved oral systemic bioavailability;
- good tolerability, for example, by limiting the side effects showed by other medication targeting broadly the 1C metabolism, such as MTX;
- low toxicity at the relevant therapeutic dose;
- distinct anti-inflammatory profiles;
- disease modifying effect.

The invention may be described by the following clauses:

Clause 1. A compound of formula (I):



(I):

wherein:

R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

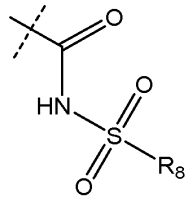
R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2;

and R_5, R_6 and R_7 are defined as follows:

(a) R_6 is  and R_7 is absent;

R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a} (for example R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a});

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

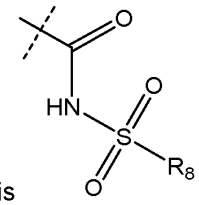
R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 (e.g. 4-8) membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 (e.g. 4-8) membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl (for example, R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl);

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or:

(b) R_7 is  : and

(i) R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a} (for example R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a});;

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(ii) R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a} (for example R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a});

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(iii) R_5 and R_6 join to form a 4-8 membered heterocyclic ring;

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 (e.g. 4-8) membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 (e.g. 4-8) membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein:

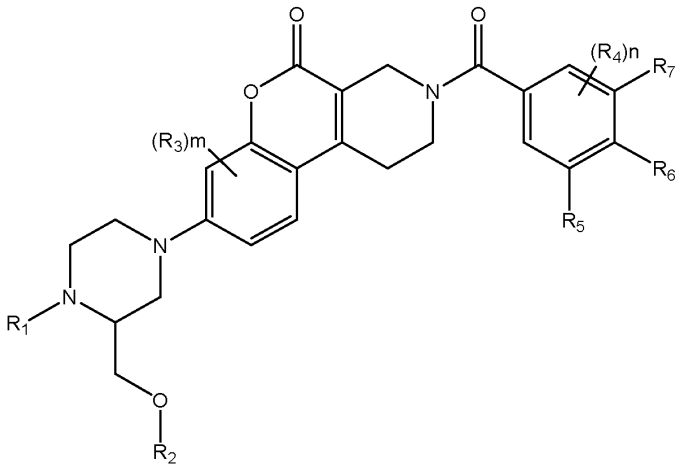
R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl (for example, R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl);

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

Clause 2. A compound of formula (I) according to clause 1:



(I):

wherein:

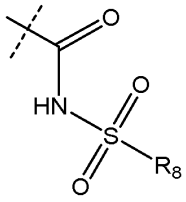
R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

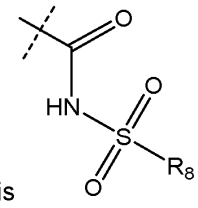
R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

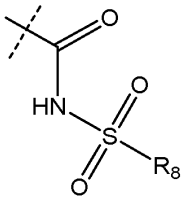
R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and 4-7 membered heterocycloalkyl;

R_6 is  and R_7 is absent; or

R_7 is  ;

wherein:

when R_6 is  and R_7 is absent:

R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

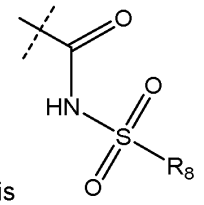
R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

or:

when R_7 is  :

R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 and R_6 join to form a 4-8 membered heterocyclic ring; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2;

or a pharmaceutically acceptable salt and/or solvate thereof.

Clause 3. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 or clause 2 wherein R_1 is C_{1-4} alkyl.

Clause 4. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 3 wherein R_1 is methyl.

Clause 5. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 or clause 2 wherein R_1 is C_{3-5} cycloalkyl.

Clause 6. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 5 wherein R_1 is cyclopropyl.

Clause 7. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 6 wherein R_2 is methyl.

Clause 8. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 or clause 2 wherein R_1 and R_2 join to form a 5-7 membered heterocycloalkyl.

Clause 9. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 8 wherein R_1 and R_2 join to form a 6 membered heterocycloalkyl.

Clause 10. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 9 wherein R_3 is C_{1-3} alkyl.

Clause 11. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 10 wherein R_3 is methyl.

Clause 12. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 9 wherein R_3 is halo.

Clause 13. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 12 wherein R_3 is chloro.

Clause 14. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 9 wherein m = 0.

Clause 15. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 13 wherein m = 1.

Clause 16. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 13 wherein m = 2.

Clause 17. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is C_{1-3} alkyl.

Clause 18. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 17 wherein R_4 is methyl.

Clause 19. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is halo.

Clause 20. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 19 wherein R_4 is selected from the group consisting of chloro and fluoro, such as fluoro.

Clause 21. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is C_{1-3} haloalkyl.

Clause 22. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 21 wherein R_4 is trifluoromethyl.

Clause 23. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is C_{1-3} alkoxy.

Clause 24. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 23 wherein R_4 is methoxy.

Clause 25. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is C_{1-3} haloalkoxy.

Clause 26. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is 4-7 membered heterocycloalkyl.

Clause 27. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 26 wherein R_4 is pyrrolidinyl.

Clause 28. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein R_4 is $NR_{4a}R_{4b}$.

Clause 29. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 28 wherein R_{4a} is H.

Clause 30. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 28 wherein R_{4a} is $C_{1\text{-}3}$ alkyl, such as methyl.

Clause 31. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 28 wherein R_{4b} is H.

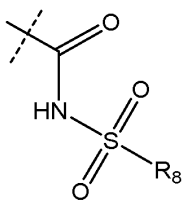
Clause 32. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 28 wherein R_{4b} is $C_{1\text{-}3}$ alkyl, such as methyl.

Clause 33. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 16 wherein n is 0.

Clause 34. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 32 wherein n is 1.

Clause 35. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 32wherein n is 2.

Clause 36. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 35 wherein:

R_6 is  and R_7 is absent.

Clause 37. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is H.

Clause 38. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is halo.

Clause 39. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 38 wherein R_5 is chloro.

Clause 40. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is C_{1-3}alkyl, such as methyl or ethyl.

Clause 41. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is C_{1-3} alkoxy, such as methoxy or ethoxy, e.g. methoxy.

Clause 42. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is C_{1-3} haloalkoxy.

Clause 43. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is SC_{1-3} alkyl.

Clause 44. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is SC_{1-3} haloalkyl.

Clause 45. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is OC_{3-10} cycloalkyl.

Clause 46. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 45 wherein R_5 is selected from the group consisting of cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, bicyclo[3.1.0]hexyloxy and 2-adamantanyloxy.

Clause 47. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is 4-7 membered heterocycloalkyl.

Clause 48. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 47 wherein R_5 is selected from the group consisting of pyrrolidinyl, piperidinyl, 3-azabicyclo[3.1.0]hexyl, 2-azabicyclo(2.2.1)heptyl and 7-azanorbornanyl.

Clause 49. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 45 to 48 wherein R_5 is unsubstituted.

Clause 50. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 45 to 48 wherein R_5 is substituted by one or more (such as one, two or three, e.g. one) R_{5a}.

Clause 51. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 50 wherein R_{5a} is halo.

Clause 52. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 51 wherein R_{5a} is fluoro.

Clause 53. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 50 wherein R_{5a} is C_{1-3} alkyl.

Clause 54. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 53 wherein R_{5a} is methyl.

Clause 55. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 50 wherein R_5 is substituted by one methyl group.

Clause 56. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 50 wherein R_5 is substituted by two R_{5a} groups selected from the group consisting of methyl and fluoro.

Clause 57. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 50 wherein two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl ring such as a C_3 cycloalkyl ring.

Clause 58. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 36 wherein R_5 is $NR_{5b}R_{5c}$.

Clause 59. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 58 wherein R_{5b} is H.

Clause 60. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 58 wherein R_{5b} is C_{1-3} alkyl.

Clause 61. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 60 wherein R_{5b} is methyl.

Clause 62. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 58 to 61 wherein R_{5c} is C_{1-3} alkyl.

Clause 63. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 62 wherein R_{5c} is selected from the group consisting of methyl and isopropyl.

Clause 64. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 58 to 61 wherein R_{5c} is C_{3-6} cycloalkyl.

Clause 65. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 64 wherein R_8 is C_{3-6} cycloalkyl.

Clause 66. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 65 wherein R_8 is cyclopropyl.

Clause 67. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 64 wherein R_8 is 4-10 (e.g. 4-8) membered heterocycloalkyl.

Clause 68. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 67 wherein R_8 is selected from the group consisting of pyrrolidinyl (e.g. pyrrolidin-1-yl) , piperidinyl (e.g. piperidin-1-yl), 7-azanorbornanyl, 3-azabicyclo[3.1.0]hexyl (e.g. 3-azabicyclo[3.1.0]hexan-3-yl) , 6-azaspiro[2.5]octyl (e.g. 6-azaspiro[2.5]octan-6-yl) and 3-oxa-6-azabicyclo[3.2.1]octyl (e.g. 3-oxa-8-azabicyclo[3.2.1]octan-8-yl), 7-azabicyclo[2.2.1]heptan-7-yl, (3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl, octahydro-2*H*-isoindol-2-yl, 2-

azaspiro[3.3]heptan-2-yl, (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl), 2-azabicyclo[2.2.1]heptan-2-yl) and 8-azabicyclo[3.2.1]octan-8-yl and for example is selected from the group consisting of pyrrolidinyl (e.g. pyrrolidin-1-yl), piperidinyl (e.g. piperidin-1-yl), 7-azanorbornanyl, 3-azabicyclo[3.1.0]hexyl (e.g. 3-azabicyclo[3.1.0]hexan-3-yl), 6-azaspiro[2.5]octyl (e.g. 6-azaspiro[2.5]octan-6-yl) and 3-oxa-6-azabicyclo[3.2.1]octyl (e.g. 3-oxa-8-azabicyclo[3.2.1]octan-8-yl),.

Clause 69. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 65 to 68 wherein R_8 is unsubstituted.

Clause 70. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 65 to 68 wherein R_8 is substituted by one or more (such as one, two or three, e.g. one) R_{8a} groups.

Clause 71. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 70 wherein R_{8a} is C_{1-3} alkyl.

Clause 72. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 71 wherein R_{8a} is methyl.

Clause 73. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 70 wherein R_{8a} is halo.

Clause 74. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 70 wherein R_{8a} is C_{1-3} haloalkyl.

Clause 75. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 70 wherein R_8 is substituted by two methyl groups.

Clause 76. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 64 wherein R_8 is $N(C_{1-3}\ alkyl)_2$.

Clause 77. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 76 wherein R_8 is selected from the group consisting of $N(CH_3)_2$ and $N(CH_3)(CH(CH_3)_2)$.

Clause 78. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 64 wherein R_8 is $NR_{8b}R_{8c}$.

Clause 79. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8b} is H.

Clause 80. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8b} is C_{1-3} alkyl, such as methyl.

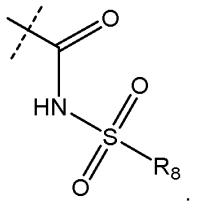
Clause 81. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8b} is C_{3-6} cycloalkyl, such as cyclopropyl or cyclopentyl.

Clause 82. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8c} is H.

Clause 83. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8c} is C_{1-3} alkyl, such as methyl.

Clause 84. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 78 wherein R_{8c} is C_{3-6} cycloalkyl, such as cyclopropyl or cyclopentyl.

Clause 85. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 43 wherein:

R_7 is 

.

Clause 86. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 85 wherein:

R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;
R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and
R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

Clause 87. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 85 wherein:

R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,
R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and
R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

Clause 88. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is H.

Clause 89. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is halo.

Clause 90. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is C_{1-3}alkyl, such as methyl or ethyl.

Clause 91. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is C_{1-3} alkoxy.

Clause 92. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is C_{1-3} haloalkoxy.

Clause 93. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is SC_{1-3} alkyl.

Clause 94. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is SC_{1-3} haloalkyl.

Clause 95. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is OC_{3-10} cycloalkyl.

Clause 96. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 95 wherein R_5 is cyclobutyloxy.

Clause 97 The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is 4-7 membered heterocycloalkyl.

Clause 98. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 95 to 96 wherein R_5 is unsubstituted.

Clause 99. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 95 to 97 wherein R_5 is substituted by one or more (such as one, two or three e.g. one) R_{5a}.

Clause 100. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 99 wherein R_{5a} is halo.

Clause 101. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 99 wherein R_{5a} is C_{1-3} alkyl.

Clause 102. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 99 wherein two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring.

Clause 103. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 86 or clause 87 wherein R_5 is $NR_{5b}R_{5c}$.

Clause 104. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 103 wherein R_{5b} is H.

Clause 105. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 103 wherein R_{5b} is C_{1-3} alkyl.

Clause 106. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 103 to 105 wherein R_{5c} is C_{1-3} alkyl.

Clause 107. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 103 to 105 wherein R_{5c} is C_{3-6} cycloalkyl.

Clause 108. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 85 wherein:

R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

Clause 109. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 85 wherein:

R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl.

Clause 110. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is H.

Clause 111. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is halo.

Clause 112. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 107 wherein R_6 is C_{1-3}alkyl, such as methyl or ethyl.

Clause 113. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is C_{1-3} alkoxy.

Clause 114. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is C_{1-3} haloalkoxy.

Clause 115. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is SC_{1-3} alkyl.

Clause 116. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is SC_{1-3} haloalkyl.

Clause 117. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is OC_{3-10} cycloalkyl.

Clause 118. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 117 wherein R_6 is cyclobutyloxy.

Clause 119. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is 4-7 membered heterocycloalkyl.

Clause 120. The compound or a pharmaceutically acceptable salt and/or solvate thereof accordingly to clause 119 wherein R_6 is pyrrolidinyl.

Clause 121. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 117 to 120 wherein R_6 is unsubstituted.

Clause 122. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 117to 120 wherein R_6 is substituted by one or more (such as one, two or three e.g. one) R_{6a}.

Clause 123. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 122 wherein R_{6a} is halo.

Clause 124. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 122 wherein R_{6a} is C_{1-3} alkyl.

Clause 125. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 122 wherein two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring.

Clause 126. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 108 or clause 109 wherein R_6 is $NR_{6b}R_{6c}$.

Clause 127. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 126 wherein R_{6b} is H.

Clause 128. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 126 wherein R_{6b} is C_{1-3} alkyl.

Clause 129. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 126 to 128 wherein R_{6c} is C_{1-3} alkyl.

Clause 130. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 126 to 128 wherein R_{6c} is C_{3-6} cycloalkyl.

Clause 131. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 85 wherein R_5 and R_6 join to form a 4-8 membered heterocyclic ring.

Clause 132. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 131 wherein R_5 and R_6 join to form an 8 membered heterocyclic ring.

Clause 133. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 132 wherein R_5 and R_6 join to form a 5,8-dioxaspiro[3.4]octanyl ring.

Clause 134. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 35 and 85 to 133 wherein R_8 is C_{3-6} cycloalkyl.

Clause 135. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 35 and 85 to 133 wherein R_8 is 4-8 membered heterocycloalkyl.

Clause 136. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 135 wherein R_8 is pyrrolidinyl.

Clause 137. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 134 to 136 wherein R_8 is unsubstituted.

Clause 138. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 134 to 136 wherein R_8 is substituted by one or more (such as one, two or three, e.g. one) R_{8a}.

Clause 139 The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 138 wherein R_{8a} is C_{1-3} alkyl.

Clause 140. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 138 wherein R_{8a} is halo.

Clause 141. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 138 wherein R_{8a} is C_{1-3} haloalkyl.

Clause 142. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 35 and 85 to 133 wherein R_8 is $N(C_{1-3}$ alkyl$)_2$.

Clause 143. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 35 and 85 to 133 wherein R_8 is $NR_{8b}R_{8c}$.

Clause 144. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8b} is H.

Clause 145. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8b} is C_{1-3} alkyl, such as methyl.

Clause 146. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8b} is C_{3-6} cycloalkyl, such as cyclopropyl or cyclopentyl.

Clause 147. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8c} is H.

Clause 148. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8c} is C_{1-3} alkyl, such as methyl.

Clause 149. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 143 wherein R_{8c} is C_{3-6} cycloalkyl, such as cyclopropyl or cyclopentyl.

Clause 150. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 149 wherein R_4 is 4-7 membered heterocycloalkyl and is attached via a nitrogen atom.

Clause 151. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 150 wherein R_5 is 4-7 membered heterocycloalkyl and is attached via a nitrogen atom.

Clause 152. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 151 wherein R_6 is 4-7 membered heterocycloalkyl and is attached via a nitrogen atom.

Clause 153. The compound or a pharmaceutically acceptable salt and/or solvate thereof according any one of clauses 1 to 152 wherein R_8 is 4-8 membered heterocycloalkyl and is attached via a nitrogen atom.

Clause 154. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 which is selected from the list consisting of:

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

(R)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

(*R*)-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopropyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopropyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-((4,4-difluorocyclohexyl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-((4,4-difluorocyclohexyl)oxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(azetidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(azetidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-((adamantan-2-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-((4,4-difluorocyclohexyl)oxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

N-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide;

N-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methyl-6-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(95 yrrolidine-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(2-azabicyclo[2.2.1]heptan-2-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(2-azabicyclo[2.2.1]heptan-2-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(5-azaspiro[2.5]octan-5-yl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

(*S*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(3-(ethoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-*2H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-5-(trifluoromethyl)benzamide;
(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;
(*R*)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;
(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-5-(trifluoromethyl)benzamide;

(*R*)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-6-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-4-carboxamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-2-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-cyclobutoxy-*N*-(((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)sulfonyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methyl-N-((1-methylcyclopropyl)sulfonyl)benzamide;

(R)-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-7-carboxamide;
(R)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((1-methylcyclopropyl)sulfonyl)-5-(trifluoromethyl)benzamide;
(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(trifluoromethoxy)benzamide;
(*R*)-2-chloro-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-2-cyclobutoxy-3-fluoro-4-(8-(4-isopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-2-(difluoromethoxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-2-cyclobutoxy-4-(8-(4-ethyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(4-cyclopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(S)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide; and
(*S*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

Clause 155. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 which is selected from the list consisting of:
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(isopropoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-(azetidin-1-yl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-amino-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;
(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;
(*R*)-*N*-(*N*-cyclopentyl-*N*-methylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-(cyclobutyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(methylamino)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(azetidin-1-yl)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-3-fluoro-N-((4-fluoropiperidin-1-yl)sulfonyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-propoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(2,2,2-trifluoroethoxy)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide;
(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide

N-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((octahydro-2*H*-isoindol-2-yl)sulfonyl)benzamide;

(*R*)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide;

(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((3,3-dimethylpyrrolidin-1-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(3,3,3-trifluoropropoxy)benzamide;

(*R*)-3-ethoxy-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((2-azabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-ethoxy-3-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-(N-cyclopentyl-N-methylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;

(*R*)-3-fluoro-N-((4-fluoropiperidin-1-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methylbenzamide;

(*R*)-5-(dimethylamino)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethyl-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-ethoxy-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-(methoxy-d3)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(dimethylamino)-5-fluoro-N-(((S)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*-cyclopropyl-N-methylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide;

2-ethoxy-5-fluoro-*N*-(((*R*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-fluoro-5-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-(((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-ethoxy-5-fluoro-*N*-(((*S*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*-cyclopropyl-*N*-methylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide; and

(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

Clause 156. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to clause 1 which is selected from the list consisting of:
(R)-N-((2-oxa-5-azaspiro[3.5]nonan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-N-((2-oxa-6-azaspiro[3.5]nonan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
R)-N-((2-oxa-6-azaspiro[3.4]octan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-N-((5-azaspiro[2.4]heptan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(piperidin-1-ylsulfonyl)benzamide;
(R)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide;
4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;
(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-3-methoxypiperidin-1-yl)sulfonyl)benzamide;

(R)-N-((2-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-3-methoxypiperidin-1-yl)sulfonyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-methoxypiperidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-5-chloro-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-N-(N,N-dimethylsulfamoyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide;

N-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-5-fluoro-2-methoxybenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-ethoxy-5-fluorobenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-N-((1-methylcyclopropyl)sulfonyl)benzamide;

(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;

N-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-N-(N,N-dimethylsulfamoyl)-5-fluorobenzamide;
N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-5-fluorobenzamide;
(R)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methyl-N-(pyrrolidin-1-ylsulfonyl)benzamide;
2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;
2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;
N-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;

(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxybenzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide;

(R)-5-chloro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-chloro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-chloro-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide; and
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

Clause 157. The pharmaceutically acceptable salt according to any one of clauses 1 to 156.

Clause 158. The pharmaceutically acceptable solvate according to any one of clauses 1 to 156.

Clause 159. The compound according to any one of clauses 1 to 156.

Clause 160. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 159 and one or more pharmaceutically acceptable diluents or carriers.

Clause 161. A compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 159 or a pharmaceutical composition according to clause 133 for use as a medicament.

Clause 162. A compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of clauses 1 to 159 or a pharmaceutical composition according to clause 158 for use in the treatment or prevention of a disease selected from the group consisting of inflammatory, autoimmune or fibrotic diseases, and cancer.

Clause 163. Use of a compound or salt and/or solvate thereof according to any one of clauses 1 to 159 or a pharmaceutical composition according to clause 160 in the manufacture of a medicament for treating or preventing a disease selected from inflammatory, autoimmune and fibrotic diseases, and cancer.

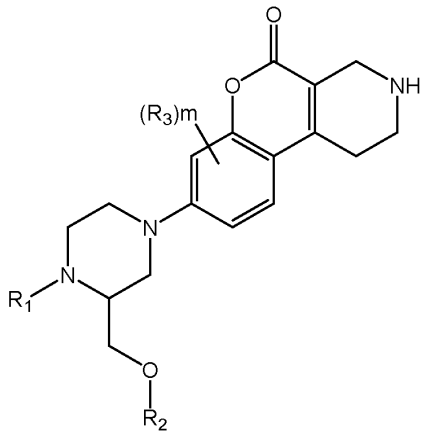
Clause 164. A method of treating or preventing a disease selected from inflammatory, autoimmune and fibrotic diseases, and cancer, which comprises administering a compound or salt and/or solvate thereof according to any one of clauses 1 to 159 or a pharmaceutical composition according to clause 160.

Clause 165. The compound for use, composition for use, use or method according to any one of clauses 162 to 164 wherein the inflammatory, autoimmune or fibrotic disease is selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, myasthenia gravis (MG), Crohn's disease, multiple sclerosis, sarcoidosis, ulcerative colitis, Celiac's disease, systemic lupus erythematosus (SLE), Sjogren's syndrome, asthma, atopic dermatitis, vitiligo, systemic sclerosis (SSC), graft versus host disease (GvHD), Type 1 diabetes, Hidradenitis suppurativa, idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD) and non-alcoholic steatohepatitis (NASH).

Clause 166. The compound for use, composition for use, use or method according to any one of clauses 162 to 164 wherein the cancer is selected from the group consisting of acute lymphoblastic leukaemia (ALL), primary central nervous system lymphoma (PCNSL), lymphoma, mycosis fungoides, refectory non-Hodgkin lymphoma (NHL), head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), bladder cancer, lymphoma, breast cancer, osteoscarcoma, gestational trophoblastic neoplasia (GTN), acute myeloid leukaemia (AML), hepatocellular carcinoma, renal cell carcinoma, colorectal cancer, lung cancer, glioma, ovarian cancer, melanoma, and solid tumours such as cervical, uterine, testicular, stomach, prostate and pancreatic tumours.

Clause 167. The compound for use, composition for use, use or method according to clause 166 wherein the cancer is selected from the group consisting of acute lymphoblastic leukaemia (ALL), primary central nervous system lymphoma (PCNSL), lymphoma, mycosis fungoides, refectory non-Hodgkin lymphoma (NHL) and acute myeloid leukaemia (AML).

Clause 168. A process for preparing a compound of formula (I), or a salt such as a pharmaceutical acceptable salt thereof, which comprises coupling a compound of formula (II):

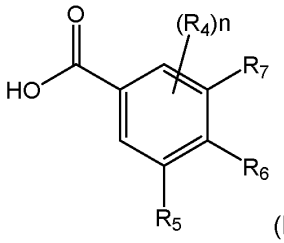


(II)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3 and m are as defined in any one of clauses 1 to 156;

with a compound of formula (III):

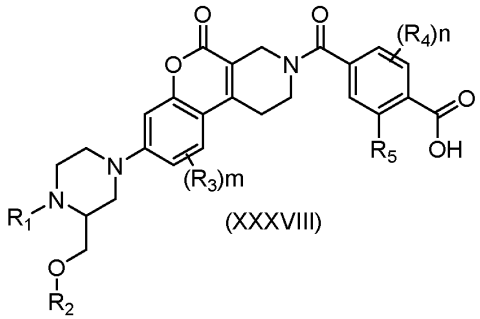


(III)

or a salt and/or solvate thereof;

wherein R_4, R_5, R_6, R_7 and n are as defined in any one of clauses 1 to 156.

Clause 169. A process for preparing a compound of formula (I), or a salt such as a pharmaceutical acceptable salt thereof, in which R_7 is absent which comprises coupling a compound of formula (XXXVIII):

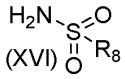


(XXXVIII)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, R_8, n and m are defined in any one of clauses 1 to 156;

with a compound of formula (XVI):

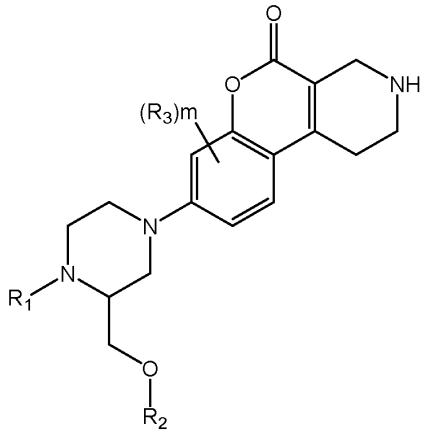


(XVI)

or a salt and/or solvate thereof;

wherein R_8 is defined in any in any one of clauses 1 to 156.

Clause 170. A compound of formula (II):

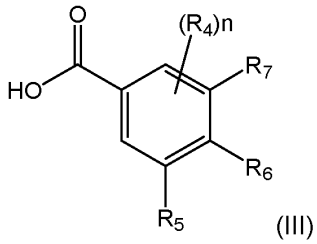


(II)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3 and m are as defined in any one of clauses 1 to 156.

Clause 171. A compound of formula (III):

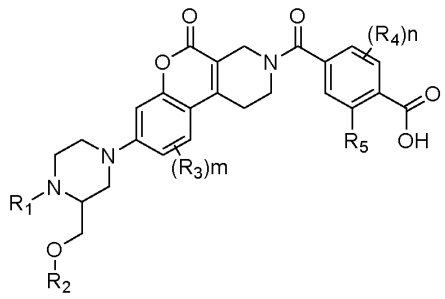


(III)

or a salt and/or solvate thereof;

wherein R_4, R_5, R_6, R_7 and n are as defined in any one of clauses 1 to 156, such as R_5 is an O-linked group such as C_{1-3} alkoxy, C_{1-3} haloalkoxy or OC_{3-10} cycloalkyl, or an N-linked group such as $NR_{5b}R_{5c}$ or N-linked 4-7 membered heterocycloalkyl.

Clause 172. A compound of formula (XXXVIII):

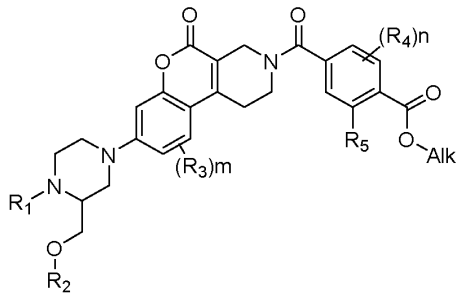


(XXXVIII)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of clauses 1 to 156.

Clause 173. A compound of formula (XXXIX):

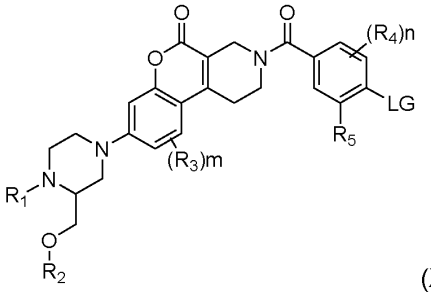


(XXXIX)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of clauses 1 to 156, and Alk is C_{1-4}alkyl.

Clause 174. A compound of formula (XXXXI):



(XXXXI)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of clauses 1 to 156, and LG is a leaving group such as halo e.g. bromo.

Abbreviations

°C	degrees centigrade
Ac	acetyl
AcOH	acetic acid
ACN	acetonitrile
AO/PI	acridine orange/propidium iodide stain
app	apparent
aq.	aqueous
br s	broad singlet
BINAP	(±)-(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Boc_2O	di-*tert*-butyldicarbonate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
ca.	circa
Cbz	(benzyloxy)carbonyl
CbzCl	benzyl chloroformate
CDI	1,1'-carbonyl diimidazole
CFSE	carboxyfluorescein succinimidyl ester
conc.	concentrated
cRPMI	complete Roswell Park Memorial Institute media
d	doublet
DAD	diode array detector
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
dFBS	dialysed fetal bovine serum
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethene
DIPEA	*N*,*N*-diisopropylethylamine
DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d6	deuterated dimethyl sulfoxide
DIPEA	*N*,*N*-diisopropylethylamine

dPBS	Dulbecco's phosphate buffered saline
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
ES^+	electrospray
FA	formic acid
FBS	fetal bovine serum
g	gram(s)
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HPLC	high-performance liquid chromatography
LDA	lithium diisopropylamide
LCMS	liquid chromatography–mass spectrometry
m	multiplet
M	molar concentration / molar mass
Me	methyl
m/z	mass to charge ratio
MeCN	acetonitrile
MeOH	methanol
MHz	(mega)hertz
min(s)	minute(s)
mL	millilitres
mmol/mM	millimole
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
$Na(Ac)_3BH$	sodium triacetoxyborohydride
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nM	nanomolar
NMM	4-methylmorpholine
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
p	quintet

PBS	phosphate buffered saline
PDA	photodiode array
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PEI	polyethylenimine
PMB	*para*-methoxybenzyl
PenStrep	mixture of penicillin G and streptomycin
PPh_3	triphenylphosphine
q	quartet
RPMI	Roswell Park Memorial Institute media
rpm	revolutions per minute
RT	room temperature
s	singlet
sat.	saturated
t	triplet
tBu_3PHBF_4	Tri-*tert*-butylphosphonium tetrafluoroborate
t-BuXPhos	2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl
^{t}BuOH	*tert*-butanol
TBTU	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TEA	triethylamine
Tf_2O	trifluoromethanesulfonic anhydride
Tf	trifluoromethanesulfonyl, i.e., CF_3SO_2-
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Tris	tris(hydroxymethyl)aminomethane hydrochloride
µL	microlitre
µM	micromolar
UPLC	ultra performance liquid chromatography
wt	weight
x g	times gravity
$ZnEt_2$	diethylzinc

EXAMPLES

Analytical Equipment

Thin layer chromatography (TLC) was performed on silica gel plates (GF254, glass, silica gel size: 400~600 mesh). Spots were visualized by UV light (214 and 254 nm) or colour reagents (iodine, $KMnO_4$ aq.). All evaporations were carried out in vacuo with a rotary evaporator.

Purification by column and flash chromatography was carried out using silica gel (200-300 mesh). Solvent systems are reported as mixtures by volume. NMR spectra were recorded on Bruker 400 MHz Avance III spectrometer fitted with a BBFO 5 mm probe, a Bruker 500 MHz Avance III HD spectrometer equipped with a Bruker 5 mm SmartProbeTM, or Jeol ECS400 at rt. ^1H chemical shifts are reported in δ values in ppm with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration.

LCMS/HPLC Instrument Details				
System	**Instrument Name**	**LC Detector**	**ELS detector**	**Mass detector**
1 (basic)	Agilent LCMS 1200	G1315D DAD	380 ELSD	Agilent G6120B
2 (acidic)	Agilent LCMS 1200	G1315C DAD	380 ELSD	Agilent G6110A
3 (acid and basic)	Waters Acquity UPLC	Waters Acquity PDA	N/A	Waters Acquity QDa

LCMS/HPLC Method Details							
Method Name	**Solvent System**	**Column**	**Gradient**	**UV range**	**Mass Range**	**Column Temp. °C**	**Flow Rate ml/min**
A (basic LCMS)	**A)** water + 10 mM NH_4HCO_3 **B)** acetonitrile	Waters X-Bridge C18 (3.5 µm, 50mm x 4.6 mm)	From 95:5 to 0:100 in 1.6 min, 0:100 for 1.4 min, from 0:100 to 95:5 in 0.1 min, 95:5 for 0.7 min.	190-400 nm	100-1800 amu	40	2.0
B (acidic LCMS)	**A)** water + 0.05% TFA] **B)** acetonitrile + 0.05% TFA	Waters X-Bridge C18 (3.5 µm, 50 mm x 4.6 mm)	From 95:5 to 0:100 in 1.6 min, 0:100 for 1.4 min, from 0:100 to 95:5 in 0.05 min, 95:5 for 0.7 min	190-400 nm	100-1100 amu	40	2.0
C (acidic LCMS)	**A)** water + 0.05% TFA] **B)** acetonitrile + 0.05% TFA	Halo C18 (2.7 µm, 30 mm x 4.6 mm)	From 95:5 to 0:100 in 0.8 min, 0:100 for 0.4 min, from 0:100 to 95:5 in 0.01 min, 95:5 for 0.2 min	190-400 nm	100-1100 amu	40	3.0
D (basic HPLC)	**A)** water + 10 mM NH_4HCO_3 **B)** acetonitrile	Waters X-Bridge C18 (3.5 µm, 150 mm x 4.6 mm)	From 95:5 to 0:100 in 10 min, 0:100 for 5 min, from 0:100 to 95:5 in 0.1 min, 95:5 for 5 min.	190-400 nm	100-1800 amu	40	1.0
E (acidic HPLC)	**A)** water + 0.05% TFA			190-400 nm	100-1100 amu	40	1.0

	B) acetonitrile + 0.05% TFA	L-column2 ODS (5.0 µm, 150mm x 4.6 mm)	From 95:5 to 0:100 in 10 min, 0:100 for 5 min, from 0:100 to 95:5 in 0.1 min, 95:5 for 5 min				
F (basic LCMS)	**A)** water + 10 mM NH_4HCO_3 **B)** acetonitrile	Waters X-Bridge C18 (2.6 µm, 50mm x 4.6 mm)	From 95:5 to 0:100 in 1.75 min, 0:100 for 0.8 min, from 0:100 to 95:5 in 0.1 min, 95:5 for 0.1 min.	190-400 nm	100-1000 amu	40	2.3
G (basic LCMS)	**A)** water + 10 mM NH_4HCO_3	Waters X-Bridge C18 (3.5 µm, 30mm x 4.6 mm)	From 95:5 to 5:95 in 1.00 min, 5:95 for 0.35 min, from 5:95 to 95:5 in 0.10 min, 95:5 for 0.05 min.	190-400 nm	100-1000 amu	40	3.0
H (basic LCMS)	**A)** water + 10 mM NH_4HCO_3 **B)** acetonitrile	Phenomenex Kinetex EVO (2.6 µm, 30 x 4.6mm)	From 95:5 to 5:95 in 1.00 min, 5:95 for 0.35 min, from 5:95 to 95:5 in 0.10 min, 95:5 for 0.05 min.	190-400 nm	100-1000 amu	40	3.0
I (basic LCMS)	**A)** NH_4HCO_3 10 mM aq. (pH 9, adjusted with NH_3) **B)** acetonitrile	Waters BEH C18 (50 x 2.1 mm, 1.7 µm)	95:5 for 0.05 min, 95:5 to 5:95 in 1.55 min, 5:95 for 0.65 min	210-400 nm	120-1000 amu	50	0.6
J (acidic LCMS)	**A)** water + 0.1% FA **B)** acetonitrile	Waters BEH C18 (50 x 2.1 mm, 1.7 µm)	95:5 for 0.05 min, 95:5 to 5:95 in 1.55 min, 5:95 for 0.65 min	210-400 nm	120-1000 amu	50	0.6
K (basic LCMS)	**A)** NH_4HCO_3 10 mM aq. (pH 9, adjusted with NH_3)	Waters Acquity CSH C18 (1.7	From 95:5 for to 5:95 in 6.5 min, 5:95 for 2.5 min.	210-400 nm	120-1250	50	0.35

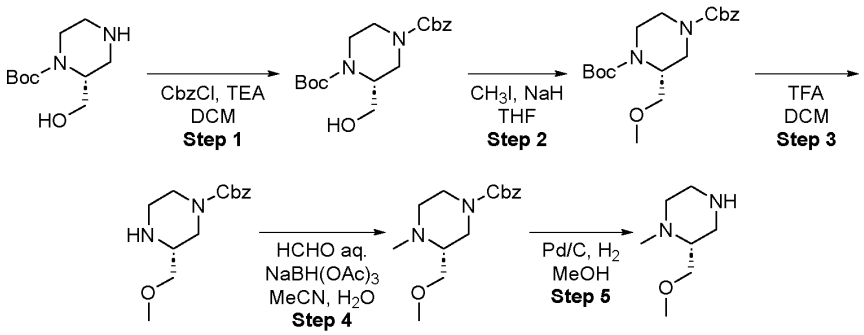
L (acidic LCMS)	**A)** water + 0.1% FA	Waters Acquity CSH C18 (1.7 µm, 100 x 2.1 mm)	From 95:5 for to 5:95 in 6.5 min, 5:95 for 2.5 min.	210-400 nm	120-1250	50	0.35
	B) acetonitrile						

Commercial Materials

All starting materials are commercially available unless otherwise stated.

Synthesis of Intermediates

Intermediate 1: (*R*)-2-(methoxymethyl)-1-methylpiperazine



Step 1

Benzylchloroformate (47.4 g, 277 mmol) was added dropwise to a solution of (*R*)-*tert*-butyl 2-(hydroxymethyl)piperazine-1-carboxylate (50.0 g, 231 mmol) and TEA (56.0 g, 555 mmol) in DCM (1.1 L) at 0 °C. The mixture was stirred at RT for 3 h. Ice water (800 mL) was added and the mixture was extracted with DCM (3x1 L). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20-50% EtOAc/petroleum ether) to afford (*R*)-4-benzyl 1-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (72.0 g, 205 mmol) as a colourless oil. LCMS (System 1, Method F) Rt = 1.59 min, m/z 251.0 $(M-100+H)^+$, 295 $(M-56+H)^+$ (ES^+).^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.38-7.29 (m, 5H), 5.15 (br s, 2H), 4.17-4.08 (m, 2H), 4.00 (s, 1H), 3.86-3.83 (m, 1H), 3.57 (m, 2H), 2.99 (m, 3H), 1.48-1.41 (s, 9H).

Step 2

Sodium hydride (60% dispersion in mineral oil, 16.4 g, 411 mmol) was added in small portions to a solution of (*R*)-4-benzyl 1-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (72.0 g, 205 mmol) in THF (822 mL) at -10 °C. The mixture was stirred at this temperature for 30 min, iodomethane (64.2 g, 452 mmol) was added and the reaction was stirred for 2 h at -10 °C. The mixture was poured into NH_4Cl aq. sat. (500 mL), and the mixture was extracted with MTBE (3x800 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20-30% MTBE/petroleum ether) to afford (*R*)-4-benzyl 1-*tert*-butyl 2-(methoxymethyl)piperazine-1,4-dicarboxylate (41.0 g, 113 mmol) as a pale-yellow oil. LCMS (System 1, Method F) Rt = 1.77 min, m/z 309.0 $(M-56+H)^+$ (ES^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.35-7.27 (m, 5H), 5.19-5.09 (m, 2H), 4.19-3.85 (m, 4H), 3.39-3.26 (m, 5H), 3.04-2.94 (m, 3H), 1.49-1.29 (s, 9H).

Step 3

To a solution of (*R*)-4-benzyl 1-*tert*-butyl 2-(methoxymethyl)piperazine-1,4-dicarboxylate (41.0 g, 113 mmol) in DCM (500 mL) was added TFA (100 mL) at RT. The reaction mixture was stirred at RT for 4 h. TFA was evaporated and the residue was partitioned between DCM (500 mL) and $NaHCO_3$ aq. sat. (300 mL). The aqueous layer was extracted with DCM (2x500 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (*R*)-benzyl 3-(methoxymethyl)piperazine-1-carboxylate (29.0 g, 110 mmol) as a yellow oil. LCMS (System 1, Method F) Rt = 1.33 min, m/z 265.2 $(M+H)^+$ (ES^+).

Step 4

To a solution of (*R*)-benzyl 3-(methoxymethyl)piperazine-1-carboxylate (29.0 g, 110 mmol) in ACN (400 mL) and water (133 mL) was added formaldehyde aq. (37%, 27.8 g, 340 mmol), the mixture was stirred at RT for 2 h. Sodium triacetoxyborohydride (46.5 g, 219 mmol) was added at 0 °C, and the mixture was stirred at RT overnight. The pH of the mixture was taken to 8 by adding $NaHCO_3$ aq. sat., ACN was evaporated under reduced pressure and the resulting aqueous solution was extracted with DCM (3x400 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford (*R*)-benzyl 3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (27.0 g, 97 mmol) as a yellow oil. LCMS (System 1, Method F) Rt = 1.45 min, m/z 279.2 $(M+H)^+$ (ES^+).

Step 5

Pd/C (10%, 2.70 g) was added to a solution of (*R*)-benzyl 3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (27.0 g, 97.0 mmol) in MeOH (750 mL), and the mixture was stirred at RT overnight under H_2. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to afford (*R*)-2-(methoxymethyl)-1-methylpiperazine (14 g, 97.0 mmol) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ: 3.44 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.45-3.41 (m, 4H), 2.96-2.85 (m, 2H), 2.72-2.63 (m, 2H), 2.48-2.42 (m, 1H), 2.18-2.09 (m, 5H).

Alternative procedure:

Step 1

Five batches were carried out in parallel: 4 x 1.49 kg and a 1.0 kg.

To a solution of tert-butyl (R)-3-(hydroxymethyl)piperazine-1-carboxylate (1.49 kg, 6.89 mol, 1.0 eq) in THF (14.9 L) was added portionwise NaH (303 g, 7.58 mol, 60%, 1.1 eq) at 20 °C. The mixture was stirred at 20 °C for 0.5 h. Methyl iodide (1.08 kg, 7.58 mol, 472 mL, 1.1 eq) was added dropwise into the mixture at 20-30 °C. The mixture was stirred at 20 °C for 0.5 h. More NaH (386 g, 9.65 mol, 60%, 1.4 eq) was slowly added into the mixture at 20 °C, the mixture was stirred at 20-30 °C for 0.5 hr. More methyl iodide (1.37 kg, 9.65 mol, 600 mL, 1.4 eq) was added dropwise to the mixture at 20 °C. The resulting mixture was stirred at 20 °C for 12 h. The reaction mixture was quenched by addition sat. aq. NH_4Cl (1.49 L) at 0 °C, diluted with more sat. aq. NH_4Cl (13.41 L) then extracted with EtOAc (14.9 L, 7.45 L). The combined organic layers were washed with brine (14.9 L), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Material from 5 batches were combined. Compound tert-butyl (R)-3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (5.80 kg, 23.7 mol, 86.1% yield) was obtained as a yellow oil.

Step 2

Three batches were carried out in parallel.

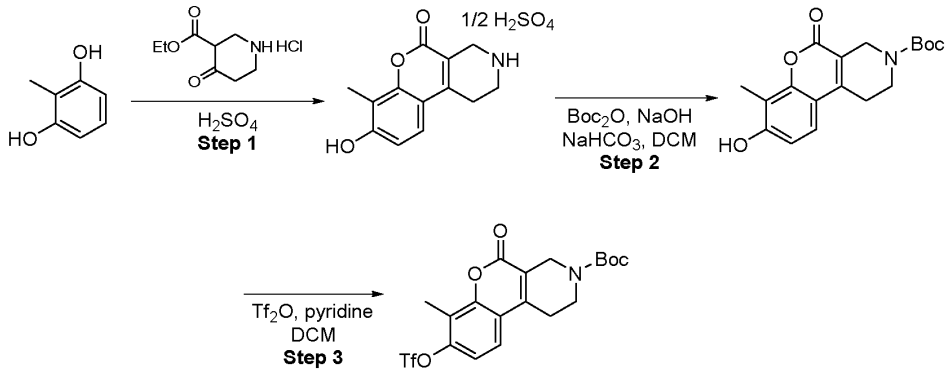
To a solution of tert-butyl (R)-3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (1.93 kg, 7.90 mol, 1.0 eq) in EtOAc (3.86 L) was added to HCl/EtOAc (4 M, 15.4 L, 7.82 eq) at 20 °C, the mixture was stirred at 20 °C for 3 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Material from 3 batches were combined. (R)-2-(methoxymethyl)-1-methylpiperazine hydrochloride (5.44 kg) was obtained as a yellow solid.

Step 3

Two batches were carried out in parallel.

To a solution of (R)-2-(methoxymethyl)-1-methylpiperazine hydrochloride (2.72 kg, 15.1 mol, 1.0 eq) in MeOH (13.6 L) was added K_2CO_3 (2.29 kg, 16.6 mol, 1.1 eq) at 10-20 °C. The mixture was stirred at 20-30 °C for 3 h. The reaction mixture was filtered, and the filtrate was concentrated at 35 °C under reduced pressure to give a residue. Residue was dissolved with DCM (13.6 L) and stirred at 20-30 °C for 0.5 h, solid was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was dissolved with DCM (10 L) and Na_2SO_4 added, suspension stirred at 20-30 °C for 0.5 h, filtered and the filtrate was concentrated under reduced pressure to give the product. Material from 3 batches were combined. (R)-2-(methoxymethyl)-1-methylpiperazine hydrochloride (2.90 kg, 20.1 mol) was obtained as brown oil.

Intermediate 2: *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



Step 1

A mixture of 2-methylbenzene-1,3-diol (25.0 g, 202 mmol) and ethyl 4-oxopiperidine-3-carboxylate hydrochloride (41.7 g, 202 mmol) in sulfuric acid (64%, 200 mL) was stirred at RT overnight. The reaction was quenched by adding ice water (300 mL) and the mixture was stirred at RT for 2 h. The precipitate was collected by filtration, washed with water and hexane, and dried under reduced pressure to afford 8-hydroxy-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one hemisulfate (46.0 g, 164 mmol) as an off-white solid. LCMS (System 2, Method B) Rt 0.38 min, m/z 232.2 $(M+H)^+$ (ES^+).

Step 2

Sodium hydroxide aq. 1 M (115 mL, 115 mmol) was added to a mixture of 8-hydroxy-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one hemisulfate (30.0 g, 107 mmol) in DCM (500 mL) and the reaction was stirred at RT for 30 min. Then $NaHCO_3$ aq. sat. (200 mL) and di-*tert*-butyl dicarbonate (25.7 g, 118 mmol) were added and the reaction was stirred at RT overnight. The organic solvent was evaporated and the resulting precipitate was recovered by filtration, washed with water, hexane, and dried to afford *tert*-butyl 7-chloro-8-hydroxy-5-oxo-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (25.0 g, 75.5 mmol) as an off-white solid. LCMS (System 2, Method B) Rt = 1.74 min, m/z 354.0 $(M+Na)^+$ (ES^+).

Step 3

A mixture *tert*-butyl 7-chloro-8-hydroxy-5-oxo-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (25.0 g, 75.5 mmol) in DCM (400 mL) was added pyridine (11.9 g, 151 mmol), the mixture was cooled to 0 °C then trifluoromethanesulfonic anhydride (21.3 g, 75.5 mmol) was added dropwise. The solution was allowed to warm to RT and stirred for 1 h. Water (300 mL) was added, and the organic phase was separated, washed with HCl aq. 0.1 N (50 mL) and brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-2% MeOH/DCM) to afford *tert*-butyl 7-methyl-5-oxo-

8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (30.0 g, 64.8 mmol) as a pale-yellow solid. LCMS: (System 2, Method B). Rt = 2.14 min, m/z 486.1 $(M+Na)^+$ (ES^+).

Alternative procedure:

Step 1

2 x 500 g batches were carried out in parallel.

To a solution of 2-methylbenzene-1,3-diol (500 g, 4.03 mol, 1.0 eq) in sulfuric acid (5.0 L, 75%) was added ethyl 4-oxopiperidine-3-carboxylate hydrochloride (920 g, 4.43 mol, 1.1 eq) at 20 °C, the reaction mixture was stirred at 30 °C for 12 h. The reaction mixture was added to ice water (20 L). The precipitate was collected by filtration, washed with water (5.0 L) and hexane (3.0 L). The filter cake was dried under reduced pressure. The crude product was used to the next step without further purification. The materials from the two batches were combined. 8-hydroxy-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one hemisulfate (3.50 kg, crude) was obtained as a white solid.

Step 2

To a suspension of 8-hydroxy-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one hemisulfate (3.15 kg, 6.42 mol, 1.0 eq) in THF (19 L) was added NaOH (1.0 M, 3.71 L) and the mixture was stirred at 25 °C for 0.5 h. $NaHCO_3$ aq. sat. (165 mL) and di-*tert*-butyl dicarbonate (1.40 kg, 6.42 mol, 1.0 eq) were added to the mixture. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated at 35 °C under reduced pressure to remove THF, the residue was filtered and washed with water (2.0 L) and hexane (4.0 L). The crude product was triturated with n-hexane/acetone 1/1 (4.0 L) at 20 °C for 12 h. *tert*-butyl 7-chloro-8-hydroxy-5-oxo-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (2.14 kg, 5.76 mol, 89.7% yield) was obtained as a white solid.

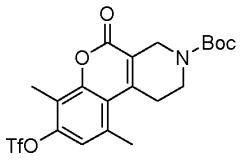
Step 3

7 batches were carried out in parallel: 5 x 330 g batches, a 290 g batch and a 200 g batch.

To a solution of *tert*-butyl 7-chloro-8-hydroxy-5-oxo-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (330 g, 996 mmol, 1.0 eq) in DCM (1.65 L) was added pyridine (197 g, 2.49 mol, 201 mL, 2.5 eq) at -10-0 °C, then trifluoromethanesulfonic anhydride (421 g, 1.49 mol, 246 mL, 1.5 eq) was added dropwise into the mixture at the same temperature. The mixture was stirred at -10-0 °C for 0.5 h until the reaction was completed by HPLC. The reaction mixture was quenched by adding water (1.65 L) at -10-0 °C then the organic phase was separated, washed with HCl (0.1 M, 0.9 L) and brine (1.65 L), dried over anhydrous Na_2SO_4, and concentrated at 35 °C under reduced pressure to give the crude product. Seven batches were combined for further

purification. The crude product was triturated with n-heptane (5.0 L) at 20 °C for 1 h. The solid was filtered and the filter cake was dried at 35 °C to obtained *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (2.64 kg, 99.0% purity, 88.2% yield) as a pale yellow solid.

Intermediate 3: *tert*-butyl 7,10-dimethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



Prepared by an analogous method to *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2) starting from 2,5-dimethylbenzene-1,3-diol (10.0 g, 73 mmol). Yield: 9.3 g, 19.5 mmol. White solid. LCMS: (System 1, Method A) Rt = 2.47 min, m/z 422.2 $(M-56+H)^+$ (ES^+).

Alternative procedure:

Step 1

3 batches were carried out in parallel: 50.0 g and 2 x 225 g.

A mixture of 2,5-dimethylbenzene-1,3-diol (225 g, 1.63 mol, 1.0 eq), ethyl 4-oxopiperidine-3-carboxylate hydrochloride (371 g, 1.79 mol, 1.1 eq, HCl), in H_2SO_4 (75%, 2250 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 30 °C for 96 h under nitrogen atmosphere. The three batched were combined and poured into ice water (6750 mL) at 0-10 °C, and the solid was recovered by filtration and washed with water (2 x 120 mL). The filter cake was dried under reduced pressure. The crude product was used to the next step without further purification. 8-hydroxy-7,10-dimethyl-1,2,3,4-tetrahydro-5H-chromeno[3,4-c]pyridin-5-one hemisulfate (1.27 kg, crude) was obtained as a white solid.

Step 2

A mixture of 8-hydroxy-7,10-dimethyl-1,2,3,4-tetrahydro-5H-chromeno[3,4-c]pyridin-5-one hemisulfate (1.15 kg, 3.58 mol, 1.0 eq) tert-butyl carbonate (687 g, 3.15 mol, 723 mL, 0.88 eq), $NaHCO_3$ (1.14 M, 890 mL, 0.28 eq) and NaOH (1.0 M, 4.30 L, 1.2 eq) in THF (16.5 L) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 15-25 °C for 12 h under nitrogen atmosphere. The solid was filtered and the filtrate concentrated under reduced pressure to give a residue. The crude product was purified by re-crystallization from 1000 mL of 1/1 acetone/n-hexane. tert-butyl 8-hydroxy-7,10-dimethyl-5-oxo-1,5-dihydro-2H-

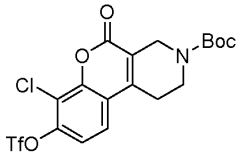
chromeno[3,4-c]pyridine-3(4H)-carboxylate (489 g, 1.42 mol, 39.5% yield) was obtained as a white solid.

Step 3

Two 239.5 g batches were carried out in parallel.

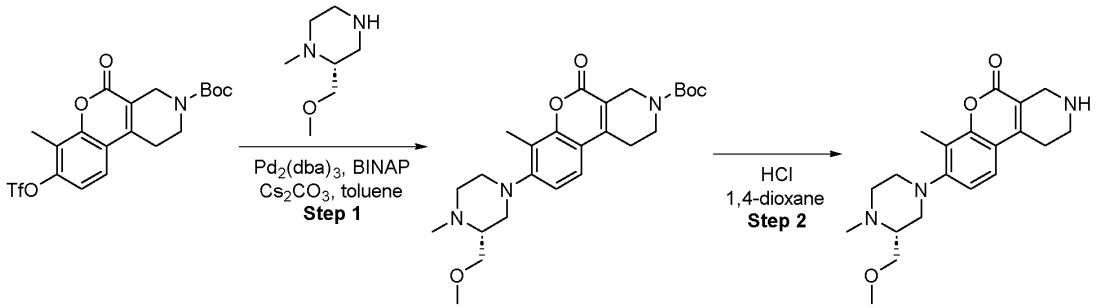
To a mixture of tert-butyl 8-hydroxy-7,10-dimethyl-5-oxo-1,5-dihydro-2H-chromeno[3,4-c]pyridine-3(4H)-carboxylate (239.5 g, 693 mmol, 1.0 eq) in DCM (2.40 L) was added pyridine (137 g, 1.73 mol, 140 mL, 2.5 eq) at -10-0 °C, followed by trifluoromethanesulfonic anhydride (293 g, 1.04 mol, 172 mL, 1.5 eq) at -10-0 °C. The mixture was stirred at -10-0 °C for 0.5 hr. The mixture was quenched by addition of water (1.12 L) at -10-0 °C, the organic phase was separated and extracted with DCM (718 mL). The combined organic phase was washed with HCl (1.0 M, 3 x 718 mL) and brine (1.12 L), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Two batches were combined for further purification. The crude product was triturated with n-heptane (1.5 L) at 25 °C for 1 hr, filtered and concentrated under reduced pressure. tert-butyl 7,10-dimethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2H-chromeno[3,4-c]pyridine-3(4H)-carboxylate (459 g, 959 mmol, 69.2% yield, 99.8% purity) was obtained as a light-yellow solid.

Intermediate 4: *tert*-butyl 7-chloro-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



Prepared by an analogous method to *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2) starting from 2-chlorobenzene-1,3-diol (20.0 g, 139 mmol). Yield: 31.0 g, mmol. Pale-yellow solid. LCMS: (System 1, Method F) Rt = 1.97 min, m/z 428.0 $(M-56+H)^+$ (ES^+).

Intermediate 5: (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



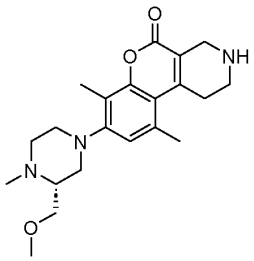
Step 1

A mixture of (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 3.73 g, 25.9 mmol), *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4H)-carboxylate (Intermediate 2, 8.0 g, 17.3 mmol), Cs_2CO_3 (11.2 g, 34.6 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.58 g, 1.73 mmol) and BINAP (2.16 g, 3.46 mmol) in toluene (87 mL) was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was cooled to RT, EtOAc was added and the mixture was filtered, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-80% EtOAc/petroleum ether then 1-5% MeOH/DCM) to afford (*R*)-*tert*-butyl 8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-4,5-dihydro-1*H*-chromeno[3,4-c]pyridine-3(2*H*)-carboxylate (7.8 g, 17.0 mmol) as a yellow solid. LCMS: (System 1, Method A). Rt = 2.19 min, 458.2 $(M+H)^+$ (ES^+).

Step 2

To a solution of (*R*)-tert-butyl 8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-4,5-dihydro-1*H*-chromeno[3,4-c]pyridine-3(2*H*)-carboxylate (7.8 g, 17.0 mmol) in MeOH (100 mL) was added HCl 4 M solution in 1,4-dioxane (100 mL). The reaction mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue was diluted with water (50 mL) and washed with DCM (2x20 mL). The pH of the aqueous layer was adjusted to pH = 7-8 by adding $NaHCO_3$ aq. sat. and washed with DCM (20 mL). The pH of the water layer was adjusted to pH = 10-11 with Na_2CO_3 aq. sat. and extracted with DCM (3x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one (3.5 g, 9.8 mmol) as a yellow solid. LCMS: (System 1, Method A). Rt = 1.48 min, 358.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.49 (d, J = 7.2 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 3.59-3.53 (m, 3H), 3.36-3.30 (m, 2H), 3.26 (s, 3H), 3.13-3.10 (m, 1H), 3.03-3.00 (m, 3H), 2.84-2.81 (m, 2H), 2.79-2.73 (m, 2H), 2.62-2.57 (m, 1H), 2.41-2.38 (m, 2H), 2.29-2.26 (m, 6H).

Intermediate 6: (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 3.6 g, 25.2 mmol) and *tert*-butyl 7,10-dimethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 3, 8.0 g, 16.8 mmol). Yield: 4.4 g, 11.8 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 1.34 min, m/z 372.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 6.80 (s, 1H), 3.58-3.53 (m, 3H), 3.34-3.30 (m, 2H), 3.26 (s, 3H), 3.11-3.08 (m, 1H), 3.01-2.94 (m, 3H), 2.90-2.88 (m, 2H), 2.82-2.77 (m, 2H), 2.65 (s, 3H), 2.61-2.56 (m, 1H), 2.39-2.35 (m, 2H), 2.28 (s, 3H), 2.20 (s, 3H)

Specific procedure:

Step 1

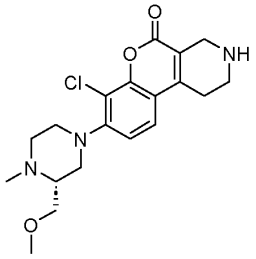
A solution of tert-butyl 7,10-dimethyl-5-oxo-8-(trifluoromethylsulfonyloxy)-4,5-dihydro-1H-chromen o[3,4-c]pyridinee-3(2H)-carboxylate (40.0 g, 83.9 mmol) in toluene (850 mL) was added Cs_2CO_3 (54.7 g, 167.7 mmol), $Pd_2(dba)_3$ (7.7 g, 8.39 mmol), BINAP (10.4 g, 16.77 mmol) and (R)-2-(methoxymethyl)-1-methylpiperazine (15.7 g, 109.0 mmol). The reaction mixture was stirred at 100 °C overnight under nitrogen atmosphere. The reaction mixture was cooled to room temperature, ethyl acetate was added and the resulting solid was filtered off. The filtrate was concentrated at 45 °C under reduced pressure and purified by silica gel column chromatography (20-80% EtOAc/petroleum ether then 1-5% MeOH/DCM) to give (R)-tert-butyl8-(3-(methoxymethyl)-4-methylpiperazin-1-y l)-7,10-dimethyl-5-oxo-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (30.0 g, 92.4% purity, 76% yield) as a yellow solid. LCMS: (System 1, Method A) Rt = 2.14 min, m/z 472.2 $(M+H)^+$ (ES^+).

Step 2

To a solution of (R)-tert-butyl 8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (30.0 g, 63.7 mmol) in dioxane (120 mL) was added HCl in dioxane (4 M, 120 mL). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated at 45 °C under reduced pressure. Water was added (200 mL) and the aqueous phase washed by DCM (2 x 80 mL). DMC layer was

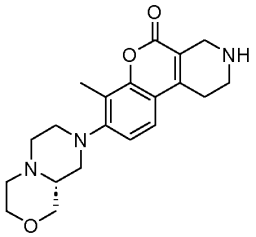
discarded. The pH was adjusted to 7~8 with $NaHCO_3$ and the aqueous phase washed by DCM (80 mL). DMC layer was discarded. The pH was adjusted to 10~11 with Na_2CO_3 and aqueous phase extracted with DCM (3 x 120 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at 35 °C under reduced pressure to give (R)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-3,4-dihydro-1H-chromen o[3,4-c]pyridin-5(2H)-one (21.0 g, >95% purity, 89% yield) as a yellow solid.

Intermediate 7: (*R*)-7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



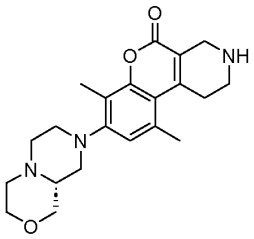
Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 671 mg, 4.7 mmol) and *tert*-butyl 7-chloro-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 4, 1.5 g, 3.1 mmol). Yield: 330 mg, 0.87 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 1.31 min, m/z 377.2 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.61 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 3.60-3.55 (m, 3H), 3.44-3.32 (m, 4H), 3.26 (s, 3H), 3.01 (br s, 2H), 2.94-2.82 (m, 2H), 2.74 (br s, 2H), 2.68-2.63 (m, 1H), 2.41-2.36 (m, 2H), 2.28 (s, 3H).

Intermediate 8: (*R*)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



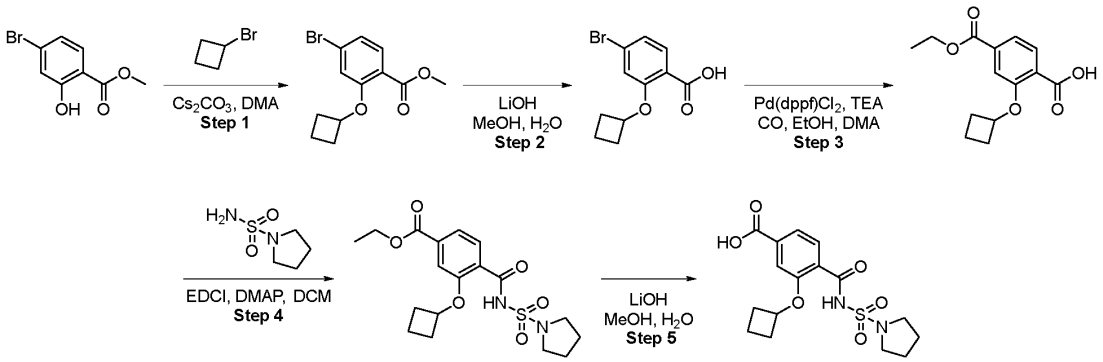
Prepared by an analogous method to Intermediate 5 starting from (*R*)-octahydropyrazino[2,1-c][1,4]oxazine (936 mg, 5.89 mmol) and *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate(Intermediate 2, 2.1 g, 5.54 mmol). Yield: 900 mg, 2.53 mmol. Yellow solid. LCMS: (System 2, Method F) Rt = 1.23 min, m/z 355.9 $(M+H)^+$ (ES^+).

Intermediate 9: (*R*)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-octahydropyrazino[2,1-c][1,4]oxazine (233 mg, 1.63 mmol) and *tert*-butyl 7,10-dimethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 3, 600 mg, 1.26 mmol). Yield: 31.0 g, mmol. Pale-yellow solid. LCMS: (System 1, Method F) Rt = 1.97 min, m/z 428.0 $(M-56+H)^+$ (ES^+).

Intermediate 10: 3-cyclobutoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

A mixture of 4-bromo-2-hydroxybenzoate (3.0 g, 13.0 mmol), bromocyclobutane (3.5 g, 26.0 mmol) and Cs_2CO_3 (8.5 g, 26.0 mmol) in DMA (30 mL) was stirred at 80 °C overnight. The reaction was cooled to RT, diluted with water (150 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 4-bromo-2-cyclobutoxybenzoate (3.0 g, 10.6 mmol) as a colourless oil. LCMS: (System 2, Method B) Rt = 2.02 min, m/z 285.0 $(M+H)^+$ (ES^+).

Step 2

A mixture of methyl 4-bromo-2-cyclobutoxybenzoate (3.0 g, 10.5 mmol) and $LiOH{\cdot}H_2O$ (1.3 g, 31.6 mmol) in MeOH (20 mL) and water (10 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure, then the pH of the mixture was adjusted to pH = 3 by adding HCl aq. 1 N The precipitate was recovered by filtration, washed with water and hexane,

and dried under reduce pressure to afford 4-bromo-2-cyclobutoxybenzoic acid (2.50 g, 9.30 mmol) as an off-white solid. LCMS: (System 1, Method A) Rt = 1.25 min, m/z 271.2 $(M+H)^+$ (ES^+).

Step 3

A mixture of 4-bromo-2-cyclobutoxybenzoic acid (1.4 g, 5.16 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.8 g, 1.04 mmol) and triethylamine (2.6 g, 25.7 mmol) in DMA (8 mL) and EtOH (30 mL) was stirred at 90 °C overnight under CO atmosphere. The reaction was cooled to RT, diluted with water (80 mL) and washed with EtOAc (3x40 mL). Then the pH of the aqueous layer was adjusted to pH = 3 by adding HCl aq. 1 N and it was extracted with EtOAc (3x40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 2-cyclobutoxy-4-(ethoxycarbonyl)benzoic acid (1.1 g, 4.16 mmol) as a brown solid which was used without further purification in the next step. LCMS: (System 1, Method A) Rt = 1.27 min, m/z 265.3 $(M+H)^+$ (ES^+).

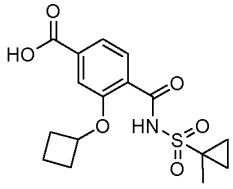
Step 4

A mixture of 2-cyclobutoxy-4-(ethoxycarbonyl)benzoic acid (600 mg, 2.27 mmol), EDCI (871 mg, 4.54 mmol), pyrrolidine-1-sulfonamide (512 mg, 3.41 mmol) and DMAP (549 mg, 4.49 mmol) in DCM (20 mL) was stirred at RT overnight. The reaction was diluted with water (20 mL) and the mixture was extracted with DCM (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-50% EtOAc/petroleum ether) to afford ethyl 3-cyclobutoxy-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoate (880 mg, 2.22 mmol) as a colourless oil. LCMS: (System 1, Method A) Rt = 1.65 min, m/z 397.3 $(M+H)^+$ (ES^+).

Step 5

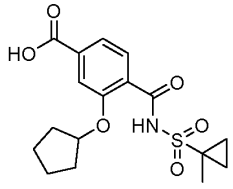
A mixture of ethyl 3-cyclobutoxy-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoate (400 mg, 1.0 mmol) and $LiOH{\cdot}H_2O$ (127 mg, 3.03 mmol) in MeOH (10 mL) and water (5 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure and the pH of the resulting aqueous solution was adjusted to pH = 3 by adding HCl aq. 1 N, the resulting solution was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 3-cyclobutoxy-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoic acid (330 mg, 0.90 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.13 min, m/z 369.2 $(M+H)^+$ (ES^+).

Intermediate 11: 3-cyclobutoxy-4-(1-methylcyclopropylsulfonylcarbamoyl)benzoic acid



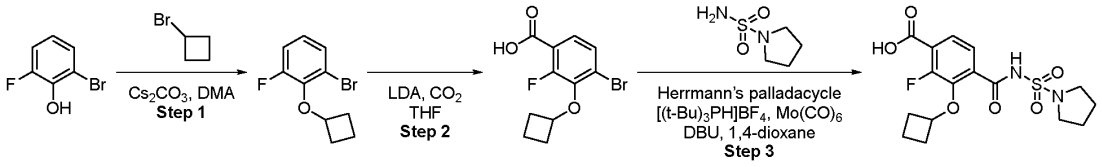
Prepared by an analogous method to Intermediate 10 starting from 4-bromo-2-hydroxybenzoate (3.0 g, 13.0 mmol) and bromocyclobutane (3.5 g, 26.0 mmol) except the Step 4 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 310 mg, 0.88 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.95 min, m/z 354.2 $(M+H)^+$ (ES^+).

Intermediate 12: 3-(cyclopentyloxy)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 10 starting from 4-bromo-2-hydroxybenzoate (5.0 g, 21.6 mmol) and bromocyclopentane (12.9 g, 86.6 mmol) except the Step 4 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 1.0 g, 2.72 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.07 min, m/z 366.0 $(M-H)^-$ (ES^-).

Intermediate 13: 3-cyclobutoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

A mixture of 2-bromo-6-fluorophenol (2.0 g, 10.5 mmol), bromocyclobutane (2.8 g, 20.9 mmol) and Cs_2CO_3 (10.2 g, 31.4 mmol) in DMA (50 mL) was stirred at RT overnight. The mixture was diluted with water (150 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford 1-bromo-2-cyclobutoxy-3-fluorobenzene (2.2 g, 8.98 mmol) as a pale-yellow oil. ^1H NMR (400 MHz, CD_3OD) δ: 7.35 (dd, J = 8.0, 1.2 Hz, 1H), 7.14-7.10 (m, 1H), 7.00-6.94 (m, 1H), 4.70-4.63 (m, 1H), 2.32-2.20 (m, 4H), 1.81-1.72 (m, 1H), 1.58-1.49 (m, 1H).

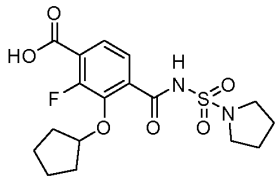
Step 2

To a solution of 1-bromo-2-cyclobutoxy-3-fluorobenzene (2.20 g, 8.98 mmol) in THF (70 mL) was slowly added LDA 2 M (5.4 mL, 10.8 mmol) at -70 °C and stirred for 1 h, then dry ice (10 g) was added slowly and the mixture was stirred at RT overnight. The reaction was quenched with NH_4Cl aq. sat. (100 mL) and partitioned with EtOAc (3x60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 4-bromo-3-cyclobutoxy-2-fluorobenzoic acid (1.6 g, 5.53 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.36 min, m/z 287.0 $(M-H)^-$ (ES^-).

Step 3

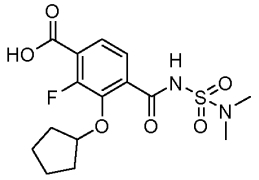
A mixture of 4-bromo-3-cyclobutoxy-2-fluorobenzoic acid (650 mg, 2.25 mmol), pyrrolidine-1-sulfonamide (1.01 g, 6.75 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)-benzyl]dipalladium (II) (Herrmann's palladacycle, 216 mg, 0.23 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (133 mg, 0.46 mmol), molybdenum hexacarbonyl (891 mg, 3.38 mmol) and DBU (1.03 g, 6.75 mmol) in 1,4-dioxane (20 mL) was stirred at 140 °C for 15 minutes under microwave irradiation. The mixture was concentrated under reduced pressure, the residue was taken in K_2CO_3 aq. 2 M (40 mL) and washed with EtOAc (3x40 mL). The pH of the aqueous layer was adjusted to pH = 4 by adding HCl aq. 1 N, then it was extracted with EtOAc (3x40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford 3-cyclobutoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (200 mg, 0.52 mmol) as a colourless oil. LCMS: (System 1, Method A) Rt = 0.99 min, m/z 385.0 $(M-H)^-$ (ES^-).

Intermediate 14: 3-(cyclopentyloxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



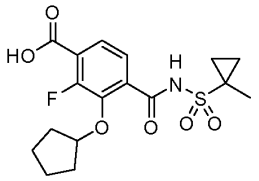
Prepared by an analogous method to Intermediate 13 starting from of 2-bromo-6-fluorophenol (50.0 g, 263 mmol) and bromocyclopentane (78.0 g, 526 mmol). Yield: 32.0 g, 79.9 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.11 min, m/z $(M-H)^-$ (ES^-).

Intermediate 15: 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



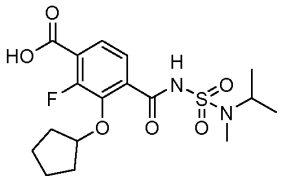
Prepared by an analogous method to Intermediate 14 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 410 mg, 1.10 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 0.96 min, m/z 373.0 $(M-H)^-$ (ES^-).

Intermediate 16: 3-(cyclopentyloxy)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



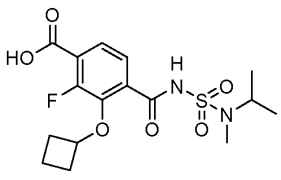
Prepared by an analogous method to Intermediate 14 except the Step 3 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 440 mg, 1.14 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.01 min, m/z 384.2 $(M-H)^-$ (ES).

Intermediate 17: 3-(cyclopentyloxy)-2-fluoro-4-(*N*-isopropyl-*N*-methylsulfamoylcarbamoyl)benzoic acid



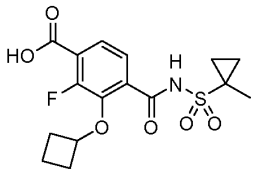
Prepared by an analogous method to Intermediate 14 except the Step 3 was carried out with *N*-methyl-*N*-isopropylsulfamoyl amide in place of pyrrolidine-1-sulfonamide. Yield: 220 mg, 0.55 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.99 min, m/z 401.0 $(M-H)^-$ (ES^-).

Intermediate 18: 3-cyclobutoxy-2-fluoro-4-((*N*-isopropyl-*N*-methylsulfamoyl)carbamoyl)benzoic acid



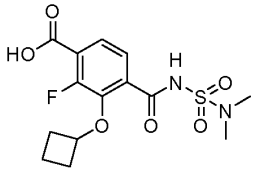
Prepared by an analogous method to Intermediate 13 except the Step 3 was carried out with *N*-methyl-*N*-isopropylsulfamoyl amide in place of pyrrolidine-1-sulfonamide. Yield: 240 mg, 0.62 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.94 min, m/z 387.0 $(M-H)^-$ (ES^-).

Intermediate 19: 3-cyclobutoxy-2-fluoro-4-(1-methylcyclopropylsulfonylcarbamoyl)benzoic acid



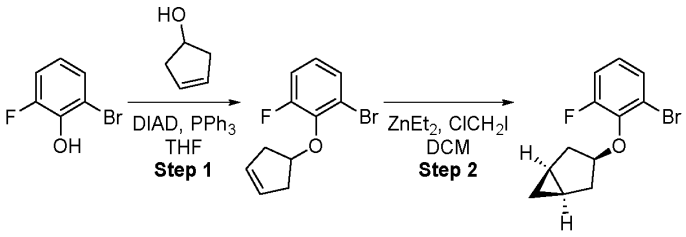
Prepared by an analogous method to Intermediate 13 except the Step 3 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 500 mg, 1.35 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.85 min, m/z 370.0 $(M-H)^-$ (ES^-).

Intermediate 20: 3-cyclobutoxy-4-(*N*,*N*-dimethylsulfamoylcarbamoyl)-2-fluorobenzoic acid



Prepared by an analogous method to Intermediate 13 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 670 mg, 1.86 mmol. White solid. LCMS: (System 2, Method B) Rt = 1.61 min, m/z 361.1 $(M-H)^-$ (ES^-).

Intermediate 21: (1*R*,3*r*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane



Step 1

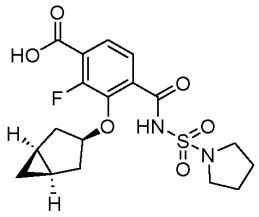
DIAD (6.8 g, 33.7 mmol) was added to a solution of 2-bromo-6-fluorophenol (3.2 g, 16.8 mmol), PPh_3 (8.8 g, 33.7 mmol) and cyclopent-3-en-1-ol (2.1 g, 25.3 mmol) in THF (150 mL) at 0 °C, the reaction mixture was stirred at RT overnight. The mixture was diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1% EtOAc/petroleum ether) to afford 1-bromo-2-(cyclopent-

3-en-1-yloxy)-3-fluorobenzene (2.1 g, 8.17 mmol) as a pale-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.47-7.45 (m, 1H), 7.35-7.30 (m, 1H), 7.10-7.05 (m, 1H), 5.77 (s, 2H), 5.06-5.03 (m, 1H), 2.67-2.50 (m, 4H).

Step 2

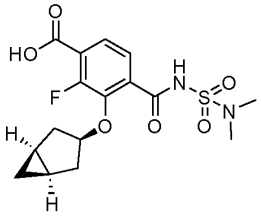
A solution of diethylzinc 1 M in heptane (24.6 mL, 24.6 mmol) in DCM (80 mL) was slowly added to a solution of chloroiodomethane (11.6 g, 65.6 mmol) in DCM (20 mL) at 0 °C and the mixture was stirred at this temperature for 1 h. Then, a solution of 1-bromo-2-(cyclopent-3-en-1-yloxy)-3-fluorobenzene (2.1 g, 8.2 mmol) in DCM (10 mL) was added and the mixture was allowed to reach RT and stirred overnight. The reaction was quenched by adding NH_4Cl aq. (50 mL) and extracted with DCM (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1% EtOAc/petroleum ether) to afford (1*R*,3*r*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane (1.7 g, 6.27 mmol) as a pale-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.46-7.43 (m, 1H), 7.33-7.27 (m, 1H), 7.08-7.02 (m, 1H), 4.81-4.78 (m, 1H), 2.18-2.11 (m, 2H), 2.05-2.01 (m, 2H), 1.36-1.30 (m, 2H), 0.86-0.83 (m, 1H), 0.54-0.50 (m, 1H).

Intermediate 22: 3-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



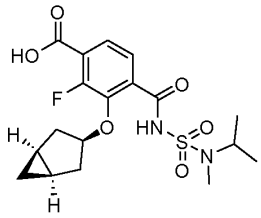
Prepared by an analogous method to Intermediate 13 (Step 2 and Step 3 only) starting from (1*R*,3*r*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane (Intermediate 21, 1.2 g, 3.8 mmol) in Step 2. Yield: 370 mg, 0.90 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.10 min, m/z 410.9 $(M-H)^-$ (ES^-).

Intermediate 23: 3-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



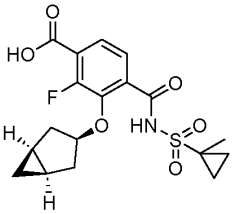
Prepared by an analogous method to Intermediate 22 except the Step 3 was carried out with *N,N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 600 mg, 1.55 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.83 min, m/z 385.4 $(M-H)^-$ (ES^-).

Intermediate 24: 3-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-fluoro-4-((*N*-isopropyl-*N*-methylsulfamoyl)carbamoyl)benzoic acid



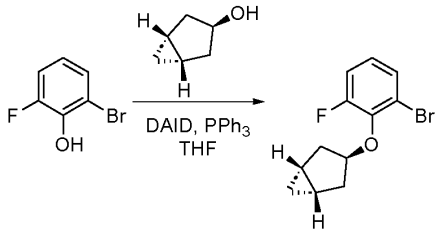
Prepared by an analogous method to Intermediate 22 except the Step 3 was carried out with *N*-methyl-*N*-isopropylsulfamoyl amide in place of pyrrolidine-1-sulfonamide. Yield: 356 mg, 0.86 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.21 min, m/z 412.8 $(M-H)^-$ (ES^-).

Intermediate 25: 3-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 22 except the Step 3 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 364 mg, 0.92 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.06 min, m/z 395.9 $(M-H)^-$ (ES^-).

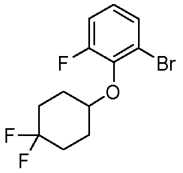
Intermediate 26: (1*R*,3*s*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane



DIAD (6.4 g, 31.6 mmol) was added to a mixture of 2-bromo-6-fluorophenol (2.0 g, 10.5 mmol), (1R,3r,5S)-bicyclo[3.1.0]hexan-3-ol (1.0 g, 10.5 mmol) and PPh_3 (8.3 g, 31.6 mmol) in THF (50 mL). The reaction was stirred at RT overnight. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine,

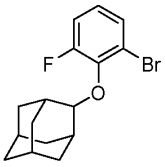
dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford (1*R*,3*s*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane (1.9 g, 7.0 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.46-7.43 (m, 1H), 7.33-7.28 (m, 1H), 7.10-7.04 (m, 1H), 4.43-4.35 (m, 1H), 2.17-2.13 (m, 2H), 2.03-1.98 (m, 2H), 1.34-1.30 (m, 2H), 0.37-0.32 (m, 1H), 0.07-0.04 (m, 1H).

Intermediate 27: 1-bromo-2-((4,4-difluorocyclohexyl)oxy)-3-fluorobenzene



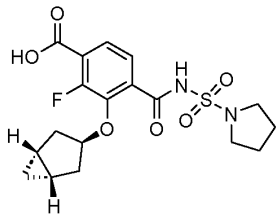
Prepared by an analogous method to Intermediate 26 starting from 2-bromo-6-fluorophenol (500 mg, 2.62 mmol) and 4,4-difluorocyclohexanol (535 mg, 3.93 mmol). Yield: 650 mg, 2.1 mmol. White solid. LCMS: (System 3, Method I). Rt = 2.14 min.

Intermediate 28: 2-(2-bromo-6-fluorophenoxy)adamantane



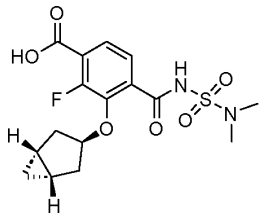
Prepared by an analogous method to Intermediate 26 starting from 2-bromo-6-fluorophenol (1.0 g, 5.24 mmol) and 2-adamantanol (1.2 g, 7.85 mmol). Yield: 700 mg, 2.2 mmol. White solid. LCMS: (System 3, Method I). Rt = 2.21 min.

Intermediate 29: 3-((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-2-fluoro-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoic acid



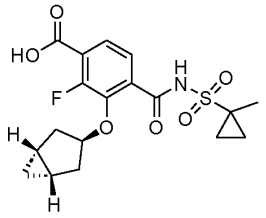
Prepared by an analogous method to Intermediate 13 (Step 2 and Step 3 only) starting from (1*R*,3*s*,5*S*)-3-(2-bromo-6-fluorophenoxy)bicyclo[3.1.0]hexane (Intermediate 26, 1.9 g, 16.7 mmol) in Step 2. Yield: 250 mg, 0.61 mmol. Pale-yellow solid. LCMS: (System 1, Method F) Rt = 0.91 min, m/z 411.0 $(M-H)^-$ (ES^-).

Intermediate 30: 3-((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-2-fluoro-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoic acid



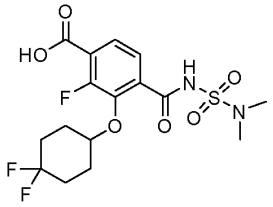
Prepared by an analogous method to Intermediate 29 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 230 mg, 0.60 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.01 min, m/z 384.8 $(M-H)^-$ (ES^-)

Intermediate 31: 3-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



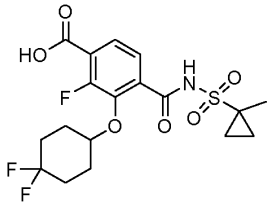
Prepared by an analogous method to Intermediate 29 except the Step 3 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 240 mg, 0.60 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.85 min, m/z 396.0 $(M-H)^-$ (ES^-)

Intermediate 32: 3-(4,4-difluorocyclohexoxy)-4-(dimethylsulfamoylcarbamoyl)-2-fluoro-benzoic acid



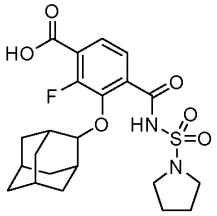
Prepared by an analogous method to Intermediate 13 (Step 2 and Step 3 only) starting from 1-bromo-2-((4,4-difluorocyclohexyl)oxy)-3-fluorobenzene (Intermediate 27, 650 mg, 2.10 mmol) in Step 2. Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 190 mg, 0.45 mmol. White solid. LCMS: (System 3, Method I) Rt = 0.80 min, m/z 423.2 $(M-H)^-$ (ES^-)

Intermediate 33: 3-(4,4-difluorocyclohexoxy)-2-fluoro-4-[(1-methylcyclopropyl)sulfonylcarbamoyl]benzoic acid



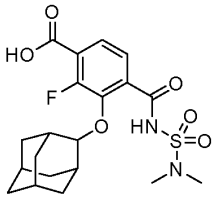
Prepared by an analogous method to Intermediate 32 except the Step 3 was carried out with 1-methylcyclopropane-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 165 mg, 0.38 mmol. Yellow solid. LCMS: (System 3, Method l) Rt = 0.98 min, m/z 434.3 $(M-H)^-$ (ES^-)

Intermediate 34: 3-((adamantan-2-yl)oxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



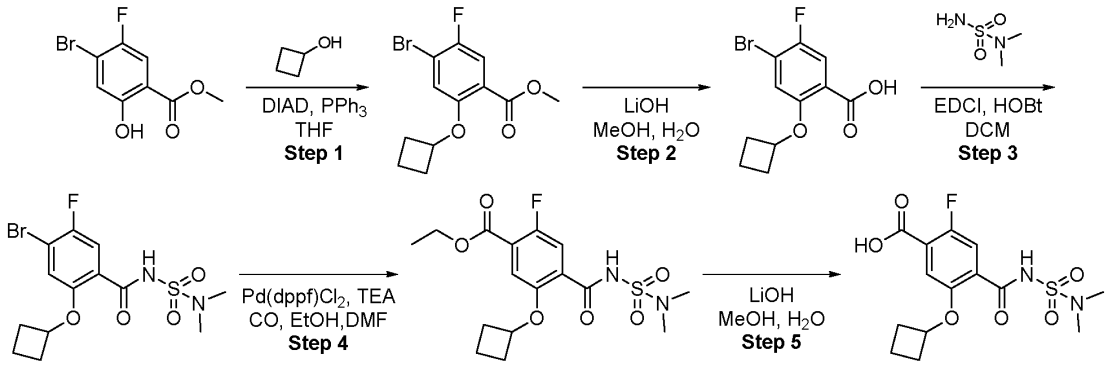
Prepared by an analogous method to Intermediate 13 (Step 2 and Step 3 only) starting from 2-(2-bromo-6-fluorophenoxy)adamantane (Intermediate 28, 700 mg, 2.15 mmol) in Step 2. Yield: 16 mg, 0.03 mmol. Yellow solid. LCMS: (System 3, Method l) Rt = 1.19 min, m/z 467.2 $(M+H)^+$ (ES^+)

Intermediate 35: 3-((adamantan-2-yl)oxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



Prepared by an analogous method to Intermediate 34 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 27 mg, 0.06 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.84 min, m/z 439.0 $(M-H)^-$ (ES^-)

Intermediate 36: 5-cyclobutoxy-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



Step 1

DIAD (1.3 mL, 6.42 mmol) was added to a mixture of methyl 4-bromo-5-fluoro-2-hydroxybenzoate (800 mg, 3.21 mmol), PPh_3 (1685 mg, 6.42 mmol) and cyclobutanol (0.38 mL, 4.82 mmol) in THF (25 mL) at 0 °C and the mixture was stirred at RT overnight. The reaction was diluted with water (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/iso-hexane) to afford methyl 4-bromo-2-cyclobutoxy-5-fluorobenzoate (619 mg, 2.04 mmol) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 5.5 Hz, 1H), 4.64 (p, J = 7.1 Hz, 1H), 3.88 (s, 3H), 2.51-2.43 (m, 2H), 2.29-2.19 (m, 2H), 1.93-1.84 (m, 1H), 1.75-1.64 (m, 1H).

Step 2

A mixture of methyl 4-bromo-2-cyclobutoxy-5-fluorobenzoate (619 mg, 2.04 mmol) and LiOH aq. 2 N (2.0 mL, 4.00 mmol) in MeOH (2 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure, then the pH of the mixture was adjusted to 3 by adding 1 N HCl aq. The precipitate was recovered by filtration, washed with water and hexane, and dried under reduce pressure to afford 4-bromo-2-cyclobutoxy-5-fluorobenzoic acid (424 mg, 1.47 mmol) as an off-white solid. LCMS: (System 3, Method I) Rt = 1.24 min, m/z 287.0 $(M-H)^-$ (ES^-)

Step 3

A mixture of 4-bromo-2-cyclobutoxy-5-fluorobenzoic acid (212 mg, 0.73 mmol), EDCI (290 mg, 1.51 mmol), pyrrolidine-1-sulfonamide (276 mg, 2.23 mmol) and DMAP (185 mg, 1.51 mmol) in DCM (4 mL) was stirred at RT overnight. The reaction was diluted with water (15 mL) and the mixture was extracted with DCM (3x15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-100% EtOAc/iso-hexane) to afford 4-bromo-2-cyclobutoxy-*N*-

(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide (175 mg, 0.43 mmol) as a white solid. LCMS: (System 3, Method I) Rt = 1.43 min, m/z 393.1 $(M-H)^-$ (ES^-).

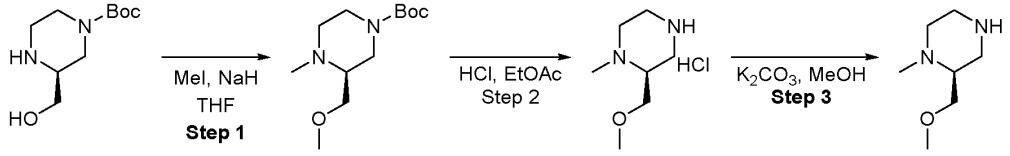
Step 4

A mixture of 4-bromo-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide (175 mg, 0.43 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (16 mg, 0.02 mmol) and triethylamine (216 mg, 2.14 mmol) in DMF (3.5 mL) and EtOH (2 mL) was stirred at 100 °C overnight under CO atmosphere. The reaction was cooled to RT, diluted with water (20 mL) and extracted with EtOAc (3x40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-80% EtOAc/iso-hexane then 1%-10% MeOH/DCM) to afford ethyl 5-cyclobutoxy-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoate (102 mg, 0.25 mmol) as a brown solid. LCMS: (System 3, Method I) Rt = 1.36 min, m/z 387.2 $(M-H)^-$ (ES^-).

Step 5

$LiOH{\cdot}H_2O$ (1.2 mL, 2.46 mmol) was added to a solution of ethyl 5-(cyclobutoxy)-2-fluoro-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoate (102 mg, 0.25 mmol) in MeOH (3.0 mL) and the reaction was stirred at RT for 1 h. The organic solvent was removed under reduced pressure and the crude product was purified by column chromatography on C_{18} (0-100% ACN/0.1% FA in water) to afford 5-cyclobutoxy-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid (41 mg, 0.11 mmol) as an off-white solid. LCMS: (System 3, Method J) Rt = 1.64 min, m/z 359.2 $(M-H)^-$ (ES^-).

Intermediate 37: (S)-2-(methoxymethyl)-1-methylpiperazine



Step 1

Sodium hydride (60% dispersion in mineral oil, 2.3 g, 57.8 mmol) was added portion wise to a solution of *tert*-butyl (*S*)-3-(hydroxymethyl)piperazine-1-carboxylate (5.0 g, 23.1 mmol) in THF (50 mL) at 0 °C for 1 h. Then iodomethane (8.2 g, 57.8 mmol) was added dropwise at 0 °C and the mixture was stirred at RT for 12 h. The reaction was quenched by adding NH_4Cl aq. sat. (30 mL) at 0 °C, the resulting aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford *tert*-butyl (*S*)-3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (6.2 g, 25.4 mmol) as a white solid which was used in the next step without further purification. ^1H NMR (400 MHz,

$CDCl_3$) δ 3.87-3.84 (m, 2H), 3.52-3.41 (m, 2H), 3.31 (s, 3H), 3.06-2.67 (m, 3H), 2.34 (s, 3H), 2.22-2.01 (m, 2H), 1.44 (s, 9H).

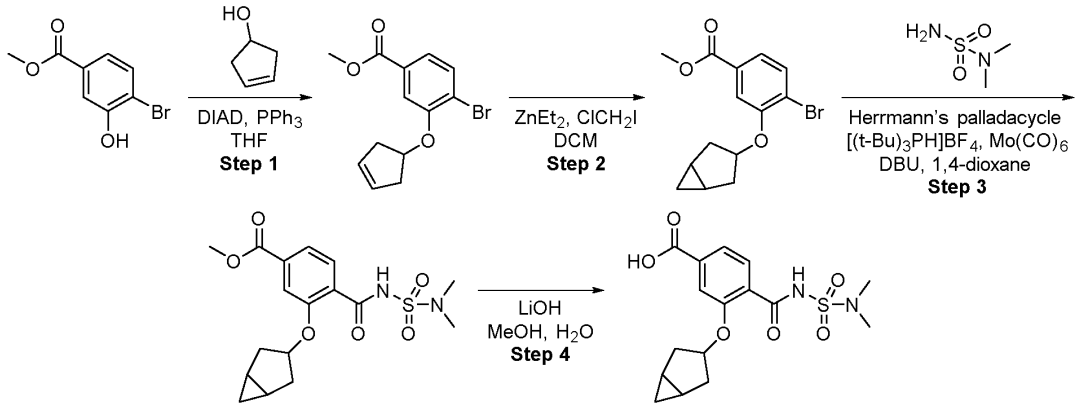
Step 2

A mixture of *tert*-butyl (*S*)-3-(methoxymethyl)-4-methylpiperazine-1-carboxylate (5.7 g, 23.1 mmol, 1.0 eq) and HCl 4 N solution in EtOAc (25 mL) in EtOAc (25 mL) was stirred at RT for 12 h. The mixture was concentrated under reduced pressure to afford (*S*)-2-(methoxymethyl)-1-methylpiperazine hydrochloride (3.00 g, 16.60 mmol) as a brown solid which was used in the next step without further purification. LCMS: (System 3, Method J) Rt = 0.33 min, m/z 145.1 $(M+H)^+$ (ES^+)

Step 3

A mixture of (*S*)-2-(methoxymethyl)-1-methylpiperazine hydrochloride (1.50 g, 8.30 mmol) and K_2CO_3 (1.26 g, 9.13 mmol, 1.1 eq) in MeOH (7.50 mL) was stirred at RT for 1 h. The reaction was partitioned between water (10 mL) and DCM (3x10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (S)-2-(methoxymethyl)-1-methylpiperazine (1.1 g, 7.63 mmol) as a black solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.44-3.48 (m, 1H), 3.30-3.35 (m, 1H), 3.24 (s, 3H), 3.10-3.14 (m, 2H), 2.78-2.85 (m, 2H), 2.63-2.69 (m, 1H), 2.39-2.46 (m, 2H), 2.22 (s, 3H),

Intermediate 38: 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



Step 1

DIAD (15.9 g, 77.9 mmol) was added to a mixture of methyl 4-bromo-3-hydroxybenzoate (6.0 g, 26.0 mmol), cyclopent-3-enol (6.6 g, 78.0 mmol) and PPh_3 (20.4 g, 77.9 mmol) in THF (300 mL) and the mixture was stirred at RT overnight. Water (300 mL) was added, and the mixture was extracted with EtOAc (3x300 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by

column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 4-bromo-3-(cyclopent-3-en-1-yloxy)benzoate (6.0 g, 20.2 mmol) as a brown solid. LCMS: (System 2, Method C) Rt = 0.86 min, m/z 297.1 2 $(M+H)^+$ (ES^+).

Step 2

Chloroiodomethane (23.6 g, 133 mmol) was added dropwise to a solution of diethylzinc 1 M in heptane (67.5 mL) in DCM (75 mL) at 0 °C, the mixture was stirred at this temperature for 30 min, then solution of methyl 4-bromo-3-(cyclopent-3-en-1-yloxy)benzoate (6.0 g, 20.2 mmol) in DCM (75 mL) was added. The mixture was stirred at RT overnight. The reaction was quenched with NH_4Cl aq. sat. (200 mL) and extracted with DCM (3x200 mL). The combined organics layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-bromobenzoate (4.5 g, 14.5 mmol) as a colorless oil. LCMS: (System 2, Method C) Rt = 0.92 min, m/z 311.2 $(M+H)^+$ (ES^+).

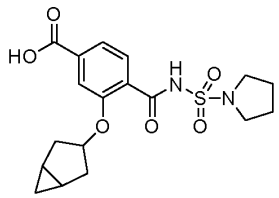
Step 3

A mixture of methyl 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-bromobenzoate (2.0 g, 6.45 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (377 mg, 1.3 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Herrmann's palladacycle, 610 mg, 0.65 mmol), molybdenum hexacarbonyl (2.6 g, 9.67 mmol), DBU (2.9 g, 19.35 mmol) and methanesulfonamide (2.4 g, 19.4 mmol) in 1,4-dioxane (50 mL) was stirred at 100 °C overnight. The reaction mixture was cooled to RT, diluted with DCM/water (5:1, 120 mL) and filtered through celite. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (0-5% MeOH/DCM) to afford methyl 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (1.3 g, 3.40 mmol) as a pale-yellow solid. LCMS: (System 2, Method F) Rt = 1.31 min, m/z 383.2 $(M+H)^+$ (ES^+).

Step 4

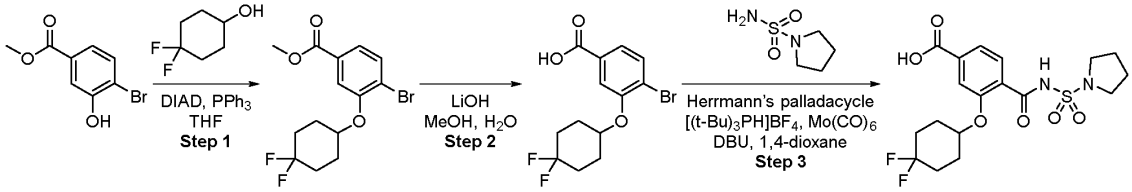
A mixture of 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (1.0 g, 2.62 mmol) in MeOH (20 mL) and water (5 mL) was added $LiOH{\cdot}H_2O$ (660 mg, 15.7 mmol), then the mixture was stirred at RT overnight. The organic solvent was removed under reduced pressure, then the pH of the mixture was adjusted to ca. 5 by adding HCl aq. 1 N and extracted with EtOAc (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid (849 mg, 2.30 mmol) as a white solid which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 1.14 min, m/z 366.8 $(M-H)^-$ (ES^-).

Intermediate 39: 3-(bicyclo[3.1.0]hexan-3-yloxy)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 38 starting from 4-bromo-3-hydroxybenzoate (6.0 g, 26.0 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of *N*,*N*-dimethylsulfamide. Yield: 1.3 g, 3.30 mmol. Pale-yellow solid. LCMS: (System 2, Method F) Rt = 1.31 min, m/z 409.2 $(M+H)^+$ (ES^+).

Intermediate 40: 3-((4,4-difluorocyclohexyl)oxy)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

DIAD (963 mg, 4.76 mmol) was added to a mixture of methyl 4-bromo-3-hydroxybenzoate (500 mg, 2.38 mmol), 4,4-difluorocyclohexanol (487 mg, 3.57 mmol) and PPh_3 (1.25 g, 4.76 mmol) in THF (12 mL) and the mixture was stirred at RT overnight. Water (50 mL) was added, and the mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 4-bromo-3-((4,4-difluorocyclohexyl)oxy)benzoate (810 mg, 2.32 mmol) as a pale-yellow solid. LCMS: (System 3, Method I) Rt = 2.07 min.

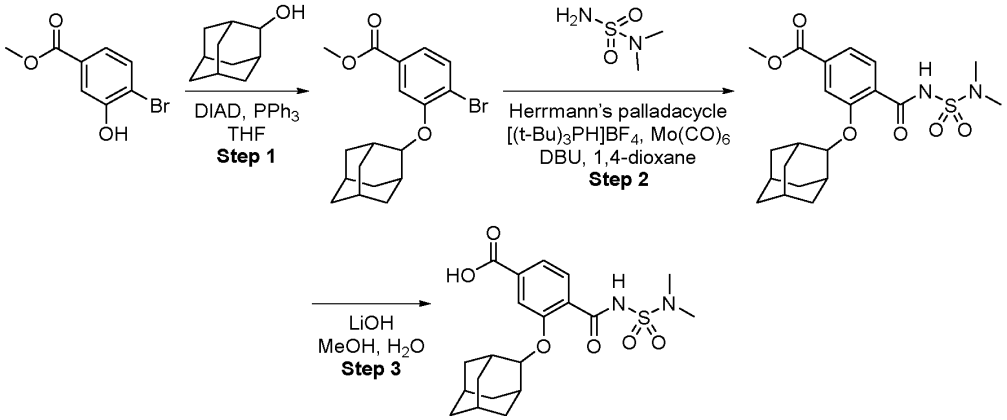
Step 2

A solution of LiOH aq. 2 M (3.5 mL, 7.0 mmol) was added to a solution of methyl 4-bromo-3-((4,4-difluorocyclohexyl)oxy)benzoate (810 mg, 2.32 mmol) in MeOH (3.5 mL). The reaction mixture was stirred at 40 °C overnight. The reaction mixture was cooled to RT, and after adjusting pH to ca. 3 with HCl aq. 1 N, extracted with EtOAc (2x30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 4-bromo-3-(4,4-difluorocyclohexoxy)benzoic acid (530 mg, 1.58 mmol) as pale-yellow solid. LCMS: (System 3, Method I) Rt = 1.38 min, m/z 334.9 $(M-H)^-$ (ES^-).

Step 3

A mixture of DBU (0.39 mL, 2.64 mmol), 4-bromo-3-(4,4-difluorocyclohexoxy)benzoic acid (295 mg, 0.88 mmol), molybdenum hexacarbonyl (594 mg, 1.32 mmol), pyrrolidine-1-sulfonamide (397 mg, 2.64 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Herrmann palladacycle, 83 mg, 0.09 mmol) and tri-*tert*-butylphosphoniumtetrafluoroborate (51 mg, 0.18 mmol) in 1,4-dioxane (4.7 mL) was stirred at 140 °C for 30 min under microwave irradiation. The mixture was dissolved in MeOH (20 mL) and concentrated under reduced pressure. The residue was diluted with K_2CO_3 aq. 2 M (30 mL) and washed with EtOAc (3x30 mL). The resulting aqueous layer was acidified to pH 1-2 by adding HCl aq. 2 N and extracted with EtOAc (3x30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 3-(4,4-difluorocyclohexoxy)-4-(pyrrolidin-1-ylsulfonylcarbamoyl)benzoic acid (33 mg, 0.08 mmol) as a white solid which was used in the next step without further purification. LCMS: (System 3, Method I) Rt = 1.71 min, m/z 431.2 $(M-H)^-$ (ES^-).

Intermediate 41: 3-((adamantan-2-yl)oxy)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

DIAD (2.1 mL, 10.5 mmol) was added to a mixture of methyl 4-bromo-3-hydroxybenzoate (1.2 g, 5.24 mmol), adamantan-2-ol (1.2 g, 7.85 mmol) and PPh_3 (2.7 g, 10.5 mmol) in THF (25 mL) and the mixture was stirred at RT overnight. Water (50 mL) was added, and the mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 3-((adamantan-2-yl)oxy)-4-bromobenzoate (49 mg, 0.12 mmol) as a pale-yellow solid. LCMS: (System 3, Method I) Rt = 1.21 min, m/z 421.1 $(M-H)^-$ (ES^-).

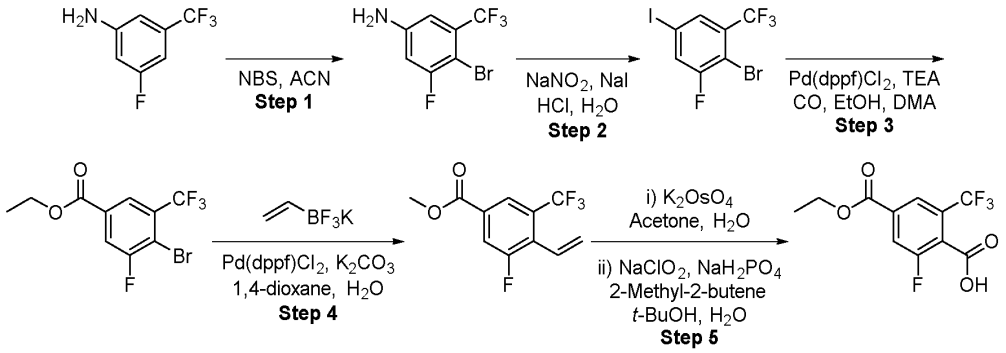
Step 2

A mixture of DBU (0.31 mL, 0.68 mmol), methyl 3-((adamantan-2-yl)oxy)-4-bromobenzoate (249 mg, 0.68 mmol), molybdenum hexacarbonyl (459 mg, 1.02 mmol), *N*,*N*-dimethylsulfamide (253 mg, 2.04 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Herrmann palladacycle, 128 mg, 0.14 mmol), tri-*tert*-butylphosphoniumtetrafluoroborate (79 mg, 0.27 mmol) in 1,4-dioxane (4.5 mL) was stirred at 140 °C for 30 min under microwave irradiation. The mixture was dissolved in MeOH (20 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10-90% EtOAc/iso-hexane) to afford methyl 3-((adamantan-2-yl)oxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (124 mg, 0.28 mmol) as a yellow solid. LCMS: (System 3, Method I) Rt = 1.62 min, m/z 435.1 $(M-H)^-$ (ES^-).

Step3

A mixture of methyl 3-((adamantan-2-yl)oxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (124 mg, 0.284 mmol) and LiOH aq. 2 M (0.43 mL, 0.85) in THF (0.4 mL) and MeOH (0.4 mL) was stirred at 40 °C overnight. The mixture was acidified to pH 1-2 by adding HCl aq. 2 N (10 mL) and extracted with EtOAc (2x30 mL). Then combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 3-(2-adamantyloxy)-4-(dimethylsulfamoylcarbamoyl)benzoic acid (49 mg, 0.12 mmol) as a pale-yellow solid which was used in the next step without further purification. LCMS: (System 3, method I) Rt = 1.21 min, m/z 421.1 $(M-H)^-$ (ES^-).

Intermediate 42: 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid



Step 1

N-Bromosuccinimide (24.8 g, 140 mmol) was added portionwise to a solution of 3-fluoro-5-(trifluoromethyl)aniline (25.0 g, 140 mmol) in ACN (500 mL) at 0 °C, then the reaction was stirred at 0 °C for 2 h. The reaction was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (10% DCM/petroleum ether) to afford 4-bromo-3-fluoro-5-(trifluoromethyl)aniline (25.0 g, 96.9) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.81-6.80 (m, 1H), 6.59 (dd, J = 9.8, 2.6 Hz, 1H), 4.00 (br s, 2H).

Step 2

A solution of $NaNO_2$ (7.4 g, 107 mmol) in water (125 mL) was added to a solution of 4-bromo-3-fluoro-5-(trifluoromethyl)aniline (25.0 g, 96.9 mmol) in HCl aq. conc. (250 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then NaI (16.0 g, 107 mmol) was added portionwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ aq. sat. (500 mL) and extracted with EtOAc (3x500 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% DCM/petroleum ether) to afford 2-bromo-1-fluoro-5-iodo-3-(trifluoromethyl)benzene (21.8 g, 59.1 mmol) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.65 (dd, J = 7.2, 1.6 Hz, 1H).

Step 3

A mixture of 2-bromo-1-fluoro-5-iodo-3-(trifluoromethyl)benzene (21.8 g, 59.1 mmol), TEA (29.9 g, 295 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (8.7 g, 11.8 mmol) in EtOH (600 mL) was stirred at 80 °C overnight under CO atmosphere. The reaction mixture was allowed to reach RT and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% DCM/petroleum ether) to afford ethyl 4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (13.1 g, 41.6 mmol) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 7.95 (dd, J = 8.2, 2.2 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

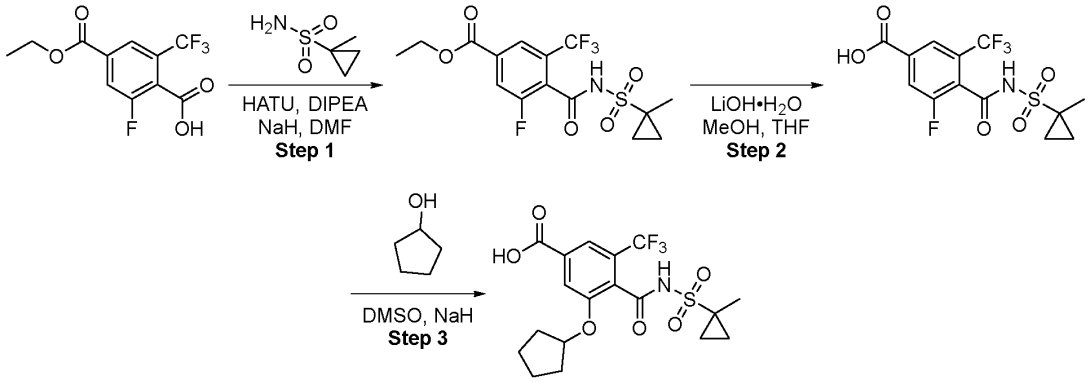
Step 4

A mixture of ethyl 4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (8.0 g, 25.4 mmol), potassium vinyltrifluoroborate (10.2 g, 76.2 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.9 g, 2.5 mmol) and K_2CO_3 (7.0 g, 50.8 mmol) in 1,4-dioxane (200 mL) and water (50 mL) was stirred at 100 °C overnight under nitrogen atmosphere. The reaction was allowed to reach RT and partitioned between water (300 mL) and EtOAc (3x300 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% DCM/petroleum ether) to afford ethyl 3-fluoro-5-(trifluoromethyl)-4-vinylbenzoate (5.0 g, 19.2 mmol) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.86 (d, J = 10.8 Hz, 1H), 6.76-6.68 (m, 1H), 5.93 (d, J = 17.6 Hz, 1H), 5.75-5.71 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

Step 5

To a solution of ethyl 3-fluoro-5-(trifluoromethyl)-4-vinylbenzoate (5.0 g, 19.2 mmol) in acetone (150 mL) and water (150 mL) was added potassium osmate(VI) dehydrate (1.4 g, 3.8 mmol), followed by $NaIO_4$ (16.41 g, 76.74 mmol) and the reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ aq. sat. and extracted with EtOAc (3x200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was dissolved in ^{t}BuOH (75 mL) and water (75 mL), and $NaH_2PO{\cdot}2H_2O$ (6.9 g, 57.6 mmol) was added, followed by $NaClO_2$ (5.2 g, 57.6 mmol) and 2-methylbut-2-ene (15 mL). The reaction mixture was stirred at RT overnight. Then, ^{t}BuOH was removed under reduced pressure, and pH of the mixture was adjusted to ca. 3 with HCl aq. 1 N. The aqueous solution was extracted with DCM (3x100 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (2.5 g, 8.92 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.67 (br s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.08 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

Intermediate 43: 3-(cyclopentyloxy)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



Step 1

A mixture of 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.7 mmol), HATU (2.6 g, 6.9 mmol) and DIPEA (3.0 g, 22.8 mmol) in DMF (50 mL) was stirred at RT for 1.5 h. After this time, 1-methylcyclopropane-1-sulfonamide (2.3 g, 17.1 mmol) was added, followed by sodium hydride (60% in mineral oil, 914 mg, 22.8 mmol). The reaction was stirred at RT overnight then poured into NH_4Cl aq. sat. (150 mL). HCl aq. 1 N (20 mL) was added and the mixture was extracted with EtOAc (3x150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford ethyl 3-

fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (1.5 g, 3.8 mmol) as a brown oil. LCMS: (System 1, Method A) Rt = 1.81 min, m/z 398.0 $(M+H)^+$ (ES^+).

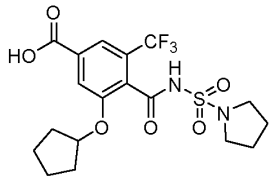
Step 2

A mixture of ethyl 3-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (500 mg, 1.26 mmol), $LiOH{\cdot}H_2O$ (207 mg, 5.04 mmol) in THF (16 mL), MeOH (4 mL) and water (4 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure, then pH of the mixture was adjusted to ca. 3 by adding HCl aq. 1 N. The precipitate was collected by filtration, washed with water then hexane and dried to afford 3-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid (400 mg, 1.08 mmol) as a brown solid.LCMS: (System 1, Method A) Rt = 0.61 min, m/z 387.0 $(M+NH_4)^+$ (ES^+).

Step 3

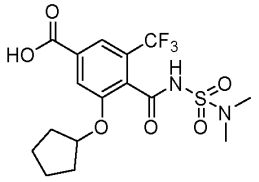
Sodium hydride (60% in mineral oil, 867 mg, 21.7 mmol) was added in small portions to a solution of 3-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid (400.0 mg, 1.08 mmol) in DMSO (15 mL). Then cyclopentanol (932 mg, 10.84 mmol) was added and the mixture was stirred at 100 °C for 30 min. The reaction mixture was allowed to reach RT and poured into NH_4Cl aq. sat. (45 mL). The pH of the solution was adjusted to ca. 8 by adding HCl aq. 1 N. The aqueous solution was extracted with EtOAc (3x60 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-(cyclopentyloxy)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid (275 mg, 0.63) as a brown solid. LCMS: (System 1, Method A) Rt = 1.08 min, m/z 453.0 $(M+NH_4)^+$ (ES^+).

Intermediate 44: 3-(cyclopentyloxy)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



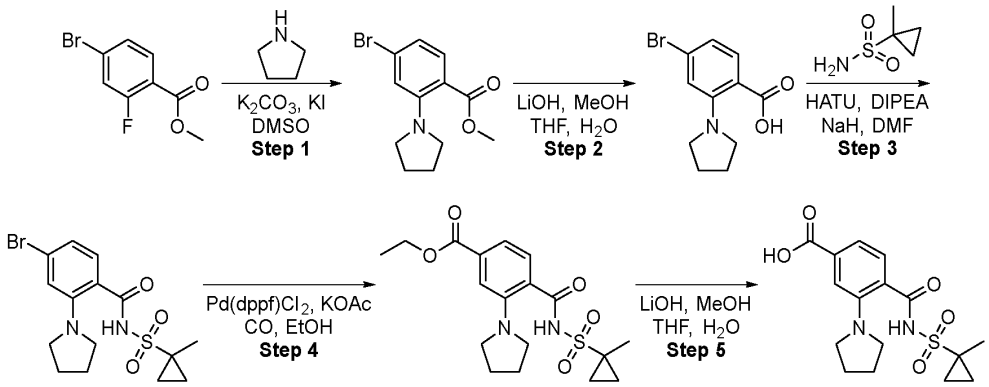
Prepared by an analogous method to Intermediate 43 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.7 mmol) except the Step 1 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 255 mg, 0.57 mmol. Brown solid. LCMS: (System 1, Method G) Rt = 0.45 min, m/z 451.1 $(M+H)^+$ (ES^+).

Intermediate 45: 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



Prepared by an analogous method to Intermediate 43 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.7 mmol) except the Step 1 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 400 mg, 0.94 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.00 min, m/z 422.8 $(M-H)^-$ (ES^-).

Intermediate 46: 4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-3-(pyrrolidin-1-yl)benzoic acid



Step 1

A mixture of methyl 4-bromo-2-fluorobenzoate (5.0 g, 21.6 mmol), K_2CO_3 (8.9 g, 64.7 mmol), KI (1.8 g, 10.8 mmol) and pyrrolidine (2.3 g, 32.3 mmol) in DMSO (100 mL) was stirred at 100 °C overnight. The reaction was allowed to reach RT and partitioned between water (200 mL) and EtOAc (3x200 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (35% DCM/petroleum ether) to afford methyl 4-bromo-2-(pyrrolidin-1-yl)benzoate (5.0 g, 17.7 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.88 min, m/z 283.8 $(M-H)^-$ (ES^-).

Step 2

A mixture of methyl 4-bromo-2-(pyrrolidin-1-yl)benzoate (5.0 g, 17.7 mmol) and $LiOH{\cdot}H_2O$ (2.9 g, 70.7 mmol) in THF (60 mL), MeOH (15 mL) and water (15 mL) was stirred at 65 °C overnight. The reaction was cooled to RT and the organic solvents were removed under reduced pressure. The pH of the resulting aqueous solution was set to ca. 3 by adding HCl aq. 1 N. The precipitate

was recovered by filtration, washed with water and hexane, and dried under reduced pressure to afford 4-bromo-2-(pyrrolidin-1-yl)benzoic acid (4.0 g, 14.8 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.09 min, m/z 269.8 $(M+H)^+$ (ES^+).

Step 3

A mixture of 4-bromo-2-(pyrrolidin-1-yl)benzoic acid (1.1 g, 4.09 mmol), HATU (1.86 g, 4.91 mmol) and DIPEA (2.11 g, 16.36 mmol) in DMF (20 mL) was stirred at RT for 1 h, then 1-methylcyclopropane-1-sulfonamide (1.7 g, 12.3 mmol) and sodium hydride (60% dispersion in mineral oil, 655 mg,16.4 mmol) were added, and the reaction was stirred at RT overnight. The pH of the crude mixture was adjusted to ca. 4 by adding HCl aq. 1 N and the mixture was extracted with EtOAc (3x25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% MeOH/DCM) to afford 4-bromo-*N*-(1-methylcyclopropylsulfonyl)-2-(pyrrolidin-1-yl)benzamide (700 mg, 1.81 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.24 min, m/z 387.3 $(M+H)^+$ (ES^+).

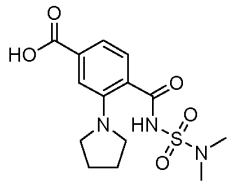
Step 4

A mixture of 4-bromo-*N*-(1-methylcyclopropylsulfonyl)-2-(pyrrolidin-1-yl)benzamide (700 mg, 1.81 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (265 mg, 0.36 mmol) and potassium acetate (532 mg, 5.43 mmol) in EtOH (15 mL) was stirred at 90 °C overnight under CO atmosphere. The mixture was dissolved in MeOH (20 mL) and concentrated under reduced pressure. The residue was dissolved in K_2CO_3 aq. 2 M (30 mL) and washed with EtOAc (3x15 mL). The resulting aqueous layer was acidified to pH 2-3 by adding HCl aq. 1 N and extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford ethyl 4-(1-methylcyclopropylsulfonylcarbamoyl)-3-(pyrrolidin-1-yl)benzoate (600 mg, 1.58 mmol) as yellow oil. LCMS: (System 1, Method A) Rt = 1.42 min, m/z 381.4 $(M+H)^+$ (ES^+).

Step 5

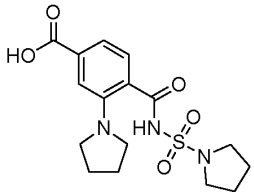
A mixture of ethyl 4-(1-methylcyclopropylsulfonylcarbamoyl)-3-(pyrrolidin-1-yl)benzoate (600 mg, 1.58 mmol) and $LiOH{\cdot}H_2O$ (259 mg, 6.32 mmol) in THF (12 mL), MeOH (3 mL) and water (3 mL) was stirred at RT overnight. The organic solvents were removed under reduced pressure. The pH of the resulting aqueous solution was set to ca. 3 by adding HCl aq. 1 N. The precipitate was recovered by filtration, washed with water and hexane, and dried under reduced pressure to afford 4-(1-methylcyclopropylsulfonylcarbamoyl)-3-(pyrrolidin-1-yl)benzoic acid (500 mg, 1.42 mmol) as a yellow solid. LCMS: (System 1, Method A) Rt = 0.73 min, m/z 353.0 $(M+H)^+$ (ES^+).

Intermediate 47: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-(pyrrolidin-1-yl)benzoic acid



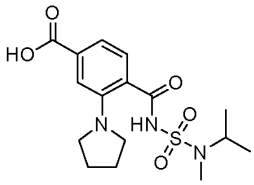
Prepared by analogous method to Intermediate 46 starting except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 320 mg, 0.94 mmol. Yellow solid. LCMS: (System 1, Method H) Rt = 0.12 min, m/z 342.1 $(M+H)^+$ (ES^+).

Intermediate 48: 3-(pyrrolidin-1-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



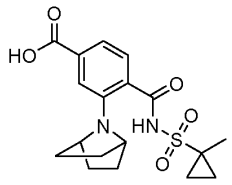
Prepared by analogous method to Intermediate 46 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 370 mg, 1.01 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.72 min, m/z 368.2 $(M+H)^+$ (ES^+).

Intermediate 49: 4-((*N*-isopropyl-*N*-methylsulfamoyl)carbamoyl)-3-(pyrrolidin-1-yl)benzoic acid



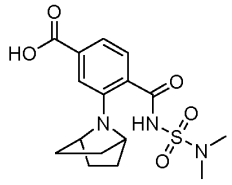
Prepared by analogous method to Intermediate 46 starting except the Step 3 was carried out with *N*-methyl-*N*-isopropylsulfamoyl amide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 820 mg, 2.22 mmol. Yellow solid. LCMS: (System 1, Method H) Rt = 0.94 min, m/z 369.8 $(M+H)^+$ (ES^+).

Intermediate 50: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



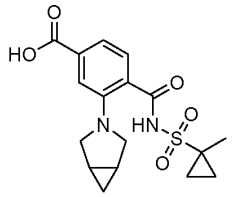
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.44 mmol) and 7-azabicyclo[2.2.1]heptane (1.25 g, 12.9 mmol). Yield: 164 mg, 0.43 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.65 min, m/z 377.2 $(M-H)^-$ (ES^-).

Intermediate 51: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



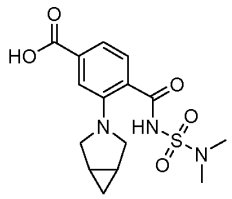
Prepared by analogous method to Intermediate 50 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 215 mg, 0.59 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.59 min, m/z 366.2 $(M-H)^-$ (ES^-).

Intermediate 52: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



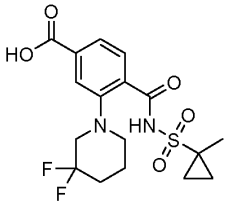
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.0 g, 8.62 mmol) and 3-azabicyclo[3.1.0]hexane (2.15 g, 25.9 mmol). Yield: 430 mg, 1.18 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.27 min, m/z 363.2 $(M-H)^-$ (ES^-).

Intermediate 53: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



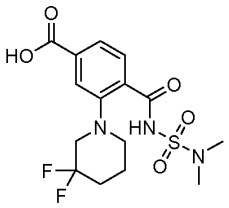
Prepared by analogous method to Intermediate 52 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 440 mg, 1.25 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.27 min, m/z 352.3 $(M-H)^-$ (ES^-).

Intermediate 54: 3-(3,3-difluoropiperidin-1-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



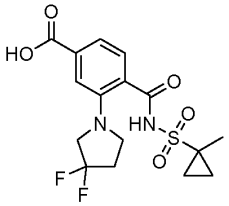
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (3.0 g, 12.9 mmol) and 3,3-difluoropiperidine(4.1 g, 25.8 mmol). Yield: 250 mg, 0.62 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.91 min, m/z 403.0 $(M-H)^-$ (ES^-).

Intermediate 55: 3-(3,3-difluoropiperidin-1-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



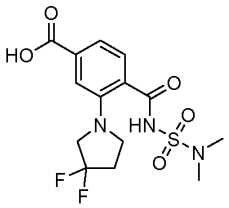
Prepared by analogous method to Intermediate 54 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 295 mg, 0.76 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.92 min, m/z 392.0 $(M+H)^+$ (ES^+).

Intermediate 56: 3-(3,3-difluoropyrrolidin-1-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



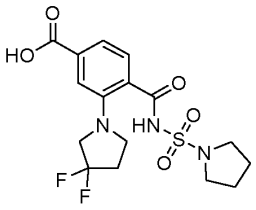
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.0 g, 8.58 mmol) and 3,3-difluoropyrrolidine hydrochloride (3.7 g, 25.8 mmol). Yield: 102 mg, 0.26 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.58 min, m/z 389.0 $(M+H)^+$ (ES^+).

Intermediate 57: 3-(3,3-difluoropyrrolidin-1-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



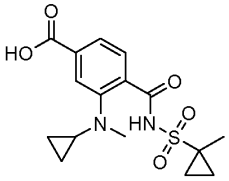
Prepared by analogous method to Intermediate 56 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 111 mg, 0.29 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.54 min, m/z 378.1 $(M-H)^-$ (ES^-).

Intermediate 58: 3-(3,3-difluoropyrrolidin-1-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



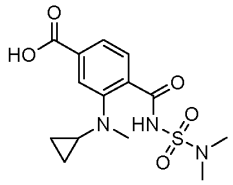
Prepared by analogous method to Intermediate 56 starting except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 130 mg, 0.32 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.61 min, m/z 404.2 $(M+H)^+$ (ES^+).

Intermediate 59: 3-(cyclopropyl(methyl)amino)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



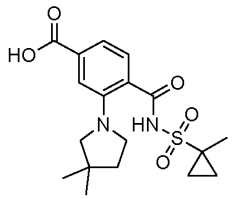
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.6 g, 6.4 mmol) and *N*-methylcyclopropanamine (1.36 g, 19.2 mmol). Yield: 215 mg, 0.61 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.80 min, m/z 353.2 $(M+H)^+$ (ES^+).

Intermediate 60: 3-(cyclopropyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



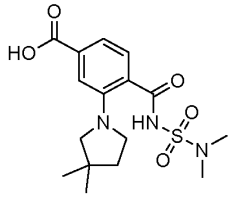
Prepared by analogous method to Intermediate 59 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 192 mg, 0.56 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.80 min, m/z 342.2 $(M+H)^+$ (ES^+).

Intermediate 61: 3-(3,3-dimethylpyrrolidin-1-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



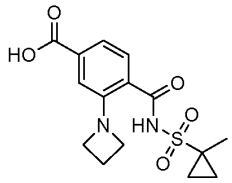
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.1 g, 8.40 mmol) and 3,3-dimethylpyrrolidine (2.5 g, 25.2 mmol). Yield: 430 mg, 1.18 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.27 min, m/z 363.2 $(M-H)^-$ (ES^-).

Intermediate 62: 3-(3,3-dimethylpyrrolidin-1-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



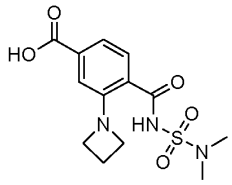
Prepared by analogous method to Intermediate 61 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 310 mg, 0.84 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.90 min, m/z 370.2 $(M+H)^+$ (ES^+).

Intermediate 63: 3-(azetidin-1-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



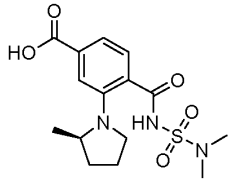
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.1 g, 8.40 mmol) and azetidine (1.44 g, 25.2 mmol). Yield: 200 mg, 0.59 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.31 min, m/z 377.0 $(M+H)^+$ (ES^+).

Intermediate 64: 3-(azetidin-1-yl) -4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



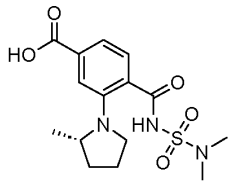
Prepared by analogous method to Intermediate 63 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 205 mg, 0.63 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.25 min, m/z 328.2 $(M+H)^+$ (ES^+).

Intermediate 65: (*R*)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-(2-methylpyrrolidin-1-yl)benzoic acid



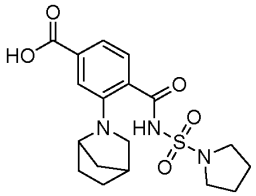
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.4 mmol) and (*R*)-2-methylpyrrolidine hydrochloride (1.6 g, 12.9 mmol) except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 355 mg, 1.18 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.84 min, m/z 356.2 $(M+H)^+$ (ES^+).

Intermediate 66: (*S*)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-(2-methylpyrrolidin-1-yl)benzoic acid



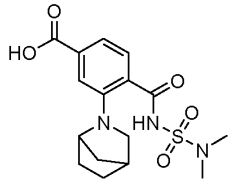
Prepared by analogous method to Intermediate 65 starting from methyl 4-bromo-2-fluorobenzoate (1.9 g, 7.60 mmol) and (*S*)-2-methylpyrrolidine (1.9 g, 22.8 mmol). Yield: 270 mg, 0.76 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.83 min, m/z 356.2 $(M+H)^+$ (ES^+).

Intermediate 67: 3-(2-azabicyclo[2.2.1]heptan-2-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



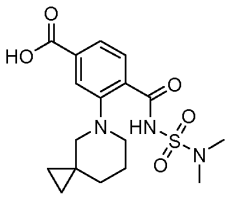
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.5 g, 10.0 mmol) and 2-azabicyclo[2.2.1]heptane (2.9 g, 30 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 460 mg, 1.17 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.83 min, m/z 394.2 $(M+H)^+$ (ES^+).

Intermediate 68: 3-(2-azabicyclo[2.2.1]heptan-2-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



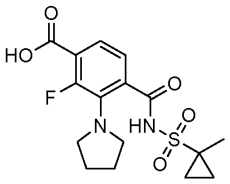
Prepared by analogous method to Intermediate 67 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 440 mg, 1.20 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.91 min, m/z 368.2 $(M+H)^+$ (ES^+).

Intermediate 69: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-(5-azaspiro[2.5]octan-5-yl)benzoic acid



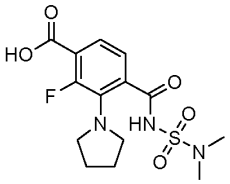
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.3 g, 5.00 mmol) and 5-azaspiro[2.5]octane (1.7 g, 15 mmol) except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 600 mg, 1.57 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 1.21 min, m/z 382.4 $(M+H)^+$ (ES^+).

Intermediate 70: 2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-3-(pyrrolidin-1-yl)benzoic acid



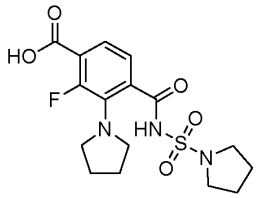
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,3-difluorobenzoate (3.0 g, 12.2 mmol) and pyrrolidine (1.74 g, 24.5 mmol). Yield: 483 mg, 1.30 mmol. White solid. LCMS: (System 1, Method F) Rt = 1.06 min, m/z 371.2 $(M+H)^+$ (ES^+).

Intermediate 71: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluoro-3-(pyrrolidin-1-yl)benzoic acid



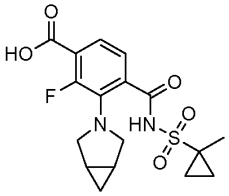
Prepared by analogous method to Intermediate 70 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 496 mg, 1.38 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.01 min, m/z 360.2 $(M+H)^+$ (ES^+).

Intermediate 72: 2-fluoro-3-(pyrrolidin-1-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



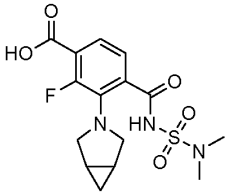
Prepared by analogous method to Intermediate 70 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 400 mg, 1.08 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.96 min, m/z 386.2 $(M+H)^+$ (ES^+).

Intermediate 73: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



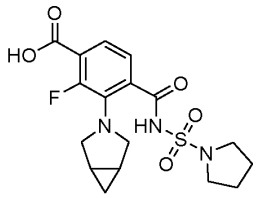
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,3-difluorobenzoate (3.0 g, 12.2 mmol) and 3-azabicyclo[3.1.0]hexane (2.9 g, 24.5 mmol). Yield: 260 mg, 0.68 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.10 min, m/z 381.2 $(M-H)^-$ (ES^-).

Intermediate 74: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



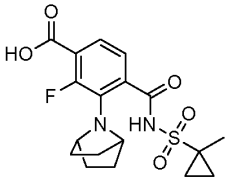
Prepared by analogous method to Intermediate 73 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 280 mg, 0.75 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.09 min, m/z 370.2 $(M-H)^-$ (ES^-).

Intermediate 75: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



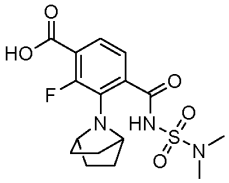
Prepared by analogous method to Intermediate 73 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 214 mg, 0.54 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 1.01 min, m/z 398.2 $(M+H)^+$ (ES^+).

Intermediate 76: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



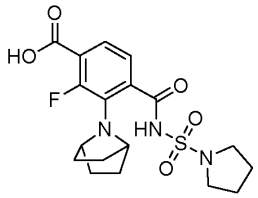
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,3-difluorobenzoate (3.1 g, 12.4 mmol) and 7-azabicyclo[2.2.1]heptane (3.61 g, 37.2 mmol). Yield: 230 mg, 0.58 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.70 min, m/z 397.0 $(M+H)^+$ (ES^+).

Intermediate 77: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



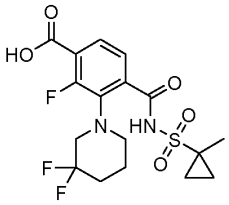
Prepared by analogous method to Intermediate 76 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 275 mg, 0.71 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.48 min, m/z 386.0 $(M+H)^+$ (ES^+).

Intermediate 78: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



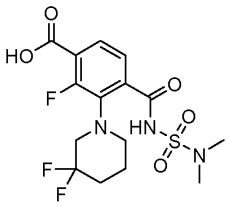
Prepared by analogous method to Intermediate 76 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 320 mg, 0.78 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.83 min, m/z 412.2 $(M+H)^+$ (ES^+).

Intermediate 79: 3-(3,3-difluoropiperidin-1-yl)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,3-difluorobenzoate (2.0 g, 7.97 mmol) and 3,3-difluoropiperidine hydrochloride (3.8 g, 23.9 mmol). Yield: 180 mg, 0.43 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.65 min, m/z 421.1 $(M+H)^+$ (ES^+).

Intermediate 80: 3-(3,3-difluoropiperidin-1-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



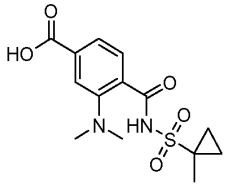
Prepared by analogous method to Intermediate 79 except the Step 3 was carried out with *N*,*N*-dimethylsulfamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 165 mg, 0.40 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.62 min, m/z 410.1 $(M+H)^+$ (ES^+).

Intermediate 81: methyl 4-bromo-2-(dimethylamino)benzoate



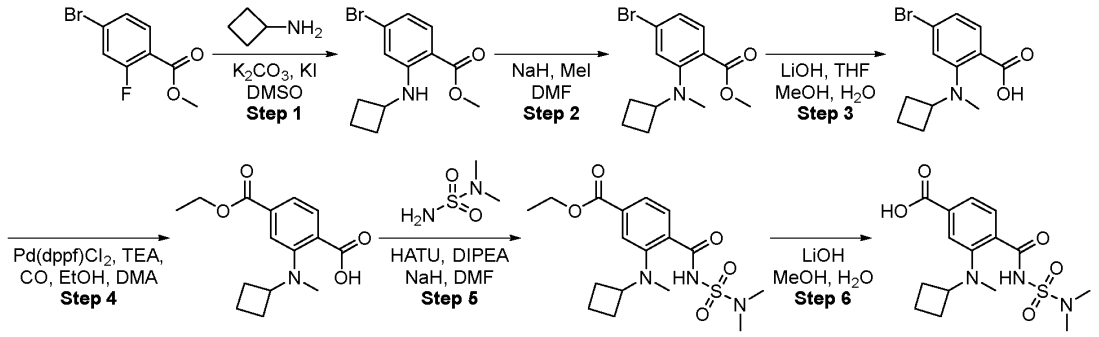
Sodium hydride (60% in mineral oil, 1.56 g, 39.12 mmol) was added to a solution of methyl 2-amino-4-bromobenzoate (1.5 g, 6.5 mmol) in DMF (14 mL) and the reaction was stirred at RT for 10 min. Iodomethane (5.6 g, 39.1 mmol) was added and the mixture was stirred at RT overnight. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (3x100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford methyl 4-bromo-2-(dimethylamino)benzoate (365 mg, 1.41 mmol) as a yellow oil. LCMS: (System 2, Method B), Rt = 1.48 min, m/z 258.0 $(M+H)^+$ (ES^+).

Intermediate 82: 3-(dimethylamino)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 46 (Steps 2 to 5) starting at Step 2 from methyl 4-bromo-2-(dimethylamino)benzoate (Intermediate 81, 340 mg, 1.39 mmol). Yield: 150 mg, 0.46 mmol. Yellow solid. LCMS: (System 2, Method B) Rt = 1.27 min, m/z 327.1 $(M+H)^+$ (ES^+).

Intermediate 83: 3-(cyclobutyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



Step 1

A mixture of methyl 4-bromo-2-fluorobenzoate (1.0 g, 4.29 mmol), K_2CO_3 (1.8 g, 12.9 mmol), KI (356 mg, 2.15 mmol) and cyclobutanamine (610 mg, 8.58 mmol) in DMSO (20 mL) was stirred at 100 °C overnight. The reaction mixture was allowed to reach RT and was partitioned between water (80 mL) and EtOAc (3x80 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (35% DCM/petroleum ether) to afford methyl 4-bromo-2-(cyclobutylamino)benzoate (1.0 g, 3.52 mmol) as a colourless oil. LCMS: (System 1, Method A) Rt = 2.69 min, m/z 284.2 $(M+H)^+$ (ES^+).

Step 2

Sodium hydride (60% dispersion in mineral oil, 422 mg, 17.6 mmol) was added in small portions to a solution of methyl 4-bromo-2-(cyclobutylamino)benzoate (1.0 g, 3.52 mmol) in DMF (15 mL) and the mixture was stirred at RT for 1 h. Iodomethane (3.5 g, 24.6 mmol) was added and the mixture was stirred at RT overnight. The mixture was poured into NH_4Cl aq. sat. (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM) to afford methyl 4-bromo-2-(cyclobutyl(methyl)amino)benzoate (950 mg, 3.19 mmol) as a pale-yellow oil. LCMS: (System 1, Method F) Rt = 2.01 min, m/z 298.2 $(M+H)^+$ (ES^+).

Step 3

A mixture of 4-bromo-2-(cyclobutyl(methyl)amino)benzoate (950 mg, 3.19 mmol) and $LiOH{\cdot}H_2O$ (668 mg, 15.9 mmol) in THF (20 mL), MeOH (5 mL) and water (5 mL) was stirred at 60 °C overnight. Organic solvents were removed under reduced pressure, then the pH of the mixture was adjusted to ca. 3 by adding HCl aq. 1 N. The precipitate was recovered by filtration, washed with water and hexane, and dried under reduced pressure to afford 4-bromo-2-(cyclobutyl(methyl)amino)benzoic acid (815 mg, 2.87 mmol) as a yellow solid. LCMS: (System 1, Method A) Rt = 1.45 min, m/z 284.1 $(M+H)^+$ (ES^+).

Step 4

A mixture of 4-bromo-2-(cyclobutyl(methyl)amino)benzoic acid (815 mg, 2.87 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (420 mg, 0.57 mmol) and TEA (1.45 g, 14.34 mmol) in DMA (5 mL) and EtOH (20 mL) was stirred at 90 °C overnight under CO atmosphere. The reaction mixture was allowed to reach RT and Na_2CO_3 aq. sat. (20 mL) was added. The reaction mixture was washed with EtOAc (3x20 mL), and after adjusting the pH of the aqueous layer to ca. 3 with HCl aq. 1 N, extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 2-(cyclobutyl(methyl)amino)-4-(ethoxycarbonyl)benzoic acid (600 mg, 2.16 mmol) as a brown solid. LCMS: (System 1, Method F) Rt = 1.23 min, m/z 276.1 $(M-H)^-$ (ES^-).

Step 5

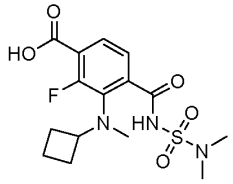
A mixture of 2-(cyclobutyl(methyl)amino)-4-(ethoxycarbonyl)benzoic acid (600 mg, 2.16 mmol), EDCI (830 mg, 4.33 mmol), DMAP (529 mg, 4.33 mmol) *N*,*N*-dimethylsulfamide (537 mg, 4.33 mmol) in DCM (20 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (20 mL) and DCM (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered

and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% MeOH/DCM) to afford ethyl 3-(cyclobutyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (320 mg, 0.83 mmol) as a brown oil. LCMS: (System 1, Method A) Rt = 2.02 min, m/z $(M+H)^+$ (ES^+).

Step 6

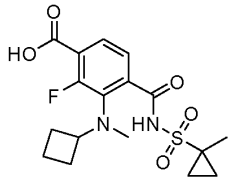
A mixture of ethyl 3-(cyclobutyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoate (320 mg, 0.83 mmol) and $LiOH{\cdot}H_2O$ (175 mg, 4.17 mmol) in MeOH (16 mL) and in water (4 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure, and the pH of the resulting aqueous solution was adjusted to ca. 3 by adding HCl aq. 1 N. The precipitate was recovered by filtration, washed with water and hexane, and dried under reduced pressure to afford 3-(cyclobutyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid (200 mg, 0.56 mmol) as a brown solid. LCMS: (System 1, Method A) Rt = 1.14 min, m/z 354.2 $(M-H)^-$ (ES^-).

Intermediate 84: 3-(cyclobutyl(methyl)amino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



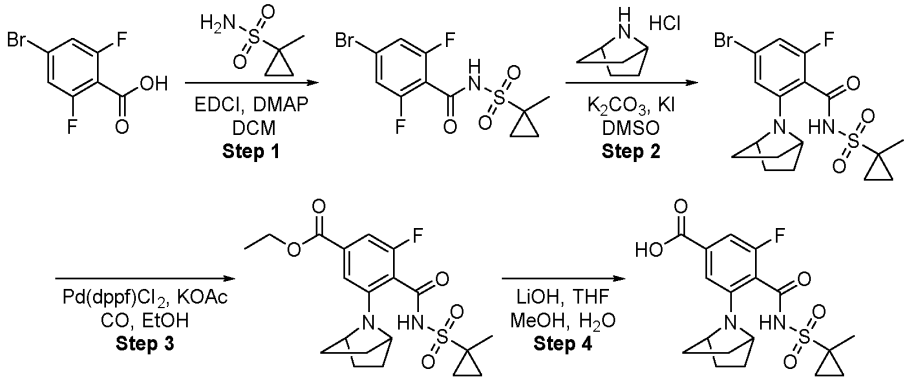
Prepared by analogous method to Intermediate 83 starting from methyl 4-bromo-2,3-difluorobenzoate (25.0 g, 106 mmol). Yield: 450 mg, 1.21 mmol. White solid. LCMS: (System 1, Method F) Rt = 1.01 min, m/z 372.3 $(M-H)^-$ (ES^-).

Intermediate 85: 3-(cyclobutyl(methyl)amino)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 83 except the Step 5 was carried out with 1-methylcyclopropane-1-sulfonamide in place of *N*,*N*-dimethylsulfamide. Yield: 450 mg, 1.17 mmol. White solid. LCMS: (System 1, Method F) Rt = 1.10 min, m/z 383.3 $(M-H)^-$ (ES^-).

Intermediate 86: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Step 1

A mixture of 4-bromo-2,6-difluorobenzoic acid (1.0 g, 4.22 mmol), 1-methylcyclopropane-1-sulfonamide (1.14 g, 8.44 mmol), EDCI (1.62 g, 8.44 mmol) and DMAP (1.03 g, 8.44 mmol) in DCM (40 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (40 mL) and DCM (3x40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-3% MeOH/DCM) to afford 4-bromo-2,6-difluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide (1.1 g, 3.00 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.07 min, m/z 353.6 $(M+H)^+$ (ES^+).

Step 2

A mixture of 4-bromo-2,6-difluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide (1.06 g, 2.99 mmol), K_2CO_3 (1.24 g, 8.98 mmol), KI (248 mg, 1.50 mmol) and 7-azabicyclo[2.2.1]heptane hydrochloride (800 mg, 5.99 mmol) in DMSO (15 mL) was stirred at 120 °C overnight. The reaction mixture was partitioned between water (60 mL) and EtOAc (3x60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford 2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-bromo-6-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide (800 mg, 1.85 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.24 min, m/z 430.7 $(M+H)^+$ (ES^+).

Step 3

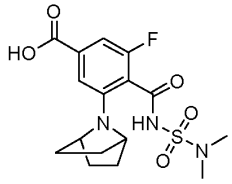
A mixture of 2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-bromo-6-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide (500 mg, 1.16 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (170 mg, 0.23 mmol) and KOAc (341 mg, 3.48 mmol) in EtOH (15 mL) was stirred at 80 °C for 5 h under CO atmosphere. The mixture was

concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (1-3% MeOH/DCM) to afford ethyl 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoate (300 mg, 0.71 mmol) as a brown oil. LCMS: (System 1, Method F) Rt = 1.22 min, m/z 425.0 $(M+H)^+$ (ES^+).

Step 4

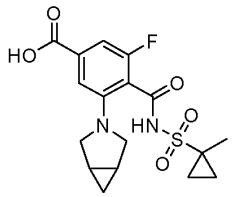
A mixture of ethyl 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoate (300 mg, 0.71 mmol) and $LiOH{\cdot}H_2O$ (148 mg, 3.53 mmol) in THF (12 mL), MeOH (3 mL) and water (3 mL) was stirred at RT overnight. The pH of the mixture was adjusted to ca. 8 by adding HCl aq. 1 N. Then the organic solves were evaporated under reduced pressure and the pH of the resulting aqueous phase was adjusted to ca. 3 by adding HCl aq. 1 N. The precipitate was collected by filtration, washed with water then hexane and dried to afford 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid (215 mg, 0.54 mmol) as a brown solid. LCMS: (System 1, Method F) Rt = 0.55 min, m/z 395.4 $(M-H)^-$ (ES^-).

Intermediate 87: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-fluorobenzoic acid



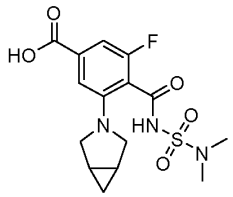
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2,6-difluorobenzoic acid (1.0 g, 4.22 mmol) and *N*,*N*-dimethylsulfamide (1.05 g, 8.44 mmol). Yield: 335 mg, 0.87 mmol. Brown solid. LCMS: (System 1, Method F) Rt = 0.38 min, m/z 384.4 $(M-H)^-$ (ES^-).

Intermediate 88: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



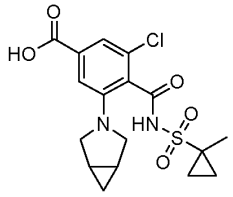
Prepared by analogous method to Intermediate 86 starting except the Step 2 was carried out with 3-azabicyclo[3.1.0]hexane hydrochloride in place of 7-azabicyclo[2.2.1]heptane hydrochloride. Yield: 265 mg, 0.69 mmol. Brown solid. LCMS: (System 1, Method F) Rt = 0.43 min, m/z 381.3 $(M-H)^-$ (ES^-).

Intermediate 89: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-fluorobenzoic acid



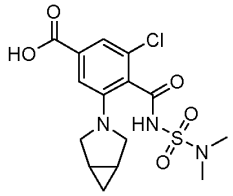
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2,6-difluorobenzoic acid (2.0 g, 8.44 mmol) and *N*,*N*-dimethylsulfamide (2.1 g, 16.9 mmol) except the Step 2 was carried out with 3-azabicyclo[3.1.0]hexane hydrochloride in place of 7-azabicyclo[2.2.1]heptane hydrochloride. Yield: 636 mg, 1.71 mmol. Brown solid. LCMS: (System 1, Method F) Rt = 0.25 min, m/z 370.3 $(M-H)^-$ (ES^-).

Intermediate 90: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-5-chloro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-chloro-6-fluorobenzoic acid (2.0 g, 7.94 mmol) and 1-methylcyclopropane-1-sulfonamide (2.1 g, 15.8 mmol) except the Step 2 was carried out with 3-azabicyclo[3.1.0]hexane hydrochloride in place of 7-azabicyclo[2.2.1]heptane hydrochloride. Yield: 394 mg, 0.99 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.52 min, m/z 397.0 $(M-H)^-$ (ES^-).

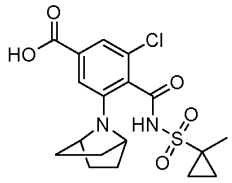
Intermediate 91: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-5-chloro-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-chloro-6-fluorobenzoic acid (2.0 g, 7.94 mmol) and *N*,*N*-dimethylsulfamide (2.10 g, 15.8 mmol) except the Step 2 was carried out with 3-azabicyclo[3.1.0]hexane hydrochloride in place of 7-

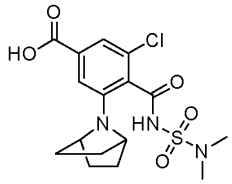
azabicyclo[2.2.1]heptane hydrochloride. Yield: 349 mg, 0.90 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.39 min, m/z 386.0 $(M-H)^-$ (ES^-).

Intermediate 92: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-5-chloro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



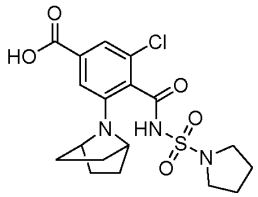
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-chloro-6-fluorobenzoic acid (1.4 g, 5.52 mmol) and 1-methylcyclopropane-1-sulfonamide (1.5 g, 11.01 mmol). Yield: 172 mg, 0.42 mmol. Brown solid. LCMS: (System 1, Method F) Rt = 0.59 min, m/z 411.1 $(M-H)^-$ (ES^-).

Intermediate 93: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-chloro-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)benzoic acid



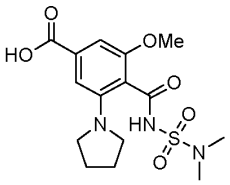
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-chloro-6-fluorobenzoic acid (3.0 g, 11.8 mmol) and *N*,*N*-dimethylsulfamide (2.9 g, 23.7 mmol). Yield: 235 mg, 0.58 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 0.77 min, m/z 399.6 $(M-H)^-$ (ES^-).

Intermediate 94: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-5-chloro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



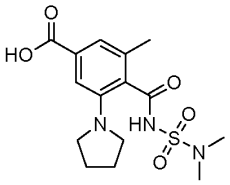
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-chloro-6-fluorobenzoic acid (600 mg, 2.37 mmol) and pyrrolidine-1-sulfonamide (1.1 g, 7.10 mmol). Yield: 340 mg, 0.54 mmol. Brown solid. LCMS: (System 1, Method F) Rt = 0.74 min, m/z 412.0 $(M-H)^-$ (ES^-).

Intermediate 95: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-methoxy-5-(pyrrolidin-1-yl)benzoic acid



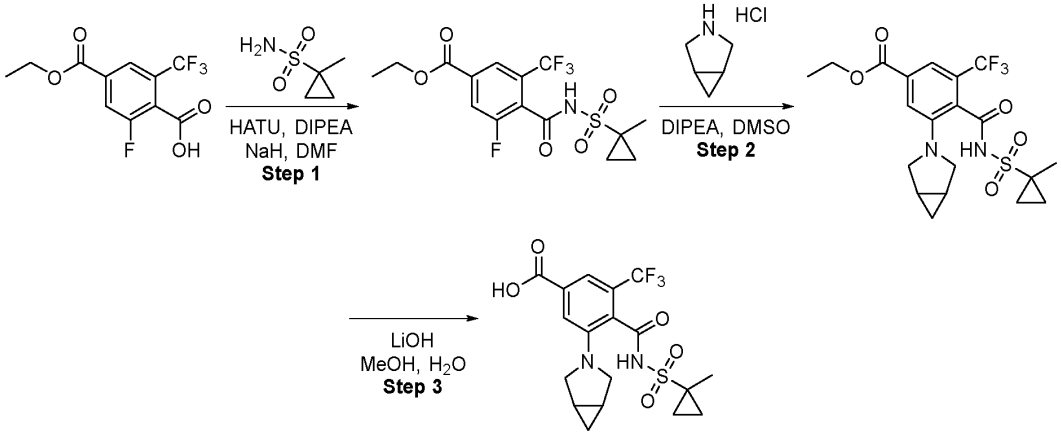
Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-fluoro-6-methoxybenzoic acid (2.1 g, 8.40 mmol) and *N*,*N*-dimethylsulfamide (3.12 g, 25.2 mmol) except the Step 2 was carried out with pyrrolidine in place of 7-azabicyclo[2.2.1]heptane hydrochloride. Yield: 700 mg, 1.88 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.54 min, m/z 372.2 $(M+H)^+$ (ES^+).

Intermediate 96: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-methyl-5-(pyrrolidin-1-yl)benzoic acid



Prepared by analogous method to Intermediate 86 starting from 4-bromo-2-fluoro-6-methylbenzoic acid (1.6 g, 6.90 mmol) and *N*,*N*-dimethylsulfamide (2.57 g, 20.7 mmol) except the Step 2 was carried out with pyrrolidine in place of 7-azabicyclo[2.2.1]heptane hydrochloride. Yield: 1.5 g, 4.22 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.30 min, m/z 339.2 $(M+H)^+$ (ES^+).

Intermediate 97: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



Step 1

A mixture of 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (1.6 g, 5.71 mmol), HATU (2.6 g, 6.85 mmol) and DIPEA (3.0 g, 22.8 mmol) in DMF (50 mL) was stirred at RT for 1.5 h. 1-methylcyclopropane-1-sulfonamide (2.31 g, 17.13 mmol) was added, followed by sodium hydride (60% dispersion in mineral oil, 914 mg, 22.84 mmol) and the reaction mixture was stirred at RT overnight. The mixture was poured into NH_4Cl aq. sat. (150 mL), HCl aq. 1 N (20 mL) and was added and the mixture was extracted with EtOAc (3x150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford ethyl 3-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (1.5 g, 3.78 mmol) as a brown oil. LCMS: (System 1, Method A) Rt = 1.81 min, m/z 398.0 $(M+H)^+$ (ES^+).

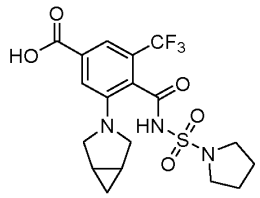
Step 2

A mixture of 3-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (630.0 mg, 1.59 mmol), DIPEA (1.02 g, 7.93 mmol) and 3-azabicyclo[3.1.0]hexane (263 mg, 3.17 mmol) in DMSO (3 mL) was stirred at 100 °C in a sealed vial for 48 h. The reaction mixture was allowed to reach RT and partitioned between water (10ml) and EtOAc (3x10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford ethyl 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (220 mg, 0.48 mmol) as a brown solid which was used in the next step without further purification. LCMS: (System 1, Method F) Rt = 1.30 min, 461.2 $(M+NH_4)^+$ (ES^+).

Step 3

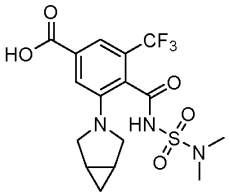
A mixture of ethyl 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoate (220 mg, 0.48 mmol) and $LiOH{\cdot}H_2O$ (78 mg, 1.91 mmol) in THF (16 mL), MeOH (4 mL) and water (4 mL) was stirred at RT overnight. The organic solvents were removed under reduced pressure, then the pH of the resulting aqueous layer was adjusted to ca. 3 by adding HCl aq. 1 N. The precipitate was recovered by filtration, washed with water and hexane, and dried under reduced pressure to afford 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid (180 mg, 0.42 mmol) as a brown solid. LCMS: (System 1, Method A) Rt = 0.99 min, 433.3 $(M+NH_4)^+$ (ES^+).

Intermediate 98: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



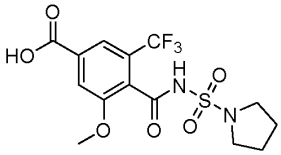
Prepared by analogous method to Intermediate 97 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 6.90 mmol) and pyrrolidine-1-sulfonamide (2.6 g, 17.13 mmol). Yield: 170 mg, 0.38 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.09 min, m/z 448.2 $(M+H)^+$ (ES^+).

Intermediate 99: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



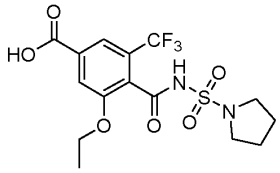
Prepared by analogous method to Intermediate 97 starting from Intermediate 42 (1.6 g, 6.90 mmol) and *N*,*N*-dimethylsulfamide (2.57 g, 20.7 mmol). Yield: 1.5 g, 4.22 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.30 min, m/z 339.2 $(M+H)^+$ (ES^+).

Intermediate 100: 3-methoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



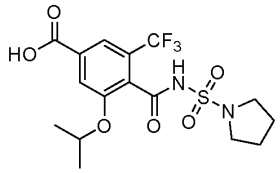
Prepared by an analogous method to Intermediate 43 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.71 mmol) except the Step 1 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide and the Step 3 was carried out with MeOH instead of cyclopentanol. Yield: 260 mg, 0.57 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.60 min, m/z 395.0 $(M-H)^-$ (ES^-).

Intermediate 101: 3-ethoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



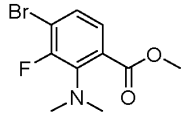
Prepared by an analogous method to Intermediate 100 except Step 3 was carried out with EtOH instead of MeOH. Yield: 270 mg, 0.66 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.80 min, m/z 409.2 $(M-H)^-$ (ES^-).

Intermediate 102: 3-isopropoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



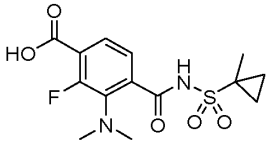
Prepared by an analogous method to Intermediate 100 except the Step 3 was carried out with isopropanol instead of MeOH. Yield: 280 mg, 0.66 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.98 min, m/z 423.0 $(M-H)^-$ (ES^-).

Intermediate 103: methyl 4-bromo-2-(dimethylamino)-3-fluorobenzoate



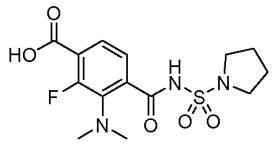
Prepared by an analogous method to Intermediate 81 starting from methyl 2-amino-4-bromo-3-fluorobenzoate (6.4 g, 160 mmol). Yield: 3.6 g, 13.1 mmol. Yellow oil. LCMS: (System 1, Method F) Rt = 1.84 min, m/z 276.0 $(M+H)^+$ (ES^+).

Intermediate 104: 3-(dimethylamino)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



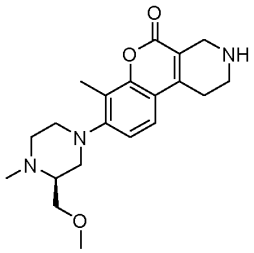
Prepared by an analogous method to Intermediate 82 starting from 2-amino-4-bromo-3-fluorobenzoic acid (Intermediate 103, 3.6 g, 13.1 mmol). Yield: 340 mg, 0.99 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.52 min, m/z 342.8 $(M-H)^-$ (ES^-).

Intermediate 105: 3-(dimethylamino)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



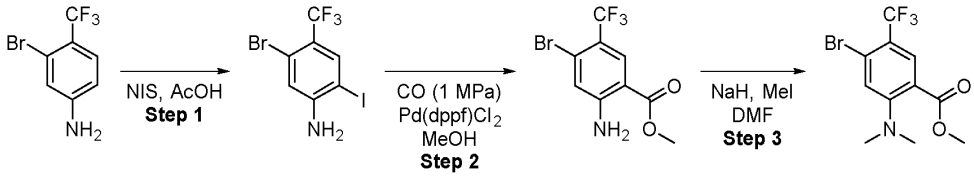
Prepared by an analogous method to Intermediate 82 starting from 2-amino-4-bromo-3-fluorobenzoic acid (Intermediate 103, 3.6 g, 13.1 mmol). Yield: 430 mg, 1.20 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.76 min, m/z 394.0 $(M+H)^+$ (ES^+).

Intermediate 106: (S)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*S*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 37, 205 mg, 1.43 mmol) and *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2, 550 mg, 1.19 mmol). Yield: 205 mg, 0.57 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.51 min, m/z 358.4 $(M+H)^+$ (ES^+).

Intermediate 107: methyl 2-amino-4-bromo-5-(trifluoromethyl)benzoate



Step 1

NIS (5.7 g, 25.1 mmol) was added to a solution of 3-bromo-4-(trifluoromethyl)aniline (5.0 g, 20.9 mmol) in AcOH (50 mL) and the reaction was stirred at RT overnight. The mixture was partitioned between water (50 mL) and EtOAc (3x50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-30% EtOAc/petroleum ether) to afford 5-bromo-2-iodo-4-

(trifluoromethyl)aniline (5.6 g,15.3 mmol) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.82 (s, 1H), 7.07 (s, 1H), 6.20 (s, 2H).

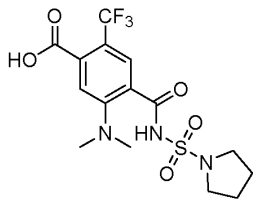
Step 2

A solution of 5-bromo-2-iodo-4-(trifluoromethyl)aniline (5.6 g, 15.3 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.2 g, 3.07 mmol) and KOAc (4.5 g, 46.0 mmol) in MeOH (100 mL) was stirred at 30 °C overnight under CO (1 Mpa) atmosphere. The reaction mixture was partitioned between Na_2CO_3 aq. sat. (15 mL) and EtOAc (3x100 mL). The pH of the aqueous layer was adjusted to pH ca. 3 with HCl aq. 1 N and the aqueous layer extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford methyl 2-amino-4-bromo-5-(trifluoromethyl)benzoate (2.8 g, 9.43 mmol) as a black solid which was used in the next step without further purification. LCMS: (System 1, Method G). Rt = 0.99 min, m/z 296.0 $(M-H)^-$ (ES^-).

Step 3

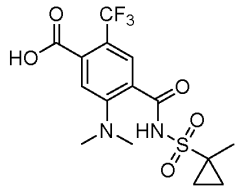
Sodium hydride (60% dispersion in mineral oil, 2.7 g, 56.6 mmol) was added to a solution of methyl 2-amino-4-bromo-5-(trifluoromethyl)benzoate (2.8 g, 9.43 mmol) in DMF (30 mL) and the reaction was stirred at RT for 10 min. Iodomethane (10.7 g, 75.4 mmol) was added and the mixture was stirred at RT overnight. The reaction was partitioned between water (100 mL) and EtOAc (3x30 mL). The combined organic layers were washed with brine (3x30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford methyl 4-bromo-2-(dimethylamino)-5-(trifluoromethyl)benzoate (2.0 g, 6.2 mmol) as yellow oil. LCMS: (System 1, Method A), Rt = 2.10 min, m/z 326.2 $(M+H)^+$ (ES^+).

Intermediate 108: 5-(dimethylamino)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-2-(trifluoromethyl)benzoic acid



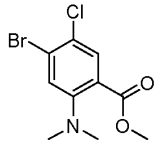
Prepared by analogous method to Intermediate 46 (Steps 2 to 5) from Intermediate 107 (2.0 g, 6.2 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 360 mg, 0.88 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.24 min, m/z 408.0 $(M-H)^-$ (ES^-).

Intermediate 109: 5-(dimethylamino)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-2-(trifluoromethyl)benzoic acid



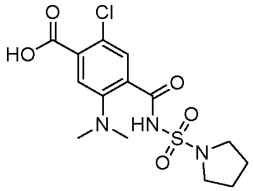
Prepared by analogous method to Intermediate 46 (steps 2 to 5) from Intermediate 107 (2.0 g, 6.2 mmol). Yield: 370 mg, 0.94 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.36 min, m/z 393.0 $(M-H)^-$ (ES^-).

Intermediate 110: methyl 4-bromo-5-chloro-2-(diethylamino)benzoate



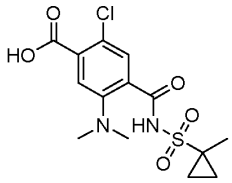
Prepared by analogous method to Intermediate 81 starting from 2-amino-4-bromo-5-chlorobenzoic acid (5.0 g, 22.1 mmol). Yield: 4.5 g, 14.4 mmol. Yellow oil. LCMS: (System 1, Method G) Rt = 1.04 min, m/z 292.0 $(M+H)^+$ (ES^+).

Intermediate 111: 2-chloro-5-(dimethylamino)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



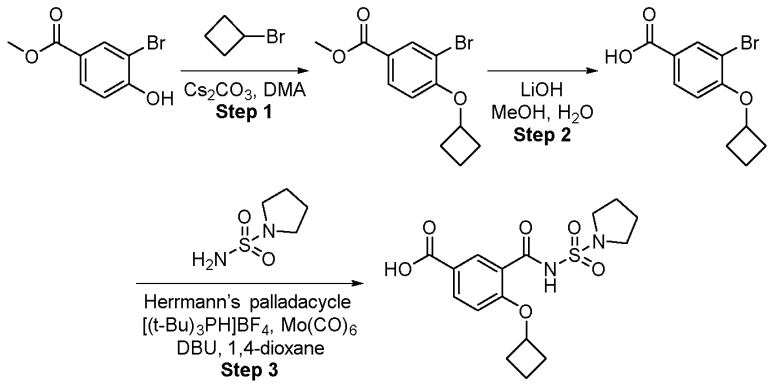
Prepared by analogous method to Intermediate 46 (steps 2 to 5) from methyl 4-bromo-5-chloro-2-(dimethylamino)benzoate (Intermediate 110, 2.5 g, 8.59 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 540 mg, 1.44 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.41 min, m/z 374.0 $(M-H)^-$ (ES^-).

Intermediate 112: 2-chloro-5-(dimethylamino)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 46 (steps 2 to 5) from methyl 4-bromo-5-chloro-2-(dimethylamino)benzoate (Intermediate 110, 2.5 g, 8.59 mmol). Yield: 510 mg, 1.41 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.23 min, m/z 359.0 $(M-H)^-$ (ES^-).

Intermediate 113: 4-cyclobutoxy-3-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

Bromocyclobutane (2.6 g, 19.6 mmol) was added to a solution of methyl 3-bromo-4-hydroxybenzoate (3.0 g, 13.0 mmol) and K_2CO_3 (3.6 g, 26.1 mmol) in DMF (30 mL) and the reaction was stirred at 80 °C overnight. The mixture was partitioned between water (100 mL) and EtOAc (3x60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 3-bromo-4-cyclobutoxybenzoate (3.5 g, 12.3 mmol) as a white solid. LCMS: (System 2, Method B) Rt = 2.09 min, m/z 285.0 $(M+H)^+$ (ES^+).

Step 2

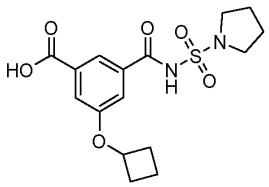
A solution of methyl 3-bromo-4-cyclobutoxybenzoate (3.5 g, 12.3 mmol) and $LiOH{\cdot}H_2O$ (2.6 g, 61.6 mmol) in MeOH (100 mL) and water (30 mL) was stirred at RT overnight. The pH of the mixture was adjusted to pH ca. 3 by adding HCl aq. 1 N. The organic solvent was evaporated under reduced pressure and the resulting precipitate was recovered by filtration, washed with

water, hexane, and dried to afford 3-bromo-4-cyclobutoxybenzoic acid (3.1 g, 11.4 mmol) as a white solid. LCMS: (System 2, Method B) Rt = 1.81 min, 271.0 $(M+H)^+$ (ES^+).

Step 3

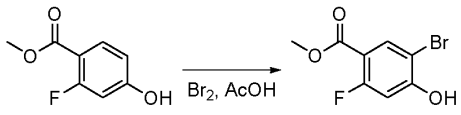
A solution of 3-bromo-4-cyclobutoxybenzoic acid (1.0 g, 3.7 mmol), pyrrolidine-1-sulfonamide (1.5 g, 11 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Herrmann's palladacycle, 341 mg, 0.4 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (217 mg, 0.70 mmol), molybdenum hexacarbonyl (968 mg, 5.5 mmol) and DBU (1.7 g, 11.0 mmol) in 1,4-dioxane (30 mL) was stirred at 100 °C for 15 minutes under microwave irradiation. Once the reaction was cooled down to RT, MeOH (30 mL) was added and solvents were removed under reduced pressure. K_2CO_3 aq. 2 M (30 mL) was added and reaction mixture washed with EtOAc (3x40 mL). The pH of the aqueous layer was adjusted to pH ca. 4-5 by adding HCl aq. 1 N, and reaction mixture extracted with EtOAc (3x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford 4-cyclobutoxy-3-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (700 mg, 1.90 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.24 min, m/z 366.8 $(M-H)^-$ (ES^-).

Intermediate 114: 3-cyclobutoxy-5-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 113 from methyl 3-bromo-5-hydroxybenzoate (3.0 g, 13.0 mmol). Yield: 410 mg, 1.11 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.14 min, m/z 366.8 $(M-H)^-$ (ES^-).

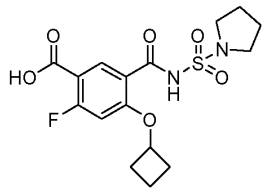
Intermediate 115: methyl 5-bromo-2-fluoro-4-hydroxybenzoate



A mixture of methyl 2-fluoro-4-hydroxybenzoate (2.0 g, 11.8 mmol) in AcOH (30 mL) was stirred at 0 °C for 10 min, then bromine (1.9 g, 35.3 mmol) was added and the reaction was allowed to reach RT and stirred overnight. The mixture was partitioned between water (100 mL) and EtOAc

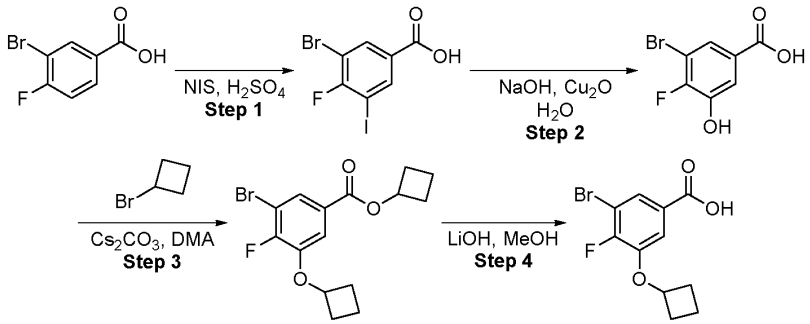
(3x60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 5-bromo-2-fluoro-4-hydroxybenzoate (800 mg, 3.23 mmol) as a white solid. LCMS: (System 1, Method F) Rt = 1.00 min, 247.0 $(M-H)^-$ (ES^-).

Intermediate 116: 4-cyclobutoxy-2-fluoro-5-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 113 from methyl 5-bromo-2-fluoro-4-hydroxybenzoate (Intermediate 115, 800 g, 3.23 mmol). Yield: 215 mg, 0.56 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.20 min, m/z 387.3 $(M+H)^+$ (ES^+).

Intermediate 117: 3-bromo-5-cyclobutoxy-4-fluorobenzoic acid



Step 1

NIS (2.3 g, 10.1 mmol) was added to a suspension of 3-bromo-4-fluorobenzoic acid (2.0 g, 9.17 mmol) in H_2SO_4 (40 mL) at 0 °C and the mixture was stirred at RT overnight. The reaction was poured into ice water (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-bromo-4-fluoro-5-iodobenzoic acid (2.2 g, 6.40 mmol) as a white solid which was used in the next step without further purification. LCMS: (System 1, Method B) Rt = 1.14 min, m/z 342.8 $(M+H)^+$ (ES^+).

Step 2

Copper(I) oxide (1.8 g, 12.80 mmol) was added to a solution of 3-bromo-4-fluoro-5-iodobenzoic acid (2.2 g, 6.40 mmol) and NaOH (1.0 g, 25.6 mmol) in water (30 mL) and the mixture was stirred at 100 °C overnight. The pH of the mixture was adjusted to ca. 3 with HCl aq. 1 N and this aqueous phase was extracted with EtOAc (3x330 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-bromo-4-fluoro-5-hydroxybenzoic acid (900 mg, 3.95 mmol) as a white solid which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 0.91 min, m/z 232.8 $(M-H)^-$ (ES^-).

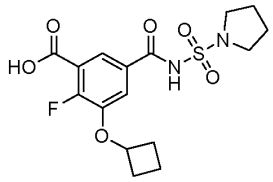
Step 3

A mixture of 3-bromo-4-fluoro-5-hydroxybenzoic acid (900 mg, 3.85 mmol), Cs_2CO_3 (2.5 g, 7.69 mmol) and bromocyclobutane (2.1 g, 15.4 mmol) in DMA (20 mL) was stirred at 60 °C overnight. The reaction was partitioned between water (60 mL) and EtOAc (3x30 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford cyclobutyl 3-bromo-5-cyclobutoxy-4-fluorobenzoate (1.1 g, 3.21 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 2.41 min, m/z 343.0 $(M+H)^+$ (ES^+).

Step 4

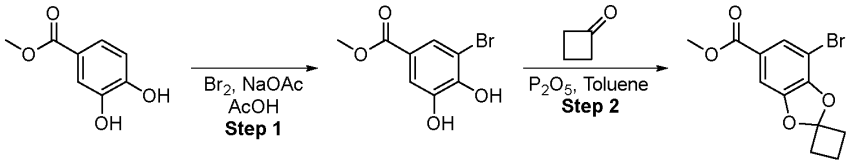
A mixture of cyclobutyl 3-bromo-5-cyclobutoxy-4-fluorobenzoate (1.1 g, 3.21 mmol) and $LiOH{\cdot}H_2O$ (811 mg, 19.3 mmol) in MeOH (20 mL) and water (5 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure and the pH of the mixture was adjusted to ca. 5 with HCl aq. 1 N and the resulting solution was extracted with EtOAc (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-bromo-5-cyclobutoxy-4-fluorobenzoic acid (900 mg, 3.11 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.41 min, m/z 286.8 $(M-H)^-$ (ES^-).

Intermediate 118: 3-cyclobutoxy-2-fluoro-5-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 36 (Steps 3 to 5 only) starting from 3-bromo-5-cyclobutoxy-4-fluorobenzoic acid (Intermediate 117, 900 mg, 3.11 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place *N*,*N*-dimethylsulfamide. Yield: 245 mg, 0.63 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.15 min, m/z 384.7 $(M-H)^-$ (ES^-).

Intermediate 119: methyl 4-bromospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-6-carboxylate



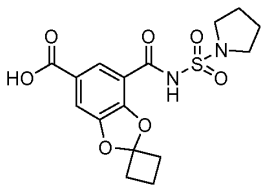
Step 1

A mixture of methyl 3,4-dihydroxybenzoate (3.0 g, 17.9 mmol) and sodium acetate (2.9 g, 35.7 mmol) in AcOH (30 mL) was stirred at 0 °C for 10 min, then bromine (8.6 g, 53.6 mmol) was added and the reaction was allowed to reach RT and stirred overnight. The mixture was partitioned between water (100 mL) and EtOAc (3x60 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 3-bromo-4,5-dihydroxybenzoate (3.0 g,12.2 mmol) as a white solid. LCMS: (System 2, Method B) Rt = 1.49 min, m/z 247.0 $(M+H)^+$ (ES^+).

Step 2

A mixture of methyl 3-bromo-4,5-dihydroxybenzoate (3.0 g, 12.2 mmol), cyclobutanone (1.3 g, 18.3 mmol) and phosphorus pentoxide (8.3 g, 58.6 mmol) in toluene (40 mL) was stirred at 75 °C overnight. The mixture was poured into water and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-30% EtOAc /petroleum ether) to afford methyl 4-bromospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-6-carboxylate (1.5 g, 4.85 mmol) as yellow oil. LCMS: (System 2, Method B) Rt = 2.10 min, m/z 299.0 $(M+H)^+$ (ES^+).

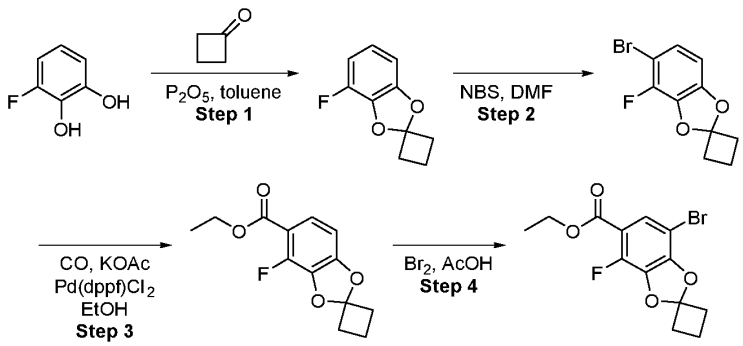
Intermediate 120: 4-((pyrrolidin-1-ylsulfonyl)carbamoyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-6-carboxylic acid



Prepared by an analogous method to Intermediate 38 (Step 3 and Step 4 only) starting from methyl 4-bromospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-6-carboxylate (Intermediate 119, 1.5 g, 4.85 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of *N*,*N*-

dimethylsulfamide. Yield: 255 mg, 0.67 mmol. White solid. LCMS: (System 2, Method F) Rt = 0.89 min, m/z 383.0 $(M+H)^+$ (ES^+).

Intermediate 121: ethyl 7-bromo-4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylate



Step 1

A mixture of 3-fluorobenzene-1,2-diol (6.0 g, 46.8 mmol), cyclobutanone (4.9 g, 70.2 mmol), phosphorus pentoxide (26.6 g, 187.2 mmol) in toluene (200 mL) was stirred at 75 °C overnight. The mixture was poured into ice-water (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-30% EtOAc/petroleum ether) to afford 4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane] (2.5 g, 13.9) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.86-6.77 (m, 3H), 2.65-2.57 (m, 4H), 1.85-1.77 (m, 2H).

Step 2

A mixture of 4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane] (2.2 g, 12.21 mmol), NBS (2.4 g, 13.4 mmol) in DMF (50 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (150 mL) and EtOAc (3x100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-50% EtOAc/petroleum ether) to afford 4-bromo-7-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane] (2.1 g, 8.14 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.20 (dd, J = 8.4, 2.8 Hz, 1H), 7.34 (dd, J = 8.4, 0.8 Hz, 1H), 2.73-2.66 (m, 4H), 1.91-1.83 (m, 2H).

Step 3

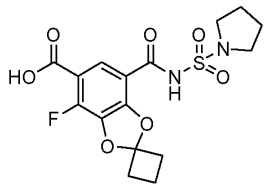
A mixture of 5-bromo-4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane (2.1 g, 8.14 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.20 g, 1.63 mmol) and KOAc (2.40

g, 24.4 mmol) in EtOH (40 mL) was stirred at 80 °C for 5 h under CO atmosphere. The reaction was allowed to reach RT and partitioned between water (40 mL) and EtOAc (3x40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-50% EtOAc/petroleum ether) to afford ethyl 4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylate (1.6 g, 6.35 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 2.11 min, m/z 253.4 $(M+H)^+$ (ES^+).

Step 4

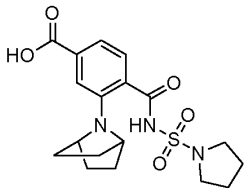
A mixture of bromine (4.1 g, 25.4 mmol), ethyl 4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylate (1.6 g, 6.35 mmol) in AcOH (20 mL) and DMF (1 mL) was stirred at 50 °C for 5 h under nitrogen atmosphere. The reaction was partitioned between water (20 mL) and EtOAc (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-50% EtOAc/petroleum ether) to afford ethyl 7-bromo-4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylate (1.6 g, 4.80 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 2.03 min, m/z 331.0 $(M+H)^+$ (ES^+).

Intermediate 122: 4-fluoro-7-((pyrrolidin-1-ylsulfonyl)carbamoyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylic acid



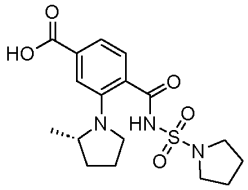
Prepared by an analogous method to Intermediate 120 starting from ethyl 7-bromo-4-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-5-carboxylate (Intermediate 121, 1.6 g, 4.80 mmol). Yield: 180 mg, 0.45 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.14 min, m/z 401.0 $(M+H)^+$ (ES^+).

Intermediate 123: 3-(7-azabicyclo[2.2.1]heptan-7-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



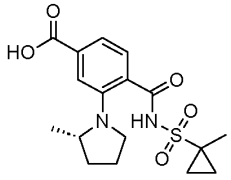
Prepared by analogous method to Intermediate 51 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 293 mg, 0.74 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.23 min, m/z 391.9 $(M-H)^-$ (ES^-).

Intermediate 124: (*S*)-3-(2-methylpyrrolidin-1-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



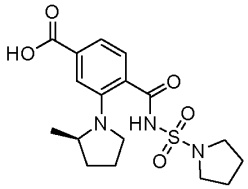
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.4 mmol) and (*S*)-2-methylpyrrolidine hydrochloride (1.6 g, 12.9 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 320 mg, 0.84 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.97 min, m/z 382.2 $(M+H)^+$ (ES^+).

Intermediate 125: (*S*)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-3-(2-methylpyrrolidin-1-yl)benzoic acid



Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.4 mmol) and (*S*)-2-methylpyrrolidine hydrochloride (1.6 g, 12.9 mmol). Yield: 300 mg, 0.82 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.88 min, m/z 367.2 $(M+H)^+$ (ES^+).

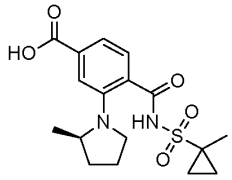
Intermediate 126: (*R*)-3-(2-methylpyrrolidin-1-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.4 mmol) and (*R*)-2-methylpyrrolidine hydrochloride (1.6 g, 12.9 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide.

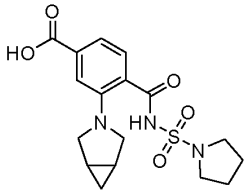
Yield: 330 mg, 0.87 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.97 min, m/z 382.2 $(M+H)^+$ (ES^+).

Intermediate 127: (*R*)-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-3-(2-methylpyrrolidin-1-yl)benzoic acid



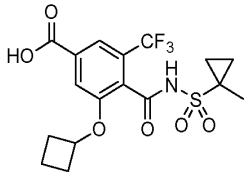
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (1.5 g, 6.4 mmol) and (*R*)-2-methylpyrrolidine hydrochloride (1.6 g, 12.9 mmol). Yield: 310 mg, 0.84 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.88 min, m/z 367.0 $(M+H)^+$ (ES^+).

Intermediate 128: 3-(3-azabicyclo[3.1.0]hexan-3-yl)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



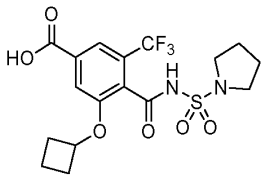
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2-fluorobenzoate (2.0 g, 8.62 mmol) and 3-azabicyclo[3.1.0]hexane (2.15 g, 25.9 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 390 mg, 1.03 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.83 min, m/z 378.0 $(M-H)^-$ (ES^-).

Intermediate 129: 3-cyclobutoxy-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



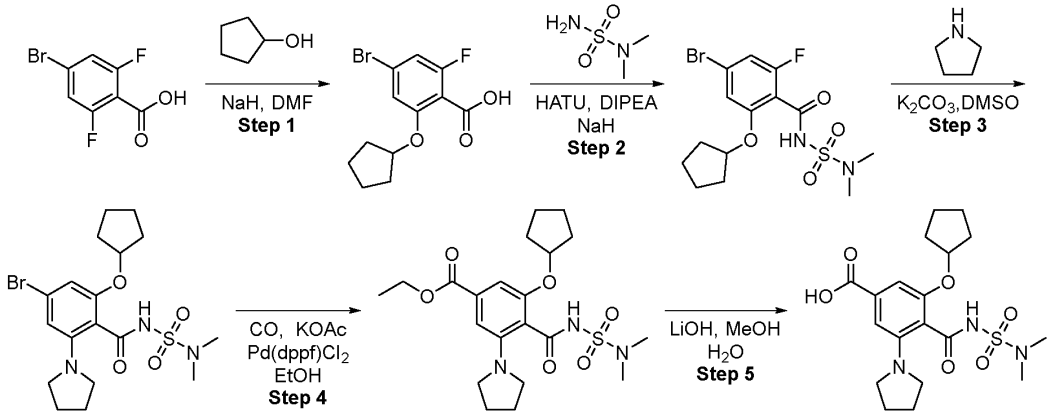
Prepared by an analogous method to Intermediate 43 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.7 mmol) except the Step 3 was carried out with cyclobutanol in place of cyclopentanol. Yield: 250 mg, 0.60 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.07 min, m/z 419.8 $(M+H)^+$ (ES^+).

Intermediate 130: 3-cyclobutoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-5-(trifluoromethyl)benzoic acid



Prepared by an analogous method to Intermediate 43 starting from 4-(ethoxycarbonyl)-2-fluoro-6-(trifluoromethyl)benzoic acid (Intermediate 42, 1.6 g, 5.7 mmol) except the Step 1 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide and the Step 3 was carried out with cyclobutanol in place of cyclopentanol. Yield: 600 mg, 1.38 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.05 min, m/z 434.6 $(M-H)^-$ (ES^-).

Intermediate 131: 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoic acid



Step 1

Sodium hydride (60% dispersion in mineral oil, 628 mg, 15.7 mmol) was added in small portions to a solution of 4-bromo-2,6-difluorobenzoic acid (3.1 g, 13.1 mmol) in DMF (50 mL). Cyclopentanol (1.2 g, 14.4 mmol) was added and the reaction was stirred at 100 °C for 2 h. The mixture was quenched with NH_4Cl aq. sat. (150 mL) and partitioned with EtOAc (3x150 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography (C_{18}, 35% ACN/H_2O) to afford 4-bromo-2-(cyclopentyloxy)-6-fluorobenzoic acid (1.6 g, 5.28 mmol) as a brown solid. LCMS: (System 1, Method A) Rt = 1.35 min, m/z 300.8 $(M-H)^-$ (ES^-).

Step 2

A mixture of 4-bromo-2-(cyclopentyloxy)-6-fluorobenzoic acid (1.6 g, 5.28 mmol), HATU (2.4 g, 6.33 mmol) and DIPEA (2.7 g, 21.1 mmol) in DMF (40 mL) was stirred at RT for 1.5 h. After this time, *N*,*N*-dimethylsulfamide (2.0 g, 15.8 mmol) was added, followed by sodium hydride (60% dispersion in mineral oil, 844 mg, 21.1 mmol), and the reaction mixture was stirred at RT overnight. The reaction mixture was poured into NH_4Cl aq. sat. (120 mL), acidified with HCl aq. 1 N (15 mL) and extracted with EtOAc (3x120 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (1-3% MeOH/DCM) to afford 4-bromo-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluorobenzamide (1.0 g, 2.44 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.64 min, m/z 409.0 $(M+H)^+$ (ES^+).

Step 3

A mixture of 4-bromo-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluorobenzamide (1.0 g, 2.44 mmol), K_2CO_3 (1.0 g, 7.33 mmol) and pyrrolidine (869 mg, 12.2 mmol) in DMSO (14 mL) was stirred at 120 °C overnight. The reaction mixture was partitioned between water (50 mL) and EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford 4-bromo-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-(pyrrolidin-1-yl)benzamide (500 mg, 1.09 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 2.14 min, m/z 460.0 $(M+H)^+$ (ES^+).

Step 4

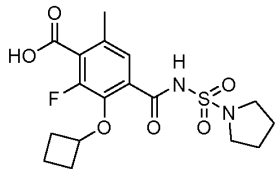
A mixture of 4-bromo-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-(pyrrolidin-1-yl)benzamide (500 mg, 1.09 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (159 mg, 0.22 mmol) and potassium acetate (320 mg, 3.26 mmol) in EtOH (15 mL) was stirred at 80 °C for 5 h under CO atmosphere. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-3% MeOH/DCM) to afford ethyl 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoate (455 mg, 1.00 mmol) as a brown oil. LCMS: (System 1, Method F) Rt = 1.58 min, 454.2 $(M+H)^+$ (ES^+).

Step 5

A solution of $LiOH{\cdot}H_2O$ (210 mg, 5.02 mmol) in water (3 mL) was added to a solution of ethyl 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoate (455 mg, 1.00 mmol) in MeOH (12 mL). The reaction mixture was stirred at RT overnight. Organic solvents were removed under reduced pressure, then the pH of the mixture was adjusted to ca. 3 with HCl aq. 1 N. The formed precipitate was collected by filtration, washed with water then hexane and

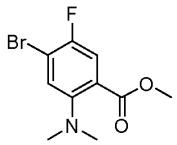
dried under reduced pressure to afford 3-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoic acid (385 mg, 0.85 mmol) as a yellow solid. LCMS: (System 1, Method A) Rt = 1.23 min, 454.2 $(M-H)^-$ (ES^-).

Intermediate 132: 3-cyclobutoxy-2-fluoro-6-methyl-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 13 starting from of 2-bromo-6-fluoro-4-methylphenol (2.0 g, 10 mmol) and bromocyclobutane (2.7 g, 20 mmol). Yield: 230 mg, 0.58 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.02 min, m/z 398.8 $(M-H)^-$ (ES^-).

Intermediate 133: methyl 4-bromo-2-(dimethylamino)-5-fluorobenzoate

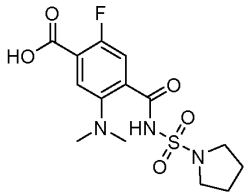


Prepared by an analogous method to Intermediate 81 starting from 2-amino-4-bromo-5-fluorobenzoic acid (5.2 g, 22.3 mmol). Yield: 2.8 g, 10.2 mmol. Yellow oil. LCMS: (System 1, Method F) Rt = 1.78 min, m/z 276.0 $(M+H)^+$ (ES^+).

Specific procedure:

To a solution of 2-amino-4-bromo-5-fluorobenzoic acid (5.2 g, 22.32 mmol) in DMF (50 mL), was added NaH (60%, 5.36 g, 133.91 mmol), and the reaction mixture was stirred at room temperature for 10 min. Methyl iodide (25.4 g, 178.54 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate extracts were washed with brine (3 x 100 mL), dried over Na_2SO_4 and concentrated to give methyl 4-bromo-2-(dimethylamino)-5-fluorobenzoate (2.8 g, 46% yield) as yellow oil. LCMS: (System 1, Method F) Rt = 1.78 min, m/z 276.0 $(M+H)^+$.

Intermediate 134: 5-(dimethylamino)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 46 (Steps 2 to 5) from methyl 4-bromo-2-(dimethylamino)-5-fluorobenzoate (Intermediate 133, 2.8 g, 10.2 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 430 mg, 1.20 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.93 min, m/z 360.3 $(M+H)^+$ (ES^+).

Specific procedure:

Step 1

To a solution of methyl 4-bromo-2-(dimethylamino)-5-fluorobenzoate (Intermediate 133, 2.8 g, 10.18 mmol) in THF/MeOH/water(16 mL/16 mL/4 mL) was added LiOH (1.7 g, 40.73 mmol), and the reaction mixture was stirred at 60 °C for 4 h. The pH of the mixture was adjusted to 8 with 1N HCl, MeOH and THF were removed at 35 °C under reduced pressure. The pH was adjusted to 3 with 1N HCl. The formed precipitate was collected by filtration, washed with water then hexane and dried at 35 °C under reduced pressure to give 4-bromo-2-(dimethylamino)-5-fluorobenzoic acid (2.6 g, 98% yield) as a yellow solid. LCMS: (System 1, Method A) Rt = 1.25 min, m/z 262.2 $(M+H)^+$.

Step 2

A solution of 4-bromo-2-(dimethylamino)-5-fluorobenzoic acid (900 mg, 3.45 mmol) HATU (1.57 g, 4.14 mmol), TEA (1.39 g, 13.79 mmol) in DMF (20 mL) was stirred at room temperature 1h. Pyrrolidine-1-sulfonamide (1.55 g, 10.34 mmol) and NaH (60%, 552 mg, 13.79 mmol) were added and the reaction mixture was stirred at room temperature overnight. The pH of the mixture was adjusted to 4 with 1N HCl and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated at 35 °C under reduced pressure to give crude material, which was purified by silica gel column chromatography (1-10% MeOH/DCM) to give 4-bromo-2-(dimethylamino)-5-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide (700 mg, 52% yield) as yellow oil. LCMS: (System 1, Method A), Rt = 1.88 min, m/z 394.0 $(M+H)^+$.

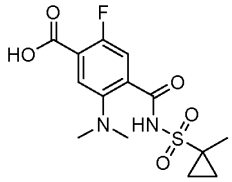
Step 3

To a solution of 4-bromo-2-(dimethylamino)-5-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide (700 mg, 1.78 mmol) in EtOH (15 mL) was added $Pd(dppf)Cl_2$ (260 mg, 0.36 mmol) and KOAc (524 mg, 5.34 mmol), then the mixture was stirred at 80 °C for 5 hours under CO atmosphere. Sat. aq. Na_2CO_3 (15 mL) was added, and the reaction mixture was extracted with EtOAc (3 x 15 mL). The pH of the aqueous layer was adjusted to 3 with 1N HCl aq. and aqueous layer extracted again with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated at 35 °C under reduced pressure to give ethyl 5-(dimethylamino)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (500 mg, 73% yield) as a black solid. LCMS: (System 1, Method F). Rt = 1.33 min, m/z 388.0 $(M+H)^+$.

Step 4

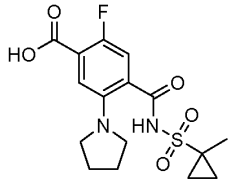
To a solution of ethyl 5-(dimethylamino)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (500 mg, 1.29 mmol) in THF (12 mL) and MeOH (3 mL) was added a solution of LiOH H_2O (212 mg, 5.17 mmol) in water (3 mL). The reaction mixture was stirred at room temperature overnight. The pH of the mixture was adjusted to 8 with 1N HCl, MeOH and THF were removed at 35 °C under reduced pressure, then pH of the mixture was adjusted to 3 with 1N HCl. The formed precipitate was collected by filtration, washed with water, hexane and dried at 35 °C under reduced pressure to give 5-(dimethylamino)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (430 mg, 93 % yield) as a yellow solid.
LCMS: (System 1, Method A). Rt = 0.93 min, m/z 360.3 $(M+H)^+$ (ES^+).

Intermediate 135: 5-(dimethylamino)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



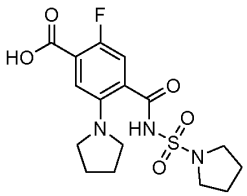
Prepared by analogous method to Intermediate 46 (Steps 2 to 5) from methyl 4-bromo-2-(dimethylamino)-5-fluorobenzoate (Intermediate 133, 2.5 g, 8.59 mmol). Yield: 400 mg, 1.16 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.35 min, m/z 345.0 $(M+H)^+$ (ES^+).

Intermediate 136: 2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoic acid



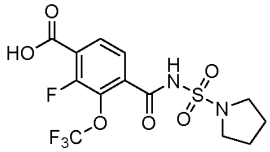
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,5-difluorobenzoate (2.5 g, 10.0 mmol) and pyrrolidine (2.13 g, 30.0 mmol). Yield: 280 mg, 0.76 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 0.69 min, m/z 369.0 $(M+H)^+$ (ES^+).

Intermediate 137: 2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5-(pyrrolidin-1-yl)benzoic acid



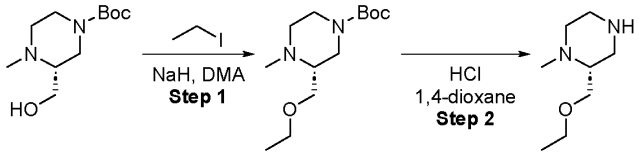
Prepared by analogous method to Intermediate 136 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 330 mg, 0.89 mmol. White solid. LCMS: (System 1, Method F) Rt = 0.66 min, m/z 371.2 $(M+H)^+$ (ES^+).

Intermediate 138: 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(trifluoromethoxy)benzoic acid



Prepared by an analogous method to Intermediate 13 (Step 3 only) starting from 4-bromo-2-fluoro-3-(trifluoromethoxy)benzoic acid (577 mg, 1.91 mmol). Yield: 160 mg, 0.40 mmol. Pale-yellow solid. LCMS: (System 1, Method I) Rt = 0.95 min, m/z 399.0 $(M+H)^+$ (ES^+).

Intermediate 139: (*R*)-2-(ethoxymethyl)-1-methylpiperazine



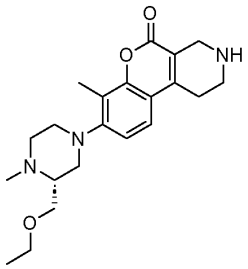
Step 1

Sodium hydride (60% dispersion in mineral oil, 208 mg, 5.21 mmol) was added in small portions to a solution of (*R*)-tert-butyl 3-(hydroxymethyl)-4-methylpiperazine-1-carboxylate (1.0 g, 4.34 mmol) in DMA (20 mL) at 0 °C and the mixture was stirred at this temperature for 30 min. Iodoethane (677 mg, 4.34 mmol) was added and the reaction was stirred at RT overnight. The mixture was partitioned between ice-water (60 mL) and EtOAc (3x60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-20% EtOAc/petroleum ether) to afford (*R*)-tert-butyl 3-(ethoxymethyl)-4-methylpiperazine-1-carboxylate (500 mg, 1.94 mmol) as a colorless oil. LCMS: (System 1, Method F) Rt = 1.50 min, m/z 259.2 $(M+H)^+$ (ES^+).

Step 2

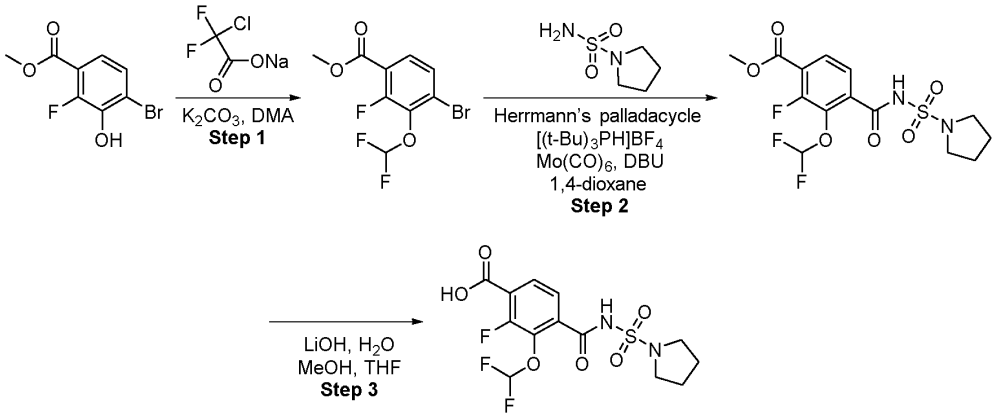
HCl 4 N in 1,4-dioxane (5 mL, 20 mmol) was added to a solution of (*R*)-*tert*-butyl 3-(ethoxymethyl)-4-methylpiperazine-1-carboxylate (500 mg, 1.94 mmol) in 1,4-dioxane (5 mL) and the reaction was stirred at RT overnight. The mixture was concentrated under reduced pressure to afford (*R*)-2-(ethoxymethyl)-1-methylpiperazine which was used without further purification. LCMS: (System 1, Method H) Rt = 0.73 min, m/z 159.3 $(M+H)^+$ (ES^+).

Intermediate 140: (*R*)-8-(3-(ethoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(ethoxymethyl)-1-methylpiperazine (Intermediate 139) and *tert*-butyl 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2, 897 mg, 1.94 mmol). Yield: 235 mg, 0.63 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.70 min, m/z 372.2 $(M+H)^+$ (ES^+).

Intermediate 141: 3-(difluoromethoxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

A mixture of methyl 4-bromo-2-fluoro-3-hydroxybenzoate (1.0 g, 4.03 mmol), K_2CO_3 (1.7 g, 12.1 mmol) and sodium 2-chloro-2,2-difluoroacetate (1.8 g, 12.1 mmol) in DMA (20 mL) was stirred at 100 °C overnight. The reaction was cooled down to RT and partitioned between water (30 mL) and EtOAc (3x30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduce pressure. The crude product was purified by column chromatography on silica gel (1% MeOH/DCM) to afford methyl 4-bromo-3-(difluoromethoxy)-2-fluorobenzoate (880 mg, 2.95 mmol) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (dd, J = 8.8, 7.2 Hz, 1H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (t, J = 73.6 Hz, 1H), 3.93 (s, 3H).

Step 2

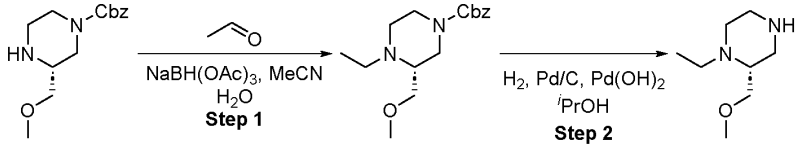
A mixture of methyl 4-bromo-3-(difluoromethoxy)-2-fluorobenzoate (880 mg, 2.95 mmol), [(t- tri-*tert*-butylphosphonium tetrafluoroborate (170 mg, 0.59 mmol), *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Herrmann's palladacycle, 277 mg, 0.30 mmol), molybdenum hexacarbonyl (1.2 g, 4.43 mmol), DBU (1.3 g, 8.85 mmol) and pyrrolidine-1-sulfonamide (1.3 g, 8.85 mmol) in dioxane (25 mL) was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was cooled to RT, DCM/water (5:1, 120 mL) was added and the mixture was filtered over celite. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (0-5% MeOH/DCM) to afford methyl 3-(difluoromethoxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (250 mg, 0.63 mmol) as a pale-yellow solid. LCMS: (System 2, Method A) Rt = 1.38 min, m/z 397.3 $(M+H)^+$ (ES^+).

Step 3

A mixture of methyl 3-(difluoromethoxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (250 mg, 0.63 mmol) and $LiOH{\cdot}H_2O$ (159 mg, 3.78 mmol) in MeOH (8 mL), water (2 mL) and THF

(2 mL) was stirred at RT overnight. Organic solvents were removed under reduced pressure and the pH of the mixture was adjusted to ca. 5 with HCl aq. 1 N. This aqueous layer was extracted with EtOAc (3x15 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-(difluoromethoxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (190 mg, 0.50 mmol) as a white solid which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 0.67 min, m/z 381.2 $(M-H)^-$ (ES^-).

Intermediate 142: (*R*)-1-ethyl-2-(methoxymethyl)piperazine



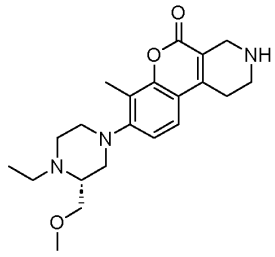
Step 1

Acetaldehyde (600 mg, 13.6 mmol) was added to a solution of (*R*)-benzyl 3-(methoxymethyl)piperazine-1-carboxylate (Step 3 Intermediate 1, 1.2 g, 4.55 mmol) in ACN/water (20 mL/5 mL) and the mixture was stirred at RT for 2 h. Sodium triacetoxyborohydride (1.9 g, 9.1 mmol) was added at 0 °C, and the reaction was stirred at RT overnight. The pH of the mixture was adjusted to ca.8 with $NaHCO_3$ aq. sat. and the organic solvents were removed under reduced pressure. The resulting aqueous phase was extracted with DCM (3x20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford (*R*)-benzyl 4-ethyl-3-(methoxymethyl)piperazine-1-carboxylate (460 mg, 1.58 mmol) as a yellow oil. LCMS: (System 1, Method F) Rt = 1.55 min, m/z 293.2 $(M+H)^+$ (ES^+).

Step 2

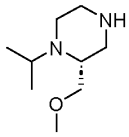
A mixture of (*R*)-benzyl 4-ethyl-3-(methoxymethyl)piperazine-1-carboxylate (460 mg, 1.58 mmol), Pd/C (20%, 92 mg),$Pd(OH)_2$ (20%, 92 mg) in isopropanol (10 mL) was stirred at RT for 2 days under H_2 atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford (*R*)-1-ethyl-2-(methoxymethyl)piperazine (210 mg, 1.33 mmol) as a yellow oil. LCMS: (System 1, Method A) Rt = 0.86 min, m/z 159.4 $(M+H)^+$ (ES^+).

Intermediate 143: (*R*)-8-(4-ethyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



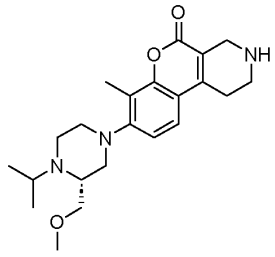
Prepared by an analogous method to Intermediate 5 starting from (*R*)-1-ethyl-2-(methoxymethyl)piperazine (Intermediate 142, 210 mg, 1.33 mmol) and 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2, 410 mg, 0.89 mmol). Yield: 160 mg, 0.43 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.60 min, m/z 372.4 $(M+H)^+$ (ES^+).

Intermediate 144: (*R*)-1-isopropyl-2-(methoxymethyl)piperazine



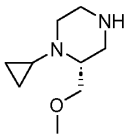
Prepared by an analogous method to Intermediate 142 starting from (*R*)-benzyl 3-(methoxymethyl)piperazine-1-carboxylate (Step 3 Intermediate 1, 1.2 g, 4.55 mmol) and acetone (791 mg, 13.6 mmol). Yield: 460 mg, 2.67 mmol. Yellow oil. LCMS: (System 1, Method F) Rt = 0.76 min, m/z 173.3 $(M+H)^+$ (ES^+).

Intermediate 145: (*R*)-8-(4-isopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



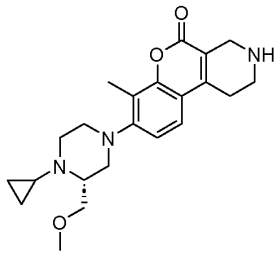
Prepared by an analogous method to Intermediate 5 starting from (*R*)-1-isopropyl-2-(methoxymethyl)piperazine (Intermediate 144, 460 mg, 2.67 mmol) and 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2, 820 mg, 1.78 mmol). Yield: 380 mg, 0.99 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.72 min, m/z 386.4 $(M+H)^+$ (ES^+).

Intermediate 146: (*R*)-1-cyclopropyl-2-(methoxymethyl)piperazine



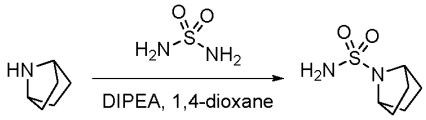
Prepared by an analogous method to Intermediate 142 starting from (*R*)-benzyl 3-(methoxymethyl)piperazine-1-carboxylate (Step 3 Intermediate 1, 1.2 g, 4.55 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (2.4 g, 13.6 mmol) except in Step 1 sodium cyanoborohydride was used instead of sodium triacetoxyborohydride and the reaction was stirred for 2 h at 70 °C instead of overnight at RT. Yield: 500 mg, 2.94 mmol. Yellow oil. LCMS: (System 1, Method A) Rt = 1.27 min, m/z 171.4 $(M+H)^+$ (ES^+).

Intermediate 147: (*R*)-8-(4-cyclopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



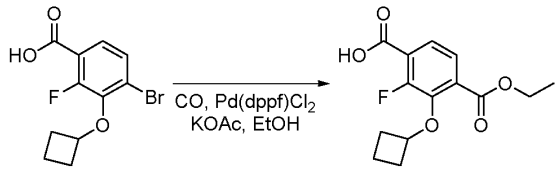
Prepared by an analogous method to Intermediate 5 starting from (*R*)-1-cyclopropyl-2-(methoxymethyl)piperazine (Intermediate 146, 500 mg, 2.94 mmol) and 7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 2, 903 mg, 1.96 mmol). Yield: 350 mg, 0.91 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.74 min, m/z 384.2 $(M+H)^+$ (ES^+).

Intermediate 148: 7-azabicyclo[2.2.1]heptane-7-sulfonamide



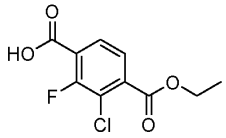
A mixture of 7-azabicyclo[2.2.1]heptane hydrochloride (6.0 g, 62.0 mmol), sulfuric diamide (8.9 g, 93 mmol) and TEA (19.1 g, 189 mmol) in DME (50 mL) was stirred at 100 °C overnight. The reaction mixture was partitioned between water (50 mL) and DCM (3x50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (40-60% EtOAc/petroleum ether) to afford 7-azabicyclo[2.2.1]heptane-7-sulfonamide (1.2 g, 6.82 mmol) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ: 6.86 (s, 2H), 4.00-3.97 (m, 2H), 1.85-1.83 (m, 4H), 1.38-1.35 (m, 4H).

Intermediate 149: 3-cyclobutoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid



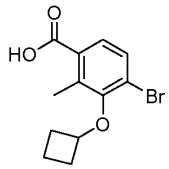
A mixture of 4-bromo-3-cyclobutoxy-2-fluorobenzoic acid (Step 2 Intermediate 13, 1.0 g, 3.48 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (509 mg, 0.70 mmol) and potassium acetate (1.02 g, 10.5 mmol) in EtOH (20 mL) was stirred at 90 °C overnight under CO atmosphere. The reaction mixture diluted with Na_2CO_3 aq. sat. (20 mL) and washed with EtOAc (3x20 mL). Then, the pH of the resulting aqueous layer was adjusted to ca. 3 with HCl aq. 1 N and the aqueous layer extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 3-cyclobutoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid (720 mg, 2.55 mmol) as yellow oil which was used in the next step without further purification. LCMS: (System 1, Method F) Rt = 1.11 min, m/z 283.0 $(M+H)^+$ (ES^+).

Intermediate 150: 3-chloro-4-(ethoxycarbonyl)-2-fluorobenzoic acid



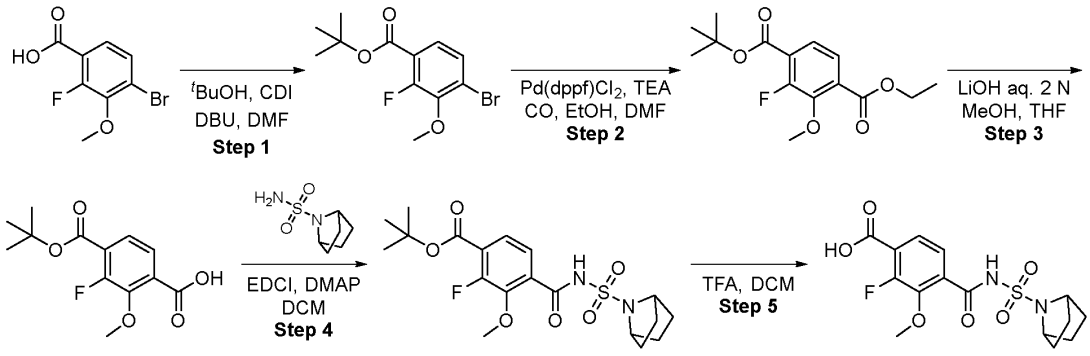
Prepared by an analogous method to Intermediate 149 starting from 4-bromo-3-chloro-2-fluorobenzoic acid (1.0 g, 3.95 mmol). Yield: 820 mg, 3.32 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.26 min, m/z 245.0 $(M+H)^+$ (ES^+).

Intermediate 151: 4-bromo-3-cyclobutoxy-2-methylbenzoic acid



Prepared by an analogous method to Intermediate 40 (Steps 1 to 2 only) starting from methyl 4-bromo-3-methoxy-2-methylbenzoate (500 g, 2.04 mmol) and cyclobutanol (184 mg, 2.45 mmol). Yield: 494 mg, 3.32 mmol. White solid. LCMS: (System 3, Method I) Rt = 1.32 min, m/z 283.0 $(M-H)^-$ (ES^-).

Intermediate 152: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoic acid



Step 1

A mixture of 4-bromo-2-fluoro-3-methoxybenzoic acid (2.7 g, 10.6 mmol) and CDI (2.6 g, 16.0 mmol) in DMF (15 mL) was stirred for 1 h at 40 °C. Then *tert*-butanol (2.0 mL, 21.3 mmol) and DBU (1.6 mL, 10.6 mmol) were added and the mixture was stirred overnight at 40 °C. The organic solvents were removed under reduced pressure. The crude product was purified by column chromatography on C18-modified silica (0-100% ACN/NH_4OH 10 mM aq.) to afford *tert*-butyl 4-bromo-2-fluoro-3-methoxy-benzoate (1.6 g, 5.08 mmol) as a pale-brown oil. LCMS: (System 3, Method I) Rt = 2.10 min.

Step 2

A mixture of *tert*-butyl 4-bromo-2-fluoro-3-methoxy-benzoate (260 mg, 0.85 mmol), TEA (0.60 mL, 4.28 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.04 mmol) in EtOH (0.9 mL) and DMF (0.9 mL) was stirred at 100 °C overnight under CO atmosphere. Organic solvents were removed under reduced pressure. The crude product was purified by column chromatography on C18-modified silica (0-100% ACN/NH_4OH aq. 10 mM) to afford 1-(*tert*-butyl) 4-ethyl 2-fluoro-3-methoxyterephthalate (165 mg, 0.55 mmol) as a brown oil. LCMS: (System 3, Method I) Rt = 1.95 min.

Step 3

LiOH aq. 2 N (0.3 mL) was added to solution of 1-(*tert*-butyl) 4-ethyl 2-fluoro-3-methoxyterephthalate (723 mg, 2.42 mmol) THF (6.1 mL) and MeOH (6.1 mL) and the reaction was stirred at RT for 2 h. Then the solvents were removed, and the crude product was purified by column chromatography on C18-modified silica (0-100% ACN/0.1% FA in water) to afford 4-*tert*-butoxycarbonyl-3-fluoro-2-methoxy-benzoic acid (116 mg, 0.43 mmol) as a yellow solid. LCMS: (System 3, Method I) Rt = 1.24 min, m/z 269.0 $(M-H)^-$ (ES^-).

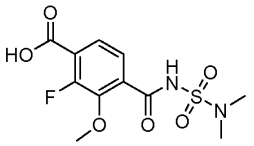
Step 4

A mixture of 4-*tert*-butoxycarbonyl-3-fluoro-2-methoxy-benzoic acid (30 mg, 0.11 mmol), 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148, 23 mg, 0.133 mmol), EDCI (43 mg, 0.22 mmol), DMAP (27 mg, 0.22 mmol) in DCM (1.1 mL) was stirred at RT overnight. The organic solvent was removed under reduced pressure and the crude product was purified by column chromatography on C18-modified silica (0-100% ACN, 0.1% FA in water) to afford *tert*-butyl 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoate (22 mg, 0.05 mmol) as a yellow solid. LCMS: (System 3, Method J) Rt = 1.96, m/z 427.4 $(M-H)^-$ (ES^-).

Step 5

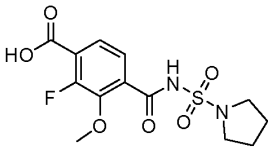
A mixture of *tert*-butyl 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoate and TFA (0.50 mL, 6.53 mmol) in DCM (1.0 mL) was stirred at RT for 1 h. The organic solvents were removed under reduced pressure and the crude product was purified by column chromatography on C18-modified silica (0-100% ACN/0.1% FA in water) to afford 4-(7-azabicyclo[2.2.1]heptan-7-ylsulfonylcarbamoyl)-2-fluoro-3-methoxy-benzoic acid (16 mg, 0.04 mmol) as a pale-yellow solid. LCMS (System 3, Method I) Rt = 0.28 min, m/z 373.1 $(M-H)^-$ (ES^-).

Intermediate 153: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluoro-3-methoxybenzoic acid



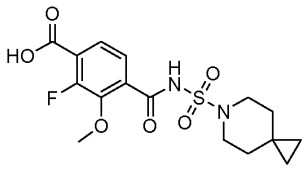
Prepared by analogous method to Intermediate 152 except the Step 4 was carried out with *N*,*N*-dimethylsulfamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 41 mg, 0.13 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.36 min, m/z 319.1 $(M-H)^-$ (ES^-).

Intermediate 154: 2-fluoro-3-methoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



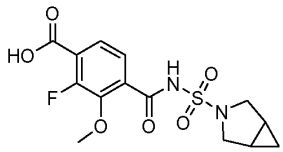
Prepared by analogous method to Intermediate 152 except the Step 4 was carried out with pyrrolidine-1-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 43 mg, 0.12 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.47 min, m/z 345.1 $(M-H)^-$ (ES^-).

Intermediate 155: 4-(((6-azaspiro[2.5]octan-6-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoic acid



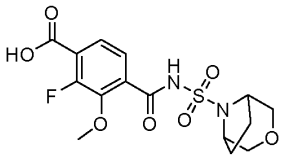
Prepared by analogous method to Intermediate 152 except the Step 4 was carried out with 6-azaspiro[2.5]octane-6-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 16 mg, 0.04 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.70 min, m/z 385.2 $(M-H)^-$ (ES^-).

Intermediate 156: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoic acid



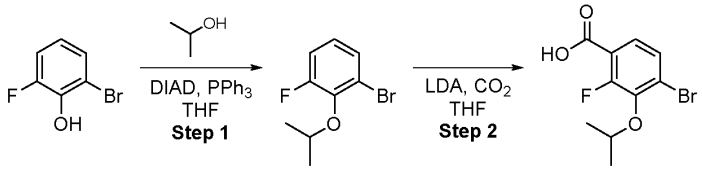
Prepared by analogous method to Intermediate 152 except the Step 4 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 20 mg, 0.06 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.52 min, m/z 357.2 $(M-H)^-$ (ES^-).

Intermediate 157: 4-(((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)carbamoyl)-2-fluoro-3-methoxybenzoic acid



Prepared by analogous method to Intermediate 152 except the Step 4 was carried out with 3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 14 mg, 0.04 mmol. Pale-brown solid. LCMS: (System 3, Method J) Rt = 1.38 min, m/z 389.1 $(M+H)^+$ (ES^+).

Intermediate 158: 4-bromo-2-fluoro-3-isopropoxybenzoic acid



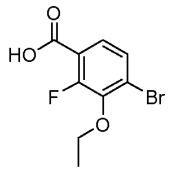
Step 1

DIAD (1.0 mL, 5.24 mmol) was added to a mixture of 2-bromo-6-fluorophenol (500 mg, 2.62 mmol), PPh_3 (1.4 mg, 5.24 mmol) and anhydrous isopropanol (0.30 mL, 3.93 mmol) in tetrahydrofuran (13 mL) at 0 °C and the reaction was stirred at RT overnight. The mixture was partitioned between water (20 mL) and EtOAc (3x20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/iso-haxene) to afford 1-bromo-3-fluoro-2-isopropoxy-benzene (490 mg, 2.10 mmol) as pale-yellow oil. LCMS (System 3, Method I) Rt = 2.04 min.

Step 2

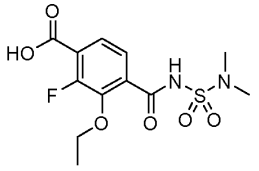
LDA (468 mg, 4.37 mmol) was added dropwise to a solution of 1-bromo-3-fluoro-2-isopropoxy-benzene (509 mg, 2.18 mmol) in tetrahydrofuran (21 mL) at -78°C and the reaction was stirred at this temperature for 1 h under nitrogen atmosphere. Dry ice pellets were added at -78°C and the resultant mixture was allowed to reach RT and stirred overnight. The reaction was quenched with $NaHCO_3$ aq. sat. (20 mL) and the resulting aqueous layer was extracted with EtOAc (3x30 mL). Then the pH of aqueous layer was adjusted to ca. 1-2 with HCl aq. 1 N and the aqueous layer extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was triturated with hexane, isolated by filtration and dried under reduced pressure to afford 4-bromo-2-fluoro-3-isopropoxy-benzoic acid (456 mg, 1.65 mmol) as off-white solid. LCMS (System 3, Method I) Rt = 1.20 min, m/z 276.9 $(M+H)^+$ (ES^+).

Intermediate 159: 4-bromo-3-ethoxy-2-fluorobenzoic acid



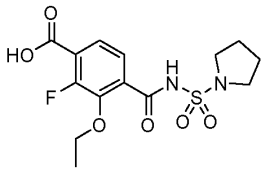
Prepared by analogous method to Intermediate 158 (only Step 2) starting from 1-bromo-2-ethoxy-3-fluorobenzene (2.7 g, 10.6 mmol). Yield: 1.6 g, 6.1 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.75 min, m/z 262.8 $(M+H)^+$ (ES^+).

Intermediate 160: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-3-ethoxy-2-fluorobenzoic acid



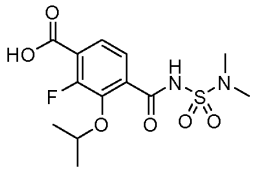
Prepared by analogous method to Intermediate 152 starting from 4-bromo-3-ethoxy-2-fluorobenzoic acid (Intermediate 159, 451 mg, 1.71 mmol) except the Step 4 was carried out with *N*,*N*-dimethylsulfamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 21 mg, 0.06 mmol. Yellow solid. LCMS: (System 3, Method J) Rt = 1.45 min, m/z 333.1 $(M-H)^-$ (ES^-).

Intermediate 161: 3-ethoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



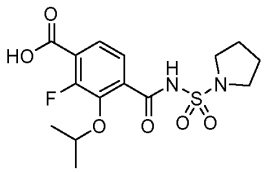
Prepared by analogous method to Intermediate 152 starting from 4-bromo-3-ethoxy-2-fluorobenzoic acid (Intermediate 159, 451 mg, 1.71 mmol) except the Step 4 was carried out with pyrrolidine-1-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 22 mg, 0.06 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.54 min, m/z 359.2 $(M-H)^-$ (ES^-).

Intermediate 162: 4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluoro-3-isopropoxybenzoic acid



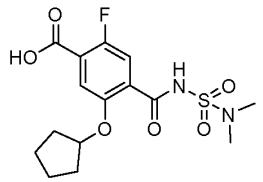
Prepared by analogous method to Intermediate 152 starting from 4-bromo-2-fluoro-3-isopropoxybenzoic acid (Intermediate 158, 456 mg, 1.65 mmol) except the Step 4 was carried out with *N*,*N*-dimethylsulfamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 12 mg, 0.03 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.52 min, m/z 347.2 $(M-H)^-$ (ES^-).

Intermediate 163: 2-fluoro-3-isopropoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



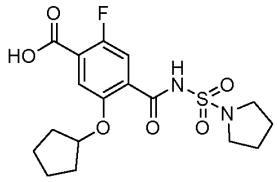
Prepared by analogous method to Intermediate 152 starting from 4-bromo-2-fluoro-3-isopropoxybenzoic acid (Intermediate 158, 456 mg, 1.65 mmol) except the Step 4 was carried out with pyrrolidine-1-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 13 mg, 0.03 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.61 min, m/z 373.2 $(M-H)^-$ (ES^-).

Intermediate 164: 5-(cyclopentyloxy)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



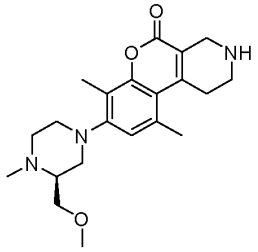
Prepared by an analogous method to Intermediate 36 starting from methyl 4-bromo-5-fluoro-2-hydroxybenzoate (800 mg, 3.21 mmol) and cyclopentanol (415 mg, 4.82 mmol). Yield: 65 mg, 0.17 mmol. White solid. LCMS: (System 3, Method I) Rt = 0.30 min, m/z 373.2 $(M-H)^-$ (ES^-).

Intermediate 165: 5-(cyclopentyloxy)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 164 except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of *N*,*N*-dimethylsulfamide. Yield: 45 mg, 0.11 mmol. White solid. LCMS: (System 3, Method I) Rt = 0.59 min, m/z 399.2 $(M-H)^-$ (ES^-).

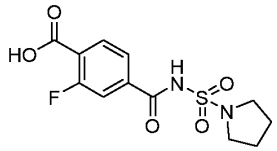
Intermediate 166: (*S*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*S*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 37, 187 mg, 1.3 mmol) and *tert*-butyl 7,10-dimethyl-5-oxo-8-(trifluoromethylsulfonyloxy)-4,5-dihydro-1*H*-chromeno[3,4-c]pyridine-3(2*H*)-carboxylate

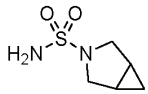
(Intermediate 3, 480 mg, 1.00 mmol). Yield: 200 mg, 0.54 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.48 min, m/z 372.3 $(M+H)^+$ (ES^+).

Intermediate 167: 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



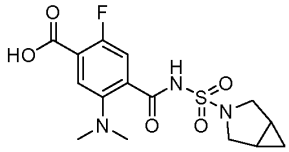
Prepared by an analogous method to Intermediate 36 (Steps 3 to 5 only) starting from 4-bromo--3-fluorobenzoic acid (1.50 g, 6.85 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place *N,N*-dimethylsulfamide. Yield: 114 mg, 0.36 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.38 min, m/z 315.2 $(M-H)^-$ (ES^-)

Intermediate 168: 3-azabicyclo[3.1.0]hexane-3-sulfonamide



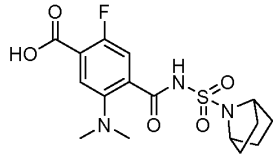
Prepared by an analogous method to Intermediate 148 starting from 3-azabicyclo[3.1.0]hexane (5.4 g, 64.6 mmol), sulfuric diamide (6.2 g, 64.6 mmol). Yield: 2.1 g, 0.91 mmol. Colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.72 (s, 2H), 3.19-3.14 (m, 4H), 1.55-1.53 (m, 2H), 0.58-0.53 (m, 1H), 0.41-0.38 (m, 1H).

Intermediate 169: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



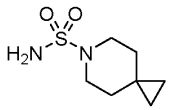
Prepared by analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of pyrrolidine-1-sulfonamide. Yield: 400 mg, 1.08 mmol. Yellow solid. LCMS: (System 1, Method F) Rt = 1.02 min, m/z 372.0 $(M+H)^+$ (ES^+).

Intermediate 170: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



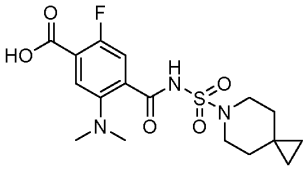
Prepared by analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 130 mg, 0.34 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.06 min, m/z 386.0 $(M+H)^+$ (ES^+).

Intermediate 171: 6-azaspiro[2.5]octane-6-sulfonamide



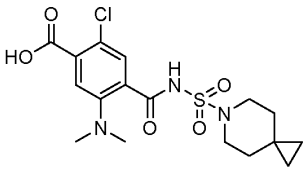
Prepared by an analogous method to Intermediate 148 starting from 6-azaspiro[2.5]octane hydrochloride (5.0 g, 45.0 mmol) and sulfuric diamide (6.5 g, 67.6 mmol). Yield: 2.5 g, 0.91 mmol. Pale-yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ: 6.69 (s, 2H), 3.01-2.99 (m, 4H), 1.41 (t, J = 5.4 Hz, 4H), 0.31 (s, 4H).

Intermediate 172: 4-(((6-azaspiro[2.5]octan-6-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



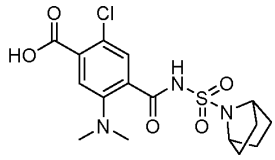
Prepared by analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with 6-azaspiro[2.5]octane-6-sulfonamide (Intermediate 171) in place of pyrrolidine-1-sulfonamide. Yield: 350 mg, 0.88 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.23 min, m/z 400.0 $(M+H)^+$ (ES^+).

Intermediate 173. 4-(((6-azaspiro[2.5]octan-6-yl)sulfonyl)carbamoyl)-2-chloro-5-(dimethylamino)benzoic acid



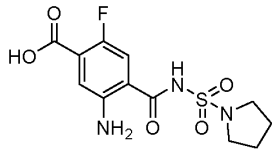
Prepared by analogous method to Intermediate 111 except the Step 3 was carried out with 6-azaspiro[2.5]octane-6-sulfonamide (Intermediate 171) in place of pyrrolidine-1-sulfonamide. Yield: 380 mg, 0.91 mmol. Yellow solid. LCMS: (System 1, Method B) Rt = 1.01 min, m/z 414.0 $(M-H)^-$ (ES^-).

Intermediate 174: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-chloro-5-(dimethylamino)benzoic acid



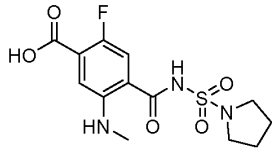
Prepared by an analogous method to Intermediate 111 except the Step 3 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 340 mg, 0.85 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.02 min, m/z 402.0 $(M+H)^+$ (ES^+).

Intermediate 175: 5-amino-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



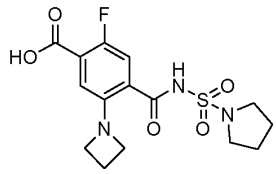
Prepared by analogous method to Intermediate 46 (Steps 3 to 5) from 2-amino-4-bromo-5-fluorobenzoic acid (1.0 g, 4.29 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 440 mg, 1.32 mmol. Yellow solid. LCMS: (System 1, Method B) Rt = 0.24 min, m/z 330.0 $(M-H)^-$ (ES^-).

Intermediate 176: 2-fluoro-5-(methylamino)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



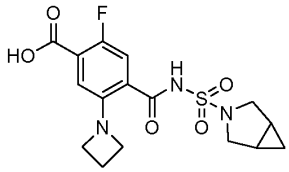
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,5-difluorobenzoate (2.1 g, 8.4 mmol) and methylamine hydrochloride (1.7 g, 25.2 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 200 mg, 0.58 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 346.3 $(M+H)^+$ (ES^+).

Intermediate 177: 5-(azetidin-1-yl)-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



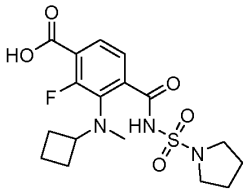
Prepared by analogous method to Intermediate 46 starting from methyl 4-bromo-2,5-difluorobenzoate (2.1 g, 8.4 mmol) and azetidine (1.4 g, 25.0 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 200 mg, 0.58 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 346.3 $(M+H)^+$ (ES^+).

Intermediate 178: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-5-(azetidin-1-yl)-2-fluorobenzoic acid



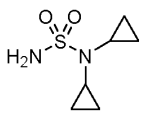
Prepared by analogous method to Intermediate 177 except the Step 3 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of 1-methylcyclopropane-1-sulfonamide. Yield: 200 mg, 0.58 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 346.3 $(M+H)^+$ (ES^+).

Intermediate 179: 3-(cyclobutyl(methyl)amino)-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



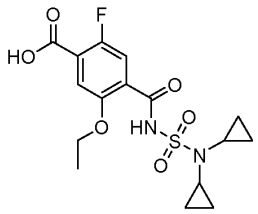
Prepared by analogous method to Intermediate 83 except the Step 5 was carried out with pyrrolidine-1-sulfonamide in place of *N*,*N*-dimethylsulfamide. Yield: 450 mg, 1.17 mmol. White solid. LCMS: (System 1, Method F) Rt = 1.10 min, m/z 383.3 $(M-H)^-$ (ES^-).

Intermediate 180: *N*,*N*-dicyclopropylsulfamide



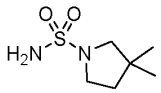
Prepared by an analogous method to Intermediate 148 starting from dicyclopropylamine hydrochloride (1.0 g, 7.48 mmol), sulfuric diamide (863 mg, 8.98 mmol). Yield: 986 mg, 5.59 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (s, 2H), 2.31-2.25 (m, 2H), 0.72-0.67 (m, 4H), 0.66-0.59 (m, 4H).

Intermediate 181: 4-((*N*,*N*-dicyclopropylsulfamoyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



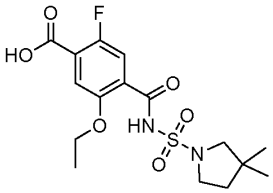
Prepared by an analogous method to Intermediate 10 starting from methyl 4-bromo-5-fluoro-2-hydroxybenzoate (3.0 g, 13.0 mmol) and iodoethane (3.5 g, 26.0 mmol) except the Step 4 was carried out with *N*,*N*-dicyclopropylsulfamide (Intermediate 180) in place of pyrrolidine-1-sulfonamide. Yield: 109 mg, 0.28 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.71 min, m/z 385.0 $(M-H)^-$ (ES^-).

Intermediate 182: 3,3-dimethylpyrrolidine-1-sulfonamide



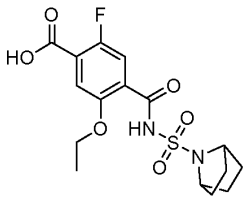
Prepared by an analogous method to Intermediate 148 starting from 3,3-dimethylpyrrolidine hydrochloride (1.0 g, 7.37 mmol), sulfuric diamide (850 mg, 8.85 mmol). Yield: 650 mg, 3.65 mmol. Brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.68 (s, 2H), 3.20 (t, J = 7.1 Hz, 2H), 2.86 (s, 2H), 1.60 (t, J = 7.1 Hz, 2H), 1.05 (s, 6H).

Intermediate 183: 4-(((3,3-dimethylpyrrolidin-1-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



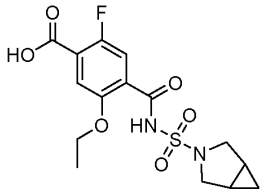
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 3,3-dimethylpyrrolidine-1-sulfonamide (Intermediate 182) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 111 mg, 0.29 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.74 min, m/z 387.0 $(M-H)^-$ (ES^-).

Intermediate 184: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



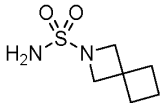
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 52 mg, 0.14 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.63 min, m/z 385.0 $(M-H)^-$ (ES^-).

Intermediate 185: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



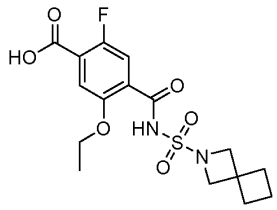
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 120 mg, 0.32 mmol. Off-white solid. LCMS: (System 3, Method I) Rt = 0.42 min, m/z 371.2 $(M-H)^-$ (ES^-).

Intermediate 186: 2-azaspiro[3.3]heptane-2-sulfonamide



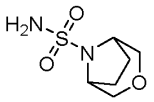
Prepared by an analogous method to Intermediate 148 starting from 2-azaspiro[3.3]heptane hydrochloride (1.0 g, 7.48 mmol), sulfuric diamide (1510 mg, 15 mmol). Yield: 1000 mg, 3.65 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (s, 2H), 3.63 (s, 4H), 2.08 (t, J = 7.6 Hz, 4H), 1.76-1.76 (m, 2H).

Intermediate 187: 4-(((2-azaspiro[3.3]heptan-2-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



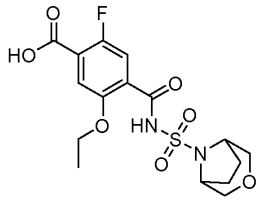
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 3-2-azaspiro[3.3]heptane-2-sulfonamide (Intermediate 186) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 120 mg, 0.31 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.72 min, m/z 385.0 $(M-H)^-$ (ES^-).

Intermediate 188: 3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonamide



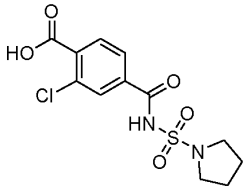
Prepared by an analogous method to Intermediate 148 starting from 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (1.5 g, 16.0 mmol), sulfuric diamide (2.0 g, 13.4 mmol). Yield: 1.6 g, 8.11 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (s, 2H), 3.90-3.85 (m, 2H), 3.54 (s, 4H), 2.06-1.99 (m, 2H), 1.80-1.75 (m, 2H).

Intermediate 189: 4-(((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



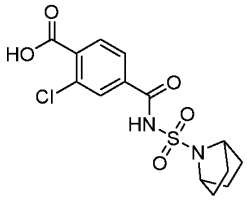
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonamide (Intermediate 188) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 177 mg, 0.44 mmol. Off-white solid. LCMS: (System 3, Method I) Rt = 1.51 min, m/z 401.0 $(M-H)^-$ (ES^-).

Intermediate 190: 2-chloro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



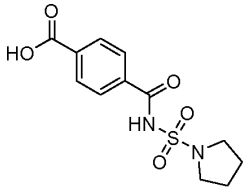
Prepared by an analogous method to Intermediate 10 (Steps 4 to 5 only) starting from 3-chloro-4-(methoxycarbonyl)benzoic acid (1.50 g, 6.85 mmol). Yield: 61 mg, 0.18 mmol. Light-brown solid. LCMS: (System 3, Method J) Rt = 1.41 min, m/z 331.2 $(M-H)^-$ (ES^-).

Intermediate 191: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-chlorobenzoic acid



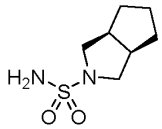
Prepared by an analogous method to Intermediate 190 except the Step 4 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of *N*,*N*-dimethylsulfamide. Yield: 61 mg, 0.18 mmol. Pale-brown oil. LCMS: (System 3, Method J) Rt = 1.41 min, m/z 331.2 $(M-H)^-$ (ES^-).

Intermediate 192: 4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 10 (Steps 4 to 5 only) starting from 4-(methoxycarbonyl)benzoic acid (0.60 g, 3.33 mmol). Yield: 540 mg, 1.81 mmol. Yellow solid. LCMS: (System 1, Method B) Rt = 0.24 min, m/z 297.0 $(M-H)^-$ (ES^-).

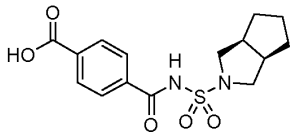
Intermediate 193: (3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrole-2(1H)-sulfonamide



Prepared by an analogous method to Intermediate 148 starting from (3a*R*,6a*S*)-octahydrocyclopenta[c]pyrrole hydrochloride (1.0 g, 6.77 mmol), sulfuric diamide (781 mg, 13.5 mmol). Yield: 1.0 g, 5.36 mmol. Pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78-6.68 (m,

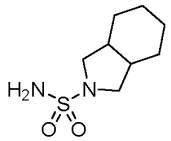
2H), 3.19-3.11 (m, 2H), 2.73-2.70 (m, 2H), 2.68-2.59 (m, 2H), 1.54-1.81 (m, 3H), 1.28-1.54 (m, 3H).

Intermediate 194: 4-((((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)sulfonyl)carbamoyl)benzoic acid



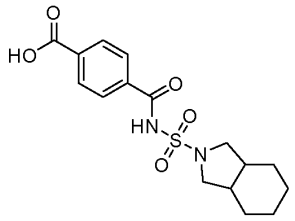
Prepared by an analogous method to Intermediate 192 except the Step 4 was carried out with (3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrole-2(1H)-sulfonamide (Intermediate 193) in place of *N*,*N*-dimethylsulfamide. Yield: 268 mg, 0.79 mmol. White solid. LCMS: (System 3, Method I) Rt = 0.93 min, m/z 337.1 $(M-H)^-$ (ES^-).

Intermediate 195: octahydro-2H-isoindole-2-sulfonamide



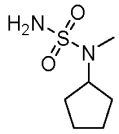
Prepared by an analogous method to Intermediate 148 starting from octahydro-1H-isoindole hydrochloride (1.9 g, 15.1 mmol), sulfuric diamide (1.7 g, 18.2 mmol). Yield: 2.3 g, 11.5 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.59 (s, 2H), 4.07-3.98 (m, 1H), 2.55 (s, 3H), 1.77-1.38 (m, 8H)

Intermediate 196: 4-(((octahydro-2H-isoindol-2-yl)sulfonyl)carbamoyl)benzoic acid



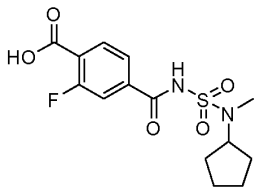
Prepared by an analogous method to Intermediate 192 except the Step 4 was carried out with octahydro-2H-isoindole-2-sulfonamide (Intermediate 195) in place of *N*,*N*-dimethylsulfamide. Yield: 215 mg, 0.61 mmol. White solid. LCMS: (System 3, Method I) Rt = 0.99 min, m/z 351.1 $(M-H)^-$ (ES^-).

Intermediate 197: *N*-cyclopentyl-*N*-methyl-sulfamide



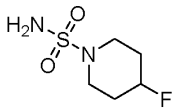
Prepared by an analogous method to Intermediate 148 starting from cyclopentylmethylamine (1.0 g, 10.1 mmol), sulfuric diamide (1.5 g, 15.1 mmol). Yield: 1.5 g, 8.2 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.59 (s, 2H), 4.07-3.98 (m, 1H), 2.55 (s, 3H), 1.77-1.38 (m, 8H).

Intermediate 198: 4-((*N*-cyclopentyl-*N*-methylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



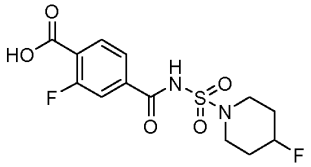
Prepared by an analogous method to Intermediate 167 except the Step 3 was carried out with *N*-cyclopentyl-*N*-methyl-sulfamide (Intermediate 197) in place of pyrrolidine-1-sulfonamide. Yield: 61 mg, 0.18 mmol. Pale-brown oil. LCMS: (System 3, Method I) Rt = 0.84 min, m/z 343.0 $(M-H)^-$ (ES^-).

Intermediate 199: 4-fluoropiperidine-1-sulfonamide



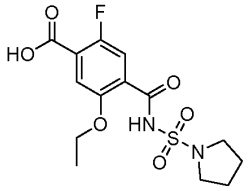
Prepared by an analogous method to Intermediate 148 starting from 4-fluoropiperidine (1.0 g, 9.7 mmol), sulfuric diamide (1.4 g, 14.5 mmol). Yield: 1.1 g, 6.2 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (s, 2H), 4.88-4.71 (m, 1H), 3.05-3.05 (m, 4H), 1.97-1.76 (m, 4H)

Intermediate 200: 2-fluoro-4-(((4-fluoropiperidin-1-yl)sulfonyl)carbamoyl)benzoic acid



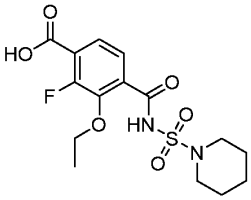
Prepared by an analogous method to Intermediate 167 except the Step 3 was carried out with 4-fluoropiperidine-1-sulfonamide (Intermediate 199) in place of pyrrolidine-1-sulfonamide. Yield: 104 mg, 0.30 mmol. Light-brown oil. LCMS: (System 3, Method J) Rt = 1.40 min, m/z 347.2 $(M-H)^-$ (ES^-).

Intermediate 201: 5-ethoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



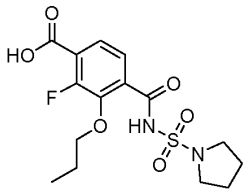
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with pyrrolidine-1-sulfonamide in place of *N*,*N*-dicyclopropylsulfamide. Yield: 181 mg, 0.50 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.72 min, m/z 361.0 $(M+H)^+$ (ES^+).

Intermediate 202: 3-ethoxy-2-fluoro-4-((piperidin-1-ylsulfonyl)carbamoyl)benzoic acid



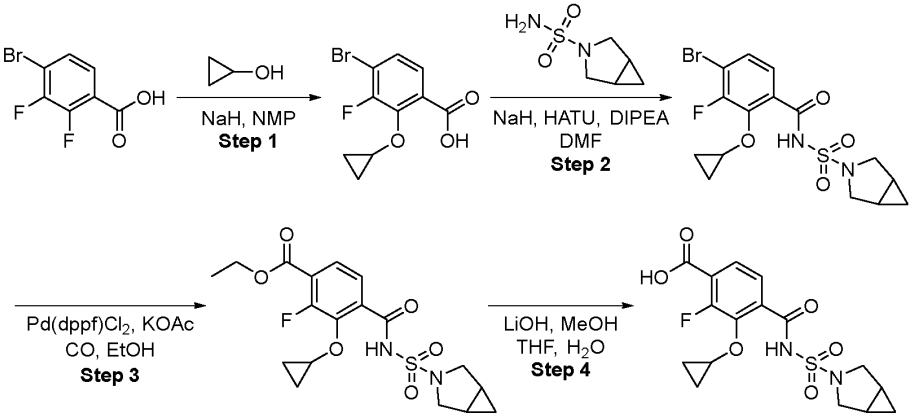
Prepared by an analogous method to Intermediate 13 starting from of 2-bromo-6-fluorophenol (6.0 g, 31.6 mmol) and iodoethane (9.9 g, 63.2 mmol) except the Step 4 was carried out with piperidine-1-sulfonamide in place of pyrrolidine-1-sulfonamide. Yield: 600 mg, 1.60 mmol. Off-white solid. LCMS: (System 1, Method A) Rt = 1.00 min, m/z 373.2 $(M-H)^-$ (ES^-).

Intermediate 203: 2-fluoro-3-propoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 13 starting from of 2-bromo-6-fluorophenol (4.0 g, 21.1 mmol) and iodopropane (7.2 g, 42.1 mmol). Yield: 600 mg, 1.6 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.93 min, m/z 373.0 $(M-H)^-$ (ES^-).

Intermediate 204: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-3-cyclopropoxy-2-fluorobenzoic acid



Step 1

Sodium hydride (60% dispersion in mineral oil, 3.9 g, 84.8 mmol) was added in small portions to a solution of 4-bromo-2,3-difluorobenzoic acid (5.0 g, 21.19 mmol) in NMP (150 mL) at RT. Then cyclopropanol (4.90 g, 84.75 mmol) was added and the mixture was stirred at RT overnight. The reaction was quenched with NH_4Cl aq. sat. (450 mL), then the pH of the mixture was adjusted to ca. 4 by adding HCl aq. 1 N. The resulting aqueous phase was extracted with EtOAc (3x200 mL). The combined organic layers were washed by brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 4-bromo-2-cyclopropoxy-3-fluorobenzoic acid (3.6 g, 13.1 mmol) as an off-white solid. LCMS: (System 1, Method A) Rt = 1.27, m/z 273 $(M-H)^-$ (ES^-).

Step 2

A mixture of 4-bromo-2-cyclopropoxy-3-fluorobenzoic acid (1.5 g, 5.5 mmol), HATU (2.5 g, 6.6 mmol) and DIPEA (2.82 g, 21.90 mmol) in DMF (50 mL) was stirred for 1 h at RT, 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168, 2.7 g, 16.4 mmol) and sodium hydride (60% dispersion in mineral oil, 876 mg, 21.9 mmol) were added and the reaction was stirred overnight at RT. The mixture was quenched with NH_4Cl aq. sat. (150 mL), then the pH of the resulting aqueous layer was adjusted to ca. 4 with HCl aq. 1 N. the reaction mixture was extracted with EtOAc (3x100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-25% EtOAc/petroleum ether) to afford *N*-(3-azabicyclo[3.1.0]hexan-3-ylsulfonyl)-4-bromo-2-cyclopropoxy-3-fluorobenzamide (850 mg, 2.03 mmol) as yellow oil. LCMS: (System 1, Method A) Rt = 1.50 min, m/z 418.9 $(M+H)^+$ (ES^+).

Step 3

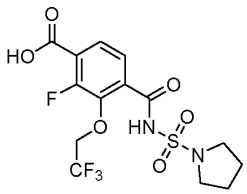
To a mixture of *N*-(3-azabicyclo[3.1.0]hexan-3-ylsulfonyl)-4-bromo-2-cyclopropoxy-3-fluorobenzamide (836 mg, 2.00 mmol) in EtOH (20 mL) was added [1,1′-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (146 mg, 0.20 mmol) and potassium acetate (588 mg, 6.00 mmol), then the mixture was stirred for 2 h at 80 °C under CO atmosphere. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (1-50% EtOAc/petroleum ether) to afford ethyl 4-((3-azabicyclo[3.1.0]hexan-3-ylsulfonyl)carbamoyl)-3-cyclopropoxy-2-fluorobenzoate (659 mg, 1.60 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.46 min, m/z 413.0 $(M+H)^+$ (ES^+).

Step 4

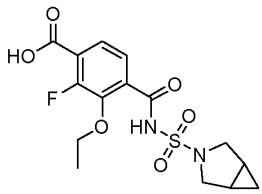
A mixture of ethyl 4-((3-azabicyclo[3.1.0]hexan-3-ylsulfonyl)carbamoyl)-3-cyclopropoxy-2-fluorobenzoate (412 mg, 1.00 mmol) and $LiOH{\cdot}H_2O$ (252 mg, 6.00 mmol) in water (3 mL) and MeOH (10 mL) was stirred for 3 h at RT. The pH of the mixture was adjusted to ca. 8 by adding HCl aq. 1 N and the organic solvents were removed under reduced pressure. The pH of the resulting aqueous phase was adjusted to ca. 3 with HCl aq. 1 N. The formed precipitate was collected by filtration, washed with water then hexane and dried under reduced pressure to afford 4-((3-azabicyclo[3.1.0]hexan-3-ylsulfonyl)carbamoyl)-3-cyclopropoxy-2-fluorobenzoic acid (360 mg, 0.94 mmol) as a yellow solid. LCMS: (System 1, Method A) Rt = 0.91 min, 383.0 $(M-H)^-$ (ES^-).

Intermediate 205: 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(2,2,2-trifluoroethoxy)benzoic acid



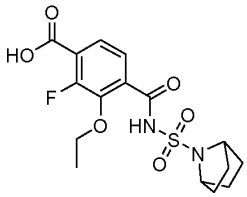
Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (1.1 g, 4.66 mmol) and 2,2,2-trifluoroethanol (2.14 g, 46.6 mmol) except the Step 2 was carried out with pyrrolidine-1-sulfonamide in place of 3-azabicyclo[3.1.0]hexane-3-sulfonamide. Yield: 230 mg, 0.56 mmol. Off-white solid. LCMS: (System 1, Method A) Rt = 0.99 min, m/z 415.0 $(M-H)^-$ (ES^-).

Intermediate 206: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-3-ethoxy-2-fluorobenzoic acid



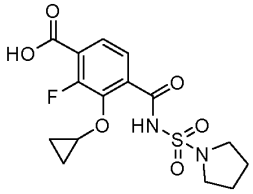
Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (11.0 g, 46.6 mmol) and ethanol (21.4 g, 466 mmol). Yield: 1.0 g, 2.69 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.76 min, m/z 372.0 $(M-H)^-$ (ES^-).

Intermediate 207: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-3-ethoxy-2-fluorobenzoic acid



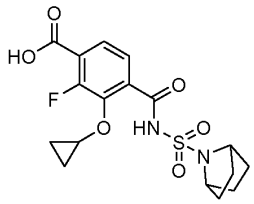
Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (11.0 g, 46.6 mmol) and ethanol (21.4 g, 466 mmol) except the Step 2 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of 3-azabicyclo[3.1.0]hexane-3-sulfonamide. Yield: 1.1 g, 2.72 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.95 min, m/z 385.0 $(M-H)^-$ (ES^-).

Intermediate 208: 3-cyclopropoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



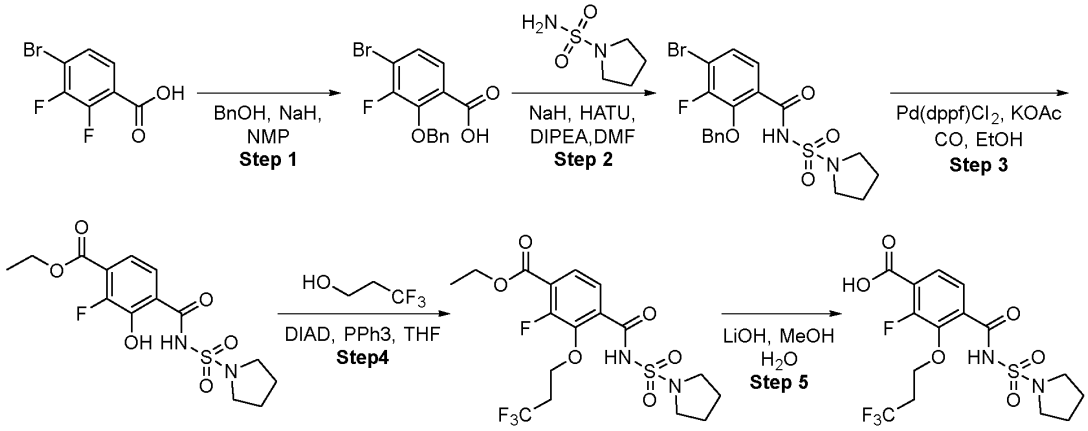
Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (5.0 g, 21.2 mmol) and cyclopropanol (4.9 g, 84.8 mmol) except the Step 2 was carried out with pyrrolidine-1-sulfonamide in place of 3-azabicyclo[3.1.0]hexane-3-sulfonamide. Yield: 300 g, 0.81 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.62 min, m/z 370.9 $(M-H)^-$ (ES^-).

Intermediate 209: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-3-cyclopropoxy-2-fluorobenzoic acid



Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (5.0 g, 21.2 mmol) and cyclopropanol (4.9 g, 84.8 mmol) except the Step 2 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of 3-azabicyclo[3.1.0]hexane-3-sulfonamide. Yield: 300 g, 0.75 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.00 min, m/z 398.8 $(M+H)^+$ (ES^+).

Intermediate 210: 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(3,3,3-trifluoropropoxy)benzoic acid



Step 1

Sodium hydride (60% dispersion in mineral oil, 2.2 g, 54.9 mmol) was added portionwise to a solution of 4-bromo-2,3-difluorobenzoic acid (2.6 g, 11.0 mmol) in NMP (40 mL) at 0 °C, then benzyl alcohol (7.1 g, 65.8 mmol) was added and the reaction was stirred at RT overnight. The mixture was poured into NH_4Cl aq. sat. (120 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/Petroleum ether) to afford 2-(benzyloxy)-4-bromo-3-fluorobenzoic acid (2.5 g, 7.69 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.39 min, m/z 324.6 $(M+H)^+$ (ES^+).

Step 2

A mixture of 2-(benzyloxy)-4-bromo-3-fluorobenzoic acid (2.4 g, 7.38 mmol), HATU (3.4 g, 8.86 mmol) and DIPEA (3.8 g, 29.5 mmol) in DMF (50 mL) was stirred at RT for 1 h, pyrrolidine-1-sulfonamide (3.3 g, 22.2 mmol) and sodium hydride (60% dispersion in mineral oil, 1.2 g, 29.5 mmol) was added, then the reaction mixture was stirred at RT for 2 h. The mixture was poured into NH_4Cl aq. sat. (150 mL), then the pH of the resulting aqueous layer was adjusted to ca. 5 with HCl aq. 1 N and extracted with EtOAc (3x120 mL). The combined organic layers were washed by brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-25% EtOAc/petroleum ether) to afford 2-(benzyloxy)-4-bromo-3-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide (1.0 g, 2.2 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.61 min, m/z 457.0 $(M+H)^+$ (ES^+).

Step 3

A mixture of 2-(benzyloxy)-4-bromo-3-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide (1.0 g, 2.2 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (160 mg, 0.22 mmol) and potassium acetate (644 mg, 6.57 mmol) in EtOH (22 mL) was stirred at 80 °C for 5 h under CO atmosphere. The organic solvent was removed under reduced pressure and the residue partitioned between water (20 mL) and EtOAc (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel column (1-50% EtOAc/Petroleum ether) to afford ethyl 2-fluoro-3-hydroxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (600 mg, 1.67 mmol) as a brown solid. LCMS: (System 1, Method A) Rt = 1.55 min, m/z 361.0 $(M+H)^+$ (ES^+).

Step 4

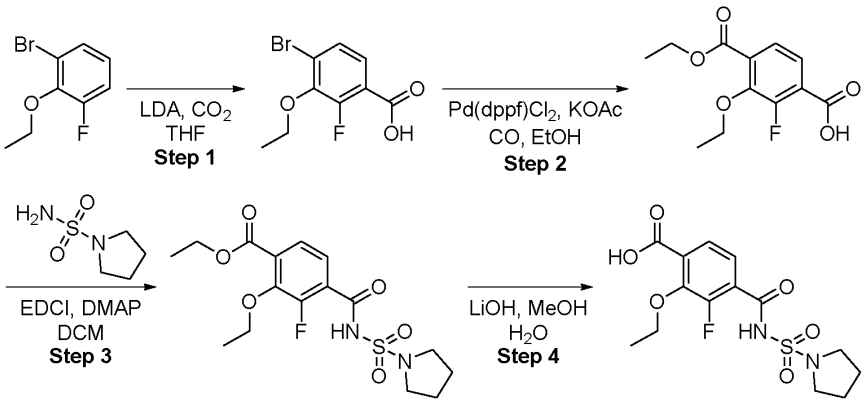
A mixture of ethyl 2-fluoro-3-hydroxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (360 mg, 1.00 mmol), 3,3,3-trifluoropropan-1-ol (171 mg, 1.50 mmol), PPh_3 (786 mg, 3.00 mmol) and DIAD (606 mg, 3.00 mmol) in THF (10 mL) was stirred at RT overnight under N_2 atmosphere. The mixture was partitioned between water (30 mL) and EtOAc (3x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-50% ethyl acetate/petroleum ether) to afford ethyl 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(3,3,3-trifluoropropoxy)benzoate (41k-6, 400 mg, 0.80 mmol) as a yellow solid. LCMS: (System 1, Method A). Rt = 1.72 min, m/z 456.7 $(M+H)^+$ (ES^+).

Step 5

A solution of $LiOH{\cdot}H_2O$ (184 mg, 4.38 mmol) and ethyl 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(3,3,3-trifluoropropoxy)benzoate (400 mg, 0.88 mmol) in MeOH (10 mL)

and water (2.5 mL) was stirred at RT overnight. The pH of the mixture was adjusted to ca. 8 by adding HCl aq. 1 N and the organic solvents was removed under reduced pressure. The aqueous residue was washed with EtOAc (3x10 mL), and the pH of the resulting aqueous layer was adjusted to ca. 3 by adding HCl aq. 1 N. the mixture was extracted with EtOAc (3x10 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)-3-(3,3,3-trifluoropropoxy)benzoic acid (45 mg, 0.11 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.03 min, m/z 426.8 $(M-H)^-$ (ES^-).

Intermediate 211: 2-ethoxy-3-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

LDA 2 N in THF (23 mL) was added to a solution of 1-bromo-2-ethoxy-3-fluorobenzene (2.5 g, 11.4 mmol) in THF (23 mL) at -78 °C and the reaction mixture was stirred at this temperature for 1 h under N_2. Dry ice pellets were added under N_2 at -78 °C and the mixture was stirred at RT overnight. The reaction was quenched with NH_4Cl aq. sat. (20 mL), the pH of the resulting aqueous layer adjusted to ca. 2 with HCl aq. 1 N and the mixture extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was triturated with hexane to afford 4-bromo-3-ethoxy-2-fluoro-benzoic acid (1.6 g, 6.08 mmol) as an off-white solid. LCMS: (System 3, Method J) Rt = 1.75 min, m/z 262.8 $(M-H)^-$ (ES^-).

Step 2

A mixture of 4-bromo-3-ethoxy-2-fluoro-benzoic acid (1.9 g, 7.15 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.1 g, 1.43 mmol) and potassium acetate (2.1 g, 21.4 mmol) in EtOH (16 mL) was stirred under CO atmosphere at 80 °C overnight. The mixture was allowed to reach RT, filtered through a pad of celite and concentrated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and HCl aq. 4 N (10 mL). The aqueous layer was extracted with EtOAc (2x20 mL) and the combined organic layers were dried

($MgSO_4$), filtered and concentrated under reduced pressure to afford 3-ethoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid (1.7 g, 6.63 mmol) as a red oil which was used without further purification in the next step. LCMS: (System 3, Method J) Rt = 1.79 min, m/z 255.0 $(M-H)^-$ (ES^-).

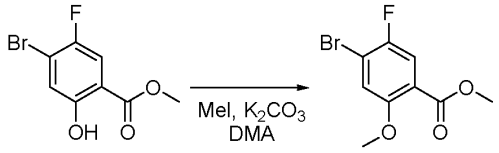
Step 3

A mixture of 3-ethoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid (250 mg, 0.98 mmol), EDCI (281 mg, 1.46 mmol), DMAP (477 mg, 3.90 mmol) and pyrrolidine-1-sulfonamide (440 mg, 2.93 mmol) in DCM (4.9 mL) was stirred at RT overnight. The reaction mixture was partitioned between $NaHCO_3$ aq. sat. (20 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (2x15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on C_{18} (0-100% ACN/0.1% formic acid in water) to afford ethyl 2-ethoxy-3-fluoro-4-(228yrrolidine-1-ylsulfonylcarbamoyl)benzoate (262 mg, 0.68 mmol) as an off-white solid. LCMS: (System 3, Method J) Rt = 1.89 min, m/z 387.3 $(M-H)^-$ (ES^-).

Step 4

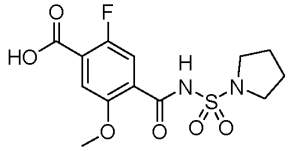
A mixture of ethyl 2-ethoxy-3-fluoro-4-(228yrrolidine-1-ylsulfonylcarbamoyl)benzoate (262 mg, 0.68 mmol) and LiOH aq. 2 N (2.7 mL) in MeOH (1.2 mL) and THF (1.2 mL) was stirred at RT for 1 h. Then the reaction was quenched with HCl aq. 1 N (20 mL) and the aqueous phase was extracted with EtOAc (2x20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2-ethoxy-3-fluoro-4-(228 yrrolidine-1-ylsulfonylcarbamoyl)benzoic acid (208 mg, 0.58 mmol) as an off-white solid. LCMS: (System 3, Method J) Rt = 1.57 min, m/z 359.2 $(M-H)^-$ (ES^-).

Intermediate 212: methyl 4-bromo-5-fluoro-2-methoxybenzoate



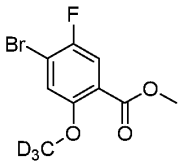
Iodomethane (1.71 g, 12.05 mmol) was added to a mixture of methyl 4-bromo-5-fluoro-2-hydroxybenzoate (2.0 g, 8.03 mmol) and K_2CO_3 (2.2 g, 16.1 mmol) in DMA (40 mL) and the mixture was stirred at RT overnight. The reaction mixture was poured into ice-water (120 mL) and extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford methyl 4-bromo-5-fluoro-2-methoxybenzoate (2.0 g, 7.60 mmol) as a yellow oil. LCMS: (System 1, Method A) Rt = 1.85 min, m/z 262.8 $(M+H)^+$ $(ES)^+$.

Intermediate 213: 2-fluoro-5-methoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



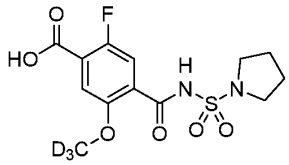
Prepared by an analogous method to Intermediate 36 (Steps 2 to 5) starting from methyl 4-bromo-5-fluoro-2-methoxybenzoate (Intermediate 212) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 320 mg, 0.92 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.42 min, m/z 346.17$(M+H)^+$ (ES^+).

Intermediate 214: methyl 4-bromo-5-fluoro-2-(methoxy-d_3)benzoate



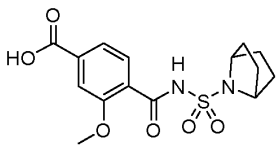
Prepared by an analogous method to Intermediate 212 starting from of methyl 4-bromo-5-fluoro-2-hydroxybenzoate (2.0 g, 8.1 mmol) and iodomethane-d_3 (1.7 g, 12.1 mmol). Yield: 1.9 g, 7.17 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.87 min, m/z 266.1 $(M+H)^+$ (ES^+).

Intermediate 215: 2-fluoro-5-(methoxy-d_3)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-5-fluoro-2-(methoxy-d_3)benzoate (Intermediate 214). Yield: 300 mg, 0.86 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 348.0 $(M-H)^-$ (ES^-).

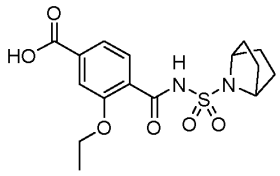
Intermediate 216: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-3-methoxybenzoic acid



Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-2-methoxybenzoate except the Step 3 was carried out with 7-azabicyclo[2.2.1]heptane-7-

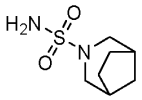
sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 280 mg, 0.79 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.73 min, m/z 355.0 $(M+H)^+$ (ES^+).

Intermediate 217: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-3-ethoxybenzoic acid



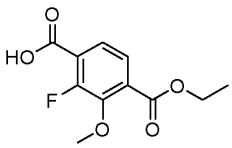
Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-2-ethoxybenzoate except the Step 3 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 290 mg, 0.79 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.05 min, m/z 369.0 $(M+H)^+$ (ES^+).

Intermediate 218: 3-azabicyclo[3.2.1]octane-3-sulfonamide



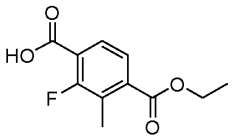
Prepared by an analogous method to Intermediate 148 starting from 3-azabicyclo[3.2.1]octane (1.0 g, 9.0 mmol), sulfuric diamide (1.3 g, 13.5 mmol). Yield: 1.3 g, 6.8 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.57 (s, 2H), 3.16-3.13 (m, 2H), 2.63 (d, J = 10.4 Hz, 2H), 2.24 (br s, 2H), 1.61-1.43 (m, 5H), 1.34-1.31 (m, 1H).

Intermediate 219: 4-(ethoxycarbonyl)-2-fluoro-3-methoxybenzoic acid



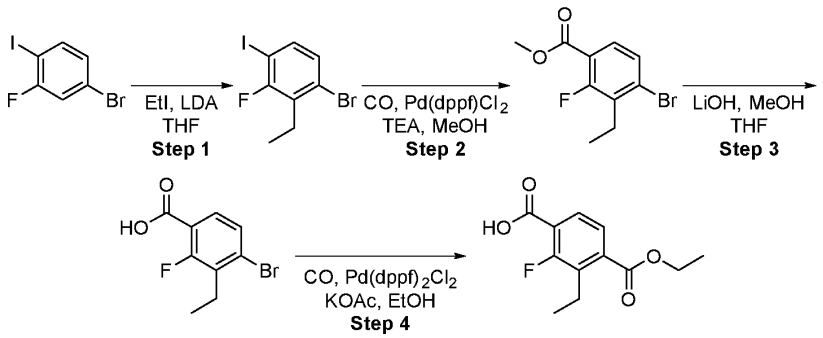
Prepared by an analogous method to Intermediate 149 starting from 4-bromo-2-fluoro-3-methoxybenzoic acid (5.4 g, 21.8 mmol). Yield: 4.4 g, 18.0 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.14 min, m/z 241.2 $(M-H)^-$ (ES^-).

Intermediate 220: 4-(ethoxycarbonyl)-2-fluoro-3-methylbenzoic acid



Prepared by an analogous method to Intermediate 149 starting from 4-bromo-2-fluoro-3-methylbenzoic acid (1.0 g, 4.29 mmol). Yield: 700 mg, 3.1 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.18 min, m/z 225.3 $(M-H)^-$ (ES^-).

Intermediate 221: 4-(ethoxycarbonyl)-3-ethyl-2-fluorobenzoic acid



Step 1

To a solution of 4-bromo-2-fluoro-1-iodobenzene (5 g, 16.7 mmol) in THF (34 mL) was slowly added LDA (2M in THF, 16.67 mL, 33.3 mmol) at -78 °C under N_2. The reaction was slowly warmed to -20 °C and stirred at this temperature for 0.5 h, then it was cooled to -78 °C. Iodoethane (8.67 g, 55.5 mmol) was added and the mixture was stirred at room temperature overnight. Saturated NH_4Cl aq. (100 mL) was added, and the mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed by brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (10% EtOAc/petroleum ether) to afford 1-bromo-2-ethyl-3-fluoro-4-iodobenzene (2 g, 6.08 mmol) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.62 (dd, J = 8.2, 7.0 Hz, 1H), 7.27 (dd, J = 8.4, 1.2 Hz, 1H), 2.80-2.74 (m, 2H), 1.11 (t, J = 7.4 Hz, 3H).

Step 2

To a solution of 1-bromo-2-ethyl-3-fluoro-4-iodobenzene (1 g, 3.05 mmol) in MeOH (30 mL) was added $Pd(dppf)Cl_2$ (223 mg, 0.31 mmol) and TEA (1.85 g, 18.3 mmol), then the mixture was stirred at room temperature overnight under CO (1 MPa). The mixture was concentrated under reduced pressure, water (30 mL) was added and the mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed by brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford ethyl methyl 4-bromo-3-ethyl-2-fluorobenzoate (550 mg, 2.11 mmol) as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ: 7.65 (d, J = 8.2, 7.6 Hz, 1H), 7.59 (dd, J = 8.2, 0.8 Hz, 1H), 3.86 (s, 3H), 2.83-2.77 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H).

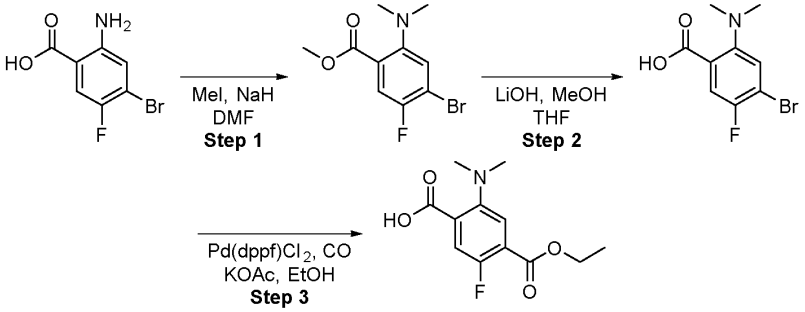
Step 3

To a solution of methyl 4-bromo-3-ethyl-2-fluorobenzoate (550 mg, 2.11 mmol) in MeOH (20 mL) was added a solution of $LiOH{\cdot}H_2O$ (534 mg, 12.7 mmol) in water (5 mL). The reaction mixture was stirred at room temperature overnight. The pH was adjusted to ca. 8 with HCl aq. 1N. MeOH was removed under reduced pressure, and pH was further adjusted to pH = 3 with HCl aq. 1N. The formed precipitate was collected by filtration, washed with water and hexane to afford 4-bromo-3-ethyl-2-fluorobenzoic acid (400 mg, 1.63 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.30 min. m/z 245.4 $(M-H)^-$ (ES^-).

Step 4

To a solution of 4-bromo-3-ethyl-2-fluorobenzoic acid (400 mg, 1.63 mmol) in EtOH (20 mL) was added $Pd(dppf)Cl_2$ (117 mg, 0.16 mmol) and potassium acetate (479 mg, 4.89 mmol), and the mixture was stirred at 80 °C overnight under CO atmosphere (1 atm). The solvent was removed under reduced pressure and K_2CO_3 aq. 2M (15 mL) was added. The aqueous layer was washed with EtOAc (3x15 ml) and the pH was adjusted to ca. 4~5 with HCl aq. 1N. The aqueous layer was extracted with EtOAc (3x15 ml) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford 4-(ethoxycarbonyl)-3-ethyl-2-fluorobenzoic acid (330 mg, 1.37 mmol) as an off-white solid. LCMS: (System 1, Method A). Rt = 1.29 min. m/z 239.2 $(M-H)^-$ (ES^-)

Intermediate 222: 2-(dimethylamino)-4-(ethoxycarbonyl)-5-fluorobenzoic acid



Step 1

Sodium hydride (60% dispersion in mineral oil, 615 mg, 25.6 mmol) was added portionwise to a solution of 2-amino-4-bromo-5-fluorobenzoic acid (1.0 g, 4.27 mmol) in DMF (9.5 mL) at 0 °C and the reaction was stirred at this temperature for 30 min. Iodomethane (2.1 mL, 34.2 mmol) was added and the reaction was stirred for 2 h at RT. The reaction was poured into water (20 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 4-bromo-2-(dimethylamino)-5-fluorobenzoate (1.0 g, 3.62 mmol) as a yellow oil which was used in the next step without further purification. LCMS: (System 3, Method J) Rt = 1.78 min, m/z 276.0 $(M-H)^-$ (ES^-).

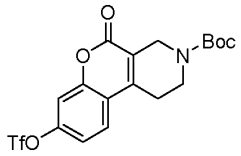
Step 2

LiOH aq. 2 N (7.3 mL, 14.5 mmol) was added to a mixture of methyl 4-bromo-2-(dimethylamino)-5-fluoro-benzoate (1.0 g, 3.62 mmol) in methanol (3.6 mL) and tetrahydrofuran (3.6 mL), and the solution was stirred at RT for 1 h. The solvents were removed, and the crude product was purified by column chromatography on C_{18} (0-100% ACN/0.1% FA in water) to afford 4-bromo-2-(dimethylamino)-5-fluorobenzoic acid (240 mg, 0.92 mmol) as a yellow solid. LCMS: (System 3, Method J) Rt = 1.18 min, m/z 262.0 $(M-H)^-$ (ES^-).

Step 3

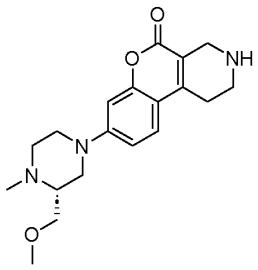
A solution of 4-bromo-2-(dimethylamino)-5-fluorobenzoic acid (2.7 g, 10.3 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (758 mg, 1.03 mmol) and potassium acetate (3.1 g, 30.9 mmol) in EtOH (52 mL) was stirred at 80 °C overnight under CO atmosphere. The reaction mixture was allowed to reach RT, filtered through a celite pad and concentrated under reduce pressure. The crude product was purified by column chromatography on C_{18} (0-100% ACN/0.1% formic acid in water) to afford 2-(dimethylamino)-4-ethoxycarbonyl-5-fluorobenzoic acid (750 mg, 2.94 mmol) as a yellow solid. LCMS: (System 3, Method J) Rt = 1.20 min, m/z 254.0 $(M-H)^-$ (ES^-).

Intermediate 223: *tert*-butyl 5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



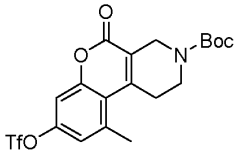
Prepared by an analogous method to Intermediate 2 starting from resorcinol (4.4 g, 40.4 mmol). Yield: 6.5 g, 14.5 mmol. Pale-yellow solid. LCMS: (System 1, Method F) Rt = 2.11 min, m/z 394.2 $(M-56+H)^+$ (ES^+).

Intermediate 224: (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



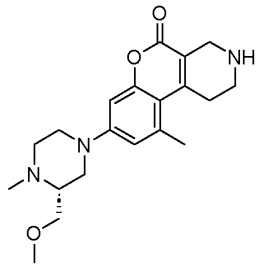
Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 1.9 g, 13.0 mmol) and *tert*-butyl 5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4H)-carboxylate (Intermediate 223, 3.9 g, 8.65 mmol). Yield: 1.9 g, 5.54 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.34 min, m/z 344.2.0 $(M+H)^+$ (ES^+).

Intermediate 225: *tert*-butyl 10-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



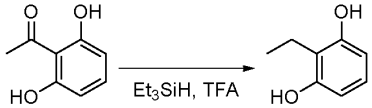
Prepared by an analogous method to Intermediate 2 starting from 5-methylresorcinol (5.0 g, 40.4 mmol). Yield: 10.0 g, 21.6 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 2.16 min, m/z 408.3 $(M-56+H)^+$ (ES^+).

Intermediate 226: (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 1.9 g, 13 mmol) and *tert*-butyl 10-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 225, 4.0 g, 8.7 mmol). Yield: 1.9 g, 5.32 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.46 min, m/z 358.2 $(M+H)^+$ (ES^+).

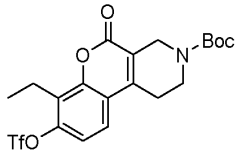
Intermediate 227: 2-ethylresorcinol



Triethylsilane (25.2 g, 217.1 mmol) was added dropwise to a solution of 1-(2,6-dihydroxyphenyl)ethanone (11.0 g, 72.4 mmol) in TFA (200 mL) at 0 °C, the reaction was stirred at RT overnight. The mixture was poured into ice-water (400 mL) and extracted with DCM (3x400

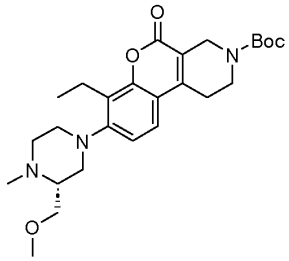
mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1% EtOAc/Petroleum ether) to afford 2-ethylbenzene-1,3-diol (8.0 g, 57.9 mmol) as a colourless oil. LCMS: (System 1, Method A) Rt = 1.30 min, m/z 137.3 $(M-H)^-$ (ES^-).

Intermediate 228: *tert*-butyl 7-ethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



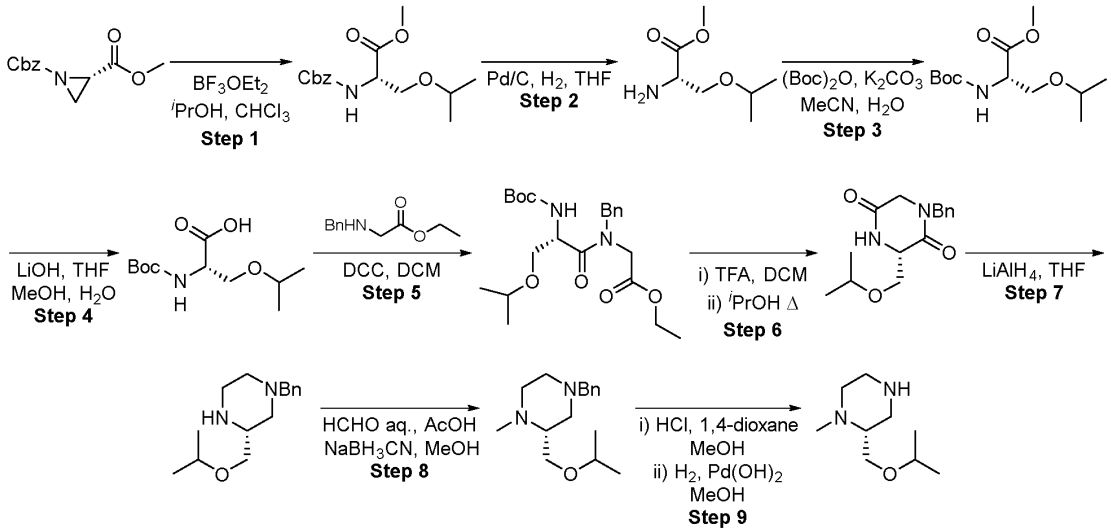
Prepared by an analogous method to Intermediate 2 starting from 2-ethylresorcinol (Intermediate 227, 5.2 g, 37.68 mmol). Yield: 3.0 g, 6.20 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 2.54 min, m/z 422.0 $(M-56+H)^+$ (ES^+).

Intermediate 229: (*R*)-7-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 671 mg, 4.65 mmol) and *tert*-butyl 7-ethyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 228, 1.5 g, 3.10 mmol). Yield: 0.6 g, 1.62 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.63 min, m/z 372.2 $(M+H)^+$ (ES^+).

Intermediate 230: (*R*)-3-(isopropoxymethyl)-1-methylpiperazine



Step 1

Boron trifluoride diethyl etherate (22 mL) was added dropwise to a solution of (*S*)-1-benzyl 2-methyl aziridine-1,2-dicarboxylate (5.0 g, 21.3 mmol) in chloroform (106 mL) and isopropanol (106 mL) and the reaction was stirred at RT overnight. The mixture was partitioned between water (200 mL) and DCM (3x200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford (*S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-isopropoxypropanoate (5.0 g, 16.9 mmol) as a yellow oil. LCMS: (System 1, Method A) Rt = 1.88 min, m/z 296.4 $(M+H)^+$ (ES^+).

Step 2

A mixture of (*S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-isopropoxypropanoate (5.0 g, 16.9 mmol) and Pd/C (10%, 1.5 g) in THF (170 mL) was stirred at RT overnight under H_2. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford (*S*)-methyl 2-amino-3-isopropoxypropanoate (2.5 g, 15.5 mmol) as a yellow oil which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 1.23 min, m/z 162.4 $(M+H)^+$ (ES^+).

Step 3

A mixture of (*S*)-methyl 2-amino-3-isopropoxypropanoate (2.5 g, 15.51 mmol), K_2CO_3 (4.3 g, 31.0 mmol) and Boc_2O (4.1 g, 18.6 mmol) in ACN (70 mL) and water (70 mL) was stirred at RT overnight. The reaction mixture was partitioned with EtOAc (3x100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford

(*S*)-methyl 2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanoate (3.0 g, 11.5 mmol) as a colourless oil. LCMS: (System 1, Method A) Rt = 1.84 min, m/z 206.2 $(M-56+H)^+$ (ES^+).

Step 4

A solution $LiOH{\cdot}H_2O$ (2.4 g, 57.4 mmol) in water (20 mL) was added to a solution of (*S*)-methyl 2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanoate (3.0 g, 11.5 mmol) in THF (80 mL) and MeOH (20 mL). The reaction mixture was stirred at RT overnight. The pH of the mixture was adjusted to ca. 8 by adding HCl aq. 1 N and the organic solvents were removed under reduced pressure. The pH of the resulting aqueous layer was adjusted to ca. 5 by adding HCl aq. 1 N and the aqueous layer extracted with EtOAc (3x40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (*S*)-2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanoic acid (2.3 g, 9.30 mmol) as a brown oil which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 1.21 min, m/z 246.2 $(M-H)^-$ (ES^-).

Step 5

A mixture of (*S*)-2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanoic acid (2.3 g, 9.30 mmol), ethyl 2-(benzylamino)acetate (1.8 g, 9.30 mmol) and DCC (1.9 g, 9.30 mmol) in DCM (90 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure. The residue was suspended in MTBE/Petroleum ether (v/v 3/1, 3x20 mL) and the solid filtered off. The filtrate was concentrated under reduced pressure to afford (*S*)-ethyl 2-(*N*-benzyl-2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanamido)acetate (3.1 g, 7.34 mmol) as a yellow oil. LCMS: (System 1, Method A) Rt = 2.31 min, m/z 423.2 $(M+H)^+$ (ES^+).

Step 6

TFA (15 mL) was added to a mixture of (*S*)-ethyl 2-(*N*-benzyl-2-((tert-butoxycarbonyl)amino)-3-isopropoxypropanamido)acetate (3.1 g, 7.34 mmol) in DCM (60 mL) and the reaction mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue dissolved in isopropanol (60 mL) and stirred at 80 °C for 2 h. The organic solvent was removed under reduced pressure and water (30 mL) was added to the residue. The pH of the resulting aqueous layer was adjusted to ca. 9 by adding 15% NaOH aq. The formed precipitate was filtered and dried under reduced pressure to afford (*S*)-1-benzyl-3-(isopropoxymethyl)piperazine-2,5-dione (1.6 g 5.79 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 1.51 min, m/z 277.4 $(M+H)^+$ (ES^+).

Step 7

Lithium aluminium hydride 2.5 N in THF (7 mL, 17.5 mmol) was added dropwise to a solution of (*S*)-1-benzyl-3-(isopropoxymethyl)piperazine-2,5-dione (1.6 g, 5.79 mmol) in THF (60 mL) at 0 °C and the reaction mixture was stirred at 60 °C for 2 h. $Na_2SO_4 \cdot 10\ H_2O$ was added portionwise and the mixture was stirred at RT for 15 min. The reaction was filtered and the filtrate was concentrated under reduced pressure to afford (*R*)-1-benzyl-3-(isopropoxymethyl)piperazine (1.28 g, 5.15 mmol) as a pale-yellow oil which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 1.61 min, 249.3 $(M+H)^+$ (ES^+).

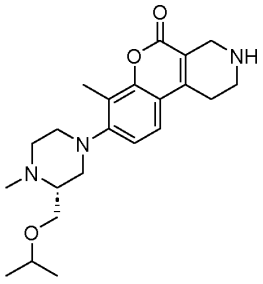
Step 8

A mixture of (*R*)-1-benzyl-3-(isopropoxymethyl)piperazine (1.3 g, 5.15 mmol), formaldehyde (37% aq. solution, 4.2 g, 51.54 mmol) and AcOH (309 mg, 5.15 mmol) in MeOH (40 mL) was stirred at RT for 30 min, then sodium cyanoborohydride (648 mg, 10.3 mmol) was added and the reaction mixture was stirred at RT overnight. The mixture was poured into $NaHCO_3$ aq. sat. (40 mL) and extracted with DCM (4x40 mL). The combined organics layers were washed by brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% MeOH/DCM) to afford (*R*)-4-benzyl-2-(isopropoxymethyl)-1-methylpiperazine (750 mg, 2.86 mmol) as a yellow oil. LCMS: (System 1, Method C) Rt = 0.83 min, m/z 263.3 $(M+H)^+$ (ES^+).

Step 9

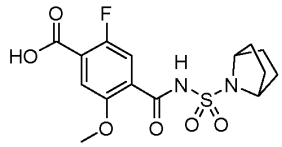
HCl 4 N in 1,4-dioxane (10 mL, 40 mmol) was added to (*R*)-4-benzyl-2-(isopropoxymethyl)-1-methylpiperazine (750 mg, 2.86 mmol) and the reaction was stirred at RT overnight. The mixture was concentrated under reduced pressure. The residue dissolved in MeOH (20 mL), $Pd(OH)_2$ (20%, 225 mg) was added and the reaction mixture was stirred at 50 °C overnight under H_2 (1.2 MPa). The mixture was filtered and the filtrate was concentrated under reduced pressure to afford (*R*)-2-(isopropoxymethyl)-1-methylpiperazine (430 mg, 2.50 mmol) as a brown oil. LCMS: (System 1, Method A) Rt = 1.08 min, m/z 173.4 $(M+H)^+$ (ES^+).

Intermediate 231: (*R*)-8-(3-(isopropoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



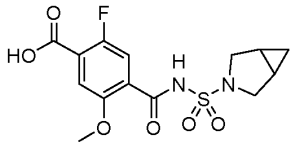
Prepared by an analogous method to Intermediate 5 starting from (*R*)-3-(isopropoxymethyl)-1-methylpiperazine (Intermediate 230, 430 mg, 2.50 mmol) and (Intermediate 2, 850 mg, 1.78 mmol). Yield: 288 mg, 0.75 mmol. Brown solid. LCMS: (System 1, Method C) Rt = 0.76 min, m/z 386.2 $(M+H)^+$ (ES^+).

Intermediate 232: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-5-methoxybenzoic acid



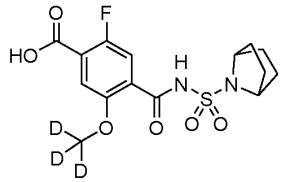
Prepared by analogous method to Intermediate 213 starting from methyl 4-bromo-5-fluoro-2-methoxybenzoate (Intermediate 212) except the Step 3 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 300 mg, 0.81 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.72 min, m/z 371.2 $(M-H)^-$ (ES^-).

Intermediate 233: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-2-fluoro-5-methoxybenzoic acid



Prepared by analogous method to Intermediate 213 starting from methyl 4-bromo-5-fluoro-2-methoxybenzoate (Intermediate 212) except the Step 3 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of pyrrolidine-1-sulfonamide. Yield: 290 mg, 0.81 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.55 min, m/z 357.2 $(M-H)^-$ (ES^-).

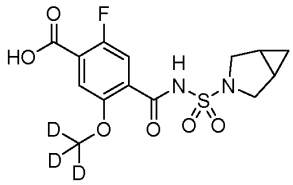
Intermediate 234: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-5-(methoxy-d_3)benzoic acid



Prepared by analogous method to Intermediate 213 starting from methyl 4-bromo-5-fluoro-2-(methoxy-d_3)benzoate (Intermediate 214) except the Step 3 was carried out with 7-

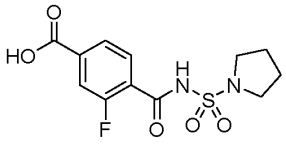
azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of pyrrolidine-1-sulfonamide. Yield: 280 mg, 0.75 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.61 min, m/z 375.6 $(M+H)^+$ (ES^+).

Intermediate 235: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-2-fluoro-5-(methoxy-d_3)benzoic acid



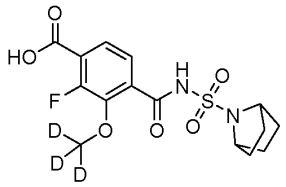
Prepared by analogous method to Intermediate 213 starting from methyl 4-bromo-5-fluoro-2-(methoxy-d_3)benzoate (Intermediate 214) except the Step 3 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of pyrrolidine-1-sulfonamide. Yield: 285 mg, 0.79 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.51 min, m/z 361.6 $(M+H)^+$ (ES^+).

Intermediate 236: 3-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic



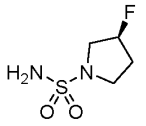
Prepared by analogous method to Intermediate 36 (Steps 3 to 5) starting from 4-bromo-2-fluorobenzoic acid (542 mg, 2.49 mmol) except the Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 1-methylcyclopropane-1-sulfonamide. Yield: 205 mg, 0.65 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.32 min, m/z 317.0 $(M+H)^+$ (ES^+).

Intermediate 237: 4-(((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)carbamoyl)-2-fluoro-3-(methoxy-d_3)benzoic acid



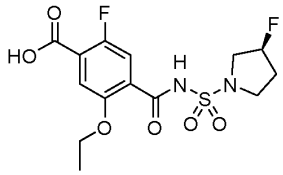
Prepared by an analogous method to Intermediate 204 starting from of 4-bromo-2,3-difluorobenzoic acid (0.5 g, 2.13 mmol) and methanol-d_3 (383 mg, 10.6 mmol) except the Step 2 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148) in place of 3-azabicyclo[3.1.0]hexane-3-sulfonamide. Yield: 250 mg, 0.67 mmol. Off-white solid. LCMS: (System 1, Method A) Rt = 0.39 min, m/z 374.0 $(M-H)^-$ (ES^-).

Intermediate 238: (*S*)-3-fluoropyrrolidine-1-sulfonamide



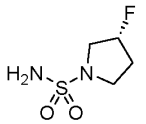
Prepared by an analogous method to Intermediate 148 starting from (*S*)-3-fluoropyrrolidine hydrochloride (1.0 g, 8.0 mmol), sulfuric diamide (918 mg, 9.6 mmol). Yield: 608 mg, 3.6 mmol. Off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.78 (s, 2H), 5.35-5.19 (m, 1H), 3.37-3.30 (m, 1H), 3.26-3.12 (m, 3H), 2.12-1.91 (m, 2H).

Intermediate 239: (*S*)-5-ethoxy-2-fluoro-4-(((3-fluoropyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



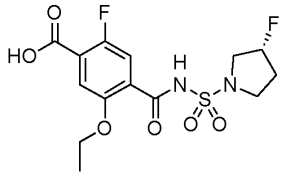
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with (*S*)-3-fluoropyrrolidine-1-sulfonamide (Intermediate 238) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 244 mg, 0.65 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.53 min, m/z 377.2 $(M-H)^-$ (ES^-).

Intermediate 240: (*R*)-3-fluoropyrrolidine-1-sulfonamide



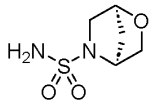
Prepared by an analogous method to Intermediate 148 starting from (*R*)-3-fluoropyrrolidine hydrochloride (2.35 g, 18.7 mmol), sulfuric diamide (1.5 g, 15.6 mmol). Yield: 1.5 g, 8.7 mmol. White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (br s, 2H), 5.31 (dq, J = 57.1, 2.2 Hz, 1H), 3.41-3.17 (m, 5H), 2.12-1.95 (m, 2H).

Intermediate 241: (*R*)-5-ethoxy-2-fluoro-4-(((3-fluoropyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



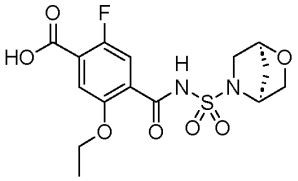
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with (*R*)-3-fluoropyrrolidine-1-sulfonamide (Intermediate 240) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 280 mg, 0.74 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.54 min, m/z 377.0 $(M-H)^-$ (ES^-).

Intermediate 242: (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane-5-sulfonamide



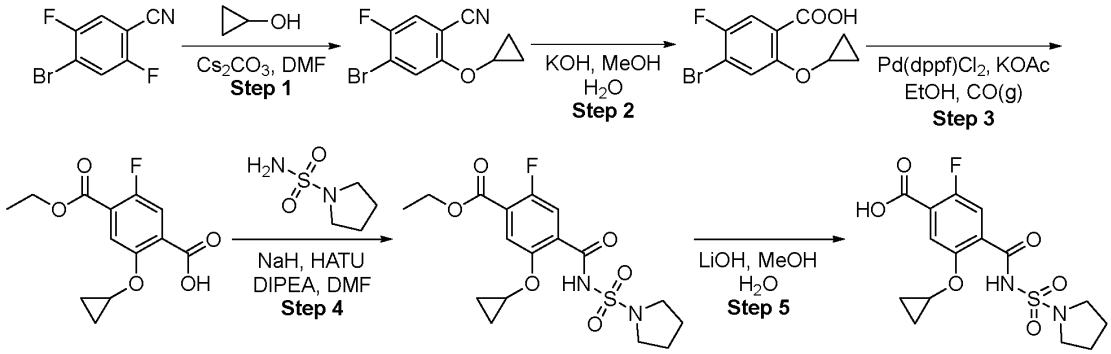
Prepared by an analogous method to Intermediate 148 starting from (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (1.0 g, 7.4 mmol), sulfuric diamide (1.1 g, 11.1 mmol). Yield: 0.9 g, 5.1 mmol. Off-white solid. ^{1}H-NMR (400 MHz, DMSO-D6) δ 6.85 (s, 2H), 4.55 (s, 1H), 4.18 (d, J = 18.8 Hz, 1H), 3.85-3.78 (m, 1H), 3.63-3.57 (m, 1H), 3.24-3.16 (m, 1H), 3.10-3.05 (m, 1H), 1.86 (dd, J = 10.1, 2.3 Hz, 1H), 1.70-1.67 (m, 1H).

Intermediate 243: 4-((((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane-5-sulfonamide (Intermediate 242) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 289 mg, 0.7 mmol. White solid. LCMS: (System 3, Method J) Rt = 1.41 min, m/z 387.0 $(M-H)^-$ (ES^-).

Intermediate 244: 5-cyclopropoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Step 1

To a solution of 4-bromo-2,5-difluorobenzonitrile (5.1 g, 23.5 mmol) in DMF (100 mL) was added Cs_2CO_3 (23.0 g, 70.5 mmol) and cyclopropanol (1.64 g, 28.2 mmol). The reaction mixture was stirred at 50 °C overnight, then cooled at RT, poured into water (300 mL) and extracted with ethyl acetate (3x300 mL). The combined organic layers were washed with brine (3x50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to afford 4-bromo-2-cyclopropoxy-5-fluorobenzonitrile (4.07 g, 15.9 mmol) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.97 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 5.6 Hz, 1H), 4.14-4.11 (m, 1H), 0.90-0.85 (m, 2H), 0.78-0.74 (m, 2H).

Step 2

To a solution of 4-bromo-2-cyclopropoxy-5-fluorobenzonitrile (4.07 g, 15.9 mmol) in MeOH/water (32 mL/8 mL) was added KOH (3.58 g, 63.8 mmol), then the reaction mixture was stirred at 80 °C overnight. The pH was adjusted to ca. 8 with HCl aq. 1N and the organic solvents were removed under reduced pressure. The pH was then adjusted to ca. 3 with HCl aq. 1N. The formed precipitate was collected by filtration, washed with water then hexane to afford 4-bromo-2-cyclopropoxy-5-fluorobenzoic acid (3.8 g, 13.8 mmol) as a yellow solid. LCMS: (System 1, Method A), Rt = 1.25 min. m/z 273.0 $[M-H]^-$ (ES^-).

Step 3

To a solution of 4-bromo-2-cyclopropoxy-5-fluorobenzoic acid (3.8 g, 13.8 mmol) in EtOH (50 mL) was added $Pd(dppf)Cl_2$ (2.03 g, 2.77 mmol) and potassium acetate (4.08 g, 41.6 mmol), and the mixture was stirred at 80 °C for 5 hours under CO atmosphere (1 atm). EtOH was removed at 45 °C under reduced pressure, saturated Na_2CO_3 aq. (50 mL) was added and the reaction mixture was extracted with EtOAc (3x50 mL). The pH of the aqueous layer was adjusted to ca. 3 with HCl aq. 1N and the aqueous layer extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford 2-cyclopropoxy-4-(ethoxycarbonyl)-5-fluorobenzoic acid (2.4 g, 8.94 mmol) as a yellow solid. LCMS: (System 1, Method A). Rt = 1.23 min. m/z 269.1 $[M+H]^+$ (ES^+).

Step 4

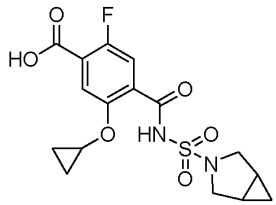
A solution of 2-cyclopropoxy-4-(ethoxycarbonyl)-5-fluorobenzoic acid (600 mg, 2.24 mmol), HATU (1.02 g, 2.69 mmol) and DIPEA (1.16 g, 9 mmol) in DMF (10 mL) was stirred at room temperature for 1 h. Pyrrolidine-1-sulfonamide (672 mg, 4.48 mmol) and NaH (60% in mineral oil, 358 mg, 9 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The mixture was poured into sat NH_4Cl aq. (30 mL), then the pH was adjusted to ca. 4 with HCl

aq. 1N and extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine (3x20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-25% EtOAc/petroleum ether) to afford ethyl 5-cyclopropoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (500 mg, 1.25 mmol) as a white solid. LCMS: (System 1, Method A), Rt = 1.44 min. m/z 401.0 $[M+H]^+$ (ES^+).

Step 5

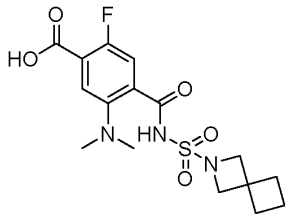
To a solution of ethyl 5-cyclopropoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoate (500 mg, 1.25 mmol) in MeOH (12 mL) was added a solution of $LiOH{\cdot}H_2O$ (205 mg, 5.00 mmol) in water (3 mL). The reaction mixture was stirred at room temperature overnight and the pH was adjusted to ca. 8 with HCl aq. 1N. The organic solvents were removed under reduced pressure and the pH was adjusted to ca. 3 with HCl aq. 1N. The formed precipitate was collected by filtration, washed with water then hexane to afford 5-cyclopropoxy-2-fluoro-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (370 mg, 0.99 mmol) as a yellow solid. LCMS: (System 1, Method A). Rt = 0.70 min. m/z 370.6 $[M-H]^-$ (ES^-).Step 1

Intermediate 245: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-5-cyclopropoxy-2-fluorobenzoic acid



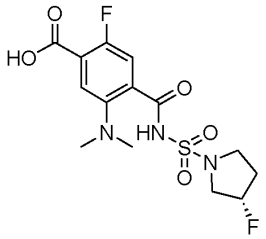
Prepared by an analogous method to Intermediate 245 except the Step 4 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168) in place of pyrrolidine-1-sulfonamide. Yield: 93 mg, 0.24 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.45 min, m/z 384.0 $(M-H)^-$ (ES^-).

Intermediate 246: 4-(((2-azaspiro[3.3]heptan-2-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



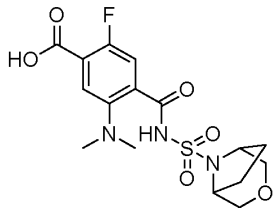
Prepared by an analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with 2-azaspiro[3.3]heptane-2-sulfonamide (Intermediate 186) in place of pyrrolidine-1-sulfonamide. Yield: 93 mg, 0.24 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.45 min, m/z 384.0 $(M-H)^-$ (ES^-).

Intermediate 247: (*S*)-5-(dimethylamino)-2-fluoro-4-(((3-fluoropyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



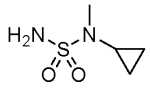
Prepared by an analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with (*S*)-3-fluoropyrrolidine-1-sulfonamide (Intermediate 238) in place of pyrrolidine-1-sulfonamide. Yield: 40 mg, 0.11 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.24 min, m/z 376.0 $(M-H)^-$ (ES^-).

Intermediate 248: 4-(((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



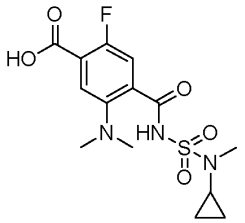
Prepared by an analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with 3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonamide (Intermediate 188) in place of pyrrolidine-1-sulfonamide. Yield: 42 mg, 0.11 mmol. Off-white. LCMS: (System 3, Method J) Rt = 1.23 min, m/z 400.0 $(M-H)^-$ (ES^-).

Intermediate 249: *N*-cyclopropyl-*N*-methylsulfamide



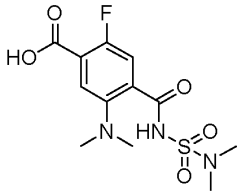
Prepared by an analogous method to Intermediate 148 starting from *N*-methylcyclopropanamine hydrochloride (1.5 g, 13.9 mmol), sulfuric diamide (1.6 g, 16.7 mmol). Yield: 0.8 g, 5.3 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.16 (s, 2H), 3.68 (s, 1H), 2.98 (s, 3H), 0.97-0.95 (m, 4H).

Intermediate 250: 4-((*N*-cyclopropyl-*N*-methylsulfamoyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



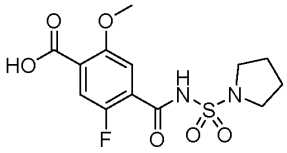
Prepared by an analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with *N*-cyclopropyl-*N*-methylsulfamide (Intermediate 249) in place of pyrrolidine-1-sulfonamide. Yield: 36 mg, 0.10 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.39 min, m/z 358.0 $(M-H)^-$ (ES^-).

Intermediate 251: 5-(dimethylamino)-4-((*N*,*N*-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



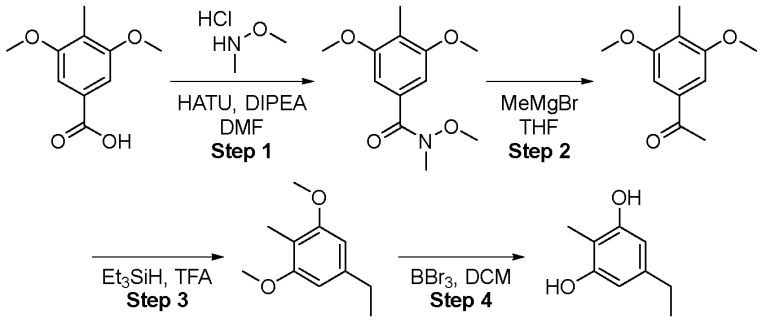
Prepared by an analogous method to Intermediate 134 specific procedure except the Step 2 was carried out with *N*,*N*-dimethylsulfamide in place of pyrrolidine-1-sulfonamide. Yield: 280 mg, 0.84 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.46 min, m/z 332.0 $[M-H]^-$ (ES^-).

Intermediate 252: 5-fluoro-2-methoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by an analogous method to Intermediate 40 starting from methyl 4-bromo-5-fluoro-2-methoxybenzoate (Intermediate 212, 2.0 g, 7.64 mmol). Yield: 500 mg, 1.44 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 345.0 $[M-H]^-$ (ES^-).

Intermediate 253: 5-ethyl-2-methylbenzene-1,3-diol



Step 1

To a solution of 3,5-dimethoxy-4-methylbenzoic acid (4 g, 20.4 mmol) in DMF (60 mL) was added HATU (8.53 g, 22.4 mmol), DIPEA (10.5 g, 81.6 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (3.96 g, 40.8 mmol) at 0 °C, then the mixture was stirred at room temperature for 4 hours. Water (180 mL) was added and the mixture was extracted with EtOAc (2x150 ml), the combined organic layers were washed with brine twice, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-2% EtOAc/petroleum ether) to afford *N*,3,5-trimethoxy-*N*,4-dimethylbenzamide (4 g, 18.2 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.70 min. m/z 239.9 $[M+H]^+$ (ES^+).

Step 2

To a solution of *N*,3,5-trimethoxy-*N*,4-dimethylbenzamide (4 g, 16.7 mmol) in THF (160 mL) was added Methylmagnesium bromide (3 N in THF, 16.7 mL) at 0 °C, then the mixture was stirred at 0 °C for 2 h under N_2 atmosphere. Sat. NH_4Cl aq. (160 mL) was added slowly and the mixture was extracted with EtOAc (3x200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% EtOAc/petroleum ether) to afford 1-(3,5-dimethoxy-4-methylphenyl)ethanone (3.2 g, 16.5 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.84 min. m/z 194.9 $[M+H]^+$ (ES^+).

Step 3

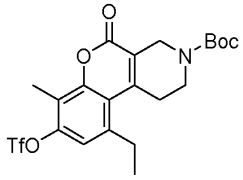
To a solution of 1-(3,5-dimethoxy-4-methylphenyl)ethanone (3.2 g, 16.5 mmol) in TFA (50 mL) was added triethylsilane (5.8 g, 49.4 mmol) dropwise at 0 °C. The solution was allowed to warm to room temperature and stirred at room temperature for 3 hours. The mixture was poured into ice-water (200 mL) slowly and extracted with DCM (3x200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product

was purified by column chromatography on silica gel (1-5% EtOAc/petroleum ether) to afford 5-ethyl-1,3-dimethoxy-2-methylbenzene (2.25 g, 12.5 mmol) as a pale yellow solid.
1H NMR (400 MHz, DMSO-d_6) δ: 6.45 (s, 2H), 3.75 (s, 6H), 2.57-2.55 (m, 2H), 1.94 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H).

Step 4

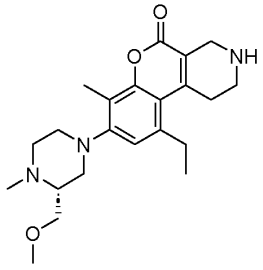
To a solution of 5-ethyl-1,3-dimethoxy-2-methylbenzene (2.25 g, 12.5 mmol) in dichloromethane (60 mL) was added BBr_3 (1 N in DCM, 62.4 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred at room temperature overnight. The mixture was poured into ice-water (150 mL) slowly and extracted with DCM (3x150 mL); the combined organic layers were dried over Na_2SO_4, filtered and concentrated reduced pressure. The crude product was purified by column chromatography on silica gel (1-40% EtOAc/petroleum ether) to afford 5-ethyl-2-methylbenzene-1,3-diol (1.5 g, 9.86 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.46 min. m/z 151.4 $[M-H]^-$ (ES^-).

Intermediate 254: *tert*-butyl 10-ethyl-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



Prepared by an analogous method to Intermediate 2 starting from 5-ethyl-2-methylbenzene-1,3-diol (Intermediate 253, 1.46 g, 9.61 mmol). Yield: 530 mg , 1.08 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 2.61 min, m/z 436.0 $(M-56+H)^+$ (ES^+).

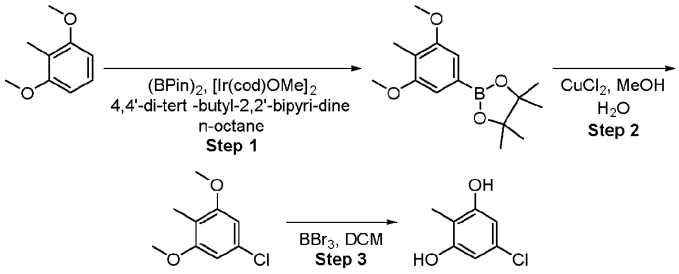
Intermediate 255: (*R*)-10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 235 mg, 1.63 mmol) and *tert*-butyl 10-ethyl-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate

(Intermediate 254, 530 mg, 1.08 mmol). Yield: 210 mg, 0.54 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.56 min, m/z 386.2 $(M+H)^+$ (ES^+).

Intermediate 256: 5-chloro-2-methylbenzene-1,3-diol



Step 1

A solution of (1,5-cyclooctadiene)(methoxy)iridium(I) dimer ($[Ir(cod)OMe]_2$, 185 mg, 0.28 mmol), 4,4'-di-tert-butyl-2,2'-bipyridine (148 mg, 0.55 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) $(BPin)_2$, 10.0 g, 39.5 mmol) in n-octane (395 mL) was stirred at RT for 15 min, then 1,3-dimethoxy-2-methylbenzene (6.0 g, 39.47 mmol) was added and the mixture was stirred at 125 °C for 3 days under N_2 atmosphere. The mixture was cooled to RT and partitioned between water (300 mL) and EtOAc (300mLx3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (n-hexane) to afford 2-(3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.0 g, 14.39 mmol) as a white solid. LCMS: (System 1, Method A) Rt = 2.18 min, m/z 279.2 $(M+H)^+$ (ES^+).

Step 2

A mixture of 2-(3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.0 g, 14.39 mmol) and copper(II) chloride (5.8 g, 43.2 mmol) in MeOH (80 mL) and water (80 ml) was stirred at 80 °C for 5 h under air atmosphere. MeOH was removed under reduced pressure, and the aqueous mixture was extracted with EtOAc (3x80mL). The combined organic layers were dried over (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% EtOAc/Petroleum ether) to afford 5-chloro-1,3-dimethoxy-2-methylbenzene (2.0 g, 10.8 mmol) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 6.69 (s, 2H), 3.78 (s, 6H), 1.95 (s, 3H).

Step 3

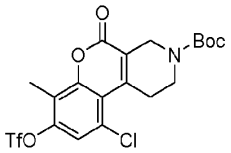
Boron tribromide 1 N solution in DCM (54 mL) was added dropwise to a solution of 5-chloro-1,3-dimethoxy-2-methylbenzene in DCM (100 mL) at 0 °C. The solution was allowed to reach RT and stirred at this temperature overnight. The mixture was slowly poured into ice-water (200 mL) and extracted with EtOAc (3x200 mL). The combined organic layers were dried (Na_2SO_4), filtered and

concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-50% EtOAc/petroleum ether) to afford 5-chloro-2-methylbenzene-1,3-diol (1.6 g, 10.1 mmol) as a pale-yellow solid. LCMS: (System 1, Method A) Rt = 1.45 min, m/z 157.2 $(M-H)^-$ (ES^-).

Alternative procedure:

To a solution of 1,3-dibromo-5-chloro-2-methylbenzene (40.0 g, 141.8 mmol) in dioxane (700 mL) and water (700 mL) was added NaOH (56.7 g, 1418 mmol), $Pd_2(dba)_3$ (3.25 g, 3.55 mmol) and t-BuXPhos (3.01 g, 7.09 mmol). The reaction mixture was stirred at 110 °C for 3 h under nitrogen atmosphere. The reaction mixture was washed with DCM (3 x 700 mL), the pH of the aqueous layer was adjusted 5 with 1 N HCl and extracted with EtOAc (3 x 700 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at 35 °C under reduced pressure to give the crude product, which was purified by silica gel column chromatography (20-80% EtOAc/petroleum ether) to give 5-chloro-2-methylbenzene-1,3-diol (20.0 g, 89% yield) as a white solid.

Intermediate 257: *tert*-butyl 10-chloro-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate



Prepared by an analogous method to Intermediate 2 starting from 5-chloro-2-methylbenzene-1,3-diol (Intermediate 256, 1.0 g, 10.13 mmol). Yield: 2.0 g, 4.0 mmol. Pale-yellow solid. LCMS: (System 1, Method A) Rt = 2.29 min, m/z 497.0 $(M-56+H)^+$ (ES^+).

Specific method:

Step 1

A solution of 5-chloro-2-methylbenzene-1,3-diol (16.0 g, 101.3 mmol) and ethyl 4-oxopiperidine-3-carboxylate hydrochloride (17.3 g, 101.3 mmol) in sulfuric acid (64%, 200 mL) was stirred at room temperature overnight. Ice water (500 mL) was added and the mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration, washed with water then hexane, dried under reduced pressure to give 10-chloro-8-hydroxy-7-methyl-3,4-dihydro-1H-chromeno[3,4-c]pyridin-5(2H)-one (16.0 g, 60% yield) as an off-white solid. LCMS: (System 1, Method A). Rt = 1.213 min, m/z 266.4 $(M+H)^+$ (ES^+).

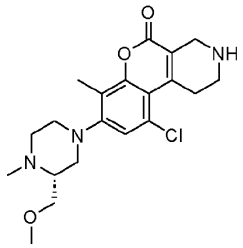
Step 2

To a suspension of 10-chloro-8-hydroxy-7-methyl-3,4-dihydro-1H-chromeno[3,4-c]pyridin-5(2H)-one (16.0 g, 60.4 mmol) in THF (500 mL) was added sat. aq. $NaHCO_3$ (500 mL) and di-tert-butyl dicarbonate (14.5 g, 66.4 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate (3 x 500 mL), the organic phase was dried over anhydrous Na_2SO_4, concentrated at 35 °C under reduced pressure to give the crude product which was dried under reduced pressure to give tert-butyl 10-chloro-8-hydroxy-7-methyl-5-oxo-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (18.0 g, 82% yield) as an off-white solid. LCMS: (System 1, Method A). Rt = 1.85 min, m/z 310.0 $(M-56+H)^+$ (ES^+).

Step 3

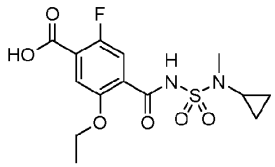
To a suspension of tert-butyl 10-chloro-8-hydroxy-7-methyl-5-oxo-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (18.0 g, 49.3 mmol) in dichloromethane (500 mL) was added pyridine (15.6 g, 197.2 mmol), the mixture was cooled to 0 °C then Tf_2O (27.8 g, 98.6 mmol) was added dropwise at 0 °C. The solution was allowed to warm to room temperature and stirred at room temperature for 1 h. Water (500 mL) was added. The organic phase was separated, washed with aq. $CuSO_4$ (3 x 500 mL), dried over anhydrous Na_2SO_4, concentrated at 35 °C under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1-5% MeOH/DCM) to give tert-butyl 10-chloro-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (20.0 g, 55% yield) as a pale yellow solid. LCMS: (System 1, Method A). Rt = 2.29 min. m/z 442.0 $(M-56+H)^+$ (ES^+).

Intermediate 258: (*R*)-10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one



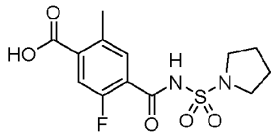
Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 871 mg, 6.0 mmol) and *tert*-butyl 10-chloro-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,5-dihydro-2*H*-chromeno[3,4-c]pyridine-3(4*H*)-carboxylate (Intermediate 257, 2.0 g, 4.0 mmol). Yield: 500 mg, 1.28 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.58 min, m/z 392.2 $(M+H)^+$ (ES^+).

Intermediate 259: 4-((*N*-cyclopropyl-*N*-methylsulfamoyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



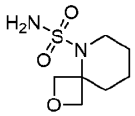
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with *N*-cyclopropyl-*N*-methylsulfamide (Intermediate 249) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 123 mg, 0.34 mmol. Off-white solid. LCMS: (System 3, Method J) Rt = 1.24 min, m/z 376.0 $(M-H)^-$ (ES^-).

Intermediate 260: 5-fluoro-2-methyl-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



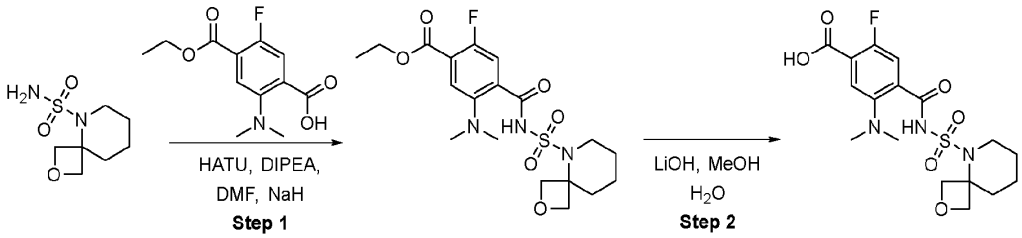
Prepared by an analogous method to Intermediate 10 (Step 3 to Step 5 only) starting from 4-bromo-2-fluoro-5-methylbenzoic acid (1.0 g, 4.29 mmol). Yield: 179 mg, 0.54 mmol. Off-White solid. LCMS: (System 3, Method J) Rt = 1.50 min, m/z 329.2 $(M-H)^-$ (ES^-)

Intermediate 261: 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide



Prepared by an analogous method to Intermediate 148 starting from 2-oxa-5-azaspiro[3.5]nonane hemioxalate (2.0 g, 5.81 mmol), sulfuric diamide (0.84 g, 8.72 mmol). Yield: 0.8 g, 3.88 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.94 (s, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.18 (d, *J* = 6.8 Hz, 2H), 3.10-3.06 (m, 2H), 1.98-1.95 (m, 2H), 1.69-1.66 (m, 2H), 1.52-1.49 (m, 2H).

Intermediate 262: 4-(((2-oxa-5-azaspiro[3.5]nonan-5-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



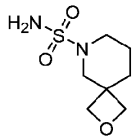
Step 1

A solution of 2-(dimethylamino)-4-(ethoxycarbonyl)-5-fluorobenzoic acid (400 mg, 1.57 mmol), HATU (715 mg, 1.88 mmol), DIPEA (810 mg, 6.28 mmol) in DMF (15 mL) was stirred at room temperature for 1 h, then 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide (647 mg, 3.14 mmol) and NaH (60%, 251 mg, 6.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The pH of the mixture was adjusted to 4 with 1N HCl aq. and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated at 35 °C under reduced pressure to give the crude materials, which was purified by column chromatography on silica gel (1-25% EtOAc/petroleum ether) to afford ethyl 4-((2-oxa-5-azaspiro[3.5]nonan-5-ylsulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoate (200 mg, 0.45 mmol) as yellow oil. LCMS: (System 1, Method A) Rt = 1.47 min, m/z 444.0 $(M+H)^+$ (ES^+).

Step 2

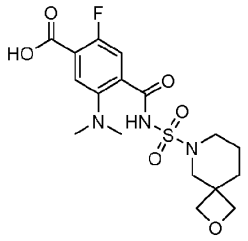
To a solution of ethyl 4-((2-oxa-6-azaspiro[3.5]nonan-6-ylsulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoate (200 mg, 0.45 mmol) in THF (5 mL) and MeOH (2 mL) was added a solution of $LiOH{\cdot}H_2O$ (76 mg, 1.80 mmol) in water (1 mL). The reaction mixture was stirred at room temperature for 3 h. The pH of the mixture was adjusted to 8 with 1N HCl aq., MeOH and THF was removed at 35 °C under reduced pressure, and the pH of the mixture was adjusted to 3 with 1N HCl aq. The formed precipitate was collected by filtration, washed with water then hexane and dried at 35 °C under reduced pressure to give 4-((2-oxa-5-azaspiro[3.5]nonan-5-ylsulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid (150 mg, 0.36 mmol) as a yellow solid. LCMS: (System 1, Method A) Rt = 1.08 min, m/z 414.0 $(M-H)^-$ (ES^-).

Intermediate 263: 2-oxa-6-azaspiro[3.5]nonane-6-sulfonamide



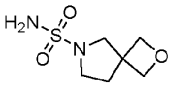
Prepared by an analogous method to Intermediate 148 starting from 2-oxa-6-azaspiro[3.5]nonane (1 g, 7.87 mmol), sulfuric diamide (1.13 g, 11.8 mmol). Yield: 1.3 g, 6.31 mmol. White solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 6.79 (s, 2H), 4.27 (d, J = 6.0 Hz, 2H), 4.21 (d, J = 6.0 Hz, 2H), 3.12 (s, 2H), 2.86 (t, J = 5.6 Hz, 2H), 1.69 (t, J = 6.0 Hz, 2H), 1.52-1.47 (m, 2H).

Intermediate 264: 4-(((2-oxa-6-azaspiro[3.5]nonan-6-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



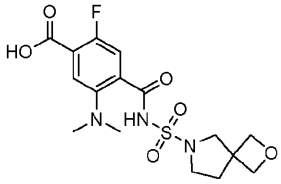
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 2-oxa-6-azaspiro[3.5]nonane-6-sulfonamide (Intermediate 263, 400mg, 1.57 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 330 mg, 0.80 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.98 min, m/z 414.0 $(M+H)^+$ (ES^+).

Intermediate 265: 2-oxa-6-azaspiro[3.4]octane-6-sulfonamide



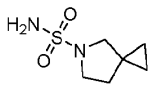
Prepared by an analogous method to Intermediate 148 starting from 2-oxa-6-azaspiro[3.4]octane (1 g, 8.85 mmol), sulfuric diamide (1 g, 10.6 mmol). Yield: 1.2 g, 6.25 mmol. Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.75 (s, 2H), 5.54 (d, J = 6.0 Hz, 2H), 4.44 (d, J = 6.0 Hz, 2H), 3.34 (s, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.11 (d, J = 6.8 Hz, 2H).

Intermediate 266: 4-(((2-oxa-6-azaspiro[3.4]octan-6-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



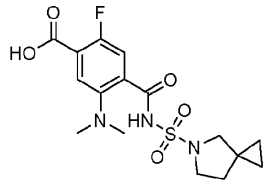
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 2-oxa-6-azaspiro[3.4]octane-6-sulfonamide (Intermediate 265, 602 mg, 3.14 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 320 mg, 0.79 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.52 min, m/z 401.7 $(M+H)^+$ (ES^+).

Intermediate 267: 5-azaspiro[2.4]heptane-5-sulfonamide



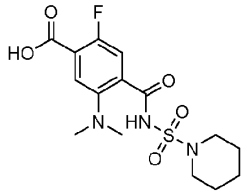
Prepared by an analogous method to Intermediate 148 starting from 5-azaspiro[2.4]heptane hydrochloride (1 g, 7.52 mmol), sulfuric diamide (1.08 g, 11.3 mmol). Yield: 0.7 g, 3.98 mmol. White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.72 (s, 2H), 3.25 (t, J = 7.2 Hz, 2H), 3.01 (s, 2H), 1.76 (t, J = 7.2 Hz, 2H), 0.61-0.52 (m, 4H).

Intermediate 268: 4-((5-azaspiro[2.4]heptan-5-ylsulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



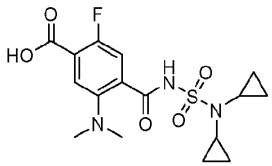
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 5-azaspiro[2.4]heptane-5-sulfonamide (Intermediate 267, 691 mg, 3.93 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 300 mg, 0.79 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.52 min, m/z 401.7 $(M+H)^+$ (ES^+).

Intermediate 269: 5-(dimethylamino)-2-fluoro-4-((piperidin-1-ylsulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with piperidine-1-sulfonamide (385 mg, 2.35 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 360 mg, 0.97 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.13 min, m/z 372.2 $(M+H)^+$ (ES^+).

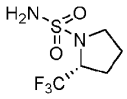
Intermediate 270: 4-((N,N-dicyclopropylsulfamoyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with *N*,*N*-dicyclopropylsulfamide (Intermediate 180, 963 mg, 5.47 mmol) in place of 2-oxa-5-

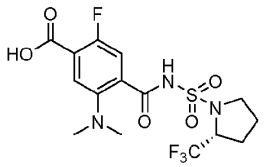
azaspiro[3.5]nonane-5-sulfonamide. Yield: 500 mg, 1.30 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.75 min, m/z 414.3 $(M+H)^+$ (ES^+).

Intermediate 271: (R)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide



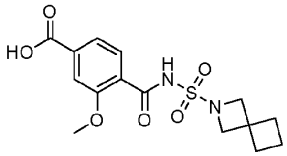
Prepared by an analogous method to Intermediate 148 starting from (R)-2-(trifluoromethyl)pyrrolidine hydrochloride (1.0 g, 5.75 mmol), sulfuric diamide (732 mg, 7.47 mmol). Yield: 0.7 g, 3. 21 mmol. White solid. ^{1}H NMR (400 MHz, DMSO) δ: 7.03 (s, 2H), 4.31-4.26 (m, 1H), 3.44-3.38 (m, 1H), 3.24-3.19 (m, 1H), 2.07-1.84 (m, 4H).

Intermediate 272: (R)-5-(dimethylamino)-2-fluoro-4-(((2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



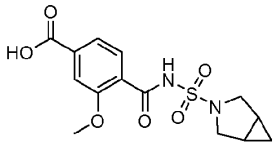
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out (R)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide (Intermediate 271, 513 mg, 2.35 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 350 mg, 0.78 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.72 min, m/z 456.3 $(M+H)^+$ (ES^+).

Intermediate 273: 4-((2-azaspiro[3.3]heptan-2-ylsulfonyl)carbamoyl)-3-methoxybenzoic acid



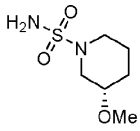
Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-2-methoxybenzoate except the Step 3 was carried out with 2-azaspiro[3.3]heptane-2-sulfonamide (Intermediate 186, 473 mg, 2.69 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 280 mg, 0.79 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.83 min, m/z 353.0 $(M-H)^-$ (ES^-).

Intermediate 274: 4-((2-azaspiro[3.3]heptan-2-ylsulfonyl)carbamoyl)-3-methoxybenzoic acid



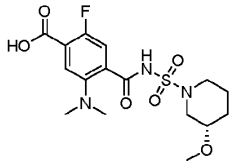
Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-2-methoxybenzoate except the Step 3 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168, 473 mg, 2.69 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 280 mg, 0.88 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.61 min, m/z 339.0 $(M-H)^-$ (ES^-).

Intermediate 275: (S)-3-methoxypiperidine-1-sulfonamide



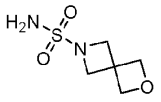
Prepared by an analogous method to Intermediate 148 starting from (S)-3-methoxypiperidine hydrochloride (1 g, 6.59 mmol), sulfuric diamide (824 mg, 8.57 mmol) Yield: 0.7 g, 3.60 mmol. White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.74 (s, 2H), 3.35-3.28 (m, 2H), 3.26 (s, 3H), 3.14-3.09 (m, 1H), 2.69-2.63 (m, 1H), 2.59-2.54 (m, 1H), 1.86-1.82 (m, 1H), 1.77-1.71 (m, 1H), 1.49-1.42 (m, 1H), 1.30-1.24 (m, 1H).

Intermediate 276: (S)-5-(dimethylamino)-2-fluoro-4-(((3-methoxypiperidin-1-yl)sulfonyl)carbamoyl)benzoic acid



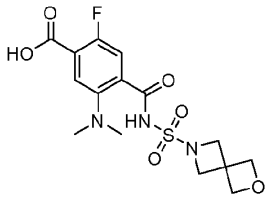
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out (S)-3-methoxypiperidine-1-sulfonamide (Intermediate 275, 457 mg, 2.35 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 320 mg, 0.79 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.94 min, m/z 402.2 $(M-H)^-$ (ES^-).

Intermediate 277: 2-oxa-6-azaspiro[3.3]heptane-6-sulfonamide



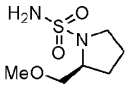
Prepared by an analogous method to Intermediate 148 starting from 2-Oxa-6-azaspiro[3.3]heptane hemioxalate (5.0 g, 17.4 mmol), sulfuric diamide (4.2 g, 43.4 mmol. Yield: 0.7 g, 4 mmol. Light yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 6.89 (s, 2H), 4.63 (s, 4H), 3.86 (s, 4H).

Intermediate 278: 4-(((2-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



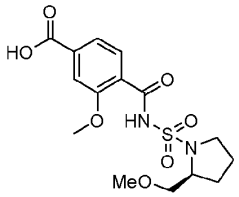
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with2-oxa-6-azaspiro[3.3]heptane-6-sulfonamide (Intermediate 277, 419 mg, 2.35 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 300 mg, 0.77 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.31 min, m/z 387.8 $(M+H)^+$ (ES^+).

Intermediate 279: (S)-2-(methoxymethyl)pyrrolidine-1-sulfonamide



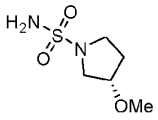
Prepared by an analogous method to Intermediate 148 starting from (S)-2-(methoxymethyl)pyrrolidine (2.0 g, 17.39 mmol) and sulfuric diamide (2.04 g, 20.87 mmol) Yield: 2.0 g, 10.3 mmol. White solid. ^{1}H NMR (400 MHz, DMSO) δ: 6.75 (s, 2H), 3.69-3.66 (m, 1H), 3.41-3.38 (m, 1H), 3.25 (s, 3H), 3.19-3.09 (m, 3H), 1.81-1.75 (m, 4H).

Intermediate 280: (S)-2-(methoxymethyl)pyrrolidine-1-sulfonamide



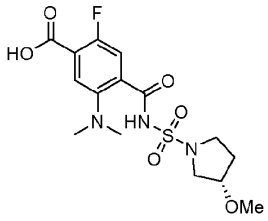
Prepared by an analogous method to Intermediate 213 starting from methyl 4-bromo-2-methoxybenzoate except the Step 3 was carried out with (S)-2-(methoxymethyl)pyrrolidine-1-sulfonamide (Intermediate 279, 520 mg, 2.68 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 320 mg, 0.86 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.87 min, m/z 371.0 $(M-H)^-$ (ES^-).

Intermediate 281: (S)-3-methoxypyrrolidine-1-sulfonamide



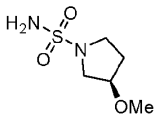
Prepared by an analogous method to Intermediate 148 starting from (S)-3-methoxypyrrolidine hydrochloride (2 g, 14.60 mmol), sulfuric diamide (2.10 g, 21.90 mmol). Yield: 1.2 g, 6.67 mmol. White solid. ^{1}H NMR (400 MHz, DMSO) δ: 6.73 (s, 2H), 3.97-3.94 (m, 1H), 3.26-3.21 (m, 4H), 3.15-3.07 (m, 3H), 1.94-1.86 (m, 2H).

Intermediate 282: (S)-5-(dimethylamino)-2-fluoro-4-(((3-methoxypyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



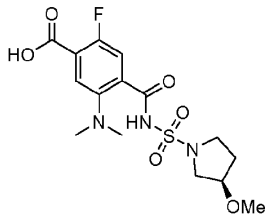
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (S)-3-methoxypyrrolidine-1-sulfonamide (Intermediate 281, 425 mg, 2.36 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 310 mg, 0.80 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.74 min, m/z 388.0 $(M+H)^+$ (ES^+).

Intermediate 283: (R)-3-methoxypyrrolidine-1-sulfonamide



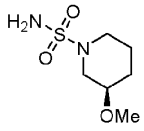
Prepared by an analogous method to Intermediate 148 starting from (R)-3-methoxypyrrolidine hydrochloride (2 g, 14.60 mmol), sulfuric diamide (2.10 g, 21.90 mmol). Yield: 1.8 g, 10.0 mmol. White solid. ^{1}H NMR (400 MHz, DMSO) δ: 6.73 (s, 2H), 3.97-3.94 (m, 1H), 3.26-3.21 (m, 4H), 3.15-3.07 (m, 3H), 1.94-1.86 (m, 2H)

Intermediate 284: (R)-5-(dimethylamino)-2-fluoro-4-(((3-methoxypyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



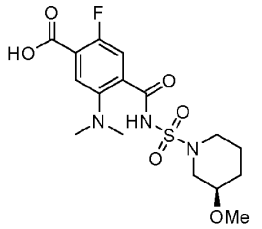
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (R)-3-methoxypyrrolidine-1-sulfonamide (Intermediate 283, 425 mg, 2.36 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 325 mg, 0.83 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.86 min, m/z 387.8 $(M+H)^+$ (ES^+).

Intermediate 285: (R)-3-methoxypiperidine-1-sulfonamide



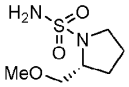
Prepared by an analogous method to Intermediate 148 starting from (R)-3-methoxypiperidine hydrochloride (1 g, 6.67 mmol), sulfuric diamide (1.28 g, 13.3 mmol). Yield: 800 mg,4.11 mmol. White solid. ^{1}H NMR (400 MHz, DMSO) δ: 6.74 (s, 2H), 3.35-3.28 (m, 2H), 3.26 (s, 3H), 3.14-3.09 (m, 1H), 2.69-2.63 (m, 1H), 2.59-2.54 (m, 1H), 1.86-1.82 (m, 1H), 1.77-1.71 (m, 1H), 1.51-1.41 (m, 1H), 1.31-1.22 (m, 1H).

Intermediate 286: (R)-5-(dimethylamino)-2-fluoro-4-(((3-methoxypiperidin-1-yl)sulfonyl)carbamoyl)benzoic acid



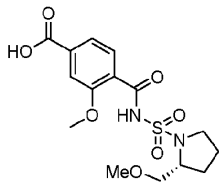
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (R)-3-methoxypiperidine-1-sulfonamide (Intermediate 285, 457 mg, 2.36 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 320 mg, 0.72 mmol. Yellow oil. LCMS: (System 1, Method A) Rt = 1.01 min, m/z 402.0 $(M-H)^-$ (ES^-).

Intermediate 287: (R)-2-(methoxymethyl)pyrrolidine-1-sulfonamide



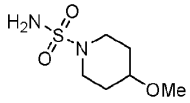
Prepared by an analogous method to Intermediate 148 starting from (R)-2-(methoxymethyl)pyrrolidine (1 g, 8.68 mmol), sulfuric diamide (0.97 g, 10 mmol). Yield: 670 mg,3.45 mmol. White solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 6.77 (s, 2H), 3.70 (s, 1H), 3.45-3.42 (m, 1H), 3.29 (s, 3H), 3.23-3.13 (m, 3H), 1.87-1.78 (m, 4H)

Intermediate 288: (R)-2-(methoxymethyl)pyrrolidine-1-sulfonamide



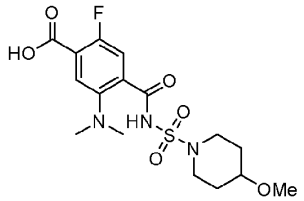
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (R)-2-(methoxymethyl)pyrrolidine-1-sulfonamide (Intermediate 287, 400 mg, 1 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 340 mg, 0.92 mmol. Off-white solid. LCMS: (System 1, Method A) Rt = 0.69 min, m/z 371.0 $(M-H)^-$ (ES^-).

Intermediate 289: 4-methoxypiperidine-1-sulfonamide



Prepared by an analogous method to Intermediate 148 starting from 4-methoxypiperidine (2 g, 17.4 mmol), sulfuric diamide (2 g, 20.9 mmol). Yield: 2 g,3.45 mmol. Light-yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ: 6.71 (s, 2H), 3.31-3.27 (m, 1H), 3.24 (s, 3H), 3.18-3.12 (m, 2H), 3.82-3.77 (m, 2H), 1.87-1.81 (m, 2H), 1.58-1.51 (m, 2H)

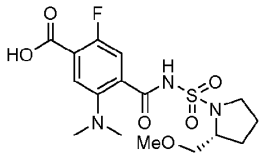
Intermediate 290: 5-(dimethylamino)-2-fluoro-4-(((4-methoxypiperidin-1-yl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 4-methoxypiperidine-1-sulfonamide (Intermediate 289, 609 mg, 3.14 mmol) in place of 2-oxa-5-

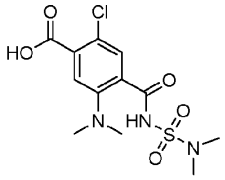
azaspiro[3.5]nonane-5-sulfonamide. Yield: 300 mg, 0.70 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.50 min, m/z 431.8 $(M+H)^+$ (ES^+).

Intermediate 291: (R)-5-(dimethylamino)-2-fluoro-4-(((2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



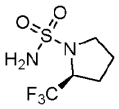
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (R)-2-(methoxymethyl)pyrrolidine-1-sulfonamide (Intermediate 287, 456 mg, 2.35 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 300 mg, 0.75 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.06 min, m/z 402.0 $(M-H)^-$ (ES^-).

Intermediate 292: 2-chloro-5-(dimethylamino)-4-((N,N-dimethylsulfamoyl)carbamoyl) benzoic acid



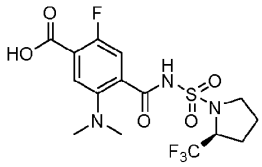
Prepared by an analogous method to Intermediate 111 except the Step 3 was carried out with *N,N*-dimethyl sulfamide (367 mg, 2.96 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 250 mg, 0.72 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.35 min, m/z 348.0 $(M-H)^-$ (ES^-).

Intermediate 293: (S)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide



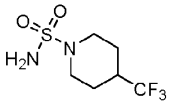
Prepared by an analogous method to Intermediate 148 starting from (S)-2-(trifluoromethyl)pyrrolidine (0.8 g, 5.75 mmol), sulfuric diamide (0.66 g, 6.9 mmol). Yield: 640 mg, 2.93 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 7.06 (s, 2H), 4.37-4.28 (m, 1H), 3.48-3.42 (m, 1H), 3.28-3.22 (m, 1H), 2.11-1.85 (m, 4H).

Intermediate 294: (S)-5-(dimethylamino)-2-fluoro-4-(((2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)carbamoyl)benzoic acid



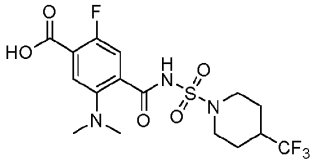
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (S)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide (Intermediate 293, 577 mg, 2.65 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 360 mg, 0.79 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.58 min, m/z 456.0 $(M+H)^+$ (ES^+).

Intermediate 295: 4-(trifluoromethyl)piperidine-1-sulfonamide



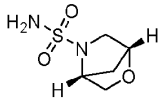
Prepared by an analogous method to Intermediate 148 starting from 4-(trifluoromethyl)piperidine (2 g, 13.1 mmol), sulfuric diamide (1.51 g, 15.1 mmol). Yield: 1.91 g, 8.22 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 6.85 (s, 2H), 3.60 (d, J = 11.9 Hz, 2H), 3.24-3.41 (1H), 2.60 (d, J = 9.6 Hz, 1H), 2.48 (s, 1H), 1.93 (d, J = 11.4 Hz, 2H), 1.57-1.47 (m, 2H).

Intermediate 296: 5-(dimethylamino)-2-fluoro-4-(((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 4-(trifluoromethyl)piperidine-1-sulfonamide (Intermediate 295, 1.27 g, 5.49 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 1.91 g, 8.22 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 1.26 min, m/z 440.0 $(M-H)^-$ (ES^-).

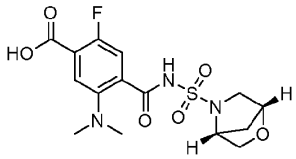
Intermediate 297: (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane-5-sulfonamide



Prepared by an analogous method to Intermediate 148 starting from (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (2.95 g, 21.7 mmol), sulfuric diamide (1.9 g, 19.8 mmol).

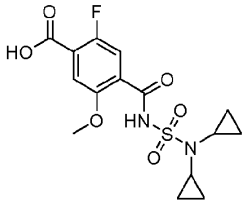
Yield: 2.68 g, 15 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 6.88 (s, 2H), 4.58 (s, 1H), 4.24 (s, 1H), 3.87 (d, J = 7.3 Hz, 1H), 3.63 (d, J = 7.8 Hz, 1H), 3.22-3.09 (m, 2H), 1.89 (dd, J = 10.1, 2.3 Hz, 1H), 1.72 (dt, J = 10.1, 1.1 Hz, 1H).

Intermediate 298: 4-((((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



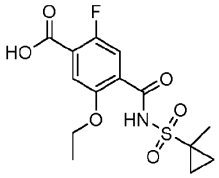
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane-5-sulfonamide (Intermediate 297, 698 mg, 3.92 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 330 mg, g, 0.86 mmol. Light-yellow solid. LCMS: (System 1, Method A) Rt = 0.43 min, m/z 386.2 $(M-H)^-$ (ES^-).

Intermediate 299: 4-((N,N-dicyclopropylsulfamoyl)carbamoyl)-2-fluoro-5-methoxybenzoic acid



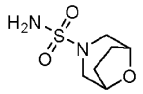
Prepared by analogous method to Intermediate 213 except the Step 3 was carried out with *N*,*N*-dicyclopropylsulfamide (Intermediate 180, 704 mg, 4 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 200 mg, 0.53 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.91 min, m/z 371.0 $(M-H)^-$ (ES^-).

Intermediate 300: 5-ethoxy-2-fluoro-4-(((1-methylcyclopropyl)sulfonyl)carbamoyl)benzoic acid



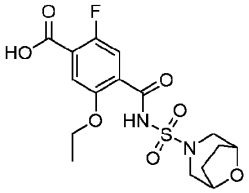
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with methylcyclopropane-1-sulfonamide (540 mg, 4 mmol) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 210 mg, 0.61 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.48 min, m/z 346.1 $(M+H)^+$ (ES^+).

Intermediate 301: 8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonamide



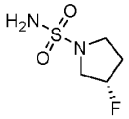
Prepared by an analogous method to Intermediate 148 starting from 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (2.0 g, 13.5 mmol), sulfuric diamide (1.95 g, 20.3 mmol). Yield: 1.5 g, 7.81 mmol. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.75 (s, 2H), 4.37 (s, 2H), 3.04-3.01 (m, 2H), 2.78-2.74 (m, 2H), 1.78-1.77 (m, 4H).

Intermediate 302: 4-((8-oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl)carbamoyl)-5-ethoxy-2-fluorobenzoic acid



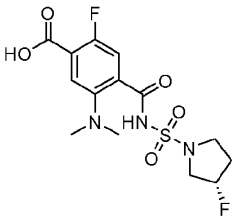
Prepared by an analogous method to Intermediate 181 except the Step 4 was carried out with 8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonamide (Intermediate 301, 768 mg, 4 mmol) in place of *N*,*N*-dicyclopropylsulfamide. Yield: 290 mg, 0.72 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.46 min, m/z 403.1 $(M+H)^+$ (ES^+).

Intermediate 303: (S)-3-fluoropyrrolidine-1-sulfonamide



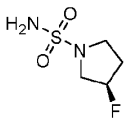
Prepared by an analogous method to Intermediate 148 starting from (S)-3-fluoro-pyrrolidine hydrochloride (3.0 g, 24.0 mmol), sulfuric diamide (3.45 g, 36 mmol). Yield: 1.9 g, 11.2 mmol. Light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.84 (s, 2H), 5.32 (d, *J* = 52.8 Hz, 1H), 3.38-3.34 (m, 1H), 3.30-3.17 (m, 3H), 2.12-1.98 (m, 2H).

Intermediate 304: (S)-5-(dimethylamino)-2-fluoro-4-(((3-fluoropyrrolidin-1-yl)sulfonyl) carbamoyl)benzoic acid



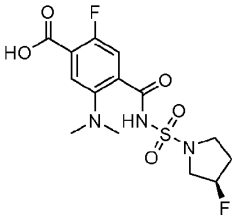
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (S)-3-fluoropyrrolidine-1-sulfonamide (Intermediate 303, 605 mg, 3.6 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 270 mg, g, 0.89 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.75 min, m/z 376.0 $(M-H)^-$ (ES^-).

Intermediate 305: (R)-3-fluoropyrrolidine-1-sulfonamide



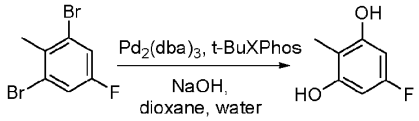
Prepared by an analogous method to Intermediate 148 starting from (R)-3-fluoro-pyrrolidine hydrochloride (3.0 g, 24.0 mmol), sulfuric diamide (3.45 g, 36 mmol). Yield: 2 g, 11.8 mmol. Light yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ: 6.84 (s, 2H), 5.32 (d, J = 52.8 Hz, 1H), 3.38-3.34 (m, 1H), 3.30-3.17 (m, 3H), 2.12-1.98 (m, 2H).

Intermediate 306: (R)-5-(dimethylamino)-2-fluoro-4-(((3-fluoropyrrolidin-1-yl)sulfonyl) carbamoyl)benzoic acid



Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (R)-3-fluoropyrrolidine-1-sulfonamide (Intermediate 303, 672 mg, 4 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 400, g, 1.06 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.67 min, m/z 375. $(M-H)^-$ (ES^-).

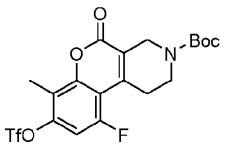
Intermediate 307: 5-fluoro-2-methylbenzene-1,3-diol



To a solution of 1,3-dibromo-5-fluoro-2-methylbenzene (5 g, 18.66 mmol) in dioxane (90 mL) and water (90 mL), was added NaOH (7.46 g, 186.62 mmol), $Pd_2(dba)_3$ (427 mg, 0.47 mmol) and t-BuXPhos (396 mg, 0.93 mmol). The reaction mixture was stirred at 110 °C for 3 h under nitrogen atmosphere. The reaction mixture was washed with DCM (3 x 150 mL). The pH of the aqueous layer was adjusted to 3 with 1 N HCl. and the aqueous layer extracted with EtOAc (3 x 200 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

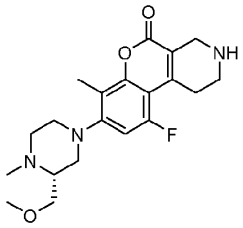
pressure to give the crude material, which was purified by silica gel column chromatography (20-80% EtOAc/petroleum ether) to give 5-fluoro-2-methylbenzene-1,3-diol (2.3 g, 37.5 mmol) as a white solid. LCMS: (System 1, Method A). Rt = 1.321 min. m/z 141.2 $(M-H)^-$ (ES^-).

Intermediate 308: tert-butyl 10-fluoro-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate



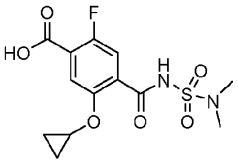
Prepared by an analogous method to Intermediate 2 starting from 5-fluoro-2-methylbenzene-1,3-diol (Intermediate 307, 2.3 g, 37.5 mmol) Yield: 1.8 g, 3.8 mmol. Pale yellow solid. LCMS: (System 1, Method A) Rt = 2.43 min, m/z 475.3 $(M+H)^+$ (ES^+).

Intermediate 309: (R)-10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-3,4-dihydro-1H-chromeno[3,4-c]pyridin-5(2H)-one



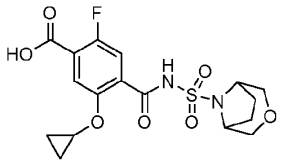
Prepared by an analogous method to Intermediate 5 starting from (*R*)-2-(methoxymethyl)-1-methylpiperazine (Intermediate 1, 449 mg, 3.12 mmol) and tert-butyl 10-fluoro-7-methyl-5-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydro-1H-chromeno[3,4-c]pyridine-3(2H)-carboxylate (Intermediate 308, 1 g, 2.08 mmol). Yield: 380 mg, 1.10 mmol. Brown solid. LCMS: (System 1, Method A) Rt = 1.60 min, m/z 376.4 $(M+H)^+$ (ES^+).

Intermediate 310: 5-cyclopropoxy-4-((N,N-dimethylsulfamoyl)carbamoyl)-2-fluorobenzoic acid



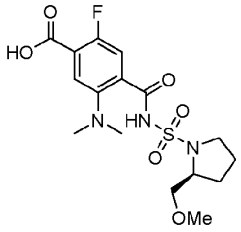
Prepared by analogous method to Intermediate 244 except the Step 4 was carried out with *N,N*-dimethyl sulfamide (741 mg, 5.96 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 400, g, 1.06 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.36 min, m/z 372.9 $(M-H)^-$ (ES^-).

Intermediate 311: 4-((3-oxa-8-azabicyclo[3.2.1]octan-8-ylsulfonyl)carbamoyl)-5-cyclopropoxy-2-fluorobenzoic acid



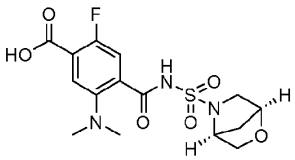
Prepared by analogous method to Intermediate 244 except the Step 4 was carried out with 3-oxa-8-azabicyclo[3.2.1]octane-8-sulfonamide (Intermediate 188, 860 mg, 4.47 mmol) in place of pyrrolidine-1-sulfonamide. Yield: 0.5 g, 1.21 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.53 min, m/z 412.8 $(M-H)^-$ (ES^-).

Intermediate 312: 5-(dimethylamino)-2-fluoro-4-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonylcarbamoyl]benzoic acid



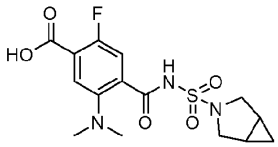
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (2S)-2-(methoxymethyl)pyrrolidine-1-sulfonamide (Intermediate 279, 152 mg, 0.78 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 87.8 mg, g, 0.22 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.45 min, m/z 402.1 $(M-H)^-$ (ES^-).

Intermediate 313: 4-((((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



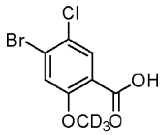
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane-5-sulfonamide (Intermediate 242, 140 mg, 0.78 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 55.9 mg, g, 0.14 mmol. Light brown oil. LCMS: (System 1, Method A) Rt = 1.15 min, m/z 386.1 $(M+H)^+$ (ES^+).

Intermediate 314: 4-(((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)carbamoyl)-5-(dimethylamino)-2-fluorobenzoic acid



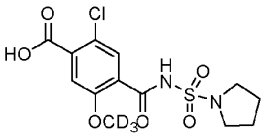
Prepared by analogous method to Intermediate 262 except the Step 1 was carried out with 3-azabicyclo[3.1.0]hexane-3-sulfonamide (Intermediate 168, 127 mg, 0.78 mmol) in place of 2-oxa-5-azaspiro[3.5]nonane-5-sulfonamide. Yield: 128 mg, g, 0.34 mmol. Light-brown oil. LCMS: (System 1, Method A) Rt = 1.47 min, m/z 370.1 $(M+H)^+$ (ES^+).

Intermediate 315: 4-bromo-5-chloro-2-(methoxy-d3)benzoic acid



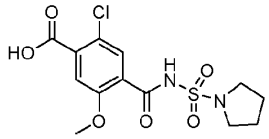
To a solution of 4-bromo-5-chloro-2-hydroxybenzoic acid (620 mg, 2.48 mmol) in DMA (20 mL), was added CD_3OD (794 mg, 24.8 mmol) and NaH (60%, 496 mg, 12.4 mmol). The reaction mixture was stirred at 80 °C for 20 min, poured into water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate extracts were washed with brine three times, dried over Na_2SO_4, filtered and concentrated to give crude material, which was purified purified by column chromatography on silica gel (1-10% EtOAc/petroleum ether) to give 4-bromo-5-chloro-2-(methoxy-d3)benzoic acid (505 mg, 1.90 mmol) as yellow oil. LCMS: (System 1, Method A) Rt = 1.21 min, m/z 266.1 $(M-H)^-$ (ES^-).

Intermediate 316: 2-chloro-5-(methoxy-d3)-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



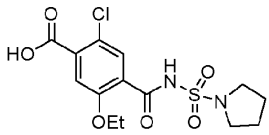
Prepared by an analogous method to Intermediate 213 starting from 4-bromo-5-chloro-2-(methoxy-d3)benzoic acid (Intermediate 315). Yield: 250 mg, 0.86 mmol. White solid. LCMS: (System 1, Method A) Rt = 0.45 min, m/z 366.0 $(M+H)^+$ (ES^+).

Intermediate 317: 2-chloro-5-methoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



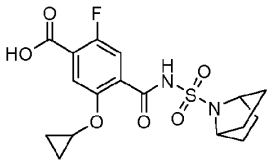
Prepared by an analogous method to Intermediate 213 starting from 4-bromo-5-chloro-2-methoxy benzoic acid (620 mg, 2.48 mmol). Yield: 260 mg, 0.86 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.47 min, m/z 363.0 $(M+H)^+$ (ES^+).

Intermediate 318: 2-chloro-5-ethoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid



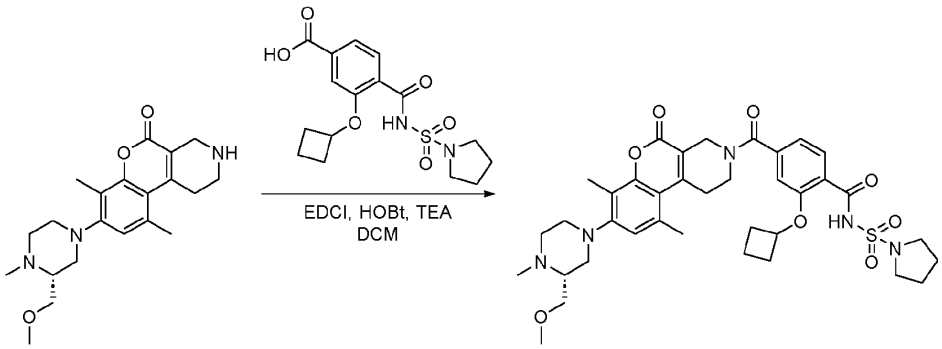
Prepared by an analogous method to Intermediate 213 starting from 4-bromo-5-chloro-2-methoxy benzoic acid (620 mg, 2.48 mmol) and ethanol (1.14 g, 24.8 mmol) in Step 1. Yield: 270 mg, 0.72 mmol. Yellow solid. LCMS: (System 1, Method A) Rt = 0.59 min, m/z 377 $(M+H)^+$ (ES^+).

Intermediate 319: 4-((7-azabicyclo[2.2.1]heptan-7-ylsulfonyl)carbamoyl)-5-cyclopropoxy-2-fluorobenzoic acid



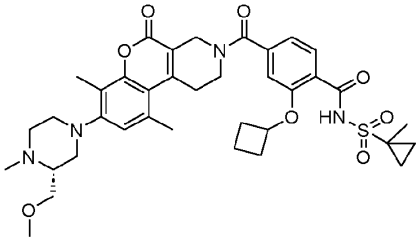
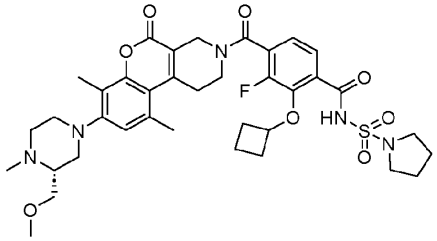
Prepared by analogous method to Intermediate 244 except the Step 4 was carried out with 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148, 788 mg, 4.48 mmol in place of pyrrolidine-1-sulfonamide. Yield: 0.34 g, 0.85 mmol. White solid. LCMS: (System 1, Method A) Rt = 1.024 min, m/z 399.0 $(M+H)^+$ (ES^+).

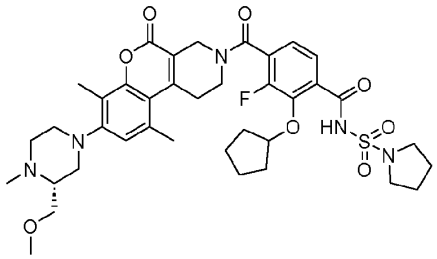
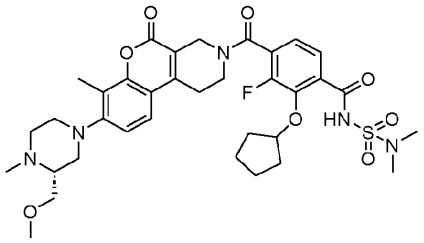
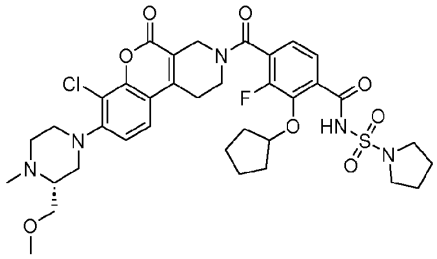
Example 1: (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide

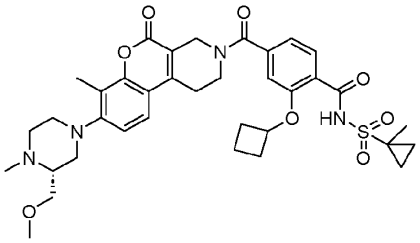
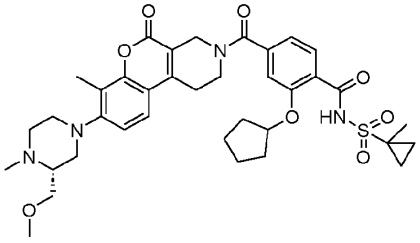
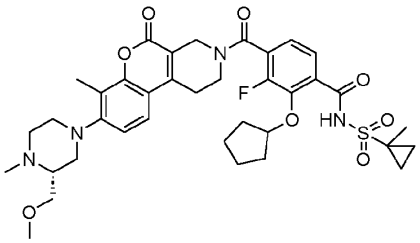


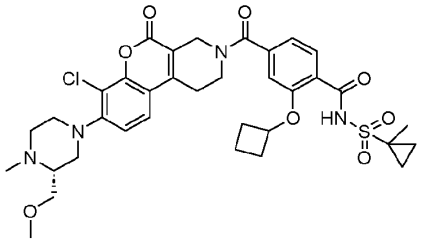
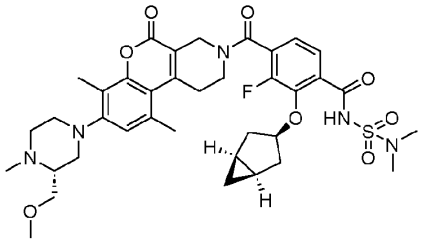
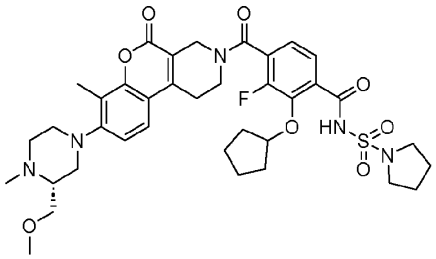
A mixture of (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyrrolid-5-one (Intermediate 6, 3.5 g, 9.4 mmol), EDCI (2.7 g, 14.1 mmol), HOBt (1.9 g, 14.1 mmol), TEA (3.8 g, 37.5 mmol) and 3-cyclobutoxy-4-((pyrrolidin-1-ylsulfonyl)carbamoyl)benzoic acid (Intermediate 10, 3.8 g, 10.3 mmol) in DCM (100 mL) was stirred at RT overnight. Water (10 mL) was added and the mixture was extracted with DCM (3x100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) and by reverse phase column chromatography (C18-modified silica, 40-60% ACN/water) to afford (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide (3.3 g, 4.6 mmol) as a white solid. HPLC: (System 1, Method D) Rt = 8.12 min, m/z 722.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.34 (br s, 1H), 7.56-7.54 (m, 1H), 7.13-7.08 (m, 1H), 7.03-6.99 (m, 1H), 6.84 (s, 1H), 4.89-4.82 (m, 1H), 4.48 (br s, 1H), 4.28 (br s, 1H), 3.83 (br s, 1H), 3.55 (dd, J = 10.0, 4.0 Hz, 1H), 3.49-3.43 (m, 5H), 3.35-3.31 (m, 1H), 3.26 (br s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.79 (m, 2H), 2.68-2.59 (m, 4H), 2.43-2.40 (m, 4H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 2.09 (br s, 2H), 1.87-1.84 (m, 5H), 1.65-1.63 (m, 1H). Mixture of rotamers.

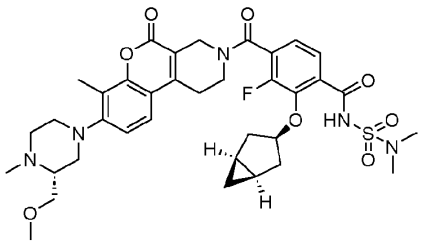
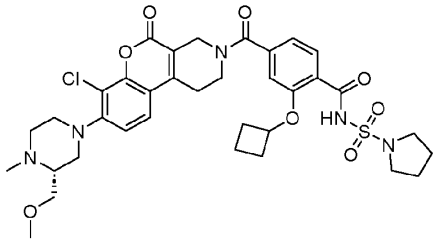
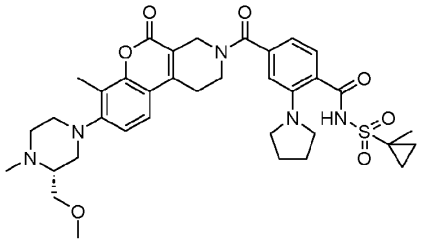
The following examples were prepared by analogous method to Example 1:

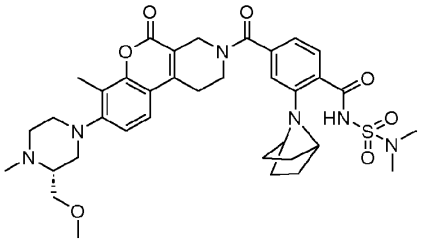
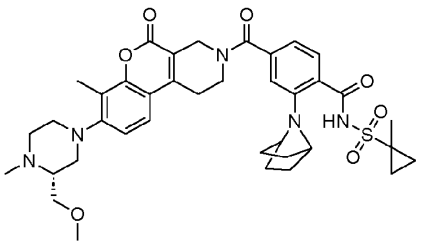
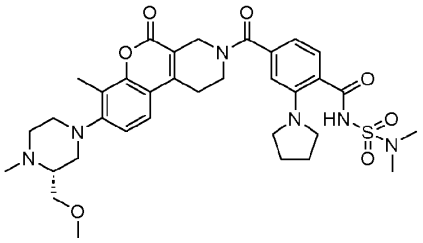
Example No.	Name / Structure / Intermediates	LCMS / ^{1}H NMR data
Example 2	(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 11 and 6	HPLC: (System 1, Method D) Rt = 7.07 min, m/z 707.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.53-7.51 (m, 1H), 7.13-7.08 (m, 1H), 7.02-6.99 (m, 1H), 6.85 (s, 1H), 4.86-4.81 (m, 1H), 4.48 (br s, 1H), 4.29 (br s, 1H), 3.83 (br s, 1H), 3.57-3.50 (m, 2H), 3.34 (br s, 5H), 3.21 (br s, 2H), 3.15-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.88-2.80 (m, 2H), 2.69-2.61 (m, 4H), 2.45 (br s, 3H), 2.33 (s, 3H), 2.24-2.19 (m, 3H), 2.14-2.09 (m, 2H), 1.82-1.80 (m, 1H), 1.65-1.62 (m, 1H), 1.54 (s, 3H), 1.46-1.43 (m, 2H), 0.96-0.94 (m, 2H). Mixture of rotamers.
Example 3	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 6	HPLC: (System 1, Method D) Rt = 7.86 min, m/z 740.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.58 (br s, 1H), 7.35-7.33 (m, 1H), 7.25-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.73-4.66 (m, 1H), 4.50 (br s, 1H), 4.17 (s, 1H), 3.88-3.86 (m, 1H), 3.57-3.54 (m, 1H), 3.45-3.37 (m, 7H), 3.27 (br s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.07-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.49-2.46 (m, 1H), 2.35 (s, 3H), 2.30-2.20 (m, 5H), 2.15-2.07 (m, 2H), 1.87-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.50-1.41 (m, 1H). Mixture of rotamers.
Example 4	(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.63 min, m/z 754.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (br s, 1H), 7.36-7.33 (m, 1H), 7.25-7.15 (m, 1H), 6.86-.684 (m, 1H), 4.87-4.82 (m, 1H), 4.50 (br s, 1H), 4.18 (s, 1H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.45-3.44 (m, 1H), 3.41-3.38 (m, 5H), 3.27 (s, 3H), 3.27-3.23 (m, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.90-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.51 (br s, 1H),2.50 (br s, 1H), 2.35 (s, 3H),

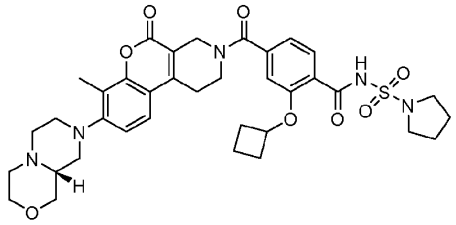
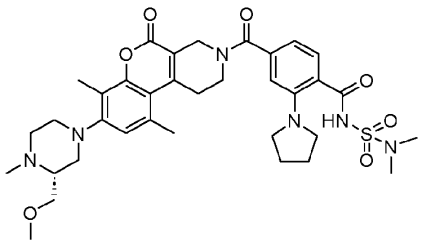
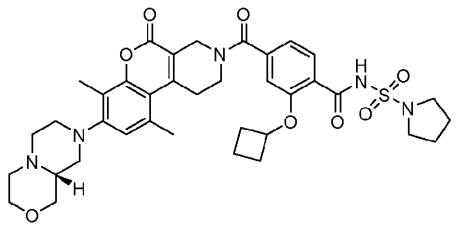
	 Synthesised from Intermediates 14 and 6	2.23-2.19 (m, 3H), 1.86-1.74 (m, 10H), 1.59-1.55 (m, 2H). Mixture of rotamers.
Example 5	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 15 and 5	HPLC: (System 1, Method D) Rt = 7.02 min, m/z 714.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.39 (br s, 1H), 7.59-7.50 (m, 1H), 7.34-7.32 (m, 1H), 7.21-7.14 (m, 1H), 7.10-7.06 (m, 1H), 4.88-4.82 (m, 1H), 4.53 (br s, 1H), 4.18 (s, 1H), 3.99-3.96 (m, 1H), 3.59-3.54 (m, 2H), 3.43-3.39 (m, 1H), 3.28 (s, 3H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 1H), 3.00-2.87 (m, 4H), 2.84-2.83 (m, 6H), 2.71-2.67 (m, 1H), 2.62-2.56 (m, 2H), 2.40 (s, 3H), 2.30-2.26 (m, 3H), 1.84-1.72 (m, 6H), 1.57-1.55 (m, 2H). Mixture of rotamers.
Example 6	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 14 and 7	HPLC: (System 1, Method D) Rt = 7.44 min, m/z 760.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br s, 1H), 7.70-7.68 (m, 1H), 7.36-7.33 (m, 1H), 7.23-7.15 (m, 2H), 4.87-4.82 (m, 1H), 4.54 (br s, 1H), 4.19 (s, 1H), 3.99-3.96 (m, 1H), 3.59-3.54 (m, 2H), 3.45-3.36 (m, 7H), 3.29-3.27 (m, 4H), 3.01-2.87 (m, 4H), 2.70 (t, J = 10.4 Hz, 1H), 2.46-2.43 (m, 1H), 2.33 (s, 3H), 1.85-1.74 (m, 10H), 1.57-1.55 (m, 2H). Mixture of rotamers.
Example 7	(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.50 min, m/z 693.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.59-7.50 (m, 2H), 7.09-7.07 (m, 2H), 6.99-6.97 (m, 1H), 4.84-4.82 (m, 1H), 4.49 (s, 1H), 4.28 (s, 1H), 3.93-3.90 (m,

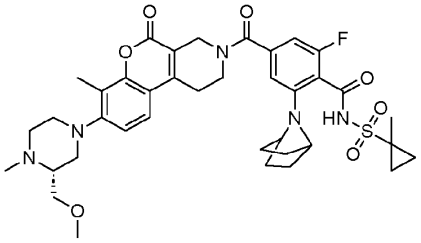
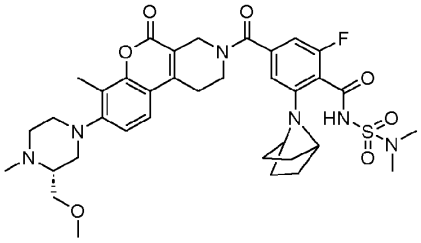
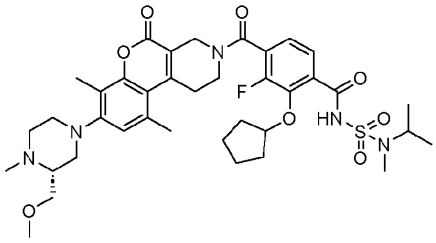
	 Synthesised from Intermediates 5 and 11	1H), 3.58-3.54 (m, 2H), 3.38-3.36 (m, 2H), 3.27 (s, 3H), 3.16-3.14 (m, 1H), 3.06-3.04 (m, 1H), 2.96-2.95(m, 2H), 2.88-2.82(m, 2H), 2.67-2.61 (m, 1H), 2.49-2.43 (m, 3H), 2.33 (s, 3H), 2.30-2.23 (m, 3H), 2.14-2.08 (m, 2H), 1.81-1.77 (m, 1H), 1.67-1.61 (m, 1H), 1.54 (s, 3H), 1.46-1.43 (m, 2H), 0.97-0.94 (s, 2H). Mixture of rotamers.
Example 8	(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 12 and 5	HPLC: (System 1, Method D) Rt = 7.97 min, m/z 707.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.23 (br s, 1H), 7.59-7.52 (m, 2H), 7.20-7.17 (m, 1H), 7.09-7.07 (m, 2H), 5.03-4.96 (m, 1H), 4.50 (s, 1H), 4.29 (s, 1H), 3.94-3.93 (m, 1H), 3.60-3.54 (m, 2H), 3.36-3.33 (m, 1H), 3.26 (s, 3H), 3.16-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.97 (br s, 2H), 2.87-2.82 (m, 2H), 2.67-2.60 (m, 1H), 2.47-2.40 (m, 2H), 2.32 (s, 3H), 2.25-2.23 (m, 3H), 1.90 (br s, 2H), 1.80-1.73 (m, 4H), 1.59-1.58 (m, 2H), 1.51 (s, 3H), 1.46-1.43 (m, 2H), 0.96-0.94 (m, 2H). Mixture of rotamers.
Example 9	(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 16 and 5	HPLC: (System 1, Method D) Rt = 7.11 min, m/z 725.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59-7.50 (m, 1H), 7.32-7.30 (m, 1H), 7.20-7.13 (m, 1H), 7.10-7.06 (m, 1H), 4.88-4.82 (m, 1H), 4.53 (br s, 1H), 4.18 (s, 1H), 3.98 (t, J = 5.6 Hz,1H), 3.59-3.54 (m, 2H), 3.46-3.42 (m, 1H), 3.29 (s, 3H), 3.20-3.18 (m, 1H), 3.09 (m, 1H), 3.00-2.98 (m, 2H), 2.91-2.86 (m, 2H), 2.73-2.64 (m, 3H), 2.45 (s, 3H), 2.30-2.26 (m, 3H), 1.83-1.72 (m, 6H), 1.56-1.54 (m, 2H), 1.48 (s, 3H), 1.40-1.39 (m, 2H), 0.88-0.84 (m, 2H). One exchangeable proton not visible. Mixture of rotamers.

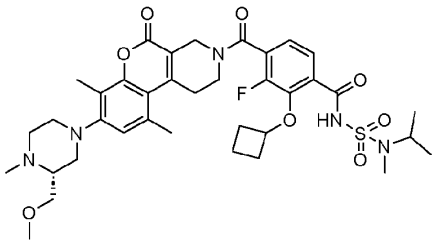
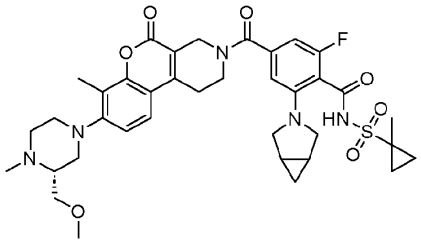
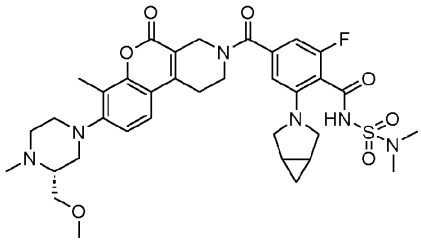
Example 10	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 11 and 7	HPLC: (System 1, Method D) Rt = 6.95 min, m/z 713.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (br s, 1H), 7.69-7.62 (m, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.00 (s, 1H), 4.84-4.83 (m, 1H), 4.50 (s, 1H), 4.29 (br s, 1H), 3.94 (br s, 1H), 3.59-3.55 (m, 2H), 3.44-3.31 (m, 7H), 2.96-2.87 (m, 4H), 2.70 (t, J = 10.0 Hz, 1H), 2.45-2.43 (m, 3H), 2.32 (s, 3H), 2.14-2.09 (m, 2H), 1.82-1.79 (m, 1H), 1.65-1.61 (m, 1H), 1.55 (s, 3H), 1.47-1.44 (m, 2H), 0.98-0.95 (m, 2H).
Example 11	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 23 and 6	HPLC: (System 1, Method D) Rt = 7.23 min, m/z 740.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.32-7.30 (m, 1H), 7.21-7.12 (m, 1H), 6.87-6.85 (m, 1H), 4.82-4.73 (m, 1H), 4.50 (br s, 1H), 4.17 (s, 1H), 3.87 (br s, 1H), 3.58-3.55 (m, 1H), 3.46-3.39 (m, 2H), 3.33 (s, 3H), 3.28-3.06 (m, 4H), 2.96-2.93 (m, 1H), 2.88-2.84 (m, 7H), 2.72-2.54 (m, 6H), 2.40 (s, 3H), 2.20-2.24 (m, 3H), 2.11-2.08 (m, 2H), 2.01-1.95 (m, 2H), 1.30 (br s, 2H), 0.70-0.63 (m, 1H), 0.47-0.43 (m, 1H). Mixture of rotamers.
Example 12	(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 14 and 5	HPLC: (System 1, Method D) Rt = 7.44 min, m/z 740.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.60-7.51 (dd, J = 28.0, 8.8 Hz, 1H), 7.36-7.33 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.06 (m, 1H), 4.87-4.81 (m, 1H), 4.53 (br s, 1H), 4.18 (s, 1H), 3.98 (t, J = 5.6 Hz, 1H), 3.58-3.55 (m, 2H), 2.40-3.39 (m, 5H), 3.27 (s, 3H), 3.18-3.16 (m, 1H), 3.08-3.06 (m, 1H), 3.00 (br s, 1H), 2.92-2.84 (m, 3H), 2.67 (t, J = 10.4 Hz, 1H), 2.55-2.51 (m, 2H), 2.37 (s, 3H), 2.30-2.26 (m, 3H), 1.85-1.73 (m, 10 H), 1.57-1.54 (m, 2H). Mixture of rotamers.

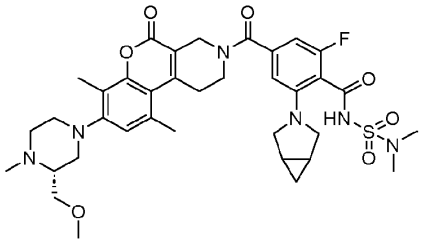
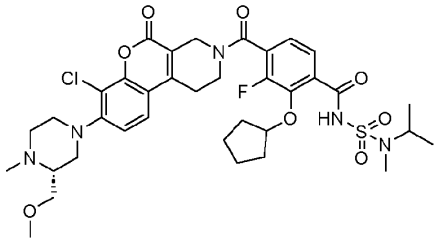
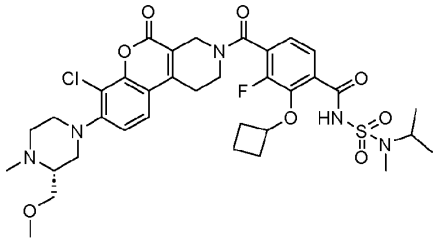
Example 13	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 23 and 5	HPLC: (System 1, Method D) Rt = 7.29 min, m/z 726.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.42 (br s, 1H), 7.59-7.50 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.18-7.06 (m, 2H), 4.82-4.73 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.98-3.96 (m, 1H), 3.59-3.54 (m, 2H), 3.43-3.40 (m, 1H), 3.28 (s, 3H), 3.19-3.17 (m, 1H), 3.10-3.07 (m, 1H), 2.99-2.87 (m, 4H), 2.84-2.83 (m, 6H), 2.71-2.57 (m, 3H), 2.40 (s, 3H), 2.30-2.26 (m, 3H), 2.12-2.07 (m, 2H), 2.01-1.95 (m, 2H), 1.32-1.28 (m, 2H), 0.69-0.63 (m, 1H), 0.46-0.42 (m, 1H). Mixture of rotamers.
Example 14	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 10 and 7	HPLC: (System 1, Method D) Rt = 7.90 min, m/z 728.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.39 (br s, 1H), 7.71-7.63 (m, 1H), 7.57-7.55 (m, 1H), 7.18-7.16 (m, 1H), 7.11-7.09 (m, 1H), 6.98 (br s, 1H), 4.86-4.83 (m, 1H), 4.50 (s, 1H), 4.28 (br s, 1H), 3.93 (br s, 1H), 3.58-3.55 (m, 2H), 3.47-3.41 (m, 5H), 3.31-3.36 (m, 5H), 2.96-2.84 (m, 4H), 2.68 (t, J = 10.8 Hz, 1H), 2.43-2.38 (m, 4H), 2.30 (s, 3H), 2.08-2.07 (m, 2H), 1.87-1.80 (m, 5H), 1.66-1.61 (m, 1H).
Example 15	(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 46 and 5	HPLC: (System 1, Method D) Rt = 6.64 min, m/z 692.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.87 (br s, 1H), 7.55-7.49 (m, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.73-6.71 (m, 2H), 4.45 (br s, 1H), 4.27 (br s, 1H), 3.89 (br s, 1H), 3.58-3.51 (m, 2H), 3.35-3.31 (m, 1H), 3.24 (s, 3H), 3.17-3.11 (m, 5H), 3.03-3.00 (m, 1H), 2.93 (br s, 2H), 2.86-2.79 (m, 2H), 2.63-2.58 (m, 1H), 2.48-2.43 (m, 2H), 2.30-2.22 (m, 6H), 1.88 (s, 4H), 1.48 (s, 3H), 1.45-1.43 (m, 2H), 0.90 (br s, 2H).

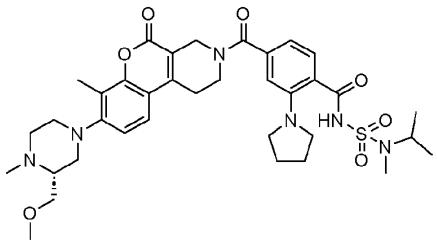
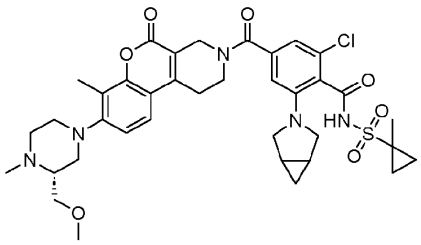
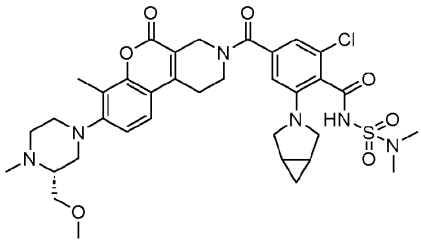
Example 16	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 51 and 5	HPLC: (System 1, Method D) Rt = 7.12 min, m/z 707.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.64 (br s, 1H), 7.53-7.48 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.01-7.00 (m, 1H), 6.92-6.88 (m, 1H), 4.45 (br s, 1H), 4.24 (br s, 1H), 4.08-4.06 (m, 2H), 3.89 (br s, 1H), 3.55-3.51 (m, 2H), 3.34-3.30 (m, 1H), 3.24 (s, 3H), 3.13-3.11 (m, 1H), 3.03-3.00 (m, 1H), 2.93 (br s, 2H), 2.85-2.79 (m, 8H), 2.63-2.58 (m, 1H), 2.45-2.40 (m, 2H), 2.30 (s, 3H), 2.26-2.22 (m, 3H), 1.69 (br s, 4H), 1.40 (br s, 4H). Mixture of rotamers.
Example 17	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 50 and 5	HPLC: (System 1, Method D) Rt = 6.83 min, m/z 718.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.67 (br s, 1H), 7.56-7.51 (m, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.02 (br s, 1H), 6.92-6.91 (m, 1H), 4.47 (br s, 1H), 4.27 (br s, 1H), 4.12-4.10 (m, 2H), 3.92 (br s, 1H), 3.57-3.54 (m, 2H), 3.37-3.33 (m, 4H), 3.16-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.95 (br s, 2H), 2.88-2.82 (m, 2H), 2.66-2.62 (m, 1H), 2.49-2.43 (m, 2H), 2.33 (s, 3H), 2.29-2.24 (m, 3H), 1.72 (br s, 4H), 1.48 (s, 3H), 1.46-1.41 (m, 6H), 0.94-0.91 (m, 2H).
Example 18	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 47 and 5	HPLC: (System 1, Method D) Rt = 6.61 min, m/z 681.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (br s, 1H), 7.54-7.49 (m, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.73-6.70 (m, 2H), 4.45 (br s, 1H), 4.27 (br s, 1H), 3.89 (br s, 1H), 3.58-3.52 (m, 2H), 3.32 (br s, 1H), 3.24 (s, 3H), 3.17-3.11 (m, 5H), 3.03-3.00 (m, 1H), 2.92 (br s, 2H), 2.86 (s, 6H), 2.86-2.79 (m, 2H), 2.63-2.57 (m, 1H), 2.47-2.41 (m, 2H), 2.29-2.22 (m, 6H), 1.88 (s, 4H).

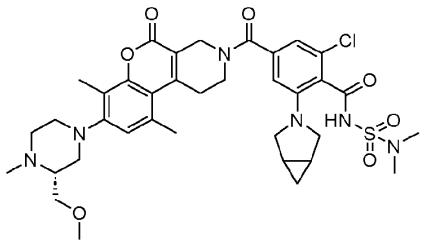
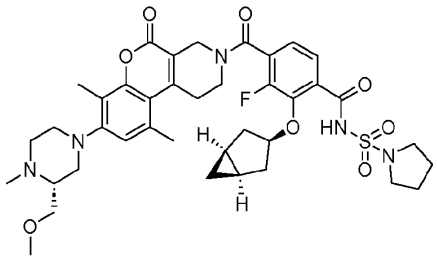
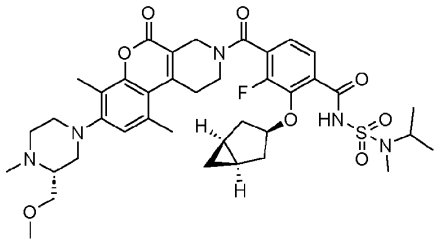
Example 19	(*R*)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 10 and 8	HPLC: (System 1, Method D) Rt = 7.91 min, m/z 706.1 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.56-7.48 (m, 2H), 7.06-7.04 (m, 2H), 6.97-6.95 (m, 1H), 4.84-4.77 (m, 1H), 4.46 (br s, 1H), 4.24 (br s, 1H), 3.90 (br s, 1H), 3.76-3.74 (m, 1H), 3.69-3.66 (m, 1H), 3.54-3.48 (m, 2H), 3.44-3.42 (m, 4H), 3.16-3.06 (m, 2H), 2.94-2.92 (m, 3H), 2.86-2.77 (m, 2H), 2.67-2.64 (m, 1H), 2.43-2.39 (m, 4H), 2.36-2.23 (m, 5H), 2.06 (br s, 2H), 1.85-1.74 (m, 5H), 1.65-1.58 (m, 1H).
Example 20	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 47 and 6	HPLC: (System 1, Method D) Rt = 6.80 min, m/z 695.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (br s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 6.82 (s, 1H), 6.76-6.69 (m, 2H), 4.43 (br s, 1H), 4.27 (br s, 1H), 3.79 (br s, 1H), 3.54-3.49 (m, 2H), 3.31 (br s, 1H), 3.23 (s, 3H), 3.17 (br s, 6H), 3.12-3.09 (m, 1H), 3.02-2.99 (m, 1H), 2.85 (s, 6H), 2.81-2.76 (m, 2H), 2.66-2.57 (m, 4H), 2.41-2.39 (m, 2H), 2.28 (s, 3H), 2.20-2.16 (m, 3H), 1.88 (br s, 4H).
Example 21	(*R*)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 10 and 9	HPLC: (System 1, Method D) Rt = 7.80 min, m/z 720.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (br s, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.10-7.07 (m, 1H), 6.99-6.95 (m, 1H), 6.82 (s, 1H), 4.85-4.78 (m, 1H), 4.45 (br s, 1H), 4.25 (br s, 1H), 3.80 (br s, 1H), 3.76-3.73 (m, 1H), 3.69-3.66 (m, 1H), 3.53-3.50 (m, 1H), 3.48-3.41 (m, 5H), 3.17-3.06 (m, 4H), 2.93-2.90 (m, 1H), 2.83-2.76 (m, 2H), 2.65-2.61 (m, 4H), 2.44-2.37 (m, 3H), 2.34-2.25 (m, 3H), 2.22-2.18 (m, 3H), 2.08-2.05 (m, 2H), 1.84-1.75 (m, 5H), 1.62-1.60 (m, 1H).

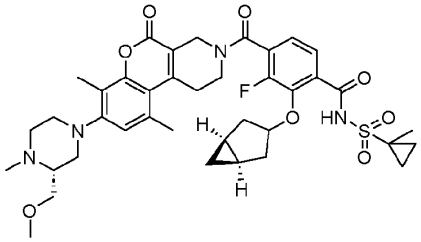
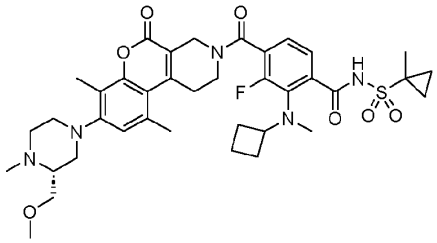
Example 22	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 86 and 5	HPLC: (System 1, Method D) Rt = 7.18 min, m/z 736.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56-7.50 (m, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.78 (s, 1H), 6.72-6.70 (m, 1H), 4.44 (br s, 1H), 4.25 (br s, 3H), 3.88 (br s, 1H), 3.56-3.53 (m, 2H), 3.43-3.37 (m, 1H), 3.32 (s, 3H), 3.16-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.93 (br s, 3H), 2.87-2.82 (m, 1H), 2.69-2.56 (m, 3H), 2.38 (s, 3H), 2.27-2.23 (m, 3H), 1.66 (br s, 4H), 1.46 (s, 3H), 1.38-1.37 (m, 6H), 0.86 (br s, 2H). One exchangeable proton not visible. Mixture of rotamers.
Example 23	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 87 and 5	HPLC: (System 1, Method D) Rt = 6.70 min, m/z 725.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.83 (br s, 1H), 7.54-7.49 (m, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.73-6.71 (m, 1H), 4.43 (br s, 1H), 4.25 (br s, 3H), 3.87 (br s, 1H), 3.56-3.52 (m, 2H), 3.38-3.35 (m, 1H), 3.25 (s, 3H), 3.15-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.93-2.83 (m, 4H), 2.81 (s, 6H), 2.67-2.62 (m, 1H), 2.54-2.51 (m, 2H), 2.35 (s, 3H), 2.27-2.23 (m, 3H), 1.65 (br s, 4H), 1.39-1.38 (m, 4H).
Example 24	(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 17 and 6	HPLC: (System 1, Method D) Rt = 8.29 min, m/z 756.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.61 (br s, 1H), 7.32-7.29 (m, 1H), 7.26-7.16 (m, 1H), 6.86-8.84 (m, 1H), 4.85-4.80 (m, 1H), 4.46 (br s, 1H), 4.18 (s, 1H), 4.11-4.06 (m, 1H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.45-3.44 (m, 1H), 3.37-3.36 (m, 1H), 3.27-3.23 (m, 4H), 3.15-3.13 (m, 2H), 3.05-3.03 (m, 1H), 2.88-2.80 (m, 5H), 2.69-2.62 (m, 4H), 2.42 (br s, 2H), 2.33 (s, 3H), 2.23-2.19 (m, 3H), 1.83-1.74 (m, 6H), 1.59-1.55 (m, 2H), 1.13-1.09 (m, 6H). Mixture of rotamers.

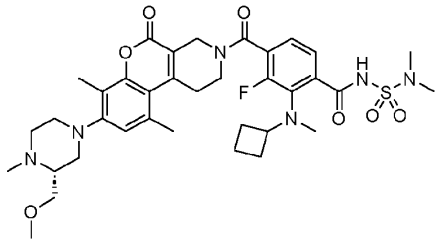
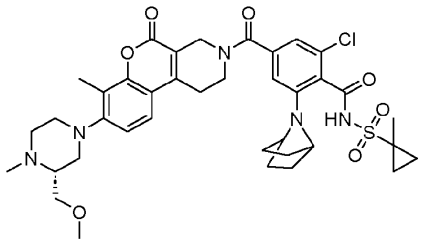
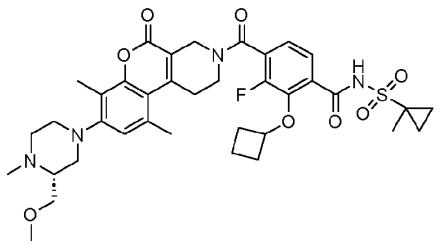
Example 25	(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 18 and 6	HPLC: (System 1, Method D) Rt = 7.92 min, m/z 742.4 $(M+H)^+$.(ES^+) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.60 (br s, 1H), 7.32-7.29 (m, 1H), 7.26-7.17 (m, 1H), 6.86-6.84 (d, J = 7.2 Hz, 1H), 4.72-4.53 (m, 1H), 4.50 (br s, 1H), 4.17 (s, 1H), 4.14-4.07 (m, 1H), 3.88-3.86 (m, 1H), 3.57-3.54 (m, 1H), 3.45 (br s, 1H), 3.38-3.34 (m, 1H), 3.27-3.23 (m, 4H), 3.15-3.13 (m, 2H), 3.06-3.03 (m, 1H), 2.88-2.81 (m, 5H), 2.69-2.59 (m, 4H), 2.46-2.41 (m, 2H), 2.33 (s, 3H), 2.30-2.19 (m, 5H), 2.16-2.08 (m, 2H), 1.71-1.66 (m, 1H), 1.50-1.41 (m, 1H), 1.15-1.12 (m, 6H). Mixture of rotamers.
Example 26	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 88 and 5	HPLC: (System 1, Method D) Rt = 6.71 min, m/z 722.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.76 (br s, 1H), 7.56-7.53 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 9.2 Hz, 1H), 6.50 (s, 1H), 4.45 (br s, 1H), 4.29 (br s, 1H), 3.90 (br s, 1H), 3.59-3.56 (m, 4H), 3.42-3.41 (m, 1H), 3.34 (br s, 2H), 3.28 (s, 3H), 3.19-3.17 (m, 1H), 3.10-3.07 (m, 1H), 2.96 (br s, 3H), 2.90-2.85 (m, 1H), 2.72-2.51 (m, 3H), 2.41 (s, 3H), 2.30-2.26 (m, 3H), 1.66-1.64 (m, 2H), 1.49 (s, 3H), 1.41 (br s, 2H), 0.89 (br s, 2H), 0.69-0.65 (m, 1H), 0.20 (br s, 1H).
Example 27	2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 89 and 5	HPLC: (System 1, Method D) Rt = 6.65 min, m/z 711.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (br s, 1H), 7.58-7.53 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.50 (s, 1H), 4.45 (br s, 1H), 4.28 (br s, 1H), 3.89 (br s, 1H), 3.58-3.55 (m, 4H), 3.42-3.41 (m, 1H), 3.32 (br s, 2H), 3.28 (s, 3H), 3.18-3.16 (m, 1H), 3.09-3.06 (m, 1H), 2.95-2.92 (m, 3H), 2.89-2.84 (m, 7H), 2.70-2.51 (m, 3H), 2.38 (s, 3H), 2.29-2.26 (m, 3H), 1.67-1.65 (m, 2H), 0.70-0.66 (m, 2H).

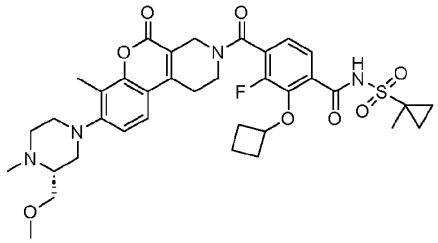
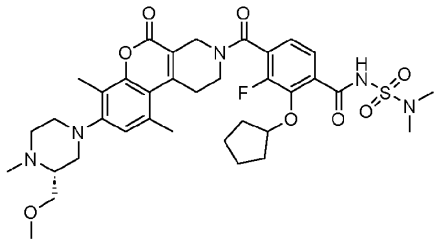
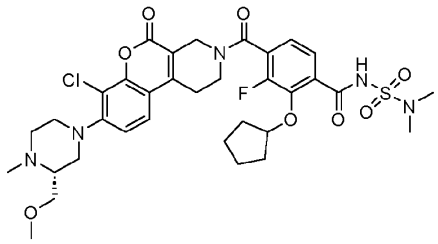
Example 28	2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 89 and 6	HPLC: (System 1, Method D) Rt = 6.89 min, m/z 725.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (br s, 1H), 6.85 (s, 1H), 6.66-6.61 (m, 1H), 6.52 (s, 1H), 4.44 (br s, 1H), 4.29 (br s, 1H), 3.79 (br s, 1H), 3.58-3.54 (m, 4H), 3.41-3.38 (m, 3H), 3.27 (s, 3H), 3.19-3.14 (m, 3H), 3.07-3.05 (m, 1H), 2.92-2.90 (m, 1H), 2.85-2.81 (m, 7H), 2.67-2.65 (m, 4H), 2.55 (br s, 2H), 2.37 (s, 3H), 2.23-2.20 (m, 3H), 1.67-1.66 (m, 2H), 0.70-0.66 (m, 1H), 0.20 (br s, 1H).
Example 29	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide  Synthesised from Intermediates 17 and 7	HPLC: (System 1, Method D) Rt = 8.22 min, m/z 762.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (br s, 1H), 7.71-7.61 (m, 1H), 7.32-7.28 (m, 1H), 7.24-7.16 (m, 2H), 4.85-4.80 (m, 1H), 4.56 (br s, 1H), 4.19 (s, 1H), 4.11-4.08 (m, 1H), 3.98 (br s, 1H), 3.58-3.55 (m, 2H), 3.45-3.42 (m, 1H), 3.34-3.27 (m, 5H), 3.01-2.86 (m, 4H), 2.81 (s, 3H), 2.72-2.67 (m, 1H), 2.50 (br s, 2H), 2.32 (s, 3H), 1.79-1.74 (m, 6H), 1.56-1.51 (m, 2H), 1.13-1.06 (m, 6H). Mixture of rotamers.
Example 30	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide  Synthesised from Intermediates 18 and 7	HPLC: (System 1, Method D) Rt = 7.75 min, m/z 748.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.67 (br s, 1H), 7.71-7.62 (m, 1H), 7.32-7.25 (m, 1H), 7.23-7.16 (m, 2H), 4.72-4.64 (m, 1H), 4.55 (br s, 1H), 4.18 (s, 1H), 4.14-4.07 (m, 1H), 3.97-3.96 (m, 1H), 3.59-3.53 (m, 2H), 3.45-3.42 (m, 1H), 3.37 (br s, 1H), 3.28-3.27 (m, 1H), 3.25 (s, 3H), 3.01-2.85 (m, 4H), 2.82 (s, 3H), 2.72-2.67 (m, 1H), 2.45 (br s, 2H), 2.32 (s, 3H), 2.27-2.19 (m, 2H), 2.16-2.08 (m, 2H), 1.71-1.66 (m, 1H), 1.51-1.43 (m, 1H), 1.15-1.13 (m, 6H). Mixture of rotamers.

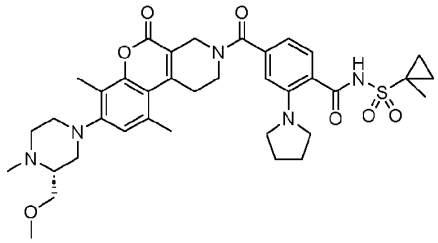
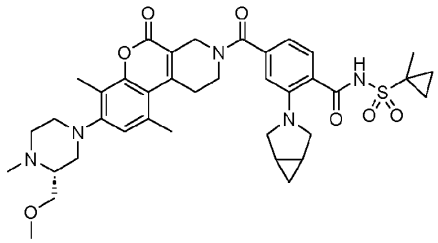
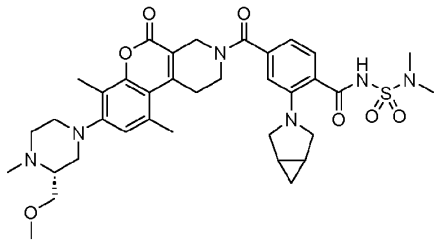
Example 31	(*R*)-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 49 and 5	HPLC: (System 1, Method D) Rt = 7.84 min, m/z 709.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.87 (br s, 1H), 7.58-7.51 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.75 (br s, 2H), 4.47 (br s, 1H), 4.29 (br s, 1H), 4.14-4.09 (m, 1H), 3.92 (br s, 1H), 3.60-3.54 (m, 2H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.19-3.12 (m, 5H), 3.05-3.02 (m, 1H), 2.95 (br s, 2H), 2.86-2.81 (m, 5H), 2.64-2.59 (m, 1H), 2.43-2.40 (m, 2H), 2.30-2.25 (m, 6H), 1.90 (br s, 4H), 1.13 (d, J = 6.4 Hz, 6H).
Example 32	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 90 and 5	HPLC: (System 1, Method D) Rt = 6.84 min, m/z 738.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.82 (br s, 1H), 7.56-7.54 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H), 6.65 (s, 1H), 4.45 (br s, 1H), 4.29 (br s, 1H), 3.89 (br s, 1H), 3.61-3.55 (m, 4H), 3.45-3.40 (m, 2H), 3.34 (br s, 1H), 3.28 (s, 3H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 1H), 2.95 (br s, 3H), 2.90-2.84 (m, 1H), 2.71-2.56 (m, 3H), 2.39 (s, 3H), 2.29-2.26 (m, 3H), 1.64-1.62 (m, 2H), 1.52 (s, 3H), 1.42 (br s, 2H), 0.87 (br s, 2H), 0.67-0.62 (m, 1H), 0.24 (br s, 1H).
Example 33	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 91 and 5	HPLC: (System 1, Method D) Rt = 6.79 min, m/z 727.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.84 (br s, 1H), 7.56-7.54 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 6.65 (s, 1H), 4.46 (br s, 1H), 4.29 (br s, 1H), 3.89 (br s, 1H), 3.60-3.55 (m, 4H), 3.41-3.38 (m, 1H), 3.34 (br s, 2H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.08-3.05 (m, 1H), 2.95-2.83 (m, 10H), 2.69-2.64 (m, 1H), 2.55 (br s, 2H), 2.37 (s, 3H), 2.29-2.26 (m, 3H), 1.65-1.64 (m, 2H), 0.68-0.63 (m, 1H), 0.23 (br s, 1H).
Example 34	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-	HPLC: (System 1, Method D) Rt = 6.93 min, 741.4 $(M+H)^+$ (ES^+).

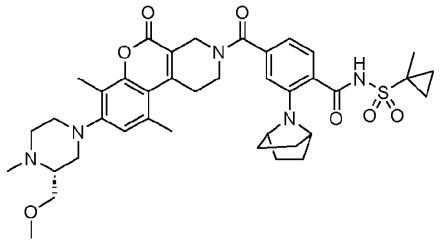
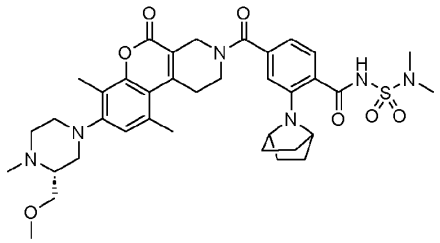
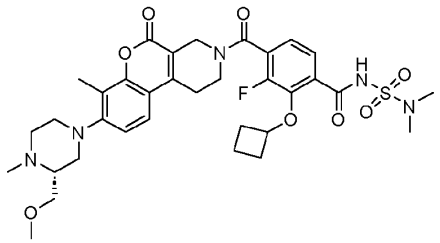
	(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 91 and 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.82 (br s, 1H), 6.85 (s, 2H), 6.67 (s, 1H), 4.45 (br s, 1H), 4.29 (br s, 1H), 3.79 (br s, 1H), 3.61-3.51 (m, 4H), 3.40-3.38 (m, 1H), 3.34 (br s, 2H), 3.27 (s, 3H), 3.24-3.14 (m, 3H), 3.09-3.05 (m, 1H), 2.88-2.81 (m, 8H), 2.68-2.64 (m, 4H), 2.51 (br s, 2H), 2.37 (s, 3H), 2.23-2.20 (m, 3H), 1.66-1.64 (m, 2H), 0.68-0.63 (m, 1H), 0.23 (br s, 1H).
Example 35	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 22 and 6	HPLC: (System 1, Method D) Rt = 7.58 min, m/z 766.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.59 (br s, 1H), 7.30-7.28 (m, 1H), 7.21-7.12 (m, 1H), 6.86-8.84 (m, 1H), 4.80-4.72 (m, 1H), 4.49 (br s, 1H), 4.17 (s, 1H), 3.88-3.85 (m, 1H), 3.57-3.54 (m, 1H), 3.46-3.44 (m, 1H), 3.41-3.38 (m, 2H), 3.36-3.35 (m, 3H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.89-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.48-2.46 (m, 2H), 2.34 (s, 3H), 2.23-2.20 (m, 3H), 2.13-2.08 (m, 2H), 2.02-1.95 (m, 2H), 1.87-1.84 (m, 4H), 1.32-1.29 (m, 2H), 0.67-0.60 (m, 1H), 0.47-0.40 (m, 1H). Mixture of rotamers.
Example 36	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 24 and 6	HPLC: (System 1, Method D) Rt = 8.10 min, m/z 768.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.67 (br s, 1H), 7.28-7.25 (m, 1H), 7.23-7.14 (m, 1H), 6.86-6.84 (m, 1H), 4.78-4.69 (m, 1H), 4.51 (br s, 1H), 4.17 (s, 1H), 4.12-4.08 (m, 1H), 3.88-3.85 (m, 1H), 3.57-3.55 (m, 1H), 3.45-3.44 (m, 1H), 3.38-3.34 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.15-3.13 (m, 2H), 3.06-3.03 (m, 1H), 2.88-2.83 (m, 2H), 2.80 (s, 3H), 2.69-2.62 (m, 4H), 2.50-2.49 (m, 2H), 2.33 (s, 3H), 2.23-2.20 (m, 3H), 2.14-2.08 (m, 2H), 2.02-1.95 (m, 2H), 1.32-1.28 (m, 2H), 1.14-1.11 (m, 6H), 0.68-0.61 (m,

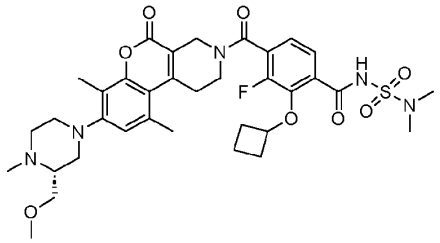
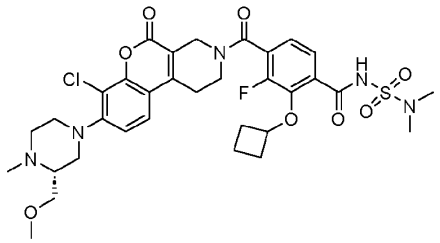
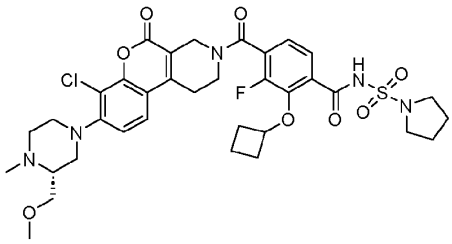
		1H), 0.47-0.40 (m, 1H). Mixture of rotamers.
Example 37	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 25 and 6	HPLC: (System 1, Method D) Rt = 7.29 min, m/z 751.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.25 (br s, 1H), 7.29-7.27 (m, 1H), 7.19-7.11 (m, 1H), 6.87-6.85 (m, 1H), 4.84-4.75 (m, 1H), 4.50 (br s, 1H), 4.18 (s, 1H), 3.87 (br s, 1H), 3.59-3.56 (m, 1H), 3.46-3.45 (m, 2H), 3.28 (s, 3H), 3.23-3.08 (m, 4H), 2.99-2.97 (m, 1H), 2.89-2.84 (m, 1H), 2.75-2.62 (m, 6H), 2.44 (s, 3H), 2.24-2.20 (m, 3H), 2.09-2.06 (m, 2H), 2.01-1.95 (m, 2H), 1.48 (s, 3H), 1.46-1.37 (m, 2H), 1.31-1.29 (m, 2H), 0.85-0.83 (m, 2H), 0.72-0.65 (m, 1H), 0.46-0.39 (m, 1H). Mixture of rotamers.
Example 38	(*R*)-2-(cyclobutyl(methyl)amino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 85 and 6	HPLC: (System 1, Method D) Rt = 8.63 min, m/z 738.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.85 (br s, 1H), 7.77-7.71 (m, 1H), 7.50-7.39 (m, 1H), 6.85 (d, J = 7.2 Hz, 1H), 4.48 (br s, 1H), 4.16 (s, 1H), 3.89-3.81 (m, 2H), 3.57-3.54 (m, 1H), 3.44 (br s, 1H), 3.38 (br s, 1H), 3.27 (s, 3H), 3.24 (br s, 1H), 3.15-3.13 (m, 2H), 3.06-3.03 (m, 1H), 2.89-2.80 (m, 2H), 2.75-2.73 (m, 3H), 2.71-2.67 (m, 2H), 2.64-2.61 (m, 2H), 2.46 (br s, 2H), 2.33 (s, 3H), 2.23-2.18 (m, 3H), 2.02 (br s, 2H), 1.94-1.85 (m, 2H), 1.68-1.59 (m, 2H), 1.55 (s, 3H), 1.50-1.48 (m, 2H), 0.97 (br s, 2H). Mixture of rotamers.
Example 39	(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	HPLC: (System 1, Method D) Rt = 9.05 min, m/z 727.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.75 (br s, 1H), 7.78-7.73 (m, 1H), 7.50-7.40 (m, 1H), 6.86-6.84 (m, 1H), 4.59-4.42 (m, 1H), 4.15 (s, 1H), 3.89-3.80 (m, 2H), 3.57-3.54 (m, 1H), 3.43 (br s, 1H), 3.37 (br s, 1H), 3.26-3.24 (m, 4H), 3.15-3.12 (m, 2H), 3.05-3.03 (m, 1H), 2.91 (s, 6H), 2.87-2.79 (m, 2H), 2.74-2.66 (m, 5H), 2.63-2.61 (m, 2H),

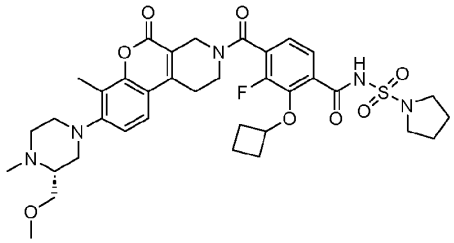
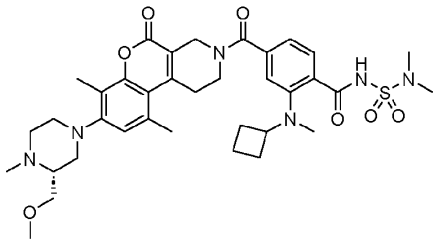
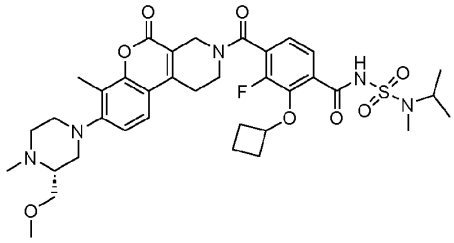
	 Synthesised from Intermediates 84 and 6	2.462.44 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 2.02 (br s, 2H), 1.92-1.83 (m, 2H), 1.68-1.59 (m, 2H). Mixture of rotamers.
Example 40	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 92 and 5	HPLC: (System 1, Method D) Rt = 7.02 min, m/z 752.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (br s, 1H), 7.58-7.53 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 0.95 (s, 2H), 4.47 (br s, 1H), 4.28 (br s, 3H), 3.90 (br s, 1H), 3.59-3.55 (m, 2H), 3.42-3.39 (m, 1H), 3.28 (s, 3H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 1H), 2.96-2.84 (m, 4H), 2.70-2.65 (m, 1H), 2.57 (br s, 2H), 2.39 (s, 3H), 2.33-2.26 (m, 3H), 1.69 (br s, 4H), 1.51 (s, 3H), 1.48-1.39 (m, 6H), 0.89 (m, 2H).
Example 41	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 19 and 6	HPLC: (System 1, Method D) Rt = 6.98 min, m/z 725.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.32 (br s, 1H), 7.31-7.29 (m, 1H), 7.22-7.13 (m, 1H), 6.87-6.85 (m, 1H), 4.74-4.67 (m, 1H), 4.50 (br s, 1H), 4.18 (s, 1H), 3.87 (br s, 1H), 3.58-3.56 (m, 1H), 3.46-3.44 (m, 2H), 3.28 (s, 3H), 3.23-3.07 (m, 4H), 2.98-2.95 (m, 1H), 2.89-2.83 (m, 1H), 2.74-2.62 (m, 6H), 2.43 (s, 3H), 2.27-2.20 (m, 5H), 2.16-2.08 (m, 2H), 1.70-1.65 (m, 1H), 1.50 (s, 3H), 1.46-1.39 (m, 3H), 0.86-0.84 (m, 2H). Mixture of rotamers.
Example 42	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 6.84 min, m/z 711.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.28 (br s, 1H), 7.60-7.51 (m, 1H), 7.31-7.29 (m, 1H), 7.20-7.13 (m, 1H), 7.11-7.09 (m, 1H), 4.74-4.66 (m, 1H), 4.53 (br s, 1H), 4.18 (s, 1H), 3.97 (t, J = 6.0 Hz, 1H), 3.59-3.54 (m,

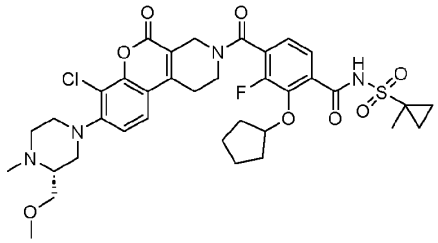
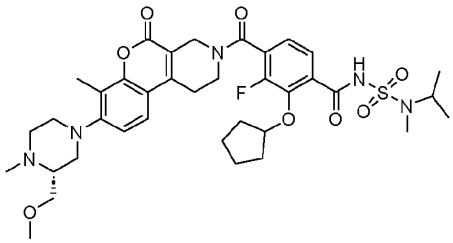
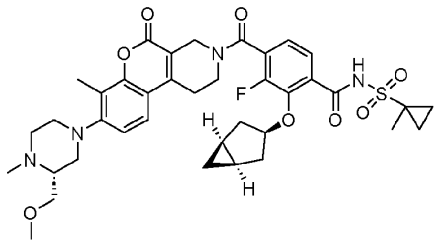
	 Synthesised from Intermediates 19 and 5	2H), 3.45-3.43 (m, 1H), 3.29 (s, 3H), 3.21-3.18 (m, 1H), 3.11-3.08 (m, 1H), 3.00-2.91 (m, 2H), 2.89-2.86 (m, 2H), 2.74-2.63 (m, 3H), 2.44 (s, 3H), 2.30-2.28 (m, 3H), 2.26-2.07 (m, 4H), 1.70-1.65 (m, 1H), 1.50 (s, 3H), 1.46-1.39 (m, 3H), 0.87-0.85 (m, 2H). Mixture of rotamers.
Example 43	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 15 and 6	HPLC: (System 1, Method D) Rt = 7.18 min, m/z 728.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.34 (d, J = 6.0 Hz, 1H), 7.23-7.14 (m, 1H), 6.86 (d, J = 7.2 Hz, 1H), 4.88-4.83 (m, 1H), 4.51 (br s, 1H), 4.18 (s, 1H), 3.87 (br s, 1H), 3.58-3.55 (m, 1H), 3.46-3.38 (m, 2H), 3.28 (s, 3H), 3.24 (br s, 1H), 3.18-3.15 (m, 2H), 3.09-3.06 (m, 1H), 2.94-2.92 (m, 1H), 2.87-2.83 (m, 7H), 2.71-2.56 (m, 6H), 2.39 (s, 3H), 2.24-2.20 (m, 3H), 1.84-1.73 (m, 6H), 1.56-1.54 (m, 2H).
Example 44	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide  Synthesised from Intermediates 15 and 7	HPLC: (System 1, Method D) Rt = 7.06 min, m/z 734.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.71-7.62 (m, 1H), 7.36-7.34 (m, 1H), 7.22-7.15 (m, 2H), 4.87-4.82 (m, 1H), 4.54 (br s, 1H), 4.19 (s, 1H), 3.98 (br s, 1H), 3.59-3.54 (m, 2H), 3.46-3.44 (m, 1H), 3.39-3.31 (m, 2H), 3.28 (s, 3H), 3.01-2.92 (m, 4H), 2.84 (s, 6H), 2.76-2.71 (m, 1H), 2.57-2.51 (m, 2H), 2.37 (s, 3H), 1.83-1.73 (m, 6H), 1.59-1.56 (m, 2H). Mixture of rotamers.
Example 45	(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide	HPLC: (System 1, Method D) Rt = 6.74 min, m/z 706.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (br s, 1H), 7.38 (m, 1H), 6.85 (s, 1H), 6.80-6.73 (m, 2H), 4.46 (br s, 1H), 4.30 (br s, 1H), 3.82 (br s, 1H), 3.57-3.52 (m, 2H), 3.38 (br s, 2H), 3.27 (s, 3H), 3.20-3.13 (m, 7H), 3.06-3.04 (m, 1H), 2.89-2.80 (m, 2H),

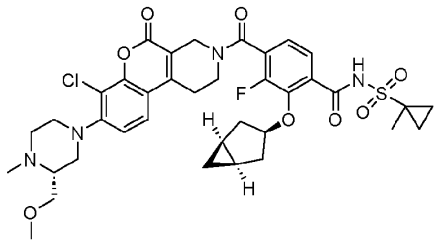
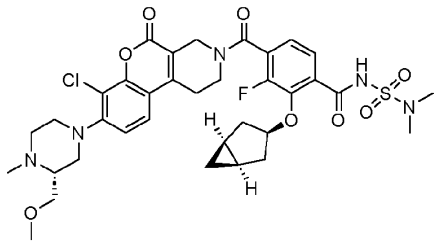
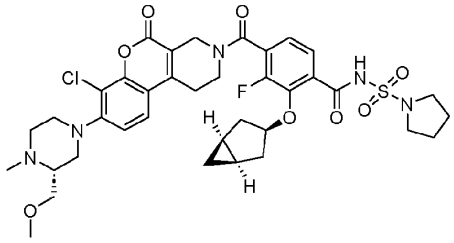
	 Synthesised from Intermediates 46 and 6	2.69-2.62 (m, 4H), 2.50 (br s, 1H), 2.34 (s, 3H), 2.23-2.19 (m, 3H), 1.91 (br s, 4H), 1.51 (s, 3H), 1.49-1.46 (m, 2H), 0.95-0.92 (m, 2H).
Example 46	2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 52 and 6	HPLC: (System 1, Method D) Rt = 6.88 min, m/z 718.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (br s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.85-6.82 (m, 3H), 4.46 (br s, 1H), 4.29 (br s, 1H), 3.82 (br s, 1H), 3.57-3.46 (m, 4H), 3.38 (br s, 1H), 3.27-3.25 (m, 5H), 3.19-3.13 (m, 3H), 3.06-3.03 (m, 1H), 2.89-2.80 (m, 2H), 2.68-2.62 (m, 4H), 2.49 (br s, 2H), 2.34 (s, 3H), 2.23-2.20 (m, 3H), 1.65-1.63 (m, 2H), 1.51 (s, 3H), 1.47-1.44 (m, 2H), 0.93 (br s, 2H), 0.66-0.61 (m, 1H), 0.30 (br s, 1H).
Example 47	2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 53 and 6	HPLC: (System 1, Method D) Rt = 6.93 min, m/z 707.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.78 (br s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.85-6.81 (m, 3H), 4.46 (br s, 1H), 4.29 (br s, 1H), 3.81 (br s, 1H), 3.57-3.45 (m, 4H), 3.37 (br s, 1H), 3.27-3.24 (m, 5H), 3.19-3.12 (m, 3H), 3.06-3.03 (m, 1H), 2.88-2.79 (m, 8H), 2.68-2.61 (m, 4H), 2.45-2.43 (m, 2H), 2.33 (s, 3H), 2.23-2.19 (m, 3H), 1.64-1.63 (m, 2H), 0.64-0.63 (m, 1H), 0.30 (br s, 1H).
Example 48	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.03 min, m/z 732.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.68 (br s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.06-7.03 (m, 1H), 6.96-6.91 (m, 1H), 6.85 (s, 1H), 4.47 (br s, 1H), 4.28 (br s, 1H), 4.14-4.10 (m, 2H), 3.82 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.38 (br s, 1H), 3.27 (s, 3H),

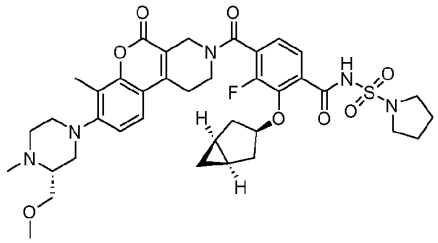
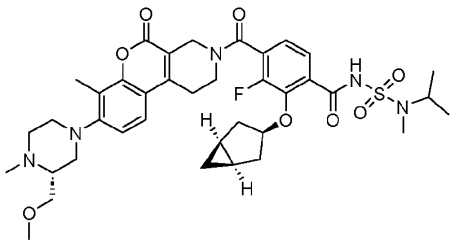
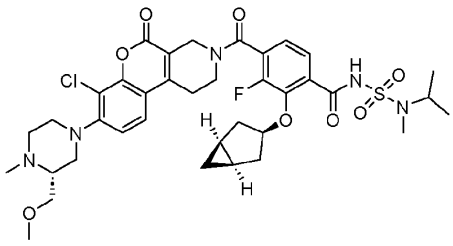
	 Synthesised from Intermediates 50 and 6	3.21 (br s, 2H), 3.15-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.88-2.80 (m, 2H), 2.68-2.61 (m, 4H), 2.50-2.46 (m, 2H), 2.33 (s, 3H), 2.23-2.19 (m, 3H), 1.73 (br s, 4H), 1.49 (s, 3H), 1.46-1.42 (m, 6H), 0.95-0.92 (m, 2H). Mixture of rotamers.
Example 49	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 51 and 6	HPLC: (System 1, Method D) Rt = 7.28 min, m/z 721.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.61 (br s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.07-7.03 (m, 1H), 6.98-6.92 (m, 1H), 6.85 (s, 1H), 4.47 (br s, 1H), 4.27 (br s, 1H), 4.13-4.09 (m, 2H), 3.82 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.35 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.15-3.12 (m, 1H), 3.04-3.02 (m, 1H), 2.87-2.79 (m, 8H), 2.68-2.60 (m, 4H), 2.45-2.43 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 1.73 (br s, 4H), 1.44 (br s, 4H).
Example 50	(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 20 and 5	HPLC: (System 1, Method D) Rt = 7.37 min, m/z 700.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.31 (br s, 1H), 7.60-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.22-7.14 (m, 1H), 7.11-7.07 (m, 1H), 4.73-4.65 (m, 1H), 4.52 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 6.0 Hz, 1H), 3.59-3.53 (m, 2H), 3.45-3.42 (m, 1H), 3.28 (br s, 3H), 3.20-3.17 (m, 1H), 3.10-3.07 (m, 1H), 2.99-2.88 (m, 4H), 2.30-2.24 (m, 6H), 2.72-2.59 (m, 3H), 2.41 (s, 3H), 2.30-2.16 (m, 5H), 2.13-2.08 (m, 2H), 1.70-1.66 (m, 1H), 1.50-1.43 (m, 1H). Mixture of rotamers.
Example 51	(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.51 min, m/z 714.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.33 (br s, 1H), 7.33 (br s, 1H), 7.22-7.17 (m, 1H), 6.86-6.85 (m, 1H), 4.71-4.68 (m, 1H), 4.50 (br s, 1H), 4.17 (s, 1H), 3.87 (br s, 1H), 3.56-3.34 (m, 5H), 3.24-3.02 (m, 5H), 2.94-

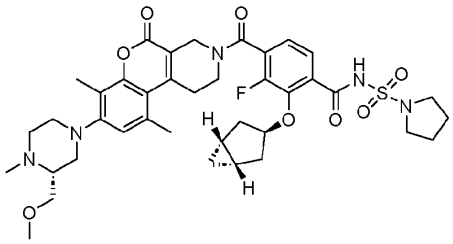
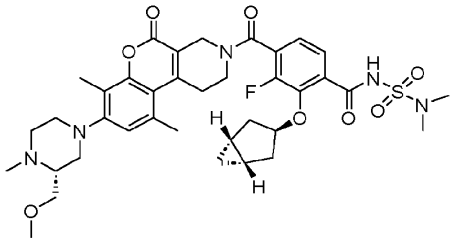
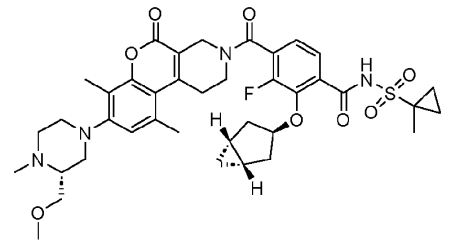
	 Synthesised from Intermediates 20 and 6	2.91 (m, 1H), 2.85 (s, 7H), 2.77-2.54 (m, 6H), 2.41 (s, 3H), 2.24-2.11 (m, 7H), 1.68 (br s, 1H), 1.45-1.41 (m, 1H). Mixture of rotamers.
Example 52	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide  Synthesised from Intermediates 20 and 7	HPLC: (System 1, Method D) Rt = 7.41 min, m/z 721.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.70-7.62 (m, 1H), 7.35-7.34 (m, 1H), 7.21-7.16 (m, 2H), 4.73-4.65 (m, 1H), 4.54 (br s, 1H), 4.19 (s, 1H), 3.97 (m, 1H), 3.59-3.56 (m, 2H), 3.47-3.31 (m, 6H), 2.99-2.93 (m, 4H), 2.86 (s, 6H), 2.77-2.72 (m, 1H), 2.61-2.55 (m, 2H), 2.38 (s, 3H), 2.24-2.11 (m, 4H), 1.71-1.69 (m, 1H), 1.48-1.43 (m, 1H). Mixture of rotamers.
Example 53	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 7	HPLC: (System 1, Method D) Rt = 7.22 min, m/z 746.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.59 (br s, 1H), 7.71-7.62 (m, 1H), 7.36-7.33 (m, 1H), 7.24-7.16 (m, 2H), 4.73-4.65 (m, 1H), 4.51 (br s, 1H), 4.18 (s, 1H), 3.97 (br s, 1H), 3.59-3.51 (m, 3H), 3.49-3.41 (m, 6H), 3.29 (br s, 1H), 3.27 (s, 3H), 3.01-2.89 (m, 4H), 2.74-2.68 (m, 1H), 2.50 (br s, 1H), 2.39 (s, 3H), 2.34-2.21 (m, 2H), 2.19-2.07 (m, 2H), 1.86 (br s, 4H), 1.71-1.66 (m, 1H), 1.50-1.44 (m, 1H). Mixture of rotamers.
Example 54	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.20 min, m/z 726.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.53 (br s, 1H), 7.60-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.24-7.16 (m, 1H), 7.10-7.06 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 6.0 Hz, 1H), 3.58-3.53 (m, 2H), 3.43-3.34 (m, 9H), 3.18-3.15 (m, 1H),

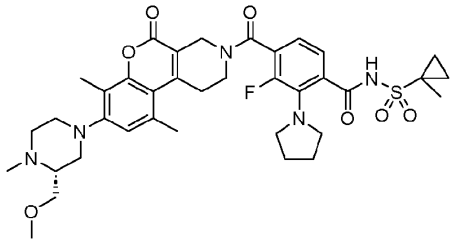
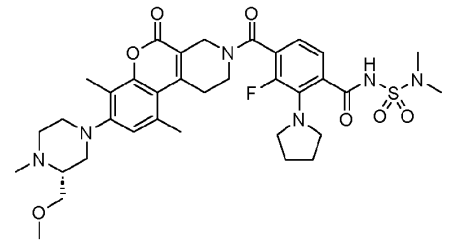
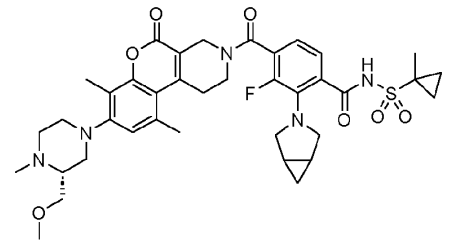
	 Synthesised from Intermediates 13 and 5	3.08-3.05 (m, 1H), 2.99 (br s, 1H), 2.91-2.83 (m, 3H), 2.68-2.63 (m, 1H), 2.51 (br s, 1H), 2.36 (s, 3H), 2.29-2.18 (m, 5H), 2.15-2.06 (m, 2H), 1.86-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.50-1.41 (m, 1H). Mixture of rotamers.
Example 55	(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 83 and 6	HPLC: (System 1, Method D) Rt = 8.90 min, m/z 709.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.72 (br s, 1H), 8.03-7.97 (m, 1H), 7.59-7.52 (m, 1H), 7.44-7.39 (m, 1H), 6.85 (s, 1H), 4.49 (br s, 1H), 4.26 (br s, 1H), 3.92-3.84 (m, 2H), 3.57-3.53 (m, 1H), 3.45 (br s, 1H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.14-3.12 (m, 1H), 3.04-3.02 (m, 1H), 2.91 (s, 6H), 2.84-2.79 (m, 2H), 2.67-2.65 (m, 6H), 2.62-2.59 (m, 1H), 2.40 (br s, 2H), 2.30 (s, 3H), 2.24-2.19 (m, 3H), 2.09-2.07 (m, 2H), 1.92-1.88 (m, 2H), 1.72-1.63 (m, 2H). Mixture of rotamers.
Example 56	(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 18 and 5	HPLC: (System 1, Method D) Rt = 7.67 min, m/z 728.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.53 (br s, 1H), 7.59-7.50 (m, 1H), 7.32-7.24 (m, 1H), 7.23-7.16 (m, 1H), 7.10-7.05 (m, 1H), 4.72-4.64 (m, 1H), 4.52 (br s, 1H), 4.17 (s, 1H), 4.12-4.08 (m, 1H), 3.98-3.96 (m, 1H), 3.58-3.53 (m, 2H), 3.38-3.34 (m, 4H), 3.17-3.14 (m, 1H), 3.07-2.99 (m, 2H), 2.89-2.85 (m, 3H), 2.82 (s, 3H), 2.67-2.61 (m, 1H), 2.50-2.46 (m, 2H), 2.33 (s, 3H), 2.29-2.19 (m, 5H), 2.16-2.07 (m, 2H), 1.71-1.66 (m, 1H), 1.50-1.43 (m, 1H), 1.15-1.13 (m, 6H). Mixture of rotamers.
Example 57	(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.08 min, m/z 745.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (br s, 1H), 7.71-7.62 (m, 1H), 7.33-7.31 (m, 1H), 7.21-7.14 (m, 2H), 4.88-4.82 (m, 1H),

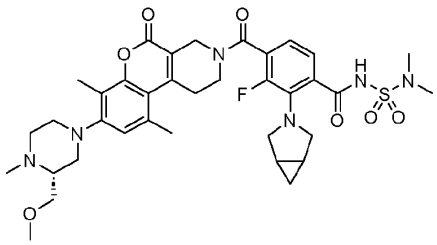
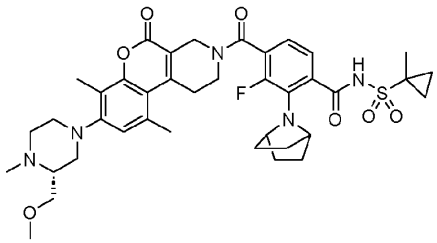
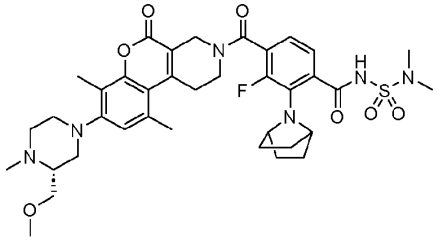
	 Synthesised from Intermediates 16 and 7	4.54 (br s, 1H), 4.20 (s, 1H), 3.98 (br s, 1H), 3.60-3.55 (m, 2H), 3.47-3.39 (m, 3H), 3.28 (s, 3H), 3.01-2.94 (m, 4H), 2.79-2.73 (m, 1H), 2.67-2.58 (m, 2H), 2.40 (s, 3H), 1.83-1.72 (m, 6H), 1.55-1.54 (m, 2H), 1.48 (s, 3H), 1.41-1.40 (m, 2H), 0.89-0.88 (m, 2H). Mixture of rotamers.
Example 58	(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 17 and 5	HPLC: (System 1, Method D) Rt = 8.13 min, m/z 741.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.69 (br s, 1H), 7.59-7.50 (m, 1H), 7.28-7.27 (m, 1H), 7.21-7.13 (m, 1H), 7.09-7.05 (m, 1H), 4.87-4.81 (m, 1H), 4.52 (br s, 1H), 4.17 (s, 1H), 4.11-4.05 (m, 1H), 3.99-3.96 (m, 1H), 3.57-3.54 (m, 2H), 3.32 (br s, 1H), 3.26 (s, 3H), 3.16-3.13 (m, 1H), 3.05-2.99 (m, 2H), 2.90-2.81 (m, 3H), 2.77 (s, 3H), 2.65-2.59 (m, 1H), 2.44-2.39 (m, 2H), 2.30-2.25 (m, 6H), 1.82-1.72 (m, 6H), 1.57-1.55 (m, 2H), 1.12-1.10 (m, 6H). mixture of rotamers.
Example 59	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 25 and 5	HPLC: (System 1, Method D) Rt = 7.14 min, m/z 737.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.24 (br s, 1H), 7.60-7.51 (m, 1H), 7.29-7.27 (m, 1H), 7.17-7.07 (m, 2H), 4.83-4.74 (m, 1H), 4.51 (br s, 1H), 4.18 (s, 1H), 3.99-3.96 (m, 1H), 3.59-3.54 (m, 2H), 3.46-3.40 (m, 1H), 3.29 (s, 3H), 3.21-3.19 (m, 1H), 3.12-3.09 (m, 1H), 2.99-2.96 (m, 2H), 2.92-2.87 (m, 2H), 2.72-2.67 (m, 3H), 2.46 (s, 3H), 2.30-2.26 (m, 3H), 2.10-2.06 (m, 2H), 2.01-1.95 (m, 2H), 1.48 (s, 3H), 1.43-1.39 (m, 2H), 1.31-1.27 (m, 2H), 0.86-0.85 (m, 2H), 0.70-1.63 (m, 1H), 0.47-0.39 (m, 1H). Mixture of rotamers.
Example 60	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-	HPLC: (System 1, Method D) Rt = 7.17 min, m/z 757.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.50 (br s, 1H), 7.71-7.62- (m, 1H), 7.28-7.27 (m, 1H), 7.21-7.10 (m, 2H), 4.84-4.75 (m, 1H),

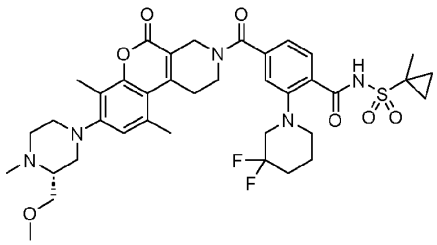
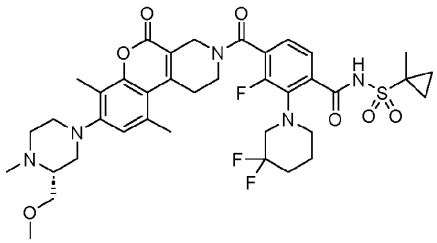
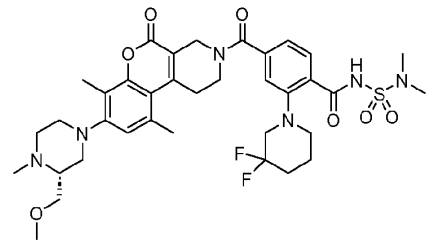
	fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 25 and 7	4.53 (br s, 1H), 4.19 (s, 1H), 3.97 (br s, 1H), 3.60-3.54 (m, 2H), 3.47-3.40 (m, 2H), 3.34 (br s, 1H), 3.28 (s, 3H), 3.00-2.93 (m, 4H), 2.77-2.72 (m, 1H), 2.68-2.51 (m, 2H), 2.39 (s, 3H), 2.10-2.05 (m, 2H), 2.01-1.94 (m, 2H), 1.48 (s, 3H), 1.45-1.38 (m, 2H), 1.31-1.29 (m, 2H), 0.85-0.82 (m, 2H), 0.71-0.65 (m, 1H), 0.45-0.39 (m, 1H). Mixture of rotamers.
Example 61	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide  Synthesised from Intermediates 23 and 7	HPLC: (System 1, Method D) Rt = 7.09 min, m/z 746.4 $(M+H)^+$ (ES^+). 1H NMR (400 MHz, DMSO-d6) δ: 11.54 (br s, 1H), 7.71-7.61 (m, 1H), 7.32-7.30 (m, 1H), 7.21-7.13 (m, 2H), 4.81-4.72 (m, 1H), 4.53 (br s, 1H), 4.19 (s, 1H), 3.97 (br s, 1H), 3.60-3.54 (m, 2H), 3.47-337 (m, 2H), 3.32 (br s, 1H), 3.28 (s, 3H), 3.00-2.93 (m, 4H), 2.85 (s, 6H), 2.77-2.71 (m, 1H), 2.60-2.51 (m, 2H), 2.38 (s, 3H), 2.13-2.08 (m, 2H), 2.01-1.95 (m, 2H), 1.32-1.30 (m, 2H), 0.69-0.63 (m, 1H), 0.47-0.43 (m, 1H). Mixture of rotamers.
Example 62	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 22 and 7	HPLC: (System 1, Method D) Rt = 7.44 min, m/z 772.4 $(M+H)^+$ (ES^+). 1H NMR (400 MHz, DMSO-d6) δ: 11.62 (br s, 1H), 7.71-7.61 (m, 1H), 7.30-7.29 (m, 1H), 7.20-7.13 (m, 2H), 4.79-4.70 (m, 1H), 4.53 (br s, 1H), 4.19 (s, 1H), 3.98-3.96 (m, 1H), 3.59-3.54 (m, 2H), 3.45-3.41 (m, 5H), 3.36-3.34 (m, 1H), 3.29-3.27 (m, 4H), 3.00-2.88 (m, 4H), 2.73-2.68 (m, 1H), 2.50-2.45 (m, 2H), 2.34 (s, 3H), 2.15-2.08 (m, 2H), 2.02-1.95 (m, 2H), 1.87-1.85 (m, 4H), 1.32-1.29 (m, 2H), 0.65-0.59 (m, 1H), 0.47-0.41 (m, 1H). Mixture of rotamers.
Example 63	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.42 min, m/z 752.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.60 (br s, 1H), 7.59-7.50 (m, 1H), 7.30-7.28 (m, 1H), 7.20-7.16 (m, 2H), 4.79-4.70 (m, 1H),

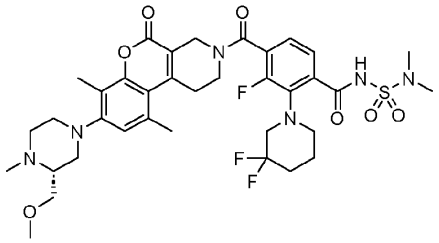
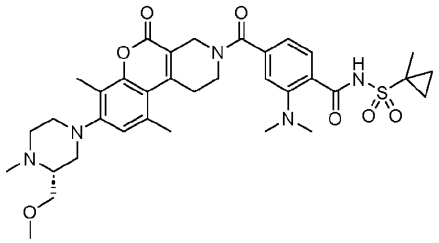
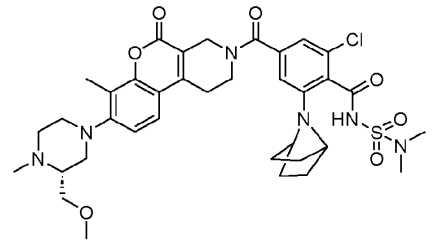
	 Synthesised from Intermediates 22 and 5	4.52 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 6.0 Hz, 1H), 3.58-3.53 (m, 2H), 3.42-3.39 (m, 5H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.08-3.00 (m, 2H), 2.89-2.83 (m, 3H), 2.68-2.66 (m, 1H), 2.54 (br s, 1H), 2.50 (br s, 1H), 2.36 (s, 3H), 2.30-2.26 (m, 3H), 2.14-2.08 (m, 2H), 2.01-1.95 (m, 2H), 1.86 (br s, 4H), 1.32-1.28 (m, 2H), 0.65-0.60 (m, 1H), 0.47-0.43 (m, 1H). Mixture of rotamers.
Example 64	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 24 and 5	HPLC: (System 1, Method D) Rt = 7.93 min, m/z 754.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (br s, 1H), 7.60-7.50 (m, 1H), 7.27-7.25 (m, 1H), 7.21-7.13 (m, 1H), 7.10-7.06 (m, 1H), 4.76-4.70 (m, 1H), 4.51 (br s, 1H), 4.17 (s, 1H), 4.12-4.08 (m, 1H), 3.97 (t, J = 5.6 Hz, 1H), 3.58-3.53 (m, 2H), 3.38-3.37 (m, 1H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-2.99 (m, 2H), 2.90-2.82 (m, 3H), 2.80 (s, 3H), 2.67-2.62 (m, 1H), 2.50 (br s, 2H), 2.34 (s, 3H), 2.29-2.26 (m, 3H), 2.14-2.06 (m, 2H), 2.01-1.94 (m, 2H), 1.32-1.28 (m, 2H), 1.14-1.12 (m, 6H), 0.66-0.62 (m, 1H), 0.47-0.43 (m, 1H). Mixture of rotamers.
Example 65	2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide  Synthesised from Intermediates 24 and 7	HPLC: (System 1, Method D) Rt = 7.93 min, m/z 774.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73 (br s, 1H), 7.71-7.61 (m, 1H), 7.27-7.25 (m, 1H), 7.21-7.14 (m, 2H), 4.78-4.70 (m, 1H), 4.52 (br s, 1H), 4.18 (s, 1H), 4.12-4.08 (m, 1H), 3.97 (br s, 1H), 3.59-3.54 (m, 2H), 3.45-3.42 (m, 1H), 3.36 (br s, 1H), 3.32-3.28 (m, 1H), 3.27 (s, 3H), 3.00-2.86 (m, 4H), 2.80 (s, 3H), 2.72-2.67 (m, 1H), 2.50-2.41 (m, 2H), 2.32 (s, 3H), 2.14-2.07 (m, 2H), 2.01-1.95 (m, 2H), 1.32-1.28 (m, 2H), 1.14-1.12 (m, 6H), 0.66-0.62 (m, 1H), 0.47-0.43 (m, 1H). Mixture of rotamers.
Example 66	2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-	HPLC: (System 1, Method D) Rt = 7.84 min, m/z 766.4 $(M+H)^+$ (ES^+).

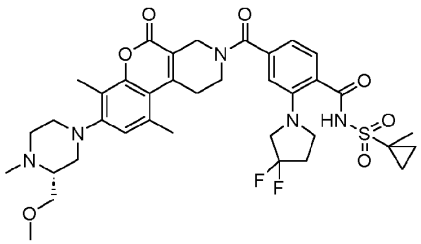
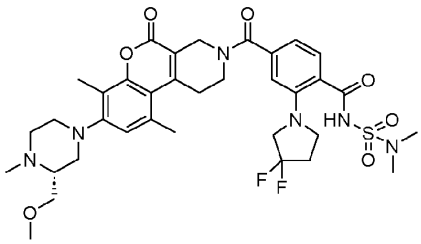
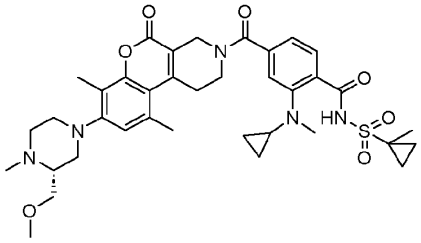
	1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 29 and 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.56 (br s, 1H), 7.34-7.31 (m, 1H), 7.26-7.16 (m, 1H), 6.86 (d, J = 6.8 Hz, 1H), 4.60-4.40 (m, 2H), 4.17 (s, 1H), 3.88-3.86 (m, 1H), 3.58-3.54 (m, 1H), 3.44-3.34 (m, 6H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.51 (br s, 2H), 2.36 (s, 3H), 2.24-2.20 (m, 3H), 2.18-2.10 (m, 2H), 1.95-1.88 (m, 2H), 1.87-1.84 (m, 4H), 1.32-1.27 (m, 2H), 0.36-0.32 (m, 1H), 0.05-0.01 (m, 1H).
Example 67	2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 30 and 6	HPLC: (System 1, Method D) Rt = 7.27 min, m/z 740.5 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.31 (br s, 1H), 7.33-7.31 (m, 1H), 7.24-7.15 (m, 1H), 6.87-6.86 (m, 1H), 4.52-4.40 (m, 2H), 4.17 (s, 1H), 3.88-3.86 (m, 1H), 3.58-3.55 (m, 1H), 3.45-3.40 (m, 2H), 3.28 (s, 3H), 3.23 (br s, 1H), 3.19-3.16 (m, 2H), 3.10-3.07 (m, 1H), 2.97-2.95 (m, 1H), 2.88-2.85 (m, 1H), 2.83-2.82 (m, 6H), 2.73-2.62 (m, 6H), 2.42 (s, 3H), 2.24-2.10 (m, 3H), 2.18-2.10 (m, 2H), 1.96-1.89 (m, 2H), 1.31-1.27 (m, 2H), 0.36-0.32 (m, 1H), 0.05-0.01 (m, 1H). Mixture of rotamers.
Example 68	2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 31 and 6	HPLC: (System 1, Method D) Rt = 7.55 min, m/z 751.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.31 (br s, 1H), 7.30-7.28 (m, 1H), 7.21-7.13 (m, 1H), 6.87-6.86 (m, 1H), 4.52-4.41 (m, 2H), 4.18 (s, 1H), 3.88-3.86 (m, 1H), 3.59-3.56 (m, 1H), 3.45-3.44 (m, 2H), 3.29 (s, 3H), 3.23-3.08 (m, 4H), 3.00-2.97 (m, 1H), 2.89-2.84 (m, 1H), 2.73-2.63 (m, 6H), 2.44 (s, 3H), 2.24-2.21 (m, 3H), 2.18-2.10 (m, 2H), 1.96-1.88 (m, 2H), 1.48 (s, 3H), 1.38 (br s, 2H), 1.31-1.27 (m, 2H), 0.85-0.83 (m, 2H), 0.35-0.31 (m, 1H), 0.03-0.00 (m, 1H). Mixture of rotamers.

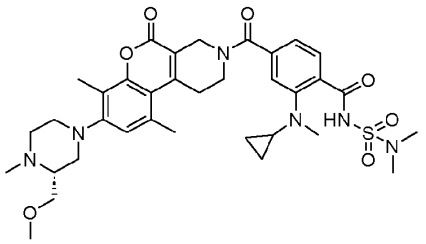
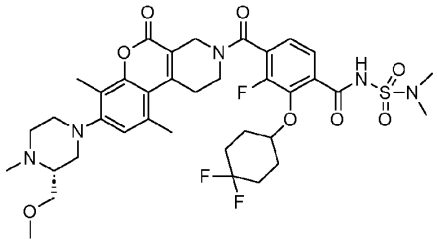
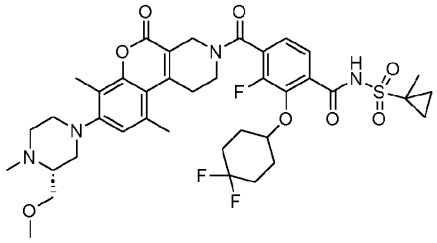
Example 69	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 70 and 6	HPLC: (System 1, Method D) Rt = 7.30 min, m/z 724.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.99 (br s, 1H), 7.44-7.37 (m, 1H), 7.12-6.99 (m, 1H), 6.86-6.84 (m, 1H), 4.57 (br s, 1H), 4.40 (br s, 1H), 3.86 (t, J = 6.4, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.39 (br s, 3H), 3.34 (br s, 2H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.19-3.16 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.51 (br s, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.93-1.86 (m, 4H), 1.50 (s, 3H), 1.44 (br s, 2H), 0.91 (br s, 2H). Mixture of rotamers.
Example 70	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 71 and 6	HPLC: (System 1, Method D) Rt = 7.54 min, m/z 713.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.84 (br s, 1H), 7.44-7.38 (m, 1H), 7.11-6.99 (m, 1H), 6.86-6.84 (m, 1H), 4.60-4.40 (m, 1H), 4.19 (br s, 1H), 3.88-3.86 (m, 1H), 3.57-3.54 (m, 1H), 3.47 (br s, 1H), 3.38 (br s, 2H), 3.32 (br s, 3H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.87-2.80 (m, 8H), 2.69-2.62 (m, 4H), 2.49 (br s, 2H), 2.34 (s, 3H), 2.23-2.20 (m, 3H), 1.93-1.87 (m, 4H). Mixture of rotamers.
Example 71	2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 73 and 6	HPLC: (System 1, Method D) Rt = 7.39 min, m/z 735.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.22 (br s, 1H), 7.38-7.33 (m, 1H), 7.19-7.10 (m, 1H), 6.87-6.85 (m, 1H), 4.62-4.38 (m, 1H), 4.18 (s, 1H), 3.86 (br s, 1H), 3.58-3.55 (m, 1H), 3.52 (br s, 1H), 3.45-3.38 (m, 3H), 3.31 (br s, 2H), 3.28 (s, 3H), 3.23 (br s, 1H), 3.17-3.05 (m, 3H), 2.93-2.91 (m, 1H), 2.87-2.82 (m, 1H), 2.73-2.69 (m, 2H), 2.68-2.54 (m, 4H), 2.38 (s, 3H), 2.24-2.20 (m, 3H), 1.57-1.54 (m, 2H), 1.50 (s, 3H), 1.44 (br s, 2H), 0.91-0.88 (m, 2H), 0.66-0.59 (m, 1H), 0.55-0.49 (m, 1H). Mixture of rotamers.

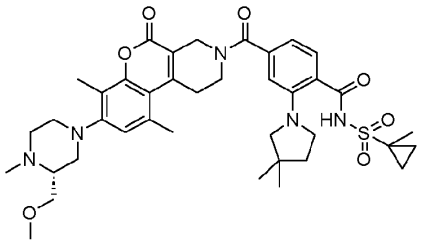
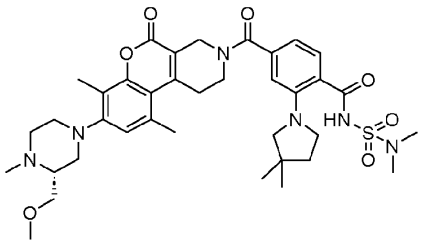
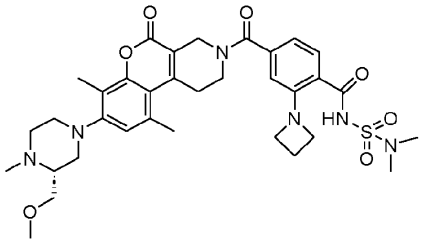
Example 72	2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 74 and 6	HPLC: (System 1, Method D) Rt = 7.55 min, m/z 724.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.21 (br s, 1H), 7.39-7.37 (m, 1H), 7.20-7.10 (m, 1H), 6.86-6.84 (m, 1H), 4.64-4.37 (m, 1H), 4.18 (s, 1H), 3.86 (br s, 1H), 3.58-3.54 (m, 1H), 3.45-3.42 (m, 2H), 3.39-3.38 (m, 2H), 3.29 (br s, 2H), 3.27-3.23 (m, 4H), 3.16-3.13 (m, 2H), 3.09-3.04 (m, 1H), 2.90-2.80 (m, 8H), 2.73-2.69 (m, 2H), 2.66-2.62 (m, 2H), 2.58 (br s, 1H), 2.43 (br s, 1H), 2.35 (s, 3H), 2.23-2.20 (m, 3H), 1.57-1.54 (m, 2H), 0.66-0.59 (m, 1H), 0.55-0.49 (m, 1H). Mixture of rotamers.
Example 73	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 76 and 6	HPLC: (System 1, Method D) Rt = 7.12 min, m/z 749.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (br s, 1H), 7.15-7.14 (m, 1H), 6.87-6.77 (m, 2H), 4.62-4.37 (m, 1H), 4.26-4.16 (m, 3H), 3.85 (br s, 1H), 3.58-3.55 (m, 1H), 3.44-3.36 (m, 2H), 3.28 (s, 3H), 3.22-3.05 (m, 4H), 2.94-2.82 (m, 2H), 2.36-2.53 (m, 6H), 2.39 (s, 3H), 2.24-2.20 (m, 3H), 1.74-1.69 (m, 4H), 1.47 (s, 3H), 1.43-1.39 (m, 6H), 0.90 (br s, 2H). Mixture of rotamers.
Example 74	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 77 and 6	HPLC: (System 1, Method D) Rt = 7.17 min, m/z 739.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.54 (br s, 1H), 7.18-7.16 (m, 1H), 6.88-6.78 (m, 2H), 4.61-4.36 (m, 1H), 4.25-4.15 (m, 3H), 3.85 (br s, 1H), 3.58-3.54 (m, 1H), 3.44-3.37 (m, 2H), 3.27 (s, 3H), 3.22 (br s, 1H), 3.16-3.04 (m, 3H), 2.91-2.80 (m, 8H), 2.69-2.62 (m, 4H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.23-2.20 (m, 3H), 1.73-1.68 (m, 4H), 1.44-1.40 (m, 4H). Mixture of rotamers.

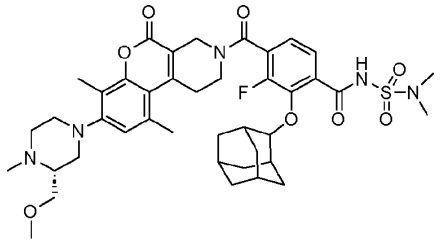
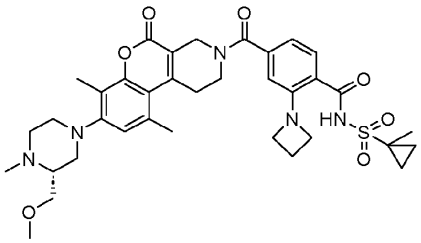
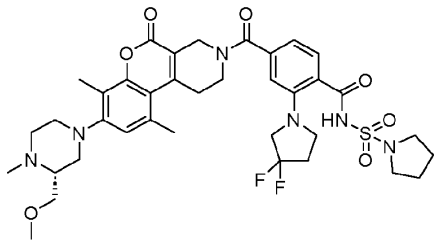
Example 75	(*R*)-2-(3,3-difluoropiperidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 54 and 6	HPLC: (System 1, Method D) Rt = 7.94 min, m/z 756.1 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.70 (br s, 1H), 7.85-7.80 (m, 1H), 7.55-7.48 (m, 1H), 7.39-7.34 (m, 1H), 6.85 (s, 1H), 4.49 (br s, 1H), 4.30 (br s, 1H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.45-3.34 (m, 3H), 3.27 (s, 3H), 3.21 (br s, 2H), 3.16-3.13 (m, 1H), 3.06 (br s, 3H), 2.88-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.50-2.47 (m, 2H), 2.33 (s, 3H), 2.24-2.19 (m, 3H), 2.04 (br s, 2H), 1.88 (br s, 2H), 1.49-1.45 (m, 5H), 0.93 (br s, 2H). Mixture of rotamers.
Example 76	(*R*)-2-(3,3-difluoropiperidin-1-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 79 and 6	HPLC: (System 1, Method D) Rt = 7.34 min, m/z 773.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (br s, 1H), 7.48-7.42 (m, 1H), 7.32-7.23 (m, 1H), 6.87-6.85 (m, 1H), 4.65-4.50 (m,1H), 4.20 (br s, 1H), 3.87 (br s, 1H), 3.59-3.53 (m, 1H), 3.46-3.43 (m, 2H), 3.43-3.38 (m, 2H), 3.35-3.28 (m, 3H), 3.28-3.11 (m, 6H), 3.10-3.00 (m, 1H), 2.97-2.83 (m, 1H), 2.80-2.62 (m, 4H), 2.62 (br s, 2H), 2.50-2.25 (br s, 3H), 2.24-2.20 (m, 3H), 2.05-1.90 (m, 2H), 1.82-1.75 (m, 2H), 1.45 (s, 3H), 1.40 (br s, 2H), 0.84 (br s, 2H). Mixture of rotamers.
Example 77	(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 55 and 6	HPLC: (System 1, Method D) Rt = 8.34 min, m/z 745.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.65 (br s, 1H), 7.88-7.86 (m, 1H), 7.56-7.49 (m, 1H), 7.41-7.39 (m, 1H), 6.85 (s, 1H), 4.49 (br s, 1H), 4.29 (br s, 1H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.47-3.36 (m, 3H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H), 3.05 (br s, 3H), 2.88 (s, 6H), 2.84-2.79 (m, 2H), 2.69-2.60 (m, 4H), 2.46-2.43 (m, 2H), 2.32 (s, 3H), 2.24-2.19 (m, 3H), 2.05 (br s, 2H), 1.88 (br s, 2H). Mixture of rotamers.

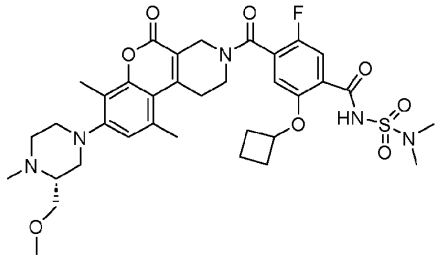
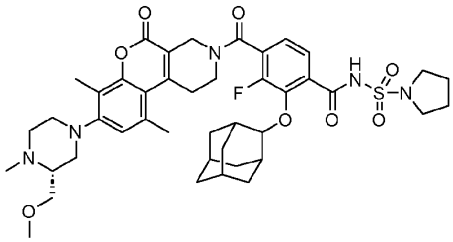
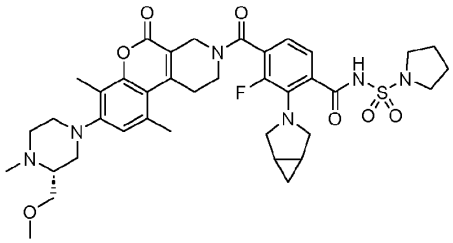
Example 78	(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 80 and 6	HPLC: (System 1, Method D) Rt = 7.46 min, m/z 762.6 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.90 (br s, 1H), 7.53-7.47 (m, 1H), 7.38-7.27 (m, 1H), 6.87-6.85 (d, J = 7.6 Hz, 1H), 4.70-4.30 (m, 1H), 4.19 (br s, 1H), 3.88 (br s, 1H), 3.58-3.55 (m, 1H), 3.48-3.45 (m, 1H), 3.46-3.38 (m, 3H), 3.34 (br s, 3H), 3.24-3.31 (m, 1H), 3.18-3.01 (m, 5H), 2.96-2.93 (m,1H), 2.87 (br s, 1H), 2.85 (s, 6H), 2.70-2.67 (m, 3H), 2.62-2.54 (m, 3H), 2.40 (br s, 3H), 2.23-2.20 (m, 3H), 2.08-1.98 (m, 2H), 1.85-1.75 (m, 2H). Mixture of rotamers.
Example 79	(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 82 and 6	HPLC: (System 1, Method D) Rt = 6.73 min, m/z 680.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 12.95 (br s, 1H), 7.65-7.58 (m, 1H), 7.31-7.21 (m, 1H), 7.16-7.06 (m, 1H), 6.84 (s, 1H), 4.48 (br s, 1H), 4.30 (br s, 1H), 3.83 (s, 1H), 3.58-3.51 (m, 2H), 3.50-3.27 (m, 3H), 3.26-3.19 (m, 3H), 3.15-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.86-2.79 (m, 8H), 2.69-2.60 (m, 4H), 2.48-2.42 (m, 2H), 2.33 (s, 3H), 2.24-2.18 (m, 3H), 1.50 (s, 3H), 1.48-1.44 (m, 2H), 0.95-0.91 (m, 2H). Mixture of rotamers.
Example 80	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 93 and 5	HPLC: (System 1, Method D) Rt = 6.78 min, m/z 741.4 $(M+H)^+$ $(ES)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.86 (br s, 1H), 7.57-7.53 (m, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.96 (s, 2H), 4.47 (br s, 1H), 4.29-4.28 (m, 3H), 3.90 (br s, 1H), 3.58-3.55 (m, 2H), 3.40.3.38 (m, 1H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.08-3.05 (m, 1H), 2.96 (br s, 2H), 2.87-2.83 (m, 8H), 2.69-2.63 (m, 1H), 2.54 (br s, 2H), 2.37 (s, 3H), 2.29-2.26 (m, 3H), 1.69 (br s, 4H), 1.42-1.40 (m, 4H).
Example 81	(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-	HPLC: (System 1, Method D) Rt = 6.85 min, m/z 741.5 $(M+H)^+$ $(ES)^+$.

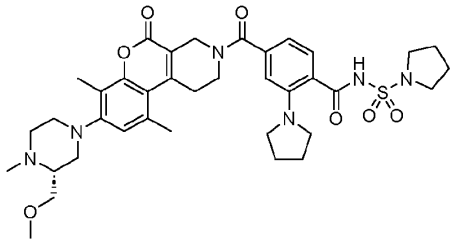
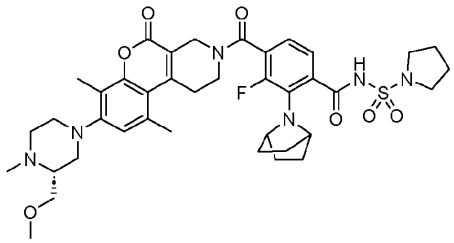
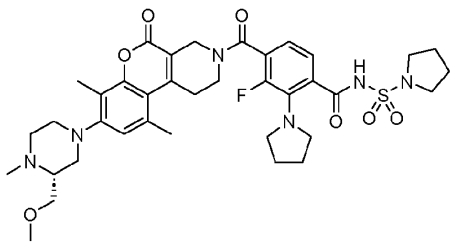
	dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 56 and 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.70 (br s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 6.90-6.86 (m, 3H), 4.47 (br s, 1H), 4.29 (br s, 1H), 3.82 (br s, 1H), 3.69-3.63 (m, 2H), 3.58-3.50 (m, 5H), 3.50-3.39 (m, 2H), 3.27 (s, 3H), 3.20-3.15 (m, 3H), 3.08-3.06 (m, 1H), 2.94-2.92 (m, 1H), 2.87-2.84 (m, 1H), 2.69-2.65 (m, 4H), 2.61-2.46 (m, 2H), 2.39 (s, 3H), 2.23-2.19 (m, 3H), 1.49 (s, 3H), 1.44 (br s, 2H), 0.87 (br s, 2H).
Example 82	(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 57 and 6	HPLC: (System 1, Method D) Rt = 6.81 min, m/z 730.5 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.70 (br s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.91-6.85 (m, 3H), 4.47 (br s, 1H), 4.29 (br s, 1H), 3.82 (br s, 1H), 3.65-3.58 (m, 2H), 3.57-3.54 (m, 1H), 3.50 (br s, 3H), 3.40-3.34 (m, 1H), 3.38 (br s, 2H), 3.27 (s, 3H), 3.19-3.14 (m, 3H), 3.10-3.04 (m, 1H), 2.95-2.89 (m, 1H), 2.86 (s, 6H), 2.85-2.79 (m, 1H), 2.69-2.64 (m, 4H), 2.57-2.53 (m, 2H), 2.37 (s, 3H), 2.24-2.19 (m, 3H).
Example 83	(*R*)-2-(cyclopropyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 59 and 6	HPLC: (System 1, Method D) Rt = 7.22 min, m/z 706.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 12.40 (br s, 1H), 7.62-7.56 (m, 1H), 7.45-7.39 (m, 1H), 7.15-7.09 (m, 1H), 6.85 (s, 1H), 4.48 (br s, 1H), 4.34 (br s, 1H), 3.84 (br s, 1H), 3.57-3.54 (m, 2H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.22 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.90 (s, 3H), 2.84-2.79 (m, 2H), 2.69-2.60 (m, 5H), 2.44-2.40 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.49 (s, 3H), 1.47-1.44 (m, 2H), 0.94 (br s, 2H), 0.72 (br s, 2H), 0.52 (br s, 2H). Mixture of rotamers.
Example 84	(*R*)-2-(cyclopropyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-	HPLC: (System 1, Method D) Rt = 7.51 min, m/z 695.4 (M+H)$^+$ (ES$^+$).

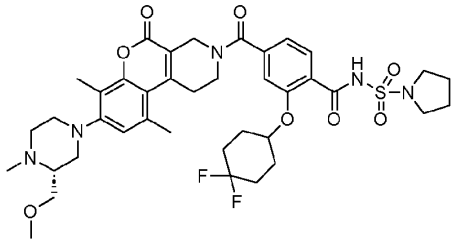
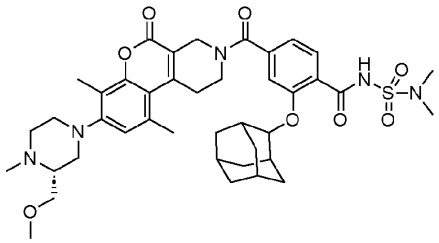
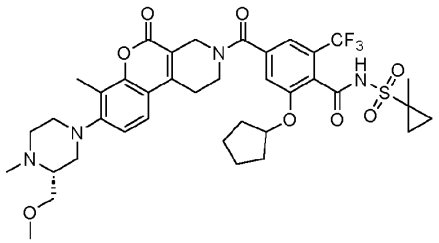
	1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 60 and 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 12.30 (br s, 1H), 7.64-7.58 (m, 1H), 7.45-7.39 (m, 1H), 7.16-7.08 (m, 1H), 6.85 (s, 1H), 4.48 (br s, 1H), 4.33 (br s, 1H), 3.84 (br s, 1H), 3.57-3.52 (m, 2H), 3.34 (br s, 1H), 3.26 (s, 3H), 3.22 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.03 (m, 1H), 2.88 (s, 9H), 2.85-2.79 (m, 2H), 2.69-2.61 (m, 5H), 2.45-2.39 (m, 2H), 2.32 (s, 3H), 2.24-2.19 (m, 3H), 0.72 (br s, 2H), 0.51 (br s, 2H). Mixture of rotamers.
Example 85	(*R*)-2-((4,4-difluorocyclohexyl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 32 and 6	UPLC: (System 3, Method K) Rt = 3.46 min, m/z 778.5 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.33-7.31 (m, 1H), 7.22-7.14 (m, 1H), 6.86-6.84 (m, 1H), 4.47-4.43 (m, 2H), 4.18 (s, 1H), 3.87 (t, J = 5.5 Hz, 1H), 3.58-3.54 (m, 1H), 3.46-3.39 (m, 3H), 3.27 (s, 3H), 3.17-3.05 (m, 3H), 2.93-2.82 (m, 2H), 2.77-2.76 (m, 6H), 2.69-2.62 (m, 6H), 2.38-2.32 (m, 3H), 2.23-2.20 (m, 3H), 2.11-2.04 (m, 2H), 1.90-1.86 (m, 6H). One exchangeable proton not observed. Mixture of rotamers.
Example 86	(*R*)-2-((4,4-difluorocyclohexyl)oxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 33 and 6	UPLC: (System 3, Method K) Rt = 3.41 min, m/z 789.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.31-7.29 (m, 1H), 7.21-7.14 (m, 1H), 6.87-6.85 (m, 1H), 4.49-4.49 (m, 2H), 4.19 (s, 1H), 3.87-3.86 (m, 1H), 3.62-3.55 (m, 1H), 3.47-3.43 (m, 2H), 3.28 (s, 3H), 3.18-3.06 (m, 3H), 2.88-2.83 (m, 1H), 2.69-2.62 (m, 6H), 2.41 (s, 3H), 2.24-2.17 (m, 3H), 2.17-2.04 (m, 2H), 1.91-1.86 (m, 8H), 1.45 (s, 3H), 1.32 (s, 2H), 0.85-0.76 (m, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 87	(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-	HPLC: (System 1, Method D) Rt = 7.23 min, m/z 734.0 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.85 (br s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.85 (s,

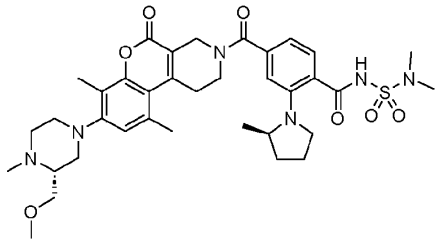
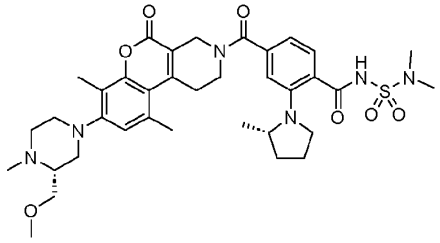
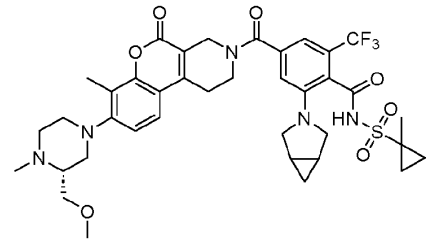
	chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 61 and 6	1H), 6.78-6.74 (m, 2H), 4.46 (br s, 1H), 4.30 (br s, 1H), 3.82 (br s, 1H), 3.57-3.54 (m, 2H), 3.34 (br s, 3H), 3.26 (s, 3H), 3.19-3.12 (m, 3H), 3.05-3.03 (m, 1H), 2.97-2.96 (m, 2H), 2.87-2.79 (m, 2H), 2.68-2.61 (m, 4H), 2.45 (br s, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 1.73 (br s, 2H), 1.51-1.48 (m, 5H), 1.06 (s, 6H), 0.91 (br s, 2H).
Example 88	(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 62 and 6	HPLC: (System 1, Method D) Rt = 7.32 min, m/z 723.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (br s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 6.77-6.73 (m, 2H), 4.46 (br s, 1H), 4.30 (br s, 1H), 3.82 (br s, 1H), 3.57-3.52 (m, 2H), 3.34 (br s, 3H), 3.26 (s, 3H), 3.20-3.12 (m, 3H), 3.05-2.96 (m, 3H), 2.88-2.79 (m, 8H), 2.68-2.60 (m, 4H), 2.42 (br s, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.74-1.71 (m, 2H), 1.07 (s, 6H).
Example 89	(*R*)-2-(azetidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 64 and 6	HPLC: (System 1, Method D) Rt = 6.44 min, m/z 681.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.70 (br s, 1H), 7.36-7.34 (m, 1H), 6.85 (s, 1H), 6.80-6.74 (m, 1H), 6.54-6.50 (m, 1H), 4.45 (br s, 1H), 4.28 (br s, 1H), 3.85-3.84 (m, 5H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.19-3.12 (m, 3H), 3.05-3.03 (m, 1H), 2.86-2.79 (m, 8H), 2.68-2.61 (m, 4H), 2.47-2.45 (m, 2H), 2.32-2.25 (m, 5H), 2.23-2.19 (m, 3H). Mixture of rotamers.
Example 90	2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC: (System 3, Method K) Rt = 4.38 min, m/z 792.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.29-7.27 (m, 1H), 7.14-7.10 (m, 1H), 6.86-6.84 (m, 1H), 4.51-4.38 (m, 2H), 4.17 (s, 1H), 3.87 (t, J = 5.7 Hz, 1H), 3.57-3.54 (m, 1H), 3.46-

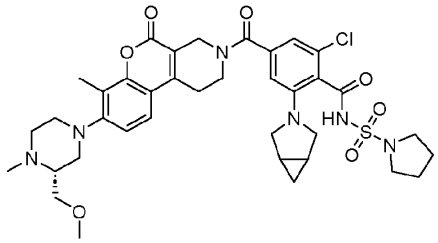
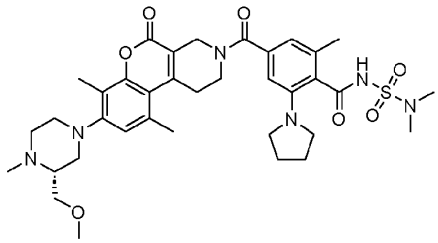
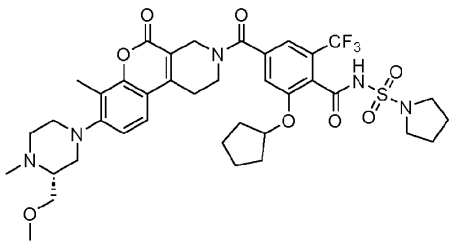
	 Synthesised from Intermediates 35 and 6	3.42 (m, 1H), 3.27 (s, 3H), 3.15-3.13 (m, 2H), 3.06-3.03 (m, 1H), 2.86-2.77 (m, 7H), 2.69-2.62 (m, 6H), 2.34-2.32 (m, 3H), 2.22 (m, 4H), 2.16-2.05 (m, 4H), 1.78-1.78 (m, 5H), 1.68-1.62 (m, 5H), 1.48 (t, J = 11.0 Hz, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 91	(*R*)-2-(azetidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 63 and 6	HPLC: (System 1, Method D) Rt = 6.51 min, m/z 692.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.71 (br s, 1H), 7.37-7.35 (m, 1H), 6.85 (s, 1H), 6.82-6.75 (m, 1H), 6.55-6.51 (m, 1H), 4.46 (br s, 1H), 4.28 (br s, 1H), 3.84-3.83 (m, 5H), 3.58-3.54 (m, 1H), 3.50 (br s, 1H), 3.37-3.34 (m, 1H), 3.29 (br s, 1H), 3.27 (s, 3H), 3.19-3.14 (m, 3H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.65 (m, 4H), 2.51 (br s, 1H), 2.36 (s, 3H), 2.33-2.26 (m, 2H), 2.24-2.19 (m, 3H), 1.49 (s, 3H), 1.47-1.44 (m, 2H), 0.93 (br s, 2H). Mixture of rotamers.
Example 92	(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 58 and 6	HPLC: (System 1, Method D) Rt = 7.05 min, m/z 757.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (br s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.93-6.84 (m, 3H), 4.47 (br s, 1H), 4.28 (br s, 1H), 3.82 (br s, 1H), 3.66-3.60 (m, 2H), 3.55-3.54 (m, 1H), 3.44 (br s, 3H), 3.51-3.49 (m, 4H), 3.37-3.34 (m, 2H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.16-3.12 (m, 1H), 3.06-3.02 (m, 1H), 2.88-2.79 (m, 2H), 2.69-2.61 (m, 4H), 2.55-2.53 (m, 1H), 2.48-2.40 (m, 2H), 2.33 (s, 3H), 2.24-2.17 (m, 3H), 1.87-1.83 (m, 4H).
Example 93	(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC (System 3, Method K) Rt = 3.87 min, m/z 714.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.75-7.70 (m, 1H), 6.96-6.89 (m, 1H), 6.80-6.78 (m, 1H), 4.89-4.77 (m, 1H), 4.52 (br s, 1H), 4.16 (br s, 1H), 3.88 (br s, 1H), 3.55-3.44

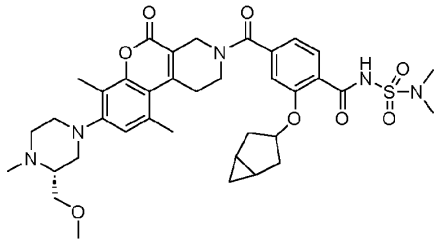
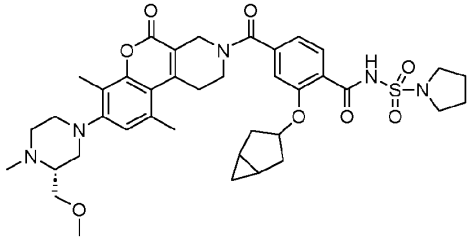
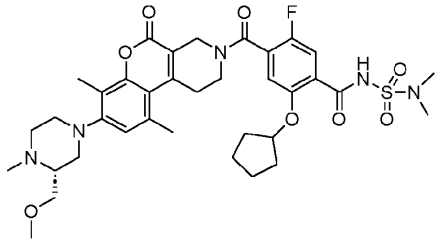
	 Synthesised from Intermediates 36 and 6	(m, 2H), 3.35-3.31 (m, 1H), 3.26 (s, 3H), 3.22-3.00 (m, 4H), 2.93 (s, 6H), 2.86-2.80 (m, 2H), 2.66-2.36 (m, 8H), 2.29-2.21 (m, 8H), 1.79-1.89 (m, 1H), 1.75-1.62 (m, 1H). One exchangeable proton not visible. Mixture of rotamers.
Example 94	2-((adamantan-2-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 34 and 6	UPLC: (System 3, Method K) Rt = 4.61 min, m/z 820.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.27-7.25 (m, 1H), 7.12-7.12 (m, 1H), 6.85-6.84 (m, 1H), 4.50-4.39 (m, 2H), 4.17 (br s, 1H), 3.87-3.87 (m, 1H), 3.57-3.53 (m, 1H), 3.46-3.39 (m, 2H), 3.25 (s, 3H), 3.14-3.11 (m, 2H), 3.04-3.01 (m, 1H), 2.84-2.79 (m, 2H), 2.71-2.64 (m, 3H), 2.60 (s, 3H), 2.44-2.32 (m, 3H), 2.29 (s, 3H), 2.23-2.13 (m, 6H), 2.08-2.05 (m, 2H), 1.79-1.79 (m, 9H), 1.68-1.61 (m, 4H), 1.50-1.44 (m, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 95	2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 75 and 6	HPLC: (System 1, Method D) Rt = 8.32 min, m/z 751.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.31 (br s, 1H), 7.41-7.36 (m, 1H), 7.20-7.11 (m, 1H), 6.86-6.84 (m, 1H), 4.60-4.38 (m, 1H), 4.18 (s, 1H), 3.86 (br s, 1H), 3.56-3.54 (m, 1H), 3.43-3.37 (m, 8H), 3.31-3.29 (m, 2H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.15-3.12 (m, 2H), 3.05-3.03 (m, 1H), 2.87-2.79 (m, 2H), 2.69-2.61 (m, 4H), 2.50-2.44 (m, 2H), 2.32 (s, 3H), 2.23-2.20 (m, 3H), 1.87-1.84 (m, 4H), 1.58-1.54 (m, 2H), 0.65-0.61 (m, 1H), 0.55-0.50 (m, 1H). Mixture of rotamers.
Example 96	(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.38 min, m/z 721.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (br s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.79-6.76 (m, 2H), 4.46 (br s, 1H),

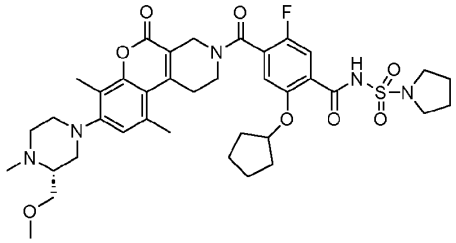
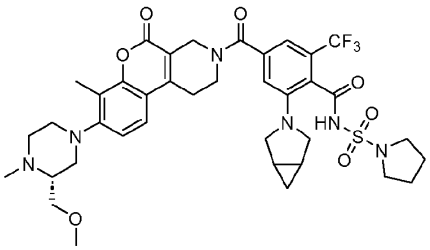
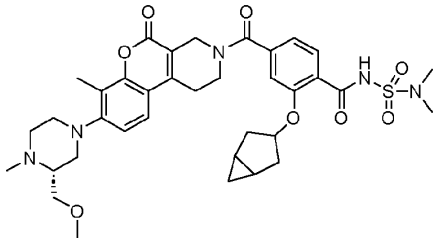
	 Synthesised from Intermediates 48 and 6	4.29 (br s, 1H), 3.82 (br s, 1H), 3.57-3.52 (m, 2H), 3.44-3.41 (m, 4H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.19 (br s, 6H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.78 (m, 2H), 2.68-2.59 (m, 4H), 2.42-2.40 (m, 2H), 2.30 (s, 3H), 2.23-2.19 (m, 3H), 1.91 (br s, 4H), 1.87-1.83 (m, 4H).
Example 97	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 78 and 6	HPLC: (System 1, Method D) Rt = 7.73 min, m/z 765.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (br s, 1H), 7.18-7.15 (m, 1H), 6.89-6.79 (m, 2H), 4.61-4.37 (m, 1H), 4.18-4.15 (m, 3H), 3.86 (br s, 1H), 3.57-3.54 (m, 1H), 3.44-3.34 (m, 6H), 3.26 (s, 3H), 3.22 (br s, 1H), 3.15-3.12 (m, 2H), 3.05-3.02 (m, 1H), 2.87-2.79 (m, 2H), 2.69-2.62 (m, 4H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 1.84-1.80 (m, 4H), 1.74-1.68 (m, 4H), 1.45-1.40 (m, 4H). Mixture of rotamers.
Example 98	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 72 and 6	HPLC: (System 1, Method D) Rt = 8.51 min, m/z 739.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.88 (br s, 1H), 7.44.738 (m, 1H), 7.13-7.10 (m, 1H), 6.86-6.84 (m, 1H), 4.59-4.41 (m, 1H), 4.19 (s, 1H), 3.86 (br s, 1H), 3.57-3.53 (m, 1H), 3.47 (br s, 1H), 3.43-3.40 (m, 4H), 3.34 (br s, 1H), 3.33-3.30 (m, 4H), 3.26 (s, 3H), 3.23 (br s, 1H), 3.14-3.12 (m, 2H), 3.05-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.69-2.61 (m, 4H), 2.45-2.43 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.93-1.87 (m, 4H), 1.84-1.80 (m, 4H). Mixture of rotamers.
Example 99	(*R*)-2-((4,4-difluorocyclohexyl)oxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	UPLC: (System 3, Method K) Rt = 4.28 min, m/z 786.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.53-7.51 (m, 1H), 7.30-7.10 (m, 2H), 6.85 (s, 1H), 4.82 (br s, 1H), 4.48-4.29 (m, 2H), 3.84 (br s, 1H), 3.57-3.50 (m, 2H), 3.39-3.39 (m, 4H), 3.26 (s, 3H), 3.21 (br s, 2H),

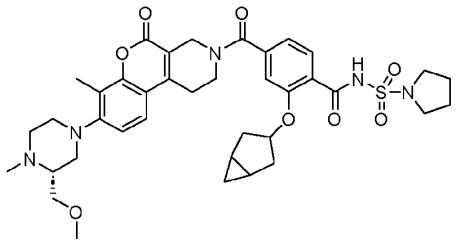
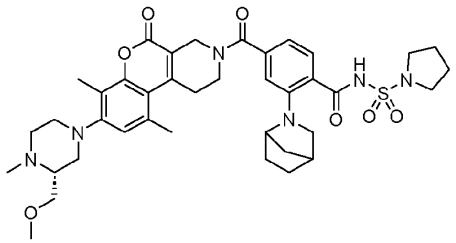
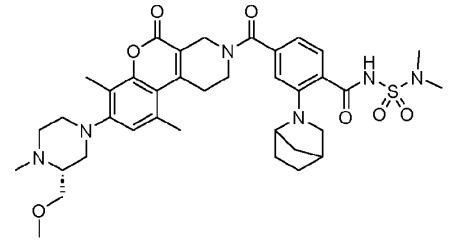
	 Synthesised from Intermediates 40 and 6	3.14-3.01 (m, 2H), 2.88-2.58 (m, 6H), 2.41-2.39 (m, 2H), 2.30 (s, 3H), 2.23-2.15 (m, 4H), 1.91-1.90 (m, 8H), 1.85-1.82 (m, 4H). One exchangeable proton not observed. Mixture of rotamers.
Example 100	2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 41 and 6	UPLC: (System 3, Method K) Rt = 4.92 min, m/z 774.4 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59-7.53 (m, 1H), 7.27-7.08 (m, 2H), 6.85 (s, 1H), 4.78-4.70 (m, 1H), 4.47-4.28 (m, 2H), 3.84 (br s, 1H), 3.57-3.49 (m, 2H), 3.26 (s, 3H), 3.21-3.21 (m, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.86 (s, 6H), 2.68-2.59 (m, 6H), 2.42-2.39 (m, 1H), 2.30-2.28 (m, 3H), 2.23-2.19 (m, 3H), 2.12 (br s, 4H), 1.91-1.71 (m, 10H), 1.52-1.49 (m, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 101	(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 43 and 5	HPLC: (System 1, Method D) Rt = 7.08 min, m/z 775.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (br s, 1H), 7.60-7.53 (m, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 7.09-7.07 (m, 1H), 5.04 (br s, 1H), 4.51 (br s, 1H), 4.29 (br s, 1H), 3.94 (br s, 1H), 3.59-3.55 (m, 2H), 3.38 (br s, 2H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.08-3.06 (m, 1H), 2.98 (br s, 2H), 2.93-2.83 (m, 2H), 2.69-2.64 (m, 1H), 2.51 (br s, 1H), 2.37 (s, 3H), 2.30-2.26 (m, 3H), 1.87-1.86 (m, 2H), 1.77-1.74 (m, 4H), 1.56 (br s, 2H), 1.50 (s, 3H), 1.42 (br s, 2H), 0.89 (br s, 2H). Mixture of rotamers.
Example 102	*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide	HPLC: (System 1, Method D) Rt = 7.75 min, m/z 709.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.56 (br s, 1H), 7.56-7.51 (m, 1H), 7.08-7.00 (m, 1H), 6.98-6.89 (m, 1H), 6.84 (s, 1H), 4.50-4.44 (m, 1H), 4.32-4.31 (m, 1H), 3.91-3.71

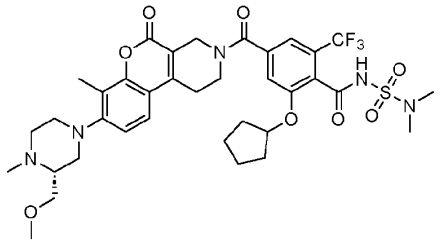
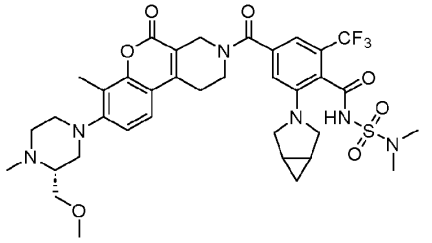
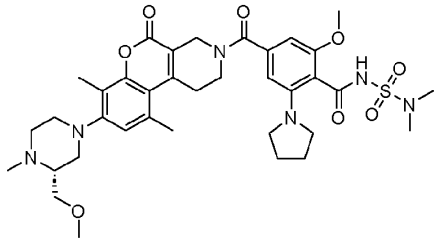
	 Synthesised from Intermediates 65 and 6	(m, 2H), 3.57-3.45 (m, 3H), 3.34 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.97 (br s, 1H), 2.88 (s, 6H), 2.84-2.79 (m, 2H), 2.68-2.59 (m, 4H), 2.44-2.42 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 4H), 1.92 (br s, 1H), 1.78 (br s, 1H), 1.60-1.56 (m, 1H), 1.10 (br s, 3H). Mixture of rotamers.
Example 103	*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide  Synthesised from Intermediates 66 and 6	HPLC: (System 1, Method D) Rt = 7.75 min, m/z 709.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.58 (br s, 1H), 7.56-7.51 (m, 1H), 7.08-6.89 (m, 2H), 6.85 (s, 1H), 4.54-4.30 (m, 2H), 3.91-3.71 (m, 2H), 3.57-3.45 (m, 3H), 3.34 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.88 (s, 6H), 2.84-2.79 (m, 2H), 2.68-2.60 (m, 4H), 2.45-2.43 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 4H), 1.92 (br s, 1H), 1.80-1.77 (m, 1H), 1.60-1.57 (m, 1H), 1.10 (br s, 3H). Mixture of rotamers.
Example 104	2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 97 and 5	HPLC: (System 1, Method D) Rt = 7.07 min, m/z 772.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.89 (br s, 1H), 7.56-7.54 (m, 1H), 7.12-7.07 (m, 3H), 4.48 (br s, 1H), 4.29 (br s, 1H), 3.92 (br s, 1H), 3.59-3.57 (m, 4H), 3.42 (br s, 1H), 3.32-3.28 (m, 6H), 3.20-3.17 (m, 1H), 3.10-3.08 (m, 1H), 2.96-2.85 (m, 4H), 2.70-2.68 (m, 2H), 2.42 (br s, 3H), 2.30-2.26 (m, 3H), 1.60 (br s, 2H), 1.46 (s, 3H), 1.42 (br s, 2H), 0.85 (br s, 2H), 0.61-0.56 (m, 1H), 0.41 (br s, 1H).
Example 105	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.12 min, m/z 753.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.98 (br s, 1H), 7.56 (br s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 6.67 (s, 1H), 4.46 (br s, 1H), 4.28 (br s, 1H), 3.89 (br s, 1H), 3.59-

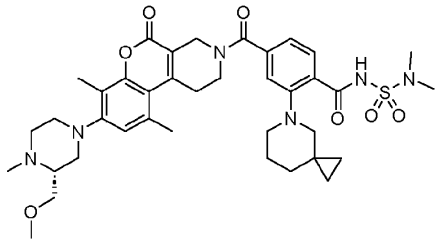
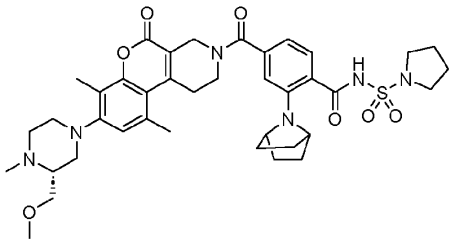
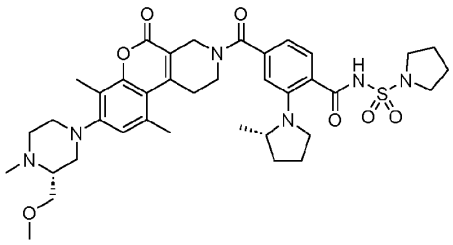
	 Synthesised from Intermediates 94 and 5	3.54 (m, 4H), 3.45 (br s, 4H), 3.38 (br s, 1H), 3.33 (br s, 2H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.95 (br s, 2H), 2.87-2.85 (m, 2H), 2.67-2.61 (m, 1H), 2.47 (br s, 2H), 2.33 (s, 3H), 2.29-2.26 (m, 3H), 1.88-1.84 (m, 4H), 1.65-1.64 (m, 2H), 0.66-0.65 (m, 1H), 0.24 (br s, 1H).
Example 106	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methyl-6-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 96 and 6	HPLC: (System 1, Method D) Rt = 6.87 min, m/z 709.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.78 (br s, 1H), 6.84 (s, 1H), 6.63-6.59 (m, 2H), 4.45-4.32 (m, 2H), 3.80 (br s, 1H), 3.57-3.54 (m, 2H), 3.37-3.34 (m, 5H), 3.26 (s, 3H), 3.19-3.12 (m, 3H), 3.06-3.02 (m, 1H), 2.89 (s, 6H), 2.84-2.79 (m, 2H), 2.67-2.60 (m, 4H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.22-2.20 (m, 3H), 1.89 (br s, 4H).
Example 107	(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 44 and 5	HPLC: (System 1, Method D) Rt = 7.53 min, m/z 790.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (br s, 1H), 7.60-7.49 (m, 2H), 7.38-7.36 (m, 1H), 7.09-7.07 (m, 1H), 5.04 (br s, 1H), 4.51-4.28 (m, 2H), 3.94 (br s, 1H), 3.58-3.54 (m, 2H), 3.42-3.40 (m, 4H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.16-3.13 (m, 1H), 3.06-2.98 (m, 3H), 2.87-2.82 (m, 2H), 2.65-2.60 (m, 1H), 2.46-2.44 (m, 2H), 2.3-2.25 (m, 6H), 1.87-1.84 (m, 6H), 1.75-1.72 (m, 4H), 1.57 (br s, 2H). Mixture of rotamers.
Example 108	2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide. Mixture of diastereomers cis/trans 83/17.	HPLC: (System 1, Method D) Rt = 7.73 min, m/z 722.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.35 (br s, 1H), 7.55-7.48 (m, 1H), 7.26-7.03 (m, 2H), 6.85 (s, 1H), 5.03-4.67 (m, 1H), 4.48-4.28 (m, 2H), 3.83 (br s, 1H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.34 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H),

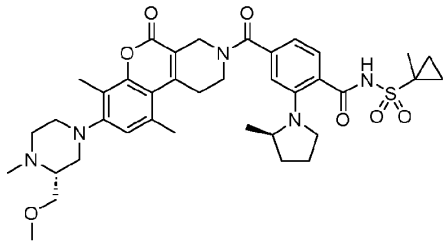
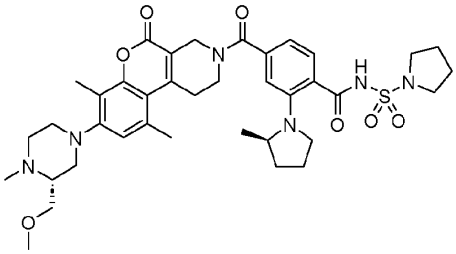
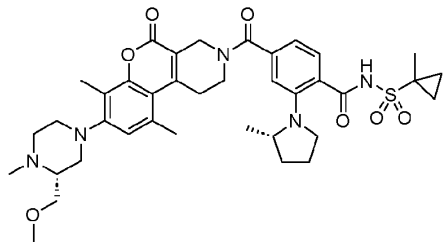
	 Synthesised from Intermediates 38 and 6	3.05-3.02 (m, 1H), 2.88-2.86 (m, 6H), 2.83-2.79 (m, 2H), 2.69-2.60 (m, 4H), 2.50-2.42 (m, 2H), 2.31 (s, 4H), 2.24-2.19 (m, 4H), 1.96-1.90 (m, 2H), 1.34 (br s, 2H), 0.56-0.17 (m, 2H). Mixture of diastereomers and rotamers.
Example 109	2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide Mixture of diastereomers cis/trans 90/10.  Synthesised from Intermediates 39 and 6	HPLC: (System 1, Method D) Rt = 8.67 min, m/z 748.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.54-7.47 (m, 1H), 7.29-7.02 (m, 2H), 6.85 (s, 1H), 5.01-4.67 (m, 1H), 4.48-4.28 (m, 2H), 3.83 (br s, 1H), 3.57-3.54 (m, 1H), 3.53 (br s, 1H), 3.49-3.43 (m, 4H), 3.30 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.02 (m, 1H), 2.84-2.79 (m, 2H), 2.69-2.59 (m, 4H), 2.42-2.40 (m, 2H), 2.36-2.19 (m, 8H), 1.95-1.86 (m, 6H), 1.33 (br s, 2H), 0.51-0.17 (m, 2H). Mixture of diastereomers and rotamers.
Example 110	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 164 and 6	UPLC: (System 3, Method K) Rt = 4.13 min, m/z 728.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.47-7.44 (m, 1H), 7.26-7.15 (m, 1H), 6.86-6.84 (m, 1H), 4.98-4.92 (m, 1H), 4.52-4.52 (m, 1H), 4.19 (s, 1H), 3.87 (t, J = 5.3 Hz, 1H), 3.57-3.54 (m, 1H), 3.47-3.47 (m, 2H), 3.25 (s, 3H), 3.15-3.03 (m, 3H), 2.86-2.80 (m, 8H), 2.69-2.61 (m, 6H), 2.33 (s, 3H), 2.27-2.20 (m, 3H), 1.91-1.70 (m, 7H), 1.58-1.57 (m, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 111	(*R*)-2-(cyclopentyloxy)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	UPLC: (System 3, Method K) Rt = 4.51 min, m/z 754.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.44-7.44 (m, 1H), 7.24-7.13 (m, 1H), 6.86-6.84 (m, 1H), 4.97-4.91 (m, 1H), 4.52-4.52 (m, 1H), 4.19 (br s, 1H), 3.87 (t, J = 5.7 Hz, 1H), 3.57-3.53 (m, 1H), 3.49-3.46 (m, 1H), 3.40-

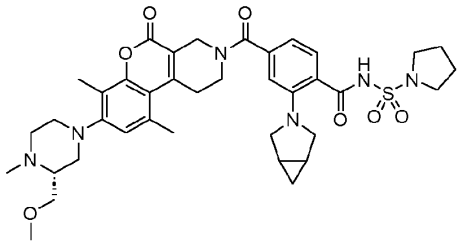
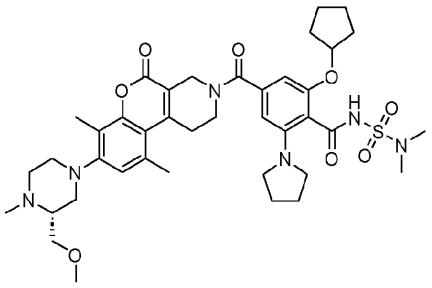
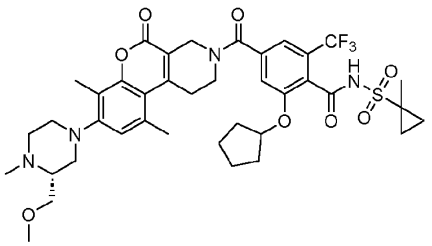
	 Synthesised from Intermediates 165 and 6	3.39 (m, 4H), 3.26 (s, 3H), 3.14-3.01 (m, 3H), 2.84-2.79 (m, 2H), 2.69-2.59 (m, 6H), 2.42-2.40 (m, 2H), 2.29 (s, 3H), 2.24-2.21 (m, 3H), 1.91-1.67 (m, 10H), 1.58-1.57 (m, 2H). One exchangeable proton not observed. Mixture of rotamers.
Example 112	2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 98 and 5	HPLC: (System 1, Method D) Rt = 7.49 min, m/z 787.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (br s, 1H), 7.59-7.54 (m, 1H), 7.14-7.07 (m, 3H), 4.48 (br s, 1H), 4.28 (br s, 1H), 3.92 (br s, 1H), 3.58-3.55 (m, 4H), 3.39-3.33 (m, 6H), 3.30 (br s, 2H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.95 (br s, 2H), 2.88-2.83 (m, 2H), 2.67-2.62 (m, 1H), 2.50 (br s, 1H), 2.34 (s, 3H), 2.29-2.26 (m, 3H), 1.87-1.84 (m, 4H), 1.61 (br s, 2H), 0.62-0.60 (m, 1H), 0.40 (br s, 1H).
Example 113	2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide. Mixture of diastereomers cis/trans 76/24.  Synthesised from Intermediates 38 and 5	HPLC: (System 1, Method D) Rt = 7.55 min, m/z 708.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.32 (br s, 1H), 7.59-7.48 (m, 2H), 7.22-7.02 (m, 3H), 5.01-4.66 (m, 1H), 4.49-4.27 (m, 2H), 3.93 (br s, 1H), 3.58-3.54 (m, 2H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.06-3.03 (m, 1H), 2.96 (br s, 2H), 2.90-2.88 (m, 6H), 2.85-2.82 (m, 2H), 2.66-2.60 (m, 1H), 2.47-2.42 (m, 2H), 2.32 (s, 3H), 2.29-2.25 (m, 5H), 1.95-1.89 (m, 2H), 1.34 (br s, 2H), 0.55-0.17 (m, 2H). Mixture of diastereomers and rotamers.
Example 114	2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide. Mixture of diastereomers cis/trans 85/15.	HPLC: (System 1, Method D) Rt = 8.45 min, m/z 734.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.57-7.47 (m, 2H), 7.23-7.00 (m, 3H), 5.00-4.69 (m, 1H), 4.49-4.27 (m, 2H), 3.93 (br s, 1H), 3.57-3.54 (m, 2H), 3.45-

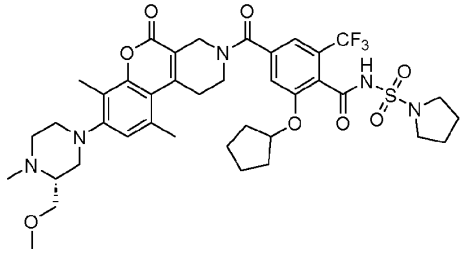
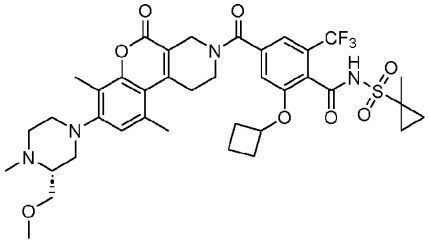
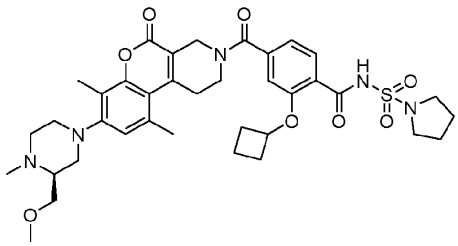
	 Synthesised from Intermediates 39 and 5	3.43 (m, 4H), 3.36 (br s, 1H), 3.26 (s, 3H), 3.16-3.13 (m, 1H), 3.05-3.03 (m, 1H), 2.96 (br s, 2H), 2.86-2.81 (m, 2H), 2.64-2.59 (m, 1H), 2.43-2.38 (m, 2H), 2.33-2.25 (m, 8H), 1.93-1.86 (m, 6H), 1.33 (br s, 2H), 0.50-0.16 (m, 2H). Mixture of diastereomers and rotamers.
Example 115	2-(2-azabicyclo[2.2.1]heptan-2-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 67 and 6	HPLC: (System 1, Method D) Rt = 7.59 min, m/z 747.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.77 (br s, 1H), 7.32-7.31 (m, 1H), 6.84 (s, 1H), 6.81-6.68 (m, 2H), 4.48-4.40 (m, 1H), 4.30-4.19 (m, 2H), 3.82 (br s, 1H), 3.57-3.53 (m, 3H), 3.46-3.44 (m, 2H), 3.39-3.37 (m, 2H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.78 (m, 2H), 2.68-2.59 (m, 4H), 2.54 (br s, 1H), 2.41-2.39 (m, 3H), 2.29 (s, 3H), 2.23-2.19 (m, 3H), 1.89-1.80 (m, 4H), 1.71-1.66 (m, 4H), 1.50-1.48 (m, 1H), 1.23 (br s, 1H). Mixture of rotamers.
Example 116	2-(2-azabicyclo[2.2.1]heptan-2-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 68 and 6	HPLC: (System 1, Method D) Rt = 7.03 min, m/z 721.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.74 (br s, 1H), 7.33-7.32 (d, J = 7.2 Hz, 1H), 6.85 (s, 1H), 6.81-6.68 (m, 2H), 4.52-4.45 (m, 1H), 4.30-4.19 (m, 2H), 3.82 (br s, 1H), 3.57-3.49 (m, 3H), 3.36 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H), 3.04-3.02 (m, 1H), 2.87 (s, 6H), 2.84-2.79 (m, 2H), 2.69-2.60 (m, 4H), 2.56 (br s, 1H), 2.45-2.40 (m, 3H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.71-1.64 (m, 4H), 1.50-1.48 (m, 1H), 1.23 (br s, 1H). Mixture of rotamers.
Example 117	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide	HPLC: (System 1, Method D) Rt = 7.10 min, m/z 764.0 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (br s, 1H), 7.60-7.53 (m, 1H), 7.50 (br s, 1H), 7.37-7.36 (m, 1H), 7.09-7.07 (m, 1H), 5.04

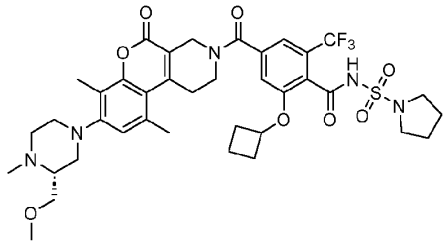
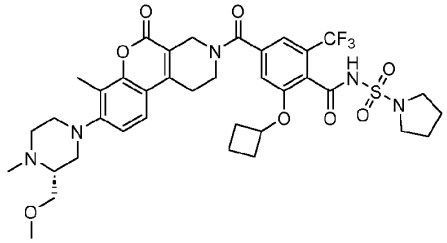
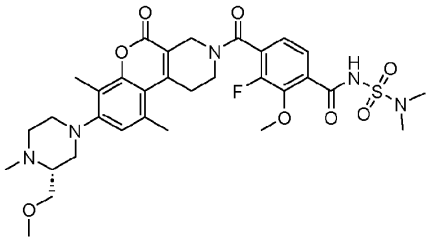
	 Synthesised from Intermediates 45 and 5	(br s, 1H), 4.51 (br s, 1H), 4.28 (br s, 1H), 3.94 (br s, 1H), 3.58-3.55 (m, 2H), 3.38 (br s, 1H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.98 (br s, 2H), 2.85-2.80 (m, 8H), 2.65 (t, J = 10.6 Hz, 1H), 2.50 (br s, 2H), 2.34 (s, 3H), 2.30-2.25 (m, 3H), 1.88-1.87 (m, 2H), 1.77-1.74 (m, 4H), 1.57 (br s, 2H).
Example 118	2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 99 and 5	HPLC: (System 1, Method D) Rt = 7.21 min, m/z 761.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.76 (br s, 1H), 7.56-7.54 (m, 1H), 7.12-7.07 (m, 3H), 4.48 (br s, 1H), 4.29 (br s, 1H), 3.92 (br s, 1H), 3.60-3.55 (m, 4H), 3.40 (br s, 1H), 3.34-3.29 (m, 2H), 3.28 (s, 3H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 1H), 2.95-2.90 (m, 3H), 2.87-2.82 (m, 7H), 2.68-2.66 (m, 1H), 2.58-2.55 (m, 2H), 2.33 (s, 3H), 2.30-2.26 (m, 3H), 1.61-1.60 (m, 2H), 0.62-0.57 (m, 1H), 0.39-0.38 (m, 1H). Mixture of rotamers.
Example 119	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 95 and 6	HPLC: (System 1, Method D) Rt = 7.14 min, m/z 725.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.75 (br s, 1H), 6.84 (s, 1H), 6.44-6.40 (m, 1H), 6.35-6.33 (m, 1H), 4.56-4.32 (m, 2H), 3.79-3.76 (m, 4H), 3.57-3.53 (m, 2H), 3.33-3.26 (m, 8H), 3.19 (br s, 2H), 3.14-3.11 (m, 1H), 3.03-3.01 (m, 1H), 2.89 (s, 6H), 2.83-2.78 (m, 2H), 2.68-2.58 (m, 4H), 2.41-2.38 (m, 2H), 2.29 (s, 3H), 2.23-2.20 (m, 3H), 1.88 (br s, 4H). Mixture of rotamers.
Example 120	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(5-azaspiro[2.5]octan-5-yl)benzamide	HPLC: (System 1, Method D) Rt = 9.56 min, m/z 735.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.82 (br s, 1H), 8.10-8.08 (m, 1H), 7.72-7.65 (m, 1H), 7.50-7.43 (m, 1H), 6.85 (s, 1H), 4.49-4.26 (m, 2H), 3.84 (br s, 1H), 3.57-3.53 (m, 1H), 3.48 (br s, 1H), 3.31 (br s, 1H), 3.26

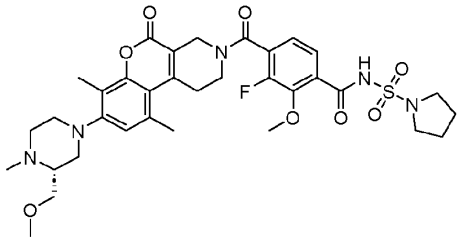
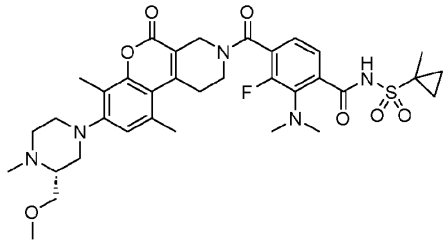
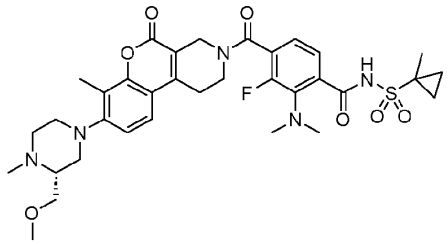
	 Synthesised from Intermediates 69 and 6	(s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.08-3.02 (m, 3H), 2.90 (br s, 7H), 2.86-2.78 (m, 3H), 2.68-2.58 (m, 4H), 2.39 (br s, 2H), 2.29 (s, 3H), 2.23-2.19 (m, 3H), 1.87 (br s, 2H), 1.44 (br s, 2H), 0.48 (br s, 2H), 0.40 (br s, 2H). Mixture of rotamers.
Example 121	(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 123	HPLC: (System 1, Method D) Rt = 8.17 min, m/z 747.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (br s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.07-7.03 (m, 1H), 6.98-6.94 (m, 1H), 6.84 (s, 1H), 4.47 (br s, 1H), 4.27 (br s, 1H), 4.11-4.07 (m, 2H), 3.84 (br s, 1H), 3.57-3.53 (m, 1H), 3.47 (br s, 1H), 3.44-3.41 (m, 4H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.79 (m, 2H), 2.68-2.59 (m, 4H), 2.42-2.40 (m, 2H), 2.30 (s, 3H), 2.23-2.19 (m, 3H), 1.86-1.83 (m, 4H), 1.73 (br s, 4H), 1.44 (br s, 4H).
Example 122	4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 124	HPLC: (System 1, Method D) Rt = 8.62 min, m/z 735.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.59 (br s, 1H), 7.52 (br s, 1H), 7.07-6.89 (m, 2H), 6.84 (s, 1H), 4.50-4.30 (m, 2H), 3.90-3.70 (m, 2H), 3.57-3.50 (m, 2H), 3.46-3.39 (m, 5H), 3.33 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-2.95 (m, 2H), 2.83-2.78 (m, 2H), 2.68-2.59 (m, 4H), 2.41-2.39 (m, 2H), 2.29 (s, 3H), 2.23-2.13 (m, 4H), 1.91-1.74 (m, 6H), 1.60-1.55 (m, 1H), 1.09 (br s, 3H).
Example 123	4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide	HPLC: (System 1, Method D) Rt = 7.58 min, m/z 720.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.78 (br s, 1H), 7.58-7.52 (m, 1H), 7.11-6.91 (m, 2H), 6.84 (s, 1H), 4.55-4.31 (m, 2H), 3.92-3.70 (m, 2H), 3.57-3.44 (m, 3H), 3.37 (br s,

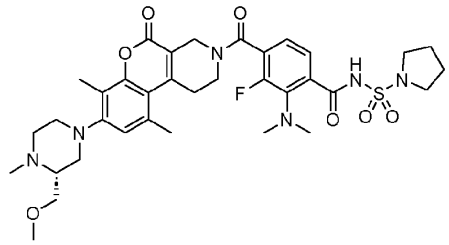
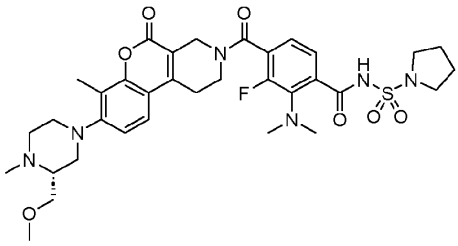
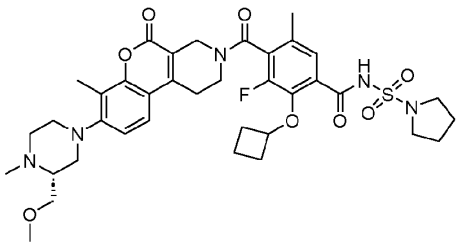
	 Synthesised from Intermediates 6 and 127	1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-2.98 (m, 2H), 2.87-2.79 (m, 2H), 2.68-2.60 (m, 4H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 4H), 1.92-1.91 (m, 1H), 1.79 (br s, 1H), 1.61-1.56 (m, 1H), 1.54-1.47 (m, 4H), 1.45-1.39 (m, 1H), 1.11 (br s, 3H), 0.97-0.90 (m, 2H). Mixture of rotamers.
Example 124	4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 126	HPLC: (System 1, Method D) Rt = 8.61 min, m/z 735.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.57 (br s, 1H), 7.55-7.50 (m, 1H), 7.07-6.89 (m, 2H), 6.84 (s, 1H), 4.50-4.30 (m, 2H), 3.92-3.69 (m, 2H), 3.57-3.53 (m, 2H), 3.47-3.41 (m, 5H), 3.31 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-2.95 (m, 2H), 2.84-2.78 (m, 2H), 2.68-2.58 (m, 4H), 2.42-2.40 (m, 2H), 2.29 (s, 3H), 2.23-2.19 (m, 4H), 1.91-1.78 (m, 6H), 1.60-1.55 (m, 1H), 1.09 (br s, 3H). Mixture of rotamers.
Example 125	4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide  Synthesised from Intermediates 6 and 125	HPLC: (System 1, Method D) Rt = 7.54 min, m/z 720.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.79 (br s, 1H), 7.58-7.53 (m, 1H), 7.11-6.92 (m, 2H), 6.85 (s, 1H), 4.50-4.31 (m, 2H), 3.90-3.70 (m, 2H), 3.57-3.44 (m, 3H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-2.98 (m, 2H), 2.87-2.79 (m, 2H), 2.68-2.60 (m, 4H), 2.46-2.43 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 4H), 1.92-1.91 (m, 1H), 1.79-1.75 (m, 1H), 1.61-1.56 (m, 1H), 1.52-1.46 (m, 4H), 1.43-1.39 (m, 1H), 1.10 (br s, 3H), 0.97-0.90 (m, 2H). Mixture of rotamers.
Example 126	2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.62 min, m/z 733.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.83 (br s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.85-6.81 (m, 3H), 4.46-4.29 (m, 2H), 3.81 (br s, 1H), 3.57-3.53 (m, 1H), 3.49-3.43 (m, 7H), 3.34

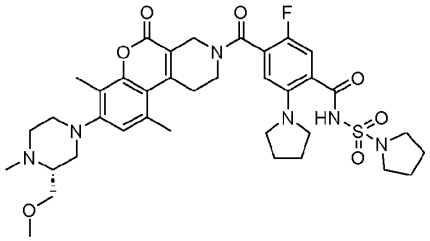
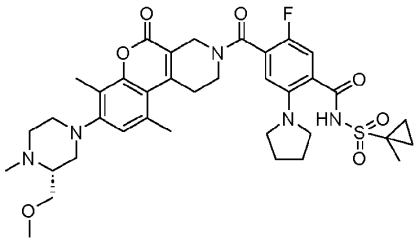
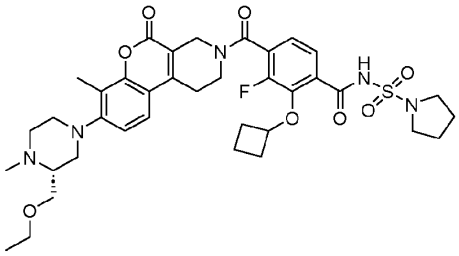
	 Synthesised from Intermediates 6 and 128	(br s, 1H), 3.26-3.24 (m, 4H), 3.19-3.12 (m, 4H), 3.04-3.02 (m, 1H), 2.84-2.79 (m, 2H), 2.68-2.59 (m, 4H), 2.43-2.41 (m, 2H), 2.30 (s, 3H), 2.23-2.19 (m, 3H), 1.88-1.85 (m, 4H), 1.64 (br s, 2H), 0.64-0.63 (m, 1H), 0.31 (br s, 1H).
Example 127	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 6 and 131	HPLC: (System 1, Method D) Rt = 8.61 min, m/z 779.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.67 (br s, 1H), 6.84 (s, 1H), 6.41-6.36 (m, 1H), 6.30-6.29 (m, 1H), 4.94-4.82 (m, 1H), 4.45 (br s, 1H), 4.33 (br s, 1H), 3.80 (br s, 1H), 3.57-3.53 (m, 2H), 3.33-3.32 (m, 1H), 3.30-3.23 (m, 7H), 3.20 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.88 (s, 6H), 2.83-2.78 (m, 2H), 2.69-2.58 (m, 4H), 2.40-2.38 (m, 2H), 2.28 (s, 3H), 2.23-2.19 (m, 3H), 1.88 (br s, 6H), 1.75-1.72 (m, 4H), 1.54 (br s, 2H). Mixture of rotamers.
Example 128	(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 43	HPLC: (System 1, Method D) Rt = 7.26 min, m/z 789.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (br s, 1H), 7.52-7.50 (m, 1H), 7.37-7.36 (m, 1H), 6.85 (s, 1H), 5.06-5.05 (m, 1H), 4.50 (br s, 1H), 4.30 (br s, 1H), 3.84 (br s, 1H), 3.58-3.51 (m, 2H), 3.33 (br s, 2H), 3.27 (s, 3H), 3.22 (br s, 2H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.63 (m, 4H), 2.51 (br s, 1H), 2.36 (s, 3H), 2.24-2.20 (m, 3H), 1.88 (br s, 2H), 1.78-1.74 (m, 4H), 1.57 (br s, 2H), 1.50 (s, 3H), 1.42 (br s, 2H), 0.89 (br s, 2H).
Example 129	(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide	HPLC: (System 1, Method D) Rt = 7.73 min, m/z 804.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (br s, 1H), 7.52-7.50 (m, 1H), 7.38-7.36 (m, 1H), 6.85 (s, 1H), 5.07-5.04 (m, 1H), 4.50 (br s, 1H), 4.29 (br s, 1H), 3.84 (br s, 1H),

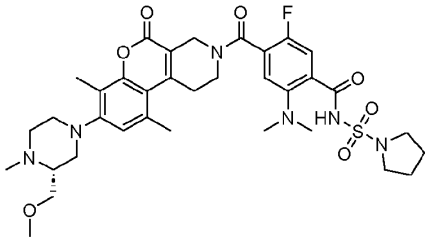
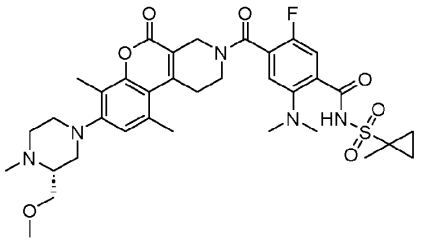
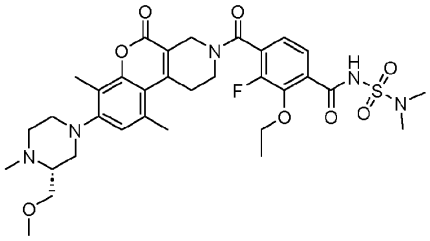
	 Synthesised from Intermediates 6 and 44	3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.41 (br s, 4H), 3.36 (br s, 1H), 3.26 (s, 3H), 3.22 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.84-2.79 (m, 2H), 2.69-2.60 (m, 4H), 2.44-2.40 (m, 2H), 2.31 (s, 3H), 2.24-2.20 (m, 3H), 1.87-1.84 (m, 6H), 1.75-1.72 (m, 4H), 1.58 (br s, 2H). Mixture of rotamers.
Example 130	(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 129	HPLC: (System 1, Method D) Rt = 7.10 min, m/z 775.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (br s, 1H), 7.39 (br s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.90-4.89 (m, 1H), 4.50 (br s, 1H), 4.29 (br s, 1H), 3.84 (br s, 1H), 3.57-3.55 (m, 1H), 3.50 (br s, 1H), 3.40-3.38 (m, 1H), 3.28 (s, 3H), 3.21-3.15 (m, 3H), 3.08-3.05 (m, 1H), 2.93-2.91 (m, 1H), 2.87-2.82 (m, 1H), 2.69 (br s, 2H), 2.65-2.56 (m, 4H), 2.44-2.38 (m, 5H), 2.24-2.20 (m, 3H), 2.10-2.05 (m, 2H), 1.81-1.79 (m, 1H), 1.63-1.60 (m, 1H),1.53 (s, 3H), 1.43 (br s, 2H), 0.89 (br s, 2H).
Example 131	(*S*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 166 and 10	UPLC (System 3, Method K) Rt = 4.19 min, m/z 722.5 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.32 (br s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.10-7.06 (m, 1H), 6.98-6.95 (m, 1H), 6.80 (s, 1H), 4.84-4.76 (m, 1H), 4.44 (br s, 1H), 4.23 (br s, 1H), 3.79 (br s, 1H), 3.51 (dd, J = 10.1, 4.1 Hz, 1H), 3.45-3.39 (m, 5H), 3.32-3.29 (m, 1H), 3.22 (s, 3H), 3.16 (br s, 2H), 3.10-3.04 (m, 1H), 3.00-2.97 (m, 1H), 2.80-2.75 (m, 2H), 2.64-2.55 (m, 4H), 2.38-2.36 (m, 4H), 2.25 (s, 3H), 2.19-2.15 (m, 3H), 2.07-2.03 (m, 2H), 1.87-1.76 (m, 5H), 1.63-1.58 (m, 1H).
Example 132	(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide	HPLC: (System 1, Method D) Rt = 7.42 min, m/z 790.0 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (br s, 1H), 7.41-7.39 (m, 1H), 7.34-7.32 (m, 1H), 6.85 (s, 1H), 4.91-4.87 (m, 1H), 4.50

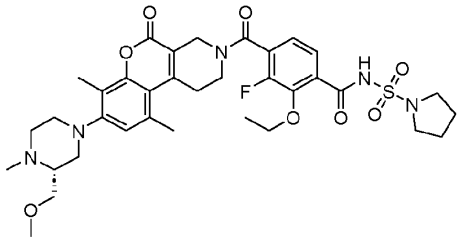
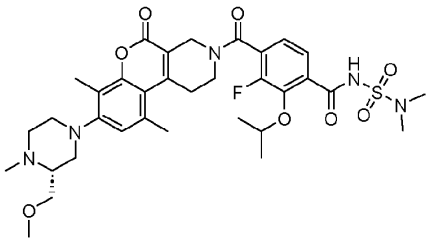
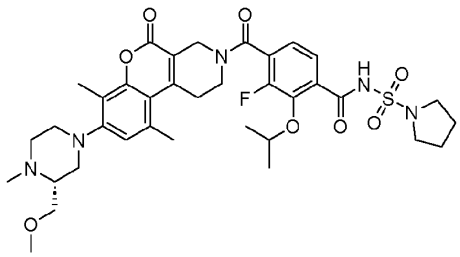
	 Synthesised from Intermediates 6 and 130	(br s, 1H), 4.27 (br s, 1H), 3.84 (br s, 1H), 3.58-3.54 (m, 1H), 3.48-3.43 (m, 5H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.03 (m, 1H), 2.87-2.79 (m, 2H), 2.69-2.63 (m, 4H), 2.45 (br s, 4H), 2.32 (s, 3H), 2.24-2.19 (m, 3H), 2.06-2.01 (m, 2H), 1.88-1.80 (m, 5H), 1.65-1.60 (m, 1H). Mixture of rotamers.
Example 133	(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 5 and 130	HPLC: (System 1, Method D) Rt = 7.26 min, m/z 775.9 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (br s, 1H), 7.58-7.52 (m, 1H), 7.40-7.39 (m, 1H), 7.31 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 4.88-4.87 (m, 1H), 4.50 (br s, 1H), 4.26 (br s, 1H), 3.94 (br s, 1H), 3.58-3.54 (m, 2H), 3.44-3.43 (m, 4H), 3.34 (br s, 1H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.06-3.04 (m, 1H), 2.99-2.96 (m, 2H), 2.85-2.82 (m, 2H), 2.66-2.61 (m, 1H), 2.48-2.45 (m, 4H), 2.33 (s, 3H), 2.30-2.25 (m, 3H), 2.05-2.01 (m, 2H), 1.86-1.79 (m, 5H), 1.64-1.61 (m, 1H). Mixture of rotamers.
Example 134	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 153	UPLC: (System 3, Method K) Rt = 3.60 min, m/z 674.80 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.34-7.32 (m, 1H), 7.23-7.15 (m, 1H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.19 (br s, 1H), 3.94-3.87 (m, 4H), 3.58-3.56 (m, 1H), 3.49-3.40 (m, 2H), 3.28-3.06 (m, 8H), 2.97-2.94 (m, 1H), 2.88-2.86 (m, 1H), 2.82-2.81 (m, 6H), 2.69-2.62 (m, 6H), 2.41 (br s, 2H), 2.24-2.20 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 135	(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.70 min, m/z 700.7 $(M+H)^+$ $(ES)^+$. 1H NMR (400 MHz, DMSO-d_6) δ: 7.33-7.31 (m, 1H), 7.25-7.17 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.19 (br s, 1H), 3.94-3.86 (m, 4H), 3.58-3.54 (m, 1H), 3.48-

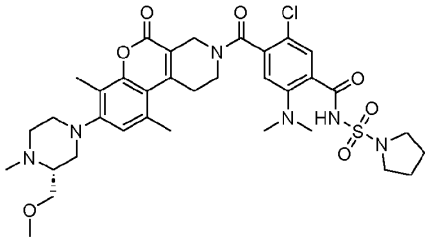
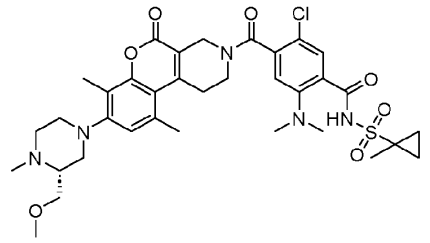
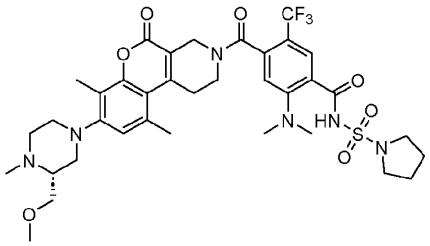
	 Synthesised from Intermediates 6 and 154	3.34 (m, 10H), 3.23-3.04 (m, 4H), 2.92-2.81 (m, 2H), 2.69-2.62 (m, 5H), 2.36 (br s, 3H), 2.24-2.20 (m, 3H), 1.86-1.82 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 136	(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 104	HPLC: (System 1, Method D) Rt = 6.88 min, m/z 698.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.81 (br s, 1H), 7.52-7.45 (m, 1H), 7.33-7.21 (m, 1H), 6.86-6.84 (m, 1H), 4.55-4.45 (m, 1H), 4.20 (s, 1H), 3.88 (br s, 1H), 3.58-3.54 (m, 1H), 3.48 (br s, 1H), 3.41-3.37 (m, 1H), 3.27 (s, 3H), 3.24 (br s, 1H), 3.17-3.14 (m, 2H), 3.08-3.05 (m, 1H), 2.93-2.90 (m, 1H), 2.86-2.85 (m, 4H), 2.81 (m, 3H), 2.70-2.62 (m, 4H), 2.55 (br s, 2H), 2.37 (s, 3H), 2.24-2.20 (m, 3H), 1.51 (m, 3H), 1.45-1.43 (m, 2H), 0.93-0.91 (m, 2H). Mixture of rotamers.
Example 137	(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 5 and 104	HPLC: (System 1, Method D) Rt = 6.88 min, m/z 684.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.86 (br s, 1H), 7.60-7.45 (m, 2H), 7.31-7.21 (m, 1H), 7.011-7.06 (m, 1H), 4.54-4.52 (m, 1H), 4.19 (s, 1H), 3.98-3.97 (m, 1H), 3.58-3.55 (m, 2H), 3.41-3.37 (m, 1H), 3.27 (s, 3H), 3.18-3.16 (m, 1H), 3.09-3.00 (m, 2H), 2.91-2.90 (m, 2H), 2.85-2.80 (m, 7H), 2.70-2.65 (m, 1H), 2.55 (br s, 2H), 2.37 (s, 3H), 2.30-2.26 (m, 3H), 1.52-1.51 (m, 3H), 1.46-1.43 (m, 2H), 0.92 (br s, 2H). Mixture of rotamers.
Example 138	(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.79 min, m/z 713.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.73 (br s, 1H), 7.53-7.46 (m, 1H), 7.36-7.24 (m, 1H), 6.86-6.84 (m, 1H), 4.61-4.42 (m, 1H), 4.19 (s, 1H), 3.87 (br s, 1H), 3.54-3.51 (m,

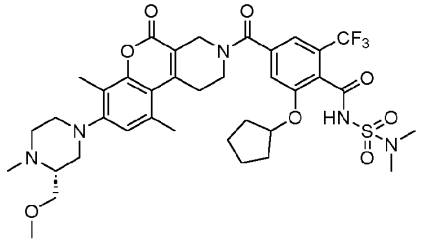
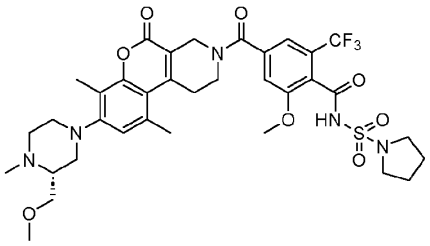
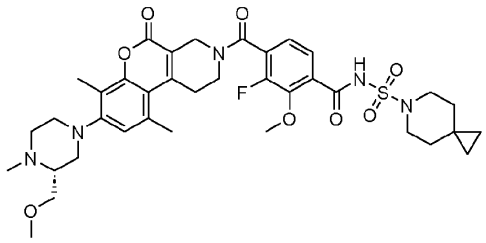
	 Synthesised from Intermediates 6 and 105	1H), 3.45-3.42 (m, 5H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.24 (br s, 1H), 3.15-3.12 (m, 2H), 3.05-3.03 (m, 1H), 2.87-2.79 (m, 8H), 2.69-2.61 (m, 4H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.23-2.20 (m, 3H), 1.86-1.85 (m, 4H). Mixture of rotamers.
Example 139	(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 5 and 105	HPLC: (System 1, Method D) Rt = 7.47 min, m/z 699.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.75 (br s, 1H), 7.60-7.45 (m, 2H), 7.33-7.23 (m, 1H), 7.10-7.05 (m, 1H), 4.55-4.52 (m, 1H), 4.19 (s, 1H), 3.97 (br s, 1H), 3.58-3.54 (m, 2H), 3.45-3.42 (m, 4H), 3.37-3.33 (m, 1H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.06-3.00 (m, 2H), 2.90-2.85 (m, 3H), 2.83-2.78 (m, 6H), 2.66-2.61 (m, 1H), 2.47-2.44 (m, 2H), 2.32 (s, 3H), 2.29-2.26 (m, 3H), 1.86-1.84 (m, 4H). Mixture of rotamers.
Example 140	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 5 and 132	HPLC: (System 1, Method D) Rt = 7.43 min, m/z 740.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (br s, 1H), 7.60-7.49 (m, 1H), 7.25-7.22 (m, 1H), 7.11-7.06 (dd, J = 10.8, 8.4 Hz, 1H), 4.66-4.49 (m, 2H), 4.10-3.91 (m, 2H), 3.58-3.55 (m, 1H), 3.53-3.50 (m, 1H), 3.43-3.37 (m, 5H), 3.34 (br s, 1H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.09-3.01 (m, 2H), 2.91-2.83 (m, 3H), 2.68-2.63 (m, 1H), 2.57 (br s, 1H), 2.35 (s, 3H), 2.29-2.26 (m, 3H), 2.24-2.19 (m, 3H), 2.17-2.03 (m, 4H), 1.87-1.84 (m, 4H), 1.69-1.64 (m, 1H), 1.49-1.40 (m, 1H). Mixture of rotamers.
Example 141	(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 8.01 min, m/z 739.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.91 (br s, 1H), 7.27-7.24 (m, 1H), 6.86-6.84 (m, 1H), 6.80-6.71 (m, 1H), 4.49 (br s, 1H), 4.20 (s, 1H), 3.86 (br s, 1H), 3.57-3.54 (m,

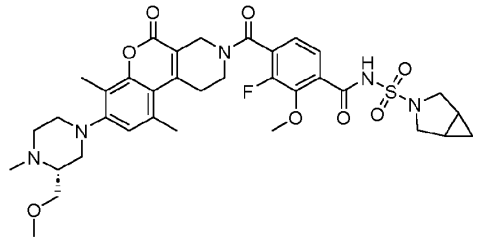
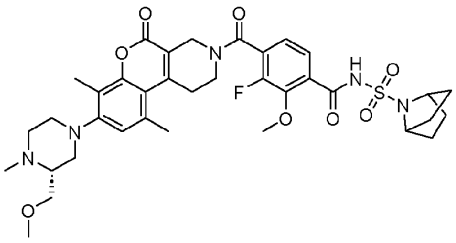
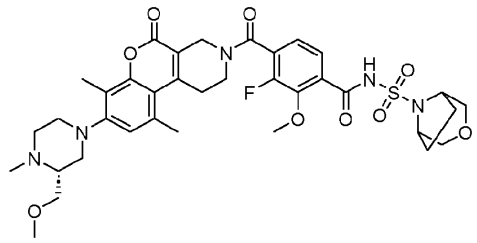
	 Synthesised from Intermediates 6 and 137	1H), 3.47-3.46 (m, 1H), 3.43-3.40 (m, 4H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.22 (br s, 1H), 3.17-3.13 (m, 6H), 3.05-3.02 (m, 1H), 2.87-2.79 (m, 2H), 2.69-2.61 (m, 4H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.23-2.19 (m, 3H), 1.90-1.83 (m, 8H). Mixture of rotamers.
Example 142	(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide  Synthesised from Intermediates 6 and 136	HPLC: (System 1, Method D) Rt = 6.91 min, m/z 724.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.89 (br s, 1H), 7.26-7.23 (m, 1H), 6.86-6.85 (m, 1H), 6.80-71 (m, 1H), 4.50 (br s, 1H), 4.20 (s, 1H), 3.86 (br s, 1H), 3.58-3.54 (m, 1H), 3.48-3.47 (m, 1H), 3.45-3.41 (m, 1H), 3.28 (s, 3H), 3.23-3.15 (m, 7H), 3.08-3.05 (m, 1H), 2.93-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.59-2.53 (m, 2H), 2.38 (s, 3H), 2.24-2.20 (m, 3H), 1.90-1.89 (m, 4H), 1.49 (s, 3H), 1.43 (br s, 2H), 0.90-0.88 (m, 2H). Mixture of rotamers.
Example 143	(*R*)-2-cyclobutoxy-4-(8-(3-(ethoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 140	HPLC: (System 1, Method D) Rt = 8.31 min, m/z 740.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.60-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.16 (m, 1H), 7.10-7.06 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (br s, 1H), 3.99-3.96 (m, 1H), 3.63-3.59 (m, 1H), 3.56-3.53 (m, 1H), 3.50-3.38 (m, 7H), 3.19-3.16 (m, 1H), 3.08-3.05 (m, 1H), 2.99 (br s, 1H), 2.89-2.84 (m, 3H), 3.68-2.63 (m, 1H), 2.52 (br s, 2H), 2.36 (s, 3H), 2.30-2.18 (m, 5H), 2.13-2.07 (m, 2H), 1.88-1.84 (m, 4H), 1.71-1.68 (m, 1H), 1.50-1.41 (m, 1H), 1.13-1.09 (m, 3H). Mixture of rotamers.
Example 144	(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.66 min, m/z 713.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.00 (br s, 1H), 7.56-7.50 (m, 1H), 7.46-7.31 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.20 (s, 1H), 3.87 (br s, 1H), 3.57-3.54 (m,

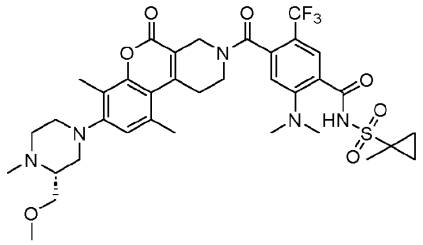
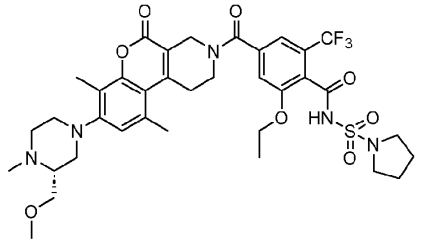
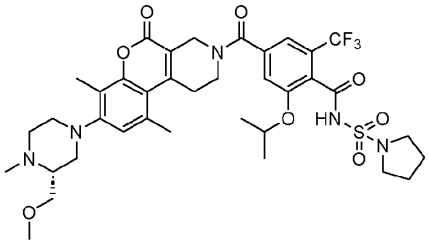
	 Synthesised from Intermediates 6 and 134	1H), 3.48-3.41 (m, 5H), 3.36 (br s, 1H), 3.26 (s, 3H), 3.23 (br s, 1H), 3.15-3.12 (m, 2H), 3.05-3.02 (m, 1H), 2.86-2.82 (m, 2H), 2.78-7.75 (m, 6H), 2.69-2.61 (m, 4H), 2.45-2.43 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.86-1.83 (m, 4H). Mixture of rotamers.
Example 145	(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 135	HPLC: (System 1, Method D) Rt = 6.88 min, m/z 698.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.33 (br s, 1H), 7.55-7.33 (m, 2H), 6.86-6.85 (m, 1H), 4.52 (br s, 1H), 4.20 (s, 1H), 3.88 (br s, 1H), 3.58-3.54 (m, 1H), 3.49-3.46 (m, 1H), 3.40-3.36 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.83 (m, 2H), 2.80 (d, J = 13.2 Hz, 6H), 2.69-2.62 (m, 4H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.36 (s, 3H), 2.24-2.20 (m, 3H), 1.50 (s, 3H), 1.45-1.42 (m, 2H), 0.91-0.89 (m, 2H). Mixture of rotamers.
Example 146	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 160	UPLC: (System 3, Method K) Rt = 3.73 min, m/z 688.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.78-7.72 (m, 1H), 7.24-7.17 (m, 1H), 6.82-6.80 (m, 1H), 4.55 (s, 1H), 4.41-4.30 (m, 2H), 4.20 (s, 1H), 3.91 (t, J = 5.7 Hz, 1H), 3.58-3.55 (m, 1H), 3.50-3.47 (m, 1H), 3.39-3.33 (m, 1H), 3.29 (s, 3H), 3.23-3.03 (m, 4H), 2.95 (s, 6H), 2.89-2.82 (m, 2H), 2.68-2.61 (m, 4H), 2.48-2.42 (m, 2H), 2.33-2.23 (m, 6H), 1.48-1.41 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 147	(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.85 min, m/z 714.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.79-7.73 (m, 1H), 7.24-7.17 (m, 1H), 6.82-6.81 (m, 1H), 4.55 (br s, 1H), 4.41-4.32 (m, 2H), 4.20 (br s, 1H), 3.91 (t, J = 5.7 Hz, 1H), 3.58-3.54 (m, 1H), 3.53-3.47 (m, 5H), 3.38-

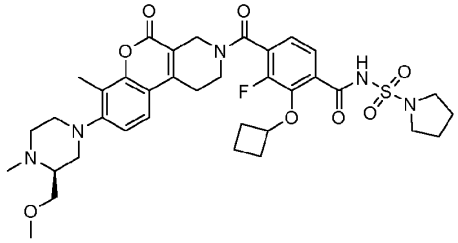
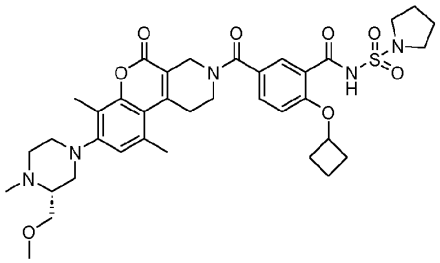
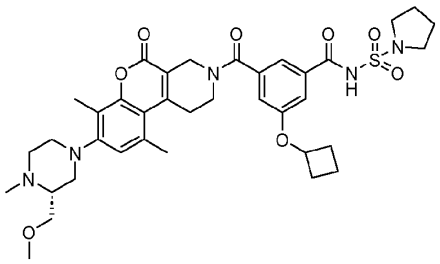
	 Synthesised from Intermediates 6 and 161	3.34 (m, 1H), 3.29 (s, 3H), 3.24-3.03 (m, 4H), 2.88-2.83 (m, 2H), 2.68-2.61 (m, 4H), 2.47-2.41 (m, 2H), 2.32-2.24 (m, 6H), 1.92-1.88 (m, 4H), 1.48-1.42 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 148	(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 162	UPLC: (System 3, Method K) Rt = 3.81 min, m/z 702.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.80-7.74 (m, 1H), 7.25-7.18 (m, 1H), 6.82-6.81 (m, 1H), 4.80-4.69 (m, 1H), 4.55 (br s, 1H), 4.20 (br s, 1H), 3.91 (t, J = 4.8 Hz, 1H), 3.58-3.55 (m, 1H), 3.49-3.47 (m, 1H), 3.38-3.33 (m, 1H), 3.29 (s, 3H), 3.22-3.03 (m, 4H), 2.95-2.95 (m, 6H), 2.89-2.83 (m, 2H), 2.68-2.61 (m, 4H), 2.47-2.42 (m, 2H), 2.33-2.24 (m, 6H), 1.41-1.36 (m, 6H). One exchangeable proton not visible. Mixture of rotamers.
Example 149	(*R*)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 163	UPLC: (System 3, Method K) Rt = 3.95 min, m/z 728.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.81-7.75 (m, 1H), 7.25-7.18 (m, 1H), 6.81-6.80 (m, 1H), 4.82-4.69 (m, 1H), 4.54 (br s, 1H), 4.19 (br s, 1H), 3.91 (br s, 1H), 3.58-3.47 (m, 6H), 3.38-3.34 (m, 1H), 3.29 (s, 3H), 3.23-3.02 (m, 4H), 2.88-2.82 (m, 2H), 2.67-2.60 (m, 4H), 2.47-2.41 (m, 2H), 2.32-2.23 (m, 6H), 1.92-1.88 (m, 4H), 1.41-1.37 (m, 6H). One exchangeable proton not visible. Mixture of rotamers.
Example 150	(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.52 min, m/z 729.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d^6) δ: 12.10 (br s, 1H), 7.52-7.47 (m, 1H), 7.13-7.02 (m, 1H), 6.87-6.84 (m, 1H), 4.66-4.36 (m, 1H), 4.10 (br s, 1H), 3.99-3.74 (m, 1H), 3.57-3.54 (m, 1H), 3.43-3.36 (m, 6H), 3.27 (s,

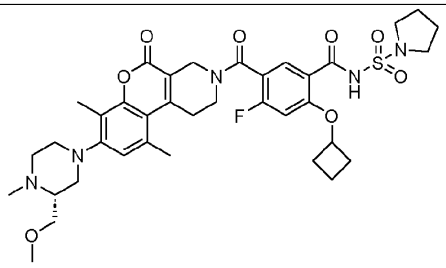
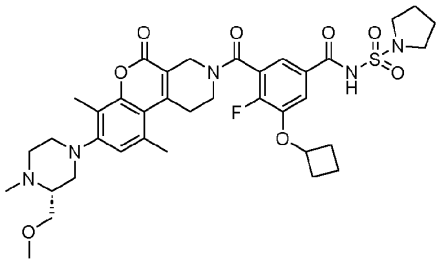
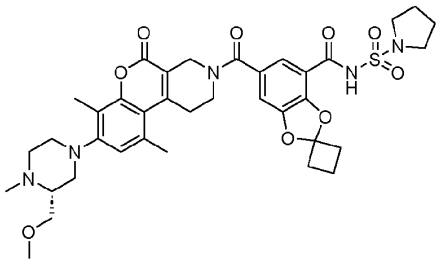
	 Synthesised from Intermediates 6 and 111	3H), 3.23-3.12 (m, 3H), 3.05-3.03 (m, 1H), 2.88-2.85 (m, 2H), 2.82-2.80 (m, 6H), 2.70-2.60 (m, 4H), 2.50-2.49 (m, 2H), 2.33 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H). Mixture of rotamers.
Example 151	(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 112	HPLC: (System 1, Method D) Rt = 6.98 min, m/z 714.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.09 (br s, 1H), 7.50-7.45 (m, 1H), 7.12-7.01 (m, 1H), 6.87-6.85 (m, 1H), 4.66-4.37 (m, 1H), 4.11 (br s, 1H), 4.01-3.73 (m, 1H), 3.58-3.55 (m, 1H), 3.45-3.38 (m, 2H), 3.28 (s, 3H), 3.21-3.05 (m, 4H), 2.99-2.87 (m, 2H), 2.84-2.82 (m, 6H), 2.70-2.55 (m, 6H), 2.39 (s, 3H), 2.24-2.20 (m, 3H), 1.49 (s, 3H), 1.43 (br s, 2H), 0.89 (br s, 2H). Mixture of rotamers.
Example 152	(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-5-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 108	HPLC: (System 1, Method D) Rt = 7.23 min, m/z 763.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.75 (br s, 1H), 7.60-7.56 (m, 1H), 6.96-6.84 (m, 2H), 4.72-4.13 (m, 2H), 3.98-3.54 (m, 2H), 3.42-3.37 (m, 6H), 3.27 (s, 3H), 3.21-2.98 (m, 4H), 2.94-2.93 (m, 6H), 2.90-2.80 (m, 2H), 2.69-2.60 (m, 4H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.24-2.19 (m, 3H), 1.86-1.83 (m, 4H). Mixture of rotamers.
Example 153	(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide	HPLC: (System 1, Method D) Rt = 7.93 min, m/z 778.0 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.79 (br s, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 6.8 Hz, 1H), 6.85 (s, 1H), 5.07-5.06 (m, 1H), 4.50 (br s, 1H), 4.30 (br s, 1H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.38-3.37 (m, 1H), 3.27 (s, 3H), 3.22

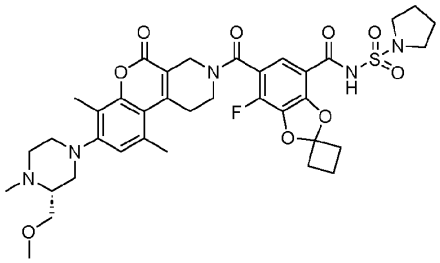
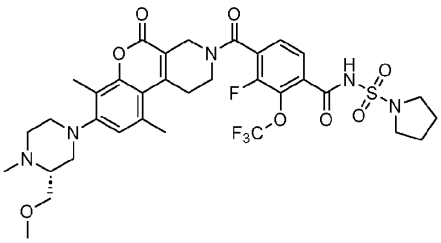
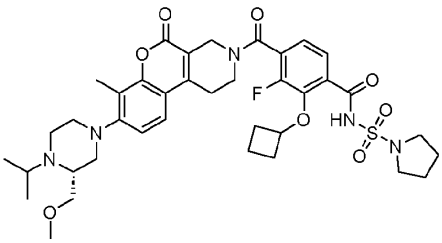
	 Synthesised from Intermediates 6 and 45	(br s, 2H), 3.16-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.86-2.81 (m, 8H), 2.69-2.63 (m, 4H), 2.49 (br s, 2H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 1.89-1.88 (m, 2H), 1.78-1.74 (m, 4H), 1.58 (br s, 2H).
Example 154	(*R*)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 100	HPLC: (System 1, Method D) Rt = 6.86 min, m/z 750.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (br s, 1H), 7.55-7.53 (m, 1H), 7.44-7.42 (m, 1H), 6.85 (s, 1H), 4.51 (br s, 1H), 4.27 (br s, 1H), 3.91 (br s, 3H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.50 (br s, 1H), 3.43-3.41 (m, 4H), 3.38-3.33 (m, 1H), 3.27 (s, 3H), 3.22 (br s, 2H), 3.16-3.13 (m, 1H), 3.06-3.03 (m, 1H), 2.88-2.80 (m, 2H), 2.69-2.63 (m, 4H), 2.49 (br s, 2H), 2.33 (s, 3H), 2.24-2.20 (m, 3H), 1.88-1.85 (m, 4H). Mixture of rotamers.
Example 155	(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 155	UPLC: (System 3, Method K) Rt = 4.07 min, m/z 738.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.71-7.65 (m, 1H), 7.24-7.17 (m, 1H), 6.83-6.81 (m, 1H), 4.55 (br s, 1H), 4.21 (br s, 1H), 4.11-4.06 (m, 3H), 3.91 (t, J = 5.7 Hz, 1H), 3.62-3.58 (m, 1H), 3.50 (t, J = 5.5 Hz, 1H), 3.46-3.38 (m, 5H), 3.30 (s, 3H), 3.24-3.05 (m, 5H), 2.96-2.88 (m, 2H), 2.74-2.68 (m, 2H), 2.61-2.51 (m, 3H), 2.40 (s, 3H), 2.28-2.24 (m, 3H), 1.49-1.46 (m, 4H), 0.36-0.35 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 156	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.79 min, m/z 711.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.65-7.60 (m, 1H), 7.20-7.14 (m, 1H), 6.82-6.81 (m, 1H), 4.55 (br s, 1H), 4.20 (br s, 1H), 4.08-4.04 (m, 3H), 3.97-3.93 (m, 1H), 3.58-3.48 (m, 6H), 3.39-3.35 (m, 1H), 3.29 (s, 3H),

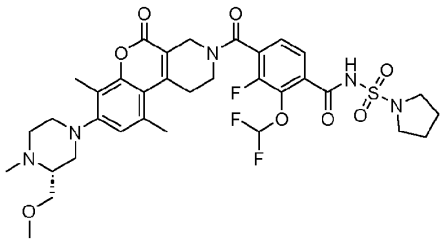
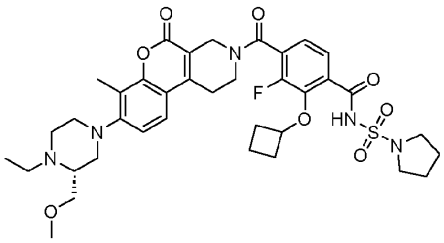
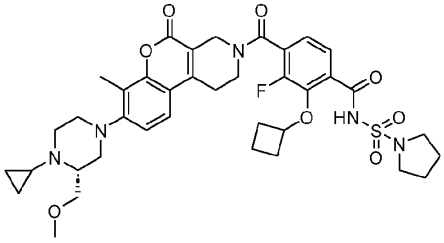
	 Synthesised from Intermediates 6 and 156	3.24-3.03 (m, 4H), 2.89-2.83 (m, 2H), 2.69-2.61 (m, 4H), 2.48-2.42 (m, 3H), 2.33-2.24 (m, 6H), 1.57 (s, 2H), 0.69-0.64 (m, 1H), 0.38-0.33 (m, 1H). One exchangeable proton not visible. Mixture of rotamers.
Example 157	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 152	UPLC: (System 3, Method K) Rt = 3.42 min, m/z 726.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.61-7.55 (m, 1H), 7.18-7.11 (m, 1H), 6.78-6.77 (m, 1H), 4.51 (br s, 1H), 4.27 (br s, 2H), 4.15 (br s, 1H), 4.04-4.01 (m, 3H), 3.87 (t, J = 5.3 Hz, 1H), 3.56-3.45 (m, 2H), 3.37-3.32 (m, 1H), 3.25 (s, 3H), 3.18-3.00 (m, 5H), 2.86-2.82 (m, 2H), 2.64-2.57 (m, 6H), 2.45-2.45 (m, 3H), 2.32 (s, 3H), 2.24-2.21 (m, 3H), 1.48-1.46 (br s, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 158	*N*-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 157	UPLC: (System 3, Method K) Rt = 3.60 min, m/z 740.9 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.58-7.53 (m, 1H), 7.16-7.10 (m, 1H), 6.79-6.78 (m, 1H), 4.52 (br s, 1H), 4.19 (br s, 3H), 4.04-4.00 (m, 3H), 3.88 (t, J = 5.5 Hz, 1H), 3.68-3.65 (m, 2H), 3.58-3.53 (m, 3H), 3.47 (t, J = 5.5 Hz, 1H), 3.37-3.32 (m, 1H), 3.31-3.24 (m, 3H), 3.19-3.01 (m, 5H), 2.87-2.81 (m, 2H), 2.67-2.58 (m, 6H), 2.48-2.45 (m, 2H), 2.32 (s, 3H), 2.25-2.21 (m, 3H), 2.03-2.01 (m, 1H) One exchangeable proton not visible. Mixture of rotamers.
Example 159	(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-5-(trifluoromethyl)benzamide	HPLC: (System 1, Method D) Rt = 6.95, m/z 748.5 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br s, 1H), 7.61-7.57 (m, 1H), 6.92-6.85 (m, 2H), 4.72-4.15 (m, 2H), 3.98-3.56 (m, 2H), 3.43-3.40 (m, 2H), 3.28 (s, 3H), 3.23-3.17 (m, 2H), 3.10-3.07 (m, 2H), 3.03-2.94 (m,

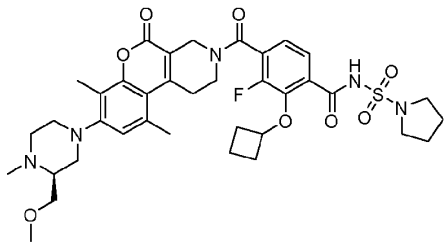
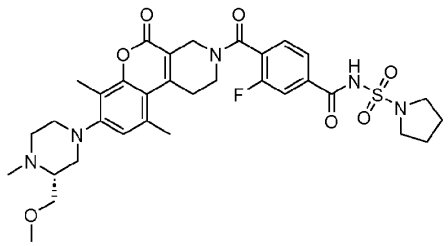
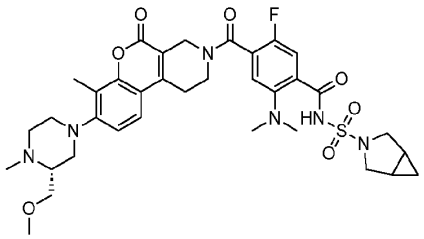
	 Synthesised from Intermediates 6 and 109	7H), 2.86 (br s, 1H), 2.70-2.60 (m, 6H), 2.42 (s, 3H), 2.24-2.20 (m, 3H), 1.47 (s, 3H), 1.42 (br s, 2H), 0.87-0.85 (m, 2H). Mixture of rotamers.
Example 160	(*R*)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 101	HPLC: (System 1, Method D) Rt = 7.06 min, m/z 764.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.87 (br s, 1H), 7.52 (br s, 1H), 7.41-7.40 (m, 1H), 6.85 (s, 1H), 4.50 (br s, 1H), 4.27 (br s, 1H), 4.19 (br s, 2H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.49-3.40 (m, 5H), 3.36-3.34 (m, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.85-2.80 (m, 2H), 2.69-2.61 (m, 4H), 2.49-2.43 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.88-1.84 (m, 4H), 1.32 (t, J = 6.8 Hz, 3H). Mixture of rotamers.
Example 161	(*R*)-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide  Synthesised from Intermediates 6 and 102	HPLC: (System 1, Method D) Rt = 7.31 min, m/z 778.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (br s, 1H), 7.56 (br s, 1H), 7.39-7.37 (m, 1H), 6.85 (s, 1H), 4.85-4.83 (m, 1H), 4.50 (br s, 1H), 4.29 (br s, 1H), 3.84 (br s, 1H), 3.57-3.54 (m, 1H), 3.49 (br s, 1H), 3.45-3.42 (m, 4H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.15-3.12 (m, 1H), 3.05-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.69-2.60 (m, 4H), 2.45-2.43 (m, 2H), 2.31 (s, 3H), 2.24-2.20 (m, 3H), 1.88-1.85 (m, 4H), 1.28 (d, J = 5.6 Hz, 6H). Mixture of rotamers.
Example 162	(*S*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 7.22 min, m/z 726.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.59-7.50 (m, 1H), 7.34-7.32 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.06 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 5.6 Hz, 1H), 3.58-3.53 (m,

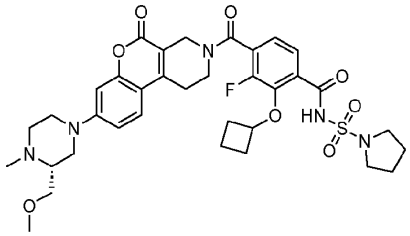
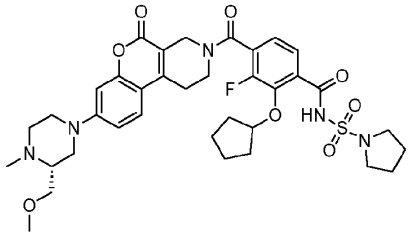
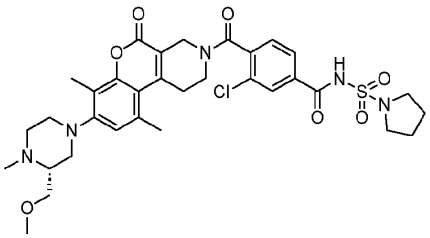
	 Synthesised from Intermediates 106 and 13	2H), 3.43-3.36 (m, 6H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.07-3.05 (m, 1H), 2.99 (br s, 1H), 2.91-2.83 (m, 3H), 2.68-2.63 (m, 1H), 2.52 (br s, 1H), 2.36 (s, 3H), 2.26-2.18 (m, 5H), 2.15-2.07 (m, 2H), 1.88-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.51-1.41 (m, 1H). Mixture of rotamers.
Example 163	(*R*)-2-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 113 and 6	HPLC: (System 1, Method D) Rt = 8.13 min, m/z 722.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.36 (br s, 1H), 7.64-7.59 (m, 2H), 7.03 (d, J = 8.8 Hz, 1H), 6.84 (s, 1H), 4.87-4.83 (m, 1H), 4.40 (br s, 2H), 3.68 (br s, 2H), 3.57-3.53 (m, 1H), 3.45-3.42 (m, 4H), 3.35-3.31 (m, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.79 (m, 2H), 2.66 (s, 3H), 2.64-2.59 (m, 1H), 2.49-2.41 (m, 4H), 2.30 (s, 3H), 2.21 (s, 3H), 2.18-2.07 (m, 2H), 1.86-1.80 (m, 5H), 1.71-1.63 (m, 1H).
Example 164	(*R*)-3-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 114 and 6	HPLC: (System 1, Method D) Rt = 7.33 min, m/z 722.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.34 (br s, 1H), 7.58 (br s, 1H), 7.46 (t, J = 2.0 Hz, 1H), 7.11 (br s, 1H), 6.86 (br s, 1H), 4.83-4.79 (m, 1H), 4.49 (br s, 1H), 4.28 (br s, 1H), 3.82 (br s, 1H), 3.58-3.50 (m, 2H), 3.44-3.43 (m, 1H), 3.33 (br s, 5H), 3.28 (s, 3H), 3.19 (br s, 3H), 3.10-3.07 (m, 1H), 2.98-2.95 (m, 1H), 2.89-2.83 (m, 1H), 2.71-2.65 (m, 5H), 2.49-2.39 (m, 5H), 2.23-2.20 (m, 3H), 2.09-2.04 (m, 2H), 1.79 (br s, 5H), 1.69-1.65 (m, 1H).
Example 165	(*R*)-2-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method D) Rt = 8.06 min, m/z 740.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.33 (br s, 1H), 7.62-7.55 (m, 1H), 6.98-6.95 (m, 1H), 6.85-6.84 (m, 1H), 4.87-4.84 (m, 1H), 4.48 (br s, 1H), 4.21 (br s, 1H), 3.81 (br s, 1H), 3.57-3.53 (m, 1H), 3.49 (br s, 1H),

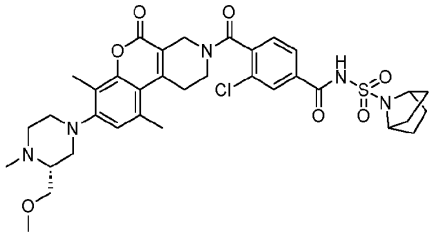
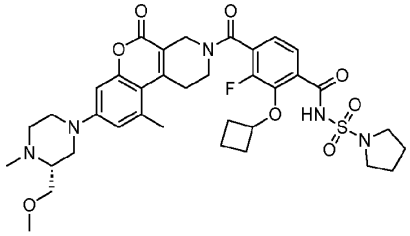
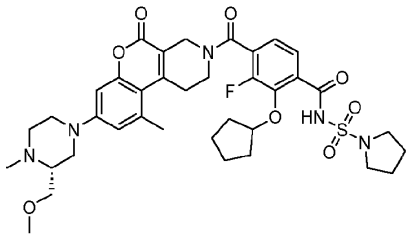
	 Synthesised from Intermediates 116 and 6	3.43-3.41 (m, 4H), 3.34 (br s, 1H), 3.32 (br s, 1H), 3.26 (s, 3H), 3.24-3.21 (m, 1H), 3.14-3.12 (m, 2H), 3.04-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.68-2.59 (m, 4H), 2.50-2.42 (m, 3H), 2.30 (s, 3H), 2.23-2.19 (m, 3H), 2.16-2.06 (m, 2H), 1.84-1.82 (m, 5H), 1.69-1.62 (m, 1H). Mixture of rotamers.
Example 166	(*R*)-3-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 118 and 6	HPLC: (System 1, Method D) Rt = 7.47 min, m/z 740.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.16 (br s, 1H), 7.62-7.54 (m, 2H), 6.88-6.86 (m, 1H), 4.89-4.86 (m, 1H), 4.51 (br s, 1H), 4.17 (br s, 1H), 3.87 (br s, 1H), 3.60-3.56 (m, 1H), 3.34 (br s, 2H), 3.30 (br s, 7H), 3.23-3.20 (m, 2H), 3.13-3.04 (m, 3H), 2.92-2.77 (m, 4H), 2.70-2.67 (m, 3H), 2.51 (br s, 3H), 2.47 (br s, 2H), 2.25-2.20 (m, 3H), 2.16-2.12 (m, 2H), 1.85-1.75 (m, 5H), 1.73-1.62 (m, 1H). Mixture of rotamers.
Example 167	(*R*)-6-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-4-carboxamide  Synthesised from Intermediates 120 and 6	HPLC: (System 1, Method D) Rt = 7.31 min, m/z 736.4 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.99 (br s, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 6.86 (s, 1H), 4.38 (br s, 2H), 3.70-3.56 (m, 3H), 3.46-3.42 (m, 1H), 3.36-3.34 (m, 4H), 3.29 (s, 3H), 3.20-3.17 (m, 3H), 3.11-3.08 (m, 1H), 3.00-2.97 (m, 1H), 2.89-2.84 (m, 1H), 2.74-2.61 (m, 10H), 2.44 (s, 3H), 2.22 (s, 3H), 1.87-1.79 (m, 6H).
Example 168	(*R*)-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-	HPLC: (System 1, Method D) Rt = 7.38 min, m/z 754.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.86 (br s, 1H), 7.37-7.30 (m, 1H), 6.86 (s, 1H),

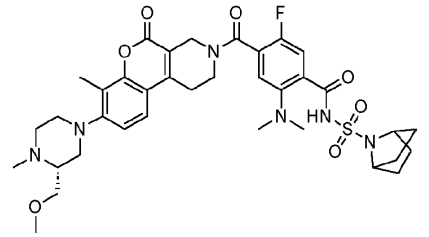
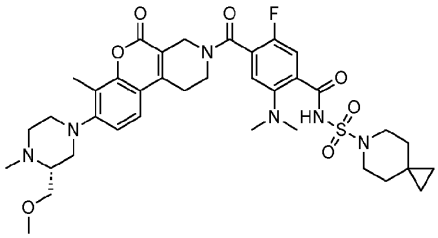
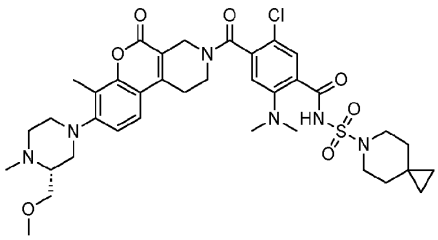
	ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-7-carboxamide  Synthesised from Intermediates 122 and 6	4.48 (br s, 1H), 4.23 (br s, 1H), 3.84 (br s, 1H), 3.59-3.45 (m, 3H), 3.29 (br s, 4H), 3.25 (s, 3H), 3.24-3.19 (m, 2H), 3.13-3.09 (m, 2H), 3.04-3.01 (m, 1H), 2.91-2.85 (m, 1H), 2.77-2.63 (m, 10H), 2.48 (br s, 3H), 2.24-2.20 (m, 3H), 1.86-1.78 (m, 6H). Mixture of rotamers.
Example 169	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(trifluoromethoxy)benzamide  Synthesised from Intermediates 138 and 6	HPLC: (System 1, Method D) Rt = 7.21 min, m/z 754.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.58-7.52 (m, 2H), 6.87-6.86 (m, 1H), 4.52 (br s, 1H), 4.18 (s, 1H), 3.90-3.87 (m, 1H), 3.60-3.57 (m, 1H), 3.47 (br s, 2H), 3.29 (s, 3H), 3.27 (br s, 5H), 3.21-3.15 (m, 2H), 3.12-3.08 (m, 2H), 3.06-2.97 (m, 1H), 2.91-2.74 (m, 3H), 2.70-2.60 (m, 4H), 2.47 (br s, 2H), 2.24-2.21 (m, 3H), 1.78 (br s, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 170	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(4-isopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 145	HPLC: (System 1, Method D) Rt = 8.13 min, m/z 754.3 $(M+H)^+$ $(ES)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.50 (br s, 1H), 7.59-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.06 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 5.6 Hz, 1H), 3.57-3.55 (m, 2H), 3.50-3.46 (m, 1H), 3.43-3.39 (m, 4H), 3.32-3.27 (m, 4H), 3.12-2.99 (m, 4H), 2.90-2.83 (m, 3H), 2.79-2.74 (m, 1H), 2.68-2.63 (m, 1H), 2.33-2.30 (m, 3H), 2.29-2.18 (m, 2H), 2.15-2.07 (m, 2H), 1.87-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.51-1.41 (m, 1H), 1.11-0.99 (m, 6H). Mixture of rotamers.
Example 171	(*R*)-2-(difluoromethoxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-	HPLC: (System 1, Method D) Rt = 7.07 min, m/z 736.3 $(M+H)^+$ $(ES)^+$.

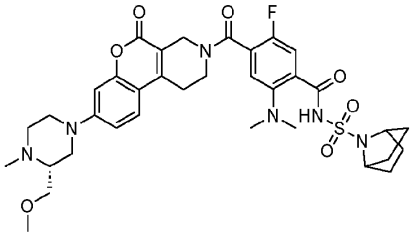
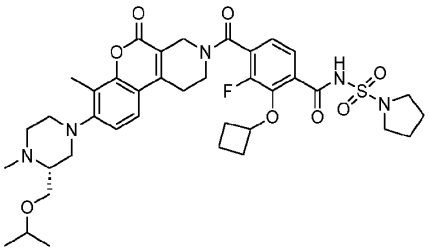
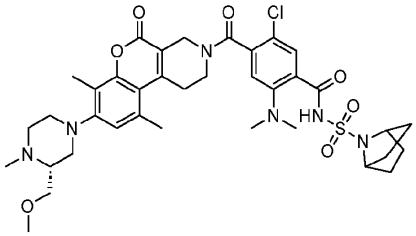
	chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 141 and 6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.05 (br s, 1H), 7.52-7.05 (m, 3H), 6.87-6.86 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.88-3.87 (m, 1H), 3.59-3.57 (m, 1H), 3.49-3.46 (m, 2H), 3.33-3.32 (m, 6H), 3.30 (s, 3H), 3.24-3.10 (m, 5H), 3.05-3.02 (m, 1H), 2.91-2.86 (m, 1H), 2.78-2.62 (m, 6H), 2.23-2.21 (m, 3H), 1.82-1.79 (m, 4H).
Example 172	(*R*)-2-cyclobutoxy-4-(8-(4-ethyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 143	HPLC: (System 1, Method D) Rt = 7.70 min, m/z 740.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.49 (br s, 1H), 7.59-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.15 (m, 1H), 7.11-7.07 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.99-3.96 (m, 1H), 3.60-3.53 (m, 2H), 3.50-3.46 (m, 1H), 3.42-3.39 (m, 4H), 3.27 (s, 3H), 3.11-2.99 (m, 3H), 2.96-2.74 (m, 6H), 2.58-2.53 (m, 2H), 2.33-2.18 (m, 5H), 2.15-2.07 (m, 2H), 1.86-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.50-1.41 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H). Mixture of rotamers.
Example 173	(*R*)-2-cyclobutoxy-4-(8-(4-cyclopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 147	HPLC: (System 1, Method D) Rt = 8.26 min, m/z 752.4 (M+H)$^+$ (ES$^+$). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.72 (br s, 1H), 7.59-7.50 (m, 1H), 7.37-7.34 (m, 1H), 7.26-7.17 (m, 1H), 7.06 (t, J = 7.6 Hz, 1H), 4.72-4.64 (m, 1H), 4.53 (br s, 1H), 4.17 (s, 1H), 3.97 (t, J = 5.6 Hz, 1H), 3.81-3.78 (m, 1H), 3.54-3.49 (m, 2H), 3.44-3.43 (m, 4H), 3.27 (s, 3H), 3.13-3.10 (m, 1H), 3.02-3.00 (m, 3H), 2.90 (br s, 1H), 2.82-2.78 (m, 2H), 2.70-2.65 (m, 1H), 2.61-2.57 (m, 1H), 2.33-2.20 (m, 5H), 2.15-2.07 (m, 2H), 1.88-1.87 (m, 4H), 1.81 (br s, 1H), 1.71-1.67 (m, 1H), 1.51-1.44 (m, 1H), 0.58-0.57 (m, 1H), 0.46-0.41 (m, 2H), 0.31-0.29 (m, 1H). Mixture of rotamers.
Example 174	(*S*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-	HPLC: (System 1, Method D) Rt = 7.39 min, m/z 740.3 (M+H)$^+$ (ES$^+$).

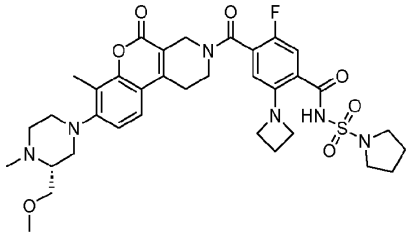
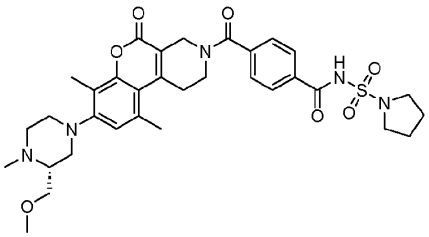
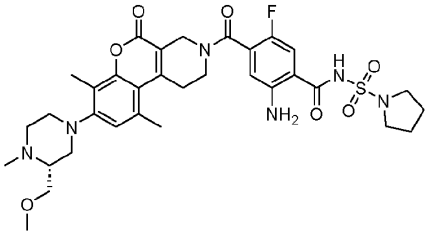
	dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 166 and 13	^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.48 (br s, 1H), 7.36-7.33 (m, 1H), 7.26-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.73-4.66 (m, 1H), 4.50 (br s, 1H), 4.17 (s, 1H), 3.88-3.86 (m, 1H), 3.58-3.54 (m, 1H), 3.45-3.37 (m, 7H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.29-2.20 (m, 5H), 2.16-2.07 (m, 2H), 1.87-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.50-1.40 (m, 1H). Mixture of rotamers.
Example 175	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 167	UPLC: (System 3, Method K) Rt = 3.68 min, m/z 668.3 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.87-7.79 (m, 2H), 7.59-7.49 (m, 1H), 6.90-6.84 (m, 1H), 4.53 (s, 1H), 4.18 (s, 1H), 3.89 (s, 1H), 3.64-3.40 (m, 3H), 3.32 (s, 11H), 3.25-3.11 (m, 5H), 2.92-2.63 (m, 6H), 2.28-2.20 (m, 3H), 1.87-1.77 (m, 4H) One exchangeable proton not visible. Mixture of rotamers.
Example 181	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 169 and 5	HPLC: (System 1, Method H) Rt = 7.59 min, m/z 711.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 13.03 (br s, 1H), 7.60-7.48 (m, 2H), 7.42-7.31 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.20 (br s, 1H), 3.98 (br s, 1H), 3.58-3.54 (m, 4H), 3.48-3.45 (m, 2H), 3.38-3.34 (m, 2H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 3.00 (br s, 1H), 2.90-2.83 (m, 3H), 2.77-2.74 (m, 6H), 2.67-2.62 (m, 1H), 2.49-2.47 (m, 1H), 2.34 (s, 3H), 2.30-2.26 (m, 3H), 1.59 (br s, 2H), 0.68-0.63 (m, 1H), 0.29-0.28 (m, 1H). Mixture of rotamers.
Example 182	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 6.89 min, m/z 712.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.56 (br s, 1H), 7.58-7.50 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.15 (m, 1H), 7.02-6.97 (m, 1H),

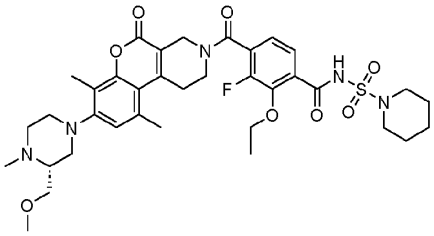
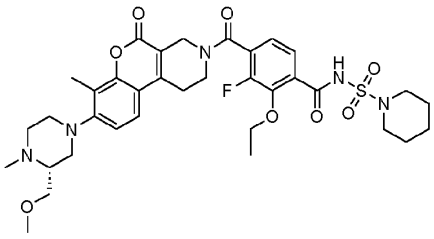
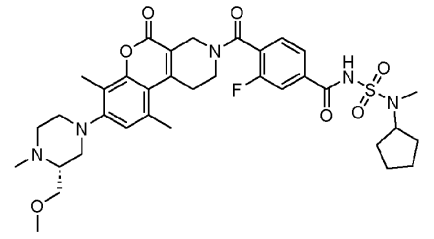
	 Synthesised from Intermediates 13 and 224	6.86-6.83 (m, 1H), 4.73-4.65 (m, 1H), 4.49 (br s, 1H), 4.13 (s, 1H), 3.97-3.94 (m, 1H), 3.82-3.74 (m, 2H), 3.56-3.51 (m, 2H), 3.43-3.37 (m, 5H), 3.29-3.28 (m, 3H), 2.99-2.94 (m, 2H), 2.87-2.84 (m, 2H), 2.80-2.74 (m, 1H), 2.36-2.31 (m, 5H), 2.27-2.18 (m, 2H), 2.15-2.07 (m, 2H), 1.86 (br s, 4H), 1.71-1.66 (m, 1H), 1.51-1.44 (m, 1H). Mixture of rotamers.
Example 183	(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 14 and 224	HPLC: (System 1, Method H) Rt = 7.14 min, m/z 726.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br s, 1H), 7.58-7.49 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.14 (m, 1H), 7.01-6.97 (m, 1H), 6.86-6.83 (m, 1H), 4.87-4.81 (m, 1H), 4.49 (br s, 1H), 4.14 (s, 1H), 3.97-3.94 (m, 1H), 3.82-3.74 (m, 2H), 3.56-3.52 (m, 2H), 3.41-3.37 (m, 5H), 3.29-3.28 (m, 3H), 2.99-2.94 (m, 2H), 2.87-2.84 (m, 2H), 2.80-2.74 (m, 1H), 2.36-2.31 (m, 5H), 1.87-1.83 (m, 4H), 1.79-1.73 (m, 6H), 1.57-1.54 (m, 2H). Mixture of rotamers.
Example 184	(*R*)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 190 and 6	UPLC: (System 3, Method K) Rt = 3.80 min, m/z 685.2 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.06-8.02 (m, 1H), 7.97-7.92 (m, 1H), 7.55-7.47 (m, 1H), 6.94-6.85 (m, 1H), 4.66-4.38 (m, 1H), 4.06 (s, 1H), 3.96-3.82 (m, 1H), 3.68-3.47 (m, 2H), 3.38-3.31 (m, 9H), 3.22-3.04 (m, 6H), 2.92-2.75 (m, 4H), 2.69 (s, 2H), 2.61 (s, 2H), 2.25-2.20 (m, 3H), 1.82-1.75 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 185	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.93 min, m/z 711.9 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.97-7.94 (m, 1H), 7.90-7.86 (m, 1H), 7.51-7.42 (m, 1H), 6.88-6.86 (m, 1H), 4.66-4.38 (m, 1H), 4.11-4.06 (m, 3H), 3.92-3.82 (m, 1H), 3.60-3.46 (m, 2H), 3.42-3.35 (m, 2H), 3.24-3.13

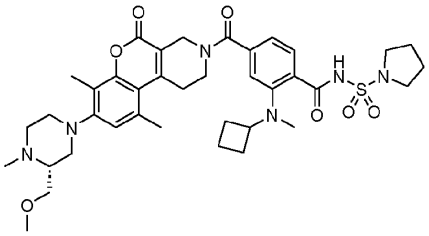
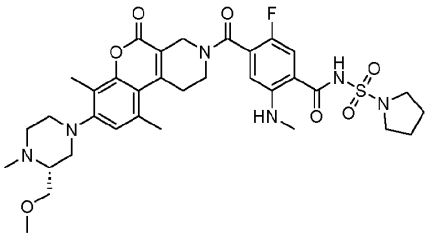
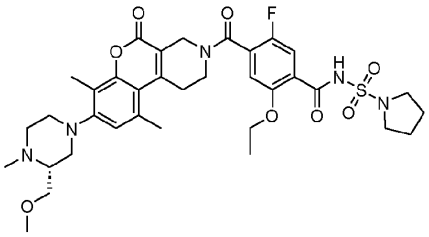
	 Synthesised from Intermediates 191 and 6	(m, 6H), 2.91-2.84 (m, 5H), 2.70-2.65 (m, 2H), 2.65-2.54 (m, 4H), 2.25-2.21 (m, 3H), 1.91-1.84 (m, 4H), 1.39-1.23 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 186	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 226	HPLC: (System 1, Method H) Rt = 7.05 min, m/z 726.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (br s, 1H), 7.36-7.25 (m, 1H), 7.24-7.16 (m, 1H), 6.81-6.79 (m, 1H), 6.69-6.65 (m, 1H), 4.75-4.64 (m, 1H), 4.48 (br s, 1H), 4.13 (s, 1H), 3.88-3.85 (m, 1H), 3.81-3.73 (m, 2H), 3.56-3.51 (m, 1H), 3.43-3.36 (m, 6H), 3.29-3.27 (m, 3H), 3.20 (br s, 1H), 3.11-3.06 (m, 1H), 2.96-2.91 (m, 1H), 2.87-2.83 (m, 1H), 2.77-2.72 (m, 1H), 2.66-2.59 (m, 3H), 2.35-2.31 (m, 5H), 2.18-2.16 (m, 2H), 2.15-2.05 (m, 2H), 1.88-1.85 (m, 4H), 1.74-1.64 (m, 1H), 1.51-1.41 (m, 1H). Mixture of rotamers.
Example 187	(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 14 and 226	HPLC: (System 1, Method H) Rt = 7.30 min, m/z 740.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br s, 1H), 7.35-7.33 (m, 1H), 7.24-7.15 (m, 1H), 6.81-6.79 (m, 1H), 6.69-6.66 (m, 1H), 4.87-4.82 (m, 1H), 4.46 (br s, 1H), 4.14 (s, 1H), 3.87-3.85 (m, 1H), 3.80-3.73 (m, 2H), 3.55-3.51 (m, 1H), 3.46-3.45 (m, 1H), 3.43-3.38 (m, 5H), 3.29-3.28 (m, 3H), 3.21 (br s, 1H), 3.11 (m, 1H), 2.96-2.91 (m, 1H), 2.86-2.83 (m, 1H), 2.77-2.71 (m, 1H), 2.66-2.59 (m, 3H), 2.33-2.30 (m, 5H), 1.85-1.74 (m, 10H), 1.59-1.55 (m, 2H). Mixture of rotamers.
Example 188	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-	HPLC: (System 1, Method H) Rt = 7.40 min, m/z 725.2 $(M+H^+)$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.97 (br s, 1H), 7.60-7.50 (m, 1H), 7.46-7.41 (m,

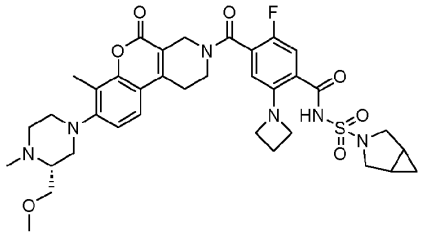
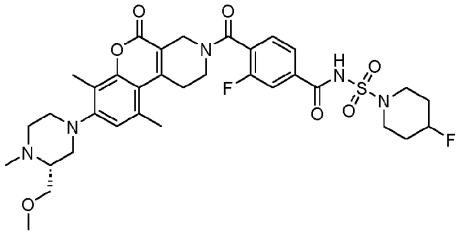
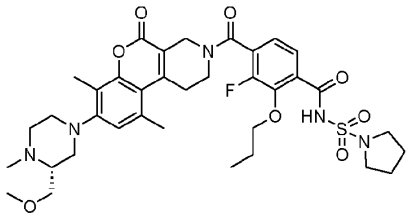
	methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 170 and 5	1H), 7.37-7.25 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.22-4.19 (m, 3H), 3.97 (br s, 1H), 3.58-3.55 (m, 2H), 3.39-3.36 (m, 2H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.99 (br s, 1H), 2.94-2.83 (m, 3H), 2.77-2.75 (m, 6H), 2.67-2.62 (m, 1H), 2.49-2.45 (m, 1H), 2.34 (s, 3H), 2.29-2.26 (m, 3H), 1.84-1.81 (m, 4H), 1.46-1.44 (m, 4H). Mixture of rotamers.
Example 189	(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 172 and 5	HPLC: (System 1, Method H) Rt = 8.28 min, m/z 739.4 ($M+H^+$) (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.08 (br s, 1H), 7.60-7.49 (m, 2H), 7.44-7.33 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.20 (br s, 1H), 3.98 (br s, 1H), 3.58-3.55 (m, 2H), 3.39-3.35 (m, 5H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 3.00 (br s, 1H), 2.90-2.83 (m, 3H), 2.79-2.76 (m, 6H), 2.68-2.62 (m, 1H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.34 (s, 3H), 2.30-2.26 (m, 3H), 1.42 (br s, 4H), 0.33 (s, 4H). Mixture of rotamers.
Example 190	(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 173 and 5	HPLC: (System 1, Method H) Rt = 7.99 min, m/z 755.3 ($M+H^+$) (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.09 (br s, 1H), 7.60-7.45 (m, 2H), 7.10-7.02 (m, 2H), 4.63-4.43 (m, 1H), 4.16-3.78 (m, 2H), 3.58-3.55 (m, 1H), 3.51-3.49 (m, 1H), 3.44-3.36 (m, 5H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.09-2.98 (m, 2H), 2.91-2.86 (m, 3H), 2.82-2.81 (m, 6H), 2.68-2.63 (m, 1H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.33-2.26 (m, 3H), 1.41-1.40 (m, 4H), 0.33-032 (m, 4H). Mixture of rotamers.
Example 191	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.03 min, m/z 711.4 ($M+H^+$) (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.08 (br s, 1H), 7.59-7.50 (m, 1H), 7.47-7.41 (m, 1H), 7.39-7.37 (m, 1H), 7.01-6.97 (m, 1H), 6.86-6.83 (m, 1H), 4.49-4.47 (m, 1H), 4.22

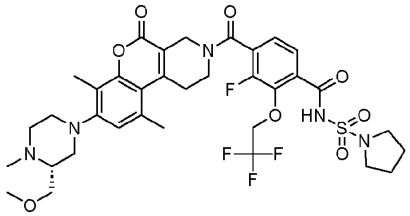
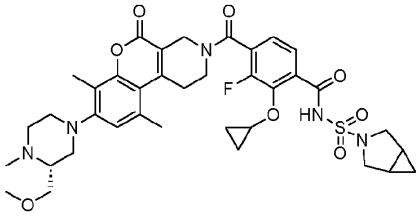
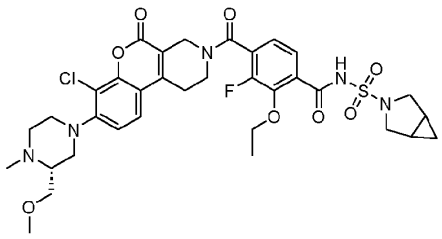
	 Synthesised from Intermediates 170 and 224	(br s, 2H), 4.16 (br s, 1H), 3.95 (br s, 1H), 3.81-3.74 (m, 2H), 3.56-3.53 (m, 2H), 3.40-3.36 (m, 1H), 3.29 (s, 3H), 2.98-2.91 (m, 2H), 2.86-2.83 (m, 2H), 2.79-2.72 (m, 7H), 2.34-2.30 (m, 5H), 1.83-1.81 (m, 4H), 1.46-1.44 (m, 4H). Mixture of rotamers.
Example 192	(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(isopropoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 13 and 231	HPLC: (System 1, Method H) Rt = 8.74 min, m/z 754.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.47 (br s, 1H), 7.60-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.05 (m, 1H), 4.73-4.65 (m, 1H), 4.53 (br s, 1H), 4.17 (br s, 1H), 4.00-3.96 (m, 1H), 3.63-3.60 (m, 1H), 3.57-3.51 (m, 2H), 3.43-3.35 (m, 5H), 3.21-3.18 (m, 1H), 3.07-3.04 (m, 1H), 2.99 (br s, 1H), 2.91-2.85 (m, 3H), 2.67-2.61 (m, 1H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.36 (s, 3H), 2.30-2.18 (m, 5H), 2.15-2.07 (m, 2H), 1.88-1.84 (m, 4H), 1.71-1.66 (m, 1H), 1.51-1.44 (m, 1H), 1.09-1.07 (m, 6H). Mixture of rotamers.
Example 193	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 174 and 6	HPLC: (System 1, Method H) Rt = 7.39 min, m/z 755.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.04 (br s, 1H), 7.40-7.35 (m, 1H), 7.08-6.97 (m, 1H), 6.89-6.84 (m, 1H), 4.66-4.36 (m, 1H), 4.21 (br s, 2H), 4.10 (br s, 1H), 4.01-3.72 (m, 1H), 3.58-3.54 (m, 1H), 3.44-3.36 (m, 3H), 3.27 (s, 3H), 3.21-3.09 (m, 3H), 3.07-3.04 (m, 1H), 2.91-2.86 (m, 2H), 2.82-2.80 (m, 6H), 2.69-2.60 (m, 4H), 2.52-2.51 (m, 1H), 2.36 (s, 3H), 2.24-2.20 (m, 3H), 1.82-1.75 (m, 4H), 1.45-1.44 (m, 4H). Mixture of rotamers.
Example 194	(*R*)-2-(azetidin-1-yl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.34 min, m/z 711.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.69 (br s, 1H), 7.59-7.50 (m, 1H), 7.25-7.22 (m, 1H), 7.10-7.06 (m, 1H), 6.51-6.44 (m, 1H),

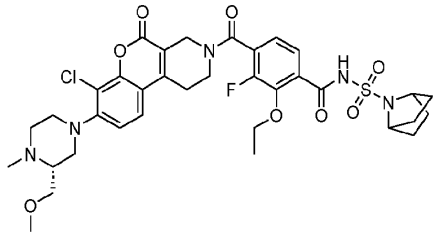
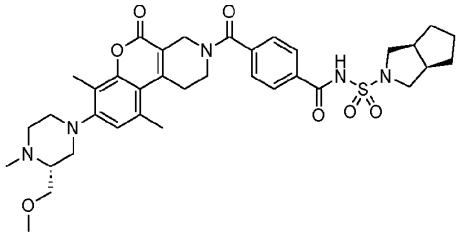
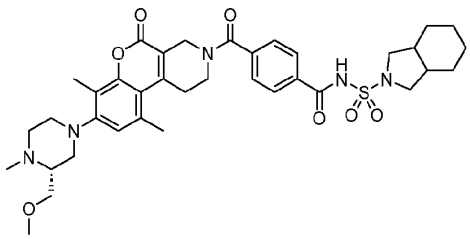
	 Synthesised from Intermediates 177 and 5	4.52 (br s, 1H), 4.19 (s, 1H), 3.95 (br s, 1H), 3.82-3.77 (m, 4H), 3.58-3.54 (m, 2H), 3.41-3.36 (m, 5H), 3.27 (s, 3H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.98 (br s, 1H), 2.90-2.83 (m, 3H), 2.67-2.62 (m, 1H), 2.50-2.49 (m, 2H), 2.34 (s, 3H), 2.29-2.23 (m, 5H), 1.85-1.82 (m, 4H). Mixture of rotamers.
Example 195	(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 192 and 6	HPLC: (System 1, Method H) Rt = 6.58 min, m/z 652.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.43 (br s, 1H), 8.01-7.99 (m, 2H), 7.57 (br s, 2H), 6.86 (s, 1H), 4.48 (br s, 1H), 4.27 (br s, 1H), 3.84 (br s, 1H), 3.59-3.55 (m, 1H), 3.50 (br s, 1H), 3.43-3.36 (m, 5H), 3.28 (s, 3H), 3.21-3.16 (m, 3H), 3.09-3.06 (m, 1H), 2.96-2.93 (m, 1H), 2.88-2.83 (m, 1H), 2.72-2.58 (m, 6H), 2.41 (s, 3H), 2.24 (br s, 3H), 1.83-1.80 (m, 4H).
Example 196	(*R*)-2-amino-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 175 and 6	HPLC: (System 1, Method H) Rt = 7.40 min, m/z 685.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.96 (br s, 2H), 7.65-7.59 (m, 1H), 6.87-6.86 (m, 1H), 6.71-6.52 (m, 1H), 4.48 (br s, 1H), 4.20 (br s, 1H), 3.84 (br s, 1H), 3.60-3.57 (m, 1H), 3.49-3.48 (m, 2H), 3.32-3.31 (m, 7H), 3.22-3.20 (m, 2H), 3.13-3.11 (m, 2H), 3.07-3.04 (m, 1H), 2.92-2.75 (m, 4H), 2.69-2.63 (m, 3H), 2.51 (s, 3H), 2.24-2.21 (m, 3H), 1.81-1.78 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 197	(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.24 min, m/z 728.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.39 (br s, 1H), 7.34-7.32 (m, 1H), 7.24-7.16 (m, 1H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.22-4.13 (m, 3H), 3.89-3.86 (m, 1H), 3.58-3.55 (m, 1H), 3.48-3.45 (m, 1H), 3.42-3.38 (m, 1H), 3.28 (s, 3H), 3.23 (br s, 5H), 3.18-3.15 (m, 2H), 3.08-3.05 (m, 1H), 2.94-2.82

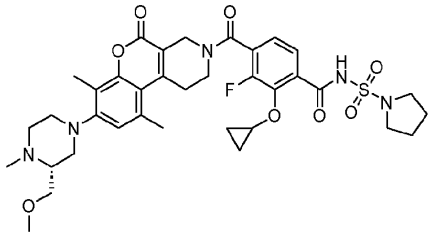
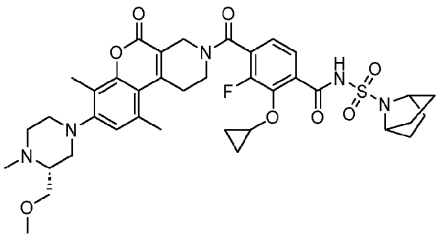
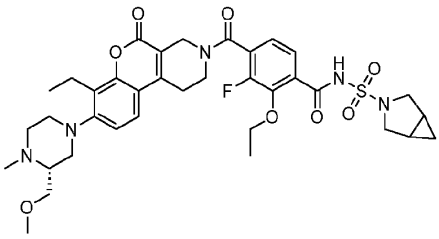
	 Synthesised from Intermediates 202 and 6	(m, 2H), 2.71-2.55 (m, 6H), 2.39 (s, 3H), 2.24-2.20 (m, 3H), 1.57-1.56 (m, 4H), 1.49-1.48 (m, 2H), 1.34-1.28 (m, 3H). Mixture of rotamers.
Example 198	(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 202 and 5	HPLC: (System 1, Method H) Rt = 7.10 min, m/z 714.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.55 (dd, J = 27.2, 8.8 Hz, 1H), 7.33 (dd, J = 8.0, 3.2 Hz, 1H), 7.22-7.15 (m, 1H), 7.08 (t, J = 8.8 Hz, 1H), 4.53 (br s, 1H), 4.22-4.13 (m, 3H), 3.99-3.96 (m, 1H), 3.59-3.55 (m, 2H), 3.42-3.38 (m, 1H), 3.28 (s, 3H), 3.24 (br s, 4H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 1H), 2.99-2.85 (m, 4H), 2.71-2.66 (m, 1H), 2.61-2.56 (m, 2H), 2.39 (s, 3H), 2.30-2.26 (m, 3H), 1.57-1.56 (m, 4H), 1.49-1.48 (m, 2H), 1.34-1.28 (m, 3H). Mixture of rotamers.
Example 199	(*R*)-*N*-(*N*-cyclopentyl-*N*-methylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 198 and 6	UPLC: (System 3, Method K) Rt = 4.08 min, m/z 698.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.84-7.76 (m, 2H), 7.59-7.54 (m, 1H), 6.72-7.01 (1H), 4.52 (s, 1H), 4.20 (d, J = 8.2 Hz, 2H), 3.88 (s, 1H), 3.59-2.98 (m, 14H), 2.91-2.62 (m, 10H), 2.22 (d, J = 16.9 Hz, 3H), 1.71-1.40 (m, 8H). One exchangeable proton not visible. Mixture of rotamers.
Example 200	(*R*)-2-(cyclobutyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 9.64 min, m/z 735.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.48 (br s, 1H), 8.02-7.97 (m, 1H), 7.57-7.50 (m, 1H), 7.43-7.36 (m, 1H), 6.85 (s, 1H), 4.49 (br s, 1H), 4.26 (br s, 1H), 3.91-3.84 (m, 2H), 3.57-3.53 (m, 1H), 3.47-3.44 (m, 5H),

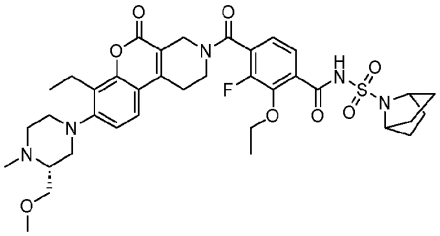
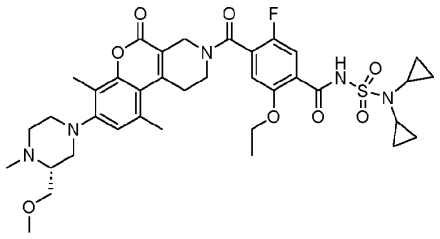
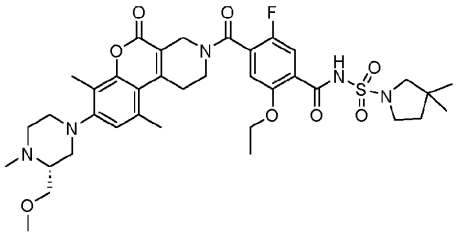
	 Synthesised from Intermediates 179 and 6	3.35 (br s, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.14-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.84-2.79 (m, 2H), 2.68-2.58 (m, 7H), 2.41-2.39 (m, 2H), 2.29 (s, 3H), 2.24-2.19 (m, 3H), 2.11-2.05 (m, 2H), 1.90-1.84 (m, 6H), 1.72-1.63 (m, 2H).
Example 201	(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(methylamino)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 176 and 6	HPLC: (System 1, Method H) Rt = 7.02 min, m/z 699.3 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (br s, 1H), 7.72-7.66 (m, 1H), 6.88-6.86 (m, 1H), 6.58-6.51 (m, 1H), 4.50 (br s, 1H), 4.20 (br s, 1H), 3.86 (br s, 1H), 3.61-3.57 (m, 1H), 3.53-3.48 (m, 2H), 3.31 (s, 3H), 3.29-3.28 (m, 4H), 3.24-3.21 (m, 2H), 3.17-3.08 (m, 3H), 2.93-2.88 (m, 2H), 2.82-2.76 (m, 5H), 2.70-2.62 (m, 3H), 2.54 (s, 3H), 2.25-2.21 (m, 3H), 1.82-1.76 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 202	(*R*)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 201 and 6	HPLC: (System 1, Method H) Rt = 7.33 min, m/z 714.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.46-7.43 (m, 1H), 7.24-7.15 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.19 (s, 1H), 4.14-4.06 (m, 2H), 3.87 (t, J = 5.2 Hz, 1H), 3.57-3.54 (m, 1H), 3.48-3.42 (m, 5H), 3.37-3.35 (m, 1H), 3.26 (s, 3H), 3.23 (br s, 1H), 3.17-3.12 (m, 2H), 3.05-3.02 (m, 1H), 2.87-2.80 (m, 2H), 2.69-2.61 (m, 4H), 2.46-2.43 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H), 1.35-1.30 (m, 3H). Mixture of rotamers.
Example 203	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(azetidin-1-yl)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.50 min, m/z 723.0 $(M+H^+)$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.60 (br s, 1H), 7.59-7.50 (m, 1H), 7.22-7.19 (m, 1H), 7.10-7.06 (m, 1H), 6.50-6.44 (m, 1H), 4.51 (br s, 1H), 4.19 (s, 1H), 3.95-3.94 (m, 1H), 3.82-3.76 (m, 4H), 3.58-3.51 (m, 4H),

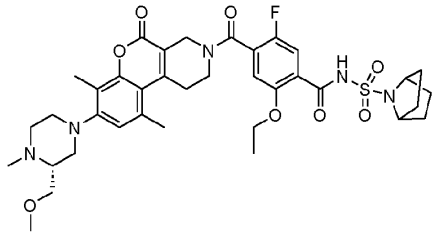
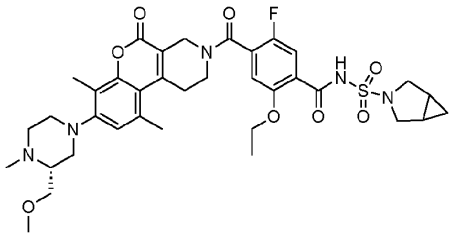
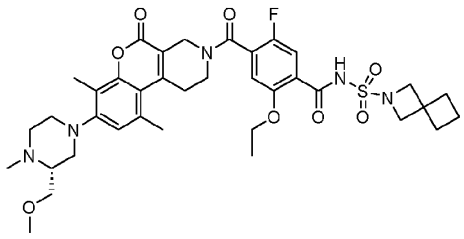
	 Synthesised from Intermediates 178 and 5	3.45-3.43 (m, 2H), 3.41-3.37 (m, 1H), 3.27 (s, 3H), 3.18-3.16 (m, 1H), 3.08-3.06 (m, 1H), 2.98 (br s, 1H), 2.93-2.84 (m, 3H), 2.70-2.65 (m, 1H), 2.55 (br s, 2H), 2.38 (s, 3H), 2.30-2.23 (m, 5H), 1.58-1.57 (m, 2H), 0.66-0.63 (m, 1H), 0.27-0.25 (m, 1H). Mixture of rotamers.
Example 204	(*R*)-3-fluoro-*N*-((4-fluoropiperidin-1-yl)sulfonyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 200 and 6	UPLC: (System 3, Method K) Rt = 3. 80 min, m/z 702.4 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.86-7.74 (m, 2H), 7.53-7.44 (m, 1H), 6.90-6.86 (m, 1H), 4.88-4.80 (m, 1H), 4.55-4.49 (m, 1H), 4.20-4.15 (m, 1H), 3.91-3.88 (m, 1H), 3.67-3.43 (m, 3H), 3.31 (s, 7H), 3.26-3.14 (m, 8H), 2.98-2.63 (m, 7H), 2.28-2.20 (m, 3H), 1.94-1.75 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 205	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-propoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 203 and 6	HPLC: (System 1, Method H) Rt = 7.28 min, m/z 728.0 $(M+H^+)$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.35-7.33 (m, 1H), 7.25-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.18 (s, 1H), 4.12-4.05 (m, 2H), 3.87 (t, J = 5.4 Hz, 1H), 3.58-3.54 (m, 1H), 3.47-3.45 (m, 1H), 3.42-3.36 (m, 5H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.52-2.50 (m, 2H), 2.36 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H), 1.74-1.67 (m, 2H), 0.99-0.93 (m, 3H). Mixture of rotamers.
Example 206	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(2,2,2-trifluoroethoxy)benzamide	HPLC: (System 1, Method H) Rt = 7.29 min, m/z 767.8 $(M+H^+)$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.20 (br s, 1H), 7.42-7.39 (m, 1H), 7.33-7.25 (m, 1H), 6.87-6.86 (m, 1H), 4.85-4.74 (m, 2H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.87 (br s, 1H), 3.59-3.57 (m, 1H), 3.48-3.45 (m, 2H), 3.34-3.33 (m, 4H), 3.29 (s, 3H), 3.24-3.18 (m,

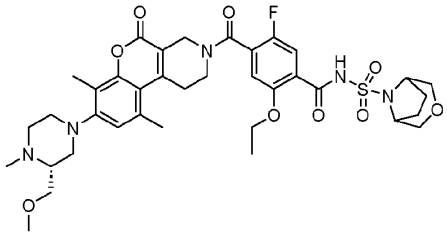
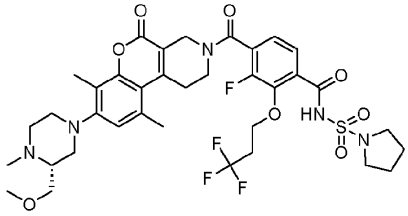
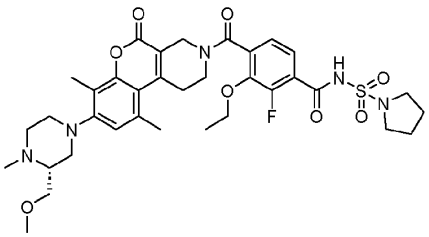
	 Synthesised from Intermediates 205 and 6	2H), 3.14-3.09 (m, 2H), 3.02-2.99 (m, 1H), 2.90-2.85 (m, 1H), 2.74-2.62 (m, 6H), 2.46 (s, 3H), 2.24-2.21 (m, 3H), 1.83-1.78 (m, 4H). Mixture of rotamers.
Example 207	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 204 and 6	HPLC: (System 1, Method H) Rt = 7.12 min, m/z 737.9 ($M+H^+$) (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (br s, 1H), 7.31-7.29 (m, 1H), 7.26-7.17 (m, 1H), 6.87-6.85 (m, 1H), 4.52 (br s, 1H), 4.30-4.24 (m, 1H), 4.19 (s, 1H), 3.89-3.87 (m, 1H), 3.59-3.55 (m, 1H), 3.50-3.40 (m, 6H), 3.28 (s, 3H), 3.24 (br s, 1H), 3.19-3.16 (m, 2H), 3.09-3.07 (m, 1H), 2.97-2.95 (m, 1H), 2.88-2.83 (m, 1H), 2.73-2.62 (m, 6H), 2.42 (s, 3H), 2.24-2.20 (m, 3H), 1.58-1.56 (m, 2H), 0.82-0.78 (m, 2H), 0.66-0.59 (m, 3H), 0.32-0.29 (m, 1H). Mixture of rotamers.
Example 208	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide  Synthesised from Intermediates 206 and 7	HPLC: (System 1, Method H) Rt = 6.95 min, m/z 731.8 ($M+H^+$) (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.59 (br s, 1H), 7.71-7.62 (m, 1H), 7.34-7.31 (m, 1H), 7.23-7.16 (m, 2H), 4.54 (br s, 1H), 4.22-4.15 (m, 3H), 3.98 (t, J = 5.8 Hz, 1H), 3.60-3.51 (m, 4H), 3.47-3.37 (m, 5H), 3.28 (s, 3H), 3.01-2.92 (m, 4H), 2.77-2.72 (m, 1H), 2.59-2.51 (m, 2H), 2.37 (s, 3H), 1.60-1.58 (m, 2H), 1.34-1.28 (m, 3H), 0.67-0.65 (m, 1H), 0.31-0.29 (m, 1H). Mixture of rotamers.
Example 209	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide	HPLC: (System 1, Method H) Rt = 6.96 min, m/z 745.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.56 (br s, 1H), 7.71-7.62 (, 1H), 7.29-7.26 (m, 1H), 7.23-7.16 (m, 2H), 4.54 (br s, 1H), 4.20-4.11 (m, 5H), 3.97 (t, J = 5.6 Hz, 1H), 3.60-3.55 (m, 2H), 3.46-3.39 (m, 3H), 3.28 (s,

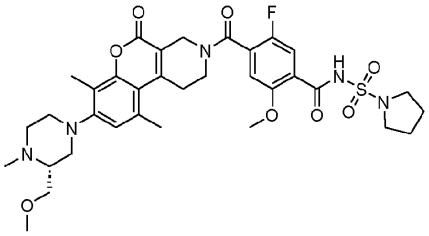
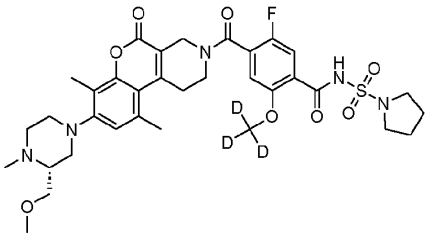
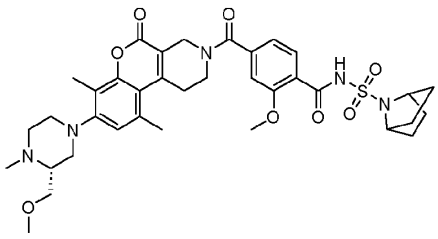
	 Synthesised from Intermediates 207 and 7	3H), 3.01-2.93 (m, 4H), 2.77-2.72 (m, 1H), 2.60-2.51 (m, 2H), 2.38 (s, 3H), 1.86-1.84 (m, 4H), 1.45-1.44 (m, 4H), 1.33-1.27 (m, 3H). Mixture of rotamers.
Example 210	*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 194 and 6	UPLC: (System 3, Method K) Rt = 3.95 min, m/z 692.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.55 (br s, 1H), 8.00-7.98 (m, 2H), 7.58 (s, 2H), 6.85 (s, 1H), 4.48 (br s, 1H), 4.27 (br s, 1H), 3.85 (br s, 1H), 3.56 (dd, J = 9.8, 3.9 Hz, 1H), 3.50-3.47 (m, 2H), 3.42-3.38 (m, 1H), 3.28-3.14 (m, 8H), 3.08-3.05 (m, 1H), 2.93-2.82 (m, 2H), 2.71-2.66 (m, 4H), 2.57-2.54 (m, 1H), 2.38 (s, 3H), 2.22-2.20 (m, 5H), 1.52-1.42 (m, 6H), 1.32-1.23 (m, 2H).
Example 211	4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((octahydro-2*H*-isoindol-2-yl)sulfonyl)benzamide  Synthesised from Intermediates 196 and 6	UPLC: (System 3, Method K) Rt = 4.04 min, m/z 706.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.00-7.98 (m, 2H), 7.56 (s, 2H), 6.86 (s, 1H), 4.47-4.28 (m, 3H), 3.86-3.84 (m, 1H), 3.58 (dd, J = 10.3, 3.0 Hz, 1H), 3.49-3.47 (m, 4H), 3.34 (s, 7H), 3.21-3.16 (m, 3H), 3.12-2.98 (m, 5H), 2.91-2.58 (m, 8H), 2.35-2.20 (m, 3H), 1.74-1.59 (m, 3H), 1.54-1.31 (m, 3H). One exchangeable proton not observed.
Example 212	(*R*)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.01 min, m/z 726.0 $(M+H^+)$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.53 (br s, 1H), 7.34-7.32 (m, 1H), 7.28-7.19 (m, 1H), 6.86-6.85 (m, 1H), 4.52 (br s, 1H), 4.28-4.23 (m, 1H), 4.23 (s, 1H), 3.89-3.87 (m, 1H), 3.58-3.54 (m, 1H), 3.46-3.45 (m, 1H), 3.40-3.37 (m, 5H), 3.27 (s, 3H), 3.24 (br s, 1H), 3.17-3.14 (m, 2H), 3.07-3.04 (m,

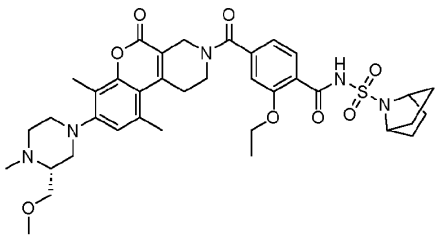
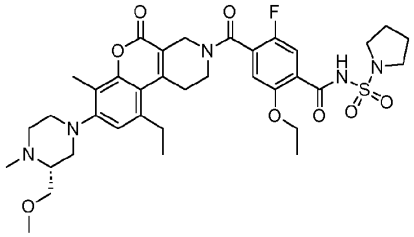
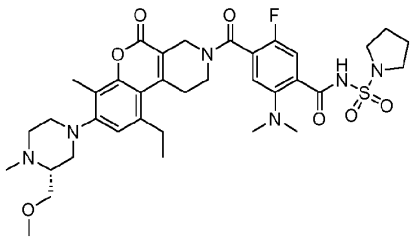
	 Synthesised from Intermediates 208 and 6	1H), 2.92-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.54-2.51 (m, 2H), 2.37 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H), 0.80-0.77 (m, 2H), 0.63-0.59 (m, 2H). Mixture of rotamers.
Example 213	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 209 and 6	HPLC: (System 1, Method H) Rt = 7.16 min, m/z 751.9 ($M+H^+$) (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.27-7.16 (m, 2H), 6.86-6.85 (m, 1H), 4.52 (br s, 1H), 4.28-4.21 (m, 1H), 4.18 (br s, 3H), 3.89-3.86 (m, 1H), 3.59-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.28 (s, 3H), 3.24 (br s, 1H), 3.18-3.16 (m, 2H), 3.09-3.06 (m, 1H), 2.96-2.93 (m, 1H), 2.88-2.83 (m, 1H), 2.72-2.58 (m, 6H), 2.41 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H), 1.43-1.41 (m, 4H), 0.81-0.77 (m, 2H), 0.61-0.57 (m, 2H). Mixture of rotamers.
Example 214	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide  Synthesised from Intermediates 206 and 229	HPLC: (System 1, Method H) Rt = 7.23 min, m/z 726.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.61-7.52 (m, 1H), 7.34-7.31 (m, 1H), 7.23-7.13 (m, 2H), 4.54 (br s, 1H), 4.22-4.13 (m, 3H), 3.97 (t, J = 5.8 Hz, 1H), 3.60-3.55 (m, 2H), 3.53-3.50 (m, 2H), 3.46-3.44 (m, 2H), 3.41-3.37 (m, 1H), 3.28 (s, 3H), 3.13-3.10 (m, 1H), 2.99-2.89 (m, 5H), 2.86-2.78 (m, 2H), 2.73-2.68 (m, 1H), 2.63-2.51 (m, 2H), 2.39 (s, 3H), 1.59-1.57 (m, 2H), 1.34-1.28 (m, 3H), 1.24-1.16 (m, 3H), 0.67-0.62 (m, 1H), 0.32-0.29 (m, 1H). Mixture of rotamers.
Example 215	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide	HPLC: (System 1, Method H) Rt = 7.23 min, m/z 740.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.61-7.52 (m, 1H), 7.28-7.26 (m, 1H), 7.21-7.13 (m, 2H), 4.53 (br s, 1H), 4.20-4.11 (m, 5H), 3.97 (t, J = 5.8 Hz, 1H),

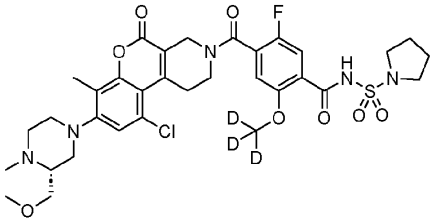
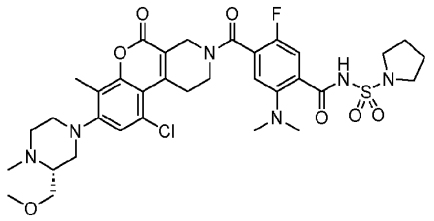
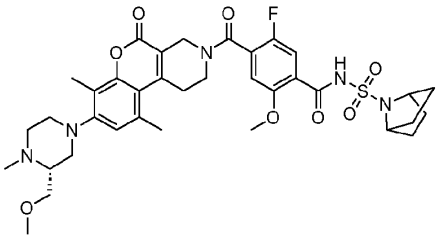
	 Synthesised from Intermediates 207 and 229	3.60-3.54 (m, 2H), 3.41-3.37 (m, 1H), 3.28 (s, 3H), 3.12-3.10 (m, 1H), 2.99-2.89 (m, 5H), 2.86-2.78 (m, 2H), 2.73-2.68 (m, 1H), 2.63-2.53 (m, 2H), 2.39 (s, 3H), 1.86-1.84 (m, 4H), 1.44-1.43 (m, 4H), 1.33-1.26 (m, 3H), 1.24-1.16 (m, 3H). Mixture of rotamers.
Example 216	(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 181 and 6	UPLC: (System 3, Method K) Rt = 4.02 min, m/z 740.7 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45-7.43 (m, 1H), 7.24-7.15 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.19 (s, 1H), 4.16-4.07 (m, 2H), 3.88-3.86 (m, 1H), 3.57-3.44 (m, 2H), 3.39-3.31 (m, 7H), 3.23-3.04 (m, 4H), 2.90-2.81 (m, 2H), 2.74-2.69 (m, 3H), 2.66-2.61 (m, 2H), 2.40-2.32 (m, 3H), 2.24-2.15 (m, 3H), 1.34-1.23 (m, 3H), 0.87-0.77 (m, 4H), 0.74-0.62 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 217	(*R*)-*N*-((3,3-dimethylpyrrolidin-1-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 183 and 6	UPLC: (System 3, Method K) Rt = 4.30 min, m/z 742.7 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (br s, 1H), 7.44-7.41 (m, 1H), 7.25-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.61 (br s, 1H), 4.19-4.07 (m, 3H), 3.88-3.86 (m, 1H), 3.59-3.53 (m, 3H), 3.48-3.44 (m, 1H), 3.36-3.31 (m, 6H), 3.23 (s, 1H), 3.16-3.12 (m, 3H), 3.05-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.69-2.61 (m, 3H), 2.46-2.38 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.69-1.65 (m, 2H), 1.36-1.27 (m, 3H), 1.06-1.05 (m, 6H). Mixture of rotamers.
Example 218	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.91 min, m/z 740.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.4 (br s, 1H), 7.39-7.35 (m, 1H), 7.22-7.21 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.21-4.04 (m, 5H), 3.87-3.85 (m, 1H), 3.57-3.54 (m, 1H), 3.47-3.44 (m, 1H), 3.41-3.34 (m, 2H), 3.26 (s, 3H), 3.22-3.03 (m, 5H),

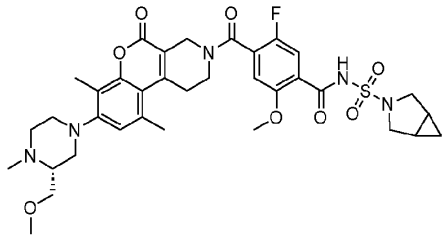
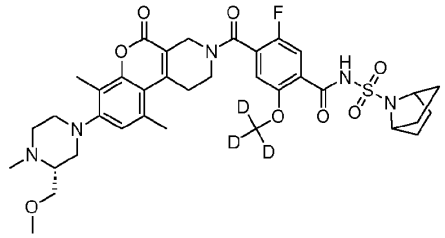
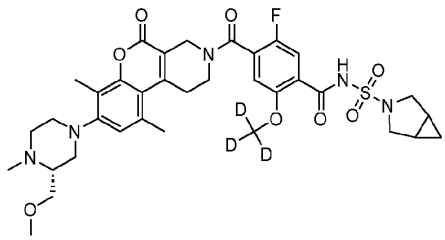
	 Synthesised from Intermediates 184 and 6	2.89-2.76 (m, 2H), 2.69-2.61 (m, 4H), 2.41-2.32 (m, 3H), 2.23-2.19 (m, 3H), 1.91-1.79 (m, 4H), 1.50-1.38 (m, 4H), 1.38-1.28 (m, 3H). Mixture of rotamers.
Example 219	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 185 and 6	UPLC: (System 3, Method K) Rt = 3.92 min, m/z 726.7 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.42-7.36 (m, 1H), 7.24-7.11 (m, 1H), 6.85-6.83 (m, 1H), 4.51 (br s, 1H), 4.19 (s, 1H), 4.14-4.05 (m, 2H), 3.87 (s, 1H), 3.57-3.42 (m, 5H), 3.35-3.32 (m, 6H), 3.14-3.01 (m, 3H), 2.84-2.79 (m, 2H), 2.68 (s, 1H), 2.65-2.59 (m, 3H), 2.43-2.39 (m, 2H), 2.33-2.30 (m, 3H), 2.23-2.19 (m, 3H), 1.57-1.50 (m, 2H), 1.36-1.31 (m, 3H), 0.64-0.59 (m, 1H), 0.33-0.29 (m, 1H). One exchangeable proton not visible. Mixture of rotamers.
Example 220	(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 187 and 6	UPLC: (System 3, Method K) Rt = 3.94 min, m/z 740.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.24 (br s, 1H), 7.42-7.40 (m, 1H), 7.23-7.15 (m, 1H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.19-4.07 (m, 3H), 4.00 (s, 4H), 3.88-3.81 (m, 1H), 3.58-3.38 (m, 3H), 3.28 (s, 3H), 3.23-3.05 (m, 4H), 2.93-2.82 (m, 2H), 2.69-2.65 (m, 3H), 2.62-2.54 (m, 3H), 2.38-2.33 (m, 3H), 2.27-2.20 (m, 3H), 2.12-2.09 (m, 4H), 1.79-1.72 (m, 2H), 1.36-1.31 (m, 3H). Mixture of rotamers.
Example 221	*N*-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	UPLC: (System 3, Method K) Rt = 3.72 min, m/z 756.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (br s, 1H), 7.36-7.34 (m, 1H), 7.20-7.12 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.19-4.04 (m, 5H), 3.87-3.85 (m, 1H), 3.61-3.54 (m, 5H), 3.48-3.45 (m, 1H), 3.39-3.35 (m, 2H), 3.27 (s, 3H), 3.23-3.04 (m, 5H),

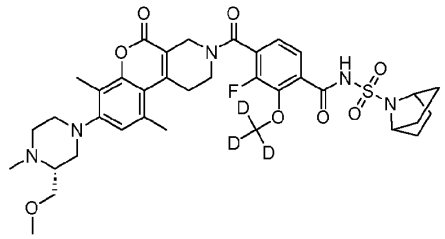
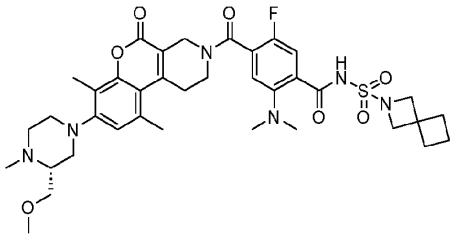
	 Synthesised from Intermediates 189 and 6	2.90-2.81 (m, 2H), 2.69-2.61 (m, 4H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 2.03-1.95 (m, 2H), 1.85-1.80 (m, 2H), 1.34-1.23 (m, 3H). Mixture of rotamers.
Example 222	(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)-2-(3,3,3-trifluoropropoxy)benzamide  Synthesised from Intermediates 210 and 6	HPLC: (System 1, Method H) Rt = 7.34 min, m/z 781.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.37-7.35 (m, 1H), 7.29-7.21 (m, 1H), 6.87-6.85 (m, 1H), 4.52 (br s, 1H), 4.36-4.29 (m, 2H), 4.19 (br s, 1H), 3.88 (t, J = 5.4 Hz, 1H), 3.58-3.55 (m, 1H), 3.48-3.47 (m, 1H), 3.43-3.36 (m, 5H), 3.28 (s, 3H), 3.24 (br s, 1H), 3.18-3.15 (m, 2H), 3.09-3.06 (m, 1H), 2.96-2.93 (m, 1H), 2.88-2.85 (m, 1H), 2.84-2.73 (m, 2H), 2.71-2.51 (m, 6H), 2.40 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.82 (m, 4H). Mixture of rotamers.
Example 223	(*R*)-3-ethoxy-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 211 and 6	UPLC: (System 3, Method K) Rt = 3.82 min, m/z 714.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35-7.33 (m, 1H), 7.25-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.35-4.00 (m, 3H), 3.89-3.86 (m, 1H), 3.62-3.45 (m, 2H), 3.42-3.37 (m, 4H), 3.35-3.32 (m, 5H), 3.23-3.03 (m, 5H), 2.94-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.34 (s, 3H), 2.23-2.20 (m, 3H), 1.91-1.81 (m, 4H), 1.33-1.15 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 224	(*R*)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide	HPLC: (System 1, Method H) Rt = 6.86 min, m/z 700.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (br s, 1H), 7.46-7.43 (m, 1H), 7.26-7.17 (m, 1H), 6.86-8.64 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.88-3.82 (m, 4H), 3.57-3.54 (m, 1H), 3.48-3.46 (m, 1H), 3.43-3.40 (m, 4H), 3.37-3.35 (m, 1H), 3.27 (s, 3H), 3.23

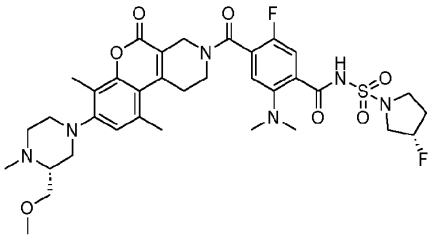
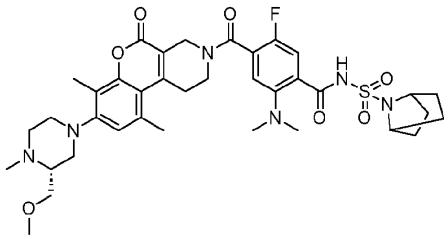
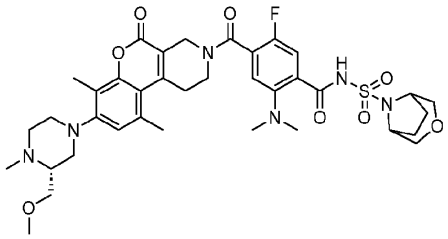
	 Synthesised from Intermediates 213 and 6	(br s, 1H), 3.15-3.13 (m, 2H), 3.05-3.02 (m, 1H), 2.87-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.49-2.44 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H). Mixture of rotamers.
Example 225	(*R*)-5-fluoro-2-(methoxy-d_3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 215 and 6	HPLC: (System 1, Method H) Rt = 6.87 min, m/z 703.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.42 (br s, 1H), 7.46-7.43 (m, 1H), 7.25-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.88 (br s, 1H), 3.57-3.54 (m, 1H), 3.48-3.46 (m, 1H), 3.43-3.40 (m, 4H), 3.37-3.35 (m, 1H), 3.27 (s, 3H), 3.25-3.23 (m, 1H), 3.15-3.13 (m, 2H), 3.05-3.03 (m, 1H), 2.87-2.80 (m, 2H), 2.69-2.62 (m, 4H), 2.47-2.44 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H). Mixture of rotamers.
Example 226	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 216 and 6	HPLC: (System 1, Method H) Rt = 7.01 min, m/z 708.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.45 (br s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.21-7.17 (m, 1H), 7.13-7.11 (m, 1H), 6.85 (s, 1H), 4.48 (br s, 1H), 4.28 (br s, 1H), 4.21 (br s, 2H), 3.87-3.84 (m, 4H), 3.57-3.50 (m, 2H), 3.36-3.33 (m, 1H), 3.26 (s, 3H), 3.21 (br s, 2H), 3.14-3.12 (m, 1H), 3.04-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.68-2.60 (m, 4H), 2.44-2.39 (m, 2H), 2.31 (s, 3H), 2.23-2.20 (m, 3H), 1.86-1.85 (m, 4H), 1.46-1.44 (m, 4H).

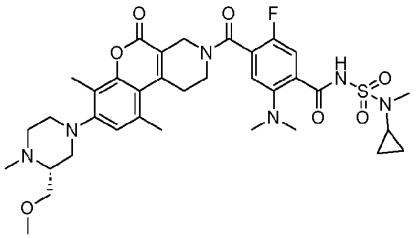
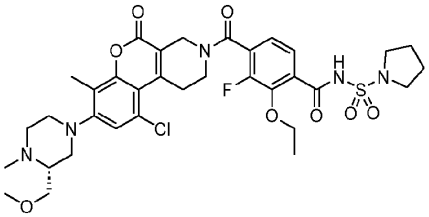
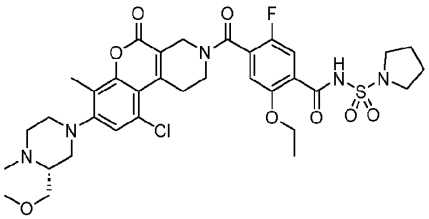
Example 227	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 217 and 6	HPLC: (System 1, Method H) Rt = 7.38 min, m/z 722.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.20-7.17 (m, 1H), 7.13-7.11 (m, 1H), 6.84 (s, 1H), 4.48 (br s, 1H), 4.28-4.23 (m, 3H), 4.15 (br s, 2H), 3.83 (br s, 1H), 3.57-3.53 (m, 1H), 3.49 (br s, 1H), 3.36-3.33 (m, 1H), 3.26 (s, 3H), 3.20 (br s, 2H), 3.14-3.12 (m, 1H), 3.04-3.02 (m, 1H), 2.86-2.79 (m, 2H), 2.68-2.60 (m, 4H), 2.44-2.39 (m, 2H), 2.31 (s, 3H), 2.23-2.19 (m, 3H), 1.87-1.85 (m, 4H), 1.46-1.45 (m, 4H), 1.35 (br s, 3H).
Example 244	(*R*)-2-ethoxy-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 201 and 255	HPLC: (System 1, Method H) Rt = 7.64 min. m/z 728.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.42 (br s, 1H), 7.47-7.43 (m, 1H), 7.25-7.17 (m, 1H), 6.89-6.87 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 1H), 4.15-4.06 (m, 2H), 3.90-3.87 (m, 1H), 3.57-3.54 (m, 1H), 3.49-3.47 (m, 1H), 3.43-3.39 (m, 4H), 3.39-3.376. (m, 1H), 3.27 (s, 3H), 3.21 (br s, 1H), 3.16-3.14 (m, 2H), 3.06-3.00 (m, 2H), 2.97-2.92 (m, 1H), 2.87-2.82 (m, 2H), 2.66-2.61 (m, 1H), 2.46-2.41 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H), 1.35-1.30 (m, 3H), 1.25-1.16 (m, 3H)
Example 245	(*R*)-2-(dimethylamino)-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 134 and 255	HPLC: (System 1, Method H) Rt = 8.10 min. m/z 727.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.98 (br s, 1H), 7.56-7.50 (m, 1H), 7.46-7.33 (m, 1H), 6.89-6.87 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.89 (br, 1H), 3.57-3.54 (m, 1H), 3.49-3.47 (m, 1H), 3.44-3.41 (m, 4H), 3.37-3.35 (m, 1H), 3.27 (s, 3H), 3.21 (br, 1H), 3.16-3.14 (m, 2H), 3.06-3.00 (m, 2H), 2.97-2.92 (m, 1H), 2.86-2.81 (m, 2H), 2.78-2.75 (m, 6H), 2.66-2.61 (m, 1H), 2.46-2.43 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H), 1.25-1.16 (m, 3H).

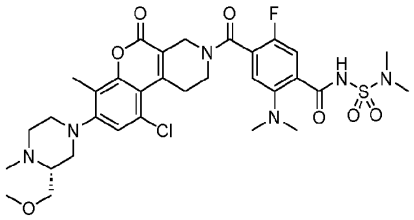
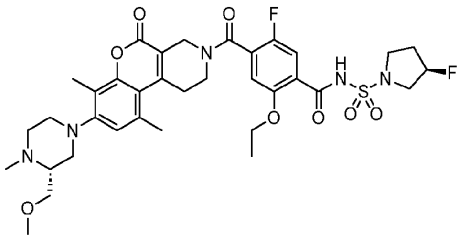
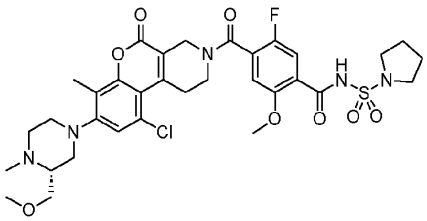
Example 246	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d_3)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 215 and 258	HPLC: (System 1, Method H) Rt = 7.24 min. m/z 723.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.45 (br s, 1H), 7.47-7.44 (m, 1H), 7.25-7.19 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (s, 1H), 4.21 (s, 1H), 3.88 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.43-3.40 (m, 4H), 3.37-3.33 (m, 3H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.68-2.65 (m, 1H), 2.45-2.42 (m, 2H), 2.31 (s, 3H), 2.25-2.21 (m, 3H), 1.86-1.83 (m, 4H).
Example 247	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 134 and 258	HPLC: (System 1, Method H) Rt = 8.23 min. m/z 734.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.08 (br s, 1H), 7.55-7.50 (m, 1H), 7.42-7.34 (m, 1H), 7.06-7.04 (m, 1H), 4.53 (s, 1H), 4.21 (s, 1H), 3.87 (br s, 1H), 3.57-3.53 (m, 1H), 3.48 (br s, 1H), 3.43-3.40 (m, 4H), 3.33 (br s, 2H), 3.26 (br s, 4H), 3.17-3.14 (m, 1H), 3.08-3.05 (m, 1H), 2.87-2.82 (m, 2H), 2.77-2.75 (m, 6H), 2.67-2.61 (m, 1H), 2.43-2.38 (m, 2H), 2.30 (s, 3H), 2.25-2.21 (m, 3H), 1.84-1.83 (m, 4H).
Example 248	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 232 and 6	HPLC: (System 1, Method H) Rt = 7.58 min, m/z 726.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.45 (br s, 1H), 7.36-7.34 (m, 1H), 7.22-7.14 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 3H), 3.87-3.80 (m, 4H), 3.57-3.54 (m, 1H), 3.48-3.46 (m, 1H), 3.39-3.35 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.49-2.45 (m, 2H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.84 (m, 4H), 1.45-1.43 (m, 4H).

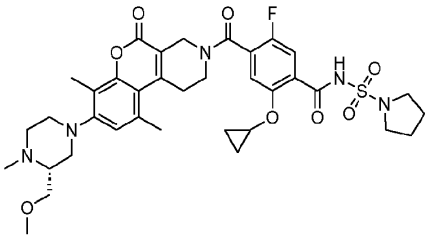
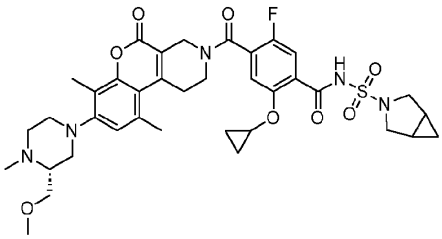
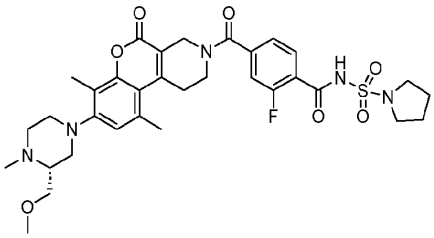
Example 249	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 233 and 6	HPLC: (System 1, Method H) Rt = 7.61 min, m/z 712.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.43-7.41 (m, 1H), 7.24-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.88-3.82 (m, 4H), 3.58-3.54 (m, 1H), 3.52-3.49 (m, 2H), 3.47-3.44 (m, 3H), 3.39-3.34 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.89-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.49-2.45 (m, 2H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 1.59-1.57 (m, 2H), 0.68-0.62 (m, 1H), 0.31-0.27 (m, 1H). Mixture of rotamers.
Example 250	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-(methoxy-d_3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 234 and 6	HPLC: (System 1, Method H) Rt = 6.93 min, m/z 729.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.37 (br s, 1H), 7.37-7.34 (m, 1H), 7.22-7.14 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 3H), 3.86 (br s, 1H), 3.58-3.54 (m, 1H), 3.48-3.46 (m, 1H), 3.39-3.35 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.51-2.50 (m, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.84 (m, 4H), 1.45-1.43 (m, 4H). Mixture of rotamers.
Example 251	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-(methoxy-d_3)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 235 and 6	HPLC: (System 1, Method H) Rt = 6.96 min, m/z 715 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.37 (br s, 1H), 7.43-7.41 (m, 1H), 7.24-7.16 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.19 (br s, 1H), 3.88 (br s, 1H), 3.58-3.54 (m, 1H), 3.53-3.50 (m, 2H), 3.47-3.45 (m, 3H), 3.39-3.35 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.51-2.50 (m, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.59-1.58 (m, 2H), 0.68-0.63 (m,

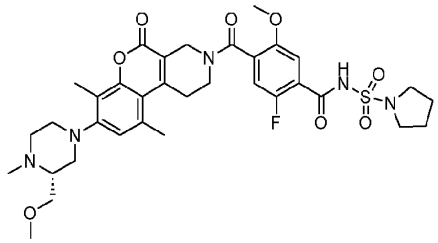
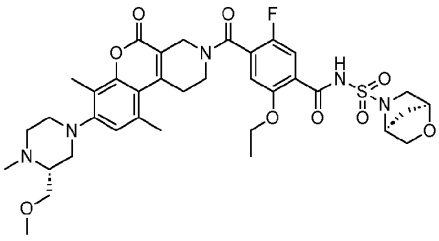
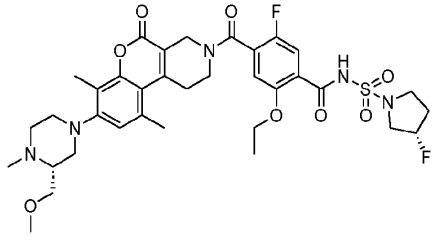
		1H), 0.31-0.29 (m, 1H). Mixture of rotamers.
Example 252	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-(methoxy-d_3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 237 and 6	HPLC: (System 1, Method H) Rt = 6.88 min, m/z 728.8 (M+H)+ (ES+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.26-7.24 (m, 1H), 7.22-7.14 (m, 1H), 6.86-6.85 (m, 1H), 4.51 (br s, 1H), 4.18 (br s, 3H), 3.87-3.85 (m, 1H), 3.58-3.55 (m, 1H), 3.48-3.46 (m, 1H), 3.43-3.39 (m, 1H), 3.28 (s, 3H), 3.23 (br s, 1H), 3.18-3.15 (m, 2H), 3.09-3.06 (m, 1H), 2.95-2.92 (m, 1H), 2.87-2.82 (m, 1H), 2.72-2.56 (m, 6H), 2.40 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.84 (m, 4H), 1.42-1.41 (m, 4H).
Example 253	(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 246 and 6	UPLC: (System 3, Method K) Rt = 4.02 min, m/z 739.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.93-7.88 (m, 1H), 7.60-7.53 (m, 1H), 6.83-6.81 (m, 1H), 4.56 (s, 1H), 4.22 (s, 1H), 4.08 (s, 4H), 3.92 (br s, 1H), 3.57 (dd, J = 9.8, 3.9 Hz, 1H), 3.49 (t, J = 5.5 Hz, 1H), 3.39-3.35 (m, 1H), 3.29 (s, 3H), 3.23-3.03 (m, 4H), 2.89-2.83 (m, 2H), 2.81-7.77 (m, 6H), 2.69-2.61 (m, 4H), 2.50-2.45 (m, 2H), 2.33 (s, 3H), 2.28-2.24 (m, 3H), 2.16-2.08 (m, 4H), 1.83-1.76 (m, 2H). One exchangeable proton not visible. Mixture of rotamers.

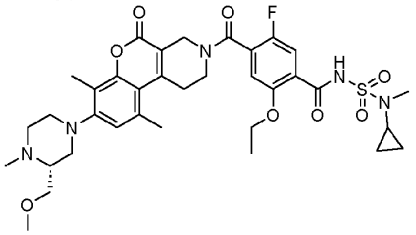
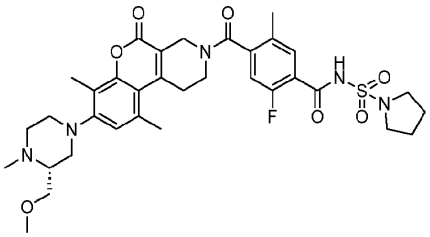
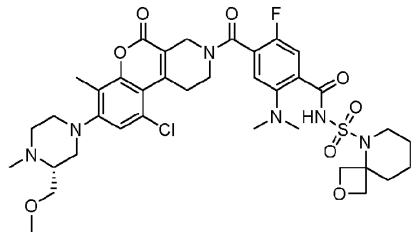
Example 254	2-(dimethylamino)-5-fluoro-*N*-(((*S*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 247 and 6	UPLC: (System 3, Method K) Rt = 3.82 min, m/z 731.8 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.90-7.85 (m, 1H), 7.60-7.53 (m, 1H), 6.82-6.80 (m, 1H), 5.36-5.22 (m, 1H), 4.55 (br s, 1H), 4.20 (br s, 1H), 3.91-3.56 (m, 5H), 3.49-3.36 (m, 2H), 3.29 (s, 3H), 3.22-3.03 (m, 4H), 2.89-2.84 (m, 2H), 2.80-2.76 (m, 6H), 2.68-2.60 (m, 4H), 2.48-2.45 (m, 2H), 2.35 (s, 3H), 2.27-2.00 (m, 6H). One exchangeable proton not visible. Mixture of rotamers.
Example 255	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 170 and 6	UPLC: (System 3, Method K) Rt = 4.01 min, m/z 739.5 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.89-7.84 (m, 1H), 7.57-5.50 (m, 1H), 6.83-6.81 (m, 1H), 4.55 (s, 1H), 4.31 (s, 2H), 4.21 (s, 1H), 3.97 (br s, 1H), 3.59-3.56 (m, 1H), 3.49-3.46 (m, 1H), 3.39-3.33 (m, 1H), 3.29 (s, 3H), 3.24-3.03 (m, 4H), 2.92-2.84 (m, 2H), 2.78-2.75 (m, 6H), 2.68-2.57 (m, 4H), 2.52-2.43 (m, 2H), 2.36 (s, 3H), 2.28-2.24 (m, 3H), 1.90-1.83 (m, 4H), 1.59-1.49 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 256	*N*-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 248 and 6	UPLC: (System 3, Method K) Rt = 3.71 min, m/z 755.7 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.89-7.84 (m, 1H), 7.58-7.51 (m, 1H), 6.81-6.80 (m, 1H), 4.54 (br s, 1H), 4.20 (br s, 3H), 3.90-3.82 (br s, 1H), 3.70-3.67 (m, 2H), 3.61-3.56 (m, 4H), 3.49-3.46 (m, 1H), 3.40-3.33 (m, 1H), 3.29 (s, 3H), 3.23-3.03 (m, 5H), 2.93-2.84 (m, 3H), 2.78-2.72 (m, 6H), 2.72-2.59 (m, 5H), 2.52-2.45 (m, 2H), 2.37 (s, 3H), 2.27-2.22 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.

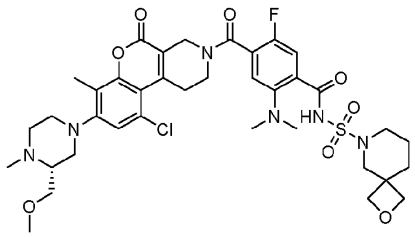
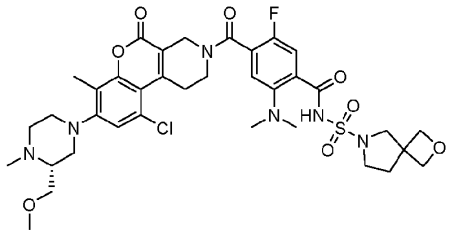
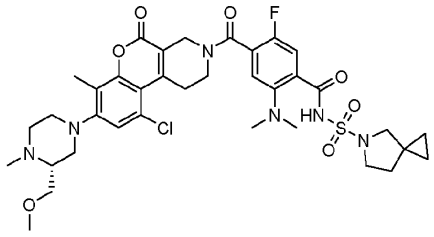
Example 257	(*R*)-*N*-(*N*-cyclopropyl-*N*-methylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 250 and 6	UPLC: (System 3, Method K) Rt = 3.96 min, m/z 713.5 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.94-7.89 (m, 1H), 7.62-7.55 (m, 1H), 6.82-6.81 (m, 1H), 4.56 (br s, 1H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.59-3.35 (m, 3H), 3.30 (s, 3H), 3.24-3.06 (m, 4H), 3.03-3.02 (m, 3H), 2.89-2.84 (m, 2H), 2.81-2.78 (m, 6H), 2.68-2.56 (m, 5H), 2.49-2.40 (m, 2H), 2.33 (s, 3H), 2.28-2.24 (m, 3H), 0.89-0.71 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.
Example 258	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 161 and 258	HPLC: (System 1, Method H) Rt = 7.29 min, m/z 733.9 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.55 (br s, 1H), 7.37-7.33 (m, 1H), 7.25-7.19 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22-4.14 (m, 3H), 3.87 (t, J = 5.6 Hz, 1H), 3.57-3.54 (m, 1H), 3.49-3.46 (m, 1H), 3.43-3.39 (m, 4H), 3.37-3.36 (m, 2H), 3.27 (s, 3H), 3.25 (br s, 1H), 3.18-3.16 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.70-2.64 (m, 1H), 2.49-2.44 (m, 2H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 1.87-1.84 (m, 4H), 1.33-1.28 (m, 3H). Mixture of rotamers.
Example 259	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 201 and 258	HPLC: (System 1, Method H) Rt = 7.70 min. m/z 733.8 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.47-7.44 (m, 1H), 7.24-7.18 (m, 1H), 7.06-7.04 (m, 1H), 4.53 (s, 1H), 4.20 (s, 1H), 4.15-4.06 (m, 2H), 3.87 (br s, 1H), 3.57-3.53 (m, 1H), 3.47-3.43 (m, 5H), 3.36-3.33 (m, 2H), 3.27 (br s, 4H), 3.17-3.14 (m, 1H), 3.08-3.06 (m, 1H), 2.87-2.83 (m, 2H), 2.67-2.62 (m, 1H), 2.44-2.39 (m, 2H), 2.31 (s, 3H), 2.25-2.21 (m, 3H), 1.85-1.83 (m, 4H) , 1.35-1.30 (m, 3H).

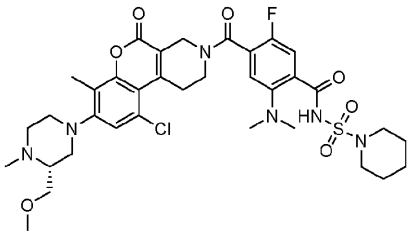
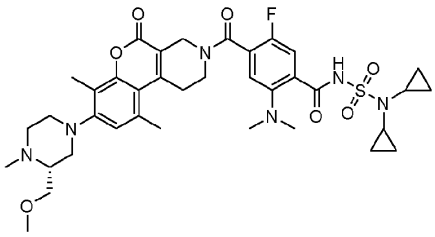
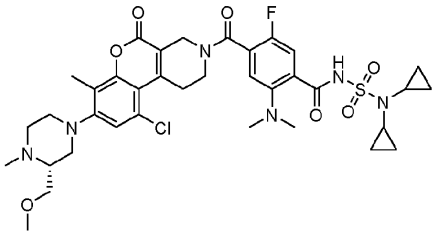
Example 260	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide  Synthesised from Intermediates 251 and 258	HPLC: (System 1, Method H) Rt = 7.42 min. m/z 707.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.14 (br s, 1H), 7.57-7.51 (m, 1H), 7.44-7.35 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (s, 1H), 4.21 (s, 1H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.38-3.36 (m, 2H), 3.27 (br, 4H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.87-2.83 (m, 8H), 2.79-2.77 (m, 6H), 2.69-2.63 (m, 1H), 2.44-2.41 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H).
Example 261	2-ethoxy-5-fluoro-*N*-(((*R*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 241 and 6	UPLC: (System 3, Method K) Rt = 3.76 min, m/z 730.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 11.19 (s, 1H), 7.41-7.39 (m, 1H), 7.22-7.14 (m, 1H), 6.86-6.84 (m, 1H), 5.36 (d, J = 53.1 Hz, 1H), 4.51 (s, 1H), 4.18 (s, 1H), 4.14-4.05 (m, 2H), 3.88-3.85 (m, 1H), 3.77-3.61 (m, 3H), 3.58-3.45 (m, 4H), 3.40-3.36 (m, 1H), 3.27 (s, 3H), 3.23-3.21 (m, 1H), 3.16-3.09 (m, 2H), 3.07-3.04 (m, 1H), 2.91-2.81 (m, 2H), 2.69-2.61 (m, 4H), 2.53 (s, 1H), 2.41-2.33 (m, 3H), 2.26-2.20 (m, 3H), 2.16-1.97 (m, 2H), 1.32 (q, J = 7.3 Hz, 3H). Mixture of rotamers.
Example 262	(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 213 and 258	HPLC: (System 1, Method H) Rt = 7.18 min. m/z 719.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.45 (br s, 1H), 7.47-7.44 (m, 1H), 7.26-7.20 (m, 1H), 7.06-7.04 (m, 1H), 4.53 (s, 1H), 4.21 (s, 1H), 3.85-3.82 (m, 4H), 3.57-3.53 (m, 1H), 3.48-3.47 (m, 1H), 3.43-3.40 (m, 4H), 3.37-3.33 (m, 2H), 3.27 (br s, 4H), 3.17-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.68-2.62 (m, 1H), 2.45-2.42 (m, 2H), 2.31 (s, 3H), 2.25-2.21 (m, 3H), 1.86-1.83 (m, 4H).

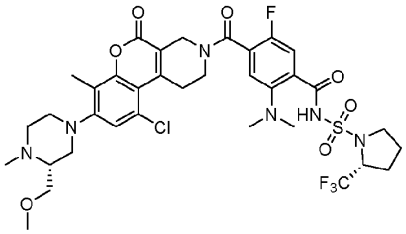
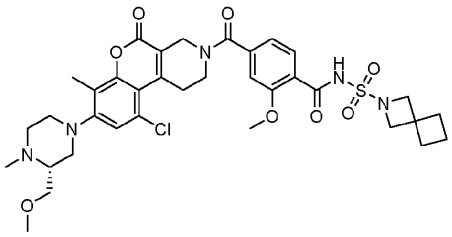
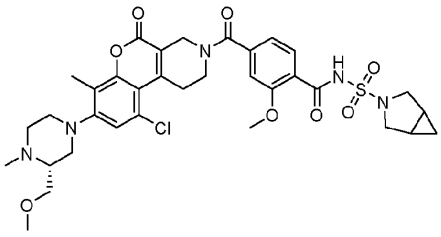
Example 263	(*R*)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 244 and 6	HPLC: (System 1, Method H) Rt = 7.17 min. m/z 726.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.39 (br s, 1H), 7.48-7.38 (m, 2H), 6.86-6.84 (m, 1H), 4.53-4.52 (m, 1H), 4.22 (s, 1H), 4.00-3.92 (m, 1H), 3.89 (br s, 1H), 3.57-3.54 (m, 1H), 3.50-3.47 (m, 1H), 3.44-3.38 (m, 4H), 3.36-3.35 (m, 1H), 3.27-3.25 (m, 4H), 3.16-3.13 (m, 2H), 3.06-3.03 (m, 1H), 2.88-2.80 (m, 2H), 2.70-2.62 (m, 4H), 2.48-2.43 (m, 2H), 2.33 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.82 (m, 4H), 0.85-0.76 (m, 2H), 0.73-0.67 (m, 2H).
Example 264	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 245 and 6	HPLC: (System 1, Method H) Rt = 7.25 min. m/z 737.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (br s, 1H), 7.47-7.38 (m, 2H), 6.86-6.85 (m, 1H), 4.53-4.52 (m, 1H), 4.22 (s, 1H), 4.00-3.92 (m, 1H), 3.89 (br s, 1H), 3.58-3.54 (m, 1H), 3.51-3.44 (m, 5H), 3.39-3.37 (m, 1H), 3.27 (s, 3H), 3.25 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.70-2.62 (m, 4H), 2.51-2.50 (m, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.59-1.57 (m, 2H), 0.85-0.72 (m, 4H), 0.67-0.62 (m, 1H), 0.30-0.26 (m, 1H).
Example 265	(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 236 and 6	HPLC: (System 1, Method H) Rt = 6.57 min, m/z 670.1 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.50 (br s, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.45 (d, J = 10.0 Hz, 1H), 7.39-7.38 (m, 1H), 6.86 (s, 1H), 4.47 (br s, 1H), 4.27 (br s, 1H), 3.83 (br 1H), 3.59-3.55 (m, 1H), 3.50 (br s, 1H), 3.45-3.41 (m, 1H), 3.38-3.36 (m, 4H), 3.28 (s, 3H), 3.22-3.16 (m, 3H), 3.10-3.07 (m, 1H), 2.98-2.95 (m, 1H), 2.89-2.83 (m, 1H), 2.74-2.61 (m, 6H), 2.42 (s, 3H), 2.24-2.20 (m, 3H), 1.83-1.81 (m, 4H).

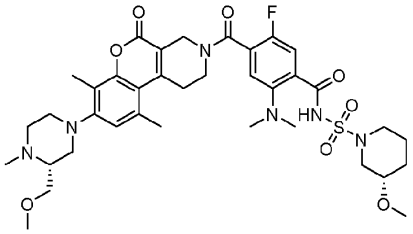
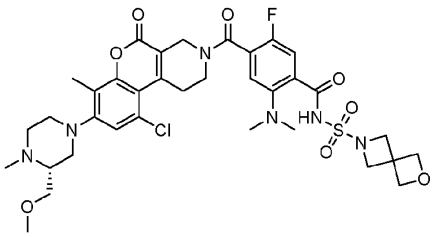
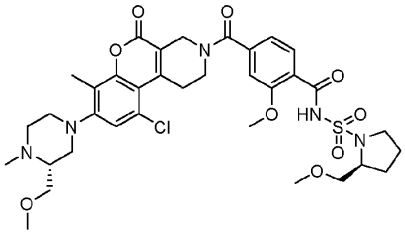
Example 266	(*R*)-2-fluoro-5-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 252 and 6	HPLC: (System 1, Method H) Rt = 6.64 min. m/z 700.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ:11.47 (br s, 1H), 7.30-7.22 (m, 2H), 6.87-6.85 (m, 1H), 4.56-4.39 (m, 1H), 4.08-4.07 (m, 1H), 3.94-3.76 (m, 4H), 3.59-3.55 (m, 1H), 3.44-3.41 (m, 2H), 3.37-3.34 (m, 4H), 3.28 (s, 3H), 3.19-3.16 (m, 2H), 3.12-3.07 (m, 2H), 2.97-2.94 (m, 1H), 2.88-2.83 (m, 1H), 2.73-2.62 (m, 6H), 2.42 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.80 (m, 4H).
Example 267	*N*-(((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 243 and 6	UPLC: (System 3, Method K) Rt = 3.59 min, m/z 742.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.76-7.72 (m, 1H), 7.15-1.10 (m, 1H), 6.83-6.81 (m, 1H), 4.62-4.56 (m, 3H), 4.27-4.18 (m, 3H), 3.92-3.89 (m, 2H), 3.73-3.68 (m, 1H), 3.58-3.55 (m, 2H), 3.51-3.44 (m, 2H), 3.39-3.35 (m, 1H), 3.31-3.30 (m, 3H), 3.23-3.04 (m, 4H), 2.89-2.82 (m, 2H), 2.69-2.62 (m, 4H), 2.46-2.40 (m, 2H), 2.32-2.25 (m, 6H), 1.85 (s, 2H), 1.49-1.43 (m, 3H). One exchangeable proton no visible. Mixture of rotamers.
Example 268	2-ethoxy-5-fluoro-*N*-(((*S*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 239 and 6	UPLC: (System 3, Method K) Rt = 3.76 min, m/z 732.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.77-7.72 (m, 1H), 7.14-7.11 (m, 1H), 6.82-6.81 (m, 1H), 5.36-5.22 (m, 1H), 4.55 (s, 1H), 4.28-4.19 (m, 3H), 3.91-3.74 (m, 3H), 3.70-3.54 (m, 3H), 3.50-3.47 (m, 1H), 3.38-3.34 (m, 1H), 3.29-3.28 (m, 3H), 3.24-3.03 (m, 4H), 2.88-2.83 (m, 2H), 2.68-2.61 (m, 4H), 2.47-2.41 (m, 2H), 2.32-2.17 (m, 8H), 1.52-1.44 (m, 3H). One exchangeable proton no visible. Mixture of rotamers.

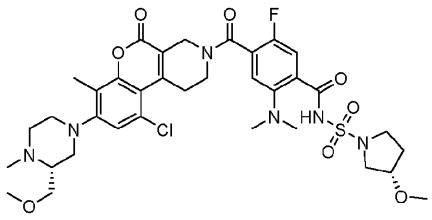
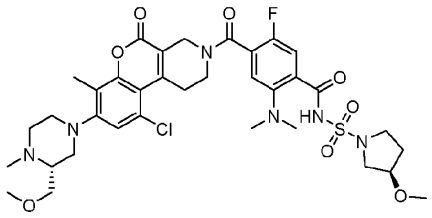
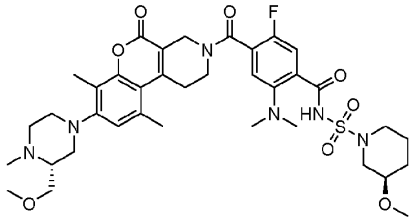
Example 269	(*R*)-*N*-(*N*-cyclopropyl-*N*-methylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 259 and 6	UPLC: (System 3, Method K) Rt = 3.86 min, m/z 714.4 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, ACN-d_3) δ: 7.79-7.75 (m, 1H), 7.17-7.12 (m, 1H), 6.83-6.79 (m, 1H), 4.55 (s, 1H), 4.29-4.21 (m, 3H), 3.91 (br s, 1H), 3.58-3.48 (m, 2H), 3.38-3.34 (m, 1H), 3.29 (s, 3H), 3.23-3.12 (m, 3H), 3.06-2.98 (m, 4H), 2.88-2.82 (m, 2H), 2.68-2.61 (m, 5H), 2.48-2.41 (m, 2H), 2.31 (s, 3H), 2.28-2.24 (m, 3H), 1.50-1.44 (m, 3H), 0.83-0.75 (m, 4H). One exchangeable proton no visible. Mixture of rotamers.
Example 270	(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 260 and 6	UPLC: (System 3, Method K) Rt = 3.69 min, m/z 684.5 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, ACN-d_3) δ: 7.69-7.64 (m, 1H), 7.16-7.10 (m, 1H), 6.84-6.82 (m, 1H), 4.68-4.36 (m, 1H), 4.08 (br s, 1H), 3.71 (s, 1H), 3.60-3.56 (m, 1H), 3.50-3.47 (m, 4H), 3.41-3.36 (m, 2H), 3.32 (s, 3H), 3.25-3.04 (m, 4H), 2.90-2.85 (m, 2H), 2.70-2.61 (m, 4H), 2.51-2.44 (m, 2H), 2.36-2.20 (m, 9H), 1.93-1.89 (m, 4H). One exchangeable proton no visible. Mixture of rotamers.
Example 271	(R)-N-((2-oxa-5-azaspiro[3.5]nonan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 262	HPLC: (System 1, Method H) Rt = 7.42 min. m/z 789.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:12.92 (br s, 1H), 7.48-7.41 (m, 1H), 7.35-7.25 (m, 1H), 7.07-7.05 (m, 1H), 4.90-4.85 (m, 2H), 3.53 (br s, 1H), 4.27-4.22 (m, 3H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.49 (br s, 1H), 3.41 (br s, 1H), 3.31-3.27 (m, 7H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.81-2.78 (m, 6H), 2.72-2.64 (m, 1H), 2.41 (br s, 2H), 2.34 (s, 3H), 2.24-2.21 (m, 3H), 1.96-1.95 (m, 2H), 1.69 (br s, 2H), 1.49 (br s, 2H).

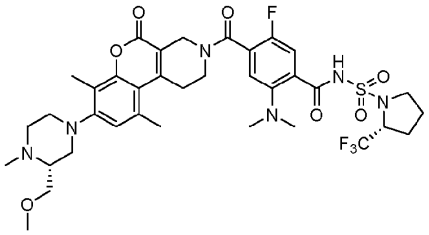
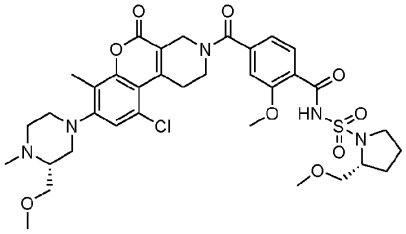
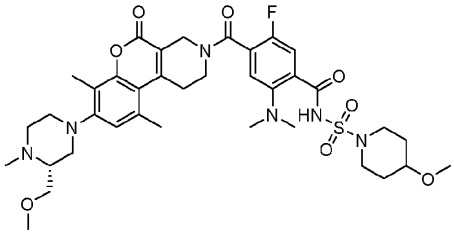
Example 272	(R)-N-((2-oxa-6-azaspiro[3.5]nonan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 264	HPLC: (System 1, Method H) Rt = 7.39 min. m/z 789.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.24 (br s, 1H), 7.55-7.49 (m, 1H), 7.543-7.35 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.30-4.21 (m, 5H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48-3.45 (m, 3H), 3.42-3.39 (m, 2H), 3.27 (br s, 4H), 3.23-3.17 (m, 3H), 3.10-3.08 (m, 1H), 2.89-2.84 (m, 2H), 2.80-2.77 (m, 6H), 2.71-2.65 (m, 1H), 2.51 (br s, 1H), 2.45 (br s, 1H), 2.35 (s, 3H), 2.25-2.21 (m, 3H), 1.75-1.73 (m, 2H), 1.51 (br s, 2H).
Example 273	(R)-N-((2-oxa-6-azaspiro[3.4]octan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 266	HPLC: (System 1, Method H) Rt = 7.08 min. m/z 774.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.05 (br s, 1H), 7.55-7.50 (m, 1H), 7.44-7.35 (m, 1H), 7.07-7.05 (m, 1H), 4.56-4.53 (m, 3H), 4.45-4.43 (m, 2H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.65 (s, 2H), 3.57-3.54 (m, 1H), 3.48-3.42 (m, 3H), 3.38-3.35 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.77-2.75 (m, 6H), 2.69-2.64 (m, 1H), 2.49-2.45 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 2.19-2.15 (m, 2H).
Example 274	(R)-N-((5-azaspiro[2.4]heptan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 268	HPLC: (System 1, Method H) Rt = 8.79 min. m/z 759.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.01 (br s, 1H), 7.56-7.50 (m, 1H), 7.44-7.34 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br, 1H), 4.22 (br s, 1H), 3.87 (br s, 1H), 3.62-3.58 (m, 2H), 3.57-3.54 (m, 1H), 3.49 (br s, 1H), 3.37-3.34 (m, 4H), 3.27 (br s, 4H), 3.17-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.78-2.76 (m, 6H), 2.68-2.65 (m, 1H), 2.45-2.39 (m, 2H), 2.31 (s, 3H), 2.25-2.21 (m, 3H), 1.85-1.75 (m, 2H), 0.62-0.55 (m, 4H).

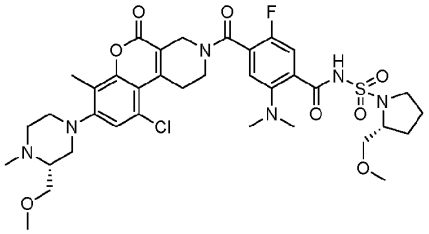
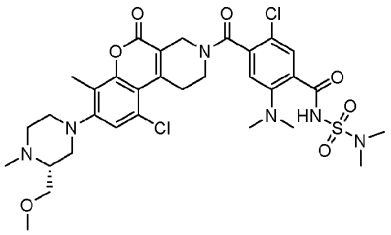
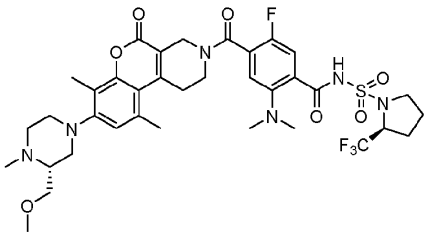
Example 275	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(piperidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 258 and 269	HPLC: (System 1, Method H) Rt = 8.45 min. m/z 746.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.09 (br s, 1H), 7.56-7.50 (m, 1H), 7.45-7.35 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.37-3.33 (m, 2H), 3.27-3.26 (m, 8H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.79-2.76 (m, 6H), 2.68-2.63 (m, 1H), 2.46-2.41 (m, 2H), 2.32 (s, 3H), 2.25-2.21 (m, 3H), 1.57 (br s, 4H), 1.50-1.49 (m, 2H).
Example 276	(R)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 270	HPLC: (System 1, Method H) Rt = 8.00 min. m/z 739.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.66 (br s, 1H), 7.62-7.41 (m, 2H), 6.86-6.85 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 1H), 3.87 (br s, 1H), 3.58-3.54 (m, 1H), 3.49-3.47 (m, 1H), 3.39-3.36 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.90-2.83 (m, 2H), 2.81-2.78 (m, 6H), 2.75-2.62 (m, 6H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 0.81 (br s, 4H), 0.70-0.65 (m, 4H).
Example 277	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 270	HPLC: (System 1, Method H) Rt = 8.47 min. m/z 759.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.74 (br s, 1H), 7.63-7.45 (m, 2H), 7.07-7.05 (m, 1H), 4.54 (br s, 1H), 4.22 (br s, 1H), 3.88 (br s, 1H), 3.57-3.54 (m, 1H), 3.49 (br, s 1H), 3.38-3.36 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.81-2.78 (m, 6H), 2.74-2.70 (m, 2H), 2.67-2.64 (m, 1H), 2.49-2.46 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 0.81-0.80 (m, 4H), 0.69-0.67 (m, 4H).

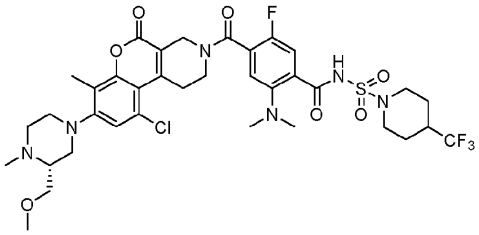
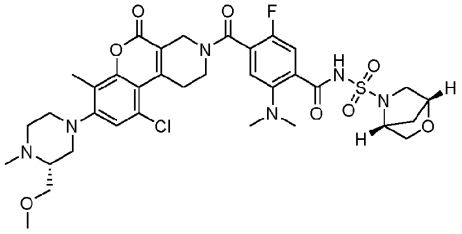
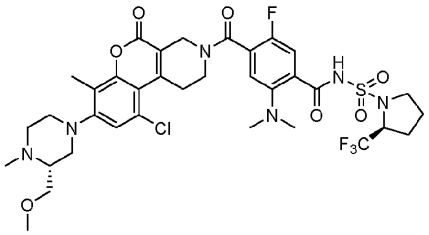
Example 278	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 272	HPLC: (System 1, Method H) Rt = 8.18 min. m/z 800.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.04 (br s, 1H), 7.51-7.47 (m, 1H), 7.39-7.33 (m, 1H), 7.09-7.07 (m, 1H), 4.94-4.90 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 3.88 (br s 1H), 3.58-3.56 (m, 1H), 3.48-3.42 (m, 3H), 3.32 (br s, 1H), 3.29 (br s, 4H), 3.26-3.21 (m, 2H), 3.18-3.12 (m, 1H), 3.02-2.96 (m, 1H), 2.94-2.87 (m, 1H), 2.82-2.79 (m, 6H), 2.77-2.75 (m, 2H), 2.69-2.62 (m, 1H), 2.46 (s, 3H), 2.26-2.22 (m, 3H), 2.15-2.06 (m, 1H), 1.98-1.88 (m, 3H).
Example 279	(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide  Synthesised from Intermediates 258 and 273	HPLC: (System 1, Method H) Rt = 7.26 min. m/z 727.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.36 (br s, 1H), 7.53-7.50 (m, 1H), 7.22 (s, 1H), 7.14-7.11 (m, 1H), 7.05 (s, 1H), 4.50 (br s, 1H), 4.32 (br s, 1H), 4.02 (s, 4H), 3.88-3.84 (m, 4H), 3.57-3.54 (m, 2H), 3.38-3.32 (m, 3H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.69-2.64 (m, 1H), 2.48-2.45 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 2.13-2.10 (m, 4H), 1.80-1.74 (m, 2H).
Example 280	N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide  Synthesised from Intermediates 258 and 274	HPLC: (System 1, Method H) Rt = 7.41 min. m/z 713.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.4 (br s, 1H), 7.52-7.51 (m, 1H), 7.22 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.05 (s, 1H), 4.49 (br s, 1H), 4.30 (br s, 1H), 3.88 (br s, 4H), 3.57-3.47 (m, 6H), 3.35-3.32 (m, 3H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.07-3.05 (m, 1H), 2.87-2.82 (m, 2H), 2.67-2.61 (m, 1H), 2.42-2.40 (m, 2H), 2.30 (s, 3H), 2.25-2.21 (m, 3H), 1.59 (br s, 2H), 0.67-0.66 (m, 1H), 0.28-0.27 (m, 1H).

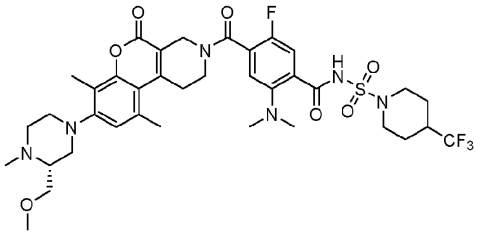
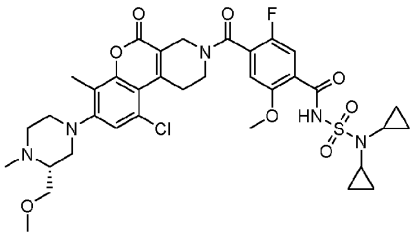
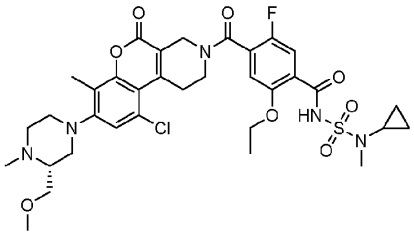
Example 281	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-3-methoxypiperidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 276	HPLC: (System 1, Method H) Rt = 7.31 min. m/z 757.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.1 (br s, 1H), 7.52-7.46 (m, 1H), 7.40-7.28 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.20 (s, 1H), 3.87 (br s, 1H), 3.57-3.53 (m, 2H), 3.47 (t, J = 5.2 Hz, 1H), 3.38-3.36 (m, 2H), 3.33 (br s, 1H), 3.27-3.26 (m, 6H), 3.23 (br s, 1H), 3.16-2.99 (m, 5H), 2.89-2.83 (m, 2H), 2.79-2.76 (m, 6H), 2.69-2.61 (m, 4H), 2.49-2.47 (m, 2H), 2.34 (s, 3H), 2.24-2.20 (m, 3H), 1.82-1.73 (m, 2H), 1.48-1.38 (m, 2H).
Example 282	(R)-N-((2-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 278	HPLC: (System 1, Method H) Rt = 6.74 min. m/z 760.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:12.96 (br s, 1H), 7.53-7.49 (m, 1H), 7.40-7.34 (m, 1H), 7.08-7.06 (m, 1H), 4.64 (s, 4H), 4.53 (br s, 1H), 4.22 (br s, 1H), 4.17-4.16 (m, 4H), 3.88 (br s, 1H), 3.59-3.55 (m, 1H), 3.49-3.46 (m, 1H), 3.42-3.40 (m, 1H), 3.31 (br s, 1H), 3.28 (br s, 4H), 3.21-3.19 (m, 1H), 3.13-3.10 (m, 1H), 2.96-2.87 (m, 2H), 2.81-2.78 (m, 6H), 2.73-2.70 (m, 1H), 2.68-2.58 (m, 2H), 2.41 (s, 3H), 2.26-2.22 (m, 3H).
Example 283	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 280	HPLC: (System 1, Method H) Rt = 7.34 min. m/z 746.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.55-7.51 (m, 1H), 7.22 (s, 1H), 7.14-7.11 (m, 1H), 7.05 (s, 1H), 4.50 (br s, 1H), 4.30-4.24 (m, 2H), 3.88-3.86 (br s, 4H), 3.57-3.43 (m, 4H), 3.36 (br, 1H), 3.30 (br s, 3H), 3.28 (br s, 4H), 3.26 (s, 3H), 3.17-3.14 (m, 1H), 3.08-3.05 (m, 1H), 2.87-2.82 (m, 2H), 2.67-2.61 (m, 1H), 2.43-2.37 (m, 2H), 2.30 (s, 3H), 2.25-2.21 (m, 3H), 1.90-1.81 (m, 4H).

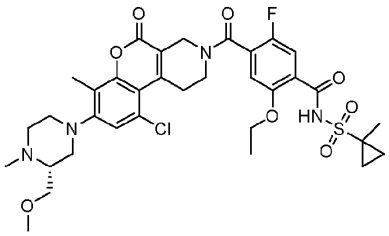
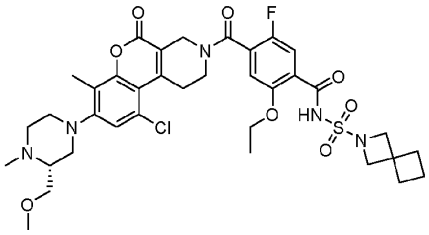
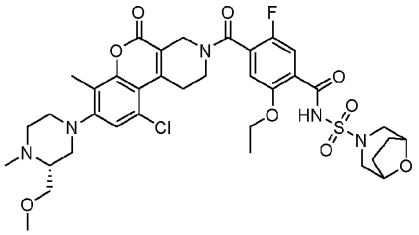
Example 284	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 282	HPLC: (System 1, Method H) Rt = 7.61 min. m/z 763.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.02 (br s, 1H), 7.54-7.48 (m, 1H), 7.43-7.34 (m, 1H), 7.07-7.04 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 4.00 (br s, 1H), 3.87 (br s, 1H), 3.57-3.54 (m, 3H), 3.48-3.40 (m, 3H), 3.39-3.33 (m, 2H), 3.27 (br s, 4H), 3.21-3.20 (m, 3H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.78-2.75 (m, 6H), 2.68-2.63 (m, 1H), 2.46-2.43 (m, 2H), 2.32 (s, 3H), 2.25-2.21 (m, 3H), 1.97-1.95 (m, 2H).
Example 285	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 284	HPLC: (System 1, Method H) Rt = 7.62 min. m/z 762.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.08 (br s, 1H), 7.54-7.48 (m, 1H), 7.42-7.33 (m, wq1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.99 (br s, 1H), 3.88 (br s, 1H), 3.56-3.51 (m, 3H), 3.48-3.40 (m, 3H), 3.38-3.33 (m, 2H), 3.27 (br s, 4H), 3.21-3.20 (m, 3H), 3.19-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.78-2.75 (m, 6H), 2.68-2.63 (m, 1H), 2.45-2.43 (m, 2H), 2.31 (s, 3H), 2.25-2.21 (m, 3H), 1.97-1.94 (m, 2H).
Example 286	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-3-methoxypiperidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 286	HPLC: (System 1, Method H) Rt = 7.29 min. m/z 757.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.10 (br s, 1H), 7.54-7.48 (m, 1H), 7.43-7.29 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 1H), 3.87 (br s, 1H), 3.58-3.53 (m, 2H), 3.48-3.46 (m, 1H), 3.38-3.33 (m, 3H), 3.27-3.26 (m, 6H), 3.23 (br s, 1H), 3.16-3.01 (m, 5H), 2.90-2.83 (m, 2H), 2.79-2.76 (m, 6H), 2.69-2.61 (m, 4H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.82-1.73 (m, 2H), 1.49-1.38 (m, 2H).

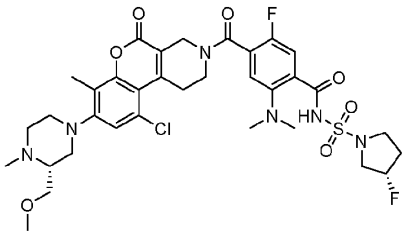
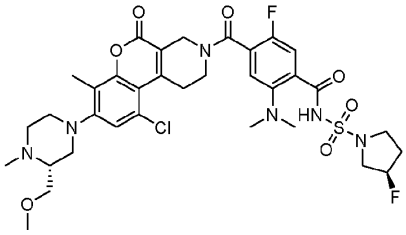
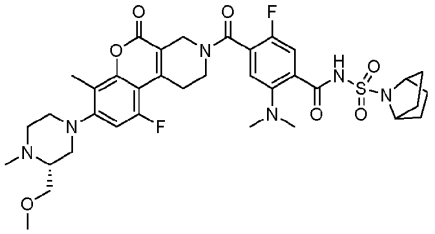
Example 287	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 272	HPLC: (System 1, Method H) Rt = 7.82 min. m/z 780.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48-7.46 (m, 1H), 7.36-7.27 (m, 1H), 6.88-6.86 (m, 1H), 4.94-4.90 (m, 1H), 4.52 (br s, 1H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.59-3.57 (m, 1H), 3.48-3.40 (m, 4H), 3.30 (br s, 4H), 3.23-3.18 (m, 2H), 3.13-3.10 (m, 2H), 3.05-3.03 (m, 1H), 2.91-2.86 (m, 1H), 2.82-2.74 (m, 8H), 2.70-2.62 (m, 4H), 3.50 (br s, 2H), 2.25-2.21 (m, 3H), 2.15-2.07 (m, 1H), 1.96-1.89 (m, 3H).
Example 288	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 288	HPLC: (System 1, Method H) Rt = 7.33 min. m/z 745.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (br s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.12 (dd, J = 7.6, 1.2 Hz, 1H), 7.05 (s, 1H), 4.49 (br s, 1H), 4.30-4.24 (m, 2H), 3.87 (br s, 4H), 3.57-3.54 (m, 1H), 3.52-3.43 (m, 3H), 3.36 (br s, 2H), 3.30-3.28 (m, 6H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.08-3.05 (m, 1H), 2.87-2.82 (m, 2H), 2.67-2.61 (m, 1H), 2.43-2.37 (m, 2H), 2.30 (s, 3H), 2.24-2.21 (m, 3H), 1.90-1.81 (m, 4H)
Example 289	(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-methoxypiperidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 290	HPLC: (System 1, Method H) Rt = 7.20 min. m/z 757.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.11 (br s, 1H), 7.53-7.47 (m, 1H), 7.45-7.30 (m, 1H), 6.86-6.84 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 1H), 3.87 (br s, 1H), 3.58-3.54 (m, 1H), 3.47-3.44 (m, 3H), 3.39-3.36 (m, 2H), 3.27 (s, 3H), 3.24 (br s, 4H), 3.16-3.11 (m, 4H), 3.06-3.04 (m, 1H), 2.90-2.83 (m, 2H), 2.79-2.76 (m, 6H), 2.69-2.62 (m, 4H), 3.51 (br s, 1H), 3.49 (br s, 1H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.89-1.84 (m, 2H), 1.56-1.51 (m, 2H).

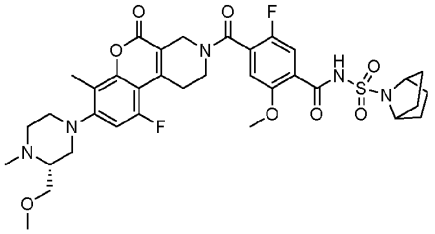
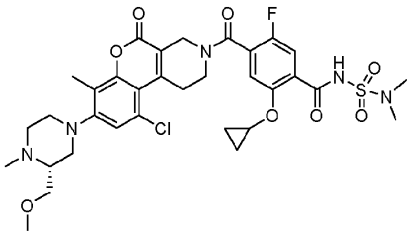
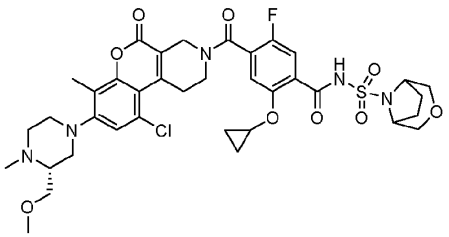
Example 290	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 291	HPLC: (System 1, Method H) Rt = 8.20 min. m/z 776.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.12 (br s, 1H), 7.57-7.51 (m, 1H), 7.45-7.36 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.27-4.21 (m, 2H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48-3.42 (m, 3H), 3.37-3.33 (m, 2H), 3.30-3.27 (m, 9H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.77-2.75 (m, 6H), 2.68-2.63 (m, 1H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.25-2.21 (m, 3H), 1.88-1.81 (m, 4H).
Example 291	(R)-5-chloro-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-N-(N,N-dimethylsulfamoyl)benzamide  Synthesised from Intermediates 258 and 292	HPLC: (System 1, Method H) Rt = 7.17 min. m/z 722.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:12.10 (br s, 1H), 7.52-7.47 (m, 1H), 7.11-7.04 (m, 2H), 4.60-4.45 (m, 1H), 4.12 (br s, 1H), 3.98-3.77 (m, 1H), 3.57-3.54 (m, 1H), 3.44-3.36 (m, 2H), 3.27 (br s, 4H), 3.18-3.16 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.81 (m, 15H), 2.70-2.64 (m, 1H), 2.50-2.47 (m, 2H), 2.34 (s, 3H), 2.25-2.21 (m, 3H).
Example 292	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 294	HPLC: (System 1, Method H) Rt = 7.77 min. m/z 780.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45-7.25 (m, 2H), 6.88-6.86 (m, 1H), 4.94-4.90 (m, 1H), 4.52 (br s, 1H), 4.21 (br, 1H), 3.87 (br s, 1H), 3.59-3.57 (m, 1H), 3.49-3.42 (m, 4H), 3.30 (br s, 4H), 3.23-3.20 (m, 2H), 3.13-3.10 (m, 2H), 3.08-3.03 (m, 1H), 2.91-2.86 (m, 1H), 2.82-2.74 (m, 8H), 2.70-2.62 (m, 4H), 3.50 (br s, 2H), 2.25-2.21 (m, 3H), 2.14-2.09 (m, 1H), 1.96-1.89 (m, 3H).

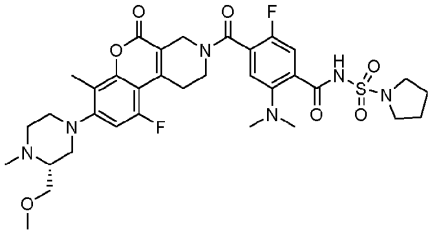
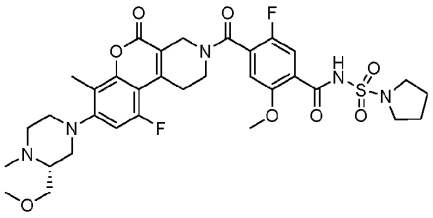
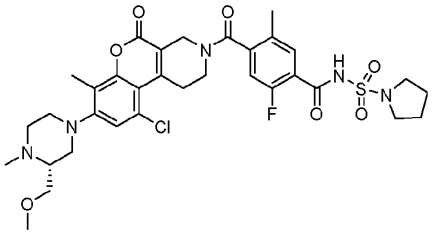
Example 293	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 296	HPLC: (System 1, Method H) Rt = 8.40 min. m/z 814.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.08 (br s, 1H), 7.52-7.46 (m, 1H), 7.42-7.34 (m, 1H), 7.08-7.06 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.88 (br s, 1H), 3.82-3.79 (m, 2H), 3.58-3.54 (m, 1H), 3.48-3.45 (m, 1H), 3.41-3.37 (m, 2H), 3.28 (br s, 5H), 3.20-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.91-2.85 (m, 4H), 2.81-2.78 (m, 6H), 2.72-2.67 (m, 1H), 2.60-2.51 (m, 2H), 2.37 (s, 3H), 2.25-2.21 (m, 3H), 1.92-1.89 (m, 2H), 1.52-1.42 (m, 2H).
Example 294	N-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 298	HPLC: (System 1, Method H) Rt = 6.92 min. m/z 760.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.05 (br s, 1H), 7.55-7.49 (m, 1H), 7.43-7.35 (m, 1H), 7.08-7.05 (m, 1H), 4.62 (br s, 1H), 4.53 (br s, 2H), 4.22 (br s, 1H), 3.87 (br s, 1H), 3.84-3.81 (m, 1H), 3.68-3.66 (m, 1H), 3.58-3.44 (m, 3H), 3.40-3.38 (m, 1H), 3.30-3.27 (m, 6H), 3.19-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.92-2.85 (m, 2H), 2.78-2.76 (m, 6H), 2.73-2.66 (m, 1H), 2.58-2.51 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 1.85-1.76 (m, 2H).
Example 295	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 294	HPLC: (System 1, Method H) Rt = 8.13 min. m/z 800.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:12.94 (br s, 1H), 7.50-7.47 (m, 1H), 7.37-7.33 (m, 1H), 7.09-7.07 (m, 1H), 4.94-4.90 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 3.87 (br s, 1H), 3.59-3.56 (m, 1H), 3.48-3.41 (m, 4H), 3.29 (br s, 4H), 3.26-3.22 (m, 2H), 3.16-3.13 (m, 1H), 3.03-3.00 (m, 1H), 2.94-2.88 (m, 1H), 2.82-2.76 (m, 8H), 2.67-2.65 (m, 1H), 2.47 (s, 3H), 2.26-2.22 (m, 3H), 2.15-2.09 (m, 1H), 1.96-1.92 (m, 3H).

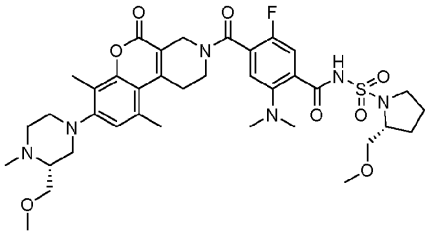
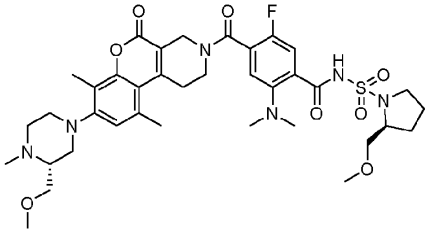
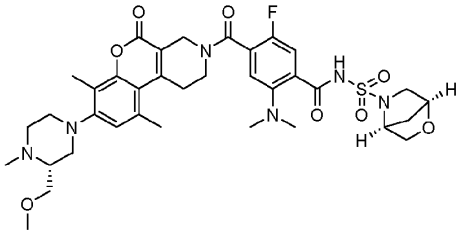
Example 296	(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 296	HPLC: (System 1, Method H) Rt = 8.07 min. m/z 814.9 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ:13.02 (br s, 1H), 7.50-7.28 (m, 2H), 6.87-6.85 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 1H), 3.87 (br s, 1H), 3.81-3.78 (m, 2H), 3.58-3.55 (m, 1H), 3.49-3.46 (m, 1H), 3.41-3.37 (m, 2H), 3.28 (s, 3H), 3.23 (br s, 1H), 3.17-3.15 (m, 2H), 3.08-3.05 (m, 1H), 2.92-2.84 (m, 4H), 2.81-2.78 (m, 6H), 2.69-2.53 (m, 6H), 2.38 (s, 3H), 2.24-2.20 (m, 3H), 1.91-1.88 (m, 2H), 1.52-1.45 (m, 2H).
Example 297	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-5-fluoro-2-methoxybenzamide  Synthesised from Intermediates 258 and 299	HPLC: (System 1, Method H) Rt = 7.50 min. m/z 746.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ:11.57 (br s, 1H), 7.45-7.42 (m, 1H), 7.24-7.19 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 3.87-3.81 (m, 4H), 3.58-3.54 (m, 1H), 3.49 (br s, 1H), 3.40-3.36 (m, 2H), 3.27 (br s, 4H), 3.19-3.17 (m, 1H), 3.10-3.08 (m, 1H), 2.91-2.84 (m, 2H), 2.73-2.66 (m, 3H), 2.55 (br s, 1H), 2.47 (br s, 1H), 2.36 (s, 3H), 2.25-2.21 (m, 3H), 0.84-0.80 (m, 4H), 0.71-0.66 (m, 4H).
Example 298	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-ethoxy-5-fluorobenzamide  Synthesised from Intermediates 259 and 258	HPLC: (System 1, Method H) Rt = 7.46 min. m/z 733.8 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ:11.48 (br s, 1H), 7.47-7.44 (m, 1H), 7.24-7.18 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 4.15-4.06 (m, 2H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.39-3.36 (m, 2H), 3.27 (br s, 4H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.92 (s, 3H), 2.89-2.84 (m, 2H), 2.70-2.65 (m, 1H), 2.62-2.58 (m, 1H), 2.51 (br s, 1H), 2.50-2.47 (m, 1H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 1.34-1.28 (m, 3H), 0.78-0.67 (m, 4H).

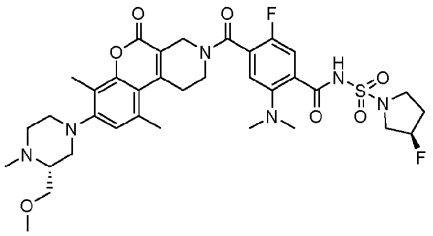
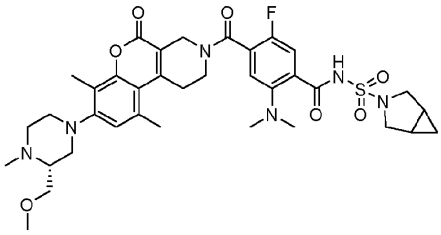
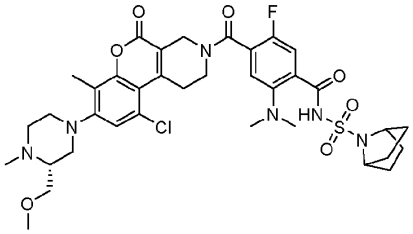
Example 299	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-N-((1-methylcyclopropyl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 300	HPLC: (System 1, Method H) Rt = 7.00 min. m/z 718.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.37 (br s, 1H), 7.44-7.41 (m, 1H), 7.23-7.18 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 4.15-4.07 (m, 2H), 3.87 (br s, 1H), 3.58-3.54 (m, 1H), 3.48-3.47 (m, 1H), 3.40-3.36 (m, 2H), 3.27 (br s, 4H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.90-2.84 (m, 2H), 2.71-2.66 (m, 1H), 2.51 (br s, 1H), 2.49 (br s, 1H), 2.35 (s, 3H), 2.25-2.21 (m, 3H), 1.52 (s, 3H), 1.44-1.41 (m, 2H), 1.34-1.30 (m, 3H), 0.94-0.91 (m, 2H).
Example 300	(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide  Synthesised from Intermediates 258 and 187	HPLC: (System 1, Method H) Rt = 8.23 min. m/z 759.6 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.32 (br s, 1H), 7.44-7.41 (m, 1H), 7.23-7.18 (m, 1H), 7.08-7.06 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 4.16-4.07 (m, 2H), 4.00 (s, 4H), 3.87 (br s, 1H), 3.58-3.54 (m, 1H), 3.48 (br s, 1H), 3.40-3.36 (m, 2H), 3.27 (br s, 4H), 3.20-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.92-2.85 (m, 2H), 2.72-2.66 (m, 1H), 2.53-2.51 (m, 2H), 2.36 (s, 3H), 2.24-2.21 (m, 3H), 2.12-2.09 (m, 4H), 1.79-1.74 (m, 2H), 1.36-1.31 (m, 3H).
Example 301	N-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide  Synthesised from Intermediates 258 and 302	HPLC: (System 1, Method H) Rt = 6.99 min. m/z 775.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.42 (br s, 1H), 7.43-7.41 (m, 1H), 7.22-7.17 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.38 (br s, 2H), 4.21 (br s, 1H), 4.12-4.07 (m, 2H), 3.86 (br s, 1H), 3.58-3.54 (m, 1H), 3.48 (b sr, 1H), 3.40-3.36 (m, 2H), 3.29-3.26 (m, 6H), 3.19-3.13 (m, 3H), 3.11-3.08 (m, 1H), 2.91-2.84 (m, 2H), 2.71-2.66 (m, 1H), 2.51 (br s, 1H), 2.50 (br s, 1H), 2.36 (s, 3H), 2.25-2.21 (m, 3H), 1.80 (br s, 4H), 1.36-1.31 (m, 3H).

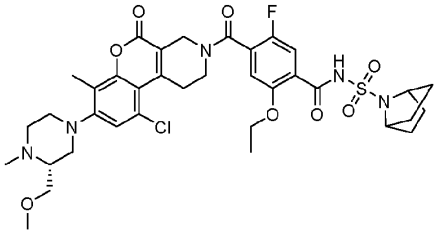
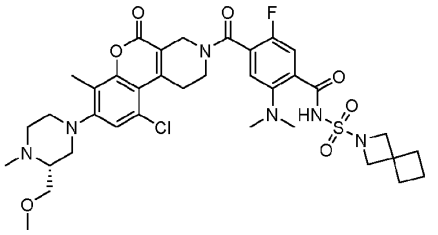
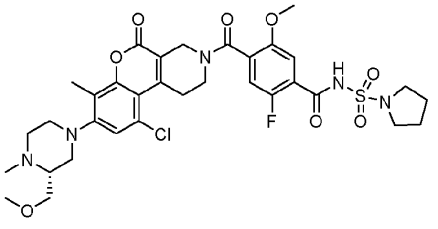
Example 302	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 304	HPLC: (System 1, Method H) Rt = 7.54 min. m/z 750.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.10 (br s, 1H), 7.53-7.33 (m, 2H), 7.07-7.05 (m, 1H), 5.42-5.29 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.75-3.66 (m, 2H), 3.63 (br s, 1H), 3.57-3.54 (m, 1H), 3.52-3.45 (m, 2H), 3.39-3.34 (m, 2H), 3.27 (br s, 4H), 3.18-3.16 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.78-2.76 (m, 6H), 2.70-2.64 (m, 1H), 2.50-2.49 (m, 2H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 2.16-2.00 (m, 2H).
Example 303	4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 258 and 306	HPLC: (System 1, Method H) Rt = 7.49 min. m/z 750.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.10 (br, s 1H), 7.53-7.33 (m, 2H), 7.07-7.05 (m, 1H), 5.42-5.29 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.87 (br s, 1H), 3.75-3.66 (m, 2H), 3.63 (br, 1H), 3.57-3.54 (m, 1H), 3.51-3.49 (m, 2H), 3.39-3.36 (m, 1H), 3.33 (br, 1H), 3.27 (br s, 4H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.88-2.84 (m, 2H), 2.78-2.76 (m, 6H), 2.70-2.65 (m, 1H), 2.50 (br, 2H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 2.16-2.01 (m, 2H).
Example 304	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 309 and 170	HPLC: (System 1, Method H) Rt = 7.43 min. m/z 773.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.07 (br s, 1H), 7.46-7.25 (m, 2H), 6.93-6.87 (m, 1H), 4.52 (br s, 1H), 4.22-4.20 (m, 3H), 3.92 (br s, 1H), 3.57-3.52 (m, 2H), 3.37-3.34 (m, 1H), 3.27 (s, 3H), 3.18-3.15 (m, 1H), 3.09-3.05 (m, 3H), 2.87-2.82 (m, 2H), 2.77-2.75 (m, 6H), 2.66-2.60 (m, 1H), 2.46-2.44 (m, 2H), 2.32 (s, 3H), 2.22-2.19 (m, 3H), 1.83-1.81 (m, 4H), 1.45-1.44 (m, 4H).

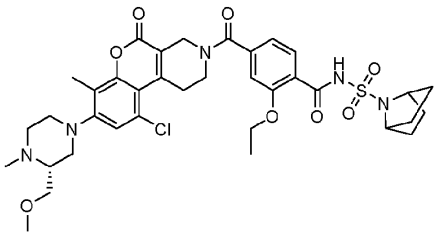
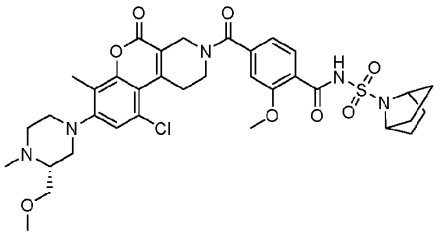
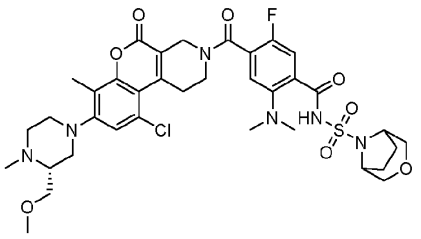
Example 305	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide  Synthesised from Intermediates 309 and 232	HPLC: (System 1, Method H) Rt = 6.99 min. m/z 730.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.38-7.34 (m, 1H), 7.21-7.15 (m, 1H), 6.93-6.88 (m, 1H), 4.53 (br s, 1H), 4.20 (br s, 3H), 3.92 (br s, 1H), 3.82-3.79 (m, 3H), 3.57-3.52 (m, 2H), 3.38-3.36 (m, 1H), 3.27 (s, 3H), 3.19-3.16 (m, 1H), 3.09-3.06 (m, 3H), 2.90-2.83 (m, 2H), 2.67-2.62 (m, 1H), 2.47-2.44 (m, 2H), 2.34 (s, 3H), 2.22-2.19 (m, 3H), 1.86-1.84 (m, 4H), 1.45-1.44 (m, 4H).
Example 306	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-N-(N,N-dimethylsulfamoyl)-5-fluorobenzamide  Synthesised from Intermediates 258 and 310	HPLC: (System 1, Method H) Rt = 7.62 min. m/z 719.8 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.35 (br s, 1H), 7.47-7.41 (m, 2H), 7.07-7.05 (m, 1H), 4.54 (br s, 1H), 4.24 (s, 1H), 3.99-3.89 (m, 2H), 3.58-3.54 (m, 1H), 3.52-3.47 (m, 1H), 3.39-3.37 (m, 2H), 3.27 (br s, 4H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.89-2.87 (m, 2H), 2.84 (s, 6H), 2.70-2.65 (m, 1H), 2.51-2.50 (m, 1H), 2.49-2.47 (m, 1H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 0.82-0.70 (m, 4H).
Example 307	N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-5-fluorobenzamide  Synthesised from Intermediates 258 and 311	HPLC: (System 1, Method H) Rt = 7.56 min. m/z 787.7 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.43 (br s, 1H), 7.44-7.39 (m, 1H), 7.37-7.35 (m, 1H), 7.08-7.06 (m, 1H), 4.54 (br s, 1H), 4.24 (s, 1H), 4.08 (br s, 2H), 3.95-3.88 (m, 2H), 3.58-3.54 (m, 5H), 3.52-3.48 (m, 1H), 3.40-3.38 (m, 2H), 3.27 (br s, 4H), 3.20-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.92-2.85 (m, 2H), 2.72-2.66 (m, 1H), 2.51-2.50 (m, 2H), 2.36 (s, 3H), 2.25-2.22 (m, 3H), 2.01-1.99 (m, 2H), 1.85-1.82 (m, 2H), 0.82-0.76 (m, 2H), 0.72-0.68 (m, 2H).

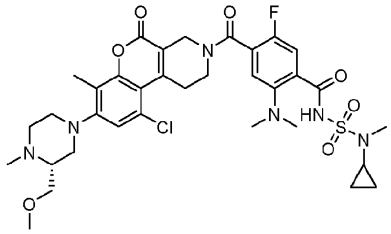
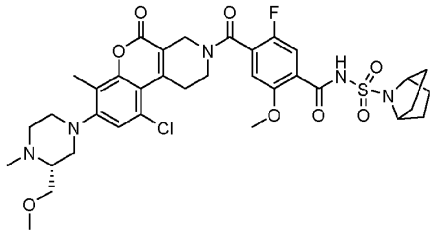
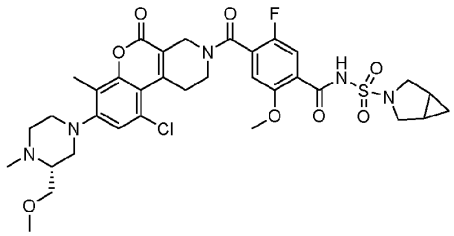
Example 308	(R)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 309 and 134	HPLC: (System 1, Method H) Rt = 7.67 min. m/z 717.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.07 (br s, 1H), 7.56-7.50 (m, 1H), 7.44-7.33 (m, 1H), 6.93-6.87 (m, 1H), 4.53 (br s, 1H), 4.20 (s, 1H), 3.92 (br s, 1H), 3.57-3.52 (m, 2H), 3.43-3.41 (m, 4H), 3.38-3.36 (m, 1H), 3.26 (s, 3H), 3.18-3.15 (m, 1H), 3.10-3.05 (m, 3H), 2.87-2.82 (m, 2H), 2.7-2.74 (m, 6H), 2.65-2.59 (m, 1H), 2.44-2.38 (m, 2H), 2.31 (s, 3H), 2.22-2.18 (m, 3H), 1.85-1.83 (m, 4H).
Example 309	(R)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 309 and 213	HPLC: (System 1, Method H) Rt = 6.82 min. m/z 704.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.46-7.43 (m, 1H), 7.23-7.17 (m, 1H), 6.93-6.87 (m, 1H), 4.53 (br s, 1H), 4.19 (s, 1H), 3.92 (br s, 1H), 3.84-3.81 (m, 3H), 3.57-3.52 (m, 2H), 3.41-3.40 (m, 4H), 3.36-3.33 (m, 1H), 3.26 (s, 3H), 3.18-3.15 (m, 1H), 3.10-3.05 (m, 3H), 2.87-2.82 (m, 2H), 2.65-2.60 (m, 1H), 2.44-2.39 (m, 2H), 2.31 (s, 3H), 2.22-2.19 (m, 3H), 1.86-1.83 (m, 4H).
Example 310	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methyl-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 258 and 260	HPLC: (System 1, Method H) Rt = 7.53 min. m/z 704.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.58 (br s, 1H), 7.57-7.54 (m, 1H), 7.35-7.28 (m, 1H), 7.08-7.05 (m, 1H), 4.65-4.42 (m, 1H), 4.11-3.72 (m, 2H), 3.58-3.54 (m, 1H), 3.45-3.36 (m, 7H), 3.28 (s, 3H), 3.20-3.14 (m, 2H), 3.11-3.08 (m, 1H), 2.93-2.85 (m, 2H), 2.73-2.67 (m, 1H), 2.56 (br s, 2H), 2.38 (s, 3H), 2.25-2.18 (m, 6H), 1.86-1.80 (m, 4H).

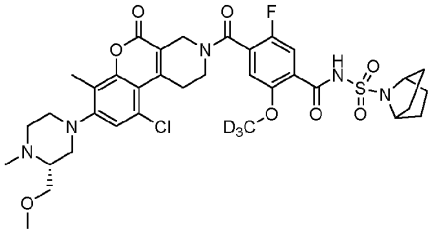
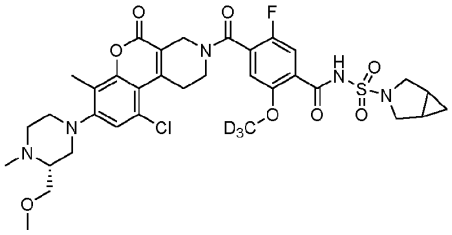
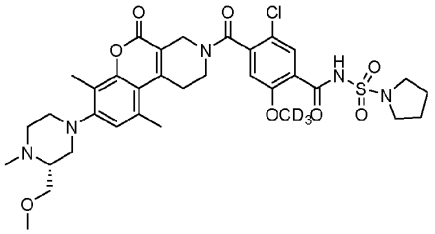
Example 311	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 291	UPLC: (System 3, Method K) Rt = 4.06 min, m/z 757.5 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, CD3CN) δ 7.91-7.86 (m, 1H), 7.59-7.52 (m, 1H), 6.83-6.81 (m, 1H), 4.56 (s, 1H), 4.30 (br s, 1H), 4.21 (s, 1H), 3.92-3.83 (br s, 1H), 3.58-3.47 (m, 4H), 3.42-3.35 (m, 3H), 3.32-3.29 (m, 6H), 3.23-3.03 (m, 4H), 2.88-2.83 (m, 2H), 2.79-2.73 (m, 6H), 2.69-2.61 (m, 4H), 2.50-2.41 (m, 2H), 2.32-2.24 (m, 7H), 2.08 (br s, 3H) One exchangeable proton not visible. Mixture of rotamers.
Example 312	2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide  Synthesised from Intermediates 6 and 312	UPLC: (System 3, Method K) Rt = 4.07 min, m/z 757.4 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, CD3CN) δ 7.93-7.83 (m, 1H), 7.60-7.53 (m, 1H), 6.84-6.83 (m, 1H), 4.57 (s, 1H), 4.31 (br s, 1H), 4.22 (s, 1H), 3.92 (br s, 1H), 3.60-3.46 (m, 4H), 3.43-3.37 (m, 3H), 3.33-3.29 (m, 6H), 3.26-3.05 (m, 4H), 2.91-2.85 (m, 2H), 2.80-2.74 (m, 6H), 2.70-2.60 (m, 4H), 2.50-2.44 (m, 2H), 2.35-2.26 (m, 7H), 2.15 (br s, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 313	N-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 313	UPLC: (System 3, Method K) Rt = 3.61 min, m/z 741.5 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, CD3CN) δ 7.88-7.83 (m, 1H), 7.55-7.48 (m, 1H), 6.83-6.82 (m, 1H), 4.60-4.56 (m, 3H), 4.21 (s, 1H), 3.93-3.89 (m, 1H), 3.72-3.67 (m, 1H), 3.58-3.54 (m, 2H), 3.50-3.34 (m, 3H), 3.31-3.29 (m, 3H), 3.25-3.03 (m, 4H), 2.88-2.82 (m, 2H), 2.83-2.76 (m, 6H), 2.69-2.61 (m, 4H), 2.48-2.39 (m, 2H), 2.32-2.22 (m, 7H), 1.85-1.81 (m, 2H). One exchangeable proton not visible. Mixture of rotamers.

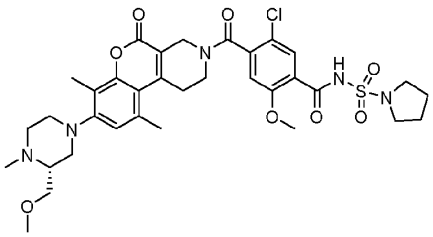
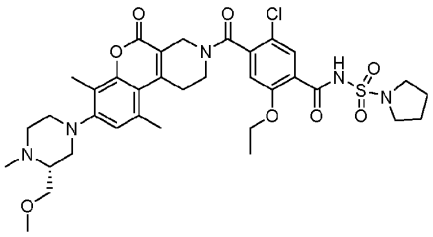
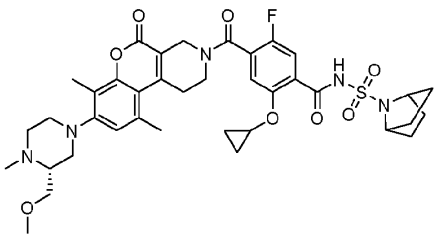
Example 314	2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 306	UPLC: (System 3, Method K) Rt = 3.82 min, m/z 731.4 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, CD3CN) δ 7.90-7.85 (m, 1H), 7.60-7.53 (m, 1H), 6.83-6.81 (m, 1H), 5.34-5.28 (m,1H), 4.56 (s, 1H), 4.20 (s, 1H), 3.91 (br s, 1H), 3.86-3.54 (m, 5H), 3.51-3.44 (m, 1H), 3.39-3.33 (m, 1H), 3.31-3.29 (m, 3H), 3.24-3.03 (m, 4H), 2.91-2.83 (m, 2H), 2.80-2.73 (m, 6H), 2.70-2.61 (m, 4H), 2.48-2.42 (m, 2H), 2.33-2.19 (m, 8H). One exchangeable proton not visible. Mixture of rotamers.
Example 315	N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 314	UPLC: (System 3, Method K) Rt = 4.08 min, m/z 725.5 $(M+H)^+$ (ES^+). ^{1}H-NMR (400 MHz, CD3CN) δ 7.92-7.87 (m, 1H), 7.59-7.52 (m, 1H), 6.84-6.82 (m, 1H), 4.56 (s, 1H), 4.21 (s, 1H), 3.93 (br s, 1H), 3.63-3.55 (m, 5H), 3.52-3.47 (m, 1H), 3.39-3.35 (m, 1H), 3.30 (s, 3H), 3.24-3.04 (m, 4H), 2.88-2.83 (m, 2H), 2.79-2.73 (m, 6H), 2.69-2.58 (m, 4H), 2.48-2.45 (m, 2H), 2.33-2.25 (m, 6H), 1.58-1.57 (m, 2H), 0.71-0.65 (m, 1H), 0.34-0.31 (m, 1H). One exchangeable proton not visible. Mixture of rotamers.
Example 316	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 170	HPLC: (System 1, Method H) Rt = 8.11 min. m/z 759.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.09 (br, s, 1H), 7.47-7.40 (m, 1H), 7.39-7.28 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 3H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.37-3.33 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.09-3.06 (m, 1H), 2.88-2.83 (m, 2H), 2.78-2.75 (m, 6H), 2.69-2.63 (m, 1H), 2.44-2.41 (m, 2H), 2.32 (s, 3H), 2.25-2.21 (m, 3H), 1.83-1.81 (m, 4H), 1.46-1.44 (m, 4H).

Example 317	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide  Synthesised from Intermediates 258 and 184	HPLC: (System 1, Method H) Rt = 8.27 min. m/z 759.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.46 (br s, 1H), 7.40-7.37 (m, 1H), 7.23-7.17 (m, 1H), 7.07-7.05 (m, 1H), 4.52 (br s, 1H), 4.22-4.20 (m, 3H), 4.13-4.05 (m, 2H), 3.87 (br s, 1H), 3.57-3.54 (m, 1H), 3.47 (br s, 1H), 3.38-3.35 (m, 1H), 3.33-3.27 (m, 5H), 3.18-3.15 (m, 1H), 3.09-3.07 (m, 1H), 2.88-2.83 (m, 2H), 2.69-2.64 (m, 1H), 2.45-2.43 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 1.87-1.85 (m, 4H), 1.46-1.44 (m, 4H), 1.35-1.29 (m, 3H).
Example 318	(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 246	HPLC: (System 1, Method H) Rt = 7.68 min. m/z 759.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.01 (br s, 1H), 7.54-7.48 (m, 1H), 7.42-7.33 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 3.98 (s, 4H), 3.87 (br s, 1H), 3.58-3.54 (m, 1H), 3.49 (br s, 1H), 3.39-3.36 (m, 1H), 3.28 (br s, 5H), 3.20-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.92-2.85 (m, 2H), 2.81-2.78 (m, 6H), 2.72-2.66 (m, 1H), 2.54-2.51 (m, 2H), 2.37 (s, 3H), 2.25-2.21 (m, 3H), 2.12-2.08 (m, 4H), 1.79-1.72 (m, 2H).
Example 319	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 258 and 252	HPLC: (System 1, Method H) Rt = 6.93 min. m/z 719.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.53 (br s, 1H), 7.32-7.26 (m, 2H), 7.08-7.06 (m, 1H), 4.49 (br s, 1H), 4.09 (br s, 1H), 3.94-3.72 (m, 4H), 3.58-3.55 (m, 1H), 3.45-3.37 (m, 6H), 3.32-3.28 (m, 4H), 3.21-3.18 (m, 2H), 3.13-3.10 (m, 1H), 2.96-2.86 (m, 2H), 2.74-2.69 (m, 1H), 2.67-2.57 (m, 2H), 2.40 (s, 3H), 2.25-2.22 (m, 3H), 1.85-1.82 (m, 4H).

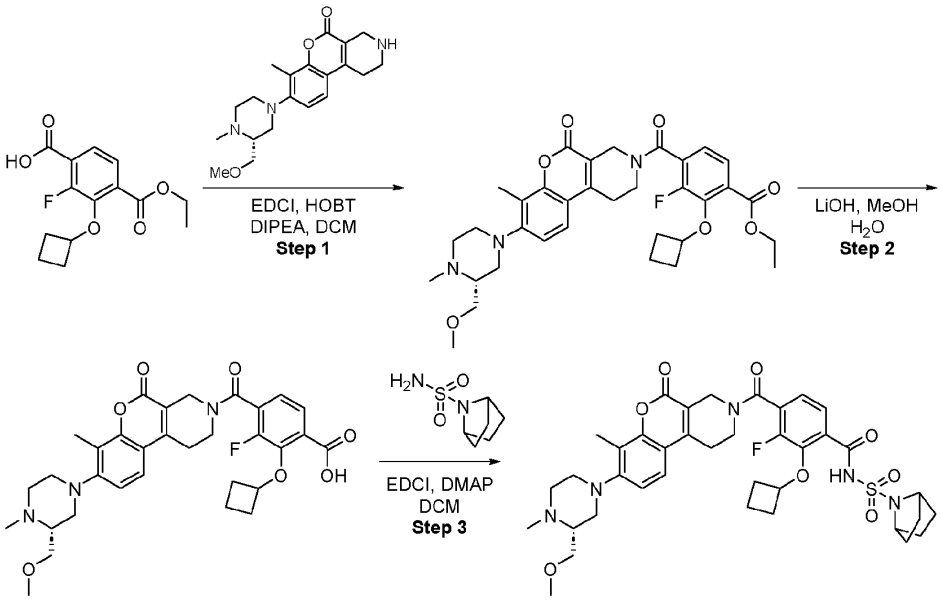
Example 320	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxybenzamide  Synthesised from Intermediates 258 and 217	HPLC: (System 1, Method H) Rt = 7.42 min. m/z 785.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.49 (br s, 1H), 7.19 (s, 1H), 7.14-7.09 (m, 1H), 7.05 (s, 1H), 4.49 (br s, 1H), 4.29 (br s, 1H), 4.22 (br s, 2H), 4.14 (br s, 2H), 3.83 (br s, 1H), 3.57-3.50 (m, 2H), 3.31 (br s, 3H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.07-3.05 (m, 1H), 2.87-2.82 (m, 2H), 2.66-2.61 (m, 1H), 2.42-2.37 (m, 2H), 2.30 (s, 3H), 2.25-2.21 (m, 3H), 1.87-1.85 (m, 4H), 1.46-1.44 (m, 4H), 1.35 (br s, 3H).
Example 321	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide  Synthesised from Intermediates 258 and 216	HPLC: (System 1, Method H) Rt = 7.22 min. m/z 727.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.48-7.45 (m, 1H), 7.21 (s, 1H), 7.14-7.10 (m, 1H), 7.05 (s, 1H), 4.49 (br s, 1H), 4.30 (br s, 1H), 4.22 (s, 2H), 3.86-3.84 (m, 4H), 3.57-3.51 (m, 2H), 3.34-3.33 (m, 1H), 3.32 (br s, 2H), 3.26 (s, 3H), 3.17-3.14 (m, 1H), 3.08-3.05 (m, 1H), 2.85 (br s, 2H), 2.67-2.62 (m, 1H), 2.43-2.41 (m, 2H), 2.30 (s, 3H), 2.25-2.21 (m, 3H), 1.86-1.84 (m, 4H), 1.46-1.45 (m, 4H)
Example 322	N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 248	HPLC: (System 1, Method H) Rt = 7.38 min. m/z 774.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.00 (br s, 1H), 7.48-7.41 (m, 1H), 7.39-7.31 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 4.13 (br s, 2H), 3.88 (br s, 1H), 3.59-3.54 (m, 5H), 3.49 (br s, 1H), 3.40-3.38 (m, 2H), 3.27 (br s, 4H), 3.19-3.17 (m, 1H), 3.11-3.08 (m, 1H), 2.92-2.84 (m, 2H), 2.79-2.76 (m, 6H), 2.71-2.66 (m, 1H), 2.54-2.51 (m, 2H), 2.36 (s, 3H), 2.25-2.21 (m, 3H), 1.95-1.89 (m, 2H), 1.85-1.82 (m, 2H).

Example 323	(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide  Synthesised from Intermediates 258 and 250	HPLC: (System 1, Method H) Rt = 8.05 min. m/z 733.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:13.45 (br s, 1H), 7.59-7.53 (m, 1H), 7.48-7.39 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.22 (br s, 1H), 3.88-3.87 (m, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.38-3.34 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.09-3.07 (m, 1H), 2.92 (s, 3H), 2.89-2.83 (m, 2H), 2.80-2.77 (m, 6H), 2.69-2.64 (m, 1H), 2.61-2.54 (m, 1H), 2.50-2.46 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 0.75-0.69 (m, 4H).
Example 324	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide  Synthesised from Intermediates 258 and 232	HPLC: (System 1, Method H) Rt = 7.21 min. m/z 746.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.38-7.34 (m, 1H), 7.22-7.17 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.20 (br s, 3H), 3.87-3.80 (m, 4H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.38-3.34 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.69-2.64 (m, 1H), 2.50-2.46 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 1.86-1.84 (m, 4H), 1.45-1.43 (m, 4H).
Example 325	N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide  Synthesised from Intermediates 258 and 233	HPLC: (System 1, Method H) Rt = 7.28 min. m/z 731.8 $(M+H)^+$ (ES^+). 11.49 (br s, 1H), 7.45-7.42 (m, 1H), 7.25-7.19 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.85-3.82 (m, 4H), 3.57-3.45 (m, 6H), 3.38-3.34 (m, 2H), 3.27 (br s, 4H), 3.18-3.16 (m, 1H), 3.09-3.07 (m, 1H), 2.89-2.83 (m, 2H), 2.69-2.64 (m, 1H), 2.50-2.45 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 1.59-1.58 (m, 2H), 0.68-0.63 (m, 1H), 0.31-0.29 (m, 1H).

Example 326	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide  Synthesised from Intermediates 258 and 234	HPLC: (System 1, Method H) Rt = 7.21 min. m/z 748.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.39-7.35 (m, 1H), 7.23-7.17 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.20 (br s, 3H), 3.86 (br s, 1H), 3.57-3.54 (m, 1H), 3.48 (br s, 1H), 3.39-3.37 (m, 2H), 3.27 (br s, 4H), 3.19-3.16 (m, 1H), 3.10-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.70-2.64 (m, 1H), 2.50-2.47 (m, 2H), 2.34 (s, 3H), 2.25-2.21 (m, 3H), 1.86-1.84 (m, 4H), 1.45-1.44 (m, 4H).
Example 327	N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide  Synthesised from Intermediates 258 and 235	HPLC: (System 1, Method H) Rt = 7.28 min. m/z 735.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.45-7.42 (m, 1H), 7.24-7.19 (m, 1H), 7.07-7.05 (m, 1H), 4.53 (br s, 1H), 4.21 (br s, 1H), 3.86 (br s, 1H), 3.57-3.45 (m, 6H), 3.38-3.34 (m, 2H), 3.27 (br s, 4H), 3.18-3.15 (m, 1H), 3.10-3.07 (m, 1H), 2.89-2.84 (m, 2H), 2.69-2.64 (m, 1H), 2.50-2.46 (m, 2H), 2.33 (s, 3H), 2.25-2.21 (m, 3H), 1.59 (br s, 2H), 0.68-0.63 (m, 1H), 0.29-0.28 (m, 1H).
Example 328	(R)-5-chloro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 316	HPLC: (System 1, Method H) Rt = 6.99 min. m/z 719.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.47 (br s, 1H), 7.59-7.57 (m, 1H), 7.28-7.20 (m, 1H), 6.87-6.84 (m, 1H), 4.70-4.35 (m, 1H), 4.09-4.08 (m, 1H), 4.01-3.76 (m, 1H), 3.57-3.54 (m, 1H), 3.42-3.37 (m, 6H), 3.26 (s, 3H), 3.24-3.23 (m, 1H), 3.18-3.03 (m, 3H), 2.87-2.79 (m, 2H), 2.70-2.61 (m, 4H), 2.45-2.42 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H).

Example 329	(R)-5-chloro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 317	HPLC: (System 1, Method H) Rt = 6.99 min. m/z 715.8 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.47 (br s, 1H), 7.59-7.57 (m, 1H), 7.29-7.20 (m, 1H), 6.87-6.84 (m, 1H), 4.70-4.65 (m, 0.5H), 4.39-4.35 (m, 0.5H), 4.10-4.09 (m, 1H), 4.01-3.96 (m, 0.5H), 3.86-3.84 (m, 3H), 3.79-3.75 (m, 0.5H), 3.57-3.54 (m, 1H), 3.42-3.36 (m, 6H), 3.26-3.23 (m, 4H), 3.19-3.09 (m, 2H), 3.05-3.03 (m, 1H), 2.87-2.79 (m, 2H), 2.70-2.61 (m, 4H), 2.47-2.42 (m, 2H), 2.32 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.83 (m, 4H).
Example 330	(R)-5-chloro-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide  Synthesised from Intermediates 6 and 318	HPLC: (System 1, Method H) Rt = 7.49 min. m/z 729.9 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.49 (br s, 1H), 7.56-7.55 (m, 1H), 7.25-7.17 (m, 1H), 6.86-6.84 (m, 1H), 4.70-4.33 (m, 1H), 4.19-4.09 (m, 3H), 4.07-3.78 (m, 1H), 3.57-3.53 (m, 1H), 3.41-3.38 (m, 6H), 3.26 (s, 3H), 3.22 (br s, 1H), 3.17-3.11 (m, 2H), 3.04-3.02 (m, 1H), 2.85-2.78 (m, 2H), 2.70-2.60 (m, 4H), 2.43-2.38 (m, 2H), 2.30 (s, 3H), 2.23-2.20 (m, 3H), 1.85-1.82 (m, 4H), 1.35-1.29 (m, 3H).
Example 331	(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Synthesised from Intermediates 6 and 319	HPLC: (System 1, Method H) Rt = 7.16 min. m/z 752.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.43 (br s, 1H), 7.45-7.34 (m, 2H), 6.86-6.85 (m, 1H), 4.53 (br s, 1H), 4.21-4.18 (m, 3H), 3.97-3.88 (m, 2H), 3.58-3.54 (m, 1H), 3.50-3.47 (m, 1H), 3.39-3.37 (m, 1H), 3.27 (s, 3H), 3.24 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.70-2.62 (m, 4H), 2.51-2.50 (m, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 1.86-1.84 (m, 4H), 1.44-1.42 (m, 4H), 0.82-0.68 (m, 4H).

Example 176: (*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide



Step 1

A mixture of 3-cyclobutoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid (Intermediate 149, 420 mg, 1.49 mmol), (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-3,4-dihydro-1*H*-chromeno[3,4-c]pyridin-5(2*H*)-one (Intermediate 5, 553 mg, 1.49 mmol), EDCI (572 mg, 2.98 mmol), HOBt (402 mg, 2.98 mmol) and DIPEA (1.2 g, 8.94 mmol) in DCM (10 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (10 mL) and DCM (3x10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1-5% MeOH/DCM) to afford (*R*)-ethyl 2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoate (600 mg, 0.97 mmol) as a brown solid. LCMS: (System 1, Method F) Rt = 1.88 min, m/z 622.3 $(M+H)^+$ (ES^+).

Step 2

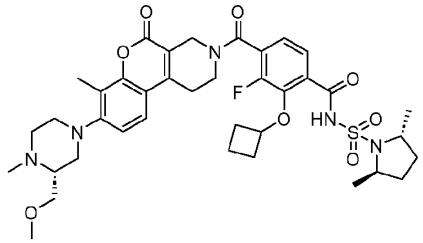
A mixture of (*R*)-ethyl 2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoate (600 mg, 0.97 mmol) and $LiOH{\cdot}H_2O$ (158 mg, 3.86 mmol) in MeOH (8 mL) was stirred at RT overnight. The organic solvents were removed under reduced pressure, the pH of mixture was adjusted to ca. 3 with HCl aq. 1 N and the aqueous layer extracted with EtOAc (7x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (*R*)-2-

cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoic acid (520 mg, 0.88 mmol) as a brown solid. LCMS: (System 1, Method A) Rt = 1.44 min, m/z 594.4 $(M+H)^+$ (ES^+).

Step 3

A mixture of (*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoic acid (255 mg, 0.43 mmol), 7-azabicyclo[2.2.1]heptane-7-sulfonamide (Intermediate 148, 227 mg, 1.29 mmol), EDCI (165 mg, 0.86 mmol) and DMAP (105 mg, 0.86 mmol) in DCM (10 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (10 mL) and DCM (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by prep-HPLC (Column: Waters X-SELECT C18 OBD 10µm 19x250mm; Flow Rate: 20 mL/min; solvent system: ACN/(10 mmol/L NH_4HCO_3/water) gradient: ACN: 30-95%; collection wavelength: 214 nm). The fractions were concentrated under reduced pressure to remove ACN, and the residue was lyophilized to afford (*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide (91 mg, 0.12 mmol) as a white solid. HPLC: (System 1, Method D) Rt = 7.26 min, m/z 752.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.43 (br s, 1H), 7.59-7.51 (m, 1H), 7.28-7.21 (m, 1H), 7.20-7.14 (m, 1H), 7.10-7.06 (m, 1H), 4.72-4.63 (m, 1H), 4.52 (br s, 1H), 4.20 (br s, 2H), 4.17 (br s, 1H), 3.97 (t, J = 6.0 Hz, 1H), 3.59-3.53 (m, 2H), 3.43-3.41 (m, 1H), 3.28(s, 3H), 3.19-3.17 (m, 1H), 3.10-3.07 (m, 1H), 2.99-2.85 (m, 4H), 2.72-2.57 (m, 3H), 2.40 (s, 3H), 2.30-2.17 (m, 5H), 2.15-2.06 (m, 2H), 1.87-1.85 (m, 4H), 1.70-1.65 (m, 1H), 1.49-1.41 (m, 5H). Mixture of rotamers.

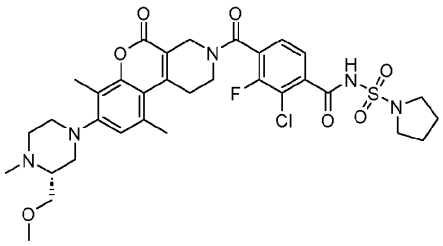
Example 177: 2-cyclobutoxy-*N*-(((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)sulfonyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide



Prepared by analogous method to Example 176 starting from 3-cyclobutoxy-4-(ethoxycarbonyl)-2-fluorobenzoic acid (Intermediate 149, 420 mg, 1.49 mmol) and (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-3,4-dihydro-1*H*-chromeno[3,4-c]pyridin-5(2*H*)-one (Intermediate

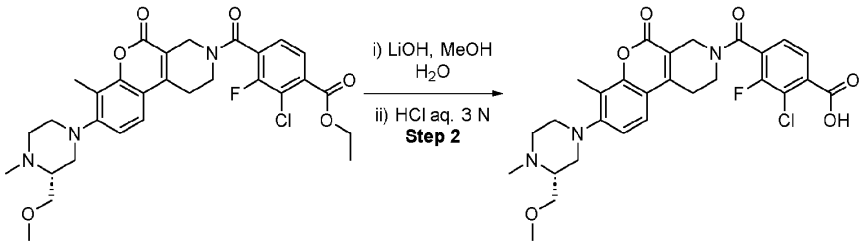
5, 553 mg, 1.49 mmol) except the Step 3 was carried out with (2*R*,5*R*)-2,5-dimethylpyrrolidine-1-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 92 mg, 0.12 mmol. White solid. HPLC: (System 1, Method D) Rt = 8.40 min, 754.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.76 (br s, 1H), 7.59-7.50 (m, 1H), 7.29-7.17 (m, 2H), 7.10-7.06 (m, 1H), 4.71-4.65 (m, 1H), 4.52 (br s, 1H), 4.27-4.24 (m, 2H), 4.17 (br s, 1H), 3.98-3.96 (m, 1H), 3.58-3.54 (m, 2H), 3.37 (br s, 1H), 3.26 (s, 3H), 3.16-3.14 (m, 1H), 3.06-2.99 (m, 2H), 2.90-2.82 (m, 3H), 2.65-2.60 (m, 1H), 2.46-2.43 (m, 2H), 2.31 (s, 3H), 2.29-2.25 (m, 4H), 2.22-2.07 (m, 5H), 1.71-1.66 (m, 1H), 1.55-1.54 (m, 2H), 1.51-1.43 (m, 1H), 1.23-1.21 (m, 6H). Mixture of rotamers.

Example 178: (*R*)-2-chloro-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide



Prepared by analogous method to Example 176 starting from 3-chloro-4-(ethoxycarbonyl)-2-fluorobenzoic acid (Intermediate 150, 246 mg, 1.00 mmol) and (*R*)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one (Intermediate 6, 352 mg, 0.95 mmol) except the Step 2 was performed as described below and Step 3 was carried out with pyrrolidine-1-sulfonamide in place of 7-azabicyclo[2.2.1]heptane-7-sulfonamide. Yield: 91 mg, 0.13 mmol. White solid. HPLC: (System 1, Method D) Rt = 6.80 min, m/z 704.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.28 (br s, 1H), 7.53-7.44 (m, 2H), 6.87-6.86 (m, 1H), 4.52 (br s, 1H), 4.19 (s, 1H), 3.89-3.86 (m, 1H), 3.59-3.56 (m, 1H), 3.48-3.46 (m, 2H), 3.36 (br s, 2H), 3.35 (br s, 1H), 3.30 (s, 3H), 3.24-3.19 (m, 3H), 3.15-3.09 (m, 2H), 3.04-3.01 (m, 1H), 2.91-2.86 (m, 1H), 2.77-2.72 (m, 2H), 2.72-2.60 (m, 4H), 2.48 (s, 3H), 2.24-2.21 (m, 3H), 1.84-1.82 (m, 4H). Mixture of rotamers.

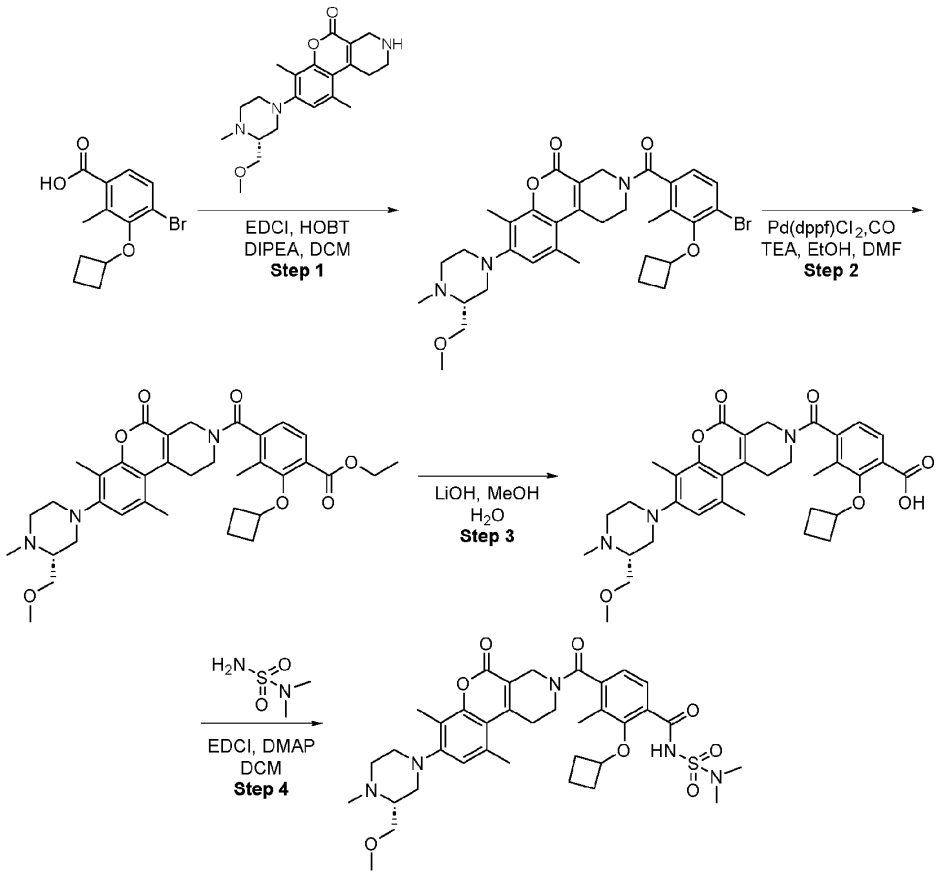
Modified Step 2



A mixture of (*R*)-ethyl 2-chloro-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoate (350 mg, 0.58 mmol) and $LiOH \cdot H_2O$ (146 mg, 3.48 mmol) in MeOH (8 mL) and H_2O (2 mL) was stirred at RT overnight. Organic solvents were removed under reduced pressure and the pH of the mixture was adjusted to ca. 5 by adding HCl aq. 1 N. The resulting aqueous layer was extracted with DCM (3x15 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give (R)-1-(4-carboxy-3-chloro-2-fluorobenzoyl)-4-(2-hydroxy-4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-3,6-dimethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (340 mg) as a yellow solid. LCMS: (System 1, Method A) Rt = 1.23 min; m/z 590.2 $(M+H)^+$ (ES^+).

(R)-1-(4-carboxy-3-chloro-2-fluorobenzoyl)-4-(2-hydroxy-4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-3,6-dimethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (340 mg, 0.58 mmol) was dissolved in HCl aq. 3 N (10 mL) and the solution stirred at RT overnight. The mixture was partitioned between water (10 mL) and DCM (3x20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford (*R*)-2-chloro-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzoic acid (280 mg, 0.49 mmol) as a yellow solid which was used in the next step without further purification. LCMS: (System 1, Method A) Rt = 1.56 min, m/z 572.3 $(M+H)^+$ (ES^+).

Example 179: (*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide



Step 1

A mixture of 4-bromo-3-(cyclobutoxy)-2-methyl-benzoic acid (Intermediate 151, 241 mg, 0.84 mmol), 8-[(3*R*)-3-(methoxymethyl)-4-methyl-piperazin-1-yl]-7,10-dimethyl-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one (Intermediate 6, 285 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI) (221 mg, 1.15 mmol), 1-hydroxybenzotriazole monohydrate (176 mg, 1.15 mmol), TEA (0.32 mL, 2.30 mmol) in DCM (5.1 mL) was stirred at RT overnight. The reaction was partitioned between water (20 mL) and DCM (3x20mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-100% EtOAc/iso-hexane and then 1-10% MeOH/DCM) to afford (*R*)-3-(4-bromo-3-cyclobutoxy-2-methylbenzoyl)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-

7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one (308 mg, 0.48 mmol) as a white solid. LCMS (System 3, method I) Rt = 2.09 min, m/z 636.2 $(M-H)^-$ (ES^-).

Step 2

A mixture of (*R*)-3-(4-bromo-3-cyclobutoxy-2-methylbenzoyl)-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-c]pyridin-5-one (302 mg, 0.473 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (17 mg, 0.02 mmol) and triethylamine (0.33 mL, 2.37 mmol) in DMF (1.2 mL) and EtOH (1.2 mL) was stirred at 100 °C overnight under CO atmosphere. The reaction was cooled to RT, diluted with EtOAc (20 mL), filtered through celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20-100% EtOAc/iso-hexane and then 1-10% MeOH/DCM) to afford ethyl (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methylbenzoate (300 mg, 0.48 mmol) as a brown solid. LCMS (System 3, method I) Rt = 2.00 min, m/z 632.4 $(M+H)^+$ (ES^+).

Step 3

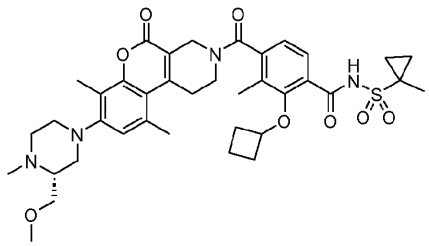
A mixture of (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methylbenzoate (300 mg, 0.48 mmol) and LiOH aq. 1 N (2.4 mL) in MeOH (2.4 mL) and THF (2.4 mL) was stirred at 40 °C overnight. Organic solvents were evaporated under reduced pressure and the pH of the aqueous phase was adjusted to ca. 4 with HCl aq. 1 N. The resulting solution was extracted with EtOAc (4x30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on C18-modified silica (5-100% ACN/0.1% formic acid in water) to afford (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methylbenzoic acid (144 mg, 0.24 mmol) as an off-white solid. LCMS (System 3, method I) Rt = 1.39 min, m/z 604.3 $(M+H)^+$ (ES^+).

Step 4

A mixture of (*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methylbenzoic acid (48 mg, 0.08 mmol), *N*,*N*-dimethylsulfamide (20 mg, 0.16 mmol), EDCI (23 mg, 0.12 mmol) and DMAP (19 mg, 0.16 mmol) in DCM (1.2 mL) was stirred at RT overnight. The reaction mixture was partitioned between water (15 mL) and DCM (3x20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by prep-HPLC (Column: Waters X-SELECT C18 OBD 10µm 19x250mm;

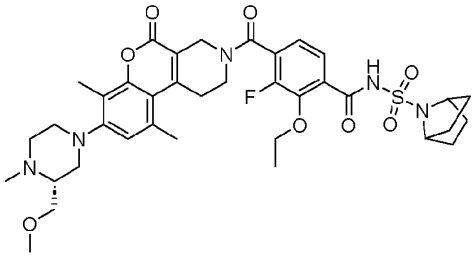
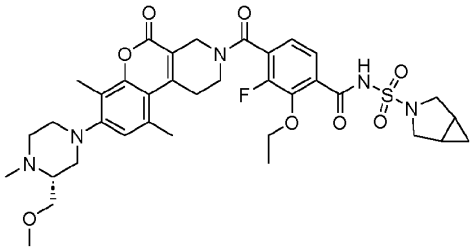
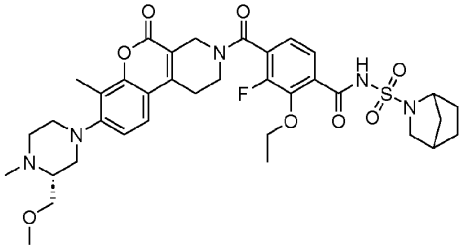
Flow Rate: 20 mL/min; solvent system: ACN/(10 mmol/L NH_4HCO_3/water) gradient: ACN: 30-95%; collection wavelength: 214 nm). The fractions were concentrated under reduced pressure to remove ACN, and the residue was lyophilized to afford (*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide (28 mg, 0.04 mmol) as a white solid. UPLC: (System 3, Method K) Rt = 3.75 min, 710.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.38-7.36 (m, 1H), 7.05-7.03 (m, 1H), 6.84 (s, 1H), 4.50 (br s, 2H), 4.08 (br s, 1H), 3.86 (br s, 1H), 3.59-3.55 (m, 1H), 3.38-3.34 (m, 2H), 3.28 (s, 3H), 3.24-3.22 (m, 1H), 3.15-3.12 (m, 2H), 3.05-3.01 (s, 2H), 2.90-2.83 (m, 8H), 2.70-2.57 (m, 5H), 2.46-2.41 (m, 1H), 2.32 (s, 3H), 2.25-2.12 (m, 8H), 1.70-1.68 (m, 1H), 1.46-1.42 (m, 1H). Mixture of rotamers.

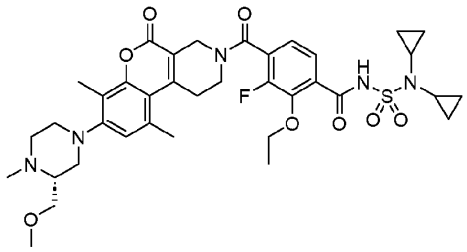
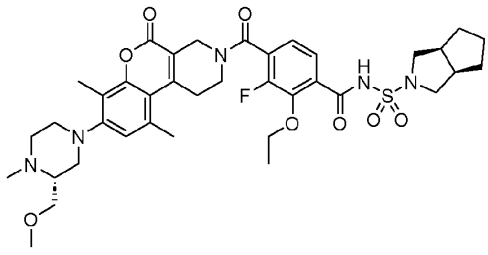
Example 180: (R)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methyl-N-((1-methylcyclopropyl)sulfonyl)benzamide

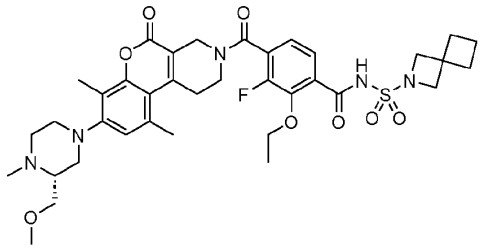
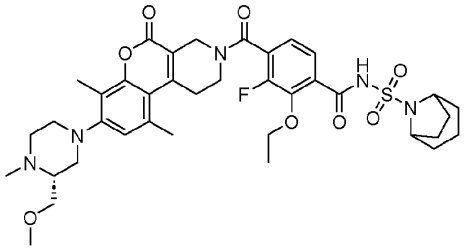


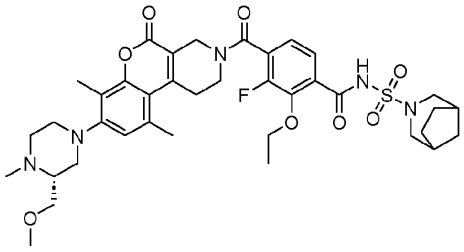
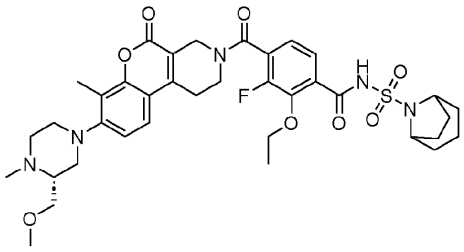
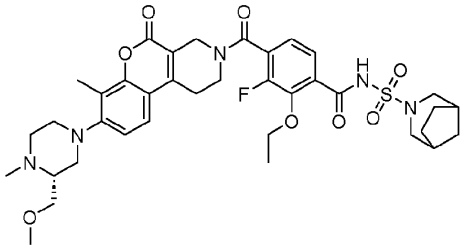
Prepared by analogous method to Example 179 except the Step 4 was carried out with 1-methylcyclopropane-1-sulfonamide in place of *N*,*N*-dimethylsulfamide. Yield: 33 mg, 0.05 mmol. White solid. UPLC: (System 3, Method K) Rt = 3.76 min, 721.3 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.36 (br s, 1H), 7.32-7.30 (m, 1H), 6.92-7.11 (m, 1H), 6.80 (s, 1H), 4.47 (br s, 2H), 4.04 (br s, 1H), 3.82 (br s, 1H), 3.55-3.52 (m, 1H), 3.35-3.31 (m, 2H), 3.25 (s, 3H), 3.21-3.18 (m, 1H), 3.11-3.08 (m, 2H), 2.99-2.97 (m, 2H), 2.85-2.80 (m, 2H), 2.65-2.58 (m, 4H), 2.41 (s, 1H), 2.30 (s, 3H), 2.22-2.09 (m, 9H), 1.66 (s, 1H), 1.51 (s, 3H), 1.46-1.43 (m, 3H), 0.88 (s, 2H). Mixture of rotamers.

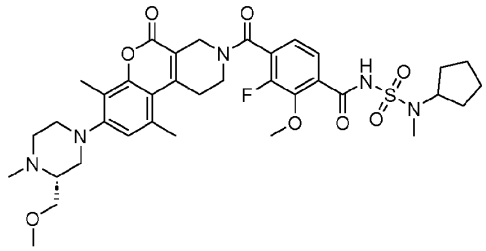
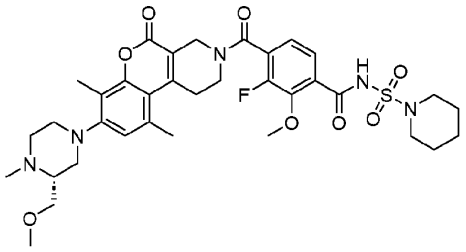
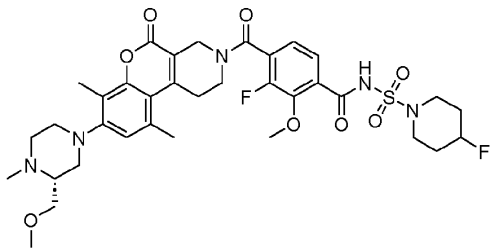
The following examples were prepared by analogous methods to Examples 176 or 178:

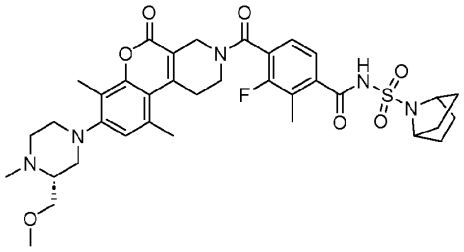
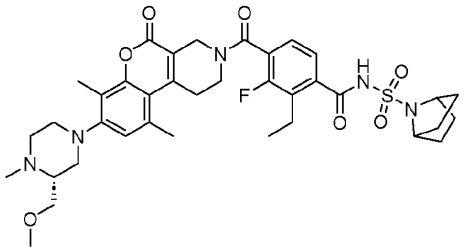
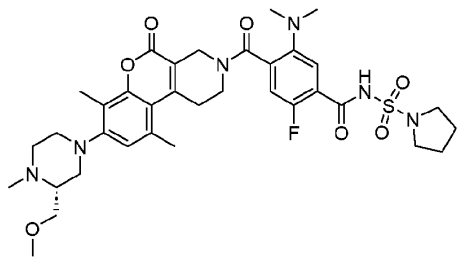
Example No.	Name / Structure / Method	LCMS / ^{1}H NMR data
Example 228	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	UPLC: (System 3, Method K) Rt = 3.88 min, 740.7 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.29-7.16 (m, 2H), 6.87-6.85 (m, 1H), 4.51 (s, 1H), 4.20-4.10 (m, 5H), 3.92-3.75 (m, 1H), 3.60-3.51 (m, 1H), 3.47-3.40 (m, 2H), 3.28 (s, 4H), 3.23-3.05 (m, 5H), 2.91-2.82 (m, 2H), 2.71-2.62 (m, 5H), 2.39 (s, 2H), 2.25-2.15 (m, 3H), 1.92-1.80 (m, 4H), 1.47-1.40 (m, 4H), 1.32-1.26 (m, 3H). One exchangeable proton not visible. Mixture of rotamers.
Example 229	*N*-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	UPLC: (System 3, Method K) Rt = 3.85 min, 726.7 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 7.35-7.30 (m, 1H), 7.24-7.15 (m, 1H), 6.90-6.85 (m, 1H), 4.51 (s, 1H), 4.22-4.10 (m, 3H), 3.90-3.82 (m, 1H), 3.58-3.31 (m, 10H), 3.23-3.05 (m, 4H), 2.93-2.82 (m, 2H), 2.69-2.54 (m, 6H), 2.41-2.34 (m, 3H), 2.27-2.18 (m, 3H), 1.60-1.53 (m, 2H), 1.34-1.23 (m, 3H), 0.72-0.59 (m, 1H), 0.35-0.25 (m, 1H). Mixture of rotamers.
Example 230	*N*-((2-azabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	HPLC: (System 1, Method H) Rt = 7.29 min, 726.2 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.54 (br s, 1H), 7.59-7.50 (m, 1H), 7.33-7.30 (m, 1H), 7.24-7.17 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.24-4.13 (m, 4H), 3.98 (t, J = 5.6 Hz, 1H), 3.58-3.55 (m, 2H), 3.45-3.43 (m, 1H), 3.39-3.35 (m, 1H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.09-3.04 (m, 2H), 3.00 (br s, 1H), 2.90-2.83 (m, 3H), 2.68-2.63 (m, 1H), 2.59 (br s, 1H), 2.50-2.46 (m, 2H), 2.35 (s, 3H), 2.29-2.26

		(m, 3H), 1.71-1.61 (m, 4H), 1.44-1.38 (m, 2H), 1.34-1.27 (m, 3H). Mixture of rotamers.
Example 231	(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	UPLC: (System 3, Method K) Rt = 3.98 min, 740.5 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.11-11.88 (br s, 1H), 7.32-7.29 (m, 1H), 7.20-7.11 (m, 1H), 6.83-6.81 (m, 1H), 4.56-4.48 (m, 1H), 4.18-4.05 (m, 3H), 3.83 (t, J = 5.7 Hz, 1H), 3.53 (dd, J = 10.3, 3.4 Hz, 1H), 3.43-3.36 (m, 2H), 3.24-3.18 (m, 4H), 3.14-3.11 (m, 2H), 3.05-3.03 (m, 1H), 2.93-2.90 (m, 1H), 2.84-2.79 (m, 1H), 2.69-2.50 (m, 8H), 2.37 (br s, 3H), 2.20-2.16 (m, 3H), 1.28-1.22 (m, 3H), 0.81-0.70 (m, 4H), 0.66-0.60 (m, 4H). Mixture of rotamers.
Example 232	2-ethoxy-3-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	UPLC: (System 3, Method K) Rt = 4.13 min, 754.7 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.28-7.26 (m, 1H), 7.19-7.10 (m, 1H), 6.82-6.80 (m, 1H), 4.48 (br s, 1H), 4.17-4.08 (m, 3H), 3.84-3.82 (m, 1H), 3.54-3.41 (m, 4H), 3.38-3.32 (m, 1H), 3.23 (s, 3H), 3.19-3.18 (m, 2H), 3.12-3.05 (m, 2H), 3.05-2.97 (m, 3H), 2.87-2.77 (m, 2H), 2.65-2.58 (m, 6H), 2.50 (s, 1H), 2.32-2.28 (m, 3H), 2.25-2.16 (m, 3H), 1.72-1.57 (m, 3H), 1.52-1.35 (m, 3H), 1.29-1.22 (m, 3H). Mixture of rotamers. One exchangeable proton not visible

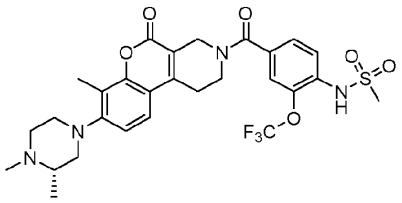
Example 233	(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	HPLC: (System 3, Method K) Rt = 3.97 min, 740.8 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.33-7.31 (m, 1H), 7.21-7.13 (m, 1H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.22-4.13 (m, 3H), 3.91-3.86 (m, 5H), 3.58-3.56 (m, 1H), 3.47-3.40 (m, 2H), 3.29 (s, 3H), 3.25-3.22 (m, 1H), 3.19-3.07 (m, 3H), 2.99-2.97 (m, 1H), 2.87 (t, J = 10.3 Hz, 1H), 2.73-2.62 (m, 6H), 2.44 (br s, 2H), 2.24-2.21 (m, 3H), 2.09 (t, J = 7.8 Hz, 4H), 1.80-1.72 (m, 2H), 1.33-1.23 (m, 4H). Mixture of rotamers. One exchangeable proton not visible
Example 234	*N*-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176	HPLC: (System 1, Method H) Rt = 7.54 min, 754.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.52 (br s, 1H), 7.30-7.17 (m, 2H), 6.86-6.84 (m, 1H), 4.51 (br s, 1H), 4.20-4.13 (m, 5H), 3.87 (t, J = 5.6 Hz, 1H), 3.58-3.54 (m, 1H), 3.46-3.45 (m, 1H), 3.39-3.35 (m, 1H), 3.27 (s, 3H), 3.23 (br s, 1H), 3.16-3.13 (m, 2H), 3.06-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.51-2.49 (m, 2H), 2.35 (s, 3H), 2.24-2.20 (m, 3H), 2.04-2.01 (m, 2H), 1.74-1.64 (m, 5H), 1.53-1.51 (m, 3H), 1.34-1.28 (m, 3H).Mixture of rotamers.
Example 235	*N*-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide	HPLC: (System 1, Method H) Rt = 7.72 min, 754.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.49 (br s, 1H), 7.34-7.32 (m, 1H), 7.26-7.17 (m, 1H), 6.86-6.85 (m, 1H), 4.50 (br s, 1H), 4.22-4.13 (m, 3H), 3.87 (t, J = 5.4 Hz, 1H), 3.58-3.54 (m, 1H), 3.48-3.45 (m, 1H), 3.40-3.38 (m, 3H), 3.27 (s, 3H), 3.24 (br s, 1H), 3.16-3.14 (m, 2H), 3.07-3.00 (m, 3H), 2.92-2.81 (m, 2H), 2.69-2.62 (m, 4H), 2.54-2.51

	 Method of Example 176.	(m, 2H), 2.36 (s, 3H), 2.27 (br s, 2H), 2.24-2.20 (m, 3H), 1.62-1.48 (m, 5H), 1.44-1.41 (m, 1H), 1.34-1.28 (m, 3H). Mixture of rotamers.
Example 236	*N*-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 176.	HPLC: (System 1, Method H) Rt = 7.39 min, m/z 740.0 $(M+H)^+$ (ES^+). 1H NMR (400 MHz, DMSO-d6) δ: 11.52 (br s, 1H), 7.59-7.50 (m, 1H), 7.30-7.26 (m, 1H), 7.24-7.16 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.20-4.12 (m, 5H), 3.99-3.96 (m, 1H), 3.58-3.55 (m, 2H), 3.40-3.37 (m, 1H), 3.27 (s, 3H), 3.17-3.15 (m, 1H), 3.08-3.05 (m, 1H), 2.99 (br s, 1H), 2.91-2.83 (m, 3H), 2.68-2.63 (m, 1H), 2.53-2.49 (m, 2H), 2.36 (s, 3H), 2.29-2.26 (m, 3H), 2.04-2.01 (m, 2H), 1.74-1.64 (m, 5H), 1.53-1.51 (m, 3H), 1.33-1.27 (m, 3H). Mixture of rotamers.
Example 237	N-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)  Method of Example 176	HPLC: (System 1, Method H) Rt = 7.56 min, m/z 740.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.44 (br s, 1H), 7.59-7.50 (m, 1H), 7.34-7.31 (m, 1H), 7.24-7.16 (m, 1H), 7.10-7.06 (m, 1H), 4.53 (br s, 1H), 4.22-4.13 (m, 3H), 3.99-3.96 (m, 1H), 3.59-3.56 (m, 2H), 3.40-3.38 (m, 3H), 3.28 (s, 3H), 3.18-3.16 (m, 1H), 3.09-3.00 (m, 4H), 2.94-2.84 (m, 3H), 2.70-2.65 (m, 1H), 2.57-2.51 (m, 2H), 2.38 (s, 3H), 2.33-2.26 (m, 5H), 1.63-1.41 (m, 6H), 1.34-1.28 (m, 3H). Mixture of rotamers.

Example 238	(*R*)-*N*-(*N*-cyclopentyl-*N*-methylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 178	UPLC: (System 3, Method K) Rt = 3.97 min, 728.6 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.31-7.17 (m, 2H), 6.89-6.82 (m, 1H), 4.51 (s, 1H), 4.25-4.15 (m, 2H), 3.94-3.86 (m, 4H), 3.57-3.33 (m, 7H), 3.23-3.03 (m, 5H), 2.90-2.82 (m, 5H), 2.66-2.60 (m, 4H), 2.35 (s, 3H), 2.25-2.16 (m, 3H), 1.78-1.48 (m, 8H). One exchangeable proton not visible. Mixture of rotamers
Example 239	(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide  Method of Example 178	HPLC: (System 1, Method H) Rt = 7.00 min, 714.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.36 (br s, 1H), 7.33-7.31 (m, 1H), 7.24-7.15 (m, 1H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.19 (s, 1H), 3.94-3.91 (m, 3H), 3.88 (t, J = 5.8 Hz, 1H), 3.58-3.55 (m, 1H), 3.49-3.46 (m, 1H), 3.43-3.39 (m, 1H), 3.28 (s, 3H), 3.23 (br s, 5H), 3.18-3.15 (m, 2H), 3.09-3.06 (m, 1H), 2.95-2.93 (m, 1H), 2.88-2.83 (m, 1H), 2.72-2.57 (m, 6H), 2.40 (s, 3H), 2.24-2.20 (m, 3H), 1.57-1.56 (m, 4H), 1.49-1.48 (m, 2H). Mixture of rotamers.
Example 240	(*R*)-3-fluoro-*N*-((4-fluoropiperidin-1-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 178	UPLC: (System 3, Method K) Rt = 3.77 min, 732.4 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, ACN-d_3) δ: 7.22-7.13 (m, 1H), 6.83-6.76 (s, 1H), 4.88-4.75 (m, 1H), 4.54 (s, 1H), 4.19 (s, 1H), 4.10-4.02 (m, 3H), 3.90 (s, 1H), 3.59-3.35 (m, 8H), 3.22-3.04 (m, 5H), 2.95-2.83 (m, 2H), 2.72-2.52 (m, 6H), 2.37-2.23 (m, 6H), 2.05-1.83 (m, 5H). One exchangeable proton no visible. Mixture of rotamers.

Example 241	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methylbenzamide  Method of Example 178	HPLC: (System 1, Method H) Rt = 6.88 min, 710.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.43 (br s, 1H), 7.37-7.30 (m, 2H), 6.87-6.85 (m, 1H), 4.51 (br s, 1H), 4.19-4.17 (m, 3H), 3.88-3.86 (m, 1H), 3.59-3.56 (m, 1H), 3.45 (br s, 2H), 3.29 (s, 3H), 3.23-3.17 (m, 2H), 3.13-3.07 (m, 2H), 2.99-2.96 (m, 1H), 2.89-2.84 (m, 1H), 2.75-2.62 (m, 6H), 2.44 (s, 3H), 2.31-2.28 (m, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H), 1.43-1.41 (m, 4H). Mixture of rotamers.
Example 242	(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethyl-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide  Method of Example 178	HPLC: (System 1, Method H) Rt = 7.11 min, 724.0 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.35 (br s, 1H), 7.37-7.26 (m, 2H), 6.87-6.85 (m, 1H), 4.52 (br s, 1H), 4.19-4.17 (m, 3H), 3.88 (br s, 1H), 3.59-3.56 (m, 1H), 3.45-3.43 (m, 2H), 3.29 (s, 3H), 3.23 (br s, 1H), 3.19-3.17 (m, 1H), 3.13-3.08 (m, 2H), 3.00-2.97 (m, 1H), 2.87-2.84 (m, 1H), 2.79-2.62 (m, 8H), 2.44 (s, 3H), 2.24-2.20 (m, 3H), 1.85-1.83 (m, 4H), 1.44-1.42 (m, 4H), 1.18-1.11 (m, 3H). Mixture of rotamers.
Example 243	(*R*)-5-(dimethylamino)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide  Method of Example 178	UPLC: (System 3, Method K) Rt = 3.77 min, 713.6 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br s, 1H), 7.21-7.10 (m, 2H), 6.88-6.84 (m, 1H), 4.56-4.39 (m, 1H), 4.20-3.99 (m, 2H), 3.68-3.54 (m, 2H), 3.46-3.34 (m, 5H), 3.27 (s, 3H), 3.18-3.00 (m, 4H), 2.90-2.81 (m, 2H), 2.74-2.69 (m, 5H), 2.67-2.61 (m, 3H), 2.58-2.53 (m, 4H), 2.35-2.32 (m, 3H), 2.22 (d, J = 12.4 Hz, 3H), 1.84-1.78 (m, 4H). One exchangeable proton not visible. Mixture of rotamers.

Reference Example 1 (RE1) corresponds to Example 5 in US2019/0284198A1 (Daiichi Sankyo Company Limited):



Biological Example 1 – MTHFD1 and MTHFD2 inhibition assay

Experimental Protocol

30 µL of each compound to be tested resuspended in DMSO (Fisher, 2212435) at a concentration of 1-100 mM was added to 2x 96 well plates (Corning U-bottom, 734-1547) and serially diluted 1 in 3 in DMSO (11x), and then further diluted 1 in 40 in distilled water. 2 µL of the serial dilutions were then quadrated in duplicate to 4x 384 well plates (Grenier Bio-One Ltd, 788096). Two columns of DMSO wells without compound were also prepared (low and high signal controls). 2x assay plates were used for the MTHFD1 and MTHFD2 assays respectively. 7 µL of assay buffer containing 200 mM Hepes (Fisher, 2212435), pH 8, 10 mM $MgCl_2$ (Sigma, M1028), 10 mM $NaPO_4$ (Sigma, 71507), 0.010% Tween20 (VWR, 663684B), and distilled water and either 30 mM NADP (MTHFD1 assay) (Alfa Aesar, S08H026) or 600 µM NAD+ (MTHFD2 assay) (Thermo Scientific, T12H054). MTHFD1 and MTHFD2 recombinant human enzymes (Gustafsson R. 2017) were added to the assay buffer at final concentrations of 200 nM and 40 nM respectively prior to addition to the compound containing wells. Assay buffer without an enzyme were added to the low signal control wells. The assay plates were then sealed and incubated on a plate shaker for 30 minutes at room temperature at 600 rpm, before additions of Folitixorin (Toronto Research Chemicals Inc, F680350) to final concentrations of 360 µM and 800 µM for MTHFD1 and MTHFD2 respectively; the plates were re-sealed and incubated again as described above for 20 minutes. The enzyme reaction was stopped with the addition of 1 µL of a MTHFD1 D/C-d/MTHFD2 dual inhibitor (any MTHFD1 D/C-d/MTHFD2 dual inhibitor with an IC_{50} of <30nM against both MTHFD1 D/C-d/MTHFD2 may be used) to a final concentration of 10 µM. NAD(P)H-GLOTM Detection system (G9061) was used to measure reduced forms of NADH and NADPH, read using Pherastar Luminescence nodule.

The results were expressed as a percentage of luminescent signal that is directly proportional to the NADPH produced by the enzyme reaction, where 0% is an enzyme free reaction and 100% is an uninhibited enzyme. Test compounds and standard (Reference Compound 1) were tested

in each experiment at several concentrations to obtain a competition curve from which its IC_{50} was calculated.

Compounds of formula (I) were tested in this assay and the IC_{50} results of those compounds tested are shown in Table 1 below. Reference Example 1 was also tested in this assay. MTHFD1 and MTHFD2 IC_{50} values and MTHFD1/MTHFD2 IC_{50} ratio thresholds (i.e. measure of the selectivity of MTHFD2 inhibition over MTHFD1) are defined below.

IC_{50} threshold:

Band	IC_{50} (μM)
A	>5
B	1 to 5
C	0.1 to <1
D	0.01 to <0.1
E	0.001 to <0.01

IC_{50} ratio threshold:

Band	MTHFD1/MTHFD2 IC_{50} Ratio
F	<3
G	3 to 9.0
H	>9.0 to 30
J	>30

Table 1 – MTHFD1 and MTHFD2 IC_{50} Values

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 1	C	C	F
Example 2	C	D	G
Example 3	D	D	F
Example 4	E	E	F
Example 5	E	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*,[1]
Example 6	E	D	F
Example 7	D	D	F
Example 8	D	D	F
Example 9	D	D	F
Example 10	D	D	F
Example 11	E	E	F
Example 12	E	E	F
Example 13	E	E	F
Example 14	D	D	F
Example 15	D	D	F
Example 16	E	E	F
Example 17	E	D	F
Example 18	D	E	G
Example 19	C	C	F
Example 20	E	E	G
Example 21	C	C	F
Example 22	E	E	F
Example 23	E	E	F
Example 24	E	E	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 25	E	E	F
Example 26	E	E	F
Example 27	E	E	F
Example 28	E	E	F
Example 29	D	D	F
Example 30	D	D	F
Example 31	D	E	G
Example 32	C	D	J
Example 33	C	D	H
Example 34	C	E	J
Example 35	E	E	F
Example 36	E	E	F
Example 37	E	E	F
Example 38	D	E	G
Example 39	D	E	G
Example 40	D	E	H
Example 41	E	E	G
Example 42	E	E	G
Example 43	E	E	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 44	E	E	F
Example 45	D	E	H
Example 46	D	E	H
Example 47	E	E	G
Example 48	E	E	F
Example 49	E	E	F
Example 50	E	E	F
Example 51	E	E	F
Example 52	E	E	F
Example 53	E	D	F
Example 54	D	D	F
Example 55	D	E	G
Example 56	E	E	F
Example 57	E	E	F
Example 58	E	E	F
Example 59	E	E	F
Example 60	E	E	F
Example 61	E	E	F
Example 62	E	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 63	E	E	F
Example 64	E	E	F
Example 65	E	D	F
Example 66	E	E	F
Example 67	E	E	F
Example 68	E	E	F
Example 69	D	D	G
Example 70	D	E	G
Example 71	D	E	F
Example 72	E	E	F
Example 73	E	E	F
Example 74	E	E	F
Example 75	E	E	G
Example 76	D	E	G
Example 77	E	E	F
Example 78	E	E	F
Example 79	D	E	H
Example 80	D	D	G
Example 81	D	E	H

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 82	D	E	G
Example 83	D	E	G H*
Example 84	D	E	G
Example 85	E	E	F
Example 86	D	D	F
Example 87	D	E	G
Example 88	E	E	F
Example 89	E	E	F
Example 90	D	D	F
Example 91	E	E	G
Example 92	D	E	H
Example 93	D	D	G
Example 94	D	D	F
Example 95	C	C	F
Example 96	E	E	G
Example 97	D	D	F
Example 98	D	E	F
Example 99	D	D	F
Example 100	D	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 101	B	C	H
Example 102	D	D	F
Example 103	E	E	G
Example 104	A	C	H
Example 105	C	C	G
Example 106	C	D	H
Example 107	B	C	G
Example 108	D	D	F
Example 109	D	D	F
Example 110	D	D	F
Example 111	D	D	F
Example 112	A	C	G
Example 113	D	C	F
Example 114	D	C	F
Example 115	D	D	F
Example 116	E	D	F
Example 117	B	C	H
Example 118	B	C	H
Example 119	C	D	G

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 120	C	D	F
Example 121	E	D	F
Example 122	D	D	F
Example 123	C	D	F
Example 124	C	C	F
Example 125	E	D	F
Example 126	D	D	F
Example 127	C	D	H
Example 128	B	D	H
Example 129	B	D	J
Example 130	B	D	J
Example 131	C	D	G
Example 132	C	D	H
Example 133	C	C	G
Example 134	D	D	G
Example 135	D	E	G
Example 136	C	D	H
Example 137	C	D	G
Example 138	C	D	H

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*,[1]
Example 139	C	C	G
Example 140	C	C	F
Example 141	D	D	F
Example 142	D	D	G
Example 143	C	D	G
Example 144	C	E	J
Example 145	C	E	J
Example 146	D	E	F
Example 147	D	E	G
Example 148	D	E	G
Example 149	D	E	F
Example 150	B	D	J
Example 151	B	D	J
Example 152	A	C	H
Example 153	B	D	H
Example 154	B	C	H
Example 155	C	D	H
Example 156	C	D	H
Example 157	C	D	H

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 158	C	D	H
Example 159	A	C	H
Example 160	B	C	H
Example 161	B	D	J
Example 162	C	C	F
Example 163	A	C	H
Example 164	A	C	H
Example 165	A	C	H
Example 166	A	C	G
Example 167	A	C	H
Example 168	A	B	F
Example 169	C	D	H
Example 170	C	D	G
Example 171	C	D	G
Example 172	D	D	F
Example 173	B	B	F
Example 174	C	D	G
Example 175	B	D	J
Example 176	D	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*,[1]
Example 177	C	C	F
Example 178	C	D	J
Example 179	C	D	G
Example 180	C	D	G
Example 181	C	D	H
Example 182	B	C	G
Example 183	A	C	H
Example 184	B	C	J
Example 185	A	C	H
Example 186	C	C	F
Example 187	A	C	H
Example 188	B	D	H
Example 189	B	C	H
Example 190	A	C	H
Example 191	A	C	G
Example 192	C	C	F
Example 193	B	D	J
Example 194	C	D	G
Example 195	B	D	J

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 196	B	D	J
Example 197	D	D	G
Example 198	C	C	F
Example 199	B	C	H
Example 200	C	D	H
Example 201	B	D	J
Example 202	C	D	H
Example 203	C	D	G
Example 204	B	D	J
Example 205	D	D	G
Example 206	D	D	F
Example 207	D	D	F
Example 208	D	D	F
Example 209	D	D	F
Example 210	B	D	J
Example 211	B	D	H
Example 212	D	E	F
Example 213	D	E	G
Example 214	D	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 215	D	C	F
Example 216	C	D	G
Example 217	C	D	G
Example 218	C	D	H
Example 219	D	D	G
Example 220	C	D	H
Example 221	C	D	H
Example 222	D	E	F
Example 223	E	E	F
Example 224	C	E	J
Example 225	C	E	J
Example 226	C	D	J
Example 227	C	E	H
Example 228	C	D	G
Example 229	D	D	G
Example 230	C	D	F
Example 231	D	D	F
Example 232	D	D	F
Example 233	D	D	F

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 234	D	D	F
Example 235	C	D	G
Example 236	D	D	F
Example 237	D	D	F
Example 238	C	D	H
Example 239	C	D	H
Example 240	C	D	H
Example 241	C	D	H
Example 242	C	D	H
Example 243	B	D	J
Example 244	C	D	J
Example 245	B	E	J
Example 246	C	E	J
Example 247	C	E	J
Example 248	C	E	J
Example 249	C	E	J
Example 250	B	E	J
Example 251	C	E	J
Example 252	C	E	J

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 253	C	E	J
Example 254	C	E	J
Example 255	B	E	J
Example 256	B	E	J
Example 257	C	E	J
Example 258	D	E	H
Example 259	C	E	J
Example 260	C	E	J
Example 261	C	E	J
Example 262	B	E	J
Example 263	D	E	J
Example 264	D	E	J
Example 265	C	E	J
Example 266	C	E	J
Example 267	C	E	J
Example 268	C	E	J
Example 269	D	E	J
Example 270	B	E	J
Example 271	B	D	H

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 272	C	D	H
Example 273	C	D	H
Example 274	C	D	H
Example 275	C	D	G
Example 276	C	D	H
Example 277	C	D	H
Example 278	C	D	H
Example 279	C	D	H
Example 280	C	D	H
Example 281	C	D	H
Example 282	C	D	H
Example 283	B	D	H
Example 284	C	D	H
Example 285	C	D	H
Example 286	C	D	J
Example 287	C	D	H
Example 288	B	D	J
Example 289	C	D	J
Example 290	C	D	J

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 291	B	D	J
Example 292	C	D	J
Example 293	C	D	J
Example 294	C	D	J
Example 295	B	D	J
Example 296	C	D	H
Example 297	C	D	H
Example 298	C	D	G
Example 299	C	D	H
Example 300	C	D	H
Example 301	C	D	J
Example 302	C	D	J
Example 303	C	E	J
Example 304	B	D	J
Example 305	B	D	J
Example 306	C	D	J
Example 307	B	D	J
Example 308	C	E	J
Example 309	B	D	J

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 310	B	D	J
Example 311	B	E	J
Example 312	C	E	J
Example 313	C	E	J
Example 314	C	E	H
Example 315	C	E	J
Example 316	B	D	J
Example 317	C	D	J
Example 318	C	E	J
Example 319	B	D	J
Example 320	C	E	J
Example 321	B	D	J
Example 322	B	E	J
Example 323	C	E	J
Example 324	C	D	J
Example 325	C	E	J
Example 326	B	E	J
Example 327	C	E	J
Example 328	B	D	J

Compound	MTHFD1 IC_{50}	MTHFD2 IC_{50}	MTHFD1/MTHFD2 IC_{50} ratio
Reference Example 1	C[1]	D[1]	G H*, [1]
Example 329	B	E	J
Example 330	C	D	J
Example 331	C	E	J

*mean value after increased number of repeats

[1] Specific values (average of multiple repeats) are: MTHFD1 IC_{50} = 0.41μM, MTHFD2 IC_{50} = 0.045 μM, MTHFD1/MTHFD2 IC_{50} ratio = 9.1.

All compounds of formula (I) which were tested in this assay showed inhibitory activity against at least MTHFD2, and certain compounds of formula (I) showed inhibitory activity against MTHFD1 and MTHFD2 as shown by the values in Table 1.

Certain compounds of formula (I) that were tested in this assay were more potent than the Reference Example 1 in the MTHFD1 assay. Certain compounds of formula (I) that were tested in this assay were more potent than the Reference Example 1 in the MTHFD2 assay. Certain compounds of formula (I) that were tested in this assay were more potent than the Reference Example 1 in the MTHFD1 and the MTHFD2 assay.

Certain compounds of formula (I) that were tested in this assay had comparable selectivity for MTHFD2 compared with Reference Example 1 as shown by the MTHFD1/MTHFD2 ratio values. Certain compounds of formula (I) that were tested in this assay were more selective for MTHFD2 than the Reference Example 1 as shown by the MTHFD1/MTHFD2 ratio values. Preferred compounds were e.g. at least 10 fold, e.g. at least 20 fold e.g. at least 30 fold, e.g. at least 50 fold, e.g. at least 100 fold selective for MTHFD2, as shown by the MTHFD1/MTHFD2 ratio values. Other preferred compounds were at least 200 fold, e.g. at least 300 fold, e.g. at least 600 fold selective for MTHFD2, as shown by the MTHFD1/MTHFD2 ratio values.

Biological Example 2 – α4β2 neuronal nicotinic receptor assay (agonist radioligand)

Experimental Protocol

The assay was purchased from Eurofins CEREP (catalogue reference 3029). Cell membrane homogenates (30 μg protein) were incubated for 120 min at 4°C with 0.6 nM [3H]cytisine in the

absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 120 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$ and 1 mM $MgCl_2$. Nonspecific binding was determined in the presence of 10 µM nicotine bitartrate. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters were dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard). The results were expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound was nicotine bitartrate. Test compounds and standard reference compound were tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} was calculated.

A number of example compounds of formula (I) were tested to evaluate their affinity for the human α4β2 neuronal nicotinic receptor expressed in transfected SH-SY5Y cells, determined in a radioligand binding assay.

The results are shown in Table 2 below. Reference Example 1 was also tested in this assay.

IC_{50} thresholds:

Band	α4β2 Nicotinic receptor IC_{50} (µM)
K	<2
L	2 to 20
M	>20 to 100
N	>100

Table 2 – α4β2 nicotinic receptor IC_{50} Values

Compound	α4β2 Nicotinic receptor IC_{50} [µM]
Reference Example 1	K
Example 1	L
Example 2	M
Example 3	M
Example 4	M
Example 12	N
Example 18	N

Compound	α4β2 Nicotinic receptor IC_{50} [μM]
Reference Example 1	K
Example 20	L
Example 24	M
Example 25	M
Example 45	M
Example 54	N
Example 69	N
Example 144	M
Example 145	N
Example 147	M
Example 150	M
Example 156	M
Example 174	M
Example 175	M

The results shown in Table 2 show that Reference Example 1 has activity against the α4β2 nicotinic receptor with an IC_{50} of <2μM whereas all the tested compounds of formula (I) displayed an α4β2 nicotinic receptor IC50 of ≥2μM and typically >20μM. Therefore, compounds of formula (I) are considerably less active against the α4β2 nicotinic receptor than Reference Example 1. These data indicate that compounds of formula (I) are not expected to exhibit off-target effects associated with α4β2 nicotinic receptor *in vivo*, unlike Reference Example 1 which displays α4β2 nicotinic receptor IC_{50} of <2μM. Therefore, such compounds of formula (I) appear to be superior to Reference Example 1 as drug candidates for development due to the lack of off-target effects observed.

Biological Example 3 – Human CD4+ T-cell proliferation assay

Stimulation by antigens promotes T cell metabolic reprogramming to meet increased biosynthetic and bioenergetic demands of the cell during inflammation. MTHFD2 is critical for activated CD4 T cells to maintain *de novo* purine synthesis and promote proliferation. MTHFD2 inhibition leads to depletion of purine pools and accumulation of purine biosynthetic intermediates as the cycle has been blocked and as a result proliferation is inhibited.

Activity in the human CD4+ T cell proliferation assay by a MTHFD2 inhibitor is an indication that the inhibitor can be used to treat inflammation and autoimmune diseases *in vivo*. Furthermore, it shows that the inhibitor is able to inhibit MTHFD2 in the mitochondria by permeating the cellular and mitochondrial membranes.

Experimental Protocol

Cryopreserved human CD4+ T cells from three donors, isolated from human blood cones using CD4+ isolation kit (StemCell, 17952), were thawed and centrifuged at 300 xg for 10 minutes at room temperature. Supernatants were decanted and pellets resuspended in 10 mL cRPMI (10% dFBS (Gibco, 26400044) + 1% PenStrep (Merk, P4333) + 1% L-glutamine (Fisher,11500626) + 25nM folic acid (Sigma, F8758) + folate free RPMI (ThermoFisher, 27016021). Cells were counted using the Auto2000 Cellometer (Nexcelom) and AOPI viability stain (Nexcelom, NEXCCS2-0106). Cells were centrifuged at 500 x g for 4 minutes at room temperature before pellets were resuspended in 1 mL of 1x dPBS (Invitrogen, 14190250). A 20 µL sample was taken as an unstained control and topped up with cRPMI. 1 vial of CFSE (Invitrogen, C34554) was reconstituted with 18 µL DMSO (Merk, D2650) and the stock was diluted 1 in 2500 in 1x dPBS to achieve final CFSE concentration of 1 µM. Cells were incubated at room temperature for 8 minutes in a rotator in the dark. 13 mL cRPMI was added to each tube and cells were centrifuged at 500 x g for 4 minutes at room temperature before pellets were resuspended in 10 mL cRPMI. Cells were counted using the Auto2000 Cellometer and AO/PI viability stain and concentration adjusted to 0.6 $x10^6$ cells/mL in cRPMI. 150 µL of cells were added to tissue culture treated 96 well U bottom plates (Corning, 734-0027) for 100k cells/well and 50 µL of 4X CD3/28 stimulatory beads (Gibco, 10548353), at 1:1 bead to cell ratio, which had been washed in 1x dPBS before use. Control wells were included for flow cytometry and edge wells were filled with 200 µL 1x dPBS. Cells were incubated at 37 °C, 5% CO_2 for 2 days before compound treatment. Compounds were added in an 8-point dose response using the Tecan D300e, concentration range 10 µM – 316 pM and Example 4 (10 µM) was added to every plate as a positive control. Cells were incubated at 37°C, 5% CO_2 for a further 2 days prior to flow staining and supernatant harvest.

On the final day plates were centrifuged at 500 x g for 4 minutes at room temperature. 125 µL of supernatants were transferred to a V bottom 96 well polystyrene plate and stored at -80 °C. Plates were gently vortexed to disrupt the cell pellets before 125 µL 1x PBS was added to each well. Plates were centrifuged at 500 x g for 4 minutes at room temperature and supernatants removed from the plates by aspirating. Plates were gently vortexed and 30 µL of live/dead stain (Invitrogen, L34975) in 1x dPBS was added and incubated for 15 minutes in the dark at 4 °C. 170 µL of flow cytometry buffer (1x dPBS + 2% FBS (Gibco, 11550356) + 2mM EDTA (Invitrogen, 15575020)) was added to each well and plates were centrifuged at 500 x g for 4 minutes before supernatants

were aspirated. Plates were gently vortexed and 100 µL of BD Cytofix fixation solution (BD Biosciences, 554655) was added to all wells and incubated for 10 minutes in the dark at 4 °C. 100 µL of flow cytometry buffer was added and plates were centrifuged at 500 x g for 4 minutes before supernatants were aspirated from the plates. Wells were resuspended in 200 µL flow cytometry buffer and plates stored at 4°C before being run on the flow cytometer.

Data was analysed using FlowJo and the compensation matrix applied to all samples. The gates were set using unstained and unstimulated samples. The data was normalised to the DMSO vehicle control, where 0% is full inhibition of proliferation. Test compounds were tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} was calculated.

Compounds of formula (I) were tested in this assay and the IC_{50} results of those compounds tested are shown in Table 3 below. Reference Example 1 was also tested in this assay. Proliferation IC_{50} values are defined below.

IC_{50} threshold:

Band	IC_{50} (µM)
A	>5
B	1 to 5
C	0.1 to <1
D	0.03 to <0.1
E	0.01 to <0.03
F	0.001 to <0.01

Table 3 – Human CD4+ T cell proliferation IC_{50} Values

Compound	Proliferation IC_{50}	Compound	Proliferation IC_{50}
Reference Example 1	D[1]	Reference Example 1	D[1]
Example 1	F	**Example 22**	E
Example 3	F	**Example 50**	F
Example 4	F	**Example 54**	E
Example 15	F	**Example 69**	F

Compound	Proliferation IC_{50}	Compound	Proliferation IC_{50}
Reference Example 1	D^1	Reference Example 1	D^1
Example 98	E	**Example 181**	E
Example 128	B	**Example 193**	D
Example 129	C	**Example 195**	B
Example 130	B	**Example 196**	A
Example 135	E	**Example 199**	C
Example 136	D	**Example 201**	C
Example 144	F	**Example 202**	E
Example 145	E	**Example 210**	A
Example 147	F	**Example 211**	B
Example 149	F	**Example 216**	E
Example 150	E	**Example 217**	E
Example 151	C	**Example 218**	D
Example 155	E	**Example 219**	E
Example 156	D	**Example 221**	D
Example 157	D	**Example 223**	F
Example 169	C	**Example 224**	D
Example 171	C	**Example 225**	D
Example 174	E	**Example 226**	D
Example 175	B	**Example 228**	F
Example 178	C	**Example 241**	C

Compound	Proliferation IC_{50}	Compound	Proliferation IC_{50}
Reference Example 1	D^1	Reference Example 1	D^1
Example 244	C	**Example 267**	C
Example 245	D	**Example 268**	F
Example 246	C	**Example 270**	B
Example 247	E	**Example 276**	F
Example 248	D	**Example 281**	F
Example 249	D	**Example 291**	D
Example 250	D	**Example 292**	F
Example 251	D	**Example 294**	E
Example 253	E	**Example 302**	E
Example 254	E	**Example 303**	E
Example 255	E	**Example 304**	E
Example 256	E	**Example 308**	F
Example 257	F	**Example 310**	D
Example 259	D	**Example 311**	F
Example 260	E	**Example 312**	E
Example 262	D	**Example 313**	D
Example 263	E	**Example 314**	F
Example 264	E	**Example 315**	F
Example 265	C	**Example 316**	D
Example 266	B	**Example 318**	E

Compound	Proliferation IC_{50}	Compound	Proliferation IC_{50}
Reference Example 1	D[1]	Reference Example 1	D[1]
Example 319	C	**Example 326**	C
Example 320	E	**Example 327**	C
Example 321	D	**Example 328**	C
Example 322	D	**Example 329**	C
Example 324	C	**Example 330**	C
Example 325	C	**Example 331**	D

[1] Specific value (average of multiple repeats) is: Proliferation IC_{50} = 0.035 μM

Most compounds of formula (I) which were tested in this assay showed inhibitory activity as shown by the values in Table 3. Certain compounds of formula (I) that were tested in this assay were more potent than the Reference Example 1.

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Miscellaneous

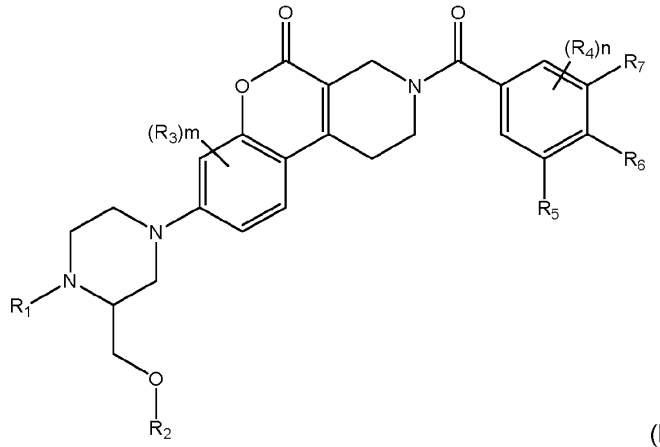
All references referred to in this application, including patent and patent applications, are incorporated herein by reference to the fullest extent possible.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

The application, of which this description and claims form part, may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

CLAIMS

Claim 1. A compound of formula (I):



(I):

wherein:

R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

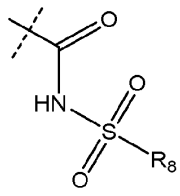
R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2;

and R_5, R_6 and R_7 are defined as follows:

(a) R_6 is  and R_7 is absent;

R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7

membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

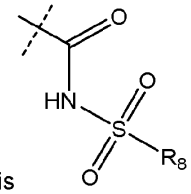
R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or:

(b) R_7 is  : and

(i) R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(ii) R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-}

$_{10}$ cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(iii) R_5 and R_6 join to form a 4-8 membered heterocyclic ring;

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-10 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-10 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein:

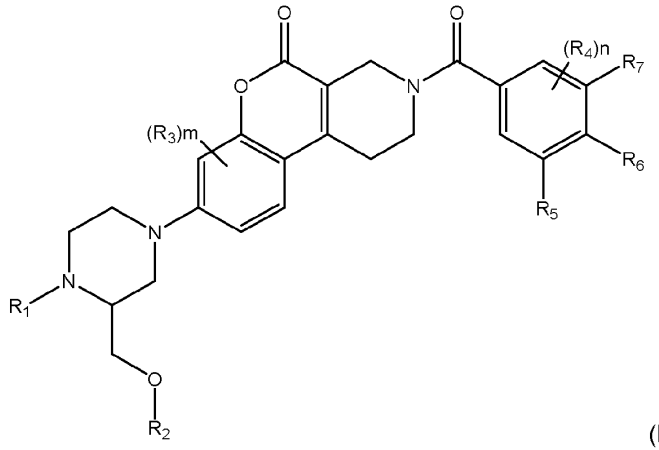
R_{8a} is selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyl substituted by OH, C_{1-2} alkyl substituted by OC_{1-2} alkyl, C_{1-3} alkoxy, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

Claim 2. A compound of formula (I) according to claim 1:



(I)

wherein:

R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $NR_{4a}R_{4b}$ and 4-7 membered heterocycloalkyl;

wherein:

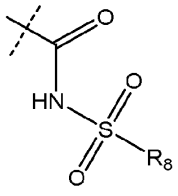
R_{4a} is selected from the group consisting of H and C_{1-3} alkyl;

R_{4b} is selected from the group consisting of H and C_{1-3} alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2;

and R_5, R_6 and R_7 are defined as follows:

(a) R_6 is  and R_7 is absent;

R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

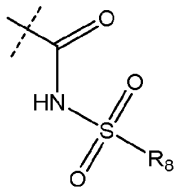
R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein:

R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or:

(b) R_7 is  : and

(i) R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(ii) R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

(iii) R_5 and R_6 join to form a 4-8 membered heterocyclic ring;

and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $NR_{8b}R_{8c}$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein:

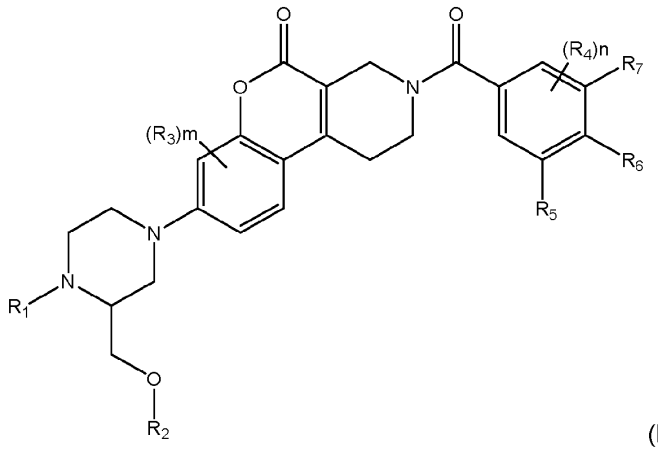
R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

R_{8b} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_{8c} is selected from the group consisting of H, C_{1-3} alkyl and C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

Claim 3. A compound of formula (I) according to claim 1:



(I):

wherein:

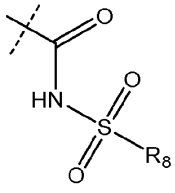
R_1 is C_{1-4} alkyl or C_{3-5} cycloalkyl;

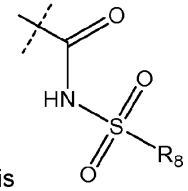
R_2 is C_{1-4} alkyl; or

R_1 and R_2 join to form a 5-7 membered heterocycloalkyl;

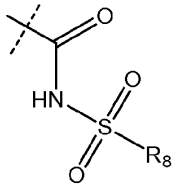
R_3 is selected from the group consisting of C_{1-3} alkyl and halo;

R_4 is selected from the group consisting of C_{1-3} alkyl, halo, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and 4-7 membered heterocycloalkyl;

R_6 is  and R_7 is absent; or

R_7 is  ;

wherein:

when R_6 is  and R_7 is absent:

R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

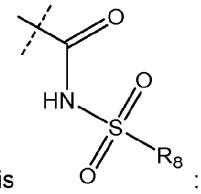
R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring;

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a}, wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

or:

when R_7 is 

:

R_6 is H and R_5 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{5b}R_{5c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{5a};

wherein:

R_{5a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{5a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{5b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{5c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 is H and R_6 is selected from the group consisting of H, halo, C_{1-3} alkoxy, C_{1-3} haloalkoxy, SC_{1-3} alkyl, SC_{1-3} haloalkyl, OC_{3-10} cycloalkyl, $NR_{6b}R_{6c}$ and 4-7 membered heterocycloalkyl, wherein the OC_{3-10} cycloalkyl and 4-7 membered heterocycloalkyl are optionally substituted by one or more R_{6a};

wherein:

R_{6a} is selected from the group consisting of halo and C_{1-3} alkyl, or two R_{6a} groups which are attached to the same carbon atom join to form a C_{3-6} cycloalkyl or 4-7 membered heterocycloalkyl ring,

R_{6b} is selected from the group consisting of H and C_{1-3} alkyl; and

R_{6c} is selected from the group consisting of C_{1-3} alkyl and C_{3-6} cycloalkyl;

or

R_5 and R_6 join to form a 4-7 membered heterocyclic ring; and

R_8 is selected from the group consisting of C_{3-6} cycloalkyl, $N(C_{1-3}$ alkyl$)_2$ and 4-8 membered heterocycloalkyl, wherein the C_{3-6} cycloalkyl and 4-8 membered heterocycloalkyl are optionally substituted by one or more R_{8a} wherein R_{8a} is selected from the group consisting of C_{1-3} alkyl, halo and C_{1-3} haloalkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2;

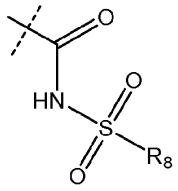
or a pharmaceutically acceptable salt and/or solvate thereof.

Claim 4. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 3 wherein R_1 is methyl and R_2 is methyl.

Claim 5. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 4 wherein m is 2 and R_3 is methyl or wherein m is 1 and R_3 is chloro.

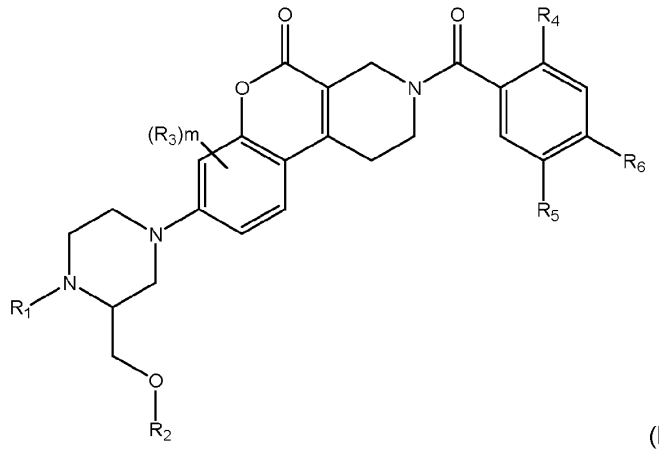
Claim 6. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 5 wherein n is 1 and R_4 is selected from the group consisting of chloro and fluoro.

Claim 7. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 6 wherein:

R_6 is  and R_7 is absent.

Claim 8. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to claim 7 wherein R_5 is C_{1-3} alkoxy e.g. methoxy or ethoxy, or OC_{3-10} cycloalkyl e.g. cyclobutyloxy or cyclopentyloxy.

Claim 9. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to claim 7 which is a compound of formula (IC):



(IC);

wherein R_1, R_2, R_3, m and R_4 are as defined in any one of claims 1 to 6, R_6 as defined in claim 7 and R_5 is methoxy, ethoxy, cyclopropyloxy or $NR_{5b}R_{5c}$ and wherein R_{5b} and R_{5c} are as defined in claim 1.

Claim 10. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 7 or claim 9 wherein R_5 is $NR_{5b}R_{5c}$ wherein R_{5b} and R_{5c} are each methyl.

Claim 11. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 10 wherein R_8 is C_{3-6} cycloalkyl e.g. cyclopropyl and R_8 is substituted by one R_{8a} group e.g. methyl, or wherein R_8 is 4-8 membered heterocycloalkyl e.g. e.g. pyrrolidinyl, 7-azanorbornanyl, 3-azabicyclo[3.1.0]hexyl, 6-azaspiro[2.5]octyl or 3-oxa-6-azabicyclo[3.2.1]octyl.

Claim 12. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to claim 11 wherein R_8 is pyrrolidinyl e.g. pyrrolidin-1-yl.

Claim 13. The compound or a pharmaceutically acceptable salt and/or solvate thereof according to claim 1 which is selected from the list consisting of:
(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

(R)-2-cyclobutoxy-4-(8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-6-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

(*R*)-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclobutoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(cyclopentyloxy)-3-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluorobenzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(*N*-isopropyl-*N*-methylsulfamoyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(((1*R*,3*s*,5*S*)-bicyclo[3.1.0]hexan-3-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropiperidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-6-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopropyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(cyclopropyl(methyl)amino)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-((4,4-difluorocyclohexyl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-((4,4-difluorocyclohexyl)oxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(3,3-dimethylpyrrolidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(azetidin-1-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-(azetidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-2-(3,3-difluoropyrrolidin-1-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
2-((adamantan-2-yl)oxy)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
2-(3-azabicyclo[3.1.0]hexan-3-yl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-((4,4-difluorocyclohexyl)oxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
2-((adamantan-2-yl)oxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

N-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide;

N-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-chloro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methyl-6-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(439 yrrolidine-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(bicyclo[3.1.0]hexan-3-yloxy)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(2-azabicyclo[2.2.1]heptan-2-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-(2-azabicyclo[2.2.1]heptan-2-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(5-azaspiro[2.5]octan-5-yl)benzamide;

(*R*)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-((*R*)-2-methylpyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-((*S*)-2-methylpyrrolidin-1-yl)benzamide;

2-(3-azabicyclo[3.1.0]hexan-3-yl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(pyrrolidin-1-yl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-(cyclopentyloxy)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-6-(trifluoromethyl)benzamide;

(*S*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(pyrrolidin-1-yl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-2-(pyrrolidin-1-yl)benzamide;
(*R*)-2-cyclobutoxy-4-(8-(3-(ethoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;
(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(*R*)-3-fluoro-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;
(*R*)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-5-(trifluoromethyl)benzamide;

(*R*)-2-(cyclopentyloxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-3-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((1-methylcyclopropyl)sulfonyl)-5-(trifluoromethyl)benzamide;

(*R*)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-isopropoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-6-(trifluoromethyl)benzamide;

(*R*)-2-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-cyclobutoxy-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-6-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-4-carboxamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-2-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-cyclobutoxy-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

2-cyclobutoxy-*N*-(((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)sulfonyl)-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-*N*-(*N*,*N*-dimethylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-2-cyclobutoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-methyl-N-((1-methylcyclopropyl)sulfonyl)benzamide;

(R)-4-fluoro-5-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclobutane]-7-carboxamide;

(R)-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((1-methylcyclopropyl)sulfonyl)-5-(trifluoromethyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(trifluoromethoxy)benzamide**;**

(*R*)-2-chloro-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-2-cyclobutoxy-3-fluoro-4-(8-(4-isopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-2-(difluoromethoxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-2-cyclobutoxy-4-(8-(4-ethyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclobutoxy-4-(8-(4-cyclopropyl-3-(methoxymethyl)piperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(S)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*S*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-chloro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(cyclopentyloxy)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-10-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((6-azaspiro[2.5]octan-6-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-cyclobutoxy-3-fluoro-4-(8-(3-(isopropoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-chloro-2-(dimethylamino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(azetidin-1-yl)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-amino-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;

(*R*)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-(*N*-cyclopentyl-*N*-methylsulfamoyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-(cyclobutyl(methyl)amino)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(methylamino)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(azetidin-1-yl)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-N-((4-fluoropiperidin-1-yl)sulfonyl)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-propoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(2,2,2-trifluoroethoxy)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(7-chloro-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(7-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluorobenzamide;

N-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-((octahydro-2*H*-isoindol-2-yl)sulfonyl)benzamide;

(*R*)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(7-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-3-fluorobenzamide;

(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((3,3-dimethylpyrrolidin-1-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)-2-(3,3,3-trifluoropropoxy)benzamide;

(*R*)-3-ethoxy-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-5-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((2-azabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*,*N*-dicyclopropylsulfamoyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-ethoxy-3-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-ethoxy-3-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-(N-cyclopentyl-N-methylsulfamoyl)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-3-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(piperidin-1-ylsulfonyl)benzamide;

(*R*)-3-fluoro-N-((4-fluoropiperidin-1-yl)sulfonyl)-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-methylbenzamide;

(*R*)-5-(dimethylamino)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-ethyl-3-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-ethoxy-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-(dimethylamino)-4-(10-ethyl-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-methoxy-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-fluoro-2-(methoxy-d3)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-3-fluoro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-(dimethylamino)-5-fluoro-N-(((S)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*-cyclopropyl-N-methylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-3-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-*N*-(*N*,*N*-dimethylsulfamoyl)-5-fluorobenzamide;

2-ethoxy-5-fluoro-*N*-(((*R*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxy-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(*R*)-2-fluoro-5-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

N-(((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-ethoxy-5-fluoro-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

2-ethoxy-5-fluoro-*N*-(((*S*)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((*R*)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-*N*-(*N*-cyclopropyl-*N*-methylsulfamoyl)-2-ethoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(*R*)-2-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2*H*-chromeno[3,4-c]pyridine-3-carbonyl)-5-methyl-*N*-(pyrrolidin-1-ylsulfonyl)benzamide;

(R)-N-((2-oxa-5-azaspiro[3.5]nonan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-N-((2-oxa-6-azaspiro[3.5]nonan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

R)-N-((2-oxa-6-azaspiro[3.4]octan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

(R)-N-((5-azaspiro[2.4]heptan-5-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(piperidin-1-ylsulfonyl)benzamide;

(R)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;

N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-3-methoxypiperidin-1-yl)sulfonyl)benzamide;

(R)-N-((2-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-methoxypyrrolidin-1-yl)sulfonyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-3-methoxypiperidin-1-yl)sulfonyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-methoxypiperidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-5-chloro-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-N-(N,N-dimethylsulfamoyl)benzamide;

2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide;

N-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-2-(trifluoromethyl)pyrrolidin-1-yl)sulfonyl)benzamide;

(R)-2-(dimethylamino)-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)benzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N,N-dicyclopropylsulfamoyl)-5-fluoro-2-methoxybenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-ethoxy-5-fluorobenzamide;

(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluoro-N-((1-methylcyclopropyl)sulfonyl)benzamide;

(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;

N-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((S)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide;

4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)benzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-N-(N,N-dimethylsulfamoyl)-5-fluorobenzamide;
N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-cyclopropoxy-5-fluorobenzamide;
(R)-2-(dimethylamino)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-fluoro-4-(10-fluoro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methyl-N-(pyrrolidin-1-ylsulfonyl)benzamide;
2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;
2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(((S)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonyl)benzamide;
N-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
2-(dimethylamino)-5-fluoro-N-(((R)-3-fluoropyrrolidin-1-yl)sulfonyl)-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-2-(dimethylamino)-5-fluoro-4-(8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;

(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxy-5-fluorobenzamide;
(R)-N-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-fluoro-5-methoxy-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-ethoxybenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-methoxybenzamide;
N-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(N-cyclopropyl-N-methylsulfamoyl)-2-(dimethylamino)-5-fluorobenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-methoxybenzamide;
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-4-(10-chloro-8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide;
N-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-4-(10-chloro-8-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)-7-methyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-5-fluoro-2-(methoxy-d3)benzamide;

(R)-5-chloro-2-(methoxy-d3)-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-chloro-2-methoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide;
(R)-5-chloro-2-ethoxy-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)-N-(pyrrolidin-1-ylsulfonyl)benzamide; and
(R)-N-((7-azabicyclo[2.2.1]heptan-7-yl)sulfonyl)-2-cyclopropoxy-5-fluoro-4-(8-(3-(methoxymethyl)-4-methylpiperazin-1-yl)-7,10-dimethyl-5-oxo-1,3,4,5-tetrahydro-2H-chromeno[3,4-c]pyridine-3-carbonyl)benzamide;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

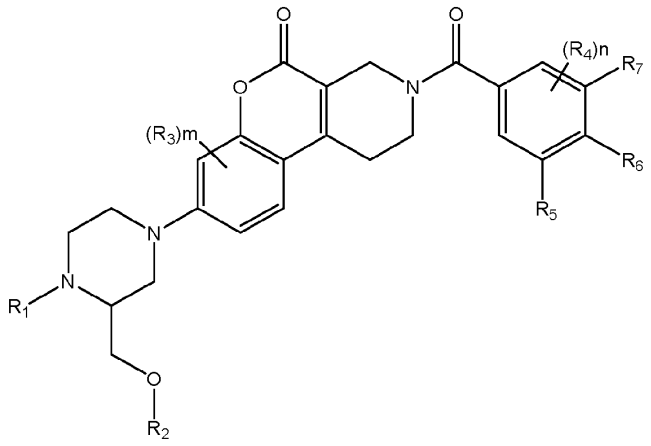
Claim 14. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 13 and one or more pharmaceutically acceptable diluents or carriers.

Claim 15. A compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 13 or a pharmaceutical composition according to claim 14 for use as a medicament.

Claim 16. A compound or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 13 or a pharmaceutical composition according to claim 14 for use in treating or preventing a disease selected from inflammatory, autoimmune and fibrotic diseases, and cancer.

Claim 17. A method of treating or preventing a disease selected from inflammatory, autoimmune and fibrotic diseases, and cancer, which comprises administering a compound or salt and/or solvate thereof according to any one of claims 1 to 13 or a pharmaceutical composition according to claim 14.

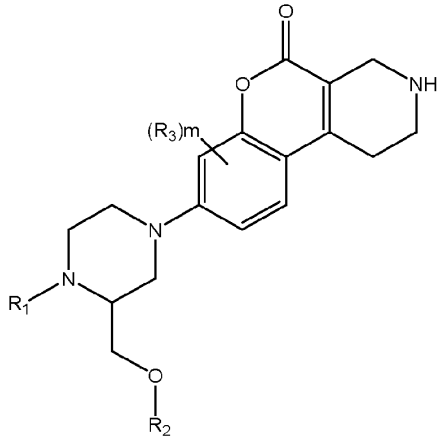
Claim 18. A process for the preparation of a compound of formula (I):



(I)

or a salt and/or solvate thereof such as a pharmaceutically acceptable salt and/or solvate thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, m and n are defined in any one of claims 1 to 13; which comprises:

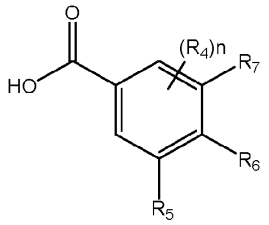
(a) coupling a compound of formula (II):



(II)

or a salt such as a pharmaceutically acceptable salt thereof;

with a compound of formula (III):



(III);

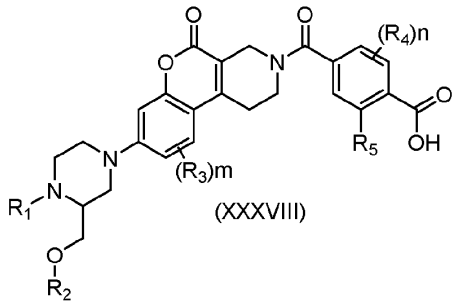
or a salt such as a pharmaceutically acceptable salt thereof;

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, m and n are defined in any one of claims 1 to 13;

or

(b) preparing a compound of formula (I) in which R_7 is absent by a process comprising

coupling a compound of formula (XXXVIII):

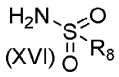


(XXXVIII)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, R_8, n and m are defined in any one of claims 1 to 13;

with a compound of formula (XVI):

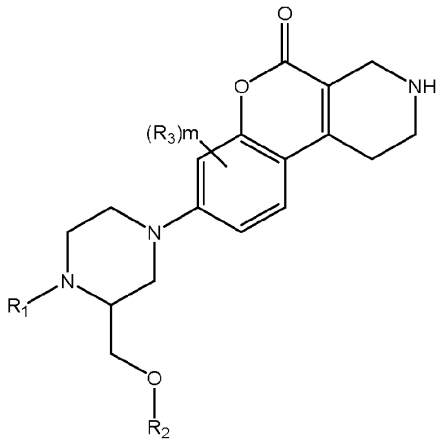


(XVI)

or a salt and/or solvate thereof;

wherein R_8 is defined in any in any one of claims 1 to 13.

Claim 19. A compound of formula (II):

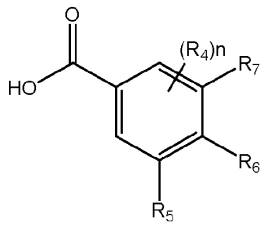


(II)

or a salt, such as a pharmaceutically acceptable salt thereof;

wherein R_1, R_2, R_3 and m are as in any one of claims 1 to 13.

Claim 20. A compound of formula (III):

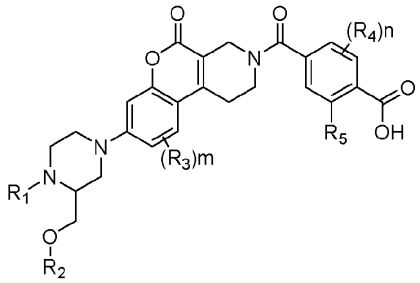


(III)

or a salt, such as a pharmaceutically acceptable salt thereof;

wherein R_4, R_5, R_6, R_7, R_8 and n are as in any one of claims 1 to 13.

Claim 21. A compound of formula (XXXVIII):

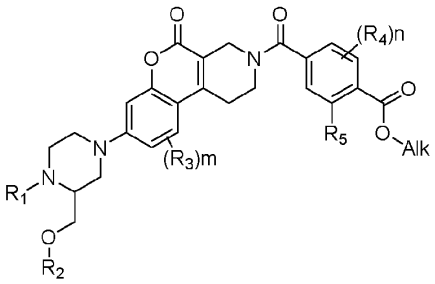


(XXXVIII)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of claims 1 to 13.

Claim 22. A compound of formula (XXXIX):

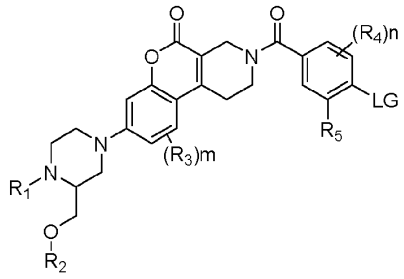


(XXXIX)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of claims 1 to 13, and Alk is C_{1-4}alkyl.

Claim 23. A compound of formula (XXXXI):



(XXXXI)

or a salt and/or solvate thereof;

wherein R_1, R_2, R_3, R_4, R_5, n and m are defined in any one of claims 1 to 13, and LG is a leaving group such as halo e.g. bromo.