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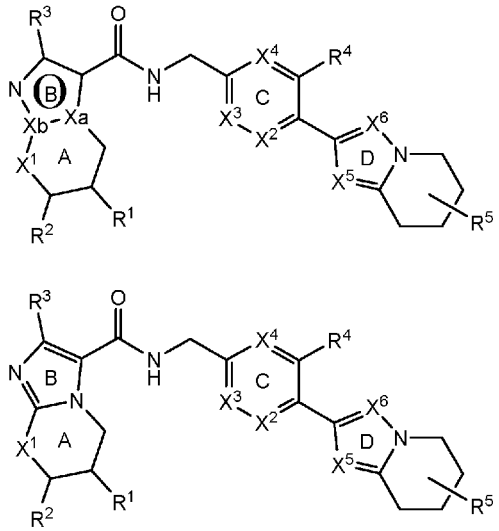
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(54) Title: IMIDAZOPYRIDINE AMIDES AND RELATED COMPOUNDS FOR USE IN THE TREATMENT OF BACTERIAL INFECTIONS



(I)

(57) Abstract: The present invention relates to the following compounds (I) wherein the integers are as defined in the description, and where the compounds may be useful as medicaments, for instance for use in the treatment of tuberculosis (e.g. in combination).

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[Continued on next page]

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IMIDAZOPYRIDINE AMIDES AND RELATED COMPOUNDS FOR USE IN THE TREATMENT OF BACTERIAL INFECTIONS

The present invention relates to novel compounds. The invention also relates to such compounds for use as a pharmaceutical and further for the use in the treatment of bacterial diseases, including diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*. Such compounds may work by interfering with ATP synthase in *M. tuberculosis*, with the inhibition of cytochrome bc_1 activity as the primary mode of action. Hence, primarily, such compounds are antitubercular agents.

BACKGROUND OF THE INVENTION

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a serious and potentially fatal infection with a world-wide distribution. Estimates from the World Health Organization indicate that more than 8 million people contract TB each year, and 2 million people die from tuberculosis yearly. In the last decade, TB cases have grown 20% worldwide with the highest burden in the most impoverished communities. If these trends continue, TB incidence will increase by 41% in the next twenty years. Fifty years since the introduction of an effective chemotherapy, TB remains after AIDS, the leading infectious cause of adult mortality in the world. Complicating the TB epidemic is the rising tide of multi-drug-resistant strains, and the deadly symbiosis with HIV. People who are HIV-positive and infected with TB are 30 times more likely to develop active TB than people who are HIV-negative and TB is responsible for the death of one out of every three people with HIV/AIDS worldwide.

Existing approaches to treatment of tuberculosis all involve the combination of multiple agents. For example, the regimen recommended by the U.S. Public Health Service is a combination of isoniazid, rifampicin and pyrazinamide for two months, followed by isoniazid and rifampicin alone for a further four months. These drugs are continued for a further seven months in patients infected with HIV. For patients infected with multi-drug resistant strains of *M. tuberculosis*, agents such as ethambutol, streptomycin, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, ciprofoxacin and ofloxacin are added to the combination therapies. There exists no single agent that is effective in the clinical treatment of tuberculosis, nor any combination of agents that offers the possibility of therapy of less than six months' duration.

There is a high medical need for new drugs that improve current treatment by enabling regimens that facilitate patient and provider compliance. Shorter regimens and those that require less supervision are the best way to achieve this. Most of the benefit from treatment comes in the first 2 months, during the intensive, or bactericidal, phase when four drugs are

given together; the bacterial burden is greatly reduced, and patients become noninfectious. The 4- to 6-month continuation, or sterilizing, phase is required to eliminate persisting bacilli and to minimize the risk of relapse. A potent sterilizing drug that shortens treatment to 2 months or less would be extremely beneficial. Drugs that facilitate compliance by requiring less intensive supervision also are needed. Obviously, a compound that reduces both the total length of treatment and the frequency of drug administration would provide the greatest benefit.

Complicating the TB epidemic is the increasing incidence of multi-drug-resistant strains or MDR-TB. Up to four percent of all cases worldwide are considered MDR-TB - those resistant to the most effective drugs of the four-drug standard, isoniazid and rifampin. MDR-TB is lethal when untreated and cannot be adequately treated through the standard therapy, so treatment requires up to 2 years of "second-line" drugs. These drugs are often toxic, expensive and marginally effective. In the absence of an effective therapy, infectious MDR-TB patients continue to spread the disease, producing new infections with MDR-TB strains. There is a high medical need for a new drug with a new mechanism of action, which is likely to demonstrate activity against drug resistant, in particular MDR strains.

The term “drug resistant” as used hereinbefore or hereinafter is a term well understood by the person skilled in microbiology. A drug resistant Mycobacterium is a Mycobacterium which is no longer susceptible to at least one previously effective drug; which has developed the ability to withstand antibiotic attack by at least one previously effective drug. A drug resistant strain may relay that ability to withstand to its progeny. Said resistance may be due to random genetic mutations in the bacterial cell that alters its sensitivity to a single drug or to different drugs.

MDR tuberculosis is a specific form of drug resistant tuberculosis due to a bacterium resistant to at least isoniazid and rifampicin (with or without resistance to other drugs), which are at present the two most powerful anti-TB drugs. Thus, whenever used hereinbefore or hereinafter “drug resistant” includes multi drug resistant.

Another factor in the control of the TB epidemic is the problem of latent TB. In spite of decades of tuberculosis (TB) control programs, about 2 billion people are infected by M. tuberculosis, though asymptomatically. About 10% of these individuals are at risk of developing active TB during their lifespan. The global epidemic of TB is fuelled by infection of HIV patients with TB and rise of multi-drug resistant TB strains (MDR-TB). The reactivation of latent TB is a high risk factor for disease development and accounts for 32% deaths in HIV infected individuals. To control TB epidemic, the need is to

discover new drugs that can kill dormant or latent bacilli. The dormant TB can get reactivated to cause disease by several factors like suppression of host immunity by use of immunosuppressive agents like antibodies against tumor necrosis factor α or interferon-γ. In case of HIV positive patients the only prophylactic treatment available for latent TB is two-three months regimens of rifampicin, pyrazinamide. The efficacy of the treatment regime is still not clear and furthermore the length of the treatments is an important constrain in resource-limited environments. Hence there is a drastic need to identify new drugs, which can act as chemoprophylatic agents for individuals harboring latent TB bacilli.

The tubercle bacilli enter healthy individuals by inhalation; they are phagocytosed by the alveolar macrophages of the lungs. This leads to potent immune response and formation of granulomas, which consist of macrophages infected with M. tuberculosis surrounded by T cells. After a period of 6-8 weeks the host immune response cause death of infected cells by necrosis and accumulation of caseous material with certain extracellular bacilli, surrounded by macrophages, epitheloid cells and layers of lymphoid tissue at the periphery. In case of healthy individuals, most of the mycobacteria are killed in these environments but a small proportion of bacilli still survive and are thought to exist in a non-replicating, hypometabolic state and are tolerant to killing by anti-TB drugs like isoniazid. These bacilli can remain in the altered physiological environments even for individual's lifetime without showing any clinical symptoms of disease. However, in 10% of the cases these latent bacilli may reactivate to cause disease. One of the hypothesis about development of these persistent bacteria is patho-physiological environment in human lesions namely, reduced oxygen tension, nutrient limitation, and acidic pH. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs.

In addition to the management of the TB epidemic, there is the emerging problem of resistance to first-line antibiotic agents. Some important examples include penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, multi-resistant salmonellae.

The consequences of resistance to antibiotic agents are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of infectivity, which increase the numbers of infected people moving in the community and thus exposing the general population to the risk of contracting a resistant strain infection.

Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted in infections with highly resistant bacterial pathogens.

Self-medication with antimicrobials is another major factor contributing to resistance. Self-medicated antimicrobials may be unnecessary, are often inadequately dosed, or may not contain adequate amounts of active drug.

Patient compliance with recommended treatment is another major problem. Patients forget to take medication, interrupt their treatment when they begin to feel better, or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed.

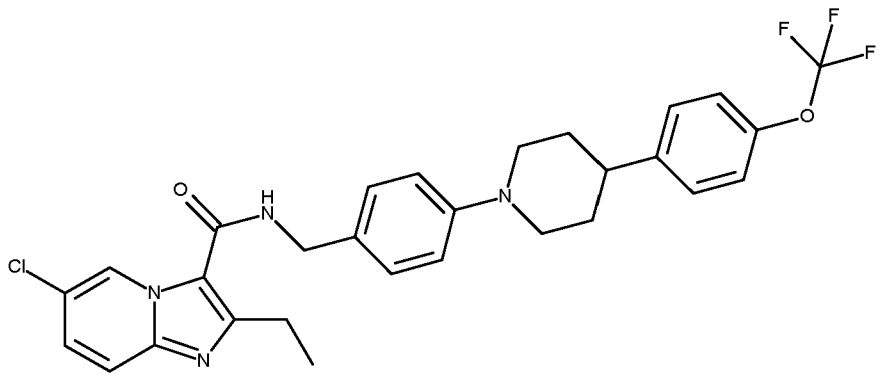
Because of the emerging resistance to multiple antibiotics, physicians are confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections impose an increasing burden for health care systems worldwide.

Therefore, there is a high need for new compounds to treat bacterial infections, especially mycobacterial infections including drug resistant and latent mycobacterial infections, and also other bacterial infections especially those caused by resistant bacterial strains.

Anti-infective compounds for treating tuberculosis have been disclosed in e.g. international patent application WO 2011/113606. Such a document is concerned with compounds that would prevent *M. tuberculosis* multiplication inside the host macrophage and relates to compounds with a bicyclic core, imidazopyridines, which are linked (e.g. via an amido moiety) to e.g. an optionally substituted benzyl group.

International patent application WO 2014/015167 also discloses compounds that are disclosed as being of potential use in the treatment of tuberculosis. Such compounds disclosed herein have a bicycle (a 5,5-fused bicycle) as an essential element, which is substituted by a linker group (e.g. an amido group), which itself may be attached to another bicycle or aromatic group. Such compounds in this document do not contain a series of more than three rings.

Journal article *Nature Medicine*, **19**, 1157-1160 (2013) by Pethe *et al* "Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis" identifies a specific compound that was tested against *M. tuberculosis*. This compound Q203 is depicted below.



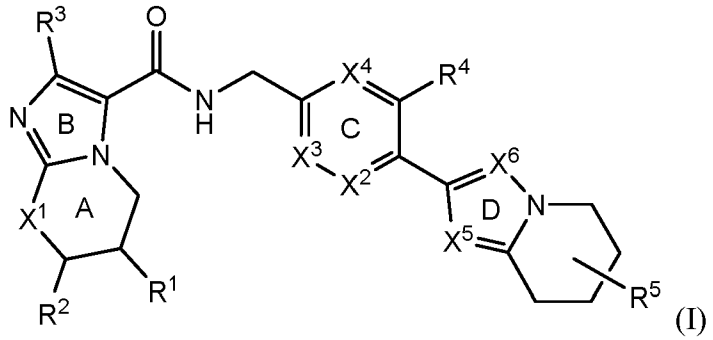
This clinical candidates is also discussed in journal article, *J. Medicinal Chemistry*, 2014, 57 (12), pp 5293-5305. It is stated to have activity against MDR tuberculosis, and have activity against the strain *M. tuberculosis* H37Rv at a MIC_{50} of 0.28 nM inside macrophages. Positive control data (using known anti-TB compounds bedaquiline, isoniazid and moxifloxacin) are also reported. This document also suggests a mode of action, based on studies with mutants. It postulates that it acts by interfering with ATP synthase in *M. tuberculosis*, and that the inhibition of cytochrome bc_1 activity is the primary mode of action. Cytochrome bc_1 is an essential component of the electron transport chain required for ATP synthesis. It appeared that Q203 was highly active against both replicating and non-replicating bacteria.

International patent application WO 2015/014993 also discloses compounds as having activity against *M. tuberculosis*, as do international patent applications WO 2014/4015167, WO 2017/001660, WO 2017/001661, WO 2017/216281, WO 2017/216283 and WO 2021/048342. International patent applications WO 2013/033070 and WO 2013/033167 disclose various compounds as kinase modulators.

The purpose of the present invention is to provide compounds for use in the treatment of bacterial diseases, particularly those diseases caused by pathogenic bacteria such as *Mycobacterium tuberculosis* (including the latent disease and including drug resistant *M. tuberculosis* strains). Such compounds may also be novel and may act by interfering with ATP synthase in *M. tuberculosis*, with the inhibition of cytochrome bc_1 activity being considered the primary mode of action.

SUMMARY OF THE INVENTION

There is now provided a compound of formula (I)



(I)

wherein

A is a 6-membered ring, which may be aromatic or non-aromatic,

X^1 represents =N- , $-CH_2-$ or $=C(R^{10a})-$;

X^2, X^3, X^4, X^5 and X^6 each independently represent =N- or $=C(R^{10b})-$;

R^1 and R^2 each independently represent a substituent selected from hydrogen, halo (e.g. Cl, F), $-R^{6c}$, $-O-R^{6d}$, $-C(=O)-R^{6e}$, $-C(=O)-N(R^6)(R^7)$, -CN and $-N(R^{6a})R^{6b}$;

R^3 represents a substituent selected from H, halo (e.g. Cl, F), and $-C_{1-3}$ alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. F) and $-O-C_{1-3}$ alkyl;

R^4 represents a substituent selected from H, F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl;

R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, and $-N(R^{11a})R^{11b}$;

R^6 and R^7 are independently selected from H and $-C_{1-3}$ alkyl;

R^{6a} and R^{6b} independently represent H, C_{1-6} alkyl or R^{6a} and R^{6b} are linked together to form a 3- to 6-membered ring;

R^{6c} and R^{6d} independently represent hydrogen or $-C_{1-4}$ alkyl optionally substituted by one or more substituents selected from halo (e.g. F), $-O-CH_3$, phenyl, $-N(R^{6a})R^{6b}$;

R^{6e} is $-C_{1-3}$ alkyl;

R^{8a} represents -CN, - C_{1-4} alkyl (linear, branched or cyclic; which alkyl group is optionally substituted by one or more substituents selected from halo, so forming e.g. $-CF_3$, $-CHF_2$, $-CF_2CH_3$), or, $-OC_{1-3}$ alkyl (optionally substituted by one or more substituents selected from halo and $-O-CH_3$);

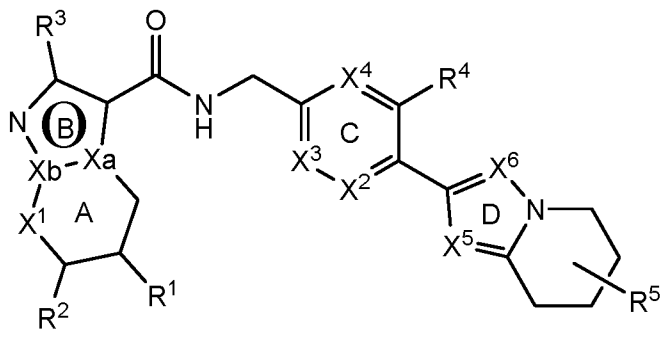
R^{8b} is hydrogen or $-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms);

R^9 represents -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F) and -O-CH_3;
R^{10a} and R^{10b} independently represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, -R^{12a}, -OR^{12b}, -$N(R^{12c})R^{12d}$ and/or -$C(O)N(R^{12e})R^{12f}$) or -O-C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -R^{12g}, -OR^{12h} and/or -$N(R^{12i})R^{12j}$);
R^{11a} and R^{11b}, independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or -$S(O)_2R^{6c}$ (where R^{6c} is defined above);
R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i} and R^{12j} independently represent hydrogen or C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);
or a pharmaceutically-acceptable salt thereof,
which compounds may be referred to herein as "compounds of the invention".

In compounds of the invention:
R^{8a} may also represent C_{1-4} alkyl optionally substituted by -OC_{1-3} alkyl (and for instance, R^5 may therefore represent -CH_2-OCH_3).

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

There is also provided a compound of formula (IA):



(IA)

wherein
A is a 6-membered ring, which may be aromatic or non-aromatic,

B is a 5-membered aromatic ring;
one of X_a and X_b represents N and the other represents C (where each N and C is linked to the appropriate number of single/double bonds);
X^1 represents =N-, $-CH_2-$ or $=C(R^{10a})-$;
X^2, X^3, X^4, X^5 and X^6 each independently represent =N- or $=C(R^{10b})-$;
R^1 and R^2 each independently represent a substituent selected from hydrogen, halo (e.g. Cl, F), $-R^{6c}$, $-O-R^{6d}$, $-C(=O)-R^{6e}$, $-C(=O)-N(R^6)(R^7)$, -CN and $-N(R^{6a})R^{6b}$;
R^3 represents a substituent selected from H, halo (e.g. Cl, F), and $-C_{1-3}$ alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. F) and $-O-C_{1-3}$ alkyl;
R^4 represents a substituent selected from H, F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl;
R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, and $-N(R^{11a})R^{11b}$;
R^6 and R^7 are independently selected from H and $-C_{1-3}$ alkyl;
R^{6a} and R^{6b} independently represent H, C_{1-6} alkyl or R^{6a} and R^{6b} are linked together to form a 3- to 6-membered ring;
R^{6c} and R^{6d} independently represent hydrogen or $-C_{1-4}$ alkyl optionally substituted by one or more substituents selected from halo (e.g. F), $-O-CH_3$, phenyl, $-N(R^{6a})R^{6b}$;
R^{6e} is $-C_{1-3}$ alkyl;
R^{8a} represents -CN, - C_{1-4} alkyl (linear, branched or cyclic; which alkyl group is optionally substituted by one or more substituents selected from halo, so forming e.g. $-CF_3$, $-CHF_2$, $-CF_2CH_3$), or, $-OC_{1-3}$ alkyl (optionally substituted by one or more substituents selected from halo and $-O-CH_3$);
R^{8b} is hydrogen or $-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms);
R^9 represents $-C_{1-4}$ alkyl optionally substituted by one or more substituents selected from halo (e.g. F) and $-O-CH_3$;
R^{10a} and R^{10b} independently represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, $-R^{12a}$, $-OR^{12b}$, $-N(R^{12c})R^{12d}$ and/or $-C(O)N(R^{12e})R^{12f}$) or $-O-C_{1-4}$ alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, $-R^{12g}$, $-OR^{12h}$ and/or $-N(R^{12i})R^{12j}$);
R^{11a} and R^{11b}, independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or $-S(O)_2R^{6c}$ (where R^{6c} is defined above);
R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i} and R^{12j} independently represent hydrogen or C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);
or a pharmaceutically-acceptable salt thereof,
which compounds may also be referred to herein as “compounds of the invention”.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid.

For the purposes of this invention solvates, prodrugs, N-oxides and stereoisomers of compounds of the invention are also included within the scope of the invention.

The term "prodrug" of a relevant compound of the invention includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form that compound in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

Prodrugs of compounds of the invention may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, *in vivo* when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesising the parent compound with a prodrug substituent. Prodrugs include compounds of the invention wherein a hydroxyl, amino, sulfhydryl, carboxy or carbonyl group in a compound of the invention is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, sulfhydryl, carboxy or carbonyl group, respectively.

Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard, H. "Design of Prodrugs" p. l-92, Elesevier, New York-Oxford (1985).

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. Positional isomers may also be embraced by the compounds of the invention. All such isomers (e.g. if a compound of the invention incorporates a double bond or a fused ring, the cis- and trans-forms, are embraced) and mixtures thereof are included within the scope of the invention (e.g. single positional isomers and mixtures of positional isomers may be included within the scope of the invention).

Compounds of the invention may also exhibit tautomerism. All tautomeric forms (or tautomers) and mixtures thereof are included within the scope of the invention. The term

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

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person.

All stereoisomers (including but not limited to diastereoisomers, enantiomers and atropisomers) and mixtures thereof (e.g. racemic mixtures) are included within the scope of the invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the

compounds of the invention. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C , ^{13}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I. Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and for substrate tissue distribution assays. Tritiated (^{3}H) and carbon-l4 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. ^{2}H may also be depicted as ^{2}D herein, and in any event both are encompassed by "hydrogen" or H according in the context of the scope of the invention. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the description/Examples hereinbelow, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). Such cycloalkyl groups may be monocyclic or bicyclic and may further be bridged. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group). In a similar way, C_{1-q} alkylene groups represent C_{1-q} alkyl linker groups, i.e. $-CH_2-$ (C_1 alkylene or methylene), $-CH_2CH_2-$, etc according to the number "q" of carbon atoms.

C_{3-q} cycloalkyl groups (where q is the upper limit of the range) that may be specifically mentioned may be monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged (so forming, for example, fused ring systems such as three fused cycloalkyl groups). Such cycloalkyl groups may be saturated or unsaturated containing one or more double bonds (forming for example a cycloalkenyl group). Substituents may be attached at any point on the cycloalkyl group. Further, where there is a sufficient number (i.e. a minimum of four) such cycloalkyl groups may also be part cyclic.

The term "halo", when used herein, preferably includes fluoro, chloro, bromo and iodo.

Heterocyclic groups when referred to herein may include aromatic or non-aromatic heterocyclic groups, and hence encompass heterocycloalkyl and hetereoaryl. Equally, "aromatic or non-aromatic 5- or 6-membered rings" may be heterocyclic groups (as well as carbocyclic groups) that have 5- or 6-members in the ring.

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between 3 and 20 (e.g. between three and ten, e.g between 3 and 8, such as 5- to 8-). Such heterocycloalkyl groups may also be bridged. Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} heterocycloalkenyl (where q is the upper limit of the range) group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo-[3.2.1]octanyl, aziridinyl, azetidinyl, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo-[3.2.1]octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, non-aromatic pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. Heterocycloalkyl mentioned herein may be stated to be specifically monocyclic or bicyclic.

Aromatic groups may be aryl or heteroaryl. Aryl groups that may be mentioned include C_{6-20}, such as C_{6-12} (e.g. C_{6-10}) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have between 6 and 12 (e.g. 6 and 10) ring carbon atoms, in which at least one ring is aromatic. C_{6-10} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydro-naphthyl. The point of attachment of aryl groups may be *via* any atom of the ring system. For example, when the aryl group is polycyclic the point of attachment may be *via* atom including an atom of a non-aromatic ring. However, when aryl groups are polycyclic (e.g.

bicyclic or tricyclic), they are preferably linked to the rest of the molecule *via* an aromatic ring. Most preferred aryl groups that may be mentioned herein are "phenyl".

Unless otherwise specified, the term "heteroaryl" when used herein refers to an aromatic group containing one or more heteroatom(s) (e.g. one to four heteroatoms) preferably selected from N, O and S. Heteroaryl groups include those which have between 5 and 20 members (e.g. between 5 and 10) and may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic (so forming, for example, a mono-, bi-, or tricyclic heteroaromatic group). When the heteroaryl group is polycyclic the point of attachment may be *via* any atom including an atom of a non-aromatic ring. However, when heteroaryl groups are polycyclic (e.g. bicyclic or tricyclic), they are preferably linked to the rest of the molecule *via* an aromatic ring. Heteroaryl groups that may be mentioned include 3,4-dihydro-1*H*-isoquinolinyl, 1,3-dihydroisoindolyl, 1,3-dihydroisoindolyl (e.g. 3,4-dihydro-1*H*-isoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 1,3-dihydroisoindol-2-yl; i.e. heteroaryl groups that are linked *via* a non-aromatic ring), or, preferably, acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiaziolyl, isothiochromanyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thiophenetyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heteroaryl groups may also be in the *N*- or *S*- oxidised form. Heteroaryl groups mentioned herein may be stated to be specifically monocyclic or bicyclic. When heteroaryl groups are polycyclic in which there is a non-aromatic ring

present, then that non-aromatic ring may be substituted by one or more =O group. Most preferred heteroaryl groups that may be mentioned herein are 5- or 6-membered aromatic groups containing 1, 2 or 3 heteroatoms (e.g. preferably selected from nitrogen, oxygen and sulfur).

It may be specifically stated that the heteroaryl group is monocyclic or bicyclic. In the case where it is specified that the heteroaryl is bicyclic, then it may consist of a five-, six- or seven-membered monocyclic ring (e.g. a monocyclic heteroaryl ring) fused with another five-, six- or seven-membered ring (e.g. a monocyclic aryl or heteroaryl ring).

Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

When "aromatic" groups are referred to herein, they may be aryl or heteroaryl. When "aromatic linker groups" are referred to herein, they may be aryl or heteroaryl, as defined herein, are preferably monocyclic (but may be polycyclic) and attached to the remainder of the molecule *via* any possible atoms of that linker group. However, when, specifically carbocylic aromatic linker groups are referred to, then such aromatic groups may not contain a heteroatom, i.e. they may be aryl (but not heteroaryl).

For the avoidance of doubt, where it is stated herein that a group may be substituted by one or more substituents (e.g. selected from C_{1-6} alkyl), then those substituents (e.g. alkyl groups) are independent of one another. That is, such groups may be substituted with the same substituent (e.g. same alkyl substituent) or different (e.g. alkyl) substituents.

All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred feature) mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

In an embodiment ring A is aromatic and:
X^1 represents =N- , or =CH-,

R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -F, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2.

Preferably, ring A is aromatic, and:
X^1 represents =N- , and/or
R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -F, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2,

In another preferred configuration ring A is aromatic,
X^1 represents =CH- , and/or
R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -F, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2.

In an alternative, ring A is non-aromatic,
X^1 represents $-CH_2-$, and/or
R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2,

It is preferred that the compound of the invention comprises:
R_3 representing a substituent selected from H, $-CF_3$, $-CHF_2$, $-CH_3$, $-CH_2CH_3$, and cyclopropyl.

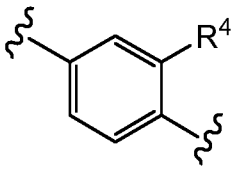
More precisely, compounds wherein ring A is non-aromatic:
X^1 represents $-CH_2-$;
R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -Cl, - OCH_3, $-NH_2$, - CH_2NH_2; and/or
R_3 represents a substituent selected from H, $-CF_3$, $-CHF_2$, $-CH_3$, $-CH_2CH_3$, and cyclopropyl.

Alternatively, in another embodiment of the invention there is provided compounds wherein:
Ring A is aromatic;
X^1 represents =N-;
R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2; and/or
R_3 represents a substituent selected from H, $-CF_3$, $-CHF_2$, $-CH_3$, $-CH_2CH_3$, and cyclopropyl.

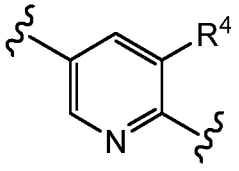
As another alternative, there is provided compounds wherein ring A is aromatic:
X^1 represents =CH-, and/or

R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2. In an embodiment $-CH_3$ may also specifically represent a deuterated isotope thereof, e.g. $-CD_3$.

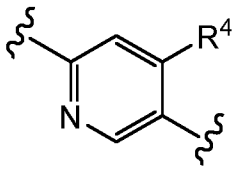
In a further aspect of the invention, there is provided a compound in which ring C is selected among:



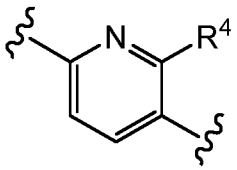
(II)



(III)



(IV)

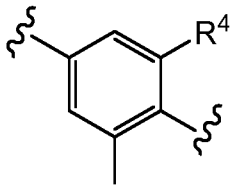


(V)

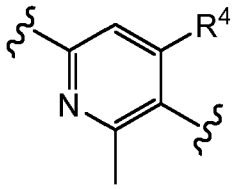
and wherein R^4 represents, as hereinbefore disclosed, a substituent selected from H, F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl.

Within this aspect, R^4 in an embodiment represents a substituent selected from H, F and $-CH_3$.

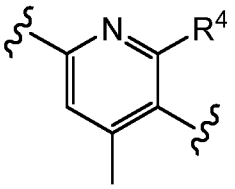
In an embodiment, Ring C may also be selected among:



(IIa)



(IVa)

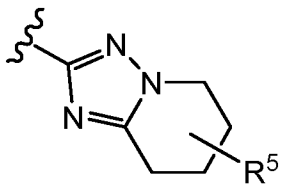


(Va)

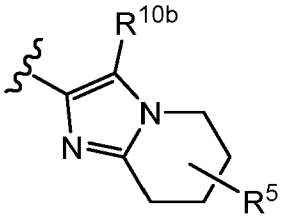
Within this aspect, R^4 in an embodiment represents a substituent selected from F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl.

Within this aspect, R^4 in another embodiment represents a substituent selected from F and $-CH_3$.

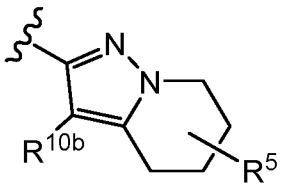
In an embodiment, the invention comprises a compound wherein ring D is selected among:



(VI)



(VII)



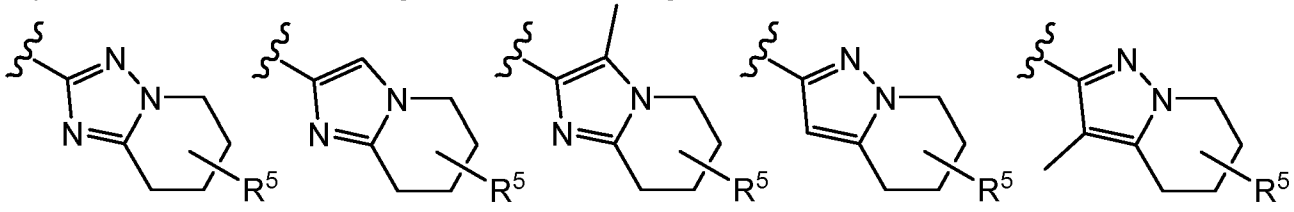
(VIII)

wherein, according to claim 1, R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, or $-N(R^{11a})R^{11b}$; and/or

R^{10b} represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, $-R^{12a}$, $-OR^{12b}$, $-N(R^{12c})R^{12d}$ and/or $-C(O)N(R^{12e})R^{12f}$) or $-O-C_{1-4}$ alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, $-R^{12g}$, $-OR^{12h}$ and/or $-N(R^{12i})R^{12j}$).

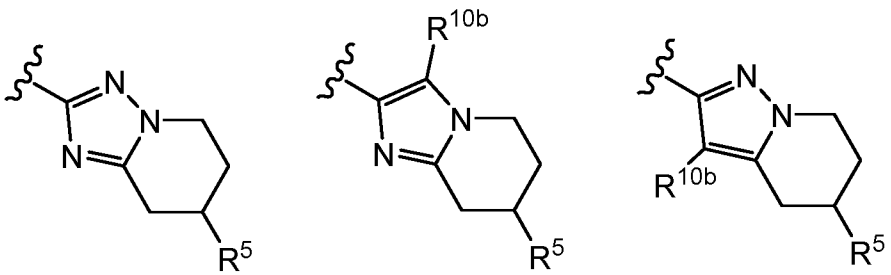
In an embodiment, there is provided compounds wherein R^{10b} represents a substituent selected from H and $-CH_3$.

In yet another embodiment, ring D is selected among:



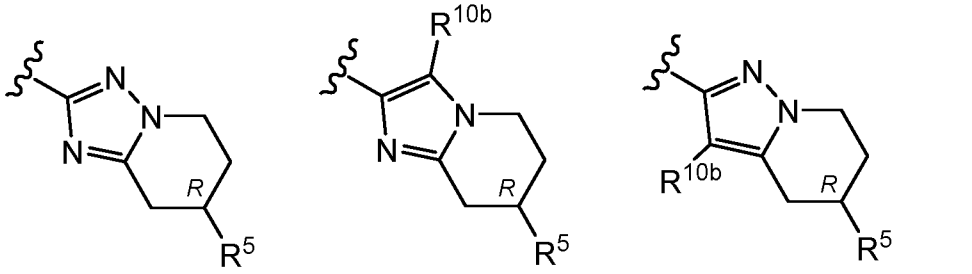
(VI) (VIIa) (VIIb) (VIIIa) (VIIIb)

Preferably ring D is selected among:



(VI') (VII') (VIII')

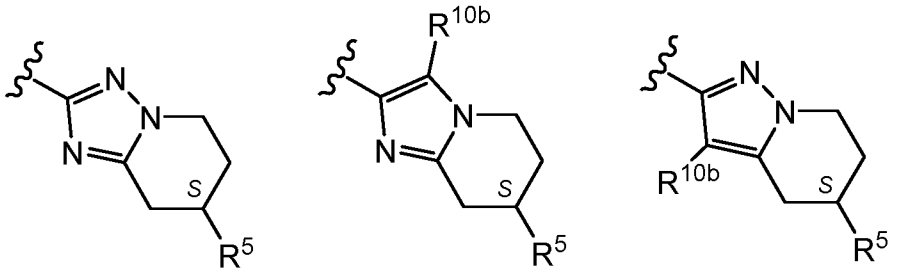
In an alternative embodiment, ring D is selected among:



(VI'-R) (VII'-R) (VIII'-R)

and the carbon atom to which R^5 is attached has a *R* configuration.

In a second alternative embodiment, ring D is selected among:

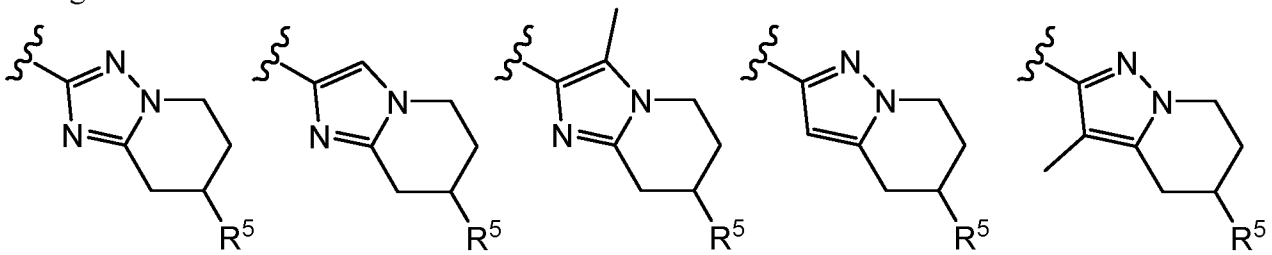


(VI'-S) (VII'-S) (VIII'-S)

and the carbon atom to which R^5 is attached has a *S* configuration.

In an embodiment, R^5 represents H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, -OH, $-OCH_3$, $-OCF_3$, $-OCH_2CH_2OCH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-NH_2$, $-NH(SO_2)CF_3$, $-N(CH_3)(SO_2)CF_3$, and $-SO_2CF_3$.

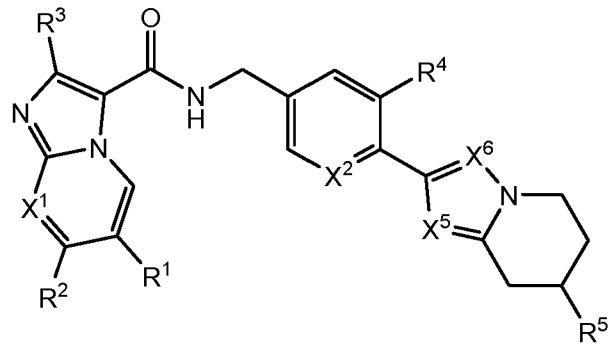
In another embodiment, the invention comprises a compound wherein ring D is selected among:



(VI') (VIIa') (VIIb') (VIIIa') (VIIIb')

and wherein R^5 represents H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, -OH, $-OCH_3$, $-OCF_3$, $-OCH_2CH_2OCH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-NH_2$, $-NH(SO_2)CF_3$, $-N(CH_3)(SO_2)CF_3$, and $-SO_2CF_3$.

Preferably the invention refers to a compound of formula (IX)



(IX)

wherein

X^1 represents =N- or =C(R^{10a})-;

X^2, X^5 and X^6 each independently represent =N- or =C(R^{10b})-;

R^1 and R^2 each independently represent a substituent selected from hydrogen, halo (e.g. Cl, F), -R^{6c}, -O-R^{6d}, -C(=O)-R^{6e}, -C(=O)-N(R^6)(R^7), -CN and -N(R^{6a})R^{6b};

R^3 represents a substituent selected from H, halo (e.g. Cl, F), -CF_3, -CHF_2, and -C_{1-3} alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. F) and -O-C_{1-3} alkyl;

R^4 represents a substituent selected from H, F, -C_{1-3} alkyl and -O-C_{1-3} alkyl;

R^5 represents H, -OH, -R^{8a}, -C(=O)-R^{8b}, -SO_2-R^9 , or -N(R^{11a})R^{11b};

R^6 and R^7 are independently selected from H and -C_{1-3} alkyl;

R^{6a} and R^{6b} independently represent H, C_{1-6} alkyl or R^{6a} and R^{6b} are linked together to form a 3- to 6-membered ring;

R^{6c} and R^{6d} independently represent hydrogen or -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F), -O-CH_3, phenyl, -N(R^{6a})R^{6b};

R^{6e} is -C_{1-3} alkyl;

R^{8a} represents -CN, - C_{1-4} alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. -CF_3 , -CHF_2), -OC_{1-3} alkyl optionally substituted by one or more substituents selected from halo and -O-CH_3;

R^{8b} is hydrogen or -C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

R^9 represents -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F) and -O-CH_3;

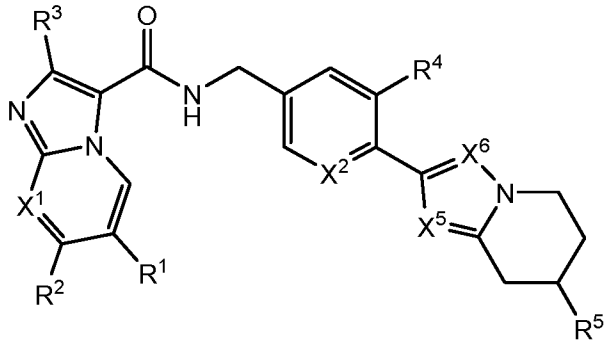
R^{10a} and R^{10b} independently represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, -R^{12a}, -OR^{12b}, -N(R^{12c})R^{12d} and/or -C(O)N(R^{12e})R^{12f}) or -O-C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -R^{12g}, -OR^{12h} and/or -N(R^{12i})R^{12j});

R^{11a} and R^{11b}, independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms); -SO_2R^{6c};

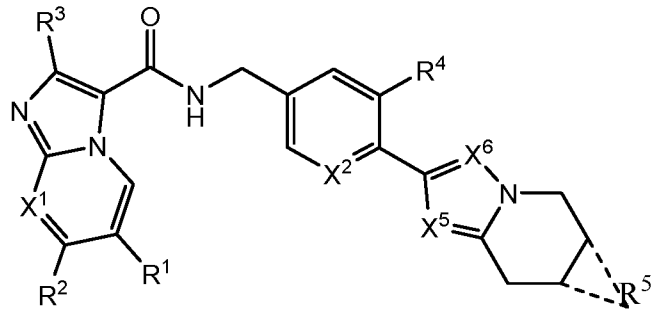
R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i} and R^{12j} independently represent hydrogen or C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

or a pharmaceutically-acceptable salt thereof.

In yet a further preferred embodiment, the invention refers to a compound of formula (IX) or formula (IXA)



(IX)



(IXA)

wherein

X^1 represents =N- or =CH-;

X^2, X^5 and X^6 each independently represent =N- , =CH- or =C(CH_3)-;

R^1 and R^2 each independently represent a substituent selected from hydrogen, -CH_3, -F, -Cl, -OCH_3, -NH_2, and - CH_2NH_2;

R^3 represents a substituent selected from H, -CF_3, -CHF_2, -CH_3, -CH_2CH_3, and cyclopropyl;

R^4 represents a substituent selected from H, F and -CH_3;

R^5 is linked to either the position *meta* or *para*- relative to the N atom in the ring system (in the compound of formula (IXA);

R^5 represents H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, cyclopropyl, -OH, -OCH_3, -OCF_3, -$OCH_2CH_2OCH_3$, -CF_3, -CHF_2, -CF_2CH_3, -NH_2, -$NH(SO_2)CF_3$, -$N(CH_3)(SO_2)CF_3$, or -SO_2CF_3,

or a pharmaceutically-acceptable salt thereof.

In an embodiment of the invention, R^5 represents or (in a further embodiment) a substituent selected from C_{1-4} alkyl (optionally substituted by one or more substituents selected from fluoro), C_{3-4} cycloalkyl (e.g. cyclopropyl), -OH and -OC_{1-4}alkyl (where the alkyl moiety is itself optionally substituted by one or more substituents selected from fluoro and -O-C_{1-2}alkyl).

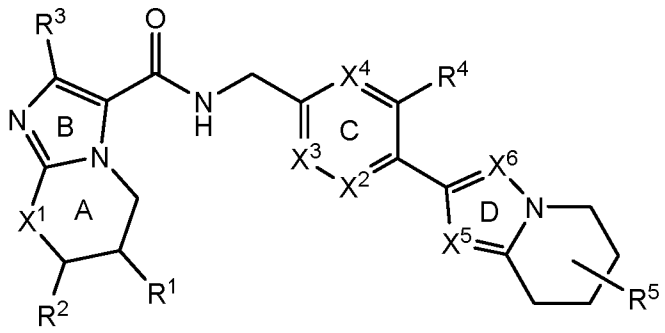
In an embodiment of the invention (including in the context of compounds of formulae (I), (IX) and (IXA):

- R^1 and R^2 independently represent H, CH_3, F, Cl or -OCH_3;
- X^1 represents =N- or =CH-;
- R^3 represents C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or C_{3-4} cycloalkyl (e.g. cyclopropyl);
- X^3 and X^4 independently represent =CH-;
- X^5 represents =CH- or =N- (and in an embodiment represents =CH-);
- R^4 represents hydrogen, F or CH_3;

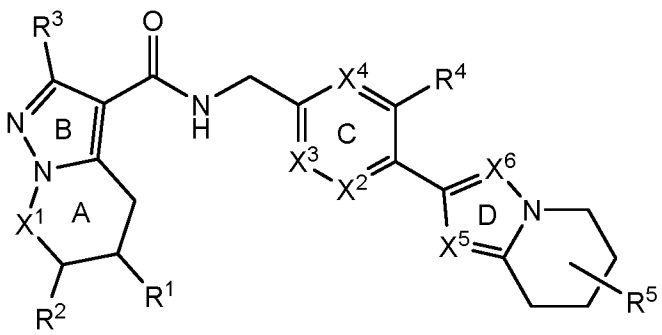
- X^5 and X^6 independently represent =N-, =CH= or =C(CH_3)- (and in a further embodiment, one of X^5 and X^6 represents =N- and the other represents =N-, =CH- or =C(CH_3)-);
- when R^5 represents a substituent, it may be at the *meta* or *para*-position relative to the requisite N atom in that bicycle; and/or
- R^5 represents H (although in an embodiment represent a substituent), -CF_3, -CH_3, -CHF_2, -OCH_3, cyclopropyl, propyl, -OH, -O-$CH_2CH_2OCH_3$ or OCF_3,

i.e. any of the above embodiments may be taken in isolation or in combination with other embodiments disclosed herein.

In separate embodiments, compounds of formula (IA) may be depicted as compounds of formula (I) or as compounds of formula (IB),



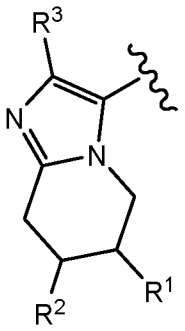
(I)

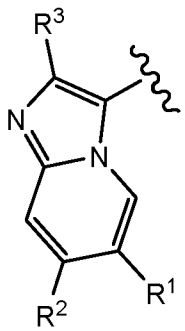


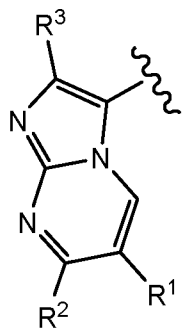
(IB)

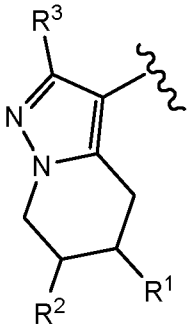
wherein all the integers are as defined herein.

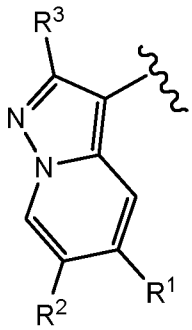
In particular embodiments, the bicycle containing rings A and B may be represented by any one of the following formulae:


(XX)


(XXII)

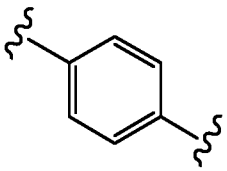

(XXIV)


(XXI)

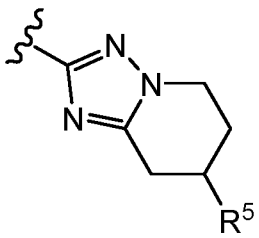

(XXIII)

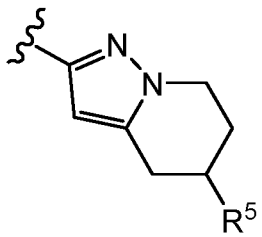
In an embodiment, R^1 and R^2 each represent hydrogen (and hence the 6-membered ring of rings depicted by (XX), (XXI), (XXII), (XXIII) and (XXIV) are unsubstituted). In another embodiment, R^3 represents C_{1-3} alkyl, such as ethyl.

In an embodiment, the C ring may represent unsubstituted phenyl, i.e. of the formula (XXX):


(XXX)

In an embodiment the D ring (or the bicycle containing the D ring) represents in separate embodiments, the formula (XXXI) or the formula (XXXII):


(XXXI)


(XXXII)

In another embodiment, R^5 represents C_{1-3} alkyl optionally substituted by one or more fluoro atoms; in a further embodiment, R^5 represents $-CF_3$.

As mentioned herein, and for the avoidance of doubt, any of the foregoing embodiments may be used in combination with the others, for instance any of the embodiments depicting rings A and B, with any of those depicting ring C, with any of those depicting ring D as well as any of the other embodiments indicated herein (such as R^5 substituents, etc).

The compounds according to the invention have surprisingly been shown to be suitable for the treatment of a bacterial infection including a mycobacterial infection, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis* (including the latent and drug resistant form thereof). The present invention thus also relates to compounds of the invention as defined hereinabove, for use as a medicine, in particular for use as a medicine for the treatment of a bacterial infection including a mycobacterial infection.

Such compounds of the invention may act by interfering with ATP synthase in *M. tuberculosis*, with the inhibition of cytochrome bc_1 activity being the primary mode of action. Cytochrome bc_1 is an essential component of the electron transport chain required for ATP synthesis.

Further, the present invention also relates to the use of a compound of the invention, as well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial infection including a mycobacterial infection.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a bacterial infection, including a mycobacterial infection, which comprises administering to the patient a therapeutically effective amount of a compound or pharmaceutical composition according to the invention.

The compounds of the present invention also show activity against resistant bacterial strains.

Whenever used hereinbefore or hereinafter, that the compounds can treat a bacterial infection it is meant that the compounds can treat an infection with one or more bacterial strains.

The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be

cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the active ingredient(s), and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage

forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

The daily dosage of the compound according to the invention will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound according to the invention is administered at a daily dosage not exceeding 1 gram, e.g. in the range from 10 to 50 mg/kg body weight.

Given the fact that the compound of formula (I) is active against bacterial infections, the present compounds may be combined with other antibacterial agents in order to effectively combat bacterial infections.

Therefore, the present invention also relates to a combination of (a) a compound according to the invention, and (b) one or more other antibacterial agents.

The present invention also relates to a combination of (a) a compound according to the invention, and (b) one or more other antibacterial agents, for use as a medicine.

The present invention also relates to the use of a combination or pharmaceutical composition as defined directly above for the treatment of a bacterial infection.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound according to the invention, and (b) one or more other antibacterial agents, is also comprised by the present invention.

The weight ratio of (a) the compound according to the invention and (b) the other antibacterial agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other antibacterial agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of the invention and another

antibacterial agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The compounds according to the invention and the one or more other antibacterial agents may be combined in a single preparation or they may be formulated in separate preparations so that they can be administered simultaneously, separately or sequentially. Thus, the present invention also relates to a product containing (a) a compound according to the invention, and (b) one or more other antibacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.

The other antibacterial agents which may be combined with the compounds of the invention are for example antibacterial agents known in the art. For example, the compounds of the invention may be combined with antibacterial agents known to interfere with the respiratory chain of Mycobacterium tuberculosis, including for example direct inhibitors of the ATP synthase (e.g. bedaquiline, bedaquiline fumarate or any other compounds that may have be disclosed in the prior art, e.g. compounds disclosed in WO2004/011436), inhibitors of ndh2 (e.g. clofazimine) and inhibitors of cytochrome bd. Additional mycobacterial agents which may be combined with the compounds of the invention are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824; delamanid; quinolones/fluoroquinolones such as for example moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, sparfloxacin; macrolides such as for example clarithromycin, amoxycillin with clavulanic acid; rifamycins; rifabutin; rifapentin; as well as others, which are currently being developed (but may not yet be on the market; see e.g. http://www.newtbdrugs.org/pipeline.php).

Compounds of the invention (including forms and compositions/combinations comprising compounds of the invention) may have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise. For instance, compounds of the invention may advantages associated with: lower cardiotoxicity; no reactive metabolite formation (e.g. that may cause toxicity issues, e.g. genotoxicity); no formation of degradants (e.g. that are undesired or may elicit unwanted side-effects); and/or faster oral absorption and improved bioavailability. Certain compounds of the invention may also have advantages over certain other compounds of the invention, for instance certain compounds (e.g. those in which R^1 and

R^2 each represent hydrogen (and hence the 6-membered ring of rings depicted by (XX), (XXI), (XXII), (XXIII) and (XXIV) are unsubstituted) may have the advantage that no or fewer undesired metabolites (e.g. oxidative metabolites) are produced (which may be observed in the case where either R^1 and/or R^2 represents a substituent, such as alkyl, e.g. methyl).

GENERAL PREPARATION

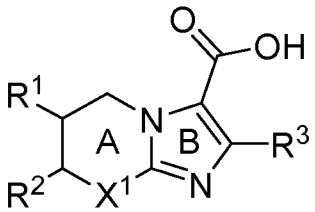
The compounds according to the invention can generally be prepared by a succession of steps, each of which may be known to the skilled person or described herein.

EXPERIMENTAL PART

Compounds of formula I may be prepared in accordance with the techniques employed in the examples hereinafter (and those methods know by those skilled in the art), for example by using the following techniques. Analogous reactions may be performed to prepare compounds of formula (IA), for instance reaction of compound (XL) as defined herein with a compound of formula (XI) and/or reaction of a compound of formula (XLI) as defined herein with a compound of formula (XIII).

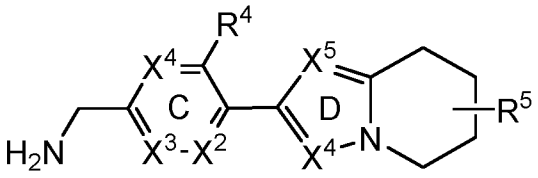
Compounds of formula (I) may be prepared by:

(i) reaction of a compound of formula (X),



(X)

in which the integers are hereinbefore defined, with a compound of formula (XI),



(XI)

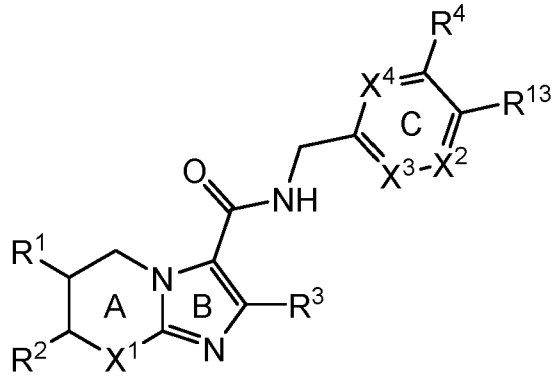
wherein the integers are as hereinbefore defined;

which reaction may be performed in the presence of a suitable coupling reagent, for instance selected from diisopropylethylamine (DIPEA), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), or a combination thereof, under

suitable conditions such as those described in the examples hereinafter; for example, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N*,*N*'-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (or hydrochloride thereof) or *N*,*N*'-disuccinimidyl carbonate), optionally in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyridine, triethylamine, dimethylaminopyridine, diisopropylamine, sodium hydroxide, potassium *tert*-butoxide and/or lithium diisopropylamide (or variants thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, trifluoromethylbenzene, dioxane or triethylamine). Alternatively, the carboxylic acid group of the compound of formula (X) may first be converted under standard conditions to the corresponding acyl chloride (e.g. in the presence of $POCl_3$, PCl_5, $SOCl_2$ or oxalyl chloride), which acyl chloride is then reacted with a compound of formula (XI), for example under similar conditions to those mentioned above;

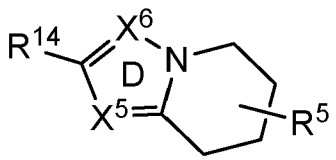
or

(ii) coupling of a compound of formula (XII),



(XII)

wherein the integers are as hereinbefore defined, and R^{13} represents a suitable group, e.g. a suitable leaving group such as chloro, bromo, iodo or a sulfonate group (for example a type of group that may be deployed for a coupling), with a compound of formula (XIII),

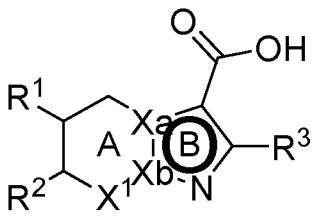


(XIII)

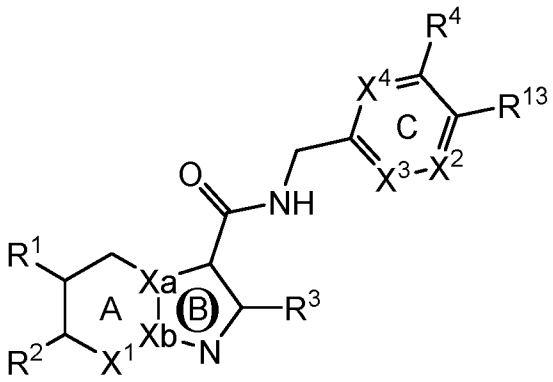
wherein R^4 is as hereinbefore defined, and R^{14} represents a suitable group, e.g. a suitable leaving group under standard conditions, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as $Pd(dba)_2$, $Pd(OAc)_2$, Cu, $Cu(OAc)_2$, CuI, $NiCl_2$ or the like, with an optional additive such as Ph_3P, X-phos or the like, in the presence of an appropriate base (e.g. t-BuONa, or the like) in a suitable solvent (e.g. dioxane or the like) under reaction conditions known to those skilled in the art.

It will be appreciated by those skilled in the art that some compounds of formula (I) may be converted to other compounds of formula (I).

Other compounds that may be used for preparation of compounds of formula (IA):



(XL)



(XLI)

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC, chiral chromatography. Individual diastereoisomers or individual enantiomers can also be obtained by Supercritical Fluid Chromatography (SCF).

The starting materials and the intermediates are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art.

EXAMPLES

1- GENERAL INFORMATION

ABBREVIATIONS

ACN: Acetonitrile
Cs_2CO_3: Cesium carbonate
DCM: Dichloromethane
DIPE: Diisopropyl ether
DIPEA: N,N-diisopropylethylamine
DMF: Dimethylformamide
DMSO: Dimethylsulfoxide
Et_2O: Diethyl ether
EtOAc: Ethyl acetate
Et_3N or TEA: Triethyl amine
h: hour
H_2: Dihydrogen gas
HATU: 1-[Bis(dimethylamino)methylene]–1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl: Hydrochloric acid
i-PrOH: Isopropyl alcohol
K_2CO_3: Potassium carbonate
LiOH: Lithium hydroxide
MeOH: methanol
MgSO4: Magnesium sulphate
min: minute
N_2: Nitrogen
$NaHCO_3$: Sodium bicarbonate
NaOH: Sodium hydroxide
NH_4Cl: Ammonium chloride
NH_4HCO_3: Ammonium bicarbonate
NMR: Nuclear magnetic resonance
$PdCl_2(PPh_3)_2$: Dichlorobis(triphenylphosphine)palladium(II)
$Pd(OAc)_2$: Palladium(II) acetate
rt: Room temperature
THF: Tetrahydrofuran
TFA: Trifluoroacetic acid
THF: Tetrahydrofuran

$PdCl_2(dppf)_2$: [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
KOtBu: Potassium tert-butoxide

MELTING POINTS

Melting points were recorded using a differential scanning calorimeter DSC 1 Mettler Toledo. Melting points were measured with a temperature gradient of 10°C per min from 25 to 350 °C. Values are peak values. Unless indicated, this method is used.
An alternative method is with open capilliary tubes on a Mettler Toledo MP50, which may be indicated at "MT". With this method, melting points are measured with a temperature gradient of 10 °C/minute. Maximum temperature is 300 °C. The melting point data is read from a digital display and checked from a video recording system.

^{1}H NMR

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer or Bruker Advance III 400 spectrometer using internal deuterium lock and equipped with reverse double-resonance (^{1}H, 13C, SEI) probe head with z gradients and operating at 400 MHz for proton and 100 MHz for carbon and a Bruker Avance 500 MHz spectrometer equipped with a Bruker 5mm BBFO probe head with z gradients and operating at 500 MHz for proton and 125 MHz for carbon.
NMR spectra were recorded at ambient temperature unless otherwise stated.
Data are reported as follow: chemical shift in parts per million (ppm) relative to TMS (δ = 0 ppm) on the scale, integration, multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sex = sextuplet, m = multiplet, b = broad, or a combination of these), coupling constant(s) J in Hertz (Hz).

ABSOLUTE CONFIGURATION

Virtual Circula Dicroism (VCD) and Infrared Spectra were used to determine absolute configuration.

Experimental

IR and VCD spectra were recorded on a dual PEM ChiralIR-2X spectrometer (Biotools Inc., Jupiter, FL). Measurements were done in DMSO-d6 with a concentration of 3.8 mg / 125 µL for A/B and E/F, 1.1 mg / 175 µL for C/D. A cell with 100µm path length and BaF_2 windows was used. Both the sample and the virtual racemate spectrum were recorded with a resolution of 4 cm^{-1}, totalling 60000 scans or 20 hours of measurement time each with both PEMs optimized at 1400 cm^{-1}. The baseline corrected VCD spectrum was obtained by combining the raw data for the enantiomer with the spectrum of the corresponding virtual racemate.

Computational

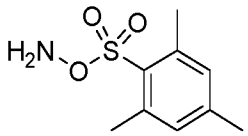
A thorough conformational search is performed at molecular mechanics level using Macromodel (version 13.3) with a mixed torsional/low-mode sampling and the OPLS4 force field. The located minima were optimized using Jaguar (version 11.2) on the B3LYP-D3/6-31G** level with a Poisson-Boltzmann continuum solvation model to mimic a DMSO solvent. All conformations within 10 kJ/mol interval were used to simulate VCD and IR spectra from calculated rotatory strength and wavenumbers (scaled by a factor 0.975) with Lorentzian curves using half width at half-height values of 4 cm^{-1}.

Assignment was done after visual comparison between experimental and measured IR and VCD spectra.

2- SYNTHESIS

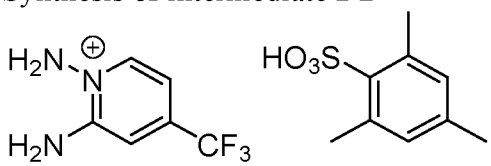
SYNTHESIS OF INTERMEDIATES I

Synthesis of intermediate **I-1**



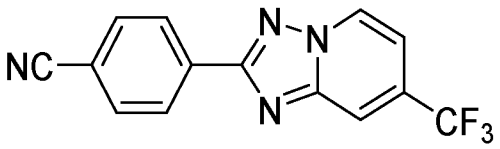
Perchloric acid [7601-90-3] was added dropwise over 15 min to a suspension of ethyl O-(2-mesitylenesulfonyl)acethydroxamate [38202-27-6] (13 g, 45.56 mmol) in 1,4-dioxane (45 mL) at 0 °C (internal temperature maintained below 15 °C). The mixture was stirred at 0 °C for 1 h. Then ice-water (45 mL) and DCM (45 mL) were added, and the organic layer was separated to yield intermediate **I-1** as a 1M DCM solution that was used in the next step without any further treatment (CAUTION, do not remove the solvent, explosive when dry).

Synthesis of intermediate **I-2**



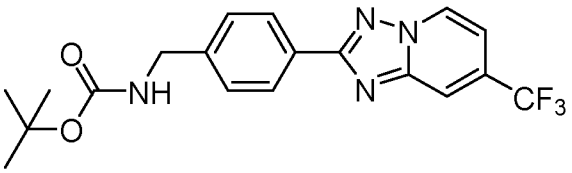
2-Amino-4-(trifluoromethyl)pyridine [106447-97-6] (2.28 g, 32.54 mmol) was added portionwise to a 1M solution of intermediate **I-1** in DCM (45.56 mL, 45.56 mmol) in a round bottom flask under nitrogen at 0 °C. The mixture was stirred at rt for 16 h. The suspension was diluted with diethyl ether (10 ml) and the solid formed was filtered off and washed with additional diethyl ether to yield intermediate **I-2** as a white solid (11.51 g, 86%).

Synthesis of intermediate **I-3**



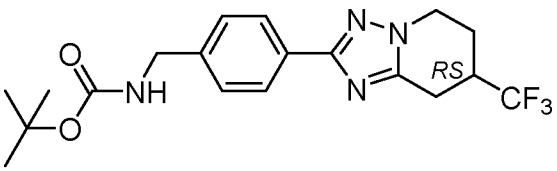
4-Cyanobenzoyl chloride [6068-72-0] (8.30 g, 21.79 mmol) was added to a solution of intermediate **I-2** (8.25 g, 21.79 mmol) in pyridine (88 mL) at 0 ºC. The mixture was stirred at 90 ºC for 16 h and then water was added. The solid formed was filtered off and washed with water (x3) and diethyl ether to yield intermediate **I-3** as a beige solid (5.03 g, 79%).

Synthesis of intermediate **I-4**



Sodium borohydride [16940-66-2] (1.99 g, 52.59 mmol) was added portionwise to a suspension of intermediate **I-3** (5.05 g, 17.53 mmol), nickel (II) chloride hexahydrate [7791-20-0] (4.17 g, 17.53 mmol) and di-tertbutyl dicarbonate [24424-99-5] (12.08 mL, 52.59 mmol) in dry methanol (60 mL) at -5 ºC under N_2. The reaction mixture was stirred at rt for 16 h. Water and 1 mL of aqueous NH_3 were added and the mixture was extracted with DCM. The combined organic layers were washed with water, separated, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 15/85). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-4** as a yellowish solid (7.50 g, 97%).

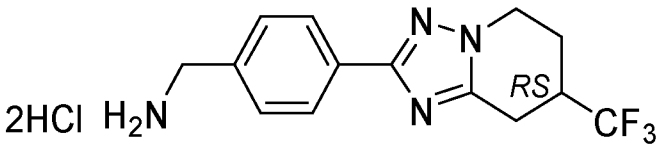
Synthesis of intermediate **I-5**



Palladium(II) hydroxide on carbon [12135-22-7] (2.17 g, 18.71 mmol) was added portionwise to a solution of intermediate I-4 (7.50 g, 17.01 mmol) in a mixture of methanol (120 mL) and EtOAc (20 mL) at 0 ºC under N2. Then H2 was added, and the mixture was stirred at rt for 18 h. Then further palladium(II)hydroxide [12135-22-7] (0.95 g, 6.81 mmol) was added at 0ºC under N2. H2 was added, and the mixture was stirred under at rt for a further 4 h. The

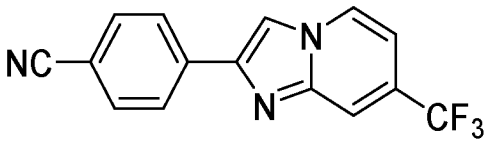
mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate I-5 as a white solid (1.78 g, 40%).

Synthesis of intermediate I-6



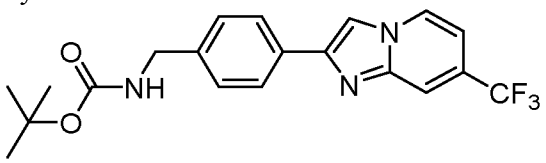
A 4 M solution of HCl in dioxane [7647-01-0] (10.52 mL, 42.08 mmol) was added to a stirred solution of intermediate I-5 (2.78 g, 7.01 mmol) in DCM (35 mL) at rt. The reaction mixture was stirred at rt for 16 h. The solvents were evaporated in vacuo to yield intermediate I-6 as a white solid used in the next step without any further purification (2.73 g, quantitative).

Synthesis of intermediate I-7



NaHCO3 (0.57 g, 6.79 mmol) was added to a stirred solution of 2-amino-4-(trifluoromethyl)pyridine [106447-97-6] (1.0 g, 6.17 mmol) and 4-(bromoacetyl)benzonitrile [20099-89-2] (1.80g, 8.02 mmol) in ethanol (12 mL) at rt. The mixture was stirred at reflux for 18 h and then water was added. The solid formed was filtered off and washed with water and diethyl ether to yield intermediate I-7 as a beige solid (1.48 g, 82%).

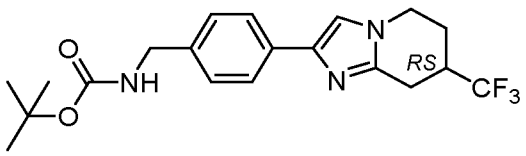
Synthesis of intermediate I-8



Sodium borohydride [16940-66-2] (0.58 g, 15.41 mmol) was added portionwise to a suspension of intermediate I-7 (1.48 g, 5.14 mmol), nickel (II) chloride hexahydrate [7791-20-0] (1.22 g, 15.41 mmol) and di-tertbutyl dicarbonate [24424-99-5] (3.54 mL, 15.41 mmol) in dry methanol (15.4 mL) at -5 °C under N2. The reaction mixture was stirred at rt for 16 h. Water and 1 mL of aqueous NH3 were added and the mixture was extracted with DCM. The

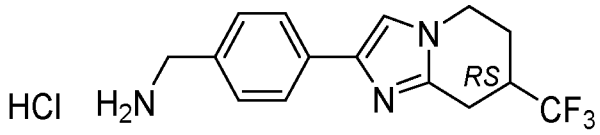
combined organic layers were washed with water, separated, dried (MgSO4), filtered and concentrated in vacuo to yield intermediate I-8 as a brown sticky oil (2.05 g, quantitative).

Synthesis of intermediate I-9



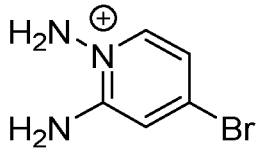
Platinum(IV) oxide [1314-15-4] (1.22 g, 5.37 mmol) was added to a solution of intermediate I-8 (2.1 g, 5.37 mmol), in a mixture of ethanol (70 mL) and dry THF (70 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 16 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield intermediate I-9 as a white solid (0.45 g, 19%).

Synthesis of intermediate I-10



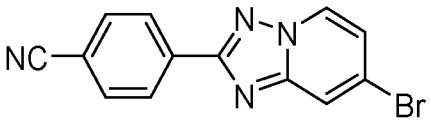
A 4 M solution of HCl in dioxane [7647-01-0] (1.33 mL, 5.31 mmol) was added to a stirred solution of intermediate I-9 (175 mg, 0.44 mmol) in DCM (2 mL) at rt. The reaction mixture was stirred at rt for 18 h. The solvents were evaporated in vacuo to yield intermediate I-10 as a yellowish solid used in the next step without any further purification (146 mg, quantitative).

Synthesis of intermediate I-11



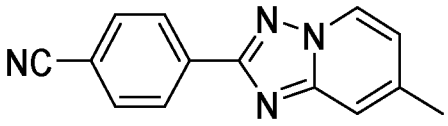
2-Amino-4-bromopyridine [84249-14-9] (5 g, 28.90 mmol) was added portionwise to a 1M solution of intermediate I-1 in DCM (57.80 mL, 57.80 mmol) in a round bottom flask under nitrogen at 0 °C. The mixture was stirred at rt for 16 h. The suspension was diluted with diethyl ether (30 ml) and the solid formed was filtered off and washed with additional diethyl ether to yield intermediate I-11 as a white solid (6.28 g, 87%).

Synthesis of intermediate I-12



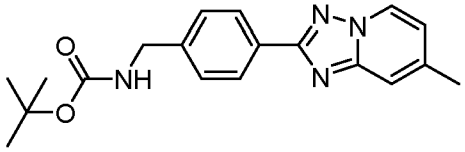
4-Cyanobenzoyl chloride [6068-72-0] (6.62 g, 40 mmol) was added to a solution of intermediate I-11 (7.77 g, 20 mmol) in pyridine (24 mL) at 0 °C. The mixture was stirred at 90 °C for 8 h and then water was added. The solid formed was filtered off and washed with water (x3) and diethyl ether to yield intermediate I-12 as a white solid (3.02 g, 46%).

Synthesis of intermediate I-13



$Pd(dppf)_2Cl_2$ [65464-05-4] (136 mg, 0.17 mmol) was added to a solution of intermediate **I-12** (0.5 g, 1.67 mmol) in a mixture of dry 1,4-dioxane (4 mL) and heptane (4 mL) in a sealed tube under N_2. Then, a 2 M solution of dimethylzinc solution in toluene [544-97-8] (2.51 mL, 5.01 mmol) was added at rt under N_2 and the mixture was stirred at 55 °C for 16h. The solvents were evaporated in vacuo and the crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-13** as an orange solid (391 mg, 99%).

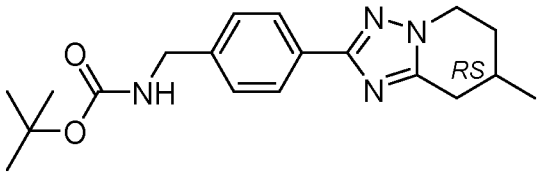
Synthesis of intermediate **I-14**



Sodium borohydride [16940-66-2] (189 mg, 5 mmol) was added portionwise to a suspension of intermediate I-13 (391 mg, 1.67 mmol), nickel (II) chloride hexahydrate [7791-20-0] (198 mg, 0.83 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.77 mL, 3.34 mmol) in a mixture of dry methanol (22 mL) and 1,4-dioxane (10 mL) at 0 °C under N2. The reaction mixture was stirred at rt for 16 h. A saturated NH4Cl aqueous solution and 1 mL of aqueous NH3 were added and the mixture was extracted with DCM. The combined organic layers were washed with water, separated, dried (MgSO4), filtered and concentrated in vacuo. The crude

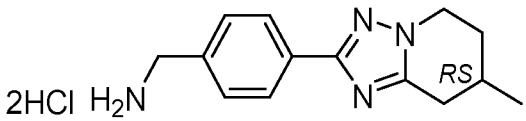
product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield intermediate I-14 as a white solid (380mg, 67%).

Synthesis of intermediate I-15



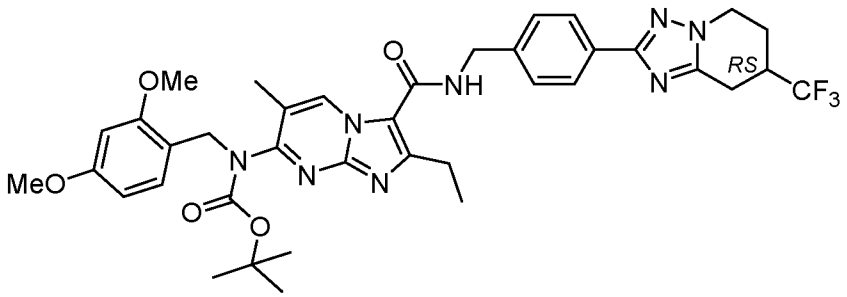
Palladium(II) hydroxide [12135-22-7] (77 mg, 0.55 mmol) was added to a solution of intermediate I-14 (370 mg, 1.1 mmol), in a mixture of methanol (5 mL) and EtOAc (1 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 16 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo to yield intermediate I-15 as a yellow solid used in the next step without any further purification (350 mg, 84%).

Synthesis of intermediate I-16



A 4 M solution of HCl in dioxane [7647-01-0] (1.55 mL, 6.2 mmol) was added to a stirred solution of intermediate I-15 (350 mg, 1.02 mmol) in DCM (15 mL) at rt. The reaction mixture was stirred at rt for 16 h. The solvents were evaporated in vacuo to yield intermediate I-16 as a white solid used in the next step without any further purification (340 mg, 99%).

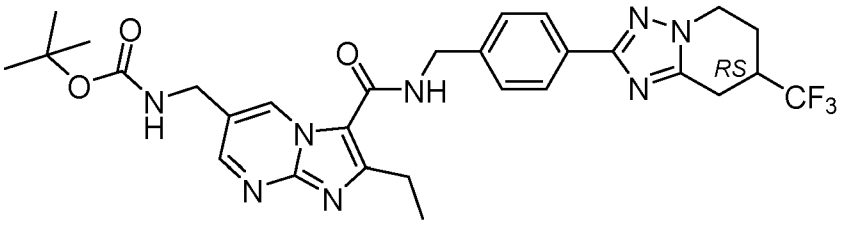
Synthesis of intermediate I-17a



Intermediate I-6 (113 mg, 0.34 mmol) was added to a stirred mixture of intermediate II-15 (160 mg, 0.34 mmol), HATU [148893-10-1] (130 mg, 0.34 mmol), and DIPEA [7087-68-5]

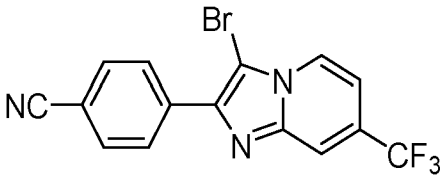
(0.24 mL, 1.36 mmol) in DMF (1.7 mL) at rt. The mixture was stirred at rt for 19 h. Then, a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The combined organic layers were dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane to 80/20). The desired fractions were collected, concentrated in vacuo to yield intermediate I-17a as a white solid (179 mg, 67%).

Synthesis of intermediate I-17b



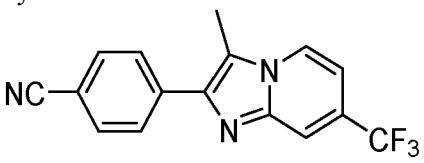
HATU [148893-10-1] (222 mg, 0.58 mmol) and DIPEA [7087-68-5] (0.54 mL, 3.08 mmol) was added to a solution of intermediate II-17d (187 mg, 0.494 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 10 min and then I-6 (187 mg, 0.49 mmol) was added, and the mixture reaction was stirred at rt for 16 h. A saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo and the excess of DMF was co-distilled with toluene (10 mL x 3). The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM from 0/100 to 30/70). The desired fractions were collected and evaporated in vacuo to yield intermediate I-17b as a beige solid (165 mg, 61%, 45% purity).

Synthesis of intermediate I-18



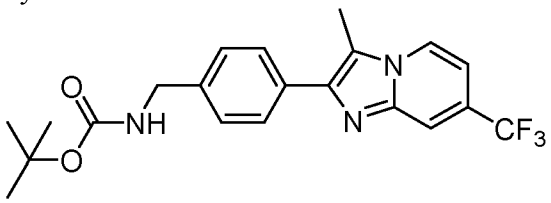
N-Bromosuccinimide [128-08-5] (205 mg, 1.15 mmol) was added portionwise to a solution of intermediate I-7a (300 mg, 1.04 mmol) and DCM (5.3 mL) at 0 °C under N2. The mixture was stirred at room temperature for 1 h. Then water was added, and the mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo to yield intermediate I-18 as a beige solid (386 mg, quantitative).

Synthesis of intermediate I-19



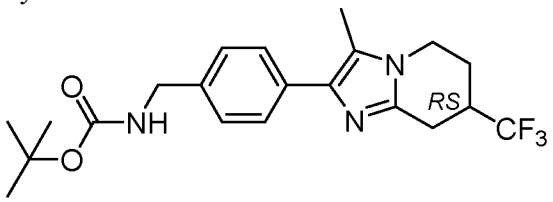
Methylboronic acid [13061-96-6] (192 mg, 2.36 mmol) and E were added to a solution of intermediate I-18 (288 mg, 0.79 mmol) in a mixture of water (0.7 mL) and 1,4-dioxane (2.6 mL) at rt. N2 was bubbled for 10 min and then tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (228 mg, 0.20 mmol) and Na2CO3 (167 mg, 1.58 mmol) were added and the mixture was stirred at 120 ºC for 17 h. Then additional methylboronic acid [13061-96-6] (47 mg, 0.39 mmol) and tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (46 mg, 0.04 mmol) were added and the mixture was stirred at 120 ºC for 16 h. Then methylboronic acid [13061-96-6] (47 mg, 0.39 mmol) and tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (46 mg, 0.04 mmol) were added and the mixture was stirred at 120ºC for 16 h. Then methylboronic acid [13061-96-6] (47 mg, 0.39 mmol) and tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (46 mg, 0.04 mmol) added and the mixture was stirred at 120ºC for a further 16 h. Water was added and the mixture was extracted with EtOAc. The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane from 0/100 to 10/90). The desired fractions were collected, and the solvent was evaporated in vacuo to yield intermediate I19 as a yellow solid (340 mg, 82%).

Synthesis of intermediate I-20



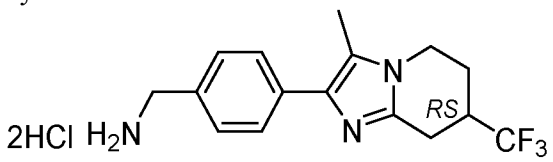
Sodium borohydride [16940-66-2] (129 mg, 3.41 mmol) was added portionwise to a suspension of intermediate I-19 (340 mg, 1.13 mmol), nickel (II) chloride hexahydrate [7791-20-0] (147 g, 1.13 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.78 mL, 3.87 mmol) in dry methanol (11 mL) at 0 ºC under N2. The reaction mixture was stirred at rt for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane to 60/40). The desired fractions were collected and concentrated in vacuo to yield intermediate I-20 as a yellow solid (207 mg, 24%).

Synthesis of intermediate I-21



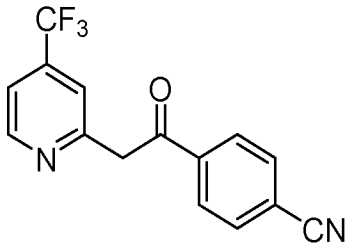
Palladium(II) hydroxide on carbon [12135-22-7] (262 mg, 0.37 mmol) was added to a solution of intermediate I-20 (505 mg g, 1.25 mmol) in methanol (8.6 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 5 h. Then more Palladium(II) hydroxide on carbon [12135-22-7] (262 mg, 0.37 mmol) was added at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 16 h. Then more Palladium(II) hydroxide on carbon [12135-22-7] (262 mg, 0.37 mmol) was added at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for a further 6 h. The mixture was filtered through a pad of celite® and the solvent was concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 55/45). The desired fractions were collected and concentrated in vacuo to yield intermediate I-21 as a white solid (428 mg, 83%).

Synthesis of intermediate I-22



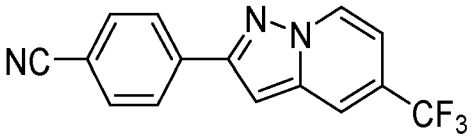
A 4 M solution of HCl in dioxane [7647-01-0] (2.7 mL, 10.8 mmol) was added to a stirred solution of intermediate I-21 (428 mg, 1.04 mmol) in DCM (3 mL) at rt. The reaction mixture was stirred at rt for 16 h. The solvents were evaporated in vacuo to yield intermediate I-22 as a white solid used in the next step without any further purification (412 mg, 97%).

Synthesis of intermediate I-23



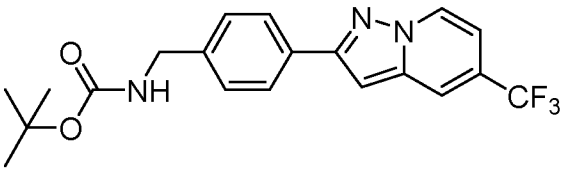
A 2.5 M solution of n-butyllithium in hexanes [109-72-8] (3 mL, 7.5 mmol) was added dropwise to a solution of 2-methyl-4-(trifluoromethyl)pyridine [106877-17-2] (800 mg, 4.9 mmol) in THF (25 mL at -78 °C under N2. The mixture was stirred at -78 °C for 30 min. Then ethyl 4-cyanobenzoate [7153-22-2] (0.96 g, 1.37 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at - 78 °C for 2 h. Water was added and the mixture was extracted with EtOAc. The crude was purified by flash column chromatography (silica; EtOAc in DCM from 0/100 to 10/90). The desired fractions were collected and the solvents evaporated in vacuo to yield intermediate I-23 as a yellow solid.

Synthesis of intermediate I-24



A 1M solution of intermediate I-1 in DCM (5.6 mL, 5.6 mmol) was added to a solution of intermediate I-23 (810 mg, 2.8 mmol) in DCM (30 mL) at rt under N2and the mixture was stirred at rt for 48 h. The reaction mixture was washed with a saturated NaHCO3 aqueous solution. The organic layer was dried (MgSO4), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (silica, EtOAc in DCM from 100/0 to 0/100). The desired fractions were combined and the solvents were removed in vacuo to yield intermediate I-24 as a yellow solid.

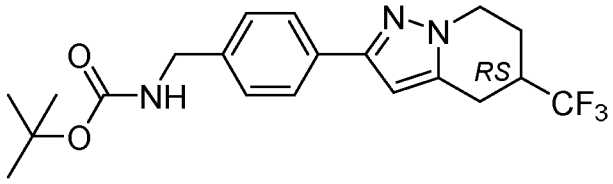
Synthesis of intermediate I-25



Sodium borohydride [16940-66-2] (137 mg, 0.66 mmol) was added portionwise to a suspension of intermediate I-24 (349 mg, 1.22 mmol), nickel (II) chloride hexahydrate [7791-20-0] (145 mg, 0.61 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.56 mL, 2.43 mmol) in a mixture of dry methanol (30 mL) and 1,4-dioxane (15 mL) at 0 °C under N2. The reaction mixture was stirred at rt for 10 min and then more nickel (II) chloride hexahydrate [7791-20-0] (145 g, 0.61 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.56 mL, 2.43 mmol) and sodium borohydride [16940-66-2] (137 mg, 0.66 mmol) were added. The mixture was stirred at rt for 16h and then a saturated NH4Cl aqueous solution and a NH3 aqueous solution (1 mL) were added, and the mixture was extracted with DCM. The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash

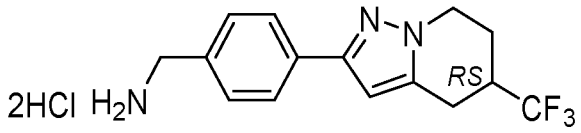
column chromatography (silica; EtOAc in heptane to 30/70). The desired fractions were collected and concentrated in vacuo to yield intermediate I-25 as a white solid (492 mg, 98%).

Synthesis of intermediate I-26



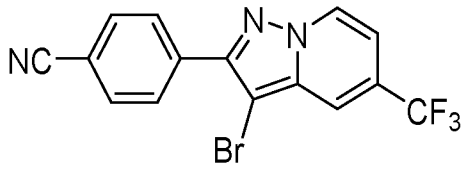
Palladium on carbon (10% w/w) 50% H2O [7440-05-3] (1 g, 0.94 mmol) was added to a solution of intermediate I-25 (492 mg g, 1.26 mmol) in a mixture of ethanol (23 mL) and THF (23 mL) at 0 °C under N2. H2 was added, and the mixture was stirred at rt for 16 h. Then more Palladium on carbon (10% w/w) 50% H2O [7440-05-3] (1 g, 0.94 mmol) was added at 0 °C under N2. H2 was added, and the mixture was stirred at rt for a further16 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate I-26 as a white solid (277 mg, 55%).

Synthesis of intermediate I-27



A 4 M solution of HCl in dioxane [7647-01-0] (1 mL, 4 mmol) was added to a stirred solution of intermediate I-26 (135 mg, 1.04 mmol) in DCM (5 mL) at rt. The reaction mixture was stirred at rt for 16 h. The solvents were evaporated in vacuo to yield intermediate I-27 as a white solid used in the next step without any further purification (126 mg, quantitative).

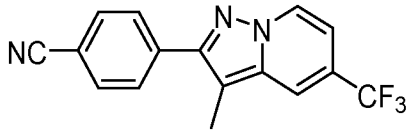
Synthesis of intermediate I-28



N-Bromosuccinimide [128-08-5] (136 mg, 0.77 mmol) was added portionwise to a solution of intermediate I-24 (200 mg, 0.7 mmol) and DCM (7 mL) at rt. The mixture was stirred at room

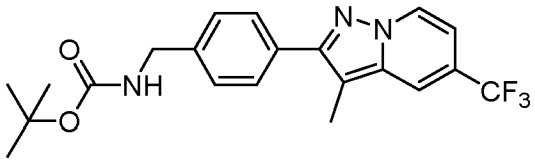
temperature for 2 h. Then water was added, and the mixture was extracted with DCM. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo and the crude product purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 15/85). The desired fractions were collected and the solvents were evaporated in vacuo to yield intermediate I-28 as a yellow solid (191 mg, 71%).

Synthesis of intermediate I-29



A 2M Dimethylzinc solution in toluene [544-97-8] (0.35 mL, 0.7 mmol) was added to a stirred solution of intermediate I-28 (170 mg, 0.46 mmol) in 1,4-dioxane (5 mL) at rt under N2. Then tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (53 mg, 0.09 mmol) and the mixture was stirred at 55 °C for 16 h. Then additional A 2M Dimethylzinc solution in toluene [544-97-8] (0.35 mL, 0.7 mmol) and tetrakis(triphenylphosphine)palladium(0) [14221-01-3] (53 mg, 0.09 mmol) were added and the mixture was stirred at 55 °C for a further 16 h. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane from 0/100 to 20/80). The desired fractions were collected, and the solvent was evaporated in vacuo to yield intermediate I-29 as a yellow solid (113 mg, 80%).

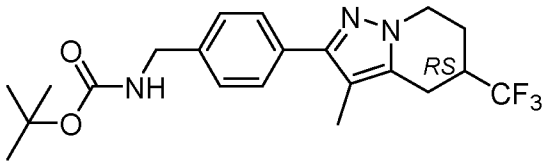
Synthesis of intermediate I-30



Sodium borohydride [16940-66-2] (43 mg, 1.12 mmol) was added portionwise to a suspension of intermediate I-29 (113 mg, 0.38 mmol), nickel (II) chloride hexahydrate [7791-20-0] (89 mg, 0.38 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.26 mL, 1.13 mmol) in a mixture of dry methanol (6 mL) and dry 1,4-dioxane (3 mL) at 0 °C under N2. The reaction mixture was stirred at rt for 16 h and then a saturated NH4Cl aqueous solution and a NH3 aqueous solution (1 mL) were added, and the mixture was extracted with DCM. The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane to 30/70).

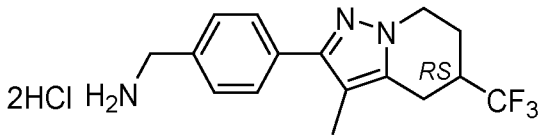
The desired fractions were collected and concentrated in vacuo to yield intermediate I-30 as a white solid (106 mg, 66%).

Synthesis of intermediate I-31



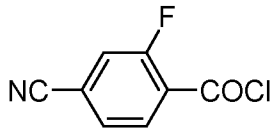
Intermediate I-31 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-26 using intermediate I-30 (90 mg, 0.22 mmol) as starting material (63 mg, 66%).

Synthesis of intermediate I-32



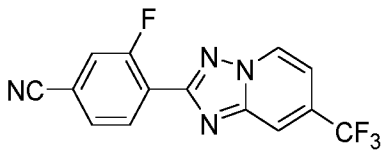
Intermediate I-32 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-27 using intermediate I-31 (63 mg, 0.15 mmol) as starting material (59 mg, 99%).

Synthesis of intermediate I-33



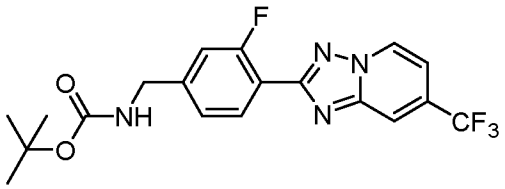
4-Cyano-2-fluorobenzoic acid [164149-28-4] (1 g, 6.06 mmol) was dissolved in dry DCM (12 mL) and cooled to 0 °C under N2. Then oxalyl chloride [79-37-8] (0.77 mL, 9.08 mmol) followed by dry DMF (0.1 mL) were added, and the mixture was stirred at rt for 1 h. The solvents were removed in vacuo to intermediate I-33 as a yellowish solid that was used in the next reaction step without any further purification (1.11 g, quantitative).

Synthesis of intermediate I-34



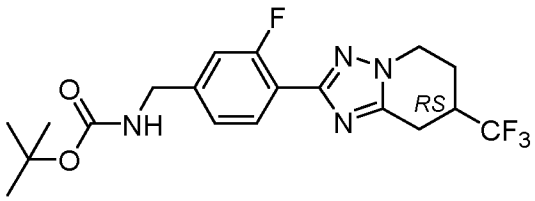
Intermediate I-34 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-3 using intermediate I-33 (1.11 g, 6.06 mmol) as starting material (0.66 g, 67%).

Synthesis of intermediate I-35



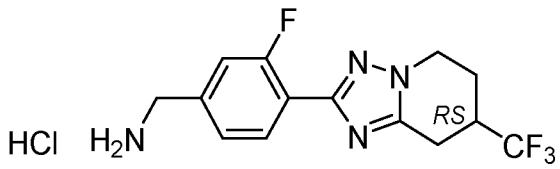
Intermediate I-35 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-4 using intermediate I-34 (0.66 g, 2.16 mmol) as starting material (0.97 g, 99%).

Synthesis of intermediate I-36



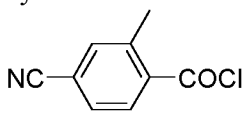
Palladium(II) hydroxide on carbon [12135-22-7] (0.33 g, 3.36 mmol) was added portionwise to a solution of intermediate I-35 (0.97 g, 3.36 mmol) in methanol (20 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 18 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate I-36 as a white solid (0.57 g, 79%).

Synthesis of intermediate I-37



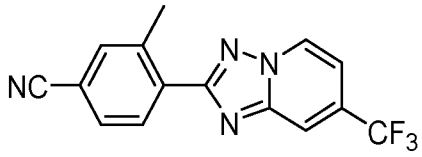
Intermediate I-37 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-6 using intermediate I-36 (0.56 g, 1.35 mmol) as starting material (0.47 g, quantitative).

Synthesis of intermediate I-38



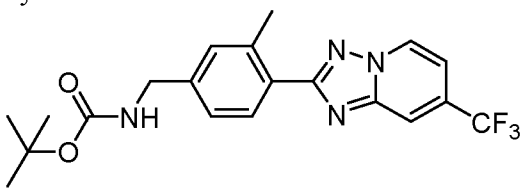
Intermediate I-38 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-33 using intermediate 4-cyano-2-methylbenzoic acid (2.5 g, 15.51 mmol) as starting material (2.79 g, quantitative).

Synthesis of intermediate I-39



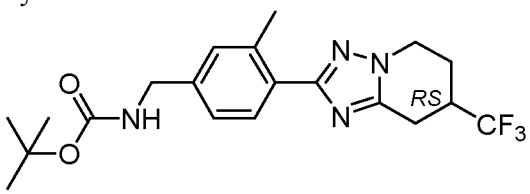
Intermediate I-39 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-3 using intermediate I-38 (2.93 g, 7.76 mmol) as starting material (1.35 g, 55%).

Synthesis of intermediate I-40



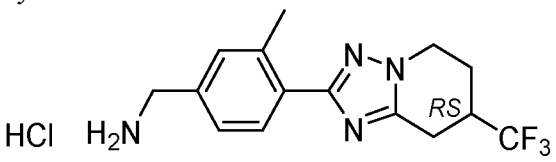
Intermediate I-40 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-14 using intermediate I-39 (1.35 g, 4.46 mmol) as starting material (0.82 g, 44%).

Synthesis of intermediate I-41



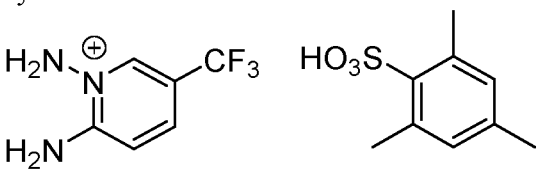
Palladium(II) hydroxide on carbon [12135-22-7] (70 mg, 0.5 mmol) was added portionwise to a solution of intermediate I-40 (0.40 g, 0.98 mmol) in a mixture of methanol (5 mL) and EtOAc (1 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 18 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo to yield intermediate I-41 as a yellow solid (0.40 g, 89%).

Synthesis of intermediate I-42



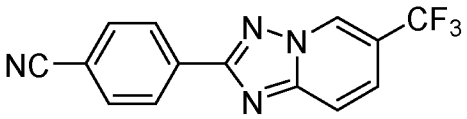
Intermediate I-42 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-6 using intermediate I-41 (0.4 g, 0.97 mmol) as starting material (0.34 g, quantitative).

Synthesis of intermediate I-43



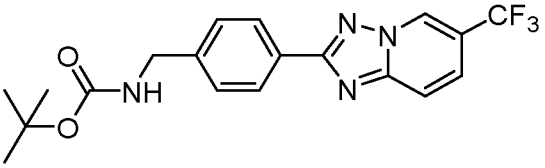
Intermediate I-42 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-2 using 2-amino-4-(trifluoromethyl)pyridine [74784-70-6] (2 g, 13.34 mmol) as starting material (3.95 g, 79%).

Synthesis of intermediate I-44



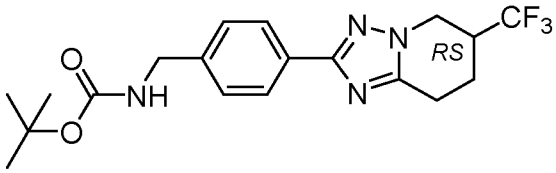
Intermediate I-44 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-3 using intermediate I-43 (3.95 g, 10.23 mmol) as starting material (2.2 g, 73%).

Synthesis of intermediate I-45



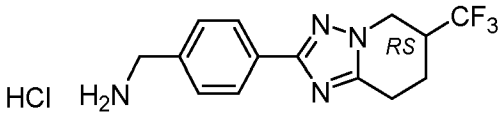
Intermediate I-45 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-4 using intermediate I-44 (2.2 g, 7.63 mmol) as starting material (1.1 g, 35%).

Synthesis of intermediate I-46



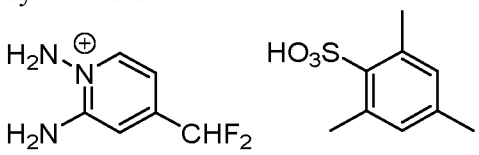
Intermediate I-46 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-26 using intermediate I-45 (0.3 g, 0.76 mmol) as starting material (196 mg, 64%).

Synthesis of intermediate I-47



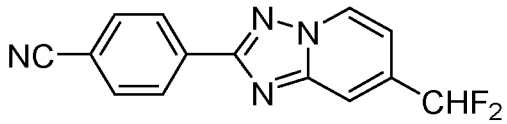
Intermediate I-47 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-6 using intermediate I-46 (196 mg, 0.49 mmol) as starting material (173 mg, quantitative).

Synthesis of intermediate I-47



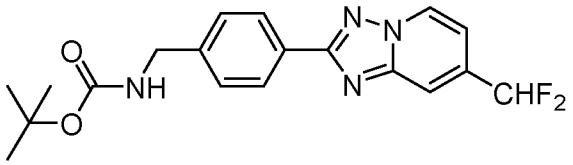
Intermediate I-47 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-2 using 4-(difluoromethyl)pyridine-2-amine [1346536-47-7] (0.5 g, 3.47 mmol) as starting material (1.27 g, 91%).

Synthesis of intermediate I-48



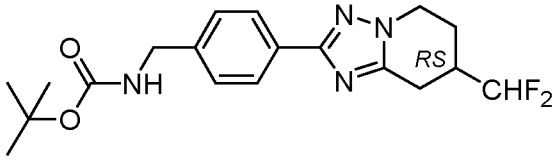
Intermediate I-48 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-3 using intermediate I-47 (1.27 g, 3.16 mmol) as starting material (0.61 g, 67%).

Synthesis of intermediate I-49



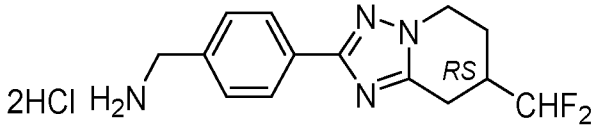
Sodium borohydride [16940-66-2] (255 mg, 6.74 mmol) was added portionwise to a suspension of intermediate I-48 (0.61 g, 2.25 mmol), nickel (II) chloride hexahydrate [7791-20-0] (0.53 mg, 2.25 mmol) and di-tertbutyl dicarbonate [24424-99-5] (1.55 mL, 6.75 mmol) in a mixture of dry methanol (12 mL) and dry 1,4-dioxane (6 mL) at 0 °C under N2. The reaction mixture was stirred at rt for 16 h and then water and a NH3 aqueous solution (3 mL) were added, and the mixture was extracted with DCM. The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane to 20/80). The desired fractions were collected and concentrated in vacuo to yield intermediate I-49 as a white solid (849 mg, 45%).

Synthesis of intermediate I-50



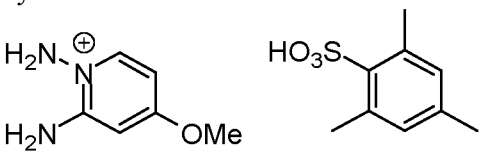
Palladium(II) hydroxide on carbon (20% w/w) 50% H2O [7440-05-3] (0.42 g, 0.60 mmol) was added portionwise to a solution of intermediate I-49 (0.97 g, 3.36 mmol) in a mixture of ethanol (13.5 mL) and dry THF (13.5 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 2 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 75/25). The desired fractions were collected and concentrated in vacuo to yield intermediate I-50 as a white solid (223 mg, 73%).

Synthesis of intermediate I-51



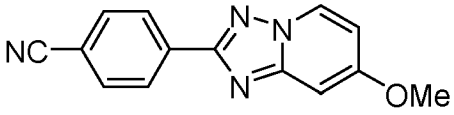
Intermediate I-51 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-6 using intermediate I-50 (223 mg, 0.59 mmol) as starting material (209 mg, quantitative).

Synthesis of intermediate I-52



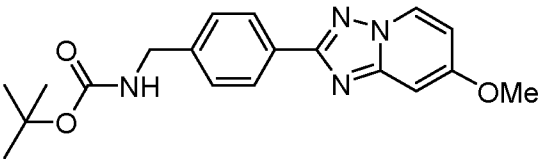
Intermediate I-52 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-2 using 2-amino-4-methoxypyridine [10201-73-7] (0.5 g, 4.03 mmol) as starting material (0.81 g, 51%, 87% purity).

Synthesis of intermediate I-53



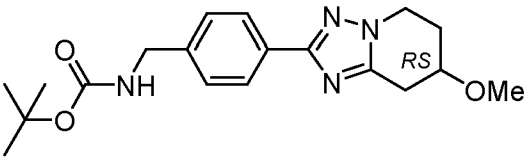
Intermediate I-53 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-3 using intermediate I-52 (0.8 g, 2.35 mmol) as starting material (0.33 g, 56%).

Synthesis of intermediate I-54



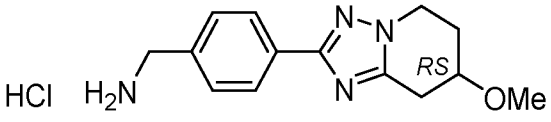
Intermediate I-54 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-4 using intermediate I-53 (0.33 g, 1.32 mmol) as starting material (0.33 g, 67%).

Synthesis of intermediate I-55



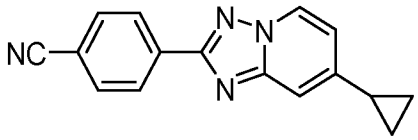
Intermediate I-55 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-36 using intermediate I-54 (0.40 g, 1.09 mmol) as starting material (0.25 g, 63%).

Synthesis of intermediate I-56



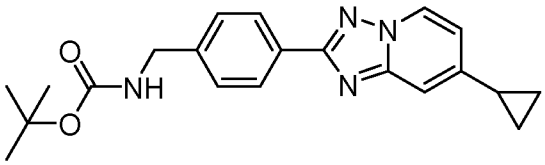
Intermediate I-56 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-6 using intermediate I-55 (0.25 g, 0.68 mmol) as starting material (201 mg, 99%).

Synthesis of intermediate I-57



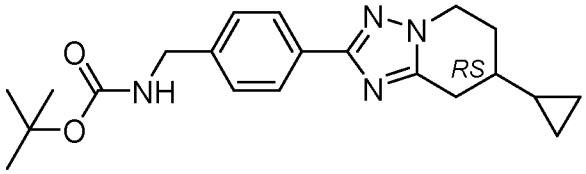
Pd(OAc)2 [3375-31-3] (19 mg, 0.08 mmol) and SPhos [657408-07-6] (34 mg, 0.08 mmol) were added to a stirred solution of intermediate I-12 (0.5 g, 1.67 mmol), cyclopropyl boronic acid [411235-57-9] (144 mg, 1.77 mmol) and K3PO4 (1.77 g, 8.36 mmol) in dry 1,4-dioxane (4 mL) in a sealed tube under N2. The mixture was stirred at 95 °C for 16h. Then water was added, and the mixture was extracted with EtOAc (x3). The combined organic layer was separated, dried (MgSO4), filtered and concentrated in vacuo to yield intermediate I-13 as a white solid (317 mg, 70%).

Synthesis of intermediate I-58



Intermediate I-58 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-14 using intermediate I-57 (287 mg, 1.1 mmol) as starting material (318 mg, 78%).

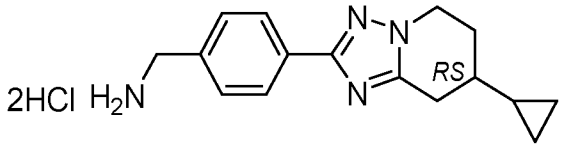
Synthesis of intermediate I-59



Palladium(II) hydroxide on carbon [12135-22-7] (31 mg, 0.11 mmol) was added to a solution of intermediate I-58 (167 mg, 0.45 mmol), in a mixture of ethanol (2 mL), THF (2 mL) and acetic acid (0.2 mL) at 0 °C under N2. Then H2 was added, and the mixture was stirred at rt for 16 h. The mixture was filtered through a pad of celite® and the solvents were concentrated

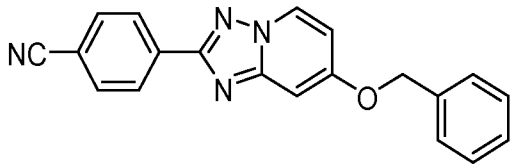
in vacuo to yield intermediate I-15 as a yellow solid used in the next step without any further purification (166 mg, 51%, 50% purity).

Synthesis of intermediate I-60



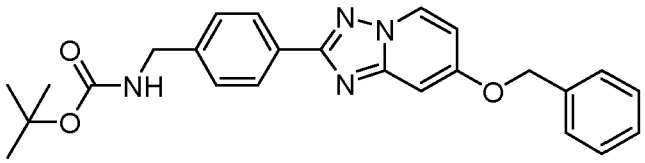
Intermediate I-60 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-16 using intermediate I-59 (166 mg, 0.45 mmol) as starting material (154 mg, 32%, 32%purity).

Synthesis of intermediate I-61



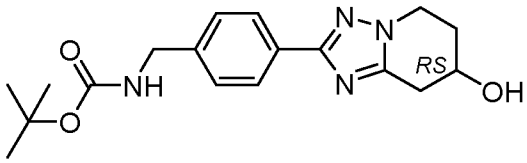
Pd(OAc)2 [3375-31-3] (170 mg, 0.76 mmol) and BredttPhos [1070663-78-3] (410 mg, 0.76 mmol) were added to a stirred solution of intermediate I-12 (3.8 g, 19.03 mmol), benzyl alcohol [100-51-6] (2 mL, 1.77 mmol) and Cs2CO3 (6.2 g, 8.36 mmol) in toluene (22 mL) in a sealed tube under N2. The mixture was stirred at 75 °C for 16h. Then water was added, and the mixture was extracted with DCM (x3). The combined organic layer was separated, dried (MgSO4), filtered and concentrated in vacuo to yield intermediate I-61 as a yellow solid (8 g, 47%, 55% purity).

Synthesis of intermediate I-62



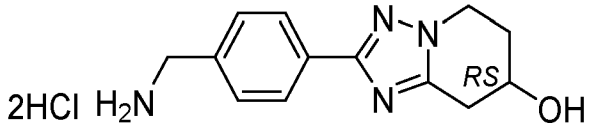
Intermediate I-62 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-4 using intermediate I-61 (3.5 g, 7.29 mmol) as starting material (0.87 g, 27%).

Synthesis of intermediate I-63



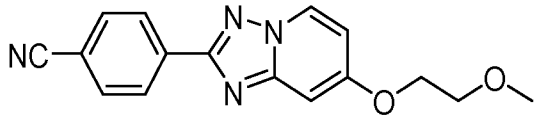
Intermediate I-63 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-9 using intermediate I-62 (0.87 g, 2.01 mmol) as starting material (488 mg, 70%).

Synthesis of intermediate I-64



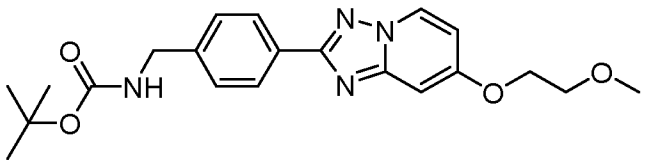
Intermediate I-64 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-5 using intermediate I-63 (100 mg, 0.29 mmol) as starting material (93 mg, quantitative).

Synthesis of intermediate I-65



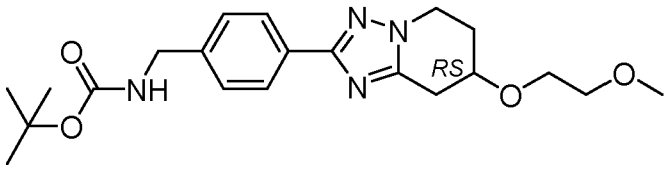
Intermediate I-65 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-61 using 2-methoxyethanol [109-86-4] (0.40 mL, 5.01 mmol) as starting material (0.97 g, 85%, 86% purity).

Synthesis of intermediate I-66



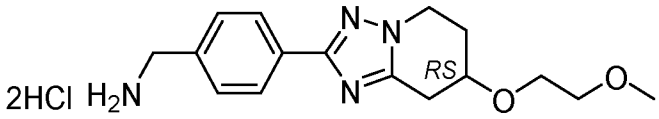
Intermediate I-66 was prepared according to an analogous procedure to the one used for the synthesis of intermediate I-4 using intermediate I-65 (0.97 g, 2.83 mmol) as starting material (0.6 g, 52%).

Synthesis of intermediate I-67



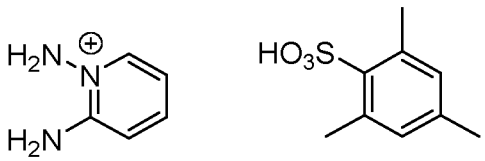
Palladium on carbon (10% w/w) 50% H_2O [7440-05-3] (0.4 g, 0.38 mmol) was added to a solution of intermediate **I-66** (200 mg g, 0.50 mmol) in a mixture of methanol (15 mL) and EtOAc (2 mL) at 0 °C under N_2. H_2 was added, and the mixture was stirred at 50 °C for 16 h. Then more Palladium on carbon (10% w/w) 50% H_2O [7440-05-3] (0.4 g, 0.38 mmol) was added at 0 °C under N_2. H_2 was added, and the mixture was stirred at rt for a further 16 h. The mixture was filtered through a pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-67** as a white solid (77 mg, 36%).

Synthesis of intermediate **I-68**



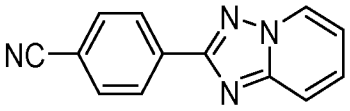
Intermediate **I-68** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-6** using intermediate **I-67** (213 mg, 0.53 mmol) as starting material (199 mg, quantitative).

Synthesis of intermediate **I-69**



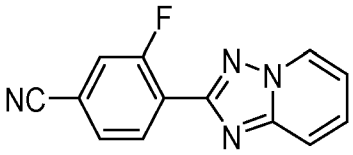
Intermediate **I-69** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-2** using 2-aminopyridine [504-29-0] (1.75 g, 18.57 mmol) as starting material (5.17 g, 89%).

Synthesis of intermediate **I-70a**



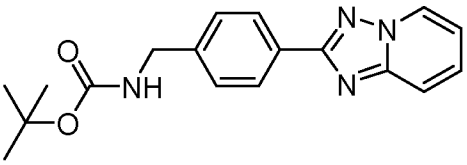
Intermediate **I-70a** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-3** using intermediate **I-69** (2 g, 6.44 mmol) as starting material (1.09 g, 76%).

Synthesis of intermediate **I-70b**



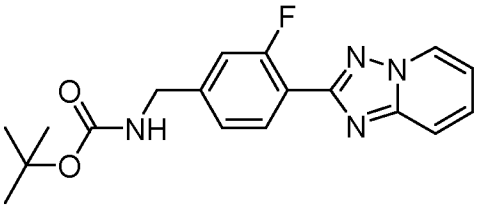
Intermediate **I-**70b was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-3** using intermediate **I-33** (3.75 g, 20.43 mmol) as starting material (1.6 g, 65%).

Synthesis of intermediate **I-71a**



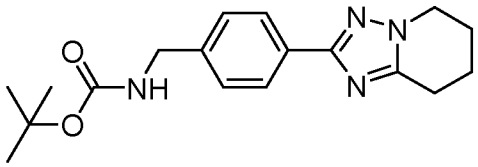
Intermediate **I-71a** was prepared **according** to an analogous procedure to the one used for the synthesis of intermediate **I-4** using intermediate **I-70a** (1.08 g, 4.90 mmol) as starting material (1.37 g, 73%, 85% purity).

Synthesis of intermediate **I-71b**



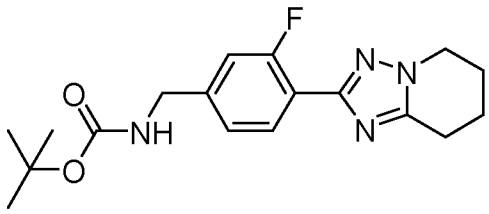
Intermediate **I-71b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-4** using intermediate **I-70b** (1.59 g, 6.67 mmol) as starting material (1.95 g, 79%).

Synthesis of intermediate **I-72a**



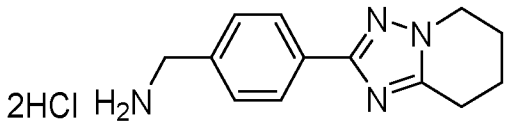
Intermediate **I-72a** was prepared according to an analogous procedure to the one used for the synthesis of **intermediate I-5** using intermediate **I-71a** (1.34 g, 3.51 mmol) as starting material (1 g, 84%).

Synthesis of intermediate **I-72b**



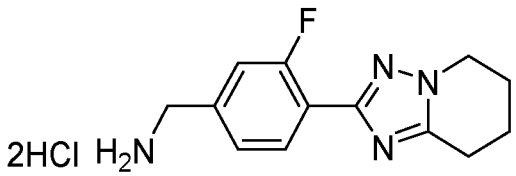
Intermediate **I-72b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-5** using intermediate **I-71b** (1.93 g, 5.19 mmol) as starting material (1.25 g, 68%).

Synthesis of intermediate **I-73a**



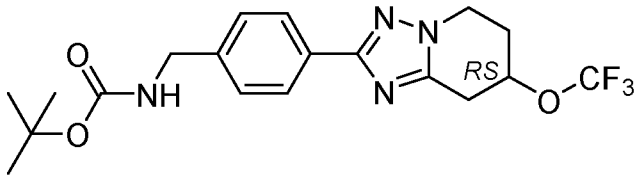
Intermediate **I-73a** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-6** using intermediate **I-72a** (1 g, 2.95 mmol) as starting material (0.93 g, quantitative).

Synthesis of intermediate **I-73b**



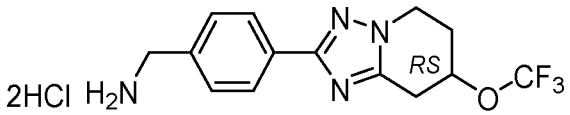
Intermediate **I-73b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-6** using intermediate **I-72b** (1.25 g, 3.5 mmol) as starting material (1.13 g, quantitative).

Synthesis of intermediate **I-74**



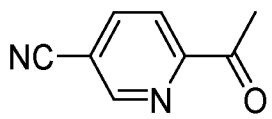
Trimethyl(trifluoromethyl)silane [81290-20-2] (0.42 uL, 2.6 mmol) was added to a mixture of intermediate **I-63** (150 mg, 0.4 mmol), N-fluoro-N'-(chloromethyl)triethylenediamine bis(tetrafluoroborate) [140681-55-6] (500 mg, 1.4 mmol), silver trifluoromethanesulfonate [2923-28-6] (700 mg, 2.7 mmol), 2-fluoropyridine (250 uL, 2.9 mmol) and potassium fluoride (230 mg, 4 mmol) in EOAc (15 mL). The reaction mixture was stirred at rt for 4 d in the dark. The reaction mixture was filtered through a celite® pad and the pad washed with EtOAc. The solvent was evaporated in vacuo, and the crude product was purified by flash column chromatography (silica, DCM/MeOH (9:1) in DCM from 100/0 to 0/100). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-74** as a yellow solid (105 mg, 47%, 80% purity).

Synthesis of intermediate **I-75**



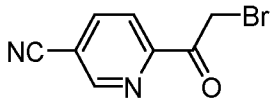
Intermediate **I-75** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-6** using intermediate **I-74** (100 mg, 0.24 mmol) as starting material (136 mg, quantitative).

Synthesis of intermediate **I-76**



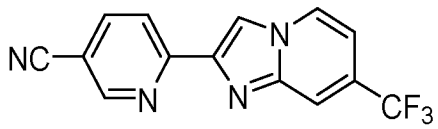
Tributyl(1-ethoxyvinyl)tin [97674-02-7] (5.9 mL, 14.46 mmol) was added to a stirred solution of 6-chloro-3-pyridinecarbonitrile [623-00-7] (2 g, 14.43 mmol) and bis(triphenylphosphine)palladium(II) chloride [13965-03-2] in dry toluene (20 mL) at rt under N_2. The mixture was stirred at 130 °C for 2 h. Then the mixture was cooled down to 0 °C with and ice bath and a 6M HCl aqueous solution (5.3 mL) was added. The mixture was stirred at rt for 1h. The reaction was cooled down to 0 °C with ice bath and the reaction was brough to pH 8 by a 4M NaOH aqueous solution and a $NaHCO_3$ saturated aqueous solution addition. The resulting suspension was filtered through a celite® pad. The filtrate was extracted with EtOAc, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-76** as a yellow solid (1.78 g, 83%).

Synthesis of intermediate **I-77**



Pyridinium tribromide [39416-48-3] (3.54 g, 11.06 mmol) was added to a solution of intermediate **I-76** (1.62 g, 11.05 mmol) in THF (50 mL) at rt. The reaction mixture was stirred at rt for 16 h and then diluted with EtOAc and a saturated $Na_2S_2O_3$ aqueous solution. The aqueous layer was extracted with EtOAc (x3) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-77** as a yellow solid (0.68 g, 25%).

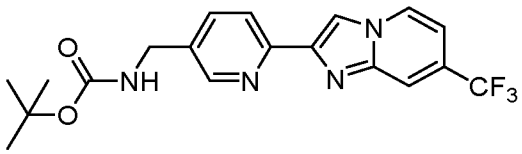
Synthesis of intermediate **I-78**



$NaHCO_3$ (218 mg, 2.60 mmol) was added to a solution of 2-amino-4-(trifluoromethyl)pyridine [106447-97-6] (375 mg, 2.31 mmol) and intermediate **I-77** (680 mg, 3.02 mmol) in ethanol (16 mL) at rt. The mixture was stirred at reflux for 16 hours. H_2O was added and the precipitate formed was filtered off and washed with water and diethyl ether. The solid was dried in vacuo to afford Intermediate **I-78** (380 mg, 57%) as a brown solid. The filtrate was extracted with DCM and the organic layer was dried ($MgSO_4$), filtered and the

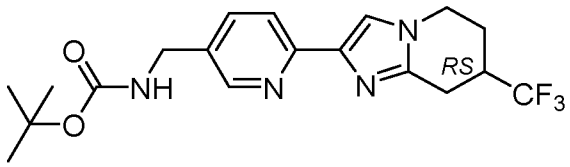
solvent concentrated in vacuo. The residue was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield further intermediate **I-78** as a yellow solid (96 mg, 14%).

Synthesis of intermediate **I-79**



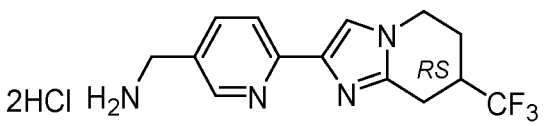
Sodium borohydride [16940-66-2] (187 mg, 4.94 mmol) was added portionwise to a suspension of intermediate **I-78** (476 mg, 1.65 mmol), nickel (II) chloride hexahydrate [7791-20-0] (393 g, 1.65 mmol) and di-tertbutyl dicarbonate [24424-99-5] (1.14 mL, 4.96 mmol) in a mixture of dry methanol (8 mL) and 1,4-dioxane (4 mL) at 0 °C under N_2. The reaction mixture was stirred at rt for 16 h. Water and 3 mL of aqueous NH_3 were added and the mixture was extracted with DCM (x3). The combined organic layers were washed with water, separated, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-79** as a brown solid (349 mg, 53%).

Synthesis of intermediate **I-80**



Intermediate **I-80** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-9** using intermediate **I-79** (306 mg, 0.78 mmol) as starting material (175 mg, 56%).

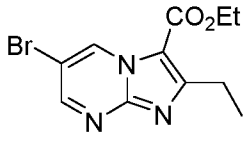
Synthesis of intermediate **I-81**



Intermediate **I-81** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-10** using intermediate **I-80** (175 mg, 0.44 mmol) as starting material (171 mg, quantitative).

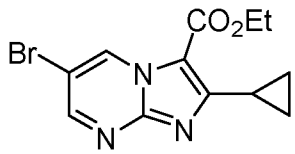
SYNTHESIS OF INTERMEDIATES II

Synthesis of intermediate **II-1a**



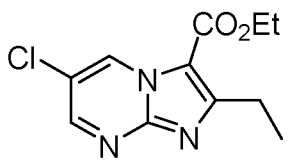
Boron trifluoride diethyl etherate [109-63-7] (0.35 mL, 2.87 mmol) was added dropwise to a solution of 2-amino-5-bromopyrimidine [7752-82-1] (5 g, 28.74 mmol), ethyl propionylacetate [4949-44-4] (6.33 mL, 43.10mmol) and (diacetoxyiodo)benzene [3240-34-4] (13.88 g, 43.09 mmol) in dry 2-methyltetrahydrofuran (125 mL), in a 2-neck round bottom flask equipped with a condenser, at rt under N_2. The mixture was stirred at 60 ºC for 16 h. A saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-1a** as a yellow solid (3.75 g, 43%).

Synthesis of intermediate **II-1b**



Intermediate **II-1b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using Ethyl-3-cyclopropyl-3-oxopropionate [24922-02-9] (3.82 mL, 25.86 mmol) as starting material (2.68 mg, 47%).

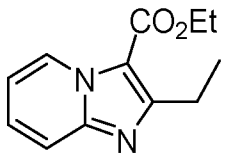
Synthesis of intermediate **II-1c**



Boron trifluoride diethyl etherate [109-63-7] (0.2 mL, 1.62 mmol) was added dropwise to a solution of 2-amino-5-chloropyrimidine [5428-89-7] (2.0 g, 15.438 mmol), ethyl propionylacetate [4949-44-4] (3.14 mL, 21.38 mmol) and (diacetoxyiodo)benzene [3240-34-

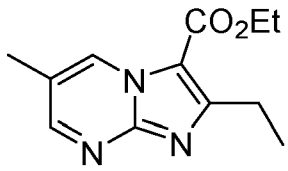
4] (7.5 g, 23.29 mmol) in dry 2-methyltetrahydrofuran (75 mL) at 0 °C under N_2. The mixture was stirred at rt for 16 h and then was poured into a 10% $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvents were evaporated in vacuo. The crude was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-1c** as a yellow solid.

Synthesis of intermediate **II-1d**



Boron trifluoride diethyl etherate [109-63-7] (66 µL, 0.53 mmol) was added dropwise to a solution of 2-aminopyridine [4949-44-4] (1 g, 10.62 mmol), ethyl propionylacetate [4949-44-4] (2.34 mL, 15.94 mmol) and (diacetoxyiodo)benzene [3240-34-4] 1.71 g, 5.31 mmol) in dry 2-methyltetrahydrofuran (25 mL), at 5 °C under N_2. The mixture was stirred at 5 °C for 15 min and then allowed to slowly warm to rt and stirred for a further 5 h. A saturated $NaHCO_3$ aqueous solution was added. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-1d** as a white solid (0.78 g, 32%).

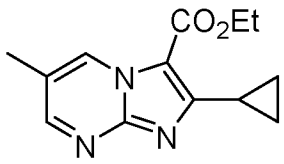
Synthesis of intermediate **II-2a**



A 2M trimethylaluminum solution in hexane [75-24-1] (22.05 mL, 44.11 mmol) was added dropwise to a solution of intermediate **II-1a** (3.78 g, 12.60mmol) and tetrakis(triphenylphosphine)-palladium(0) [14221-01-3] in dry THF (90 mL) at rt under N_2 and the mixture was stirred at 65 °C for 2 h. The mixture was cooled to 0 °C and diluted with DCM. Then 10 mL of water was added dropwise. The resulting mixture was filtered through of pad of celite ® and the pad was washed with EtOAc. Then anhydrous $MgSO_4$ was added to the filtrate. The filtrate was filtered, and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 40/60). The

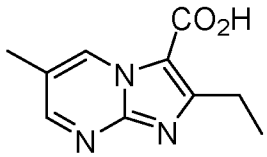
desired fractions were collected and concentrated in vacuo to intermediate **II-2a** as a yellow solid (2.45 g, 75%).

Synthesis of intermediate **II-2b**



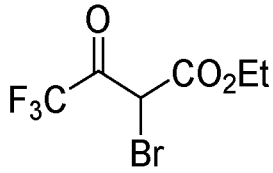
Intermediate **II-2b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using intermediate **II-1b** (2.57 mL, 8.10 mmol) as starting material (1.46 mg, 72%).

Synthesis of intermediate **II-3a**



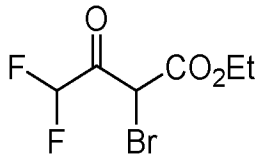
Sodium hydroxide [1310-73-2] (1.13 g, 28.29 mmol) was added to a solution of intermediate **II-2a** in a mixture of ethanol (74 mL) and water (19 mL) at rt. The mixture was stirred at 50 °C for 2 h. The reaction mixture was brought to pH 7 by a 1M HCl aqueous solution addition and concentrated in vacuo to yield intermediate **II-3a** as a pale orange solid used in next step without any further purification (2.76 g, quantitative, 90% purity).

Synthesis of intermediate **II-4a**



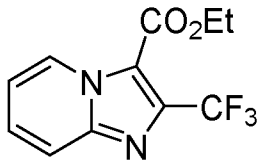
N-Bromosuccinimide [128-08-5] (14.69 g, 82.56 mmol) was added to a stirred solution of ethyl 4,4,4-trifluoroacetoacetate [372-31-6] (14.48 g, 78.63 mmol) in DMSO (72 mL). The reaction mixture was stirred at rt for 1 hour. A saturated NH_4Cl aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to yield intermediate **II-4a** as a colourless oil used in the next step without any further purification (14.1 g, 55%, 80% purity).

Synthesis of intermediate **II-4b**



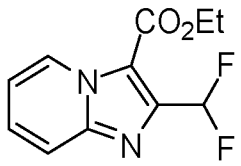
Bromine [7726-95-6] (0.70 mL, 13.75 mmol) was added dropwise to a mixture of ethyl 4,4-difluoroacetoacetate [7726-95-6] (1.8 mL, 13.75 mmol), $CaCO_3$ (1.6 g, 15.95 mmol) in dry methanol (20 mL) at 0 °C. The mixture was stirred at rt for 1 h and then concentrated in vacuo. The crude product was triturated with diethyl ether, the solid formed was filtered off and the filtrate was concentrated in vacuo to yield **II-4b** as a yellow oil (3.37, quantitative).

Synthesis of intermediate **II-5a**



2-Aminopyridine [504-29-0] (3.2 g, 34 mmol) was added to a stirred solution of intermediate **II-4a** (18 g, 68.43 mmol) in ethanol (100 mL) at rt in a sealed tube. The reaction mixture was stirred at 80 °C for 48 hours and then the solvent was evaporated in vacuo. A saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 100/0 to 80/20). The desired fractions were collected and concentrated in vacuo to intermediate **II-5a** as a pale yellow solid (2.0 g, 22%).

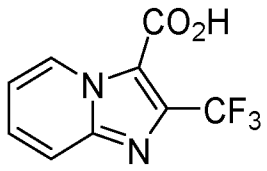
Synthesis of intermediate **II-5b**



2-Aminopyridine [504-29-0] (0.51 g, 5.44 mmol) was added to a stirred solution of intermediate **II-4b** (2 g, 8.16 mmol) in ethanol (30 mL) at rt. The reaction mixture was stirred at 65 °C for 16 hours. A saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography

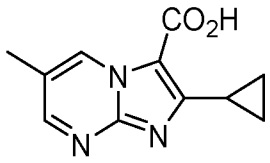
(silica; EtOAc in heptane 100/0 to 40/26). The desired fractions were collected and concentrated in vacuo to intermediate **II-5a** as a colourless solid (0.81 g, 59%).

Synthesis of intermediate **II-6a**



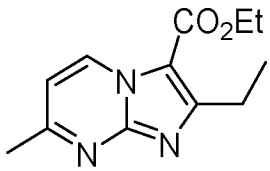
A 1M solution of aqueous sodium hydroxide [1310-73-2] (1.32 mL, 1.32 mmol) was added to a solution of intermediate **II-5a** (113 mg, 0.44 mmol) in a mixture of ethanol (3 mL) and water (1 mL) at rt. The mixture was stirred at rt for 16 h. The reaction mixture was brought to pH 5 by a 1M HCl aqueous solution addition and concentrated in vacuo to yield intermediate **II-6a** as a white solid used in next step without any further purification (101 mg, quantitative).

Synthesis of intermediate **II-6b**



Intermediate **II-6b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-6a** using intermediate **II-2b** (120 mg, 0.49 mmol) as starting material (106 mg, quantitative).

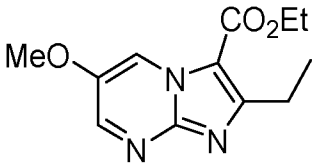
Synthesis of intermediate **II-7a**



$KHCO_3$ (688 mg, 6.87 mmol) and ethyl propionylacetate [4949-44-4] (0.98 mL, 6.87 mmol) were added to a stirred solution of 2-amino-4-methylpyrimidine [108-52-1] (500 mg, 4.58 mmol) in dry ACN (9.18 mL) at rt in a sealed tube. The reaction mixture was stirred at 80 °C for 16 hours and then a saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered and

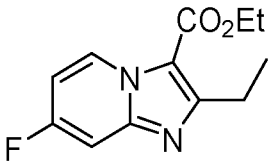
concentrated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to intermediate **II-7a** as a brown solid (206 mg, 19%).

Synthesis of intermediate **II-7b**



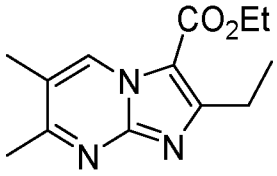
Intermediate **II-7b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7a** using 2-amino-4-methylpyrimidine [13418-77-4] (500 mg, 4 mmol) as starting material (407 mg, 40%).

Synthesis of intermediate **II-7c**



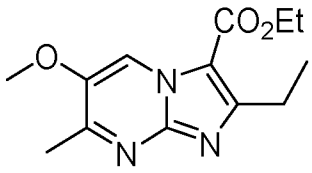
Ethyl propionylacetate [4949-44-4] (1.87 mL, 12.71 mmol) and tetrabromoethane [558-13-4] (11.24 g, 33.90 mmol) were added to a stirred solution of 4-fluoro-2-aminopiridine [944401-77-8] (1 g, 8.47 mmol) in dry ACN (15.25 mL) at rt in a sealed tube. The reaction mixture was stirred at 80 °C for 20 hours and then additional Ethyl propionylacetate [4949-44-4] (1.24 mL, 8.47 mmol) and tetrabromoethane [558-13-4] (2.81 g, 8.48 mmol). The reaction mixture was stirred at 80 °C for 5 hours and then additional Ethyl propionylacetate [4949-44-4] (0.62 mL, 4.24 mmol) and tetrabromoethane [558-13-4] (1.41 g, 4.24 mmol). The reaction mixture was stirred at 80 °C for a further 16 hours and then was poured onto a 10% $NaHCO_3$ aqueous solution and extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to intermediate **II-7c** as a pale yellow solid (529 mg, 25%).

Synthesis of intermediate **II-7d**



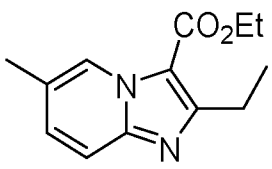
$KHCO_3$ (610 mg, 69 mmol) and ethyl propionylacetate [4949-44-4] (0.87 mL, 6.09 mmol) were added to a stirred solution of 4,5-dimethyl-2-pyrimidinamine [1193-74-4] (500 mg, 4.06 mmol) in dry ACN (8.14 mL). Then bromotrichloromethane [75-62-7] (1.2 mL, 12.18 mmol) was and the reaction mixture was stirred at 80 °C for 16 hours and then additional Ethyl propionylacetate [4949-44-4] (0.43 mL, 3.04 mmol) and bromotrichloromethane [75-62-7] (0.6 mL, 6.09 mmol) were added. The reaction mixture was stirred at 80 °C for a further 16 hours and then a saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 2/98). The desired fractions were collected and concentrated in vacuo to intermediate **II-7d** as a brown solid (219 mg, 20%).

Synthesis of intermediate **II-7f**



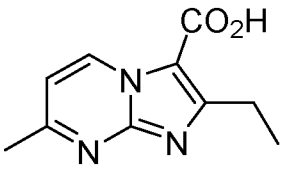
Intermediate **II-7f** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d** using 5-methoxy-4-methylpyrimidin-2amine [1749-71-9] (0.5 g, 3.59 mmol) as starting material (0.23 g, 24%).

Synthesis of intermediate **II-7g**



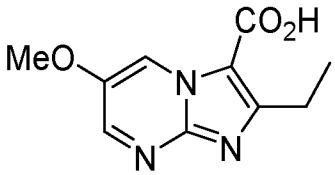
Intermediate **II-7g** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d** using 5-methyl-pyridin-2-ylamine [1603-41-4] (5 g, 46.24 mmol) as starting material (8.85 g, 82%).

Synthesis of intermediate **II-8a**



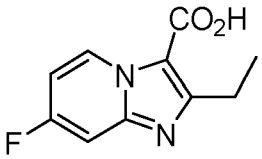
Sodium hydroxide [1310-73-2] (72 mg, 1.8 mmol) was added to a solution of intermediate **II-7a** (140 mg, 0.6 mmol) in a mixture of ethanol (4.7 mL) and water (1.2 mL) at rt. The mixture was stirred at 50 ºC for 2 h. The reaction mixture was brought to pH 7 by a 1M HCl aqueous solution addition and concentrated in vacuo to yield intermediate **II-8a** as a pale orange solid used in next step without any further purification (2.76 g, quantitative, 90% purity).

Synthesis of intermediate **II-8b**



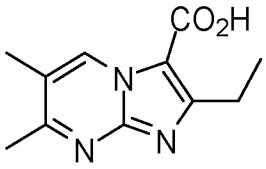
Intermediate **II-8b** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-7b** (150 mg, 0.6 mmol) as starting material (135 mg, quantitative).

Synthesis of intermediate **II-8c**



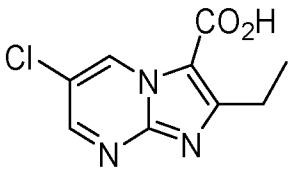
Intermediate **II-8c** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-7c** (248 mg, 1.04 mmol) as starting material (219 mg, quantitative).

Synthesis of intermediate **II-8d**



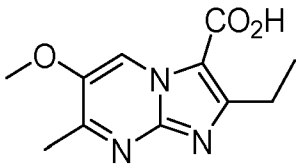
Intermediate **II-8d** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-7d** (110 mg, 0.44 mmol) as starting material (115 mg, 99%).

Synthesis of intermediate **II-8e**



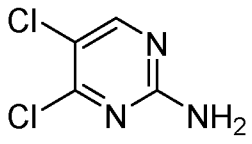
A 15% K_2CO_3 aqueous solution (1.2 mL, 1.30 mmol) was added to a solution of intermediate **II-1d** (143 mg, 0.56 mmol) in EtOH (1.5 mL) at rt in a screw cap vial. The mixture was stirred at 90 °C for 16 h and then was brought to pH 3-4 by a 2M HCl aqueous solution addition. The solvents were evaporated in vacuo to yield intermediate **II-8e** as a brownish solid (108 mg, 85%).

Synthesis of intermediate **II-8f**



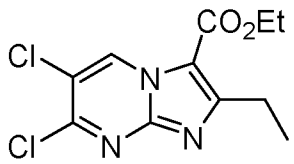
Intermediate **II-8f** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-7f** (95 mg, 0.36 mmol) as starting material (112 mg, quantitative).

Synthesis of intermediate **II-9**



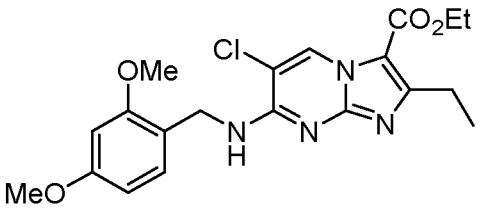
Trichloroisocyanuric acid [87-90-1] (1.54 g, 7.72 mmol) was added to a solution of 2-amino-4-chloropyrimidine [3993-78-0] (2 g, 15.44 mmol) and acid acetic (2 mL, 34.94 mmol) in water (18 mL) at rt. Then the mixture was stirred at 50 ºC for 15 h and then cooled to rt and poured into a flask containing ice. The mixture was basified by addition of a 10M NaOH aqueous solution and stirred for 4 h. The solid formed was collected by filtration and washed with water (14 mL). The solid was suspended in 24 ml of a 0.5M NaOH aqueous solution and stirred for 1 h. The solid was collected by filtration and washed with 24 ml of water. The solid was dissolved with EtOAc and concentrated in vacuo. Then diethyl ether was added, and the mixture concentrated again in vacuo again to yield intermediate **II-9** as a beige solid (1.7 g, 60%).

Synthesis of intermediate **II-10**



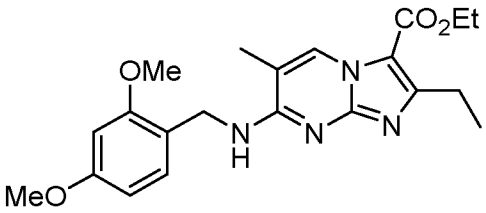
Ethyl propionylacetate [4949-44-4] (2.43 mL, 16.59 mmol) and (diacetoxyiodo)benzene [3240-34-4] (5.01 g, 15.54 mmol) were added to a solution of intermediate **II-9** (1.7 g, 10.37 mmol) in dry 2-methyltetrahydrofuran (49.4 mL) at 0 ºC under N_2. Then boron trifluoride diethyl etherate [109-63-7] (0.13 mL, 1.03 mmol) was added dropwise. The mixture was stirred at 5 ºC for 5 min and then at rt for 2 h. Further ethyl propionylacetate [4949-44-4] (1.21 mL, 8.29 mmol), (diacetoxyiodo)benzene [3240-34-4] (2.50 g, 7.78 mmol) and boron trifluoride diethyl etherate [109-63-7] (0.06 mL, 0.48 mmol) were added at 0 ºC and the mixture was stirred at 5 ºC for 5 min and then at rt for 2 h. The mixture was poured into a 10% $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 15/85). The desired fractions were collected and concentrated in vacuo. The residue was repurified by reverse phase HPLC (Phenomenex Gemini; C18 100x30mm 5µm Column; from 59% (25mM NH_4HCO_3) / 41% (ACN: MeOH 1:1) to 17% (25mM NH_4HCO_3) / 83% (ACN: MeOH 1:1). The desired fractions were collected and concentrated in vacuo to remove the organic solvents and the resulting aqueous layer was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo to intermediate **II-10** as a white solid (510 mg, 16%).

Synthesis of intermediate **II-11**



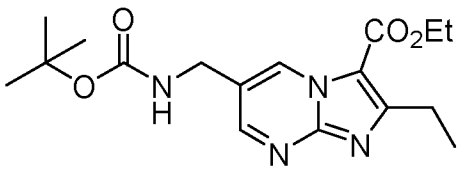
2,4-Dimethoxybenzylamine [20781-20-8] (0.36 mL, 2.4 mmol) was added to a solution of intermediate **II-10** (485 mg, 1.6 mmol) in dry 1,4-dioxane at rt. The suspension was stirred at rt for 2 h. and then more 2,4-dimethoxybenzylamine [20781-20-8] (0.18 mL, 1.2 mmol) was added and the mixture was stirred at 50 ºC for 16 h. The solvent was removed in vacuo and then water was added, and the mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 25/75). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-11** as a white solid (544 mg, 80%).

Synthesis of intermediate **II-12a**



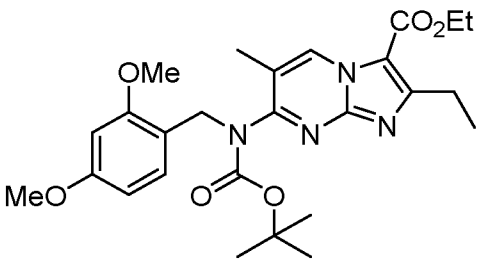
Methylboronic acid [13061-96-6] (37 mg, 0.62 mmol) and K_3PO_4 (176 mg, 0.83 mmol) were added to a solution of intermediate **II-11** in a mixture of water (0.33 mL and toluene (1.66 mL). The mixture was purged with N_2 for 10 min and then Palladium(II) acetate [3375-31-3] (9 mg, 0.042 mmol) and SPhos [657408-07-6] (26 mg, 0.062 mmol) were added at rt and the reaction mixture was stirred at 110 ºC for 2 hours. The solvents were removed under vacuum and the crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-12a** as a colourless oil.

Synthesis of intermediate **II-12b**



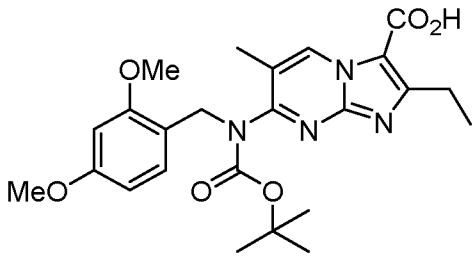
Experiment set-up in 6 batches of 50 mg of intermediate II-1a each.
A mixture of intermediate II-1a (250 mg, 0.85 mmol), potassium (((tert-butoxycarbonyl)amino)methyl)trifluoroborate [1314538-55-0] (240 mg, 1 mmol), [4,4'-bis (1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride [1034901-50-2] (35 mg, 0.085 mmol), Ir[dF(CF3)ppy]2(dtbbpy)PF6 [870987-63-6] (25 mg, 0.02mmol), Cs2CO3 (430 mg, 1.3 mmol) in dioxane (4 mL) in a screw top vial was degassed by bubbling N2 for 5 min. Then the vial was sealed, and the reaction mixture was irradiated with blue LED light at rt for 48 h. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried (MgSO4), filtered, and the solvent evaporated in vacuo. The crude was purified by flash column chromatography (silica, EtOAc in heptane from 00/100 to 100/0). The desired fractions were collected and the solvents removed in vacuo to yield intermediate II-12b as a yellow solid (160 mg, 23%, 50% purity).

Synthesis of intermediate **II-13**



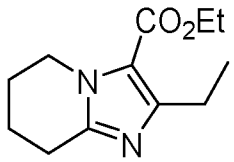
Di-tertbutyl dicarbonate [24424-99-5] (0.12 mL, 0.51 mmol) was added to a stirred solution of intermediate **II-12a** (136 mg, 0.34 mmol), triethylamine [121-44-8] (0.14 mL, 1,02 mmol) and 4-(dimethylamino)pyridine [1122-58-3] (2 mg, 0.017 mmol), in 1,4-dioxan (1.16 mL) at rt. The mixture was stirred at rt for 16 h and then more triethylamine [121-44-8] (47 µL, 0.34 mmol) and di-tertbutyl dicarbonate [24424-99-5] (78 µL, 0.34 mmol) were added and the mixture was stirred at 50 °C for 20 h. Additional triethylamine [121-44-8] (71 µL, 0.51 mmol) and di-tertbutyl dicarbonate [24424-99-5] (117 µL, 0.51 mmol) were added and the mixture was stirred at 80 °C for 2h. Then more triethylamine [121-44-8] (94 µL, 0.68 mmol), 4-(dimethylamino)pyridine [1122-58-3] (2 mg, 0.017 mmol) and di-tertbutyl dicarbonate [24424-99-5] (117 µL, 0.51 mmol) were added and the reaction mixture was stirred at 100 °C for a further 16 h. The reaction mixture was diluted with water and brine and extracted with DCM (x3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane from 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield intermediate **II-14** as a beige solid (170 mg, 86%, 86% purity).

Synthesis of intermediate **II-15**



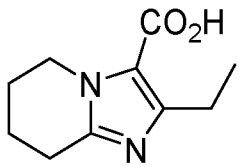
Lithium hydroxide monohydrate [1310-66-3] (43 mg, 1.02 mmol) was added to a solution of intermediate **II-14** (170 mg, 0.34 mmol) in a mixture of ethanol (5.12 mL) and water (1.71 mL) at rt. The reaction mixture was stirred at rt for 16 h. Then the mixture was brough to pH 7 by a 1M HCl aqueous solution addition. The solvent was evaporated in vacuo to yield intermediate **II-15** as an orange solid that was used in the next step without any further purification (198 mg, quantitative).

Synthesis of intermediate **II-16**



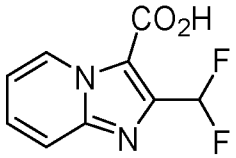
Platinum(IV) oxide [1314-15-4] (73 mg, 0.32 mmol) was added to a stirred solution of intermediate **II-1d** (0.78 g, 3.56 mmol) in methanol (8 mL) under N_2. Then a concentrated HCl aqueous solution (2 µ was added, and the resulting suspension was stirred at room temperature under H_2 atmosphere for 16 h. The reaction was filtered through a pad of celite® and the filtrate was evaporated in vacuo to yield intermediate **II-16** as a colourless oil (785 mg, 94%).

Synthesis of intermediate **II-17a**



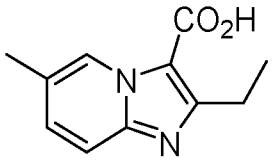
Lithium hydroxide monohydrate [1310-66-3] (85 mg, 2.02 mmol) was added to a stirred solution of intermediate **II-16** (300 mg, 1.35 mmol), in a mixture of ethanol (5 mL) and water (2 mL) at rt. The mixture was stirred at 50 ºC for 16 h and then the solvents were evaporated in vacuo to yield intermediate **II-17a** as a brown solid (262 mg, quantitative).

Synthesis of intermediate **II-17b**



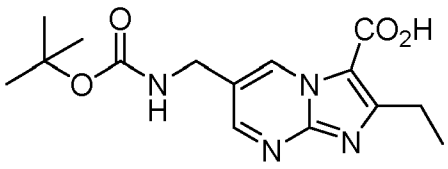
Lithium hydroxide monohydrate [1310-66-3] (29 mg, 0.69 mmol) was added to a stirred solution of intermediate **II-5b** (111 mg, 0.46 mmol), in a mixture of THF (4 mL) and water (1.5 mL) at rt. The mixture was stirred at rt for 16 h and then neutralized by a 1M HCl aqueous solution addition. The solvents were evaporated in vacuo to yield intermediate **II-17b** as a white solid (120 mg, quantitative).

Synthesis of intermediate **II-17c**



Lithium hydroxide monohydrate [1310-66-3] (135 mg, 3.23 mmol) was added to a stirred solution of intermediate **II-Id** (250 mg, 1.08 mmol), in a mixture of ethanol (4.4 mL) and water (2.2 mL) at rt. The mixture was stirred at 50 ºC for 16 h and then neutralized by a 1M HCl aqueous solution addition. The solvents were evaporated in vacuo to yield intermediate **II-17c** as an orange solid (448 mg, quantitative).

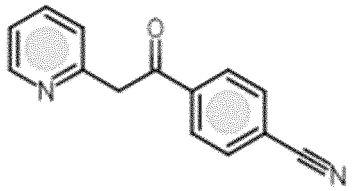
Synthesis of intermediate **II-17d**



Sodium hydroxide (61 mg, 0.3 mmol), was added to a solution of intermediate II-12b (172 mg, 0.49 mmol) at rt. The mixture was stirred at rt for 16 h. The reaction mixture was brought to pH 7 by addition of a 1M HCl aqueous solution and the solvent was evaporated in vacuo to yield intermediate II-17d as a yellow solid that was used in the next step without any further purification (187 mg, 80%, 80% purity)

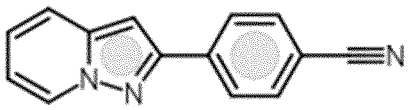
SYNTHESIS OF INTERMEDIATES I

Synthesis of intermediate **I-82**



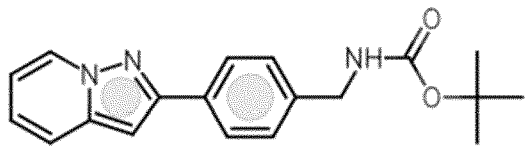
Intermediate **I-82** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-23** using 2-Methylpyridine [109-06-8] (2.1 mL, 2.13 mmol) and Ethyl 4-cyanobenzoate [7153-22-2] (4.1 g, 23.4 mmol) as starting material. (1.8 g, 36%) as a bright yellow solid.

Synthesis of intermediate **I-83**



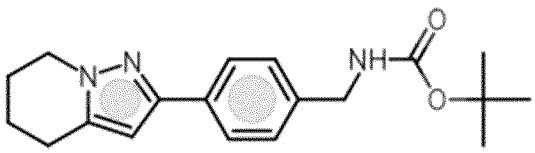
Intermediate **I-83** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-24** using 2 intermediate **I-23** (1.8 g, 8.1 mmol) and intermediate **I-1** (5.8 g, 20.2 mmol) as starting material. (179 mg, 9.6%) as a yellow solid.

Synthesis of intermediate **I-84**



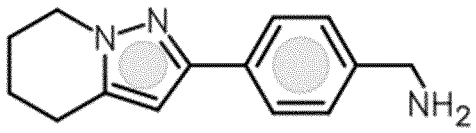
Intermediate **I-84** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-25** using intermediate **I-83** (176 mg, 0.8 mmol) as starting material. (219 mg, 83.5%) as a white solid.

Synthesis of intermediate **I-85**



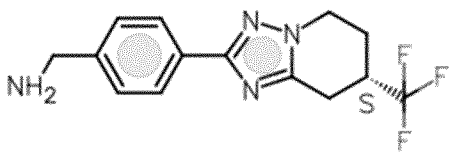
Intermediate **I-85** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-26** using intermediate **I-84** (206 mg, 0.6 mmol) as starting material. (100 mg, 47.5%) as a pale yellow solid.

Synthesis of intermediate **I-86**

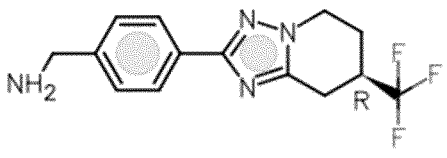


Intermediate **I-86** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-27** using intermediate **I-85** (97 mg, 0.3 mmol) as starting material. (89 mg, 99.1%) as a white solid.

Synthesis of intermediates **I-87 (S)** and **I-88 (R)**



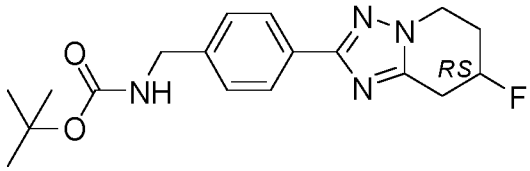
HCl



HCl

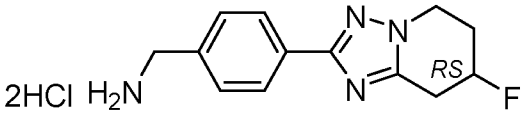
Intermediate **I-6** (3 g, 8.125 mmol) was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux Cellulose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 100ml/min of CO_2 (65%) - Methanol (40%) + 0.1% DEA, at 30 °C, BPR 150 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under vacuo to yield intermediate **I-87 (S)** (1.3 g, 42.7%) and intermediate **I-88 (R)** (1.1 g, 34.7%) as white solids.

Synthesis of intermediate **I-89**



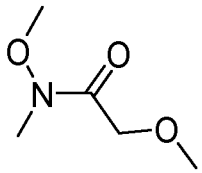
(Diethylamino)sulfur trifluoride [38078-09-0] (58 uL, 0.439 mmol) as added dropwise at -78 °C to a solution of **I-63** (72 mg, 0.210 mmol) in anhydrous DCM (3 mL). The reaction mixture was slowly warmed up to rt for 2h. Saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with DCM (x3). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo to yield intermediate **I-89** (72 mg, 95%) as a yellow solid

Synthesis of intermediate **I-90**



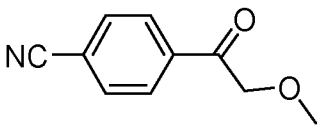
HCl 4M in dioxane (369 uL, 1.476 mmol) was added to a stirred solution of **I-89** (85 mg, 0.245 mmol) in DCM (3 mL) in a round bottom flask at rt. The reaction mixture was stirred at rt for 16 h. The reaction was concentrated in vacuo to yield intermediate **I-90** (78 mg, 99%) as a white solid.

Synthesis of intermediate **I-91**



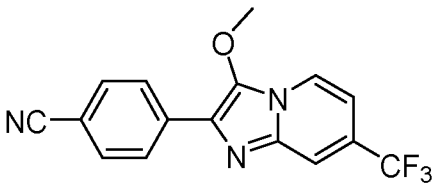
To a solution of 2-methoxyacetyl chloride [38870-89-2] (2.1 mL, 22.969 mmol) in DCM (25 mL) cooled to 0ºC, was added N,O-Dimethylhydroxylamine hydrochloride [6638-79-5] (1.5 g, 24.557 mmol) and triethylamine [121-44-8] (9.6 mL, 68.876 mmol) and the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield intermediate **I-91** (1.6 g, 52%) as a yellow oil.

Synthesis of intermediate **I-92**



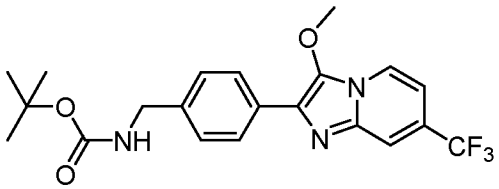
Iso-propyl magnesium chloride 2M solution in THF [1068-55-9] (4.9 mL, 9.8 mmol) was added to an ice-cooled solution on 4-iodobenzonitrile [3058-39-7] (1.9 g, 8.296 mmol) in anhydrous THF (17 mL). The solution was stirred at this temperature for 10 minutes and then cooled to -78 ºC. An ice-cooled solution of intermediate **I-91** (1.6 g, 12.017 mmol) in anhydrous THF (8 mL) was added dropwise and the reaction was stirred at -78 ºC for 1h. Then it was stirred at rt for 1h. The reaction mixture was treated with ammonium chloride solution and extracted with DCM. The organic phase was dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, 25 g, Heptane/EtOAc 100:0 to 60:40). The desired fractions were collected to yield intermediate **I-92** (920 mg, 63%) as a white solid.

Synthesis of intermediate **I-93**



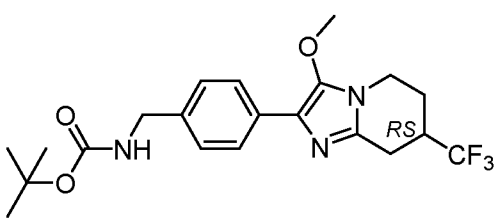
A sealed tube was charged with intermediate **I-92** (965 mg, 5.509 mmol), 2-amino-4-(trifluoromethyl)pyridine [106447-97-6] (2.7 g, 16.655 mmol), iodine [7553-56-2] (2.8 g, 11.032 mmol) and 1,2-dichloroethane (110 mL). The reaction mixture was stirred at 100 °C for 30 min. The mixture was diluted with an aqueous saturated sodium bisulfite solution and then extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give a red solid, that was purified by flash chromatography (silica, 80 g, ethyl acetate in heptane from 0/100 to 50/50). The desired fractions were collected and the solvents evaporated in vacuo to yield intermediate **I-93** (1.4 g, 61%) as an orange solid.

Synthesis of intermediate **I-94**



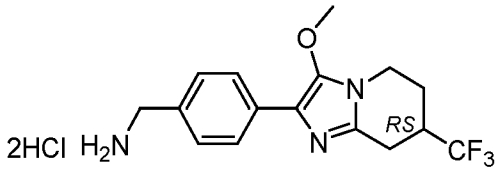
$NaBH_4$ [16940-66-2] (358 mg; 9.463 mmol) was added portionwise to a suspension of intermediate **I-93** (1.3 g; 3.155 mmol), Nickel (II) chloride hexahydrate [7791-20-0] (750 mg; 3.155 mmol) and di-tertbutyl dicarbonate [24424-99-5] (2.2 mL; 9.463 mmol) in MeOH (13 mL) and 1,4-dioxane (6 mL) in a round bottom flask under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. H_2O and 25 % aqueous ammonia were added, and the mixture was extracted with DCM. The combined organic layers were separated and dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark orange oil, that was purified by flash chromatography (silica 80 g, ethyl acetate in DCM from 0/100 to 10/90). The desired fractions were collected to yield intermediate **I-94** (834 mg, 61%) as light-yellow solid.

Synthesis of intermediate **I-95**



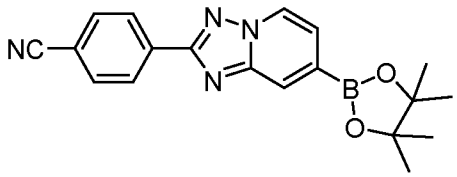
In a round bottom flask under nitrogen atmosphere Pd/C [7440-05-3] (300 mg, 0.282 mmol) was added to a solution of intermediate **I-94** (340 mg, 0.807 mmol) in methanol (12 mL) and ethyl acetate (3.2 mL) at 0 °C. The mixture was stirred under H_2 atmosphere [1333-74-0] at 50°C for 16 hours. The mixture was filtered through of pad of celite® and the solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica, 25g, EtOAc in Heptane 0/100 to 50/50) and the desired fractions were collected to yield intermediate **I-95** (53 mg, 15%) as a white solid.

Synthesis of intermediate **I-96**



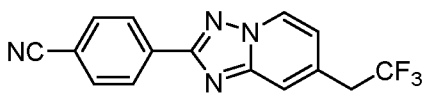
HCl 4M in 1,4-dioxane [7647-01-0] (330 µL, 1.312 mmol) was added to a solution of intermediate **I-95** (53 mg, 0.125 mmol) and VILL_scobos_124_1 (40 mg, 0.094) in dichloromethane (2 mL) in a round bottom flask at rt. The mixture was stirred at rt for 18 h. The mixture was concentrated in vacuo to yield intermediate **I-96** (88 mg, 99%) as yellow solid.

Synthesis of intermediate **I-97**



In a screw cap vial, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ [95464-05-4] (600 mg, 0.7355 mmol) was added to a solution of intermediate **I-12** (2 g, 6.68 mmol), bis(pinacolato)diboron [73183-34-3] (3.3 g, 13.13 mmol) and potassium acetate [127-08-2] (2.67 g, 27.2 mmol) in dry 1,4-dioxane (20 mL) while nitrogen was bubbling for 10 min. Then, the mixture was stirred at 80 °C for 16 h. The mixture was filtered through of a pad of celite®, rinsed with EtOAc. The solvent was concentrated in vacuo to yield intermediate **I-97** (2.43 g, 79 %) as a brown solid.

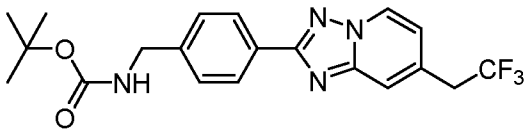
Synthesis of intermediate **I-98**



A solution of intermediate **I-97** (2.43g, 1.44 mmol) and 1-Iodo-2,2,2-trifluoroethane [353-83-3] (1.38 mL, 14 mmol) in 1,4-dioxane (52 ml) was added to a suspension of $Pd_2(dba)_3$ [51364-51-3] (64 mg, 0.07 mmol), XantPhos [161265-03-8] (162 mg, 0.28 mmol) and

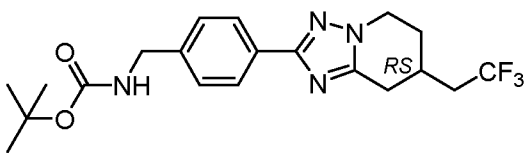
Cesium carbonate [534-17-8] (4.5 g, 14.0 mmol) under nitrogen at rt. The mixture was stirred at rt for 1 min, then water (2.5 mL) was added. The mixture was stirred at 80°C for 12 h. The mixture was cooled to rt. The mixture was diluted with water and extracted with AcOEt. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; AcOEt in heptane 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-98** (700 mg, 23%) as brown solid.

Synthesis of intermediate **I-99**



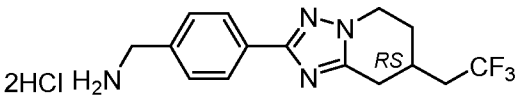
Sodium borohydride [16940-66-2] (264 mg, 6.9 mmol) was added portionwise to a suspension of intermediate **I-98** (700 mg, 2.3 mmol), Nickel(II) chloride hexahydrate [7791-20-0] (552 mg, 2.3 mmol) and Di-tertbutyl dicarbonate [24424-99-5] (1.6 mL, 6.9 mmol) in methanol (33 mL) and 1,4-dioxane (15 mL) in a round bottom flask at 0 °C. The reaction mixture was stirred at rt for 16 h. Water and aqueous NH_3 were added, and the mixture was extracted with DCM (x3). The crude product was purified by flash column chromatography (dry load on silica, 80 g; EtOAc in heptane (from 0/100 to 30/60)). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-99** (404 mg, 37 %) as a brown solid.

Synthesis of intermediate **I-100a**



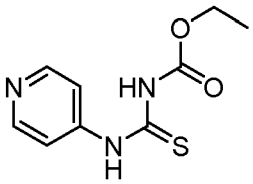
$Pd(OH)_2$ [12135-22-7] (41 mg, 0.058 mmol) was added to a solution of yield intermediate **I-99** (25 mg, 0.058 mmol) in MeOH (3 mL) and EtOAc (1 mL) in a round bottom flask under nitrogen atmosphere at 0 °C. The mixture was stirred under H_2 atmosphere [1333-74-0] at rt for 16 hours. The mixture was filtered through of pad of celite© and solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica 25g; EtOAc in Heptane from 0/100 to 80/20). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-100a** (155 mg, 43%) as a white solid.

Synthesis of intermediate **I-100b**



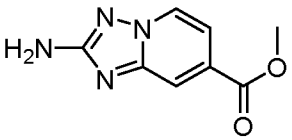
HCl 4M in 1,4-dioxane [7647-01-0] (0.56 mL, 2.26 mmol, 4M) was added to a solution of intermediate **I-100a** (155 mg, 0.38 mmol) in DCM (3 mL) in a round bottom flask at rt. The mixture was stirred at rt for 16h. The mixture was concentrated in vacuo to yield intermediate **I-100b** (152 mg, 95%) as a white solid.

Synthesis of intermediate **I-101**



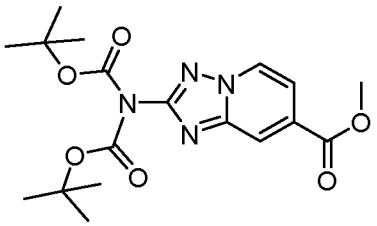
In a round bottom flask, ethoxycarbonyl isothiocyanate (9.300 mL, 78.851 mmol) was added to a solution **of** methyl 2-aminopyridine-4-carboxylate (10 g, 65.724 mmol) in 1,4-dioxane (70 mL) at rt. The mixture was stirred at rt for 16 hours. The solvent was removed in vacuo and the crude was triturated with diethyl ether, the solid was filtered and dried in vacuo to yield intermediate **I-101** (19.356 g, 99%) as a yellow solid.

Synthesis of intermediate **I-102**



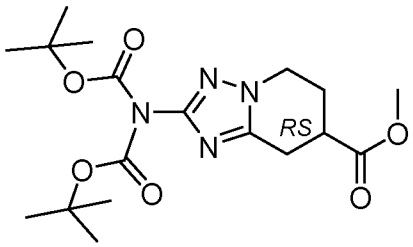
In a round bottom flask, a mixture of intermediate **I-101** (19.356 g, 68.322 mmol), hydroxylamine hydrochloride (27.461 g, 395.176 mmol), DIPEA (42.1 mL, 241.707 mmol) and methanol (180 mL) was stirred at 66 °C for 16 hours. The solvent was removed in vacuo and the residue was washed with water. The solid was collected by filtration and washed with diethyl ether. Then the product was dried under vacuo to yield intermediate **I-102** (7.857 g, 57%) as a grey solid.

Synthesis of intermediate **I-103**



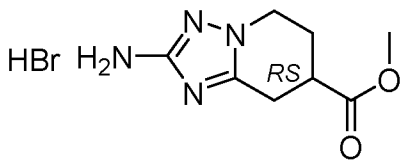
In a round bottom flask, di-tertbutyl dicarbonate [24424-99-5] (23.5 mL, 102.292 mmol) was added to a solution of intermediate **I-102** (7.857 g, 40.885 mmol), 4-(dimethylamino)pyridine (504 mg, 4.125 mmol) and triethylamine (11.4 mL, 81.791 mmol) in acetonitrile (100 mL) at rt. The mixture was stirred at 70 °C for 8 hours. The reaction mixture was diluted with H_2O and brine and extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give a dark oil. The crude product was purified by flash column chromatography (silica, 80 g; (AcOEt in heptane from 0/100 to 35/65)). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-103** (11.520 g, 71%) as a brown solid.

Synthesis of intermediate **I-104**



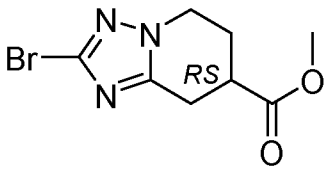
Pd/C [7440-05-3] (6.5 g, 6.1 mmol) was added to a solution of intermediate **I-103** (4 g, 10.1 mmol) in methanol (60 mL) and ethyl acetate (20 mL) in a round bottom flask under nitrogen atmosphere at 0 °C. The mixture was stirred under H_2 atmosphere [1333-74-0] at 50 °C for 16h. Pd/C [7440-05-3] (3.2 g, 3.0 mmol) was added to the reaction under nitrogen atmosphere at 0 °C. The mixture was stirred under H_2 atmosphere [1333-74-0] at 50 °C for 16 h. The reaction was filtered through pad of celite ®. Solvent was concentrated in vacuo to give a colorless oil. The crude product was purified by flash column chromatography (silica 120 g; EtOAc in heptane 0/100 to 60/40). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-104** (2.6 g, 61%) as a white solid.

Synthesis of intermediate **I-105**



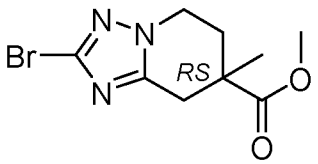
HBr [10035-10-6] (4.3 mL, 38 mmol) was added to a solution of yield intermediate **I-104** (5.0 g, 12.6 mmol) in dichloromethane (38 mL) in a round bottom flask at rt. The mixture was stirred at rt for 16 h. HBr [10035-10-6] (4.3 mL, 38 mmol) was added to the reaction and the mixture was stirred at rt for 2 h. The mixture was concentrated in vacuo to yield intermediate **I-105** (3.642 g, 99%) as a white solid.

Synthesis of intermediate **I-106**



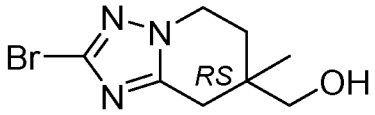
In a round bottom flask, hydrobromic acid [10035-10-6] (9.100 mL, 50.1 mmol) was added to a stirred suspension of intermediate **I-105** (3.6 g, 12.3 mmol) and acetic acid [64-19-7] (11 mL, 192.1 mmol) at 0 ºC. Then sodium nitrite [7632-00-0] (1.0 g, 14.5 mmol) was dissolved in water (19 mL) and added dropwise at 0 ºC. The reaction mixture was stirred at 0 ºC for 2h. Then Copper (I) Bromide [7787-70-4] (448 mg, 3.1 mmol) was added at 0 ºC and the mixture was heated at 90 ºC for 16 h. The reaction was cooled, and methanol (50 mL) was added at rt. The mixture was stirred at 65 ºC for 16h. The reaction mixture was cooled, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with DCM (x3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield intermediate **I-106** as a yellowish oil (2.33 g, 69%).

Synthesis of intermediate **I-107**



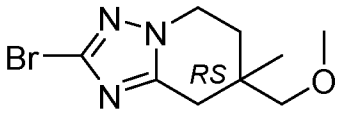
In a round bottom flask, LiHDMS [4039-32-1] (7.7 mL, 7.7 mmol) was added at -78 ºC under N_2 atmosphere to a solution of intermediate **I-106** (1 g, 3.845 mmol) in anhydrous THF (50 mL). The mixture was stirred at -78 ºC for 15 min and then was stirred at 0 ºC for 15 min. After, Iodomethane (0.6 mL, 9.638 mmol) was added at -78 ºC and the mixture was stirred at rt. The mixture was diluted with DCM and excess reactants are consumed by the addition of a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine and concentrated in vacuo to yield intermediate **I-107** as a pale-yellow solid (1.16 mg, 99.1 %).

Synthesis of intermediate **I-108**



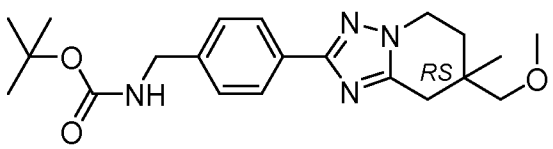
$LiBH_4$ [16949-15-8] (131 mg, 5.713 mmol) was added to a solution of intermediate **I-107** (1.16 g, 3.809 mmol) in dry THF (60 mL) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM and excess reactants are consumed by the addition of a saturated aqueous solution of NH_4Cl. The crude product was purified by flash column chromatography (silica 20 g; EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-108** as a white solid (345 mg, yield: 36.4 %).

Synthesis of intermediate **I-109**



Sodium hydride [7646-69-7] (59 mg, 1.475 mmol) was added to a solution of intermediate **I-108** (200 mg, 0.813 mmol) in DMF (10 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min followed by the addition of iodomethane [74-88-4] (76 uL, 1.221 mmol). The reaction mixture was stirred at room temperature for 16 hours. Sodium hydride [7646-69-7] (33 mg, 0.825 mmol) and iodomethane [74-88-4] (25 uL, 0.402 mmol) were added to the mixture at 0 °C. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with DCM and excess reactants are consumed by the addition of a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine and concentrated in vacuo to yield intermediate **I-109** as a yellow solid (212 mg, yield: 99.3 %).

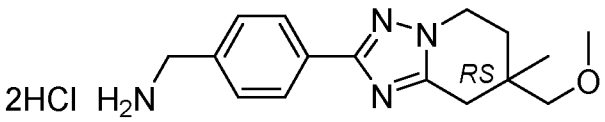
Synthesis of intermediate **I-110**



In a glass pressure tube, tert-butyl N-{[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}carbamate [330794-35-9] (301 mg, 0.903 mmol), Cs_2CO_3 [534-17-8] (584 mg, 1.792 mmol) and Pd(dppf)Cl2 [95464-05-4] (100 mg, 0.122 mmol) were added to a solution of intermediate **I-109** (212 mg, 0.815 mmol) in dioxane (6.4 mL) and water (2.6 mL)

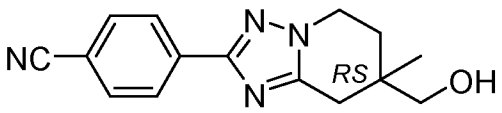
while bubbling with N_2. The reaction mixture was stirred at 90 °C for 16 hours. Water was added and then the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica 25 g; DCM:MeOH 9:1 in DCM 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-110** as a brown wax (277 mg, yield: 87.1%).

Synthesis of intermediate **I-111**



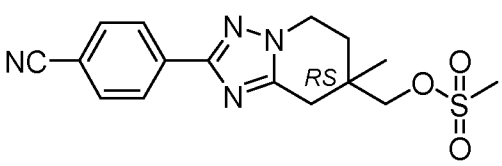
A 4M solution of HCl in 1,4-dioxane [7647-01-0] (1.1 mL, 4.4 mmol) was added to a stirred solution of intermediate **I-110** (277 mg, 0.710 mmol) in DCM (5 mL) in a round bottom flask at room temperature. The reaction mixture was stirred at room temperature for 5 min. A 4M solution of HCl in 1,4-dioxane [7647-01-0] (1.1 mL, 4.4 mmol) was added to the reaction. The mixture was stirred at room temperature for 6 hours. The crude product was concentrated in vacuo to yield intermediate **I-111** as a brown solid (255 mg, yield: 99.0 %).

Synthesis of intermediate **I-112**



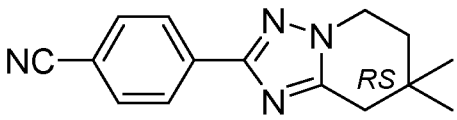
In a glass pressure tube, 4-cyanophenylboronic acid [126747-14-6] (525 mg, 3.57 mmol), Cs_2CO_3 [534-17-8] (2.30 g, 7.06 mmol) and Pd(dppf)Cl2 [95464-05-4] (395 mg, 0.48 mmol) were added to a solution of intermediate **I-108** (790 mg, 3.42 mmol) in 1,4-dioxane (20 mL) and water (8 mL) while bubbling with N_2. The reaction mixture was stirred at 90 °C for 16 hours. Water was added and then the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica 25 g; EtOAc in DCM 0/100 to 80/20). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-112** as a pale brown solid (490 mg, 55 %).

Synthesis of intermediate **I-113**



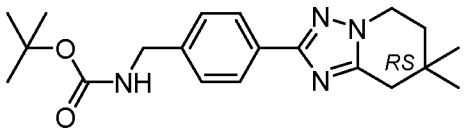
Methanesulfonyl chloride [124-63-0] (0.18 mL, 2.33 mmol) was added dropwise to a stirred solution of intermediate **I-112** (485 mg, 1.81 mmol), triethylamine [121-44-8] (0.37 mL, 0.280 mmol) and DMAP [1122-58-3] (12 mg, 0.10 mmol) in DCM (25 mL). The mixture was stirred at room temperature for 16 hours. The mixture was diluted with water and extracted with DCM (x3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield intermediate **I-113** as a pale brown solid (562 mg, 89 %).

Synthesis of intermediate **I-114**



Zinc powder [7440-66-6] (526 mg, 8.04 mmol) and sodium iodide [7681-82-5] (483 mg, 3.22 mmol) were added to a solution of intermediate **I-113** (560 mg, 1.62 mmol) in DMF (15 mL). The reaction mixture was stirred at 110 ºC for 18 hours. Zinc powder [7440-66-6] (5 eq., 526 mg, 8.04 mmol) and sodium iodide [7681-82-5] (2 eq., 483 mg, 3.22 mmol) were added to the reaction mixture and was stirred at 110 ºC for 6 hours. Zinc powder [7440-66-6] (5 eq., 526 mg, 8.04 mmol) and sodium iodide [7681-82-5] (2 eq., 483 mg, 3.22 mmol) were added to the reaction mixture and was stirred at 110 ºC for 21 hours. The reaction mixture was filtered, and the filtrate was diluted with water and extracted with EtOAc (x 3). The combined organic layers were concentrated in vacuo to yield intermediate **I-114** (375 mg, 83 %) as a yellow solid.

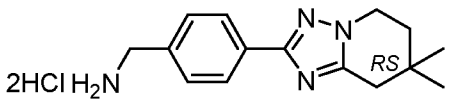
Synthesis of intermediate **I-115**



In a round bottom flask, sodium borohydride [16940-66-2] (167 mg, 4.41 mmol) was added portionwise to a suspension of intermediate **I-114** (375 mg, 1.49 mmol), Nickel (II) chloride hexahydrate [7791-20-0] (267 mg, 1.12 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.51 mL, 2.22 mmol) in dry methanol (20 mL) and dioxane (10 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 18 hours. Water and aqueous NH_3 were added and the mixture was stirred for 10 min. The mixture was filtered through of pad of celite® and washed with MeOH and was concentrated in vacuo the MeOH. Then, the mixture was extracted with DCM (x 3). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvents were concentrated in vacuo. The crude product was purified by flash column

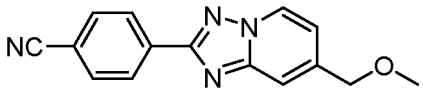
chromatography (silica, 25 g; EtOAc in DCM 0/100 to 50/50). The desired fractions were collected and the solvents evaporated in vacuo to yield intermediate **I-115** as a white solid (291 mg, 53 %).

Synthesis of intermediate **I-116**



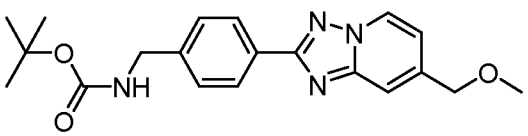
To a stirred solution of intermediate **I-115** (194 mg, 0.54 mmol) in DCM (2 ml), a 4 M solution of HCl in 1,4-dioxane [7647-01-0] (1.1 ml, 4.4 mmol), was added at room temperature and the resulting mixture was stirred for 16 hours at room temperature. The solvents were removed under high vacuo to yield intermediate **I-116** as a white solid (179 mg, 99 %).

Synthesis of intermediate **I-117**



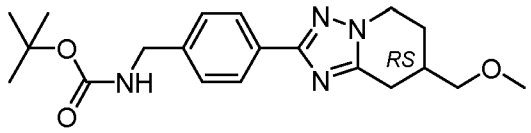
In a screw cap vial, Cs_2CO_3 [534-17-8] (3.8 mg, 11.66 mmol) was added to a solution of intermediate **I-12** (876 mg, 2.92 mmol) and potassium methoxymethyltrifluoroborate [910251-11-5] (946 mg, 5.9 mmol) in 1,4-dioxane (7.5 mL) and water (1 mL) at rt while bubbling N_2. Then, the mixture was bubbled with N_2 for 10 min. RuPhos Pd G3 [1445085-77-7] (245 mg, 0.29 mmol) and RuPhos [787618-22-8] (140 mg, 0.3 mmol) were added at rt and the mixture was bubbled with N_2 for 10 min. Then, the mixture was stirred at 100 °C for 16 h. The reaction was filtered through a pad of celite® and the solvent was evaporated in vacuo. The crude was purified by flash column chromatography [silica 80g; AcOEt in heptane from 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo. The product was repurified by flash column chromatography [silica 2x25g; AcOEt in DCM from 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-117** as a white solid (324 mg, 41%).

Synthesis of intermediate **I-118**



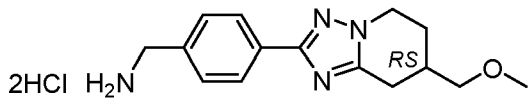
Sodium borohydride [16940-66-2] (140 mg, 3.7 mmol) was added portionwise to a suspension of intermediate **I-117** (324 g, 1.22 mmol), nickel(II) chloride hexahydrate [7791-20-0] (350 mg, 1.47 mmol) and di-tertbutyl dicarbonate [24424-99-5] (0.85 mL, 2.87 mmol) in methanol (20 mL) and dioxane (10 mL) in a round bottom flask at 0 °C. The reaction mixture was stirred at rt for 16 h. Water and 3 ml of aqueous NH_3 were added and the mixture was extracted with DCM (x3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica 25g; AcOEt in heptane from 0/100 to 70/30). The desired fractions were collected and concentrated in vacuo to afford intermediate **I-118** as a brown solid (336 mg, yield: 73.6 %).

Synthesis of intermediate **I-119**



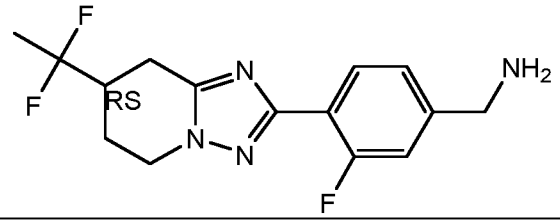
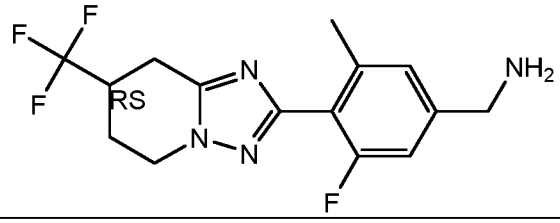
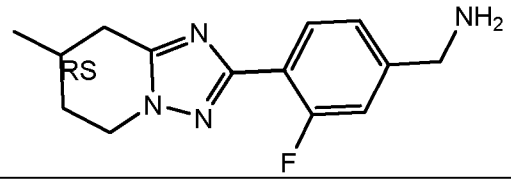
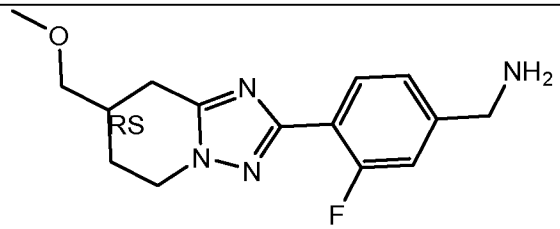
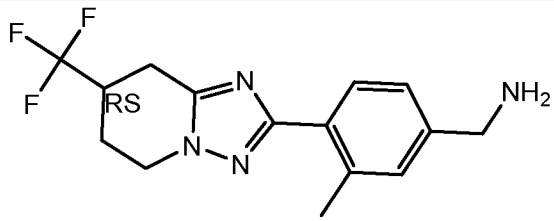
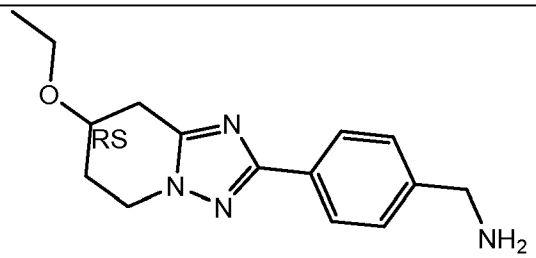
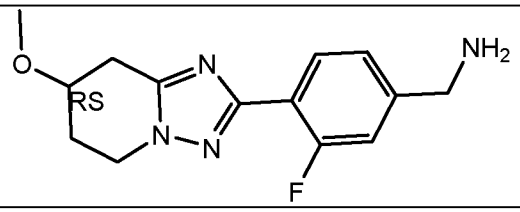
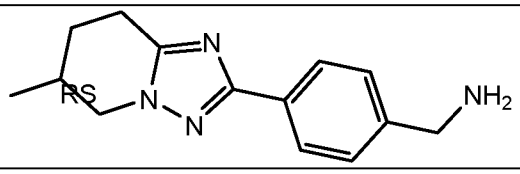
$Pd(OH)_2$ [12135-22-7] (1.0 eq., 119 mg, 0.847 mmol) was added to a solution of intermediate **I-118** (311 mg, 0.844 mmol) in methanol (11.8 ml) and ethyl acetate (6.2 ml) in a round bottom flask under nitrogen atmosphere at 0 °C. The mixture was stirred under H_2 atmosphere at room temperature for 18 hours. The mixture was filtered through of pad of celite and solvents were concentrated in vacuo. The crude product was purified by flash column chromatography (silica 25g; EtOAc in DCM from 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield intermediate **I-119** as a white solid (289 mg, 91%).

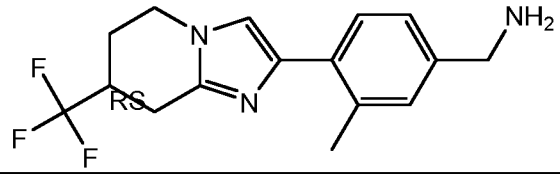
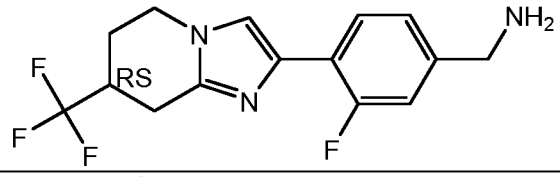
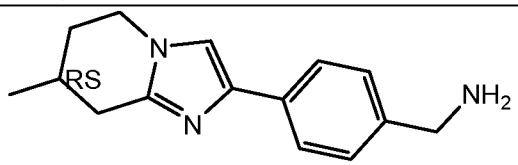
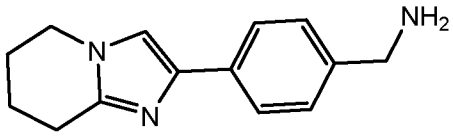
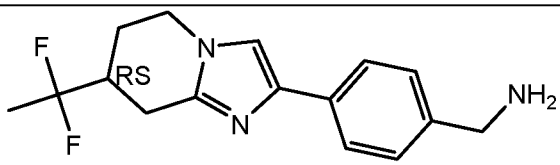
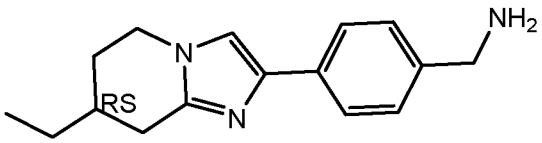
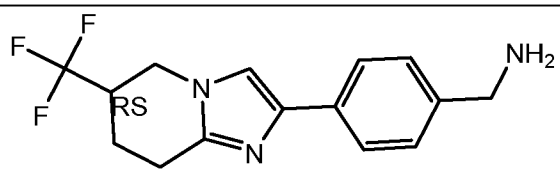
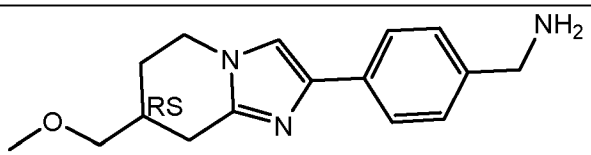
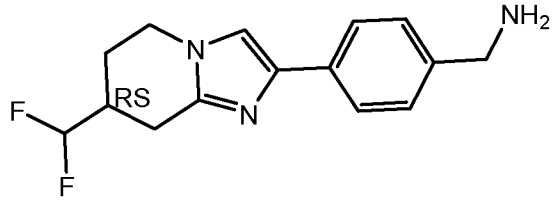
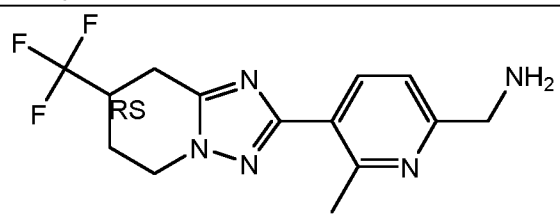
Synthesis of intermediate **I-120**

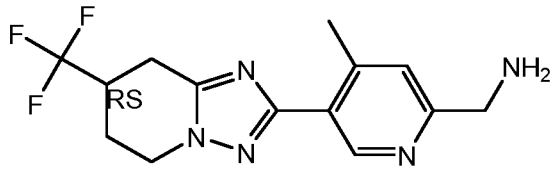
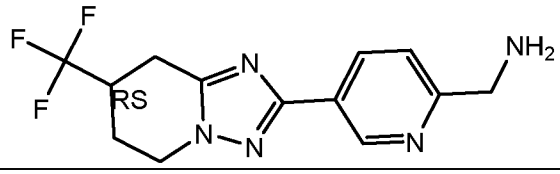
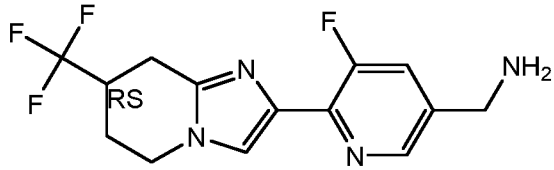
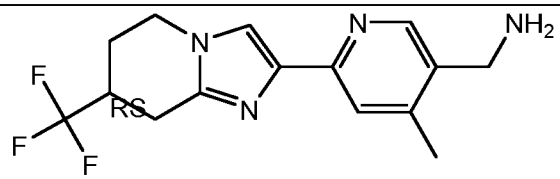
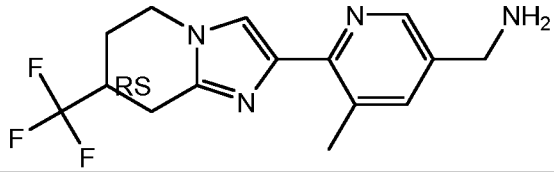
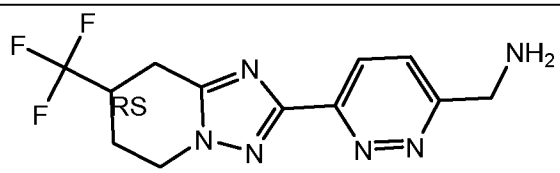
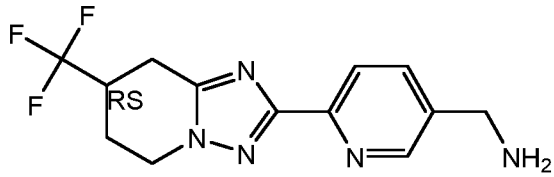
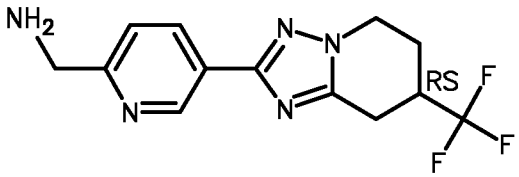
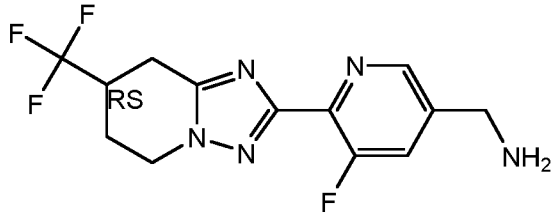


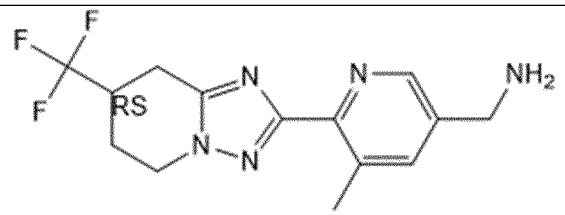
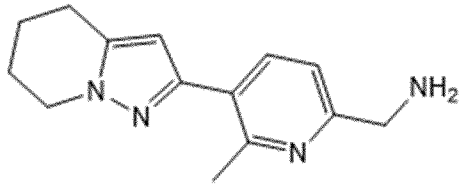
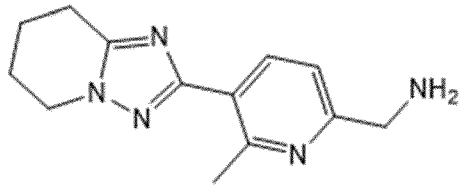
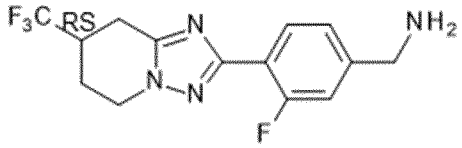
HCl in Dioxane [7647-01-0] (1.16 mL, 4.639 mmol) was added to a solution of intermediate **I-119** (288 mg, 0.773 mmol) in dichloromethane (6 mL) in a round bottom flask at rt. The mixture was stirred at rt for 4 h. The mixture was concentrated in vacuo to yield intermediate **I-120** as a white solid (251 mg, yield: 93%).

Intermediates included in next table were synthesized following similar methods as described previously.

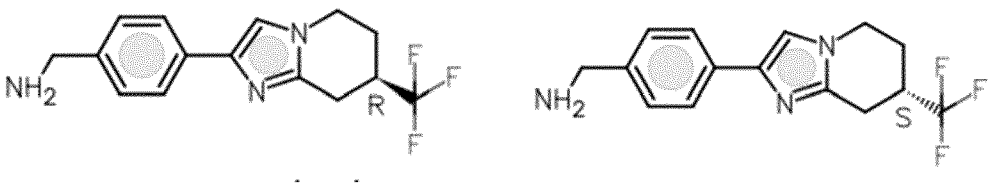
Structure	Intermediate Number
	**I-121**
	**I-122**
	**I-123**
	**I-124**
	**I-125**
	**I-126**
	**I-127**
	**I-128**

Structure	Intermediate Number
	**I-129**
	**I-130**
	**I-131**
	**I-132**
	**I-133**
	**I-134**
	**I-135**
	**I-136**
	**I-137**
	**I-138**

Structure	Intermediate Number
	**I-139**
	**I-140**
	**I-141**
	**I-142**
	**I-143**
	**I-144**
	**I-145**
	**I-146**
	**I-147**

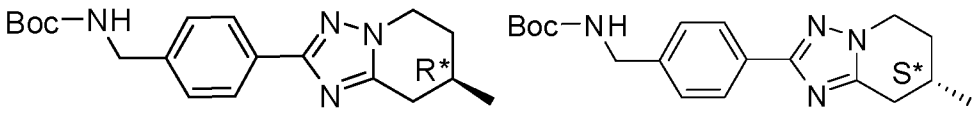
Structure	Intermediate Number
	**I-148**
	**I-149**
	**I-150**
	**I-150b**

Synthesis of intermediates **I-151a and I-151b**



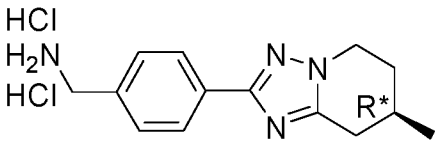
Intermediates **I-151a** and **I-151b** were prepared according to an analogous procedure to the one used for the synthesis of intermediates **I-6a** and **I-6b** using intermediate **I-10** (2.2 g, 7.4 mmol) as starting material. Intermediate **I-151a** (508 mg, 998% purity, 22.9%) and intermediate **I-151b** (415 mg, 92% purity, 17.4%) were obtained as a white solid.

Synthesis of intermediates **I-152a and I-152b**



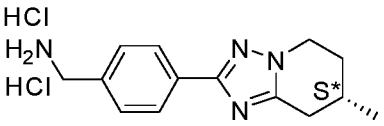
Intermediate **I-14** (394 g, 1150.55 mmol) was purified by chiral SFC system using an Phenomenex Lux Cellulose-SZ 50mm long x30mm I.D. 3 µm particle size, on gradient mode at 100ml/min from CO_2 /Methanol from 10/90 to 50/50 + 20mM NH_3, at 35 °C, BPR 2200 psi. Acquisition frequency was set to 220 nm for the DAD detector. This resulted to afford intermediate **I-152a** (144 g, 36.55%, separated two times by SFC) as a white solid and intermediate **I-152b** (161 g, 40.86%) as a white solid.

Synthesis of intermediates **I-153**



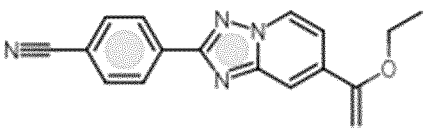
Into a 5 L 4-necked round-bottom flask was added intermediate **I-152a** (144 g) and DCM (3.2 L) at room temperature. To the above mixture was added HCl (gas) in 1,4-dioxane (705 mL, 4.0 M) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with DCM (2x1 L). This resulted in **I-153** (142.4 g, 96.08%) as a light yellow solid.

Synthesis of intermediates **I-154**



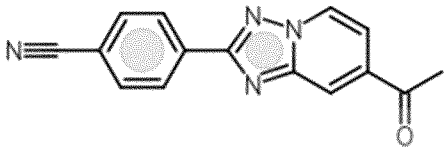
Intermediate **I-154** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-153** using intermediate **I-152b** (161 g, 470.151 mmol) as starting material. (142.4 g, 96.08%) as a light yellow solid.

Synthesis of intermediate **I-155**



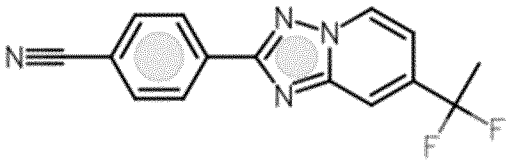
Intermediate **I-155** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-76** using intermediate **I-12** (4.5 g, 15 mmol) as starting material. (4.2 g, 95%) as a light brown solid.

Synthesis of intermediate **I-156**



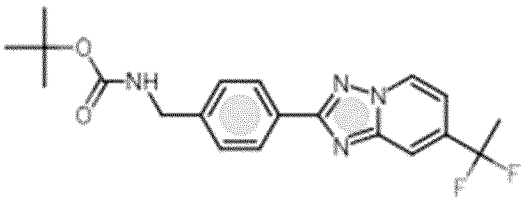
An aqueous solution 6M of HCl (82 mL, 492 mmol) was added to a solution of **I-155** (4.193 g, 14.443 mmol) in Dioxane (15 mL) in a round bottom flask at rt. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water, basified to pH 11 with an aqueous NaOH 6 N solution and extracted with DCM (x3). The combined organic layers were separated, dried (MgSO4), filtered and the solvents evaporated under vacuo to yield intermediate **I-156** (3.665 g, 92%) as a brown solid.

Synthesis of intermediate **I-157**



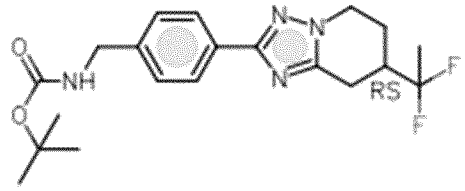
In a round bottom flask, DAST [38078-09-0] (1.755 mL, 13.280 mmol) was added dropwise to a solution of intermediate **I-156** (1.161 g, 4.427 mmol) in dichloroethane dry (33 mL) at 0 ºC under nitrogen atmosphere. The mixture reaction was stirred at 45 ºC for 120 hours. The mixture was diluted with NaHCO3 aq. sat. at 0 ºC and extracted with DCM. The combined organic layers were washed with brine and dried over MgSO4, filtered and concentrated. The crude product was purified by flash column chromatography (dry on load, silica 80 g; EtOAc in heptane 0/100 to 0/100). The desired fractions were collected and concentrated to afford intermediate **I-157** (337 mg, 26 %) as a brown solid.

Synthesis of intermediate **I-158**



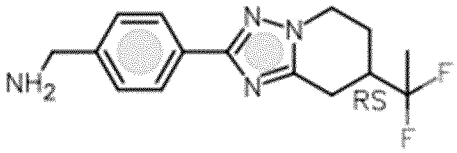
Intermediate **I-158** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-4** using intermediate **I-157** (922 mg, 3.2 mmol) as starting material. (870 mg, 67.7%) as a white solid.

Synthesis of intermediate **I-159**



Intermediate **I-159** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-5** using intermediate **I-158** (805 mg, 2 mmol) as starting material. (651 mg, 83.4%) as a white solid.

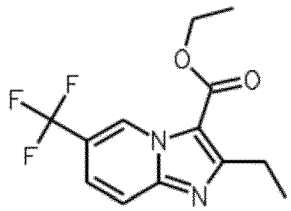
Synthesis of intermediate **I-160**



Intermediate **I-160** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **I-6** using intermediate **I-159** (651 mg, 1.7 mmol) as starting material. (614 mg, quantitative) as a white solid.

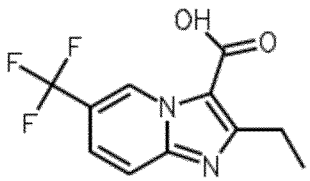
SYNTHESIS OF INTERMEDIATES II

Intermediate **II-18**



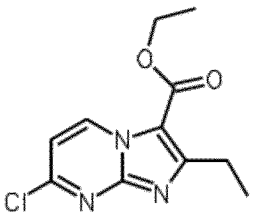
Intermediate **II-18** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a,** using 2-amino-5-(trifluoromethyl)pyridine [74784-70-6] (3 g, 18.5 mmol) as starting material. **II-18** was obtained as a orange solid (1.7 g, 28%, 88% purity).

Intermediate **II-19** – LiCl salt



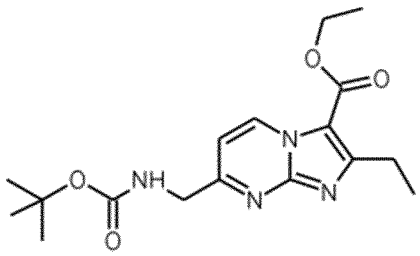
Lithium hydroxide monohydrate [1310-66-3] (77 mg, 1.8 mmol) was added to a stirred solution of Intermediate **II-18** (190mg, 0.6 mmol), in a mixture of ethanol and water (1:1) 10 mL at room temperature. The reaction mixture was stirred at room temperature or at 50 °C for 16 h and then neutralized by a solution of HCl (1M, aq.). The solvents were evaporated in vacuo to yield intermediate **II-19** (189 mg, quant.).

Intermediate **II-20**



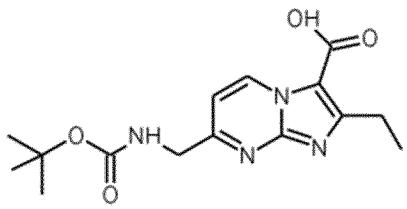
Intermediate **II-20** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a,** using 2-amino-4-chloropyrimidine [3993-78-0]. (2 g, 15.4 mmol) as starting material. Intermediate **II-20** was obtained as a yellow solid (1.8 g, 44.7%).

Intermediate **II-21**



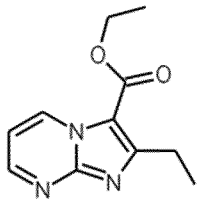
Intermediate **II-21** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-12b**, using intermediate **II-20** (300 mg, 1.2 mmol) as starting material. Intermediate **I-21** was obtained as a yellow solid (90 mg, 85% purity, 18.6 %).

Intermediate **II-22** - NaCl salt



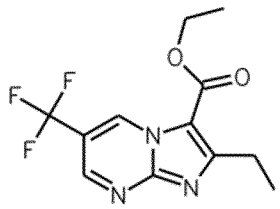
Intermediate **II-22** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using **II-21** (120 mg, 0.3 mmol) as starting material. Intermediate **I-22** was obtained as a yellow solid (120 mg, 90% purity, 97.4%).

Intermediate **II-23**



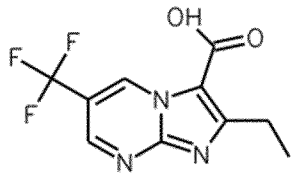
Intermediate **II-23** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a,** using 2-aminopyrimidine [109-12-6]. (5 g, 52.6 mmol) as starting material. Intermediate **II-23** was obtained as an orange solid (8.7 g, 74.5%).

Intermediate **II-24**



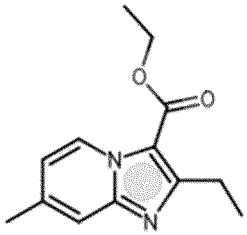
Intermediate **II-24** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a,** using 5-(Trifluoromethyl) pyrimidin-2-amine [69034-08-8] (1.2 g, 7.4 mmol) as starting material. Intermediate **II-24** was obtained as a yellow solid (825 mg, 90% purity, 35.1%).

Intermediate **II-25**



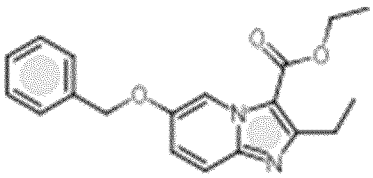
In a round bottom flask, concentrated hydrochloric acid [7647-01-0] (5 mL) was added to Intermediate **II-24** (250 mg, 0.870 mmol) and the reaction mixture was stirred at 85°C for 30 h. Additional concentrated hydrochloric acid [7647-01-0] (2 mL) was added to the reaction mixture and it was stirred at 90°C for 46 h. The solvent was concentrated in vacuo to yield intermediate **II-25** (226 mg, yield: 70%) as a brown solid.

Synthesis of intermediate **II-26**



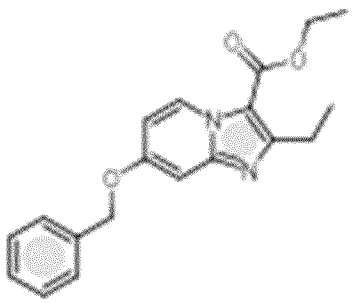
Intermediate **II-26** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 2-amino-4-picoline [695-34-1] (3 g, 27.7 mmol) as starting material. **II-26** was obtained as an orange solid (4.7 g, 71.9%).

Synthesis of intermediate **II-27**



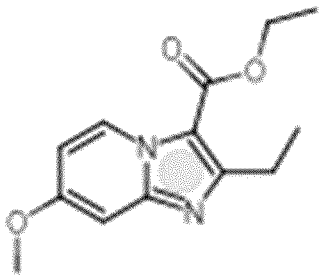
Intermediate **II-27** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 5-(benzyloxy)pyridin-2-amine [96166-00-6] (1 g, 5 mmol) as starting material. Intermediate **II-27** was obtained as an orange solid (1.1 g, 62.1%).

Synthesis of intermediate **II-28**



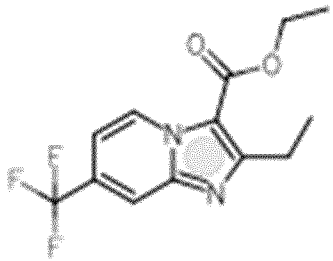
Intermediate **II-28** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 4-(benzyloxy)pyridin-2-amine [85333-26-2] (0.8 g, 4.2 mmol) as starting material. Intermediate **II-28** was obtained as a yellow solid (1.1 g, 84.3%).

Synthesis of intermediate **II-29**



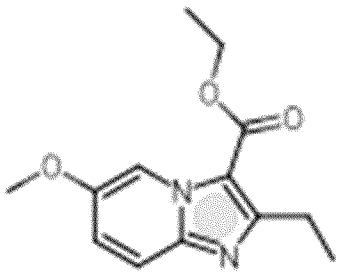
Intermediate **II-29** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 2-amino-4-methoxypyridine [10201-73-7] (5 g, 40.3 mmol) as starting material (6.7 g, 67%).

Synthesis of intermediate **II-30**



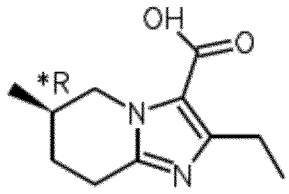
Intermediate **II-**30 was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 4-(trifluoromethyl)-2-pyridinylamine [106447-97-6] (5 g, 30.8 mmol) as starting material. **II-30** was obtained as a yellow solid (3.61 g, 56.8%).

Synthesis of intermediate **II-31**



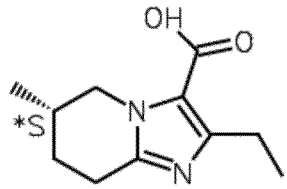
Intermediate **II-31** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 2-amino-5-methoxypyridine [10167-97-2] (2 g, 16.1 mmol) as starting material. **II-31** was obtained as an orange solid (2.3 g, 56.4%).

Synthesis of intermediate **II-32**



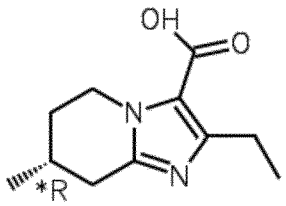
Intermediate **II-32** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-**17a using intermediate **II-40 (R*)** (142 mg, 0.6 mmol) as starting material. Intermediate **II-32** was obtained as a white oil (126 mg, quant.).

Synthesis of intermediate **II-33**



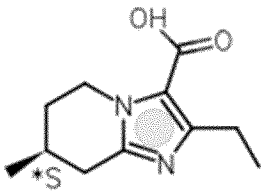
Intermediate **II-33** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a,** using intermediate **II-39 (S*)** (142 mg, 0.6 mmol) as starting material. Intermediate **II-33** was obtained as a white oil (126 mg, quant.).

Synthesis of intermediate **II-34** - LiCl salt



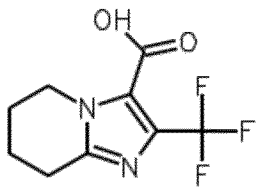
Intermediate **II-34** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a,** using intermediate **II-44 (R*)** (124 mg, 0.5 mmol) as starting material. Intermediate **II-34** was obtained as a pale yellow solid (131 mg, 98.8%).

Synthesis of intermediate **II-35** - LiCl salt



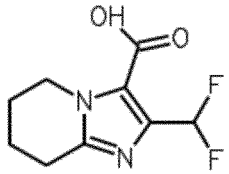
Intermediate **II-35** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a,** using intermediate **II-45 (S*)** (121 mg, 0.5 mmol) as starting material. Intermediate **II-35** was obtained as a pale yellow solid (127 mg, 99%).

Synthesis of intermediate **II-36** - LiCl salt



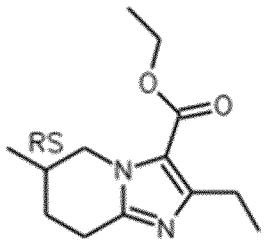
Intermediate **II-36** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a,** using intermediate **II-48** (160 mg, 0.6 mmol) as starting material. **II-36** was obtained as a white solid (215 mg, 96.5%).

Synthesis of intermediate **II-37** - LiCl salt



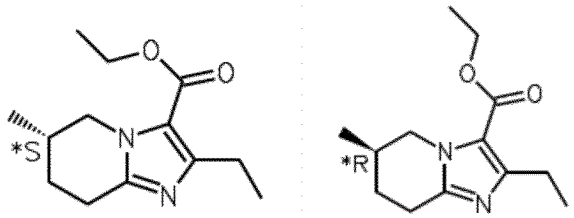
Intermediate **II-37** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a,** using intermediate **II-98** (130 mg, 0.5 mmol) as starting material. **I-37** was obtained as a white solid (144 mg, 99.4%).

Synthesis of intermediate **II-38**



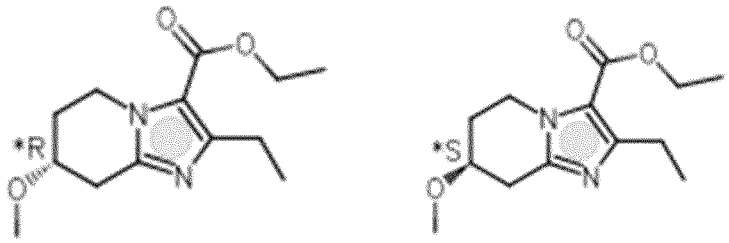
Intermediate **II-38** (939 mg, 91%, pale yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-7g** (1 g, 4.3 mmol) as starting material.

Synthesis of intermediates **II-39 (S*)** and **II-40 (R*)**



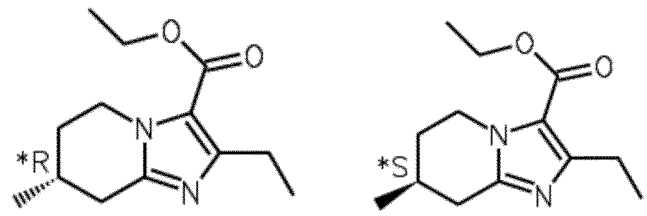
A batch of intermediates **II-38** (939 mg, 4 mmol) was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux Cellulose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 100ml/min of CO2 (65%) - Isopropanol (35%) + 0.1% DEA, at 30 ºC, BPR 150 Bar. Acquisition frequency was set to 252 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under vacuo to yield intermediate **II-39 (S*)** (243 mg, 25.6%) and intermediate **II-40 (R*)** (270 mg, 28.5%) as pale yellow oils.

Synthesis of intermediates **II-41 (R*)** and **II-42 (S*)**



Intermediates **II-41 (R*)** and **II-42 (S*)** were prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-39 (S*)** and **II-40 (R*)** using intermediate **II-50** (512 mg, 2 mmol) as starting material. It were obtained intermediate **II-41 (R*)** (164 mg, 31.7%) and intermediate **II-42 (S*)** (164 mg, 31.7%) as white solids.

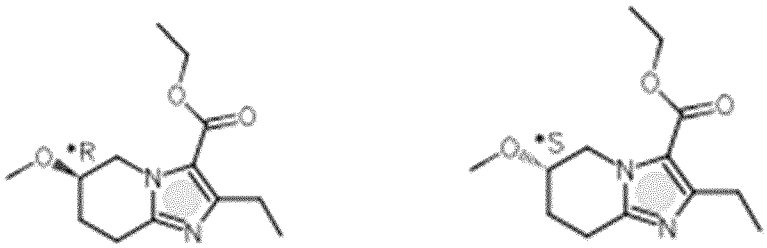
Synthesis of intermediates **II-43, II-44 (R*)** and **II-45 (S*)**



Platinum(IV) oxide [1314-15-4] (177 mg, 0.8 mmol) was added to a stirred solution of intermediate **II-7e** (1 g, 4.3 mmol) in methanol (9.5 mL) under N_2. Then a concentrated HCl aqueous solution (2.5 µL was added, and the resulting suspension was stirred at 50 ºC under

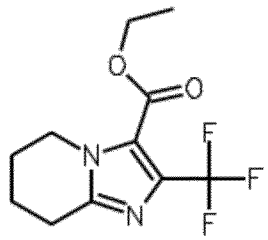
H_2 atmosphere for 16 h. The reaction was filtered through a pad of celite® and the filtrate was evaporated in vacuo to yield intermediate **II-43** as light beige solid (1 g, 96%).
Intermediate **II-43** was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux Cellulose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 100ml/min of CO_2 (65%) - Isopropanol (10%) + 0.1% DEA, at 30ºC, BPR 150 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under vacuo to yield intermediate **II-44 (R*)** (372 mg, 35.8%) and intermediate **II-45 (S*)** (364 mg, 35.1%) as light yellow solids.

Synthesis of intermediate **II-46 (R*)** and **II-47 (S*)**



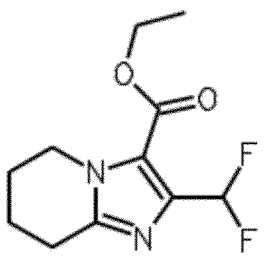
Intermediates **II-46 (R*)** (161 mg, 31.4%) and **II-47 (S*)** (103 mg, 20.1%) were prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-31** (500 mg, 2 mmol) as starting material.

Synthesis of intermediate **II-48**



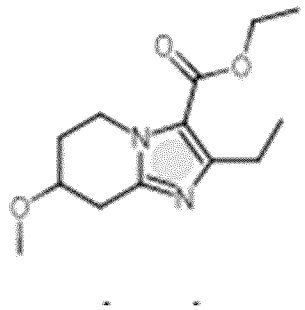
Intermediate **II-48** (845 mg, 63.3%, colourless oil) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-5a** (1.3 g, 5.4 mmol) as starting material.

Synthesis of intermediate **II-49**



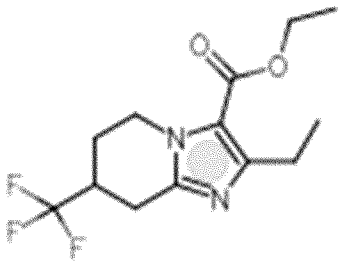
Intermediate **II-49** (670 mg, 43.5%, colourless oil) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-5b** (1.5 g, 5.8 mmol) as starting material.

Synthesis of intermediate **II-50**



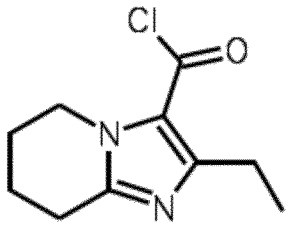
Intermediate **II-50** (512 mg, 75%, colourless oil) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-29** (665 mg, 2.7 mmol) as starting material.

Synthesis of intermediate **II-51**



Intermediate **II-51** (698 mg, 73.4%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16** from intermediate **II-30** (938 mg, 3.3 mmol) as starting material.

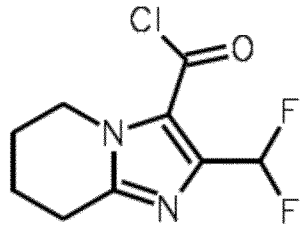
Synthesis of intermediate **II-52**



In a round bottom flask, thionyl chloride (120 mL, 1.645 mol) was added dropwise to intermediate **II-17a** (8 g, 41.188 mmol) at room temperature. The reaction mixture was stirred

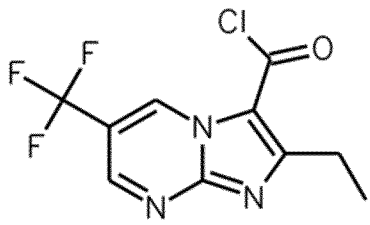
at 60 °C for 2 hours. Toluene was added and the mixture was concentrated in vacuo to yield intermediate **II-52** (8.8 g, 99.5%) as a yellow solid.

Synthesis of intermediate **II-53**



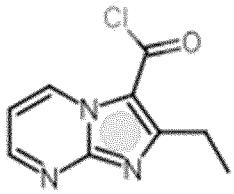
Intermediate **II-53** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-52** from intermediate **II-37** (144 mg, 0.5 mmol) as starting material. Intermediate **II-53** (154 mg, 99.8%) was obtained as a light orange solid.

Synthesis of intermediate **II-54**



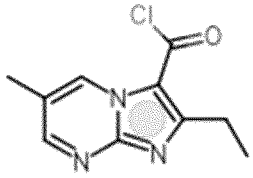
Intermediate **II-54** (242 mg, 70% purity, 100%, dark brown solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-52** from intermediate **II-25** (226 mg, 0.6 mmol) as starting material. Intermediate **II-54** (242 mg, 70% purity, 100%) was obtained as a dark brown solid

Synthesis of intermediate **II-55**



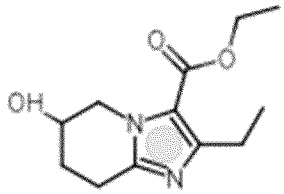
Intermediate **II-55**) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-52** from intermediate **II-83** (10 g, 0.6 mmol) as starting material. Intermediate **II-55** (11.5 g, 95% purity, 100%) was obtained as a dark brown solid

Synthesis of intermediate **II-56**



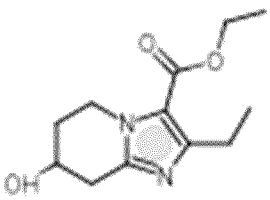
Intermediate **II-56** (470 mg, 89.5%, light orange solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-52** from intermediate **II-3a** (472 mg, 2.3 mmol) as starting material. Intermediate **II-56** (470 mg, 89.5%) was obtained as a light orange solid.

Synthesis of intermediate **II-57**



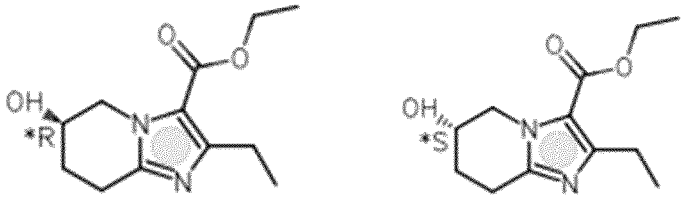
In a vial, a mixture dry EtOH/THF (1:1) (30 mL) was added to intermediate **II-7h** (1.068 g, 3.292 mmol) and Pd/C 10% (700.8 mg, 0.7 mmol). The vial was placed in a steel vessel, purged 3 times with hydrogen gas and pressurised with 10 bar hydrogen. The mixture was stirred at 30 °C for 19 h and under 20 bar hydrogen at 30 °C for 4 h. The reaction mixture was filtered and the solvent evaporated. The crude material was purified by flash chromatography (silica, MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents removed in vacuo to yield intermediate **II-57** (340 mg, 41.2 %) as an off-white solid.

Synthesis of intermediate **II-58**



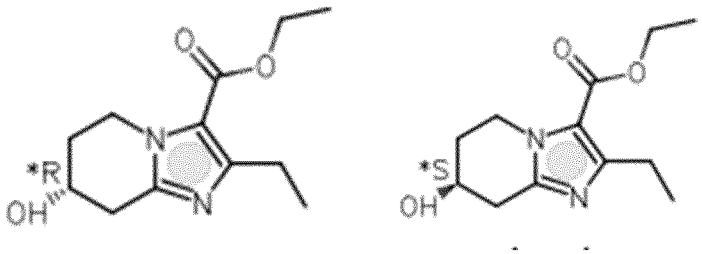
Intermediate **II-58** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-57** using intermediate **II-28** (1 g, 3.2 mmol) as starting material. Intermediate **II-58** (540 mg, 69.4%) was obtained as a pale yellow solid.

Synthesis of intermediate **II-59 (R*) and II-60 (S*)**



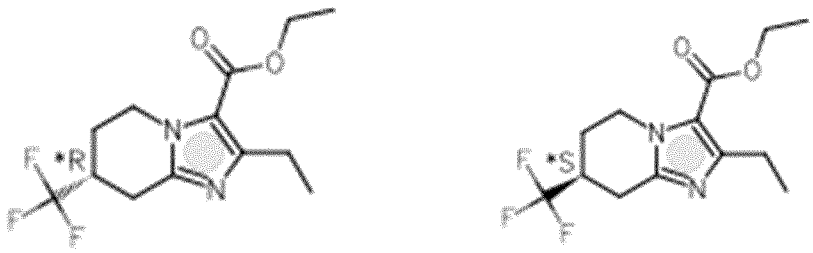
Intermediate **II-57** (200 mg, 0.8 mmol) was separated by SFC (Jasco SFC prep system using an amylose-1 column, 250*30mm, 5µm, isocratic mode 100 ml/min of CO_2 (20%) / MeOH (80%) / DEA (0.1%) at 30 °C 150 bars). Acquisition frequency was set to 220 nm for the DAD detector. Each fraction was diluted with an aqueous saturated $NaHCO_3$ solution and then extracted with DCM (x2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield intermediate **II-59 (R*)** (72 mg, 35.6%) and intermediate **II-60 (S*)** (73 mg, 36.1%).

Synthesis of intermediate **II-61 (R*)** and **II-62 (S*)** (VILL_mcalles_1382_1 and 2)



Intermediate **II-61 (R*)** (72 mg, 36.3%) and intermediate **II-62 (S*)** (59 mg, 29.8%) were prepared according to an analogous procedure to the one used for the synthesis of intermediates **II-59 (R*)** and **II-60 (S*)** using intermediate **II-58** (200 mg, 0.8 mmol) as starting material.

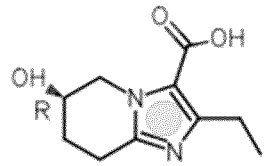
Synthesis of intermediate **II-63 (R*) and II-64 (S*)**



Intermediates **II-63 (R*)** (235 mg, 32.9%, white solid) and **II-64 (S*)** (232 mg, 32.8%, white solid) were prepared according to an analogous procedure to the one used for the synthesis of

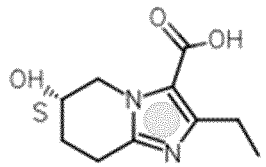
intermediates **II-59 (R*)** and **II-60 (S*)** using intermediate **II-51** (700 mg, 2.4 mmol) as starting material.

Synthesis of intermediate **II-65- -** NaCl salt



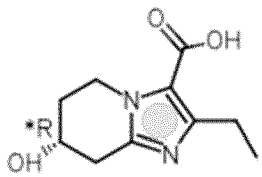
Intermediate **II-65** (81.2 mg, quantitative, orange pale solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-59 (R*)** (72 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-66** - NaCl salt



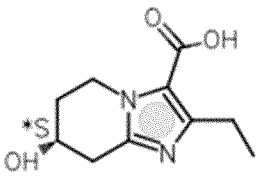
Intermediate **II-66** (82 mg, quantitative, yellowish pale solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-60 (S*)** (73 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-67** - NaCl salt



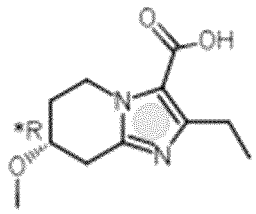
Intermediate **II-67** (78.9 mg, 99%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-61 (R*)** (70 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-68** - NaCl salt



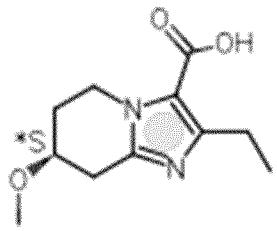
Intermediate **II-68** (70 mg, quantitative, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-62 (S*)** (59 mg, 0.2 mmol) as starting material.

Synthesis of intermediate **II-69** - NaCl salt



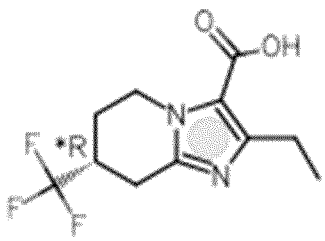
Intermediate **II-69** (70 mg, 98.9%, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-41 (R*)** (60 mg, 0.2 mmol) as starting material.

Synthesis of intermediate **II-70** - NaCl salt



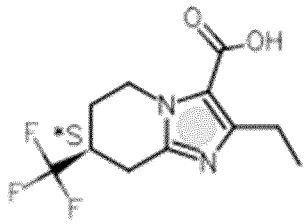
Intermediate **II-70** (89.6 mg, 99%, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-42 (S*)** (80 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-71** - NaCl salt



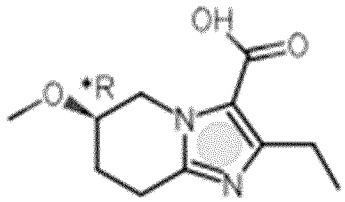
Intermediate **II-71** (92 mg, 98.9%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-63 (R*)** (80 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-72** - NaCl salt



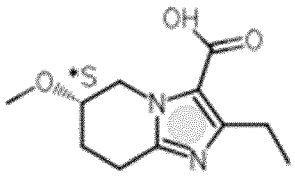
Intermediate **II-72** (88.4 mg, 99%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-64 (S*)** (80 mg, 0.3 mmol) as starting material.

Synthesis of intermediate **II-73** - NaCl salt



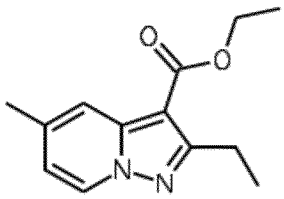
Intermediate **II-73** (113 mg, 98.8%, beige solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-46 (R*)** (100 mg, 0.4 mmol) as starting material.

Synthesis of intermediate **II-74** - NaCl salt



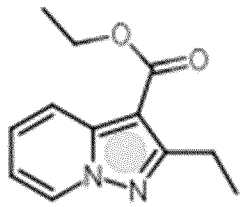
Intermediate **II-74** (112 mg, 95%, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-47 (S*)** (100 mg, 0.4 mmol) as starting material.

Synthesis of Intermediate **II-75**



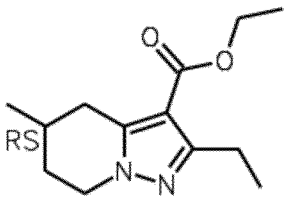
4-Methylpyridine [108-89-4] (0.50 ml, 5. mmol) was added to a solution of o-(2,4-dinitrophenyl)hydroxylamine [17508-17-7] (1.00 g, 5.02 mmol) in ACN (25 ml). The reaction mixture was stirred at 40 °C for 24 hours. Solvents were removed in vacuo and the reaction mixture was dissolved in DMF (25 ml). Ethyl 2-pentynoate [55314-57-3] (1.00 ml, 7.36 mmol) and $K2CO_3$ (2.09 g, 15.12 mmol) were added and the reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with EtOAc (75 ml), washed with water and brine, dried (anhydrous MgSO4), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 50/50). The desired fractions were collected and the solvents removed in vacuo to yield intermediate **II-75** (655 mg, 55%) as a yellow solid.

Synthesis of intermediate **II-76**



Intermediate **II-76** (652 mg, 46.9%, yellowish solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-75** using 1-aminopyridin-1-ium iodide [6295-87-0] (1.4 g, 6.3 mmol) as starting material.

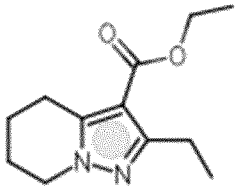
Synthesis of Intermediate **II-77**



Platinum(IV) oxide [1314-15-4] (66 mg, 0.29 mmol) was added to a stirred solution of intermediate **II-75** (655 mg, 2.82 mmol) in EtOH (6 mL) under nitrogen atmosphere. Then HCl (concentrated, aq.) (5 µl) was added, and the resulting suspension was stirred at 60 °C under nitrogen atmosphere for 16 hours. Platinum(IV) oxide (66 mg, 0.29 mmol) was added

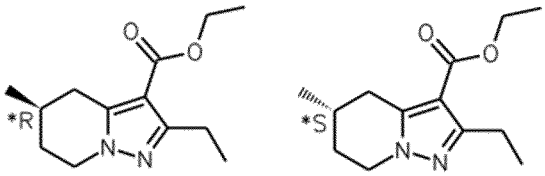
and the reaction mixture was stirred at 60 °C under nitrogen atmosphere for another 18 hours. The reaction was not complete and platinum (IV) oxide (66 mg, 0.29 mmol) was added four times over 30 hours, the reaction mixture being stirred at 60 °C. The reaction mixture was filtered over a pad of celite® and the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 50/50) to afford intermediate **II-77** as a pale yellow solid (432 mg, 64%).

Synthesis of intermediate **II-78**



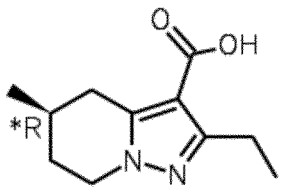
Intermediate **II-78** (653 mg, 97.7%, a white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-77** using intermediate **II-76** (650 mg, 3 mmol) as starting material.

Synthesis of intermediate **II-79 (R*)** and **II-80 (S*)**



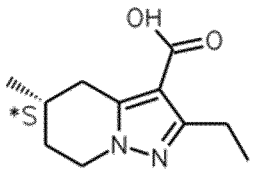
Intermediates **II-79 (R*)** (161 mg, 36.9%) and **II-80 (S*)** (165 mg, 37.8%) were prepared according to an analogous procedure to the one used for the synthesis of intermediates **II-59 (R*)** and **II-60 (S*)** using intermediate **II-77** (432 mg, 0.8 mmol) as starting material.

Synthesis of intermediate **II-81** - NaCl salt



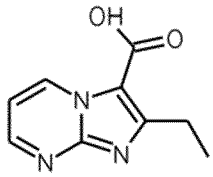
Intermediate **II-81** (122 mg, 92%, pale yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-79 (R*)** (140 mg, 0.6 mmol) as starting material.

Synthesis of intermediate **II-82** - NaCl salt



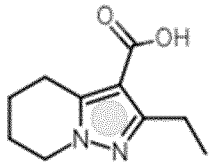
Intermediate **II-82** (197 mg, 99.4%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-80 (S*)** (158 mg, 0.7 mmol) as starting material.

Synthesis of intermediate **II-83**



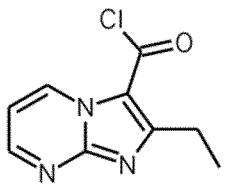
Intermediate **II-83** (22 g, 99.9%, pale yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-23** (25 g, 112.9 mmol) as starting material.

Synthesis of intermediate **II-84** - NaCl salt



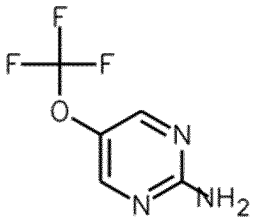
Intermediate **II-84** (133 mg, 99%, pale yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-78** (80 mg, 112.9 mmol) as starting material.

Synthesis of intermediate **II-85**



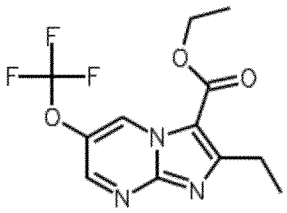
Intermediate **II-85** (26.9 g, quantitative, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-52** from intermediate **II-83** (24 g, 125.5 mmol) as starting material.

Intermediate **II-86**



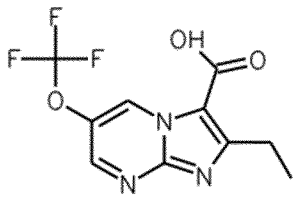
In a sealed tube a mixture of 2-Chloro-5-(trifluorometoxy)pyrimidine [1261812-52-5] (300 mg, 1.436 mmol) and ammonium hydroxide [1336-21-6] (13 mL, 83.926 mmol) was stirred at 85 °C for 16 hours. The solvent was evaporated in vacuo to yield intermediate **II-86** (295 mg, 94%) as a white solid.

Intermediate **II-87**



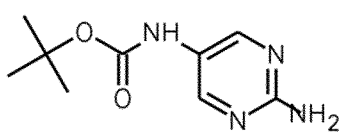
Intermediate **II-87** (69 mg, 72% purity, 12.1%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using intermediate **II-86** (295 mg, 1.4 mmol) as starting material.

Intermediate **II-88** - NaCl salt



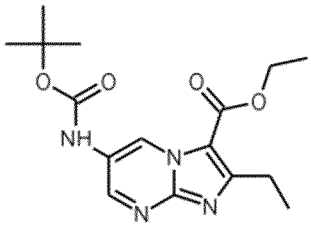
Intermediate **II-88** (53 mg, 97.8 %) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-87** (53 mg, 0.2 mmol) as starting material.

Intermediate **II-89**



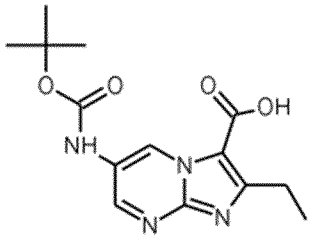
Pd/C [7440-05-3] (0.2 g, 0.188 mmol) was added to a solution of 2-Amino-5-nitropyrimidine [3073-77-6] (1 g, 7.138 mmol) in methanol (16 mL) in a round bottom flask under nitrogen atmosphere at 0°C. The mixture was stirred under H_2 atmosphere [1333-74-0] at rt for 16 h. Then, Di-tertbutyl dicarbonate [24424-99-5] (2.04 mL, 6.786 mmol) wad added at 0 °C and the mixture was stirred at 0 °C for 6h. The reaction was filtered through pad of celite. The solvent was concentrated in vacuo to give a colorless oil. The crude product was purified by flash column chromatography (silica 80 g; AcOEt in heptane 0/100 to 60/40). The desired fractions were collected and concentrated in vacuo to yield Intermediate **II-89** (1.052 g, 69%) as a yellow solid.

Synthesis of intermediate **II-90**



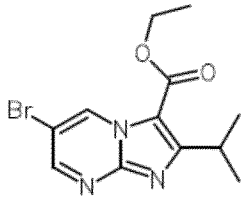
Intermediate **II-90** (127 mg, 20%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-89** (400 mg, 1.9 mmol) as starting material.

Synthesis of intermediate **II-91** - NaCl salt



Intermediate **II-91** (183 mg, 99.6%, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-90** (160 mg, 0.5 mmol) as starting material.

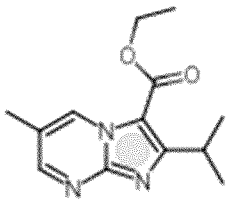
Synthesis of intermediate **II-92**



Intermediate **II-92** (464 mg, 25%,yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using 2-amino-5-

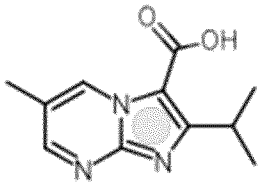
bromopyrimidine [7752-82-1] (1 g, 5.7 mmol) and ethyl isobutyrylacetate [7152-15-0] (1.5 mL, 8.6 mmol) as starting material.

Synthesis of intermediate **II-93**



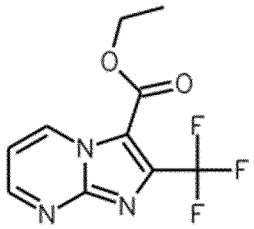
Intermediate **II-93** (331 mg, 95.9%, yellow solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using intermediate **II-92** (454 mg, 1.4 mmol) as starting material.

Synthesis of intermediate **II-94** - KCl salt



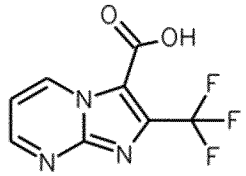
Aqueous potassium carbonate (1.1 mL, 1.20 mmol) was added to a solution of intermediate **II-93** (130 mg, 0.50 mmol) in Ethanol (3.0 mL) at room temperature. The mixture was stirred at 90 °C for 16 h. Aqueous potassium carbonate (1.4 mL, 1.52 mmol) was added to the mixture, and it was stirred at 90 °C for 1 h. The solution was acidified with HCl 1 M until pH = 7 and the solvent was concentrated in vacuo to yield intermediate **II-94** (147 mg, 82 %) as a yellowish solid.

Synthesis of intermediate **II-95**



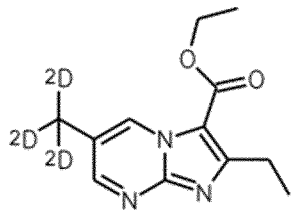
Intermediate **II-95** (1.8 g, 95%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using 2-Aminopyrimidine [109-12-6] (2.5 g, 25.5 mmol) and Ethyl 4,4, 4-trifluoroacetoacetate [372-31-6] (4.6 mL, 25.5 mmol) as starting material.

Synthesis of intermediate **II-96** - Li salt



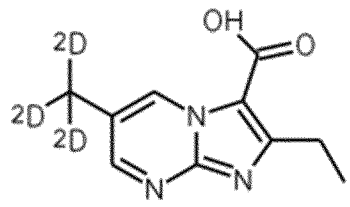
Intermediate **II-96** (174 mg, 80% purity, 83.4%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-17a** using intermediate **II-95** (158 mg, 0.6 mmol) as starting material.

Synthesis of intermediate **II-97**



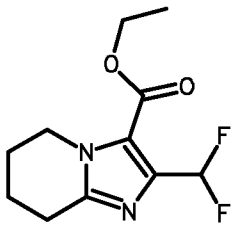
In a round bottom flask, $Zn(CD_2)_3$ (850 mg, 8.37 mmol) in solution in Et_2O was added to a mixture of $Pd(dppf)_2Cl_2$ (560 mg, 0.69 mmol) and intermediate **II-92** (2.0 g, 6.7 mmol) in anhydrous dioxane (50 ml) under nitrogen atmosphere. The reaction mixture was stirred at 55 °C for 16 hours. A solution of $NaHCO_3$ (sat., aq.) was added dropwise at 0°C. The solid was filtered off and washed with a solution of DCM and MeOH (9:1). The organic layer was dried (anhydrous MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, 80 g, gradient: EtOAc in heptane from 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to afford intermediate **II-97** (1.2 g, 72%). as a brown solid.

Synthesis of intermediate **II-98** - NaCl salt



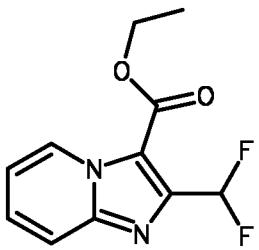
Intermediate **II-98** (223 mg, 99.8%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-97** (200 mg, 0.8 mmol) as starting material.

Synthesis of intermediate **II-98**



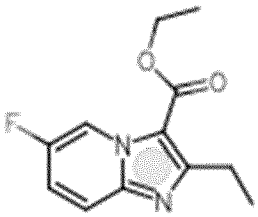
Intermediate **II-98** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-16,** using intermediate **II-99** (1.3 g, 5.41 mmol) as starting material. **I-98** was obtained as a colourless oil (845 mg, 63%).

Synthesis of intermediate **II-99**



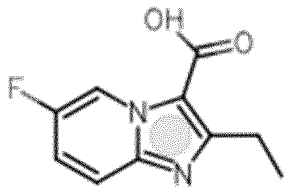
Intermediate **II-99** (0.23 g, 24%) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-7d,** using 2-Aminopyridine [504-29-0] (1.32 g, 14.02 mmol) as starting material.

Synthesis of intermediate **II-100**



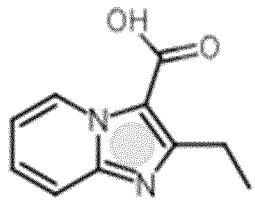
Intermediate **II-100** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-1a** using Ethyl propionylacetate [4949-44-4] (500mg, 4.5 mmol) and 2-Amino-5-fluoropyridine [21717-96-4] (983 uL, 6.7 mmol) as starting material. (573 mg, 53.8%) as yellowish solid.

Synthesis of intermediate **II-101** - KCl salt



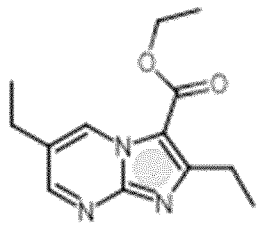
Intermediate **II-101** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-3a** using intermediate **II-100** (180 mg, 0.8 mmol) as starting material. (215 mg, 98.8%) as yellow solid.

Synthesis of intermediate **II-102** - LiCl salt



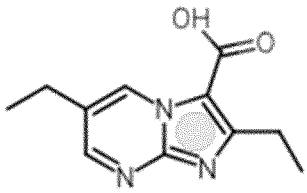
Intermediate **II-102** (149 mg, 99.9%, white solid) was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8e** using intermediate **II-1d** (133 mg, 0.6 mmol) as starting material.

Synthesis of intermediate **II-103**



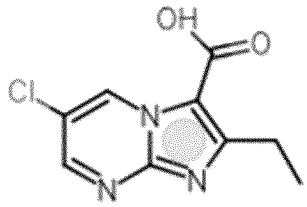
Intermediate **II-103** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-2a** using intermediate **II-1a** (500 mg, 1.6 mmol) as starting material. Intermediate **II-103** (135 mg, 34.3%) was obtained as a yellow solid.

Synthesis of intermediate **II-104** - NaCl salt



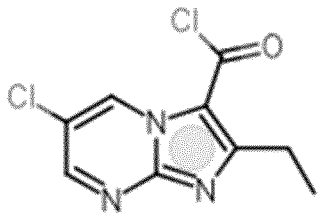
Intermediate **II-104** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-8a** using intermediate **II-103** (110 mg, 0.4 mmol) as starting material. Intermediate **II-104** (116 mg, 99%) was obtained as a yellow solid.

Synthesis of intermediate **II-105** - KCl salt



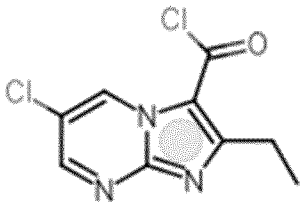
Intermediate **II-105** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-94** using intermediate intermediate **II-1c** (485 mg, 1.9 mmol) as starting material. Intermediate **II-105** (1.2 g, 95.4%) was obtained as a yellow solid.

Synthesis of intermediate **II-106** - KCl salt



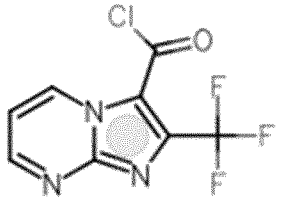
Intermediate **II-106** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-25** using intermediate intermediate **II-105** (1.2 g, 1.8 mmol) as starting material. Intermediate **II-106** (1.3 g, 99.9%) was obtained as a brown solid.

Synthesis of intermediate **II-107** - LiCl salt



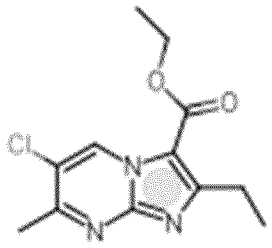
Intermediate **II-107** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-25** using intermediate **II-37** (144 mg, 0.5 mmol) as starting material. Intermediate **II-107** (154 mg, 99.8%) was obtained as a light orange solid.

Synthesis of intermediate **II-108** - KCl salt



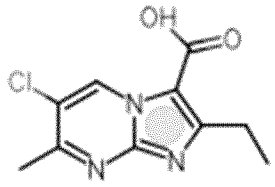
Intermediate **II-108** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-25** using intermediate intermediate **II-96** (207 mg, 0.7 mmol) as starting material. Intermediate **II-108** (230 mg, 99.5%) was obtained as a light orange solid.

Synthesis of intermediate **II-109**



In a round bottom flask, iron(III) acetylacetonate [14024-18-1] (237 mg, 0.65 mmol) was added to a solution of intermediate **II-10** (1.88 g, 6.52 mmol) in anhydrous THF (27 ml) and NMP (2.2 ml) under nitrogen atmosphere at 0 °C. Methylmagnesium bromide (3M solution in Et_2O, 4.35 ml, 13.05 mmol) was added. The reaction mixture was stirred at 0 °C for 3 hours. A solution of NH4Cl (sat., aq.) was added and the mixture was extracted with EtOAc. The organic layer was dried (anhydrous MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, 80 g, gradient: EtOAc in heptane from 0/100 to 65/35). The desired fractions were collected and concentrated in vacuo to afford intermediate **II-109** as a sticky orange oil (215 mg, 12%).

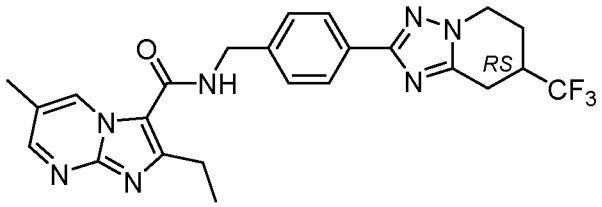
Synthesis of intermediate **II-110** - KCl salt



Intermediate **II-110** was prepared according to an analogous procedure to the one used for the synthesis of intermediate **II-94** using intermediate **II-109** (290 mg, 1 mmol) as starting material. Intermediate **II-110** (337 mg, 100%) was obtained as a yellowish solid.

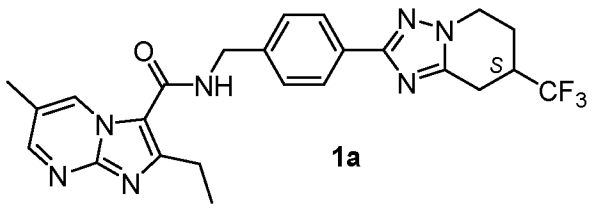
SYNTHESIS OF FINAL COMPOUNDS

Synthesis of Compound **1ab**

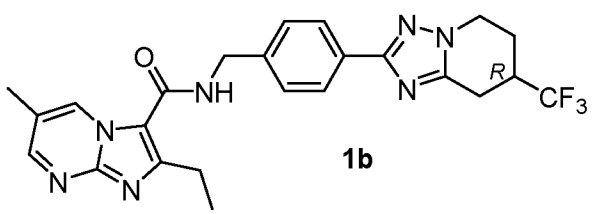


HATU [148893-10-1] (3.84 g, 10.1 mmol) and DIPEA [7087-68-5] (8.21 mL, 41.13 mmol) were added to a solution of intermediate II-3a (2.76 g, 9.43 mmol) in DMF (160 mL) at rt and the mixture was stirred for 10 min. Then, intermediate I-6 (2.49 g, 6.73 mmol) was added, and the mixture reaction was stirred at rt for a further 1 h. Then, a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM (x3). The combined organic extracts were dried (MgSO4), filtered and the solvents were evaporated in vacuo. The crude product was triturated with a saturated NaHCO3 aqueous solution and filtered. The solid was washed with water (x3), DCM (x3) and finally with diethyl ether to yield final compound 1ab as a white solid (1.59 g, 48%). The mother liquors were concentrated in vacuo and purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 30/70). The desired fractions were collected, concentrated in vacuo to yield some two additional fractions of compound 1ab as a pale brown solid (0.27 g, 8%) and as white solid (0.44 g, 13%).
1H NMR (400 MHz, DMSO) δ 9.16 (d, J = 1.0 Hz, 1H), 8.55 – 8.47 (m, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.8, 3.7 Hz, 1H), 4.17 (td, J = 12.1, 4.8 Hz, 1H), 3.27 – 3.12 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.4, 11.9 Hz, 1H), 2.34 (s, 3H), 2.30 (d, J = 2.3 Hz, 1H), 2.20 – 2.02 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **1a and 1b**



1a



1b

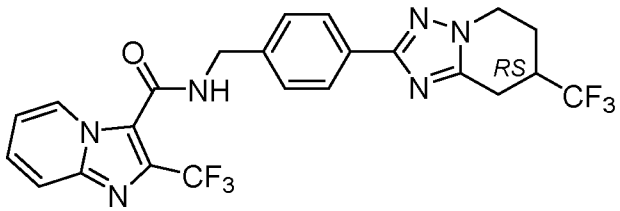
A batch of compound 1ab (0.32 mg, 0.66 mmol), prepared according to an analogous procedure to the one outlined above, was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux Cellulose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 30ml/min of CO2 (55%) – Methanol (45%) + 0.1% diethylamine, at 30 ºC,

BPR 150 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under vacuo. The residues were triturated with diethyl ether to yield compounds 1a (90 mg) and 1b (68 mg) as white solids.

Compound 1a 1H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.6, 3.7 Hz, 1H), 4.17 (td, J = 12.1, 4.8 Hz, 1H), 3.23 – 3.15 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.94 – 2.85 (m, 1H), 2.34 (s, 3H), 2.31 (s, 1H), 2.11 (qd, J = 11.4, 5.7 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Compound 1b 1H NMR (400 MHz, DMSO) δ 9.16 (d, J = 1.1 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 6.1 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.9, 3.8 Hz, 1H), 4.17 (td, J = 12.0, 4.6 Hz, 1H), 3.24 – 3.14 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.5, 12.1 Hz, 1H), 2.34 (s, 3H), 2.31 (s, 1H), 2.18 – 2.06 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

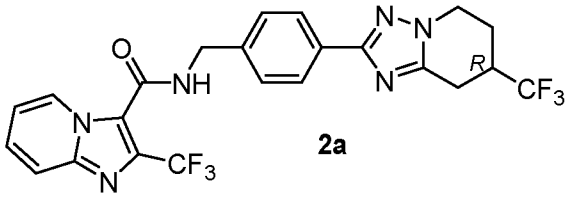
Synthesis of Compound **2ab**



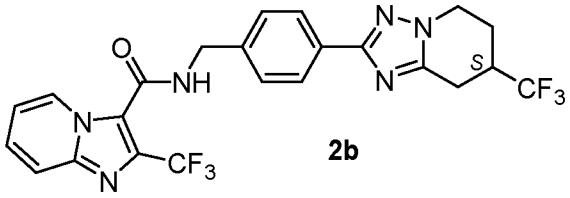
HATU [148893-10-1] (275 mg, 0.72 mmol) was added to a mixture of intermediate I-6 (120 mg, 0.36 mmol), intermediate II-6a (100 mg, 0.43 mmol) and DIPEA [7087-68-5] (0.37 mL, 2.17 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then, a 1 M Na2CO3 aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The desired fractions were collected, concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 100x30mm 5µm Column; from 72% [0.1% HCOOH] - 28% [ACN:MeOH (1:1)] to 36% [0.1% HCOOH] - 64% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 2ab as a brown solid (122 mg, 65%).

1H NMR (400 MHz, DMSO) δ 9.33 (t, J = 5.8 Hz, 1H), 8.57 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 9.1 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.20 (t, J = 6.5 Hz, 1H), 4.59 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.9, 3.5 Hz, 1H), 4.18 (td, J = 11.9, 4.7 Hz, 1H), 3.25 – 3.14 (m, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.18 – 2.09 (m, 1H).

Synthesis of Compounds **2a and 2b**



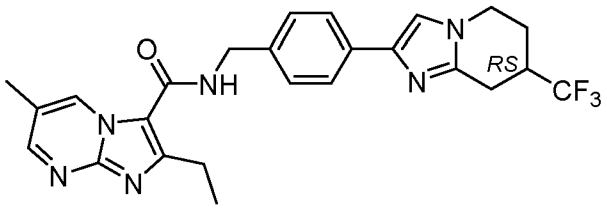
2a



2b

A batch of compound 2ab (350 mg, 0.69 mmol), prepared according to an analogous procedure to the one outlined above, was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux i-Amylose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 30ml/min of CO2 (60%) – Ethanol (40%) + 0.1% diethylamine, at 30 ºC, BPR 120 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under high vacuo. The residues were triturated with diethyl ether to yield compounds 2a (87 mg) and 2b (89 mg) as white-off solids.
Compound 2a 1H NMR (400 MHz, DMSO) δ 9.33 (t, J = 5.8 Hz, 1H), 8.57 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 9.1 Hz, 1H), 7.61 – 7.50 (m, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.20 (dd, J = 9.9, 3.9 Hz, 1H), 4.59 (d, J = 5.4 Hz, 2H), 4.33 (dd, J = 12.5, 3.6 Hz, 1H), 4.18 (td, J = 12.2, 4.9 Hz, 1H), 3.20 (d, J = 13.5 Hz, 2H), 2.93 (dd, J = 17.6, 12.1 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.12 (qd, J = 11.6, 6.0 Hz, 1H).
Compound 2b 1H NMR (400 MHz, DMSO) δ 9.34 (d, J = 5.4 Hz, 1H), 8.57 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 9.2 Hz, 1H), 7.55 (dd, J = 12.0, 3.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.20 (t, J = 6.9 Hz, 1H), 4.59 (d, J = 5.2 Hz, 2H), 4.33 (dd, J = 12.7, 3.4 Hz, 1H), 4.24 – 4.10 (m, 1H), 3.20 (d, J = 13.5 Hz, 2H), 2.93 (dd, J = 17.6, 12.3 Hz, 1H), 2.33 (dd, J = 6.4, 4.4 Hz, 1H), 2.12 (qd, J = 11.5, 5.8 Hz, 1H).

Synthesis of Compound **3ab**

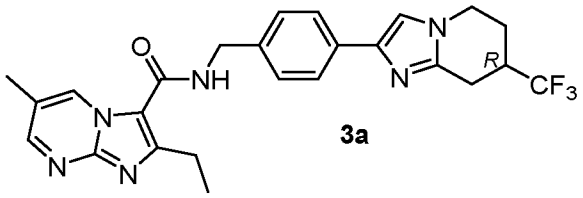


HATU [148893-10-1] (286 mg, 0.52 mmol) was added to a mixture of intermediate I-10 (125 mg, 0.86 mmol), intermediate II-3a (93 mg, 0.45 mmol) and DIPEA [7087-68-5] (0.38 mL, 2.26 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then, a 1 M Na2CO3 aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The

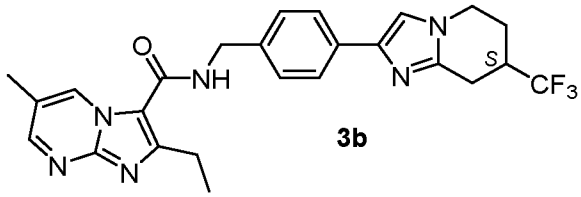
desired fractions were collected, concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 100x30mm 5µm Column; from 70% [25mM NH4HCO3] - 30% [ACN:MeOH (1:1)] to 27% [25mM NH4HCO3] - 73% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 3ab as a white solid (12 mg, 7%).

1H NMR (400 MHz, DMSO) δ 9.15 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.16 (dd, J = 12.5, 3.6 Hz, 1H), 3.98 (td, J = 12.2, 4.6 Hz, 1H), 3.12 – 3.05 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.78 (dd, J = 17.3, 12.8 Hz, 1H), 2.34 (s, 3H), 2.23 (d, J = 11.3 Hz, 1H), 1.95 (ddd, J = 24.8, 11.9, 5.6 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **3a and 3b**



3a



3b

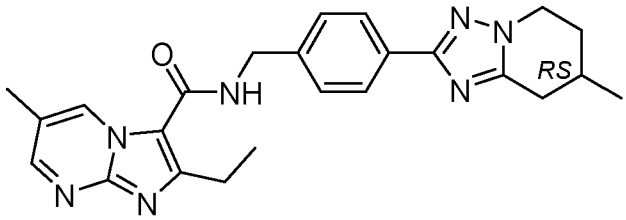
A batch of compound 3ab (350 mg, 0.69 mmol), prepared according to an analogous procedure to the one outlined above, was purified by chiral SFC on a Jasco SFC prep system using an Phenomenex Lux Amylose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 30ml/min of CO2 (50%) – 2-propanol (50%) + 0.1% diethylamine, at 30 °C, BPR 120 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected, evaporated, and dried under high vacuo. Both SFC-eluting products were repurified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo. The first SFC eluting peak product was triturated with a mixture 1:1 of DIPE/DCM and dried under high vacuo at 60 °C and then triturated with DIPE and dried under high vacuo to yield compound 3a as an off-white solid (40 mg). The second SFC eluting peak product was triturated a mixture 1:1 of DIPE/DCM and dried under high vacuo at 60 °C to yield compound 3b as an off-white solid (71 mg).

Compound 3a 1H NMR (400 MHz, DMSO) δ 9.15 (d, J = 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.17 (dd, J = 12.6, 3.3 Hz, 1H), 3.98 (td, J = 12.2, 4.6 Hz, 1H), 3.14 – 3.05 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.79 (dd, J = 17.3, 12.6 Hz, 1H), 2.34 (s, 3H), 2.24 (d, J = 11.3 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Compound 3b 1H NMR (400 MHz, DMSO) δ 9.19 – 9.11 (m, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 4.52

(d, J = 5.9 Hz, 2H), 4.17 (dd, J = 12.6, 3.5 Hz, 1H), 3.98 (td, J = 12.1, 4.5 Hz, 1H), 3.15 – 3.05 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.79 (dd, J = 17.4, 12.6 Hz, 1H), 2.34 (s, 3H), 2.28 – 2.19 (m, 1H), 2.03 – 1.87 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

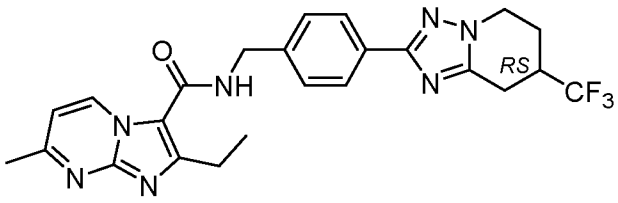
Synthesis of Compound **4ab**



Intermediate I-16 (150 mg, 0.48 mmol) was added to a stirred mixture of intermediate II-3a (189 mg, 0.67 mmol), HATU [148893-10-1] (272 mg, 0.72 mmol), and DIPEA [7087-68-5] (0.58 mL, 3.33 mmol) in DMF (10 mL) at rt. The mixture was stirred at rt for 16 h. Then, a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM (3x). The combined organic layers were dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 100/0). The desired fractions were collected, concentrated in vacuo and the residue triturated with DIPE to yield compound 4ab as a white solid (105 mg, 49%).

1H NMR (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.50 (dd, J = 7.1, 4.1 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.22 (ddd, J = 12.6, 5.6, 2.8 Hz, 1H), 4.15 – 4.01 (m, 1H), 3.08 – 2.93 (m, 3H), 2.47 – 2.39 (m, 1H), 2.37 – 2.31 (m, 3H), 2.05 (dt, J = 18.1, 13.1 Hz, 2H), 1.74 (dtd, J = 13.4, 10.9, 5.8 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **5ab**

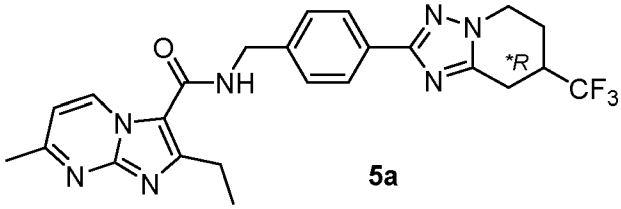


Intermediate I-6 (130 mg, 0.33 mmol) was added to a stirred mixture of intermediate II-8a (167 mg, 0.60 mmol), HATU [148893-10-1] (191 mg, 0.50 mmol), and DIPEA [7087-68-5] (0.41 mL, 2.34 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then, a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (2x). The combined organic layers were dried (MgSO4), filtered and the solvents evaporated

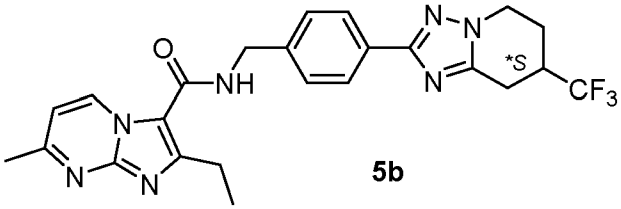
in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 30/70). The desired fractions were collected, concentrated in vacuo to yield compound 5ab as a white solid (92 mg, 56%).

1H NMR (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.46 (t, J = 5.5 Hz, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.44 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 7.0 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.39 – 4.09 (m, 2H), 3.19 (d, J = 13.1 Hz, 2H), 3.01 (q, J = 7.4 Hz, 2H), 2.97 – 2.88 (m, 1H), 2.55 (s, 3H), 2.32 (d, J = 11.3 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.27 (t, J = 7.4 Hz, 3H).

Synthesis of Compounds **5a and 5b**



5a



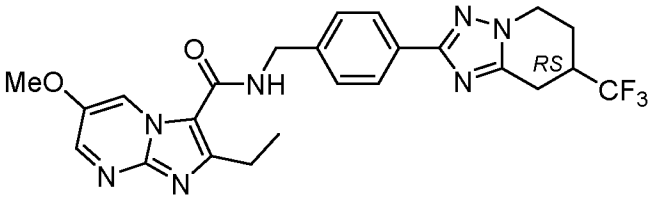
5b

A batch of compound 5ab (1.34 g, 2.87 mmol), prepared according to an analogous procedure to the one outlined above, was purified by chiral SFC method on a Jasco SFC prep system using an i-Cellulose-C column (Regis Technologies) 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 100ml/min of CO2 (65%) - methanol (45%), at 30 °C, BPR 150 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected and concentrated in vacuo to yield compound 5a (430 mg, 79%) and compound 5b (420 mg, yield = 77 %) as white solids.

Compound 5a 1H NMR (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.45 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.8, 3.8 Hz, 1H), 4.26 – 4.07 (m, 1H), 3.24 – 3.13 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.96 – 2.85 (m, 1H), 2.55 (s, 3H), 2.32 (d, J = 10.8 Hz, 1H), 2.11 (ddd, J = 17.3, 12.2, 5.8 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Compound 5b 1H NMR (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.45 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.37 – 4.26 (m, 1H), 4.23 – 4.11 (m, 1H), 3.19 (d, J = 13.3 Hz, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.2, 11.8 Hz, 1H), 2.55 (s, 3H), 2.30 (t, J = 10.4 Hz, 1H), 2.20 – 2.03 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

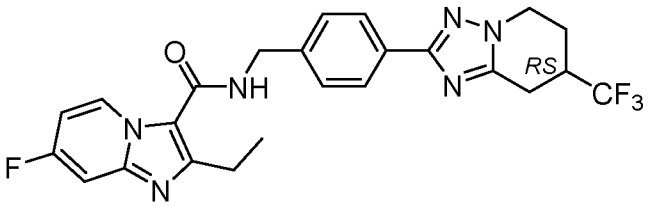
Synthesis of Compound **6ab**



Intermediate I-6 (130 mg, 0.33 mmol) was added to a stirred mixture of intermediate II-8b (171 mg, 0.60 mmol), HATU [148893-10-1] (176 mg, 0.46 mmol), and DIPEA [7087-68-5] (0.38 mL, 2.16 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then, a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (2x). The combined organic layers were dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 30/70). The desired fractions were collected, concentrated in vacuo to yield compound 6ab as a white solid (113 mg, 67%).

1H NMR (400 MHz, DMSO) δ 8.97 (d, J = 3.0 Hz, 1H), 8.52 (d, J = 3.0 Hz, 1H), 8.47 (t, J = 5.8 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.37 – 4.28 (m, 1H), 4.23 – 4.11 (m, 1H), 3.86 (s, 3H), 3.21 (s, 1H), 3.17 (d, J = 5.2 Hz, 1H), 3.03 (q, J = 7.5 Hz, 2H), 2.98 – 2.87 (m, 1H), 2.32 (d, J = 8.7 Hz, 1H), 2.19 – 2.02 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **7ab**

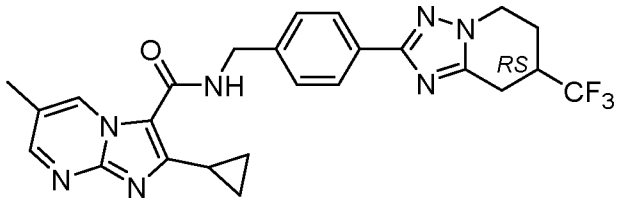


HATU [148893-10-1] (450 mg, 1.18 mmol) was added to a mixture of intermediate I-6 (196 mg, 0.59 mmol), intermediate II-8c (100 mg, 0.43 mmol) and DIPEA [7087-68-5] (0.6 mL, 3.53 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then, a 1 M NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH (9:1) in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield compound 7ab as an off-white solid (97 mg, 34%).

1H NMR (400 MHz, DMSO) δ 9.03 (dd, J = 7.5, 6.2 Hz, 1H), 8.46 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.49 (dd, J = 9.8, 2.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.06 (td, J = 7.6,

2.7 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.8, 3.6 Hz, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.26 – 3.13 (m, 2H), 2.99 (dd, J = 15.0, 7.5 Hz, 2H), 2.95 – 2.87 (m, 1H), 2.37 – 2.26 (m, 1H), 2.11 (qd, J = 11.4, 5.8 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H).

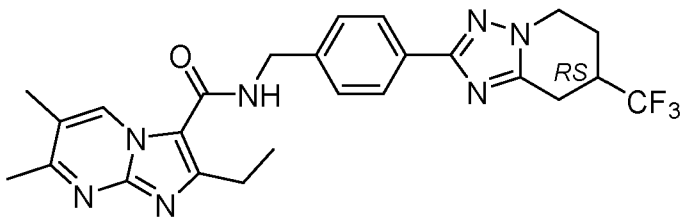
Synthesis of Compound **8ab**



HATU [148893-10-1] (306 mg, 0.81 mmol) was added to a mixture of intermediate I-6 (134 mg, 0.40 mmol), intermediate II-6b (105 mg, 0.48 mmol) and DIPEA [7087-68-5] (0.41 mL, 2.42 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then the mixture was washed with a 1 M Na2CO3 aqueous solution and brine and extracted with EtOAc. The organic layer was dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 100x30mm 5µm Column; from 59% [0.1% HCOOH] - 41% [ACN:MeOH (1:1)] to 17% [0.1% HCOOH] - 83% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo and the residue was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0) to yield compound 8ab as a white solid (13 mg, 6%).

1H NMR (400 MHz, DMSO) δ 9.18 (s, 1H), 8.64 (t, J = 5.8 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.32 (dd, J = 12.4, 4.1 Hz, 1H), 4.20 – 4.11 (m, 1H), 3.19 (d, J = 13.3 Hz, 2H), 2.92 (dd, J = 17.6, 12.2 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.32 (s, 3H), 2.31 – 2.28 (m, 1H), 2.11 (ddd, J = 24.4, 11.6, 5.7 Hz, 1H), 1.06 (d, J = 6.4 Hz, 4H).

Synthesis of Compound **9ab**

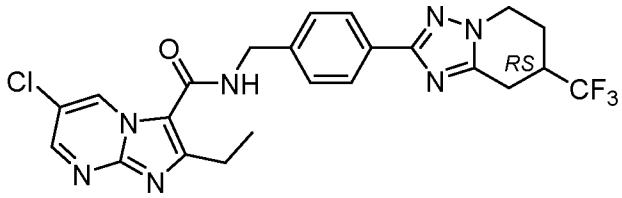


HATU [148893-10-1] (114 mg, 0.30 mmol) was added to a mixture of intermediate I-6 (100 mg, 0.30 mmol), intermediate II-8d (114 mg, 0.52 mmol) and DIPEA [7087-68-5] (0.21 mL,

1.20 mmol) in DMF (1.5 mL) at rt. The mixture was stirred at rt for 19 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 2/98). The desired fractions were collected and concentrated in vacuo to yield compound 9ab as a white solid (15 mg, 6%).

1H NMR (400 MHz, DMSO) δ 9.06 (s, 1H), 8.42 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.56 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.7, 3.8 Hz, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.23 – 3.15 (m, 2H), 2.99 (q, J = 7.6 Hz, 2H), 2.96 – 2.87 (m, 1H), 2.51 (s, 3H), 2.35 – 2.29 (m, 1H), 2.27 (s, 3H), 2.17 – 2.08 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

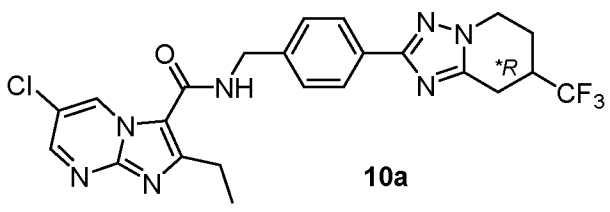
Synthesis of Compound **10ab**



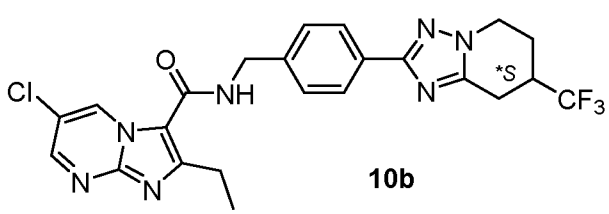
A mixture of intermediate II-8e (105 mg, 0.42 mmol), HATU [148893-10-1] (229 mg, 0.60 mmol) and DIPEA [7087-68-5] (0.31 mL, 1.80 mmol) in DMF (7.8 mL) was stirred at rt for 10 min and then intermediate I-6 (100 mg, 0.30 mmol) was added. The mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was triturated with DIPE, dissolved in DCM, and extracted with a saturated NaHCO3 aqueous solution. The organic layer was dried (MgSO4), filtered and evaporated in vacuo to yield compound 10ab as a white solid (15 mg, 10%).

1H NMR (400 MHz, DMSO) δ 9.43 (d, J = 2.6 Hz, 1H), 8.69 (d, J = 2.6 Hz, 1H), 8.62 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.6, 4.2 Hz, 1H), 4.17 (td, J = 11.9, 4.8 Hz, 1H), 3.19 (d, J = 13.1 Hz, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.8, 12.3 Hz, 1H), 2.32 (d, J = 10.5 Hz, 1H), 2.11 (qd, J = 12.0, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **10a and 10b**



10a

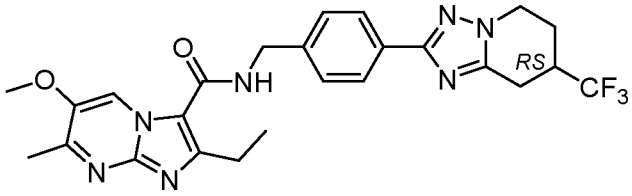


10b

A batch of compound 10ab, prepared according to an analogous procedure to the one outlined above starting from intermediate I-6 (0.74 g, 1.89 mmol), was purified by chiral SFC method on a Jasco SFC prep system using an Phenomenex Lux Cellulose-1 250mm long x30mm I.D. 5 µm particle size, on isocratic mode at 30ml/min of CO2 (50%) – methanol (40%) + 0.1% diethylamine, at 30°C, BPR 150 Bar. Acquisition frequency was set to 220 nm for the DAD detector. The desired fractions were collected and concentrated in vacuo to yield compound 10a (107 mg, 11%) and compound 10b (118 mg, yield = 12 %) as beige solids.

Compound 10a 1H NMR (400 MHz, DMSO) δ 9.43 (d, J = 2.6 Hz, 1H), 8.68 (d, J = 2.6 Hz, 1H), 8.62 (t, J = 5.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.9, 3.6 Hz, 1H), 4.17 (td, J = 12.2, 4.9 Hz, 1H), 3.23 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.32 (dd, J = 10.8, 2.1 Hz, 1H), 2.20 – 2.03 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).
Compound 10b 1H NMR (400 MHz, DMSO) δ 9.43 (d, J = 2.6 Hz, 1H), 8.68 (d, J = 2.6 Hz, 1H), 8.62 (t, J = 5.9 Hz, 1H), 7.94 (t, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 13.1, 3.4 Hz, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.24 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.5, 12.1 Hz, 1H), 2.32 (dd, J = 10.9, 2.1 Hz, 1H), 2.19 – 2.04 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

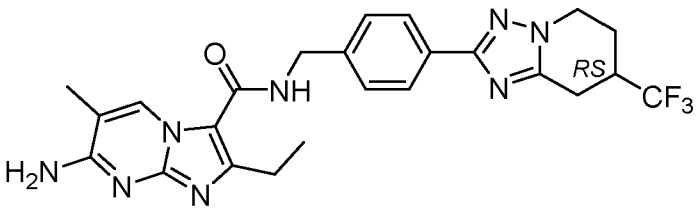
Synthesis of Compound **11ab**



Intermediate I-6 (110 mg, 0.33 mmol) was added to a solution of intermediate II-8f (106 mg, 0.36 mmol), HATU [148893-10-1] (189 mg, 0.50 mmol) and DIPEA [7087-68-5] (0.40 mL, 2.31 mmol) in DMF (4 mL) at rt. The mixture was stirred at rt for 19 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (2x). The combined organic layers were dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH (9:1) in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield compound 11ab as a pale orange solid (27 mg, 15%).
1H NMR (400 MHz, DMSO) δ 8.88 (s, 1H), 8.36 (t, J = 5.6 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.17 (td, J = 12.0, 4.7

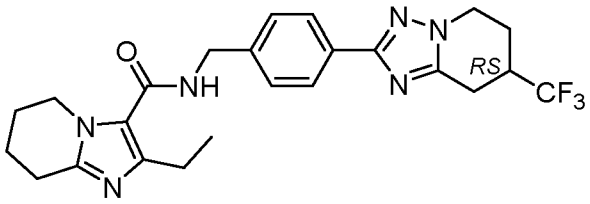
Hz, 1H), 3.86 (s, 3H), 3.23 – 3.14 (m, 2H), 3.00 (q, J = 7.4 Hz, 2H), 2.97 – 2.86 (m, 1H), 2.46 (s, 3H), 2.36 – 2.27 (m, 1H), 2.19 – 2.05 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **12ab**



Trifluoroacetic acid [76-05-1] (2.7 mL, 36.35 mmol) was added to intermediate I-17a (179 mg, 0.24 mmol) at 0 °C. The mixture was stirred at rt for 1 h. The mixture was neutralized with a saturated NaHCO3 aqueous solution and extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by reverse phase HPLC (Phenomenex Gemini C18 30x100mm 5µm Column; from 95% [0.1% HCOOH] - 5% [ACN:MeOH (1:1)] to 63% [0.1% HCOOH] - 37% [ACN:MeOH (1:1)]). The desired fractions were collected, then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo to dryness and the solid was triturated with DIPE and n-pentane to yield compound 12ab as a white solid (30 mg, 24%). 1H NMR (400 MHz, DMSO) δ 8.74 (s, 1H), 8.06 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 6.86 (s, 2H), 4.52 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.5, 3.9 Hz, 1H), 4.17 (td, J = 12.1, 4.7 Hz, 1H), 3.23 – 3.15 (m, 2H), 2.98 – 2.91 (m, 1H), 2.87 (q, J = 7.5 Hz, 2H), 2.33 (d, J = 11.5 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.06 (s, 3H), 1.22 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **13ab**

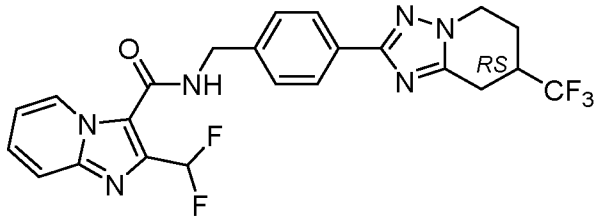


HATU [148893-10-1] (570 mg, 1.5 mmol) was added to a mixture of intermediate I-6 (250 mg, 0.75 mmol), intermediate II-17a (248 mg, 1.28 mmol) and DIPEA [7087-68-5] (0.21 mL, 1.20 mmol) in DMF (10 mL) at rt. The mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH (9:1)

in DCM 0/100 to 40/60). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 100x30mm 5µm Column; from 95% [0.1% HCOOH] - 5% [ACN:MeOH (1:1)] to 63% [0.1% HCOOH] - 37% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 13ab as a white solid (79 mg, 22%)

1H NMR (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.17 (td, J = 12.0, 4.9 Hz, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.18 (dd, J = 9.5, 8.3 Hz, 2H), 2.92 (dd, J = 17.6, 12.2 Hz, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.36 – 2.27 (m, 1H), 2.18 – 2.03 (m, 1H), 1.91 – 1.73 (m, 4H), 1.10 (t, J = 7.5 Hz, 3H).

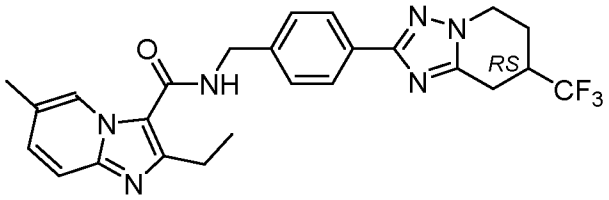
Synthesis of Compound **14ab**



Intermediate I-6 (110 mg, 0.33 mmol) was added to a solution of intermediate II-17b (120 mg, 0.46 mmol), HATU [148893-10-1] (189 mg, 0.50 mmol) and DIPEA [7087-68-5] (0.4 mL, 2.31 mmol) in DMF (4 mL) at rt. The mixture was stirred at rt for 72 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (x2). The organic layer was washed with brine, separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/methanol 9:1 in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 21.2x100mm 5µm Column; from 72% [(65mM NH4OAc) + ACN (90:10) pH 7] – 28% (ACN/methanol 1:1) to from 36% [(65mM NH4OAc) + ACN (90:10) pH 7] – 28% (ACN/methanol 1:1). The desired fractions were collected and concentrated in vacuo to yield compound 14ab as a white solid (41 mg, 25%).

1H NMR (400 MHz, DMSO) δ 9.04 (t, J = 5.7 Hz, 1H), 8.82 (d, J = 7.0 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 9.1 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.48 (s, 1H), 7.45 (s, 1H), 7.35 (t, J = 53.8 Hz, 1H), 7.17 (td, J = 6.9, 1.1 Hz, 1H), 4.59 (d, J = 5.7 Hz, 2H), 4.37 – 4.29 (m, 1H), 4.23 – 4.13 (m, 1H), 3.24 – 3.16 (m, 2H), 2.93 (dd, J = 17.8, 12.3 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.18 – 2.05 (m, 1H).

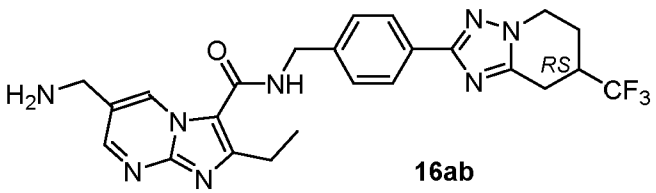
Synthesis of Compound **15ab**



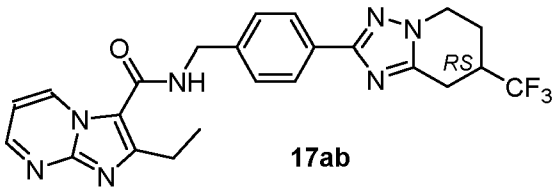
HATU [148893-10-1] (420 mg, 1.10 mmol) was added to a mixture of intermediate I-6 (234 mg, 0.55 mmol), intermediate II-17c (440 mg, 1.06 mmol) and DIPEA [7087-68-5] (0.6 ml, 3.31 mmol) in DMF (4 ml) and the mixture was stirred at rt for 24. The mixture was washed with a saturated NaHCO3 aqueous solution and extracted with DCM. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was washed with toluene twice and then purified by flash column chromatography over silica gel (20; MeOH in DCM 0/100 to 5/95). The desired fractions were collected and concentrated in vacuo and the residue triturated sequentially with DIPE:DCM (9:1), DIPE:DCM (1:9), DIPE:DCM (1:1) and Et2O. The solid was dried in vacuo and repurified by reverse phase HPLC (Phenomenex Gemini C18 30x100mm 5µm Column; from 70% [25mM NH4HCO3] - 30% [ACN:MeOH (1:1)] to 27% [25mM NH4HCO3] - 73% [ACN:MeOH (1:1)]). The desired fractions were collected, concentrated, and dried at 60 °C under vacuum to yield compound 15ab as a white solid (69 mg, 26%).

1H NMR (400 MHz, DMSO) δ 8.81 (s, 1H), 8.40 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.25 (dd, J = 9.1, 1.7 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.37 – 4.28 (m, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.24 – 3.11 (m, 2H), 3.03 – 2.95 (m, 2H), 2.92 (dd, J = 16.0, 10.6 Hz, 1H), 2.36 – 2.32 (m, 1H), 2.31 (s, 3H), 2.18 – 2.04 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **16ab** and Compound **17ab**



16ab



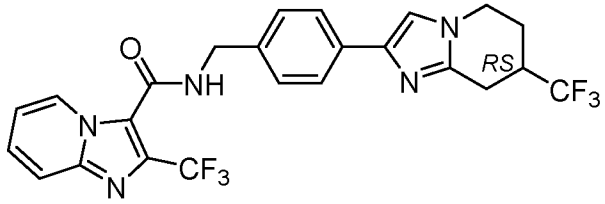
17ab

A 4M HCl dioxane solution (0.42 mL, 1.66 mmol) was added to a stirred solution of intermediate I-17b (165 mg, 0.28 mmol) in DCM (5 mL) at rt. The reaction mixture was stirred at rt for 16 h and then the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography (silica, 12; DCM/MeOH/NH3 9:1:0.1 in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield compound 16ab as a brown solid (33 mg, 23%) and compound 17ab as a white solid (35 mg, 27%).

Compound 16ab 1H NMR (400 MHz, DMSO) δ 9.24 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.52 (t, J = 5.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.32 (dd, J = 11.7, 4.4 Hz, 1H), 4.17 (td, J = 12.0, 4.9 Hz, 1H), 3.80 (s, 2H), 3.24 – 3.13 (m, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.4, 12.0 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.19 – 2.02 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Compound 17ab 1H NMR (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.56 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 6.9, 4.2 Hz, 1H), 4.59 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.7, 3.8 Hz, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.25 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.5, 12.0 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.20 – 2.05 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

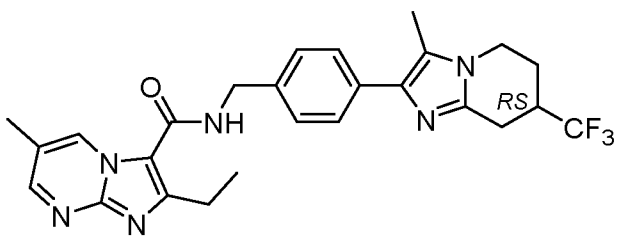
Synthesis of Compound **18ab**



Intermediate I-10 (122 mg, 0.33 mmol) was added to a solution of intermediate II-6a (132 mg, 0.57 mmol), HATU [148893-10-1] (126 mg, 0.33 mmol) and DIPEA [7087-68-5] (0.23 mL, 1.33 mmol) in DMF (1.7 mL) at rt. The mixture was stirred at rt for 3 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was washed with brine, separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 80/20). The desired fractions were collected and concentrated in vacuo to yield compound 18ab as a white solid (85 mg, 48%).

1H NMR (400 MHz, DMSO) δ 9.28 (t, J = 5.7 Hz, 1H), 8.56 (d, J = 7.0 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.21 (t, J = 6.9 Hz, 1H), 4.54 (d, J = 5.8 Hz, 2H), 4.17 (dd, J = 12.9, 3.5 Hz, 1H), 3.99 (td, J = 11.9, 4.4 Hz, 1H), 3.17 – 3.03 (m, 2H), 2.79 (dd, J = 17.3, 12.6 Hz, 1H), 2.24 (d, J = 11.5 Hz, 1H), 2.06 – 1.93 (m, 1H).

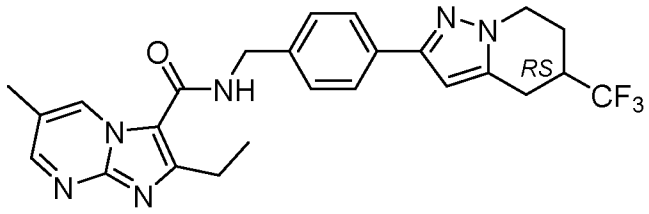
Synthesis of Compound **19ab**



Intermediate I-22 (200 mg, 0.52 mmol) was added to a solution of intermediate II-3a (140 mg, 0.58 mmol), HATU [148893-10-1] (199 mg, 0.52 mmol) and DIPEA [7087-68-5] (0.37 mL, 2.1 mmol) in DMF (2.9 mL) at 0 °C under N2. The mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was washed with brine, separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 2/98). The desired fractions were collected and concentrated in vacuo to yield compound 19ab as a white solid (127 mg, 48%).

1H NMR (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.48 (t, J = 6.0 Hz, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.54 (d, J = 5.8 Hz, 2H), 4.11 – 4.03 (m, 1H), 3.79 (td, J = 12.0, 4.7 Hz, 1H), 3.09 – 2.98 (m, 4H), 2.75 (dd, J = 17.0, 12.5 Hz, 1H), 2.34 (d, J = 0.4 Hz, 3H), 2.33 – 2.23 (m, 4H), 1.94 (ddd, J = 24.6, 11.7, 5.6 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

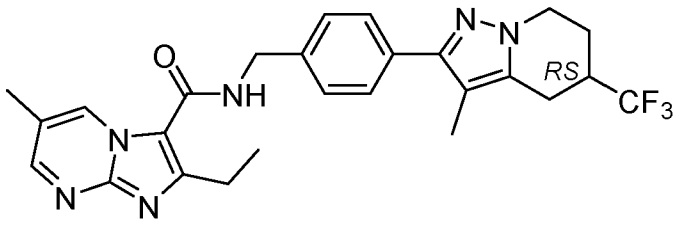
Synthesis of Compound **20ab**



Intermediate I-27 (126 mg, 0.34 mmol) was added to a solution of intermediate II-3a (120 mg, 0.41 mmol), HATU [148893-10-1] (194 mg, 0.51 mmol) and DIPEA [7087-68-5] (0.42 mL, 2.39 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase (Phenomenex Gemini C18 30x100mm 5µm Column; from 59% [25mM NH4HCO3] - 41% [ACN:MeOH (1:1)] to 17% [25mM NH4HCO3] - 83% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 20ab as a white solid (85 mg, 51%).

1H NMR (400 MHz, DMSO) δ 9.18 – 9.11 (m, 1H), 8.53 – 8.45 (m, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.52 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 4.30 (dd, J = 12.9, 3.6 Hz, 1H), 4.11 (td, J = 12.3, 4.8 Hz, 1H), 3.13 (dd, J = 15.9, 4.0 Hz, 1H), 3.02 (q, J = 7.5 Hz, 3H), 2.79 (dd, J = 15.8, 11.2 Hz, 1H), 2.34 (s, 3H), 2.27 (dd, J = 13.3, 2.2 Hz, 1H), 2.04 (qd, J = 11.8, 5.7 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

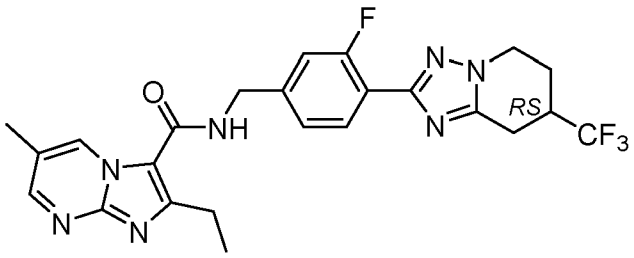
Synthesis of Compound **21ab**



Intermediate I-32 (59 mg, 0.15 mmol) was added to a solution of intermediate II-3a (63 mg, 0.22), HATU [148893-10-1] (88 mg, 0.23 mmol) and DIPEA [7087-68-5] (0.19 mL, 1.08 mmol) in DMF (3 mL) at rt. The mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase (Phenomenex Gemini C18 30x100mm 5µm Column; from 70% [0.1% HCOOH] - 30% [ACN:MeOH (1:1)] to 27% [0.1% HCOOH] - 73% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 21ab as a white solid (25 mg, 32%).

1H NMR (400 MHz, DMSO) δ 9.19 – 9.13 (m, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.50 – 8.47 (m, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 4.56 (d, J = 5.8 Hz, 2H), 4.31 – 4.22 (m, 1H), 4.07 (td, J = 12.3, 4.6 Hz, 1H), 3.08 – 2.96 (m, 4H), 2.72 – 2.60 (m, 1H), 2.34 (s, 3H), 2.30 – 2.22 (m, 1H), 2.08 (s, 3H), 2.06 – 1.93 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

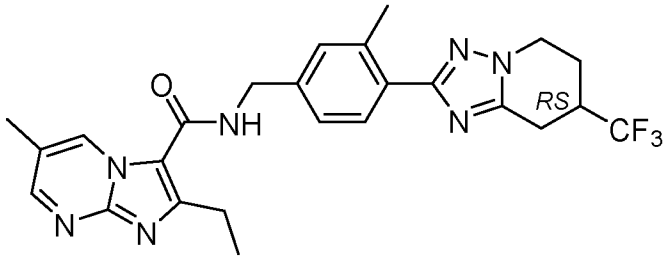
Synthesis of Compound **22ab**



HATU [148893-10-1] (434 mg, 1.14 mmol) was added to a mixture of intermediate I-37 (200 mg, 0.57 mmol), intermediate II-3a (140 mg, 0.68 mmol) and DIPEA [7087-68-5] (0.58 mL, 3.42 mmol) in DMF (10 mL) at rt. The mixture was stirred at rt for 16 h and then a 1M Na2CO3 aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was separated, washed with brine, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica;

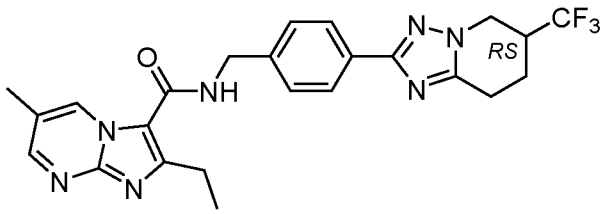
EtOAc in heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 81% [0.1% HCOOH] - 19% [ACN:MeOH (1:1)] to 45% [0.1% HCOOH] - 55% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 22ab as a white solid (122 mg, 42%).
1H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 8.68 (s, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.11 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 9.8 Hz, 2H), 4.75 (d, J = 5.8 Hz, 2H), 4.51 (dd, J = 12.7, 3.9 Hz, 1H), 4.35 (td, J = 12.1, 4.8 Hz, 1H), 3.40 – 3.31 (m, 2H), 3.20 (q, J = 7.5 Hz, 2H), 3.10 (dd, J = 17.6, 12.2 Hz, 1H), 2.66 (s, 3H), 2.47 (s, 1H), 2.29 (ddd, J = 23.7, 11.2, 5.2 Hz, 1H), 1.46 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **23ab**



HATU [148893-10-1] (0.44 g, 1.16 mmol) was added to a mixture of intermediate I-42 (0.2 g, 0.58 mmol), intermediate II-3a (0.18 g, 0.89 mmol) and DIPEA [7087-68-5] (0.59 mL, 3.47 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 16 h and then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was separated, washed with brine, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was washed with toluene and triturated with DCM. The precipitate was collected, and the mother liquor was concentrated in vacuo and the residue was by flash column chromatography (silica; EtOAc in heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 70% [25mM NH4HCO3] - 30% [ACN:MeOH (1:1)] to 27% [25mM NH4HCO3] - 73% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo and the solid obtained combined with the solid previously obtained to yield compound 23ab as a white solid (108 mg, 37%).
1H NMR (400 MHz, DMSO) δ 9.15 (s, 1H), 8.51 (s, 2H), 7.87 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 4.54 (d, J = 5.7 Hz, 2H), 4.34 (dd, J = 12.3, 4.2 Hz, 1H), 4.18 (td, J = 12.0, 4.6 Hz, 1H), 3.20 (d, J = 13.4 Hz, 2H), 3.03 (dd, J = 14.9, 7.5 Hz, 2H), 2.93 (dd, J = 17.3, 12.1 Hz, 1H), 2.58 (s, 3H), 2.34 (s, 3H), 2.31 (s, 1H), 2.13 (ddd, J = 24.9, 12.2, 5.9 Hz, 1H), 1.29 (t, J = 7.4 Hz, 3H).

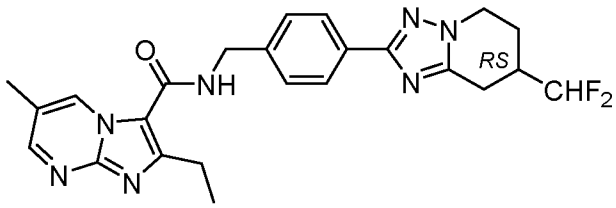
Synthesis of Compound **24ab**



Intermediate II-3a (173 mg, 0.49 mmol) was added to a solution of intermediate I-47 (173 mg, 0.64 mmol), HATU [148893-10-1] (282 mg, 0.74 mmol) and DIPEA [7087-68-5] (0.60 mL, 3.46 mmol) in DMF (5 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with EtOAc (x2). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield compound 24ab as a white solid (149 mg, 62%).

1H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 8.51 (s, 2H), 7.95 (d, J = 7.9 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 4.57 (s, 2H), 4.51 – 4.42 (m, 1H), 4.19 (t, J = 11.2 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.17 (s, 1H), 3.08 – 2.99 (m, 2H), 2.98 – 2.89 (m, 1H), 2.34 (s, 3H), 2.25 (d, J = 11.8 Hz, 1H), 2.09 – 1.95 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H).

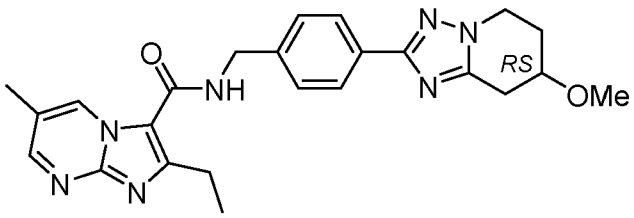
Synthesis of Compound **25ab**



Intermediate I-51 (120 mg, 0.34 mmol) was added to a solution of intermediate II-3a (151 mg, 0.52 mmol), HATU [148893-10-1] (194 mg, 0.51 mmol) and DIPEA [7087-68-5] (0.42 mL, 2.38 mmol) in DMF (3 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with EtOAc (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield compound 25ab as a beige solid (89 mg, 55%).

1H NMR (400 MHz, DMSO) δ 9.20 – 9.12 (m, 1H), 8.56 – 8.45 (m, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 6.20 (td, J = 56.2, 4.1 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.35 – 4.26 (m, 1H), 4.13 (td, J = 12.1, 4.9 Hz, 1H), 3.10 – 2.97 (m, 3H), 2.85 – 2.73 (m, 1H), 2.70 – 2.56 (m, 1H), 2.34 (s, 3H), 2.20 (d, J = 13.5 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

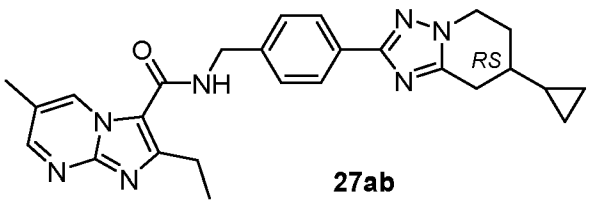
Synthesis of Compound **26ab**



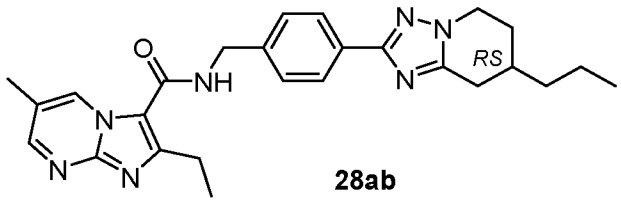
HATU [148893-10-1] (523 mg, 1.37 mmol) was added to a mixture of intermediate I-56 (202 mg, 0.68 mmol), intermediate II-3a (239 mg, 1.16 mmol) and DIPEA [7087-68-5] (0.7 mL, 4.1 mmol) in DMF (5 mL) at rt. The mixture was stirred at rt for 18 h and then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with DCM. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo and the residue was dissolved in a mixture 95/5 of DCM and methanol and the solution was extracted with a saturated NaHCO3 aqueous solution. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The residue was triturated with DIPE/DCM (9:1) and DIPE/DCM (1:1) and dried in vacuo to yield compound 26ab as a white solid (179 mg, 58%).

1H NMR (300 MHz, DMSO) δ 8.35 (s, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 4.28 – 3.99 (m, 4H), 3.95 (d, J = 3.9 Hz, 1H), 3.33 (s, 3H), 3.15 – 2.91 (m, 2H), 2.34 – 2.09 (m, 2H).

Synthesis of Compound **27ab** and Compound **28ab**



27ab



28ab

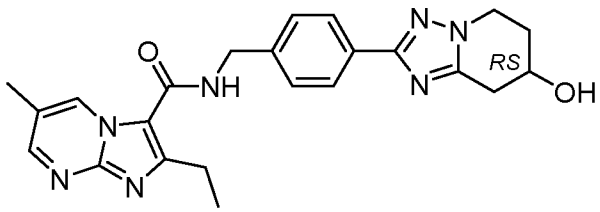
Intermediate I-60 (154 mg, 0.45 mmol) was added to a solution of intermediate II-3a (575 mg, 1.96 mmol), HATU [148893-10-1] (803 mg, 2.11 mmol) and DIPEA [7087-68-5] (1.71 mL, 9.86 mmol) in DMF (4 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with EtOAc (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was purified by reverse phase HPLC (Phenomenex Gemini C18 30x100mm 5µm Column; from 72% [0.1% HCOOH] - 28% [ACN:MeOH (1:1)] to 36% [0.1% HCOOH] - 64% [ACN:MeOH

(1:1)]). The desired fractions were collected and concentrated to yield compounds 27ab (28 mg, 14%) and 28ab (84 mg, 40%) as white solids.

Compound 27ab 1H NMR (400 MHz, DMSO) δ 9.19 – 9.12 (m, 1H), 8.55 – 8.46 (m, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.30 – 4.18 (m, 1H), 4.10 – 3.99 (m, 1H), 3.08 – 2.96 (m, 3H), 2.71 – 2.59 (m, 1H), 2.34 (d, J = 0.6 Hz, 3H), 2.20 – 2.08 (m, 1H), 2.01 – 1.84 (m, 1H), 1.28 (t, J = 7.5 Hz, 4H), 0.81 – 0.71 (m, 1H), 0.51 – 0.41 (m, 2H), 0.28 – 0.15 (m, 2H).

Compound 28ab 1H NMR (400 MHz, DMSO) δ 9.16 (dd, J = 2.4, 1.1 Hz, 1H), 8.54 – 8.46 (m, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.27 – 4.16 (m, 1H), 4.12 – 4.00 (m, 1H), 3.07 – 2.95 (m, 3H), 2.46 – 2.40 (m, 1H), 2.34 (d, J = 0.6 Hz, 3H), 2.16 – 2.05 (m, 1H), 1.97 (s, 1H), 1.80 – 1.66 (m, 1H), 1.45 – 1.34 (m, 4H), 1.28 (t, J = 7.5 Hz, 3H), 0.98 – 0.85 (m, 3H).

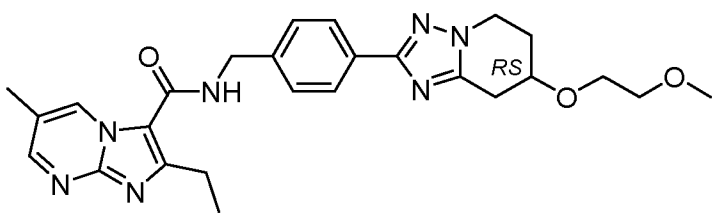
Synthesis of Compound **29ab**



Intermediate I-64 (92 mg, 0.32 mmol) was added to a solution of intermediate II-3a (85 mg, 0.27 mmol), HATU [148893-10-1] (103 mg, 0.27 mmol) and DIPEA [7087-68-5] (0.33 mL, 1.88 mmol) in DMF (3 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was washed with water and triturated with n-pentane and DCM to yield compound 29ab as a pale brown solid (77 mg, 66%).

1H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 8.50 (dd, J = 7.6, 4.1 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 5.21 (d, J = 3.4 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 4.26 (s, 1H), 4.17 (t, J = 6.2 Hz, 2H), 3.09 – 2.97 (m, 3H), 2.79 (dd, J = 17.0, 4.9 Hz, 1H), 2.34 (s, 3H), 2.18 – 1.98 (m, 2H), 1.27 (q, J = 7.8 Hz, 3H).

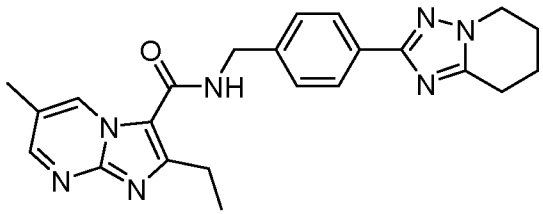
Synthesis of Compound **30ab**



Intermediate I-68 (199 mg, 0.41 mmol) was added to a solution of intermediate II-3a (134 mg, 0.49 mmol), HATU [148893-10-1] (156 mg, 0.41 mmol) and DIPEA [7087-68-5] (0.5 mL, 2.85 mmol) in DMF (3 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The rude product was purified by flash column chromatography (silica; DCM/MeOH 9:1 in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield compound 30ab as a yellow solid (83 mg, 40%).

1H NMR (400 MHz, DMSO) δ 9.16 (d, J = 1.0 Hz, 1H), 8.50 (dd, J = 7.1, 4.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.22 – 4.03 (m, 3H), 3.70 – 3.56 (m, 2H), 3.43 (t, J = 4.7 Hz, 2H), 3.22 (s, 3H), 3.10 (dd, J = 17.1, 4.2 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.1, 4.4 Hz, 1H), 2.34 (s, 3H), 2.29 – 2.20 (m, 1H), 2.15 (dt, J = 13.4, 6.6 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

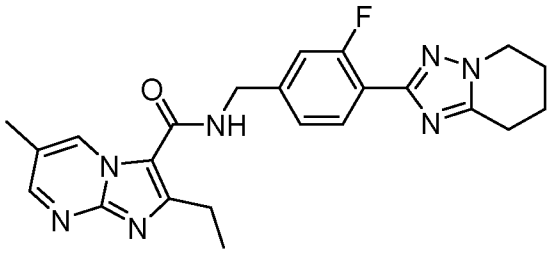
Synthesis of Compound **31ab**



DMF (10 mL) was added to intermediate II-3a (0.19 g, 0.67 mmol) at rt and the mixture was stirred at rt for 10 min. Then, DIPEA [7087-68-5] (0.58 ml, 3.33 mmol) was added and the mixture was stirred at rt for a further 10 min. Then, HATU [148893-10-1] (0.26 g, 0.69 mmol) was added to the mixture at rt and the mixture was stirred at rt for 10 min. Finally intermediate I-73a (0.21 g, 0.42 mmol) was added to the mixture and the reaction mixture was stirred for at rt for 18 hours more. The mixture was diluted with an aqueous saturated NaHCO3 solution and then extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The excess of DMF was co-distilled with toluene (100 ml x 3). The residue was dissolved in DCM and the organic phase was washed with a saturated NaHCO3 aqueous solution. The organic layer was dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 5/95). The desired fractions were collected and concentrated in vacuo. The solid was triturated with diethyl ether and drops of DCM and dried in vacuo to yield compound 31ab as a white solid (128 mg, 72%).

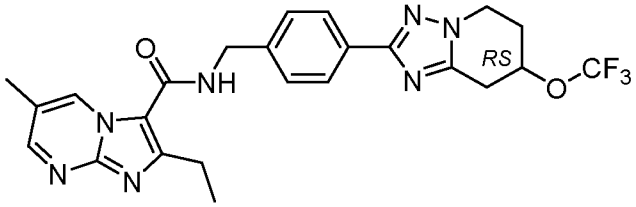
1H NMR (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.50 (dd, J = 7.4, 4.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.05 – 1.98 (m, 2H), 1.94 – 1.85 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **32ab**



Compound 32ab was prepared according to an analogous procedure to the one used for the synthesis of compound 31ab using intermediate I-73b (150 mg, 0.45 mmol) as starting material (116 mg, 59%).
1H NMR (400 MHz, DMSO) δ 9.17 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (dd, J = 9.1, 4.2 Hz, 2H), 7.94 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 9.8 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.07 – 1.98 (m, 2H), 1.96 – 1.85 (m, 2H), 1.29 (t, J = 7.5 Hz, 3H).

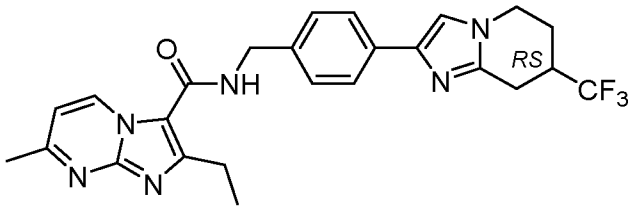
Synthesis of Compound **33ab**



Intermediate I-75 (100 mg, 0.26 mmol) was added to a solution of intermediate II-3a (110 mg, 0.39 mmol), HATU [148893-10-1] (100 mg, 0.26 mmol) and DIPEA [7087-68-5] (0.32 mL, 1.82 mmol) in DMF (3 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with DCM (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo and the residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 30x100mm 5µm; from 70% [25mM NH4HCO3] - 30% [ACN:MeOH (1:1)] to 27% [25mM NH4HCO3] - 73% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 33ab as a yellow solid (10 mg, 7%).
1H NMR (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (dd, J = 6.6, 4.2 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 5.25 – 5.19 (m, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.31 (dt, J = 11.2, 5.5 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.36 (dd, J = 17.4, 4.4 Hz, 1H), 3.17

(dd, J = 17.3, 4.9 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.40 (dd, J = 11.3, 5.6 Hz, 2H), 2.34 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H).

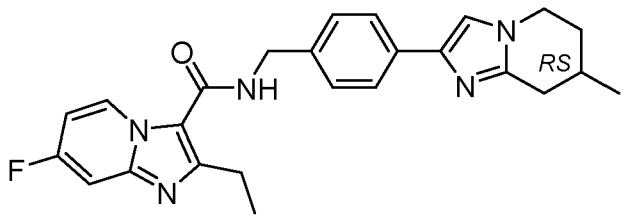
Synthesis of Compound **34ab**



Intermediate I-10 (202 mg, 0.52 mmol) was added to a solution of intermediate II-8a (200 mg, 0.73 mmol), HATU [148893-10-1] (297 mg, 0.78 mmol) and DIPEA [7087-68-5] (0.64 mL, 3.65 mmol) in DMF (10 mL). The reaction mixture was stirred at rt for 16 hours, diluted with a saturated NaHCO3 aqueous solution and extracted with DCM. The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield compound 34ab as a beige solid (177 mg, 69%).

1H NMR (400 MHz, DMSO) δ 9.18 (d, J = 7.0 Hz, 1H), 8.42 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H), 4.20 – 4.11 (m, 1H), 4.05 – 3.90 (m, 1H), 3.12 – 3.04 (m, 2H), 2.99 (q, J = 7.5 Hz, 2H), 2.83 – 2.72 (m, 1H), 2.54 (s, 3H), 2.27 – 2.18 (m, 1H), 2.01 – 1.85 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **35ab**

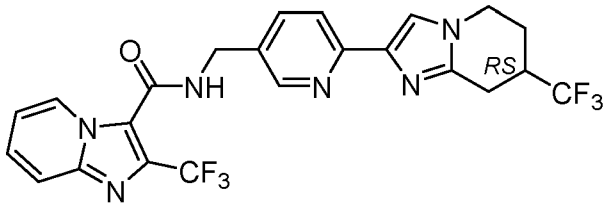


HATU [148893-10-1] (440 mg, 1.15 mmol) was added to a mixture of I-16 (160 mg, 0.57 mmol), II-8c (180 mg, 0.86 mmol) and DIPEA [7087-68-5] (0.6 ml, 3.53 mmol) in DMF (6 ml) and the mixture was stirred at rt for 20 hours. The mixture was washed with a 1M NaHCO3 aqueous solution and extracted with DCM. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The excess of DMF was co-distilled with toluene (100 ml x 3). The residue was dissolved in DCM and the organic phase was washed with a saturated NaHCO3 aqueous solution. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was triturated

with DCM:DIPE 1:1 to yield a white solid. The solid was dried in vacuo and purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo and the residue was triturated with DCM:DIPE 1:1 to yield compound 35ab as a white solid (50 mg, 22%).

1H NMR (400 MHz, DMSO) δ 9.03 (dd, J = 7.4, 6.2 Hz, 1H), 8.45 (t, J = 5.9 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.49 (dd, J = 9.8, 2.6 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.06 (td, J = 7.7, 2.7 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.22 (ddd, J = 12.6, 5.6, 2.9 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.29 (s, 1H), 3.05 – 2.92 (m, 3H), 2.09 (d, J = 5.4 Hz, 1H), 2.05 (dd, J = 13.7, 2.7 Hz, 1H), 1.74 (dtd, J = 13.4, 10.8, 5.8 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **36ab**



HATU [148893-10-1] (229 mg, 0.6 mmol) and DIPEA [7087-68-5] (0.56 mL, 3.22 mmol) were added to a solution of intermediate II-6a (202 mg, 0.74 mmol) in DMF (5 mL) at rt. The mixture was stirred 10 min and then, intermediate I-81 (171 mg, 0.46 mmol) was added, and the reaction mixture was stirred at rt for 16 h. Then a saturated NaHCO3 aqueous solution was added, and the mixture was extracted with EtOAc (x3). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The excess of DMF was co-distilled with toluene (10 mL x 3). The solid was dissolved in DCM and extracted with a saturated NaHCO3 aqueous solution. The organic phase was separated, dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, DCM/MeOH 9:1 in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo. The residue was repurified by reverse phase HPLC (Phenomenex Gemini C18 30x100mm 5µm; from 95% [0.1% HCOOH] - 5% [ACN:MeOH (1:1)] to 63% [0.1% HCOOH] - 37% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo to yield compound 36ab as white solid (41 mg, yield: 17%).

1H NMR (400 MHz, DMSO) δ 9.30 (t, J = 5.8 Hz, 1H), 8.57 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 7.85 – 7.73 (m, 3H), 7.66 (s, 1H), 7.59 – 7.52 (m, 1H), 7.20 (td, J = 6.9, 1.0 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.27 – 4.16 (m, 1H), 4.00 (td, J = 12.3, 4.5 Hz, 1H), 3.17 – 3.04 (m, 2H), 2.80 (dd, J = 17.4, 12.6 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.04 – 1.89 (m, 1H).

SYNTHESIS OF FINAL COMPOUNDS

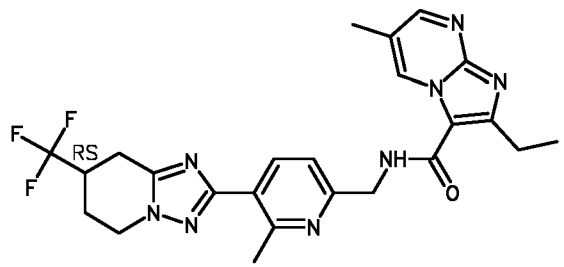
METHOD A: Coupling reaction between carboxylic acid derivative and amine derivative

General procedure

HATU [CAS 148893-10-1] (1.5 to 2.5 eq.) was added to a mixture of carboxylic acid intermediate (1.4 to 4 eq.) and DIPEA (5 to 7 eq.) in DMF. The amine intermediate (1 eq.) was added and the reaction mixture was stired at room temperature for 18 hours. The mixture was washed with a solution of $NaHCO_3$ (sat., aq.) and extracted with an appropirate solvent (DCM or EtOAc). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and the solvents were removed in vacuo.
The crude product was pruified to afford the desired compounds.
Purification techniques used were flash column chromatography (silica, eluent: DCM/MeOH (9:1) in DCM, MeOH in DCM or EtOAc in heptane), reverse phase chromatography or preparative HPLC. Other purification technique may be used if needed, as for example trituration (DIPE, DCM, Et_2O).
It is understood that several purification techniques may be employed in order to get the desired compounds with high purity degree.

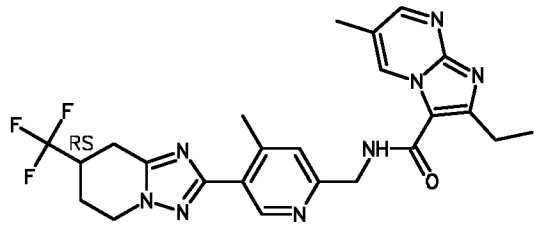
The following compounds were obtained through Method A:

Synthesis of Compound **37**



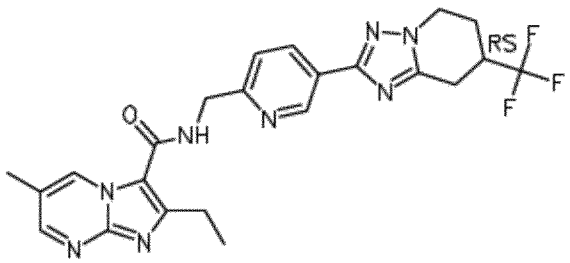
Compound **37** was synthesized from intermediates **II-3a** and **I-138** and obtained as an off-white solid (37.5 mg, 21%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 5.8 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 4.65 (d, J = 5.7 Hz, 2H), 4.37 (dd, J = 12.5, 3.9 Hz, 1H), 4.21 (td, J = 11.7, 4.5 Hz, 1H), 3.22 (d, J = 12.6 Hz, 2H), 3.09 (q, J = 7.5 Hz, 2H), 2.95 (dd, J = 17.7, 12.3 Hz, 1H), 2.81 (s, 3H), 2.34 (s, 3H), 2.33 (s, 1H), 2.13 (dtd, J = 17.2, 11.3, 5.7 Hz, 1H), 1.33 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **38**



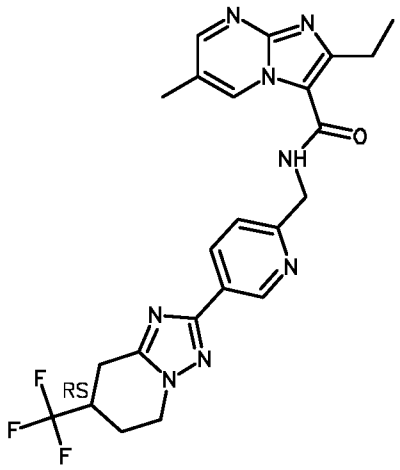
Compound **38** was synthesized from intermediates **II-3a** and **I-139** and obtained as a white solid (41.7 mg, 24%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (d, J = 1.1 Hz, 1H), 8.96 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.52 – 8.49 (m, 1H), 7.34 (s, 1H), 4.65 (d, J = 5.8 Hz, 2H), 4.37 (dd, J = 12.8, 3.7 Hz, 1H), 4.21 (td, J = 12.2, 4.8 Hz, 1H), 3.27 – 3.18 (m, 2H), 3.07 (q, J = 7.5 Hz, 2H), 2.96 (dd, J = 17.8, 12.3 Hz, 1H), 2.60 (s, 3H), 2.34 (s, 3H), 2.32 (d, J = 2.0 Hz, 1H), 2.13 (dtd, J = 16.9, 11.3, 5.5 Hz, 1H), 1.32 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **39**



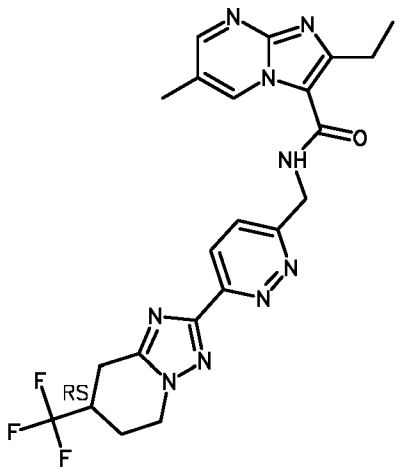
Compound **39** was synthesized from intermediates **II-3a** and **I-146** and obtained as a-white solid (7.6 mg, 11%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (dd, J = 2.2, 1.1 Hz, 1H), 9.10 (d, J = 1.8 Hz, 1H), 8.52 (t, J = 4.7 Hz, 2H), 8.29 (dd, J = 8.2, 2.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 4.69 (d, J = 5.8 Hz, 2H), 4.42 – 4.30 (m, 1H), 4.27 – 4.13 (m, 1H), 3.26 – 3.16 (m, 2H), 3.07 (q, J = 7.5 Hz, 2H), 3.00 – 2.90 (m, 1H), 2.38 – 2.31 (m, 4H), 2.22 – 2.06 (m, 1H), 1.32 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **40**



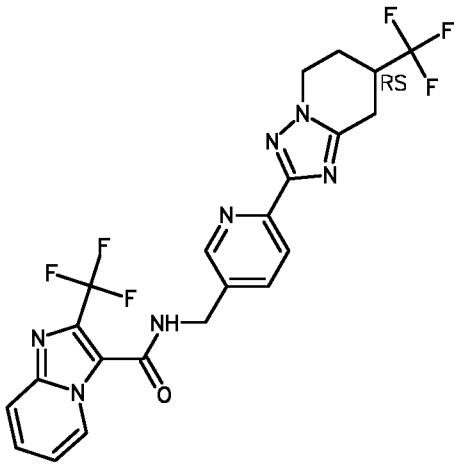
Compound **40** was synthesized from intermediates **II-8a** and **I-146** and obtained as a white solid (48.8 mg, 29%). **^{1}H NMR** (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.46 (t, J = 6.0 Hz, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 9.8 Hz, 2H), 7.06 (d, J = 7.1 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.42 – 4.26 (m, 1H), 4.18 (td, J = 12.0, 4.8 Hz, 1H), 3.18 (d, J = 4.1 Hz, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.98 – 2.88 (m, 1H), 2.55 (s, 3H), 2.41 – 2.21 (m, 1H), 2.21 – 1.95 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **41**



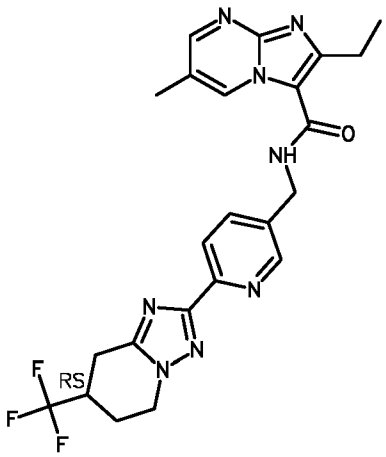
Compound **41** was synthesized from intermediates **II-3a** and **I-144** and obtained as white solid (21.3 mg, 49%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (dd, J = 2.3, 1.1 Hz, 1H), 8.63 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 4.89 (s, 2H), 4.47 – 4.20 (m, 2H), 3.29 – 3.15 (m, 3H), 3.06 (q, J = 7.5 Hz, 2H), 3.04 – 2.94 (m, 1H), 2.34 (d, J = 0.7 Hz, 3H), 2.22 – 2.09 (m, 1H), 1.31 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **42**



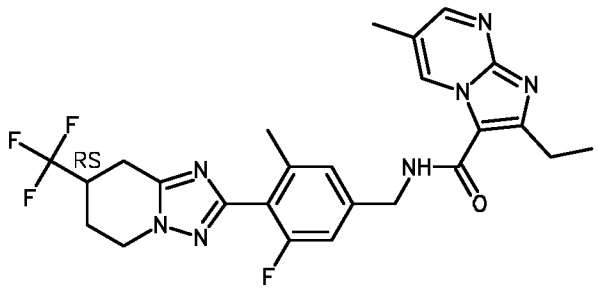
Compound **42** was synthesized from intermediates **II-6a** and **I-145** and obtained as a beige solid (67.2 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 9.36 (t, J = 5.7 Hz, 1H), 8.65 (d, J = 1.8 Hz, 1H), 8.59 (d, J = 7.0 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 8.1, 2.2 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.21 (td, J = 6.9, 1.0 Hz, 1H), 4.63 (d, J = 5.6 Hz, 2H), 4.36 (dd, J = 12.8, 3.6 Hz, 1H), 4.21 (td, J = 12.2, 4.9 Hz, 1H), 3.25 – 3.15 (m, 2H), 3.01 – 2.89 (m, 1H), 2.34 – 2.30 (m, 1H), 2.13 (qd, J = 11.6, 5.8 Hz, 1H).

Synthesis of Compound **43**



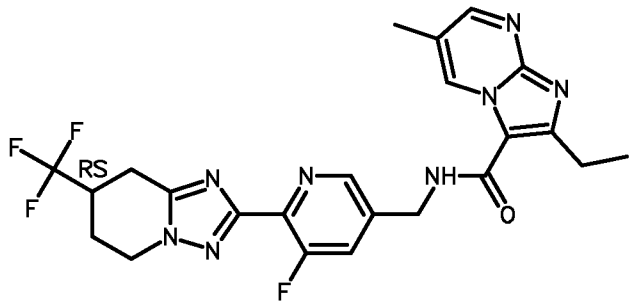
Compound **43** was synthesized from intermediates **II-3a** and **I-145** and obtained as a white solid (66.9 mg, 35%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (s, 1H), 8.65 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 6.0 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 8.1, 2.2 Hz, 1H), 4.60 (d, J = 5.8 Hz, 2H), 4.36 (dd, J = 13.1, 3.9 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.22 (s, 1H), 3.18 (d, J = 4.9 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.94 (dd, J = 17.6, 12.2 Hz, 1H), 2.34 (s, 3H), 2.33 – 2.31 (m, 1H), 2.13 (ddd, J = 17.0, 11.0, 5.4 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **44**



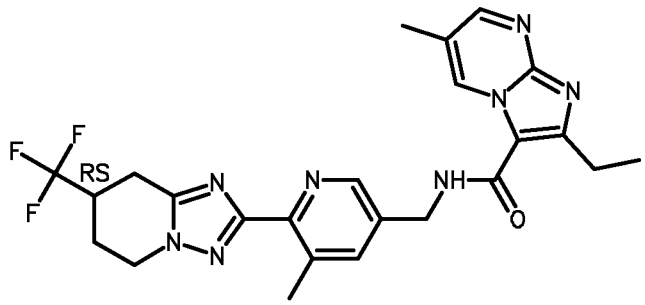
Compound **44** was synthesized from intermediates **II-3a** and **I-122** and obtained as a white solid (117 mg, 47%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.52 (d, J = 2.3 Hz, 1H), 8.50 (d, J = 5.9 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 10.7 Hz, 1H), 4.54 (d, J = 5.8 Hz, 2H), 4.35 (dd, J = 12.7, 3.6 Hz, 1H), 4.20 (td, J = 12.0, 4.5 Hz, 1H), 3.23 (s, 1H), 3.18 (d, J = 4.1 Hz, 1H), 3.04 (q, J = 7.5 Hz, 2H), 2.94 (dd, J = 16.5, 10.6 Hz, 1H), 2.34 (s, 3H), 2.33 – 2.27 (m, 1H), 2.25 (s, 3H), 2.14 (ddd, J = 24.6, 11.4, 5.7 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **45**



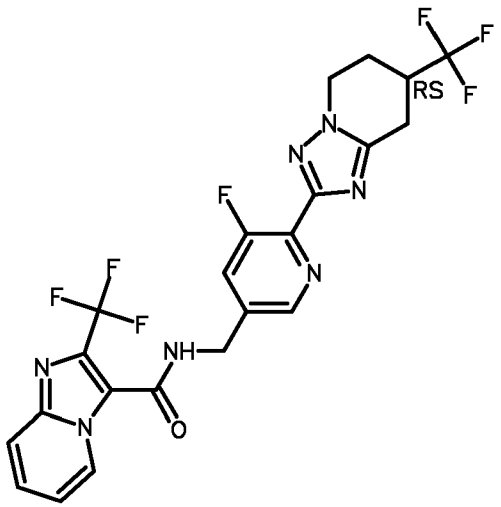
Compound **45** was synthesized from intermediates **II-3a** and **I-141** and obtained as a white solid (50.1 mg, 59%). **^{1}H NMR** (400 MHz, DMSO) δ 9.18 (dd, J = 2.3, 1.1 Hz, 1H), 8.55 (s, 1H), 8.52 (q, J = 4.7 Hz, 2H), 7.82 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 5.8 Hz, 2H), 4.37 (dd, J = 11.7, 4.7 Hz, 1H), 4.26 – 4.17 (m, 1H), 3.25 – 3.17 (m, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.96 (dd, J = 17.5, 12.0 Hz, 1H), 2.33 (d, J = 5.5 Hz, 4H), 2.15 (tt, J = 11.6, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **46**



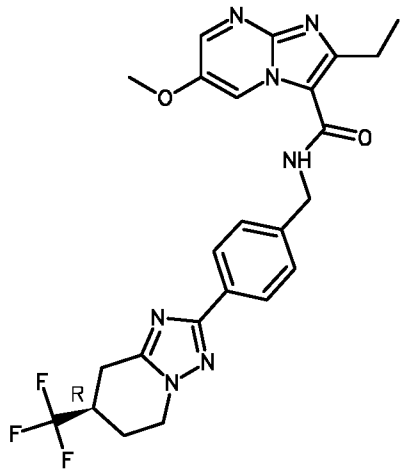
Compound **46** was synthesized from intermediates **II-3a** and **I-143** and obtained as a white solid (125.8 mg, 57%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.4, 1.1 Hz, 1H), 8.56 – 8.51 (m, J = 8.1, 4.1 Hz, 2H), 8.49 (s, 1H), 7.70 (s, 1H), 4.57 (d, J = 5.8 Hz, 2H), 4.36 (dd, J = 13.0, 3.5 Hz, 1H), 4.20 (tt, J = 12.1, 6.1 Hz, 1H), 3.30 (s, 3H), 3.26 – 3.15 (m, J = 12.1 Hz, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.95 (dd, J = 17.3, 12.0 Hz, 1H), 2.34 (d, J = 0.7 Hz, 3H), 2.33 – 2.30 (m, 1H), 2.20 – 2.08 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **47**



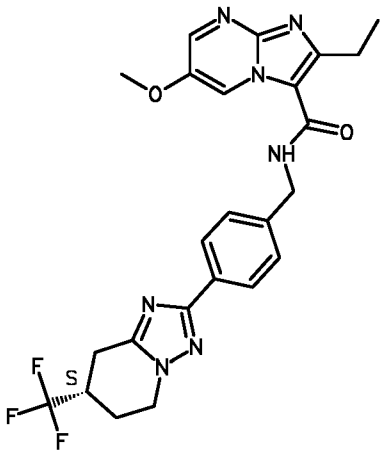
Compound **47** was synthesized from intermediates **II-6a** and **I-147** and obtained as a white solid (20.5 mg, 10%). **^{1}H NMR** (400 MHz, DMSO) δ 9.36 (t, J = 5.8 Hz, 1H), 8.62 (d, J = 7.0 Hz, 1H), 8.55 (s, 1H), 7.83 – 7.78 (m, 2H), 7.60 – 7.55 (m, 1H), 7.21 (td, J = 6.9, 1.1 Hz, 1H), 4.67 (d, J = 5.4 Hz, 2H), 4.38 (dd, J = 12.6, 3.5 Hz, 1H), 4.26 – 4.18 (m, 1H), 3.26 – 3.18 (m, 2H), 2.97 (dd, J = 17.6, 12.3 Hz, 1H), 2.34 (d, J = 10.9 Hz, 1H), 2.15 (qd, J = 11.5, 5.8 Hz, 1H).

Synthesis of Compound **48**



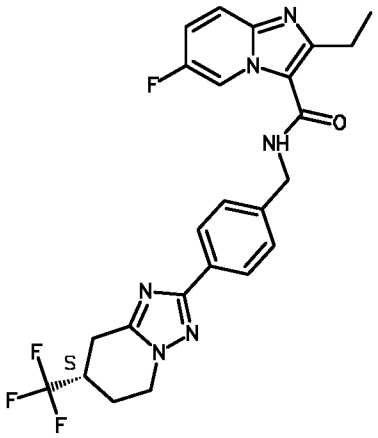
Compound **48** was synthesized from intermediates **II-8b** and **I-88** and obtained as a white solid (1.28 g, 63%). **^{1}H NMR** (400 MHz, DMSO) δ 8.97 (d, J = 3.1 Hz, 1H), 8.52 (d, J = 3.1 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 5.7 Hz, 2H), 4.38 – 4.27 (m, 1H), 4.17 (td, J = 12.1, 4.8 Hz, 1H), 3.86 (s, 3H), 3.26 – 3.13 (m, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.19 – 2.03 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **49**



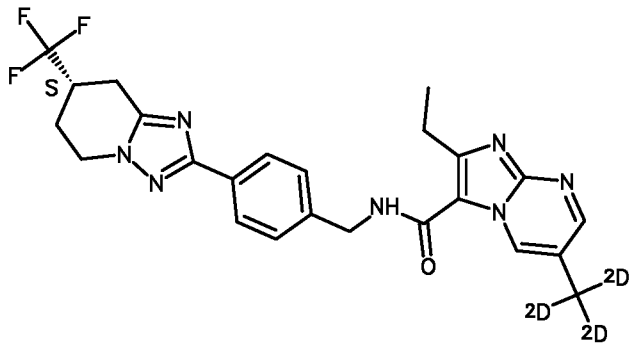
Compound **49** was synthesized from intermediates **II-8b** and **I-87** and obtained as a a white solid (1.10 g, 55%). **^{1}H NMR** (400 MHz, DMSO) δ 8.97 (d, J = 3.1 Hz, 1H), 8.52 (d, J = 3.1 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 5.9 Hz, 2H), 4.37 – 4.26 (m, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.86 (s, 3H), 3.18 (dd, J = 9.5, 8.3 Hz, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.17 – 2.04 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **50**



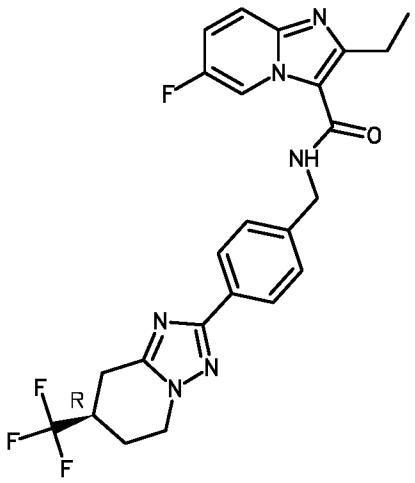
Compound **50** was synthesized from intermediates **II-101** and **I-87** and obtained as a beige solid (225 mg, 86%). **^{1}H NMR** (400 MHz, DMSO) δ 9.08 – 9.04 (m, 1H), 8.47 (t, J = 5.7 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.69 (dd, J = 9.8, 5.4 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 5.6 Hz, 2H), 4.33 (dd, J = 12.7, 3.7 Hz, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.23 – 3.15 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.5, 12.1 Hz, 1H), 2.32 (dd, J = 10.9, 2.1 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **51**



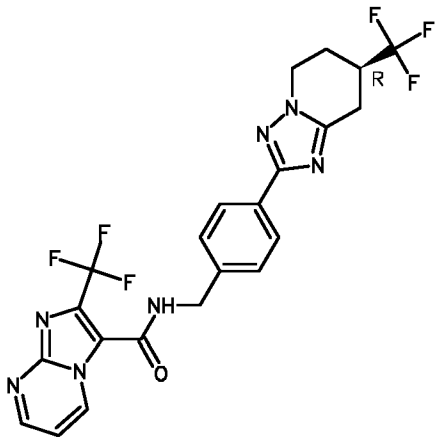
Compound **51** was synthesized from intermediates **II-98** and **I-87** and obtained as a white solid (264 mg, 97%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (d, J = 2.4 Hz, 1H), 8.54 – 8.48 (m, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.37 – 4.28 (m, 1H), 4.17 (td, J = 12.0, 4.9 Hz, 1H), 3.23 – 3.15 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.6, 12.2 Hz, 1H), 2.32 – 2.28 (m, 1H), 2.17 – 2.05 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **52**



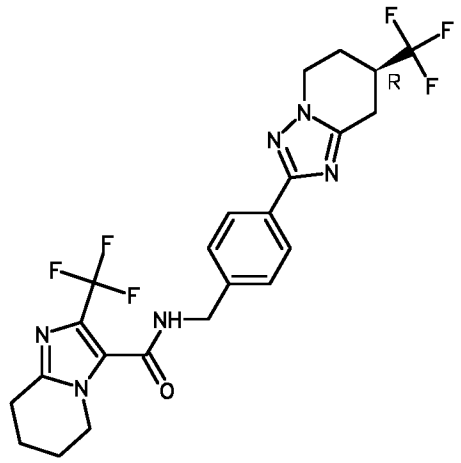
Compound **52** was synthesized from intermediates **II-101** and **I-88** and obtained as a white solid (239 mg, 92%). **^{1}H NMR** (400 MHz, DMSO) δ 9.07 (dd, J = 5.1, 2.3 Hz, 1H), 8.47 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.70 (dd, J = 9.8, 5.3 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.45 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 3.7 Hz, 2H), 4.33 (dd, J = 12.8, 3.5 Hz, 1H), 4.17 (td, J = 12.2, 4.7 Hz, 1H), 3.24 – 3.16 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.3, 11.9 Hz, 1H), 2.35 – 2.28 (m, 1H), 2.12 (ddd, J = 24.5, 11.5, 5.7 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **53**



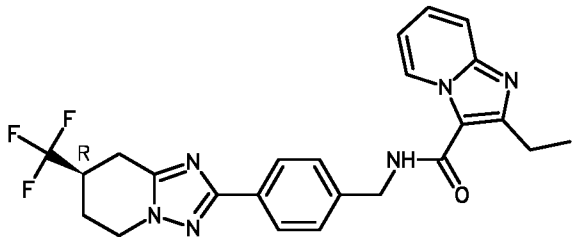
Compound **53** was synthesized from intermediates **II-96** and **I-88** and obtained as a a yellow solid (22.1 mg, 12%). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (t, J = 5.8 Hz, 1H), 9.05 (dd, J = 7.0, 2.0 Hz, 1H), 8.85 (dd, J = 4.1, 2.0 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.36 (dd, J = 7.0, 4.1 Hz, 1H), 4.61 (d, J = 5.7 Hz, 2H), 4.37 – 4.31 (m, 1H), 4.23 – 4.14 (m, 1H), 3.25 – 3.15 (m, 3H), 2.99 – 2.89 (m, 1H), 2.19 – 2.06 (m, 1H). 1H overlapped by solvent signal.

Synthesis of Compound **54**



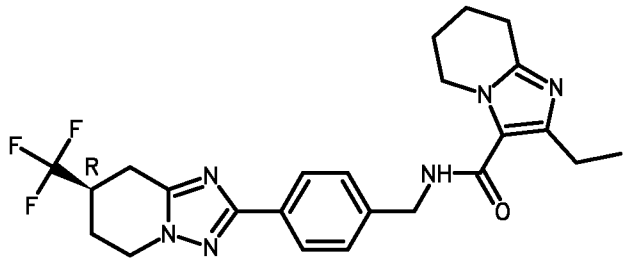
Compound **54** was synthesized from intermediates **II-36** and **I-88** and obtained as a pale yellow solid (61.9 mg, 32.5%). **^{1}H NMR** (400 MHz, DMSO) δ 9.14 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.48 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.8, 3.5 Hz, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.93 (t, J = 5.8 Hz, 2H), 3.24 – 3.14 (m, 2H), 2.93 (dd, J = 17.5, 12.1 Hz, 1H), 2.78 (t, J = 6.3 Hz, 2H), 2.34 – 2.28 (m, 1H), 2.12 (qd, J = 11.5, 5.8 Hz, 1H), 1.91 (d, J = 4.2 Hz, 2H), 1.88 – 1.79 (m, 2H).

Synthesis of Compound **55**



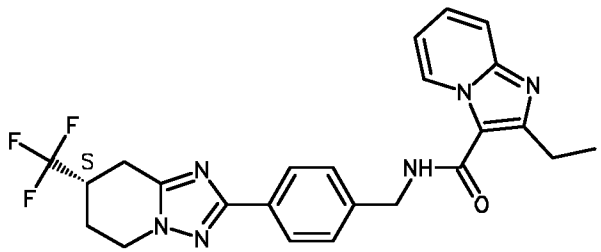
Compound **55** was synthesized from intermediates **II-8b** and **I-88** and obtained as a white solid (126.1 mg, 66%). **^{1}H NMR** (400 MHz, DMSO) δ 8.99 (dt, J = 7.0, 1.0 Hz, 1H), 8.43 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.64 – 7.57 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.41 – 7.33 (m, 1H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.37 – 4.27 (m, 1H), 4.17 (td, J = 11.9, 4.7 Hz, 1H), 3.26 – 3.12 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.19 – 2.05 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **56**



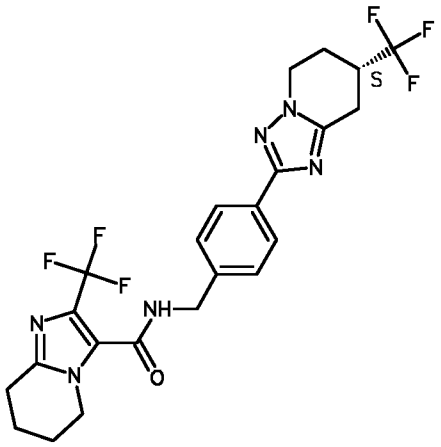
Compound **56** was synthesized from intermediates **II-17a** and **I-88** and obtained as a a white solid (130 mg, 66%). **^{1}H NMR** (400 MHz, DMSO) δ 8.33 (t, J = 5.6 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.37 – 4.27 (m, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 4.01 (t, J = 5.8 Hz, 2H), 3.26 – 3.12 (m, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.73 (t, J = 6.2 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.37 – 2.27 (m, 1H), 2.18 – 2.05 (m, 1H), 1.93 – 1.75 (m, 4H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **57**



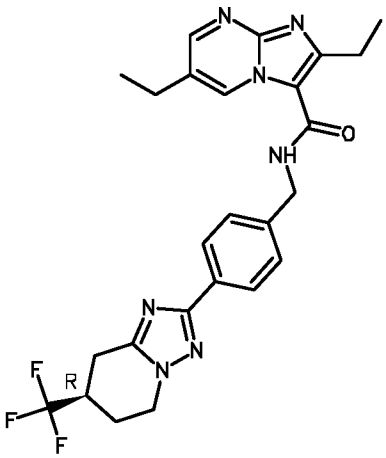
Compound **57** was synthesized from intermediates **II-102** and **I-87** and obtained as a white solid (158 mg, 81%). **^{1}H NMR** (400 MHz, DMSO) δ 8.99 (d, J = 6.9 Hz, 1H), 8.45 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 13.0, 3.4 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.25 – 3.15 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.6, 12.2 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.18 – 2.05 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **58**



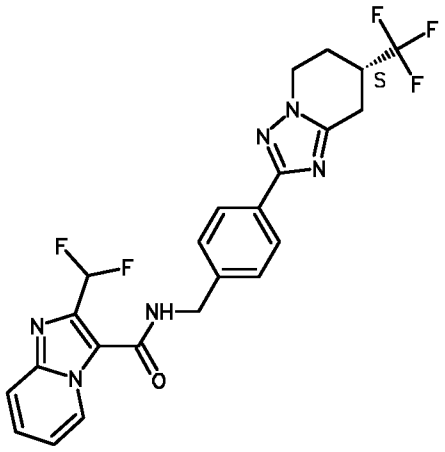
Compound **58** was synthesized from intermediates **II-36** and **I-87** and obtained as a a beige solid (95 mg, 42%). **^{1}H NMR** (400 MHz, DMSO) δ 9.14 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.48 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.9, 3.5 Hz, 1H), 4.17 (td, J = 12.1, 4.8 Hz, 1H), 3.93 (t, J = 5.8 Hz, 2H), 3.26 – 3.12 (m, 2H), 2.93 (dd, J = 18.0, 12.3 Hz, 1H), 2.78 (t, J = 6.3 Hz, 2H), 2.32 – 2.28 (m, 1H), 2.12 (qd, J = 11.6, 5.9 Hz, 1H), 1.91 (d, J = 4.4 Hz, 2H), 1.88 – 1.79 (m, 2H).

Synthesis of Compound **59**



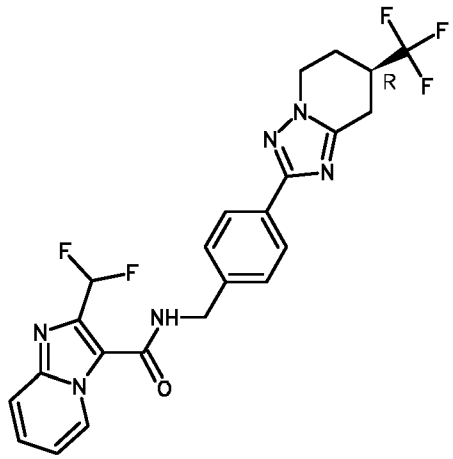
Compound **59** was synthesized from intermediates **II-104** and **I-88** and obtained as a a white solid (85.9 mg, 56%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (d, J = 2.4 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.52 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 5.9 Hz, 2H), 4.34 (dd, J = 12.8, 4.1 Hz, 1H), 4.23 – 4.13 (m, 1H), 3.24 – 3.14 (m, 2H), 3.04 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.8, 12.5 Hz, 1H), 2.72 (q, J = 7.2 Hz, 2H), 2.33 – 2.29 (m, 1H), 2.18 – 2.06 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **60**



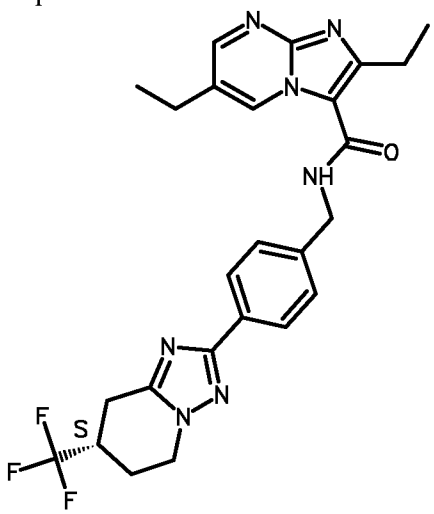
Compound **60** was synthesized from intermediates **II-17b** and **I-87** and obtained as a a pale yellow solid (287 mg, 36%). **^{1}H NMR** (400 MHz, DMSO) δ 9.06 (s, 1H), 8.83 (d, J = 6.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 9.1 Hz, 1H), 7.53 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 53.9 Hz, 1H), 7.17 (td, J = 6.9, 1.1 Hz, 1H), 4.59 (s, 2H), 4.37 – 4.28 (m, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.25 – 3.15 (m, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.18 – 2.04 (m, 1H).

Synthesis of Compound **61**



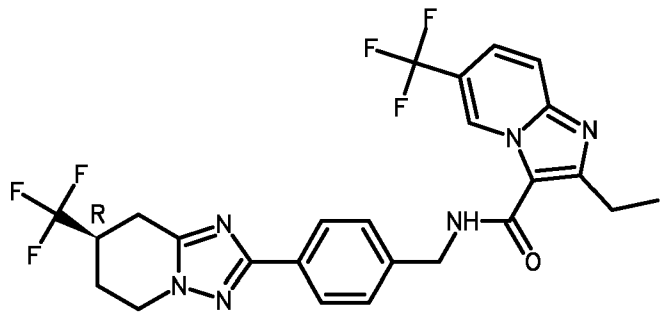
Compound **61** was synthesized from intermediates **II-17b** and **I-88** and obtained as a beige solid (376 mg, 47%). **^{1}H NMR** (400 MHz, DMSO) δ 9.05 (t, J = 5.6 Hz, 1H), 8.82 (d, J = 7.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.76 (dd, J = 9.1, 1.0 Hz, 1H), 7.53 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.35 (t, J = 53.8 Hz, 1H), 7.17 (td, J = 6.9, 1.2 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H), 4.40 – 4.27 (m, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.21 – 2.03 (m, 1H).

Synthesis of Compound **62**



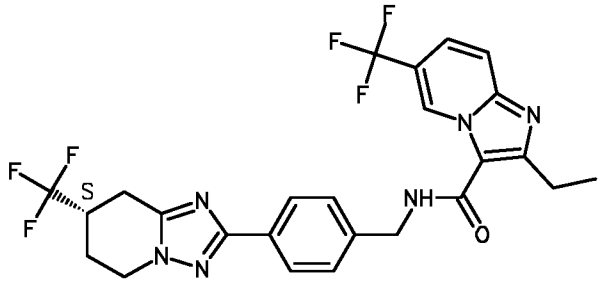
Compound **62** was synthesized from intermediates **II-104** and **I-87** and obtained as a a white solid (69.7 mg, 44%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 2.5 Hz, 1H), 8.51 (t, J = 5.7 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.8, 3.7 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.23 – 3.15 (m, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.7, 12.1 Hz, 1H), 2.74 – 2.68 (m, 2H), 2.36 – 2.27 (m, 1H), 2.11 (qd, J = 11.5, 5.8 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **63**



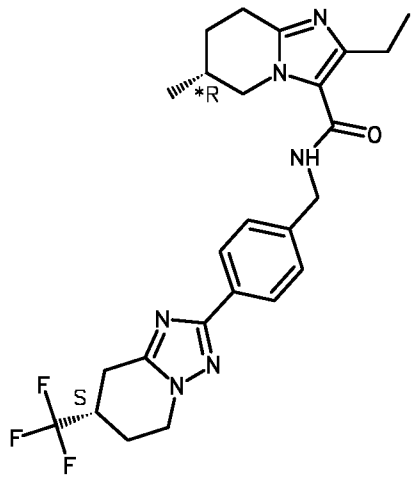
Compound **63** was synthesized from intermediates **II-19** and **I-88** and obtained as a white solid (115 mg, 51%). **^{1}H NMR** (400 MHz, DMSO) δ 9.44 (s, 1H), 8.65 (t, J = 5.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 9.4 Hz, 1H), 7.66 (dd, J = 9.4, 1.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 4.60 (d, J = 5.9 Hz, 2H), 4.37 – 4.30 (m, 1H), 4.24 – 4.13 (m, 1H), 3.25 – 3.16 (m, 2H), 3.06 (q, J = 7.5 Hz, 2H), 2.98 – 2.88 (m, 1H), 2.33 – 2.28 (m, 1H), 2.17 – 2.07 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **64**



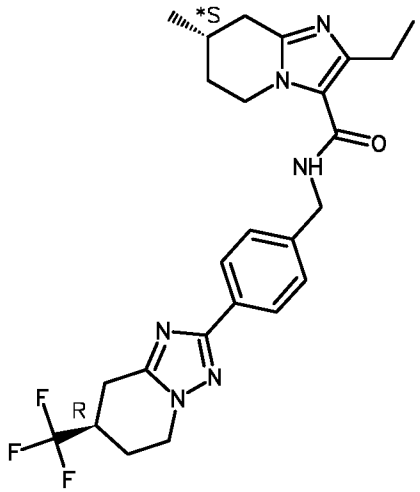
Compound **64** was synthesized from intermediates **II-19** and **I-87** and obtained as a white solid (82.4 mg, 55%). **^{1}H NMR** (400 MHz, DMSO) δ 9.43 (s, 1H), 8.64 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 9.4 Hz, 1H), 7.65 (dd, J = 9.4, 1.9 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 5.9 Hz, 2H), 4.37 – 4.29 (m, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.24 – 3.14 (m, 2H), 3.09 – 3.00 (m, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.18 – 2.05 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **65**



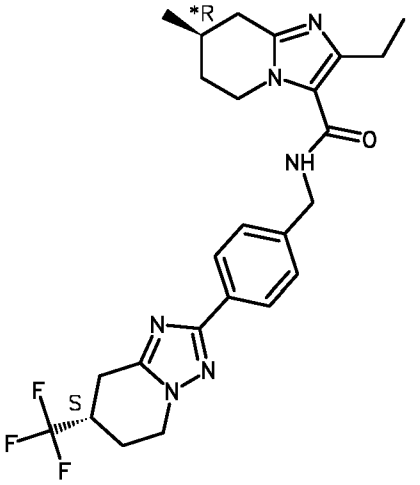
Compound **65** was synthesized from intermediates **II-32** and **II-104** and obtained as a white solid (108.3 mg, 54%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.1 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.45 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.8, 3.7 Hz, 1H), 4.23 – 4.11 (m, 2H), 3.46 (dd, J = 12.7, 10.7 Hz, 1H), 3.27 – 3.12 (m, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.79 (ddd, J = 17.0, 5.5, 2.8 Hz, 1H), 2.73 – 2.59 (m, 3H), 2.32 (dd, J = 10.8, 2.2 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.98 (d, J = 5.6 Hz, 1H), 1.87 (d, J = 12.1 Hz, 1H), 1.46 (qd, J = 11.5, 5.8 Hz, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **66**



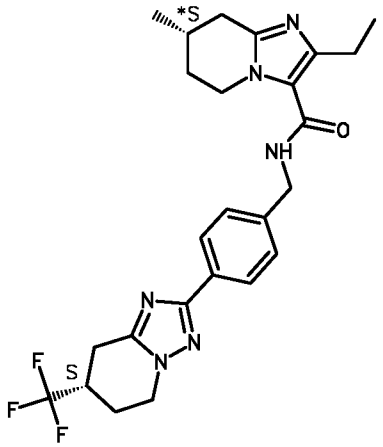
Compound **66** was synthesized from intermediates **II-35** and **I-88** and obtained as a beige solid (126.7 mg, 69%). **^{1}H NMR** (400 MHz, DMSO) δ 8.26 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.32 (dd, J = 12.9, 3.6 Hz, 1H), 4.22 – 4.11 (m, 2H), 3.91 – 3.80 (m, 1H), 3.23 – 3.13 (m, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.84 (dd, J = 16.4, 4.9 Hz, 1H), 2.64 (dt, J = 8.3, 6.8 Hz, 2H), 2.35 – 2.23 (m, 2H), 2.18 – 2.05 (m, 1H), 2.00 – 1.89 (m, 2H), 1.53 (qd, J = 11.3, 5.6 Hz, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **67**



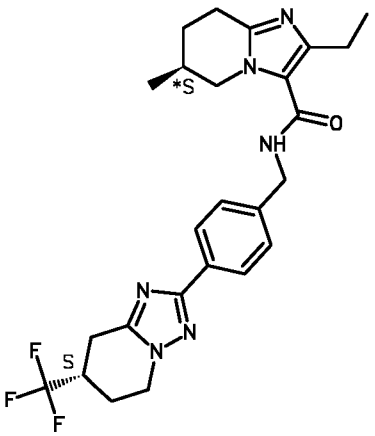
Compound **67** was synthesized from intermediates **II-34** and **I-87** and obtained as a white solid (123 mg, 64%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.38 – 4.29 (m, 1H), 4.22 – 4.13 (m, 2H), 3.93 – 3.82 (m, 1H), 3.24 – 3.14 (m, 2H), 2.98 – 2.88 (m, 1H), 2.88 – 2.80 (m, 1H), 2.68 – 2.61 (m, 2H), 2.38 – 2.24 (m, 2H), 2.19 – 2.05 (m, 1H), 2.01 – 1.87 (m, 2H), 1.59 – 1.46 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **68**



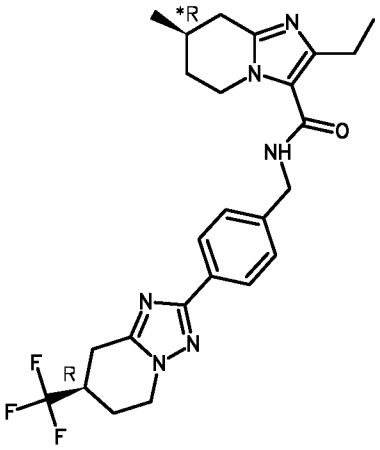
Compound **68** was synthesized from intermediates **II-35** and **I-87** and obtained as a white solid (121.2 mg, 64%). **^{1}H** NMR (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.22 – 4.12 (m, 2H), 3.91 – 3.82 (m, 1H), 3.25 – 3.13 (m, 2H), 2.99 – 2.88 (m, 1H), 2.87 – 2.79 (m, 1H), 2.69 – 2.60 (m, 2H), 2.37 – 2.23 (m, 2H), 2.18 – 2.04 (m, 1H), 2.01 – 1.87 (m, 2H), 1.58 – 1.47 (m, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **69**



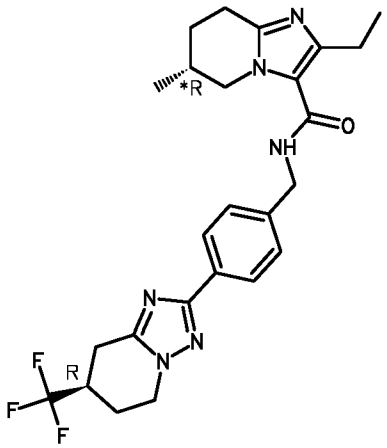
Compound **69** was synthesized from intermediates **II-33** and **I-87** and obtained as a beige solid (89 mg, 45%). **^{1}H NMR** (400 MHz, DMSO) δ 8.26 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.52 – 4.39 (m, 2H), 4.32 (dd, J = 12.8, 3.7 Hz, 1H), 4.23 – 4.10 (m, 2H), 3.46 (dd, J = 12.8, 10.6 Hz, 1H), 3.24 – 3.12 (m, 2H), 2.98 – 2.86 (m, 1H), 2.80 (ddd, J = 17.0, 5.5, 2.9 Hz, 1H), 2.73 – 2.60 (m, 3H), 2.32 (dd, J = 10.7, 2.1 Hz, 1H), 2.11 (qd, J = 11.5, 5.9 Hz, 1H), 2.00 (dd, J = 14.2, 6.3 Hz, 1H), 1.87 (d, J = 11.8 Hz, 1H), 1.46 (qd, J = 11.5, 5.8 Hz, 1H), 1.11 (t, J = 7.5 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **70**



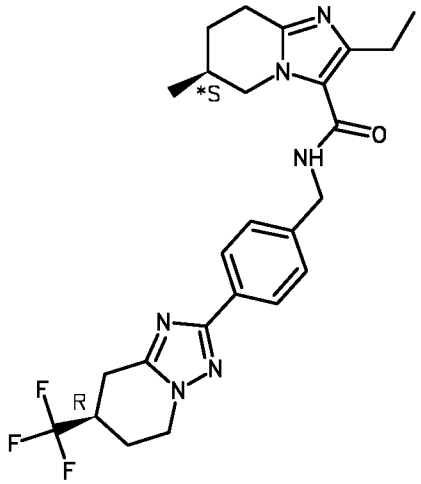
Compound **70** was synthesized from intermediates **II-34** and **I-88** and obtained as a white solid (118.6 mg, 61%). **^{1}H NMR** (400 MHz, DMSO) δ 8.26 (t, J = 5.8 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.36 – 4.26 (m, 1H), 4.21 – 4.13 (m, 2H), 3.87 (td, J = 13.0, 4.5 Hz, 1H), 3.25 – 3.14 (m, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.84 (dd, J = 16.2, 5.1 Hz, 1H), 2.68 – 2.60 (m, 2H), 2.36 – 2.25 (m, 2H), 2.18 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.59 – 1.46 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **71**



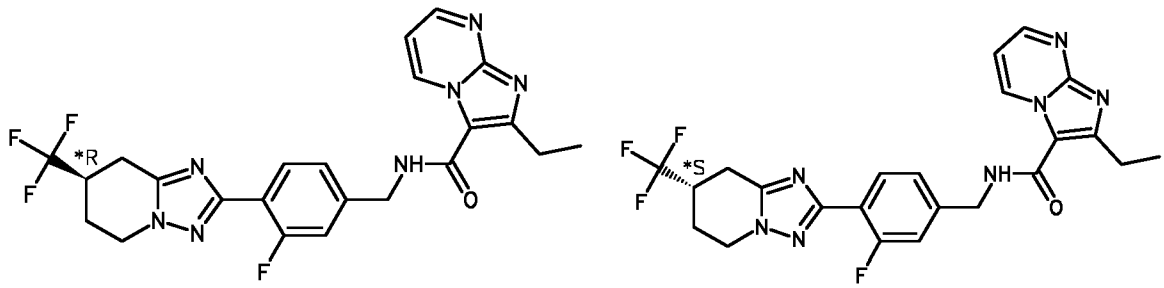
Compound **71** was synthesized from intermediates **II-32** and **I-88** and obtained as a white solid (79.5 mg, 37%). **^{1}H NMR** (400 MHz, DMSO) δ 8.29 – 8.24 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 5.9 Hz, 2H), 4.37 – 4.29 (m, 1H), 4.22 – 4.14 (m, 2H), 3.47 (dd, J = 12.8, 10.7 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.93 (dd, J = 17.5, 12.2 Hz, 1H), 2.80 (ddd, J = 16.9, 5.5, 2.8 Hz, 1H), 2.74 – 2.61 (m, 3H), 2.37 – 2.29 (m, 1H), 2.12 (qd, J = 11.4, 5.7 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.88 (d, J = 11.7 Hz, 1H), 1.46 (qd, J = 11.6, 5.7 Hz, 1H), 1.11 (t, J = 7.5 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **72**



Compound **72** was synthesized from intermediates **II-33** and **I-88** and obtained as a beige solid (101.4 mg, 59%). **^{1}H NMR** (400 MHz, DMSO) δ 8.27 – 8.22 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.9, 3.5 Hz, 1H), 4.21 – 4.12 (m, 2H), 3.46 (dd, J = 12.8, 10.7 Hz, 1H), 3.23 – 3.14 (m, 2H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.80 (ddd, J = 17.0, 5.4, 2.8 Hz, 1H), 2.72 – 2.60 (m, 3H), 2.32 (dd, J = 10.8, 2.1 Hz, 1H), 2.18 – 2.05 (m, 1H), 2.03 – 1.92 (m, 1H), 1.88 (dd, J = 11.3, 2.5 Hz, 1H), 1.52 – 1.40 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

Synthesis of Compounds **73** and **74**



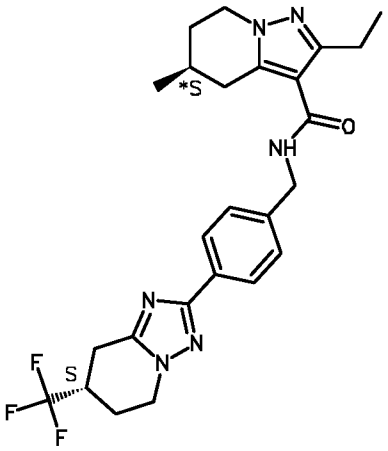
Isomers **73** and **74** were synthesized from intermediates **II-83** and **I-37**, and after SFC separation (Jasco SFC prep system, *i*-cellulose column (Phenomenex) 250*30nm, 5mm particle size, isocratic mode at 100 ml/min of CO2 (50%) / EtOH (50%) / diethylamine (0.1%) at 30 °C, 150 bars) it were obtained **73** (R*) (111.4 mg, 35%) and **74** (S*) (109.5 mg, 34%) as beige solids.

73: **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.57 (t, J = 6.0 Hz, 1H), 7.95 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 9.3 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.59 (d, J = 5.9 Hz, 2H), 4.40 – 4.28 (m, 1H), 4.24 – 4.11 (m, 1H), 3.26 –

3.14 (m, 2H), 3.06 (q, J = 7.5 Hz, 2H), 2.94 (dd, J = 17.7, 12.3 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.19 – 2.06 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

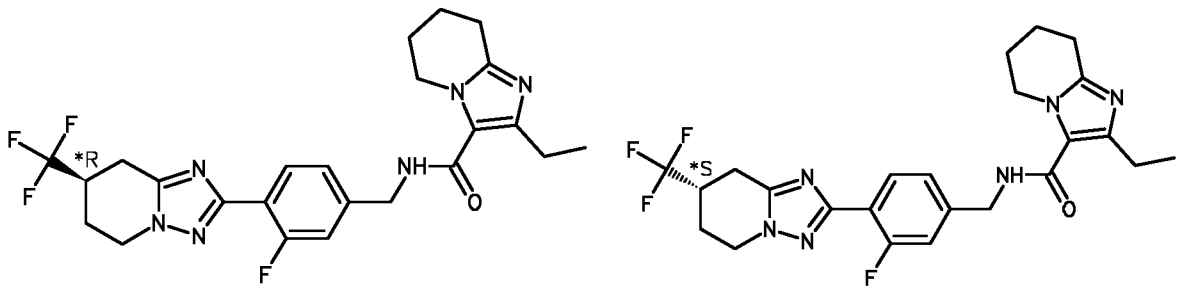
74: **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.55 (t, J = 6.0 Hz, 1H), 7.95 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 9.4 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.59 (d, J = 5.9 Hz, 2H), 4.42 – 4.28 (m, 1H), 4.18 (td, J = 12.0, 4.7 Hz, 1H), 3.27 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.94 (dd, J = 17.7, 12.3 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.19 – 2.05 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **75**



Compound **75** was synthesized from intermediates **II-82** and **I-87** and obtained as a white solid (150.1 mg, 65.6%). **1H NMR** (400 MHz, DMSO) δ 7.93 (d, J = 8.2 Hz, 2H), 7.84 (t, J = 6.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 4.48 – 4.37 (m, 2H), 4.35 – 4.29 (m, 1H), 4.21 – 4.05 (m, 2H), 3.96 – 3.88 (m, 1H), 3.23 – 3.15 (m, 2H), 3.05 (dd, J = 16.6, 4.5 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.70 (q, J = 7.5 Hz, 2H), 2.47 – 2.41 (m, 1H), 2.35 – 2.28 (m, 1H), 2.11 (qd, J = 11.5, 5.9 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.68 – 1.56 (m, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H).

Synthesis of Compounds **76** and **77**

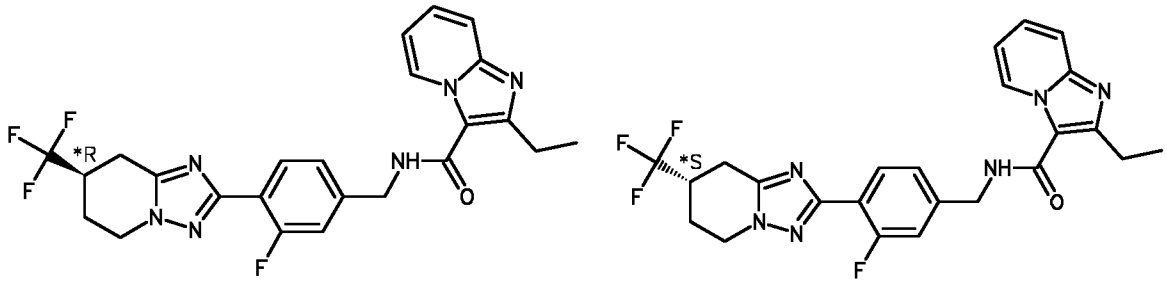


Isomers **76** and **77** were synthesized from intermediates **II-17a** and **I-6,** and after SFC separation (Jasco SFC prep system, *i*-cellulose column (Phenomenex) 250*30nm, 5mm particle size, isocratic mode at 100 ml/min of CO2 (50%) / EtOH (50%) / diethylamine (0.1%) at 30 °C, 150 bars) it were obtained **76** (R*) (64.8 mg, 24%) and **77** (S*) (70.5 mg, 26%) as white solids.

76: **^{1}H NMR** (400 MHz, DMSO) δ 8.28 (t, J = 6.0 Hz, 1H), 7.93 (dd, J = 9.8, 6.1 Hz, 1H), 7.22 (dd, J = 9.4, 4.8 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.35 (dd, J = 12.8, 3.7 Hz, 1H), 4.18 (td, J = 12.1, 4.9 Hz, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.25 – 3.14 (m, 2H), 2.94 (dd, J = 17.6, 12.1 Hz, 1H), 2.71 (dd, J = 11.4, 5.3 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 2.32 (ddd, J = 8.7, 4.8, 2.3 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.90 – 1.71 (m, 4H), 1.11 (t, J = 7.5 Hz, 3H).

77: **^{1}H NMR** (400 MHz, DMSO) δ 8.28 (t, J = 6.0 Hz, 1H), 7.94 (dd, J = 10.2, 5.8 Hz, 1H), 7.23 (dd, J = 9.4, 4.9 Hz, 2H), 4.47 (d, J = 6.0 Hz, 2H), 4.35 (dd, J = 12.8, 3.6 Hz, 1H), 4.19 (td, J = 12.0, 4.8 Hz, 1H), 4.00 (t, J = 5.8 Hz, 2H), 3.28 – 3.12 (m, 2H), 2.94 (dd, J = 17.6, 12.2 Hz, 1H), 2.72 (t, J = 6.2 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 2.33 (ddd, J = 8.8, 4.8, 2.5 Hz, 1H), 2.13 (ddd, J = 24.9, 11.5, 5.8 Hz, 1H), 1.83 (dd, J = 25.1, 4.6 Hz, 4H), 1.12 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **78** and **79**

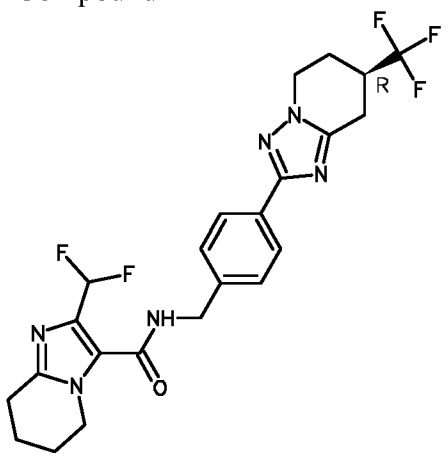


Isomers **78** and **79** were synthesized from intermediates **I-37** and **II-85**, and after SFC separation (Jasco SFC prep system, amylose column (Regis Technologies) 250*30mm, 5mm particle size, isocratic mode at 40 ml/min of CO2 (35%) / EtOH (65%) / diethylamine (0.1%) at 30 °C, 120 bars) it were obtained **78** (R*) (76 mg, 20%) and **79** (S*) (62.6 mg, 16%) as white solids.

78: **^{1}H NMR** (400 MHz, DMSO) δ 9.00 (d, J = 6.9 Hz, 1H), 8.45 (t, J = 5.9 Hz, 1H), 7.95 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.31 (s, 1H), 7.28 (d, J = 3.1 Hz, 1H), 7.02 (td, J = 6.9, 1.2 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.39 – 4.30 (m, 1H), 4.18 (td, J = 11.8, 4.5 Hz, 1H), 3.25 – 3.15 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.98 – 2.89 (m, 1H), 2.36 – 2.29 (m, 1H), 2.18 – 2.07 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

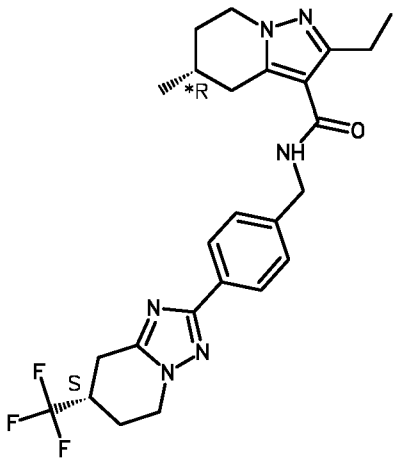
79: **^{1}H NMR** (400 MHz, DMSO) δ 9.00 (d, J = 7.0 Hz, 1H), 8.45 (t, J = 6.0 Hz, 1H), 7.95 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.39 (dd, J = 7.9, 6.6 Hz, 1H), 7.31 (s, 1H), 7.28 (d, J = 3.4 Hz, 1H), 7.03 – 6.99 (m, 1H), 4.58 (d, J = 6.2 Hz, 2H), 4.34 (d, J = 11.6 Hz, 1H), 4.23 – 4.14 (m, 1H), 3.24 – 3.17 (m, 2H), 3.03 (t, J = 7.5 Hz, 2H), 2.98 – 2.88 (m, 1H), 2.35 – 2.28 (m, 1H), 2.20 – 2.05 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **80**



Compound **80** was synthesized from intermediates **I-87 (R)** and **II-37** and obtained as a white solid (123.3 mg, 60%). **^{1}H NMR** (400 MHz, DMSO) δ 8.82 (t, J = 5.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.95 (t, J = 54.3 Hz, 1H), 4.48 (d, J = 5.9 Hz, 2H), 4.36 – 4.29 (m, 1H), 4.23 – 4.12 (m, 1H), 4.04 (t, J = 5.5 Hz, 2H), 3.23 – 3.14 (m, 2H), 2.93 (dd, J = 17.7, 12.0 Hz, 1H), 2.79 (t, J = 6.3 Hz, 2H), 2.32 (d, J = 7.6 Hz, 1H), 2.19 – 2.05 (m, 1H), 1.90 (d, J = 4.9 Hz, 2H), 1.83 (d, J = 4.7 Hz, 2H).

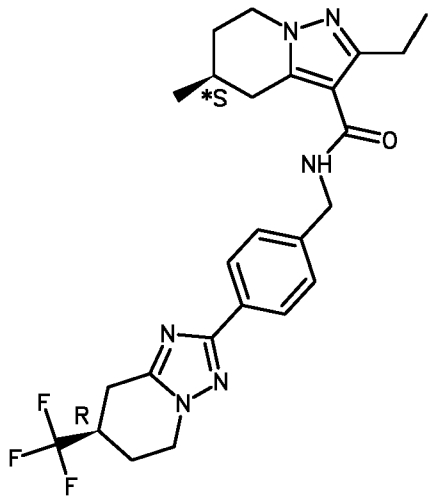
Synthesis of Compound **81**



Compound **81** was synthesized from intermediates **I-87 (S)** and **II-81** and obtained as a pale yellow oil (134.1 mg, 73%). **^{1}H NMR** (400 MHz, DMSO) δ 7.93 (d, J = 8.3 Hz, 2H), 7.83 (t, J = 6.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 4.49 – 4.37 (m, 2H), 4.36 – 4.27 (m, 1H), 4.18 (dd, J

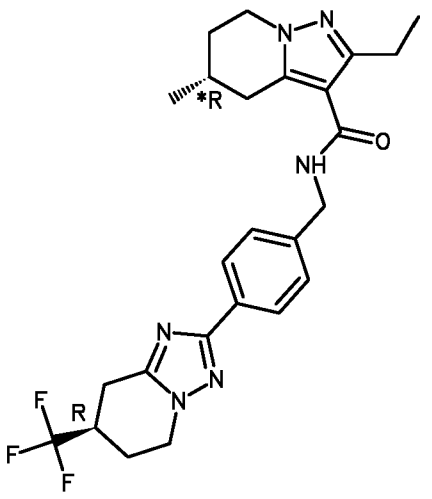
= 11.6, 4.8 Hz, 1H), 4.10 (dtd, J = 10.7, 8.2, 5.2 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.26 – 3.13 (m, 2H), 3.05 (dd, J = 16.5, 4.4 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.74 – 2.66 (m, 2H), 2.48 – 2.40 (m, 1H), 2.37 – 2.27 (m, 1H), 2.19 – 2.05 (m, 1H), 1.98 (t, J = 12.7 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.62 (ddd, J = 24.1, 11.3, 5.7 Hz, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **82**



Compound **82** was synthesized from intermediates **I-87 (R)** and **II-82** and obtained as a pale yellow solid (134.1 mg, 73%). **^{1}H** NMR (400 MHz, DMSO) δ 7.93 (d, J = 8.2 Hz, 2H), 7.83 (t, J = 6.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 4.43 (d, J = 4.4 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.22 – 4.06 (m, 2H), 3.98 – 3.87 (m, 1H), 3.24 – 3.14 (m, 2H), 3.05 (dd, J = 16.7, 4.2 Hz, 1H), 2.92 (dd, J = 17.6, 12.1 Hz, 1H), 2.70 (q, J = 7.5 Hz, 2H), 2.48 – 2.41 (m, 1H), 2.32 (dd, J = 11.1, 2.1 Hz, 1H), 2.19 – 2.05 (m, 1H), 2.01 – 1.84 (m, 2H), 1.69 – 1.55 (m, 1H), 1.13 – 1.02 (m, 6H).

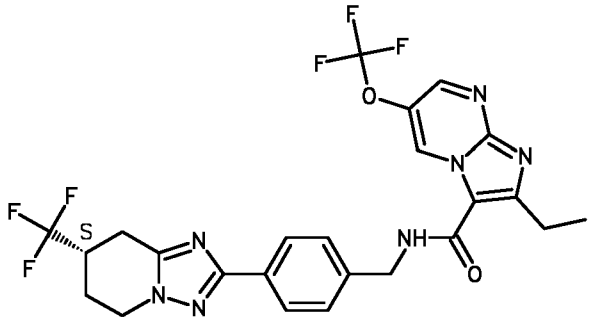
Synthesis of Compound **83**



Compound **83** was synthesized from intermediates **I-87 (R)** and **II-81** and obtained as a pale yellow solid (134.1 mg, 73%). **^{1}H NMR** (400 MHz, DMSO) δ 7.93 (d, J = 8.3 Hz, 2H), 7.83

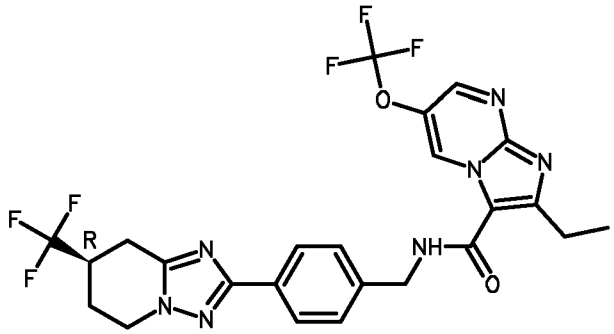
(t, J = 6.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 4.49 – 4.37 (m, 2H), 4.32 (dd, J = 12.8, 3.7 Hz, 1H), 4.17 (td, J = 12.1, 5.0 Hz, 1H), 4.09 (ddd, J = 12.8, 5.4, 2.7 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.25 – 3.13 (m, 2H), 3.05 (dd, J = 16.6, 4.4 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.70 (q, J = 7.5 Hz, 2H), 2.48 – 2.40 (m, 1H), 2.32 (dd, J = 11.1, 2.1 Hz, 1H), 2.11 (qd, J = 11.5, 5.9 Hz, 1H), 1.97 (d, J = 16.3 Hz, 1H), 1.91 (d, J = 5.6 Hz, 1H), 1.62 (qd, J = 11.3, 5.7 Hz, 1H), 1.10 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **84**



Compound **84** was synthesized from intermediates **I-87 (S)** and **II-88** and obtained as a white solid (17.1 mg, 27%). **^{1}H NMR** (400 MHz, DMSO) δ 9.54 (d, J = 2.3 Hz, 1H), 8.83 (d, J = 2.6 Hz, 1H), 8.65 (t, J = 5.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.9, 3.6 Hz, 1H), 4.17 (td, J = 11.9, 4.8 Hz, 1H), 3.24 – 3.15 (m, 2H), 3.08 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.3 Hz, 1H), 2.32 (dd, J = 10.7, 2.0 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

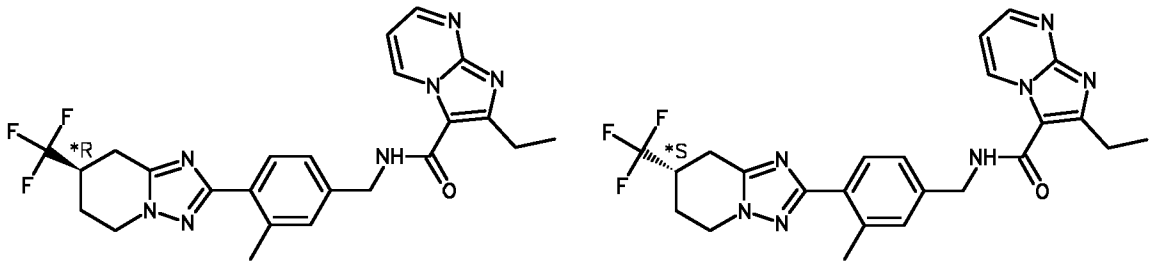
Synthesis of Compound **85**



Compound **85** was synthesized from intermediates **I-87 (R)** and **II-88** and obtained as a white solid (20.7 mg, 26%). **^{1}H NMR** (400 MHz, DMSO) δ 9.54 (d, J = 2.7 Hz, 1H), 8.83 (d, J = 2.8 Hz, 1H), 8.65 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.59 (d, J = 5.9 Hz, 2H), 4.36 – 4.29 (m, 1H), 4.17 (td, J = 12.1, 4.7 Hz, 1H), 3.23 – 3.15 (m,

2H), 3.08 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.18 – 2.05 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **86** and **87**

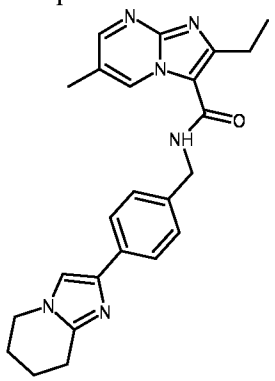


Isomers **86** and **87** were synthesized from intermediates **I-37** and **II-85**, and after SFC separation (Jasco SFC prep system, i-cellulose column (Regis Technologies) 250*30mm, 5mm particle size, isocratic mode at 40 ml/min of CO2 (50%) / EtOH (50%) / diethylamine (0.1%) at 30 °C, 120 bars) it were obtained **86** (R) (83.9 mg, 33%) and **87** (S) (82.4 mg, 33%) as beige solids.

86: **^{1}H NMR** (400 MHz, DMSO) δ 9.32 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 6.9, 4.2 Hz, 1H), 4.55 (d, J = 5.9 Hz, 2H), 4.41 – 4.29 (m, 1H), 4.18 (td, J = 12.1, 4.9 Hz, 1H), 3.26 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.4, 12.0 Hz, 1H), 2.58 (s, 3H), 2.36 – 2.27 (m, 1H), 2.20 – 2.06 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

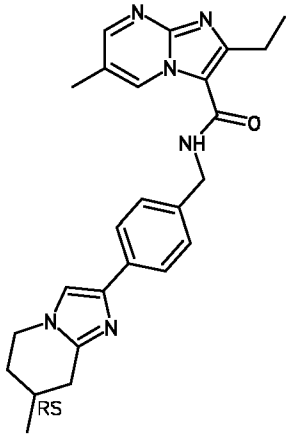
87: **^{1}H NMR** (400 MHz, DMSO) δ 9.32 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 6.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.55 (d, J = 5.9 Hz, 2H), 4.39 – 4.28 (m, 1H), 4.18 (td, J = 12.0, 4.8 Hz, 1H), 3.26 – 3.14 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.4, 12.0 Hz, 1H), 2.58 (s, 3H), 2.38 – 2.28 (m, 1H), 2.20 – 2.07 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **88**



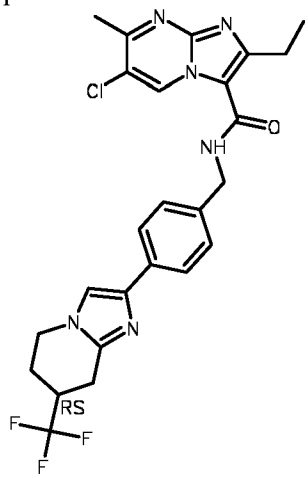
Compound **88** was synthesized from intermediates **I-132** and **II-3a** and obtained as a white solid (75.4 mg, 39%). **^{1}H NMR** (400 MHz, DMSO) δ 9.14 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 8.46 (t, J = 5.9 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.42 (s, 1H), 7.32 (d, J = 8.1 Hz, 2H), 4.51 (d, J = 5.8 Hz, 2H), 3.95 (t, J = 5.7 Hz, 2H), 3.00 (q, J = 7.5 Hz, 2H), 2.74 (t, J = 6.2 Hz, 2H), 2.34 (s, 3H), 1.95 – 1.80 (m, 4H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **89**



Compound **89** was synthesized from intermediates **I-131** and **II-3a** and obtained as a white solid (64.1 mg, 37%). **^{1}H NMR** (400 MHz, DMSO-d6) δ 9.15 (dd, J = 2.1, 1.0 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 6.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 4.51 (d, J = 5.9 Hz, 2H), 4.05 (ddd, J = 12.5, 5.4, 2.7 Hz, 1H), 3.89 (td, J = 11.7, 4.6 Hz, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.88 (dd, J = 17.2, 5.6 Hz, 1H), 2.33 (d, J = 5.0 Hz, 4H), 2.07 – 1.90 (m, 2H), 1.60 (dtd, J = 13.7, 11.3, 5.8 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H).

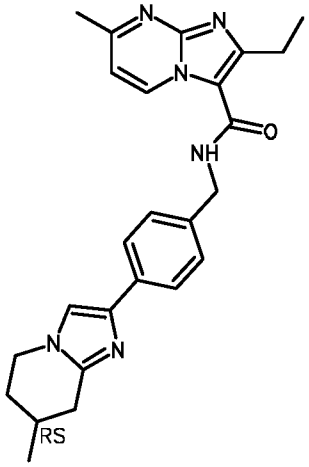
Synthesis of Compound **90**



Compound **90** was synthesized from intermediates **II-110** and **II-8e** and obtained as a white solid (94.5 mg, 21%). **^{1}H NMR** (400 MHz, DMSO) δ 9.35 (s, 1H), 8.49 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 4.51 (d, J = 5.8 Hz, 2H), 4.23

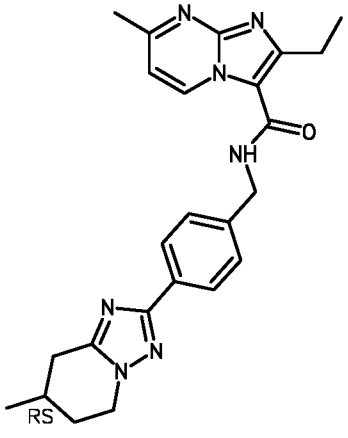
– 4.10 (m, 1H), 3.98 (td, J = 12.1, 4.4 Hz, 1H), 3.11 – 3.04 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.77 (dd, J = 17.3, 12.7 Hz, 1H), 2.61 (s, 3H), 2.23 (d, J = 11.2 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **91**



Compound **91** was synthesized from intermediates **I-131** and **II-8a** and obtained as a white solid (120 mg, 53%). **^{1}H NMR** (400 MHz, DMSO) δ 9.18 (d, J = 7.0 Hz, 1H), 8.41 (t, J = 5.9 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.43 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 4.50 (d, J = 5.8 Hz, 2H), 4.05 (ddd, J = 12.4, 5.4, 2.8 Hz, 1H), 3.88 (td, J = 11.9, 4.7 Hz, 1H), 2.99 (q, J = 7.5 Hz, 2H), 2.87 (dd, J = 16.4, 4.9 Hz, 1H), 2.54 (s, 3H), 2.32 (dd, J = 16.3, 10.3 Hz, 1H), 2.05 – 1.90 (m, 2H), 1.67 – 1.52 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H).

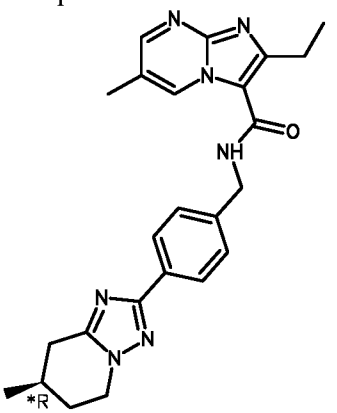
Synthesis of Compound **92**

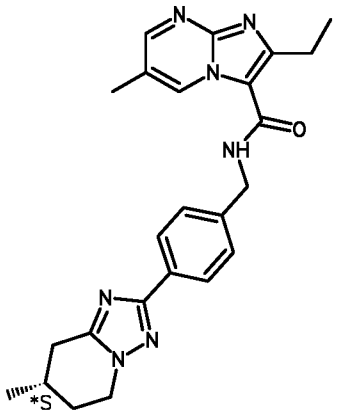


Compound **92** was synthesized from intermediates **I-16** and **II-8a** and obtained as a white solid (90.1 mg, 41%). **^{1}H NMR** (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.45 (t, J = 5.8 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 4.56 (d, J = 5.8 Hz, 2H), 4.27 – 4.17 (m, 1H), 4.15 – 3.96 (m, 1H), 3.05 – 2.93 (m, 3H), 2.55 (s,

3H), 2.47 – 2.40 (m, 1H), 2.15 – 1.99 (m, 2H), 1.81 – 1.67 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **93** and **94**



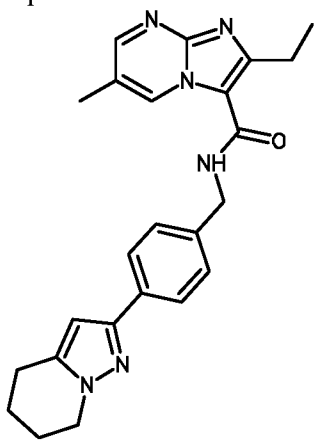


Isomers **93** and **94** were synthesized from intermediates **I-16** and **II-3a**, and after SFC separation (SFC prep system, amylose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode of CO2 (50%) / EtOH (50%) / diethylamine (0.1%) it were obtained compound **93** (R*) (542 mg, 39%) and intermediate **94** (S*) (543 mg, 40%) as beige solids.

93: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 8.51 – 8.48 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 4.22 (ddd, J = 12.5, 5.6, 2.8 Hz, 1H), 4.15 – 4.02 (m, 1H), 3.06 – 2.99 (m, 2H), 2.99 – 2.94 (m, 1H), 2.48 – 2.40 (m, 1H), 2.34 (s, 3H), 2.14 – 1.96 (m, 2H), 1.82 – 1.66 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

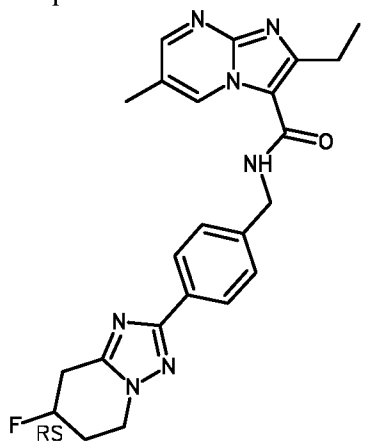
94: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (d, J = 1.2 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.51 – 8.48 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 4.22 (ddd, J = 12.7, 5.9, 3.0 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.02 (q, J = 7.5 Hz, 2H), 3.00 – 2.93 (m, 1H), 2.45 – 2.39 (m, 1H), 2.34 (s, 3H), 2.12 – 1.93 (m, 2H), 1.82 – 1.67 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H).

Synthesis of Compound **95**



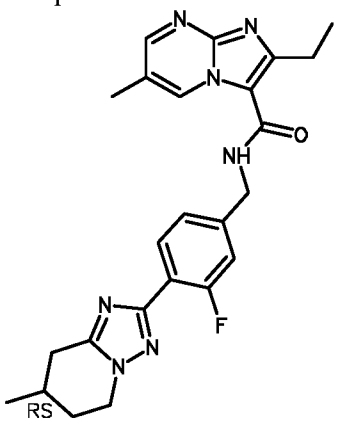
Compound **95** was synthesized from intermediates **I-86** and **II-3a** and obtained as a white solid (63.7 mg, 51%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (d, J = 1.2 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.41 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 4.07 (t, J = 6.1 Hz, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.76 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.01 – 1.94 (m, 2H), 1.84 – 1.74 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **96**



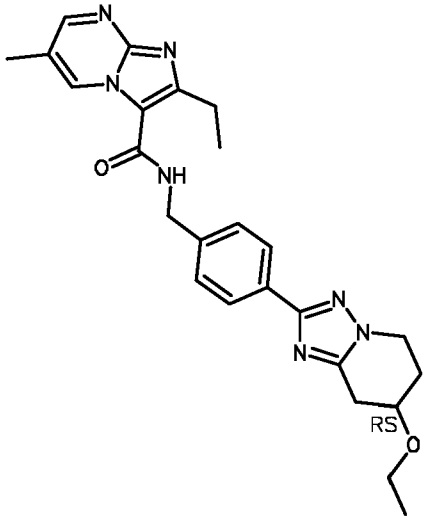
Compound **96** was synthesized from intermediates **I-89** and **II-3a** and obtained as a white solid (21.4 mg, 20 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.2, 1.1 Hz, 1H), 8.50 (dd, J = 9.8, 4.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 5.49 – 5.28 (m, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.38 – 4.09 (m, 2H), 3.29 – 3.15 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.46 – 2.22 (m, 2H), 2.34 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **97**



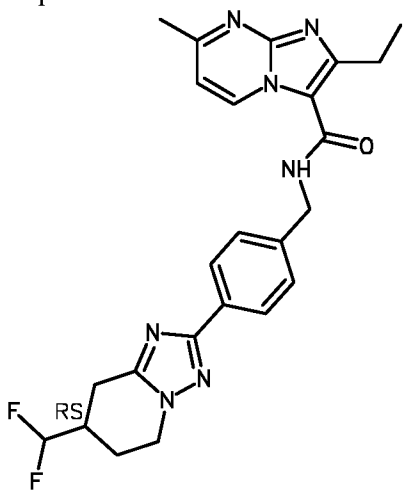
Compound **97** was synthesized from intermediates **I-16** and **II-3a** and obtained as a white solid (115 mg, 41%). **^{1}H NMR** (400 MHz, DMSO) δ 9.17 (d, J = 1.1 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.49 (t, J = 5.9 Hz, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 6.5 Hz, 1H), 7.27 (s, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.24 (ddd, J = 12.6, 5.6, 2.9 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.08 – 2.93 (m, 3H), 2.48 – 2.42 (m, 1H), 2.34 (s, 3H), 2.20 – 2.01 (m, 2H), 1.75 (dtd, J = 13.4, 10.8, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **98**



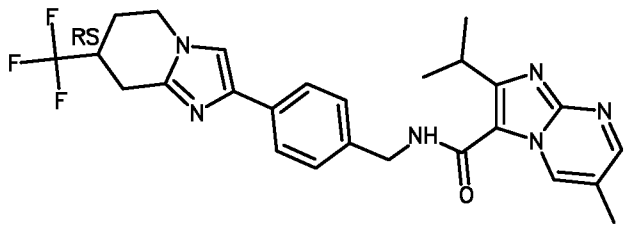
Compound **98** was synthesized from intermediates **I-126** and **II-3a** and obtained as a white solid (213 mg, 58%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (s, 1H), 8.50 (dd, J = 10.7, 4.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.22 – 4.07 (m, 2H), 4.07 – 4.00 (m, 1H), 3.64 – 3.47 (m, 2H), 3.10 (dd, J = 17.1, 4.3 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.1, 4.6 Hz, 1H), 2.34 (s, 3H), 2.27 – 2.11 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H).

Synthesis of Compound **99**



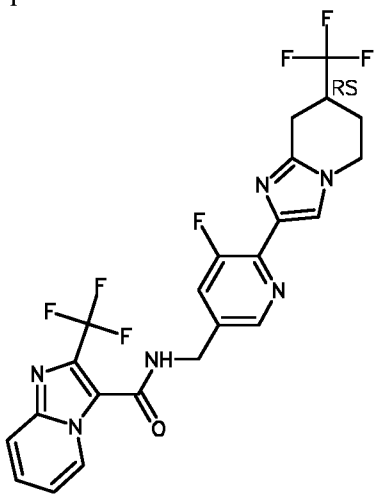
Compound **99** was synthesized from intermediates **I-51** and **II-8a** and obtained as a beige solid (85 mg, 66%). **^{1}H NMR** (400 MHz, DMSO) δ 9.20 (d, J = 7.0 Hz, 1H), 8.46 (t, J = 5.8 Hz, 1H), 7.93 (s, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 6.20 (td, J = 56.3, 3.9 Hz, 1H), 4.56 (d, J = 5.7 Hz, 2H), 4.40 – 4.24 (m, 1H), 4.13 (td, J = 12.1, 4.8 Hz, 1H), 3.09 – 2.95 (m, 3H), 2.79 (dd, J = 16.7, 10.8 Hz, 1H), 2.71 – 2.58 (m, 1H), 2.55 (s, 3H), 2.20 (d, J = 11.9 Hz, 1H), 2.03 – 1.83 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **100**



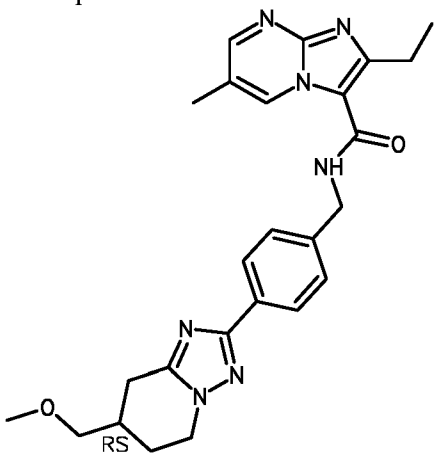
Compound **100** was synthesized from intermediates **I-81** and **II-94** and obtained as a yellow solid (78.3 mg, 46%). **^{1}H NMR** (400 MHz, DMSO) δ 9.06 (dd, J = 2.3, 1.1 Hz, 1H), 8.56 (t, J = 5.9 Hz, 1H), 8.50 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.16 (dd, J = 12.6, 3.5 Hz, 1H), 3.98 (td, J = 12.2, 4.6 Hz, 1H), 3.65 – 3.50 (m, 1H), 3.19 – 3.01 (m, 2H), 2.78 (dd, J = 17.3, 12.6 Hz, 1H), 2.33 (s, 3H), 2.28 – 2.19 (m, 1H), 2.06 – 1.86 (m, 1H), 1.28 (d, J = 6.7 Hz, 6H).

Synthesis of Compound **101**



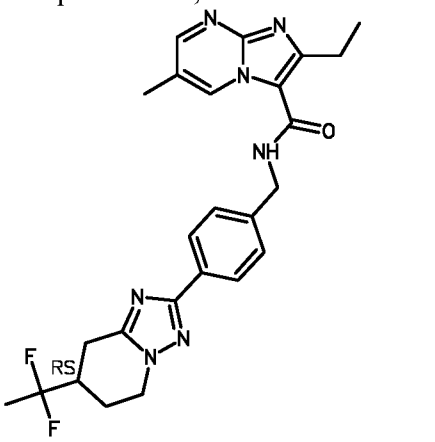
Compound **101** was synthesized from intermediates **I-135** and **II-6a** and obtained as a beige solid (47.2 mg, 23%). **^{1}H** NMR (400 MHz, DMSO) δ 9.33 (t, J = 5.6 Hz, 1H), 8.60 (d, J = 7.0 Hz, 1H), 8.43 (s, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.57 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 7.21 (td, J = 6.9, 1.1 Hz, 1H), 4.61 (d, J = 5.5 Hz, 2H), 4.29 – 4.19 (m, 1H), 4.06 – 3.95 (m, 1H), 3.15 – 3.06 (m, 2H), 2.81 (dd, J = 17.4, 12.8 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.06 – 1.89 (m, 1H).

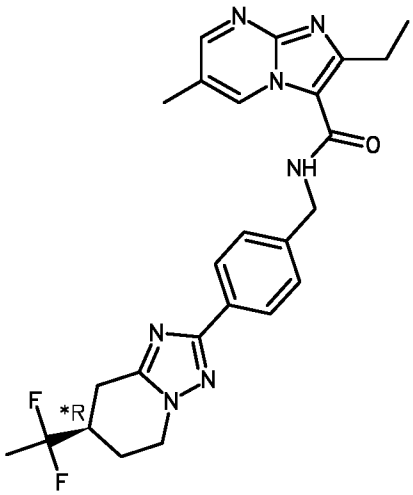
Synthesis of Compound **102**

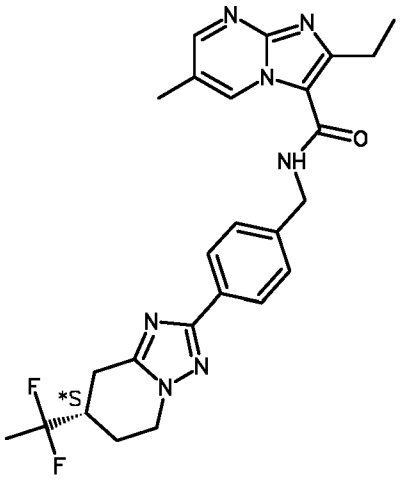


Compound **102** was synthesized from intermediates **I-120** and **II-3a** and obtained as a pale orange solid (105.1 mg, 57%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.4, 1.1 Hz, 1H), 8.54 – 8.47 (m, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.23 (ddd, J = 12.7, 5.5, 3.0 Hz, 1H), 4.08 (td, J = 11.7, 4.7 Hz, 1H), 3.38 (dq, J = 6.0, 2.9 Hz, 2H), 3.29 (s, 3H), 3.06 – 2.93 (m, 3H), 2.60 – 2.53 (m, 1H), 2.33 (dd, J = 6.1, 1.3 Hz, 3H), 2.31 – 2.24 (m, 1H), 2.13 (d, J = 13.4 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.27 (q, J = 7.1 Hz, 3H).

Synthesis of Compound **103**, **104** and **105**







Racemic compound **103** was synthesized from intermediates **I-133** and **II-3a** and obtained as a white solid (128 mg, 80%).

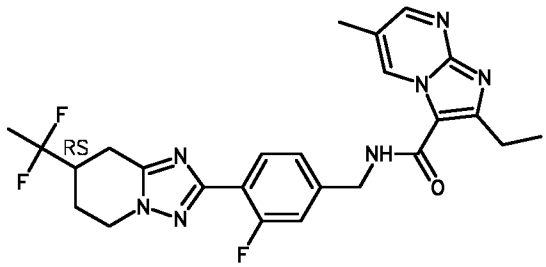
Isomers were separated by SFC (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) to obtain compound **104** (*R) and compound **105** (*S) as white solids.

103: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.54 – 8.46 (m, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.30 (dd, J = 12.7, 3.5 Hz, 1H), 4.12 (td, J = 12.0, 4.6 Hz, 1H), 3.09 (dd, J = 16.6, 4.0 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.79 (dd, J = 16.5, 11.5 Hz, 1H), 2.69 – 2.64 (m, 1H), 2.34 (s, 3H), 2.29 – 2.21 (m, 1H), 2.02 – 1.90 (m, 1H), 1.71 (t, J = 19.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H).

104: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (dd, J = 7.0, 4.2 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.30 (dd, J = 12.6, 3.8 Hz, 1H), 4.12 (td, J = 12.1, 4.6 Hz, 1H), 3.09 (dd, J = 16.5, 4.1 Hz, 1H), 3.01 (t, J = 7.5 Hz, 2H), 2.79 (dd, J = 16.5, 11.4 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.33 (d, J = 5.5 Hz, 3H), 2.25 (dd, J = 13.5, 2.1 Hz, 1H), 1.96 (ddd, J = 25.1, 11.7, 5.7 Hz, 1H), 1.71 (t, J = 19.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H).

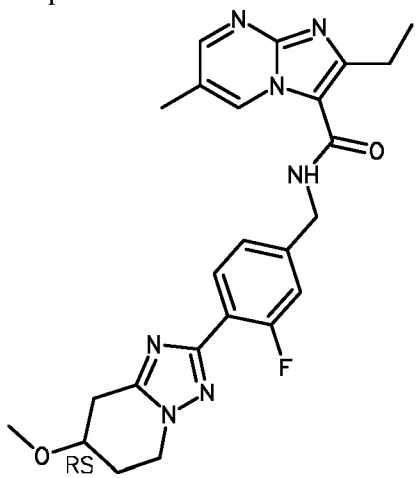
105: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.4, 1.1 Hz, 1H), 8.51 (dd, J = 6.9, 4.2 Hz, 2H), 7.98 – 7.91 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.34 – 4.25 (m, 1H), 4.12 (td, J = 12.1, 4.6 Hz, 1H), 3.09 (dd, J = 16.6, 3.9 Hz, 1H), 3.01 (t, J = 7.5 Hz, 2H), 2.79 (dd, J = 16.5, 11.3 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.34 (t, J = 2.7 Hz, 3H), 2.25 (dd, J = 13.5, 2.3 Hz, 1H), 1.96 (ddd, J = 25.2, 11.7, 5.7 Hz, 1H), 1.71 (t, J = 19.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **106**



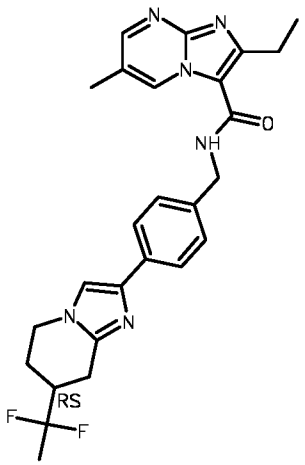
Compound **106** was synthesized from intermediates **I-121** and **II-3a** and obtained as a beige solid (96.2 mg, 48%). **^{1}H NMR** (400 MHz, DMSO) δ 9.17 (s, 1H), 8.52 (s, 2H), 7.94 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 9.6 Hz, 2H), 4.58 (s, 2H), 4.37 – 4.28 (m, 1H), 4.19 – 4.07 (m, 1H), 3.15 – 3.07 (m, 1H), 3.03 (dd, J = 14.8, 7.4 Hz, 2H), 2.87 – 2.74 (m, 1H), 2.74 – 2.60 (m, 1H), 2.34 (s, 3H), 2.26 (d, J = 11.6 Hz, 1H), 2.06 – 1.91 (m, 1H), 1.71 (t, J = 19.5 Hz, 3H), 1.29 (t, J = 7.4 Hz, 3H).

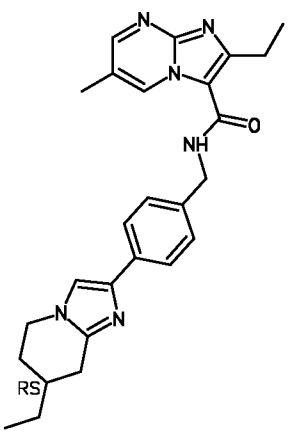
Synthesis of Compound **107**



Compound **107** was synthesized from intermediates **I-56** and **II-3a** and obtained as an orange solid (87.2 mg, 43%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 – 9.10 (m, 1H), 8.54 – 8.48 (m, 2H), 7.93 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 9.8 Hz, 2H), 4.58 (d, J = 5.5 Hz, 2H), 4.25 – 4.06 (m, 2H), 3.99 – 3.90 (m, 1H), 3.32 (s, 3H), 3.10 (dd, J = 17.2, 4.2 Hz, 1H), 3.03 (dd, J = 15.0, 7.5 Hz, 2H), 3.00 – 2.94 (m, 1H), 2.34 (s, 3H), 2.30 – 2.12 (m, 2H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **108** and **109**



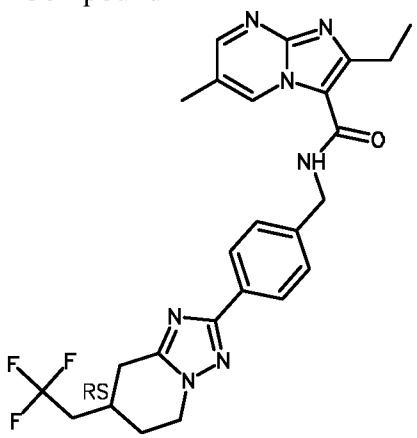


Compounds **108** and **109** were synthesized from intermediates **I-133** and **II-3a**. Purification of the crude mixture delivered compound **108** (CF2) as a white solid (21.4 mg, 40%) and compound **109** (Et) as a yellow solid (12.1 mg, 25%).

108: **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (s, 1H), 8.52 (d, J = 2.2 Hz, 1H), 8.47 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.49 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 4.52 (d, J = 5.7 Hz, 2H), 4.15 (dd, J = 12.4, 3.9 Hz, 1H), 3.93 (dt, J = 12.2, 6.1 Hz, 1H), 3.01 (dt, J = 12.5, 6.2 Hz, 3H), 2.71 – 2.60 (m, 1H), 2.58 – 2.54 (m, 1H), 2.35 (s, 3H), 2.18 (d, J = 12.0 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.70 (t, J = 19.5 Hz, 3H), 1.34 – 1.26 (m, 3H).

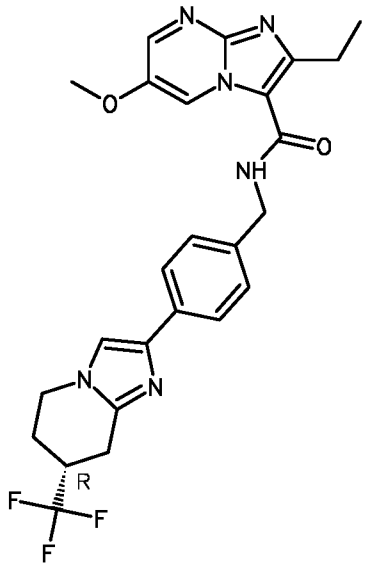
109: **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (dd, J = 2.4, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.46 (t, J = 6.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.43 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 4.51 (d, J = 5.8 Hz, 2H), 4.06 (ddd, J = 12.4, 5.5, 3.0 Hz, 1H), 3.87 (td, J = 11.9, 4.6 Hz, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.91 (dd, J = 16.5, 3.9 Hz, 1H), 2.34 (t, J = 1.8 Hz, 4H), 1.77 (s, 1H), 1.58 (ddd, J = 23.9, 11.0, 5.4 Hz, 1H), 1.46 – 1.36 (m, 2H), 1.27 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.1 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H).

Synthesis of Compound **110**



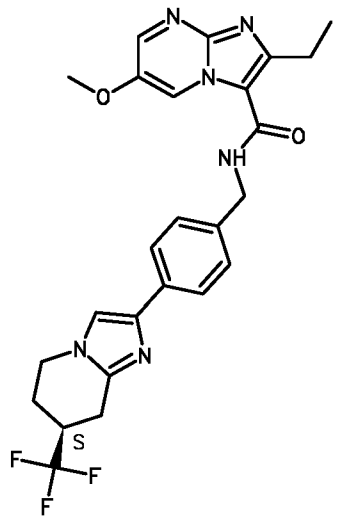
Compound **110** was synthesized from intermediates **I-100b** and **II-3a** and obtained as a white solid (76.2 mg, 39%). **^{1}H NMR** (400 MHz, DMSO) δ 9.17 (s, 1H), 8.55 – 8.48 (m, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 5.8 Hz, 2H), 4.31 – 4.22 (m, 1H), 4.18 – 4.08 (m, 1H), 3.13 – 2.99 (m, 3H), 2.74 – 2.65 (m, 1H), 2.40 (s, 1H), 2.35 (s, 3H), 2.19 (d, J = 12.9 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H). CH2 signal overlapped by DMSO signal. Confirmed by HSQC.

Synthesis of Compound **111**



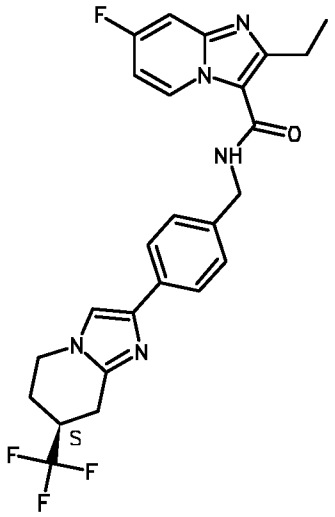
Compound **111** was synthesized from intermediates **I-151a (R)** and **II-8b** and obtained as a white solid (90.2 mg, 65%). **^{1}H NMR** (400 MHz, DMSO) δ 8.95 (d, J = 2.8 Hz, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.44 (t, J = 5.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 4.53 (d, J = 5.4 Hz, 2H), 4.21 – 4.12 (m, 1H), 3.98 (td, J = 12.1, 4.3 Hz, 1H), 3.86 (s, 3H), 3.12 – 3.06 (m, 2H), 3.05 – 2.97 (m, 2H), 2.77 (dd, J = 17.2, 12.7 Hz, 1H), 2.23 (d, J = 12.0 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.27 (t, J = 7.4 Hz, 3H).

Synthesis of Compound **112**



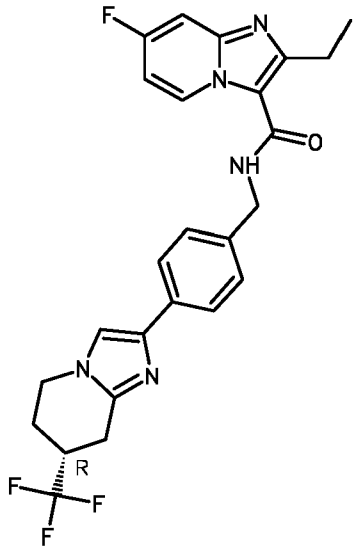
Compound **112** was synthesized from intermediates **II-8b** and **I-151b (S)** and obtained as a white solid (45.1 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 8.95 (d, J = 3.1 Hz, 1H), 8.52 (d, J = 3.1 Hz, 1H), 8.44 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.53 (d, J = 5.9 Hz, 2H), 4.19 – 4.13 (m, 1H), 3.98 (td, J = 12.4, 4.9 Hz, 1H), 3.86 (s, 3H), 3.12 – 2.95 (m, 4H), 2.77 (dd, J = 17.4, 12.9 Hz, 1H), 2.23 (d, J = 11.1 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **113**



Compound **113** was synthesized from intermediates **I-151b (S)** and **II-8c** and obtained as an a pink solid (71.8 mg, 49%). **^{1}H NMR** (400 MHz, DMSO) δ 9.06 – 8.98 (m, 1H), 8.42 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 7.9 Hz, 1H), 7.49 (dd, J = 9.8, 2.3 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.06 (td, J = 7.6, 2.7 Hz, 1H), 4.51 (d, J = 5.9 Hz, 2H), 4.21 – 4.11 (m, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.14 – 3.03 (m, 2H), 3.01 – 2.93 (m, 2H), 2.78 (dd, J = 17.4, 12.7 Hz, 1H), 2.23 (dd, J = 13.2, 2.2 Hz, 1H), 1.95 (qd, J = 11.8, 5.5 Hz, 1H), 1.26 (td, J = 7.5, 3.1 Hz, 3H).

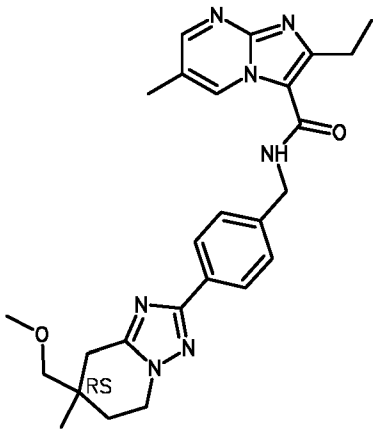
Synthesis of Compound **114**



Compound **114** was synthesized from intermediates **I-151a (R)** and **II-8c** and obtained as a beige solid (63.9 mg, 48%). **^{1}H NMR** (400 MHz, DMSO) δ 9.02 (dd, J = 7.4, 6.2 Hz, 1H), 8.42 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.49 (dd, J = 9.9, 2.4 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.06 (td, J = 7.6, 2.7 Hz, 1H), 4.51 (d, J = 5.7 Hz, 2H), 4.21 – 4.10

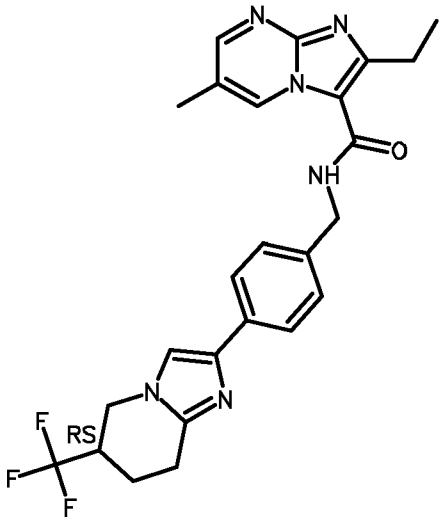
(m, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.15 – 3.02 (m, 2H), 2.97 (q, J = 7.5 Hz, 2H), 2.77 (dd, J = 17.3, 12.6 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.03 – 1.88 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **115**



Compound **115** was synthesized from intermediates **I-111** and **II-3a** and obtained as a pale orange solid (98.9 mg, 57%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.4, 1.1 Hz, 1H), 8.54 – 8.47 (m, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.21 – 4.07 (m, 2H), 3.29 (s, 3H), 3.22 (s, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.78 (d, J = 17.1 Hz, 1H), 2.63 (d, J = 17.0 Hz, 1H), 2.34 (s, 3H), 1.99 (dt, J = 13.9, 6.8 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.00 (s, 3H).

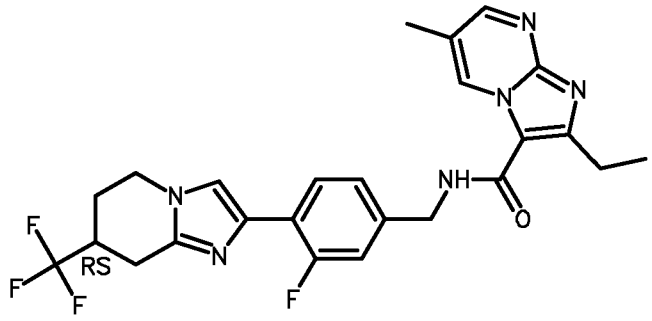
Synthesis of Compound **116**



Compound **116** was synthesized from intermediates **I-135** and **II-3a** and obtained as a white solid (61.3 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 6.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.50 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.30 (dd, J = 12.4, 5.2 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.20 (s, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.97 – 2.88 (m, 1H), 2.83 (ddd, J = 16.8, 11.1, 6.0 Hz, 1H),

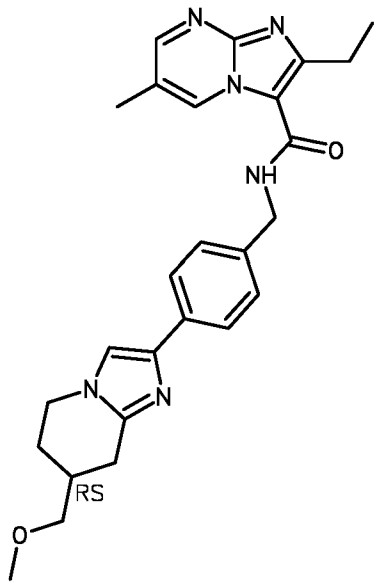
2.34 (s, 3H), 2.24 – 2.14 (m, 1H), 1.92 (ddd, J = 24.3, 11.3, 5.8 Hz, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **117**



Compound **117** was synthesized from intermediates **I-130** and **II-3a** and obtained as a white solid (102 mg, 65%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.48 (s, 1H), 7.98 (t, J = 8.2 Hz, 1H), 7.43 (d, J = 4.3 Hz, 1H), 7.26 – 7.18 (m, 2H), 4.53 (s, 2H), 4.27 – 4.17 (m, 1H), 3.99 (td, J = 12.2, 4.5 Hz, 1H), 3.17 – 3.06 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 17.4, 12.7 Hz, 1H), 2.34 (s, 3H), 2.28 – 2.20 (m, 1H), 1.95 (qd, J = 11.9, 5.6 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

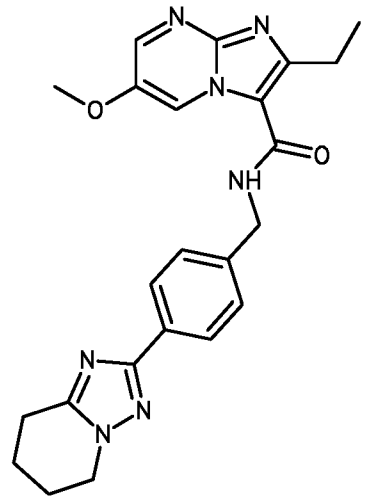
Synthesis of Compound **118**



Compound **118** was synthesized from intermediates **I-136** and **II-3a** and obtained as a white solid (78.8 mg, 24%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 4.51 (d, J = 5.7 Hz, 2H), 4.11 – 4.02 (m, 1H), 3.95 – 3.83 (m, 1H), 3.37 – 3.33 (m,

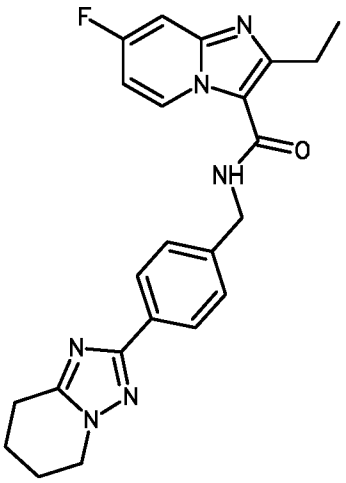
2H), 3.29 (s, J = 1.9 Hz, 3H), 3.01 (q, J = 7.5 Hz, 2H), 2.86 (dd, J = 16.5, 4.3 Hz, 1H), 2.41 (dd, J = 16.5, 10.6 Hz, 1H), 2.34 (d, J = 0.6 Hz, 3H), 2.24 – 2.13 (m, 1H), 2.08 – 1.97 (m, 1H), 1.71 – 1.57 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **119**



Compound **119** was synthesized from intermediates **I-73a** and **II-8b** and obtained as a beige solid (96.6 mg, 48%). **^{1}H NMR** (400 MHz, DMSO) δ 8.97 (d, J = 2.9 Hz, 1H), 8.52 (d, J = 2.9 Hz, 1H), 8.47 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 4.58 (d, J = 4.8 Hz, 2H), 4.13 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 3.03 (q, J = 7.5 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.06 – 1.97 (m, 2H), 1.95 – 1.86 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H).

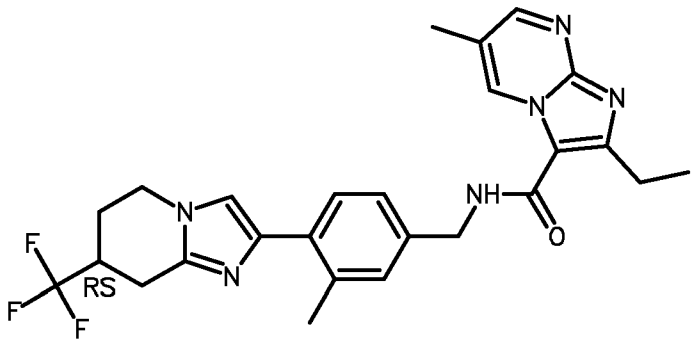
Synthesis of Compound **120**



Compound **120** was synthesized from intermediates **I-73a** and **II-101** and obtained as a white solid (100.5 mg, 51%). **^{1}H NMR** (400 MHz, DMSO) δ 9.04 (dd, J = 7.5, 6.2 Hz, 1H), 8.46 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 9.8, 2.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.07 (td, J = 7.6, 2.7 Hz, 1H), 4.57 (d, J = 5.7 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 2.99 (q, J

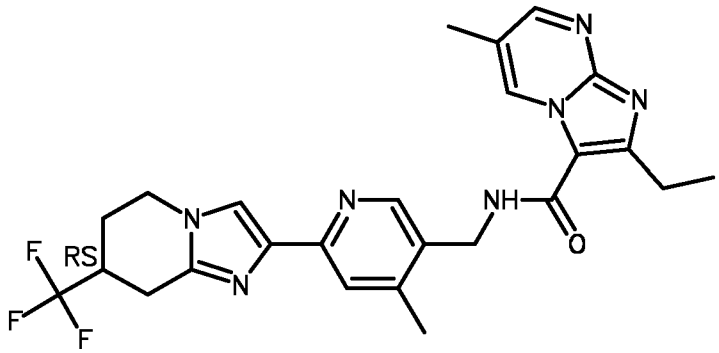
= 7.5 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.06 – 1.99 (m, 2H), 1.95 – 1.87 (m, 2H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **121**



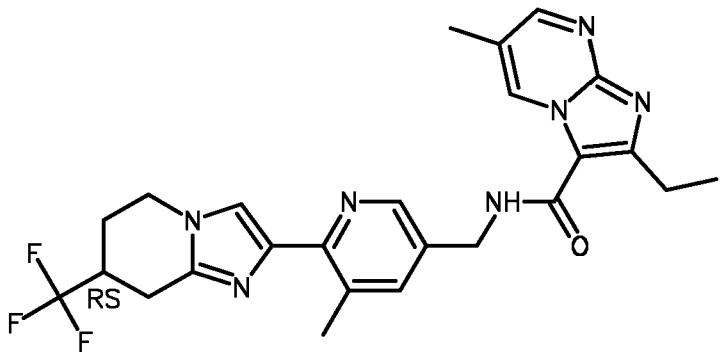
Compound **121** was synthesized from intermediates **I-129** and **II-3a** and obtained as a white solid (87.1 mg, 38%). **^{1}H NMR** (400 MHz, DMSO) δ 9.14 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 8.47 (t, J = 5.2 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.31 (s, 1H), 7.19 (d, J = 4.5 Hz, 2H), 4.50 (d, J = 4.4 Hz, 2H), 4.20 (dd, J = 12.5, 3.8 Hz, 1H), 4.00 (td, J = 12.2, 4.5 Hz, 1H), 3.12 – 3.05 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.79 (dd, J = 17.2, 12.6 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H), 2.24 (d, J = 13.4 Hz, 1H), 1.96 (qd, J = 11.9, 5.4 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **122**



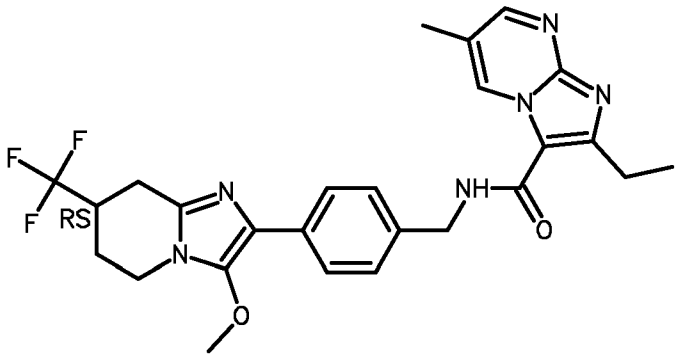
Compound **122** was synthesized from intermediates **I-142** and **II-3a** and obtained as a white solid (78.6 mg, 42%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (s, 1H), 8.84 (s, 1H), 8.52 (d, J = 2.3 Hz, 1H), 8.48 (t, J = 5.7 Hz, 1H), 7.46 (s, 1H), 7.24 (s, 1H), 4.61 (d, J = 5.7 Hz, 2H), 4.22 (dd, J = 12.8, 3.5 Hz, 1H), 4.02 (td, J = 12.3, 4.5 Hz, 1H), 3.21 – 2.98 (m, 4H), 2.81 (dd, J = 17.2, 12.6 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 3H), 2.25 (d, J = 11.3 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.32 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **123**



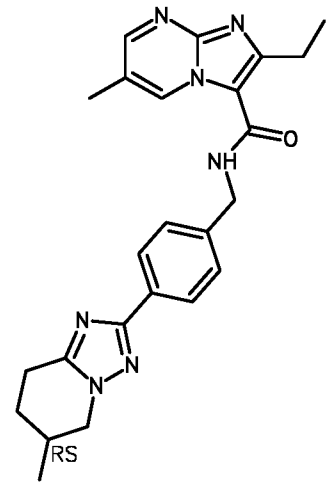
Compound **123** was synthesized from intermediates **I-143** and **II-3a** and obtained as a beige solid (47.2 mg, 26%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (dd, J = 2.4, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 8.36 (d, J = 1.9 Hz, 1H), 7.58 (s, 1H), 7.55 (d, J = 1.6 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H), 4.27 – 4.18 (m, 1H), 4.00 (td, J = 12.2, 4.6 Hz, 1H), 3.18 – 3.05 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 17.2, 12.5 Hz, 1H), 2.61 (s, 3H), 2.34 (d, J = 0.6 Hz, 3H), 2.29 – 2.19 (m, 1H), 2.03 – 1.88 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **124**



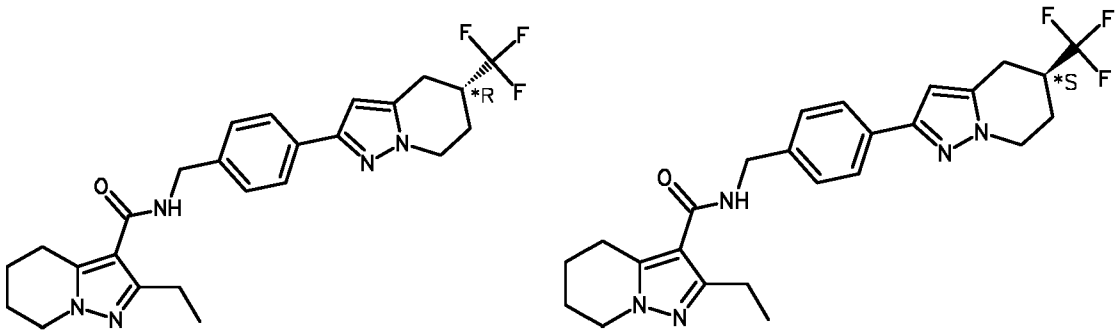
Compound **124** was synthesized from intermediates **I-96** and **II-3a** and obtained as a white solid (60.3 mg, 48%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.47 (t, J = 5.9 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.10 – 3.98 (m, 1H), 3.85 (dd, J = 12.0, 4.6 Hz, 1H), 3.81 (s, 3H), 3.06 – 2.94 (m, 4H), 2.73 (dd, J = 15.9, 11.4 Hz, 1H), 2.34 (s, J = 6.1 Hz, 3H), 2.26 (d, J = 11.4 Hz, 1H), 1.99 – 1.84 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **125**



Compound **125** was synthesized from intermediates **I-16** and **II-3a** and obtained as a white solid (136.6 mg, 58%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (s, 1H), 8.51 (s, 2H), 7.94 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 4.57 (d, J = 5.0 Hz, 2H), 4.28 – 4.19 (m, 1H), 3.69 (t, J = 11.0 Hz, 1H), 3.02 (dd, J = 14.6, 7.2 Hz, 2H), 2.88 (dd, J = 40.3, 13.9 Hz, 2H), 2.34 (s, 3H), 2.20 (s, 1H), 1.96 (s, 1H), 1.60 (d, J = 6.8 Hz, 1H), 1.28 (t, J = 7.3 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H).

Synthesis of Compound **126** and **127**

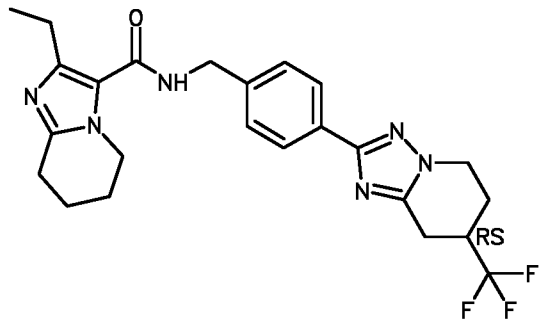


Isomers **126** and **127** were synthesized from intermediates **I-27** and **II-84**, after SFC separation (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) it were obtained **126** (R*) (37.4 mg, yield: 24 %) and compound **127** (S*) (40.3 mg, yield: 26 %) as white solids.

126: **^{1}H NMR** (400 MHz, DMSO) δ 7.82 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.51 (s, 1H), 4.40 (d, J = 6.0 Hz, 2H), 4.34 – 4.25 (m, 1H), 4.11 (td, J = 12.3, 4.7 Hz, 1H), 3.98 (t, J = 6.0 Hz, 2H), 3.18 – 3.08 (m, 1H), 3.09 – 2.95 (m, 1H), 2.89 (t, J = 6.3

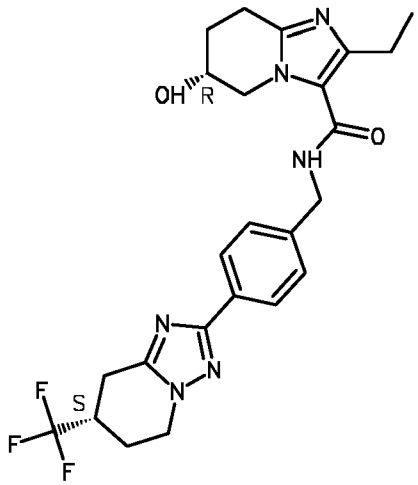
Hz, 2H), 2.79 (dd, J = 15.8, 11.1 Hz, 1H), 2.70 (q, J = 7.5 Hz, 2H), 2.31 – 2.22 (m, 1H), 2.04 (qd, J = 11.8, 5.7 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.81 – 1.67 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H).
127: **^{1}H NMR** (400 MHz, DMSO) δ 7.82 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.51 (s, 1H), 4.40 (d, J = 6.0 Hz, 2H), 4.33 – 4.25 (m, 1H), 4.11 (td, J = 12.3, 4.8 Hz, 1H), 3.98 (t, J = 6.0 Hz, 2H), 3.13 (dd, J = 15.8, 3.7 Hz, 1H), 3.08 – 2.96 (m, 1H), 2.88 (t, J = 6.3 Hz, 2H), 2.79 (dd, J = 15.8, 11.2 Hz, 1H), 2.70 (q, J = 7.5 Hz, 2H), 2.27 (dd, J = 13.2, 2.3 Hz, 1H), 2.03 (ddd, J = 25.0, 11.8, 5.7 Hz, 1H), 1.95 – 1.88 (m, 2H), 1.80 – 1.72 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **128**



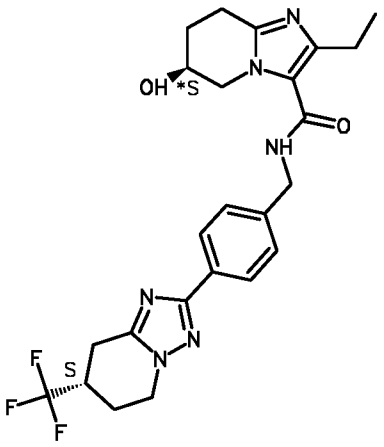
Compound **128** was synthesized from intermediates **I-47** and **II-17a** and obtained as a white solid (78.9 mg, 22%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, *J* = 6.0 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.17 (td, *J* = 12.0, 4.9 Hz, 1H), 3.99 (t, *J* = 5.8 Hz, 2H), 3.18 (dd, *J* = 9.5, 8.3 Hz, 2H), 2.92 (dd, *J* = 17.6, 12.2 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.36 – 2.27 (m, 1H), 2.18 – 2.03 (m, 1H), 1.91 – 1.73 (m, 4H), 1.10 (t, *J* = 7.5 Hz, 3H).

Synthesis of Compound **129**



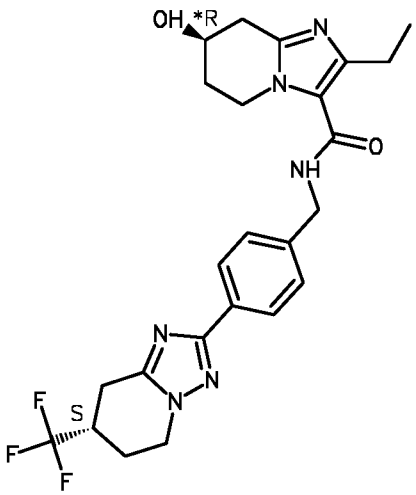
Compound **129** was synthesized from intermediates **I-87 (S)** and **II-65** and obtained as a white solid (22.4 mg, 18%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 5.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 5.12 (d, J = 3.2 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 4.37 – 4.30 (m, 1H), 4.19 (dd, J = 11.9, 4.9 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.87 (dd, J = 13.1, 4.5 Hz, 1H), 3.20 (d, J = 12.9 Hz, 1H), 2.93 (dd, J = 17.5, 12.1 Hz, 1H), 2.81 (dd, J = 15.7, 8.9 Hz, 1H), 2.74 – 2.61 (m, 4H), 2.34 (dt, J = 3.8, 1.9 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.86 (d, J = 4.8 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **130**



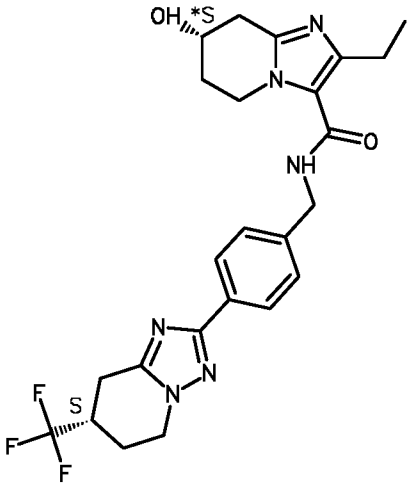
Compound **130** was synthesized from intermediates **I-87 (S)** and **II-66** and obtained as a white solid (69.2 mg, 65%). **^{1}H NMR** (400 MHz, DMSO) δ 8.36 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 5.16 (d, J = 3.2 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 4.32 (dd, J = 11.3, 4.2 Hz, 1H), 4.21 – 4.05 (m, 3H), 3.89 (dd, J = 13.2, 4.1 Hz, 1H), 3.24 – 3.14 (m, 2H), 2.97 – 2.63 (m, 5H), 2.36 – 2.28 (m, 1H), 2.18 – 2.05 (m, 1H), 1.87 (dd, J = 11.4, 5.9 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **131**



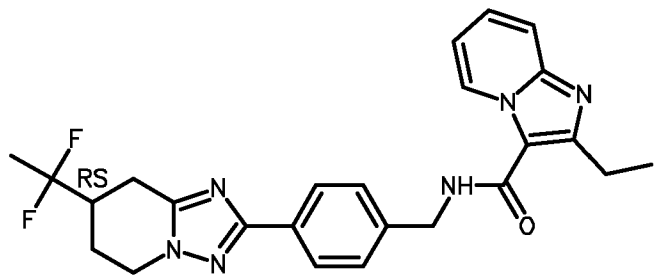
Compound **131** was synthesized from intermediates **I-87 (S)** and **II-67** and obtained as a white solid (79.4 mg, 63%). **^{1}H NMR** (400 MHz, DMSO) δ 8.28 (t, J = 5.9 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 5.06 (d, J = 3.4 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 4.38 – 4.27 (m, 1H), 4.18 (dd, J = 11.7, 4.9 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.07 – 4.00 (m, 2H), 3.24 – 3.12 (m, 2H), 3.00 – 2.85 (m, 2H), 2.69 – 2.59 (m, 3H), 2.37 – 2.25 (m, 1H), 2.18 – 2.05 (m, 1H), 2.00 – 1.91 (m, 1H), 1.92 – 1.81 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **132**



Compound **132** was synthesized from intermediates **I-87 (S)** and **II-68** and obtained as an orange solid (43 mg, 43%). **^{1}H NMR** (400 MHz, DMSO) δ 8.31 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 5.08 (d, J = 3.3 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.8, 3.6 Hz, 1H), 4.22 – 4.13 (m, 1H), 4.13 – 3.97 (m, 3H), 3.24 – 3.14 (m, 2H), 2.99 – 2.86 (m, 2H), 2.71 – 2.56 (m, 3H), 2.38 – 2.27 (m, 1H), 2.11 (ddd, J = 24.7, 11.5, 5.8 Hz, 1H), 2.01 – 1.82 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H).

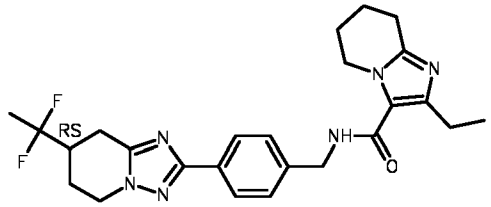
Synthesis of Compound **133**



Compound **133** was synthesized from intermediates **I-160** and **II-102** and obtained as a white solid (53.4 mg, 52%). **^{1}H NMR** (400 MHz, DMSO) δ 8.99 (dt, J = 7.0, 1.1 Hz, 1H), 8.45 (t, J

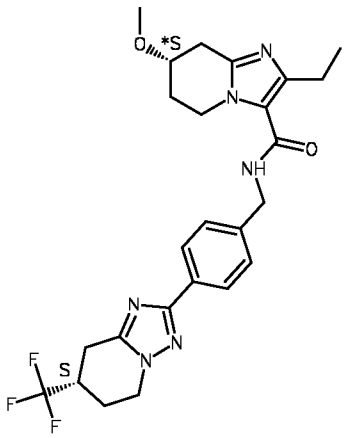
= 6.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.61 (dt, J = 9.0, 1.1 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (ddd, J = 8.9, 6.8, 1.3 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.38 – 4.21 (m, 1H), 4.12 (td, J = 12.3, 4.8 Hz, 1H), 3.10 (dd, J = 16.6, 3.9 Hz, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 16.5, 11.4 Hz, 1H), 2.73 – 2.57 (m, 1H), 2.26 (dd, J = 13.4, 2.0 Hz, 1H), 1.96 (tt, J = 18.9, 6.5 Hz, 1H), 1.72 (t, J = 19.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **134**



Compound **134** was synthesized from intermediates **I-160** and **II-17a** and obtained as a white solid (50 mg, 49%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.34 – 4.27 (m, 1H), 4.11 (td, J = 12.1, 4.7 Hz, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.09 (dd, J = 16.6, 3.9 Hz, 1H), 2.79 (dd, J = 16.4, 11.4 Hz, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.64 (q, J = 7.5 Hz, 3H), 2.25 (dd, J = 13.4, 2.1 Hz, 1H), 1.96 (ddd, J = 25.2, 11.8, 5.8 Hz, 1H), 1.89 – 1.77 (m, 4H), 1.71 (t, J = 19.5 Hz, 3H), 1.10 (t, J = 7.5 Hz, 3H).

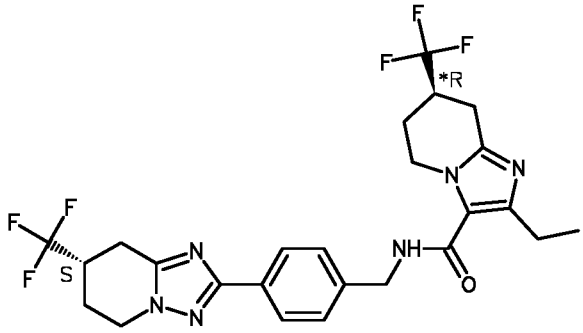
Synthesis of Compound **135**



Compound **135** was synthesized from intermediates **I-87 (S)** and **II-70** and obtained as a white solid (39 mg, 29%). **^{1}H NMR** (400 MHz, DMSO) δ 8.28 (t, J = 6.0 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.37 – 4.25 (m, 1H), 4.17 (td, J = 11.9, 4.7 Hz, 1H), 4.10 – 4.01 (m, 1H), 4.01 – 3.90 (m, 1H), 3.84 – 3.76 (m, 1H), 3.29 (s, 3H), 3.23 – 3.14 (m, 2H), 2.99 – 2.87 (m, 2H), 2.78 (dd, J = 16.9, 4.9 Hz, 1H), 2.64 (q, J = 7.5

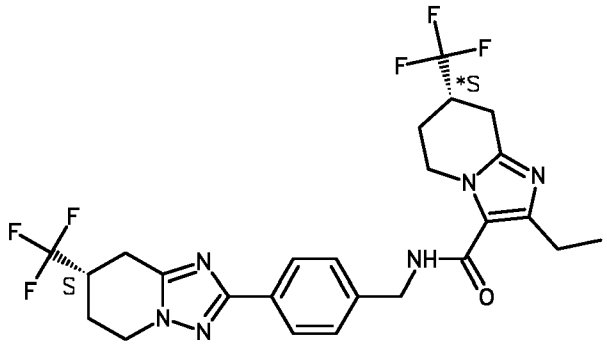
Hz, 2H), 2.36 – 2.26 (m, 1H), 2.19 – 2.07 (m, 1H), 2.07 – 1.98 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **136**



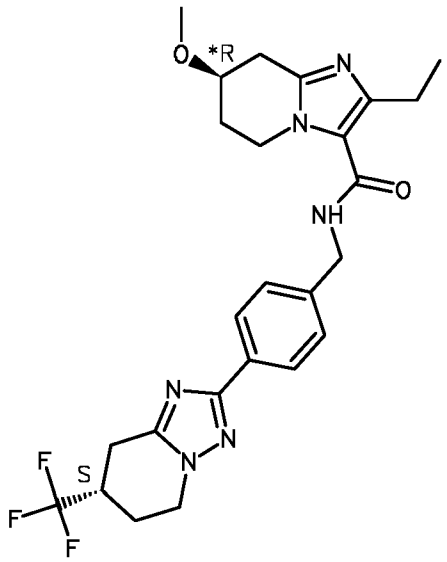
Compound **136** was synthesized from intermediates **I-87 (S)** and **II-71** and obtained as a white solid (65 mg, 61%). **^{1}H NMR** (400 MHz, DMSO) δ 8.32 (t, J = 5.9 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 6.1 Hz, 2H), 4.35 – 4.26 (m, 2H), 4.17 (td, J = 11.9, 4.9 Hz, 1H), 3.95 (td, J = 12.7, 4.4 Hz, 1H), 3.22 – 3.15 (m, 2H), 3.06 – 2.99 (m, 2H), 2.92 (dd, J = 17.5, 11.9 Hz, 1H), 2.78 – 2.63 (m, 3H), 2.31 (ddd, J = 6.9, 4.2, 2.1 Hz, 1H), 2.23 – 2.18 (m, 1H), 2.17 – 2.05 (m, 1H), 1.92 – 1.81 (m, 1H), 1.12 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **137**



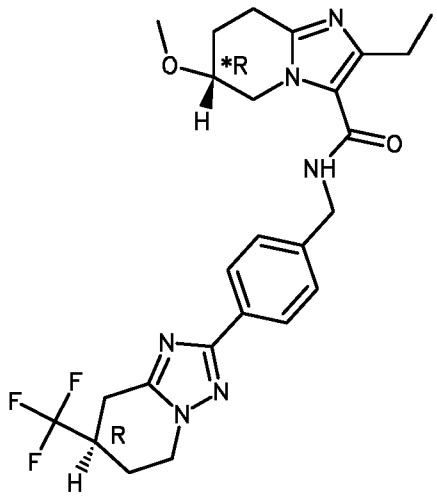
Compound **137** was synthesized from intermediates **I-87 (S)** and **II-72** and obtained as a white solid (85 mg, 79%). 1H **NMR** (400 MHz, DMSO) δ 8.33 (t, J = 5.8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.47 (d, J = 5.7 Hz, 2H), 4.40 – 4.25 (m, 2H), 4.24 – 4.10 (m, 1H), 4.05 – 3.87 (m, 1H), 3.26 – 3.14 (m, 2H), 3.11 – 2.99 (m, 2H), 2.99 – 2.87 (m, 1H), 2.82 – 2.60 (m, 3H), 2.39 – 2.26 (m, 1H), 2.26 – 2.05 (m, 2H), 1.93 – 1.80 (m, 1H), 1.13 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **139**



Compound **139** was synthesized from intermediates **I-87 (S)** and **II-69** and obtained as a white solid (49 mg, 68%). **^{1}H NMR** (400 MHz, DMSO) δ 8.28 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 4.11 – 4.02 (m, 1H), 4.00 – 3.90 (m, 1H), 3.83 – 3.76 (m, 1H), 3.29 (s, 3H), 3.22 – 3.15 (m, 2H), 2.99 – 2.87 (m, 2H), 2.78 (dd, J = 16.9, 4.8 Hz, 1H), 2.64 (q, J = 7.5 Hz, 2H), 2.37 – 2.27 (m, 1H), 2.18 – 2.06 (m, 1H), 2.06 – 1.97 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H).

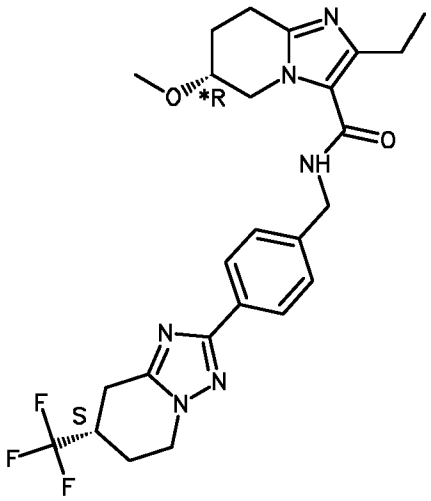
Synthesis of Compound **140**



Compound **140** was synthesized from intermediates **I-88 (R)** and **II-73** and obtained as a white solid (37 mg, 23%). **^{1}H NMR** (400 MHz, DMSO) δ 8.27 – 8.23 (m, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.21 – 4.00 (m, 3H), 3.84 – 3.80 (m, 1H), 3.28 (s, 3H), 3.22 – 3.15 (m, 2H), 2.92 (dd, J = 17.8, 12.3

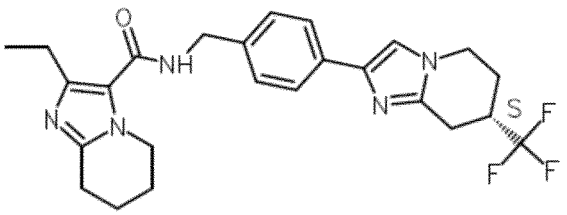
Hz, 1H), 2.74 – 2.60 (m, 4H), 2.32 (d, J = 7.8 Hz, 1H), 2.18 – 1.84 (m, 3H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **141**



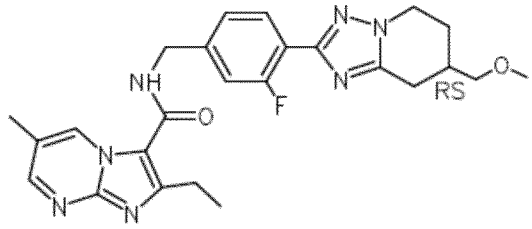
Compound **141** was synthesized from intermediates **I-87 (S)** and **II-73** and obtained as a white solid (71 mg, 44%). **^{1}H NMR** (400 MHz, DMSO) δ 8.26 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.32 (dd, J = 12.5, 3.8 Hz, 1H), 4.22 – 4.00 (m, 3H), 3.85 – 3.79 (m, 1H), 3.28 (s, 3H), 3.22 – 3.14 (m, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.73 – 2.60 (m, 4H), 2.36 – 2.28 (m, 1H), 2.18 – 2.03 (m, 2H), 1.94 – 1.84 (m, 1H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **142**



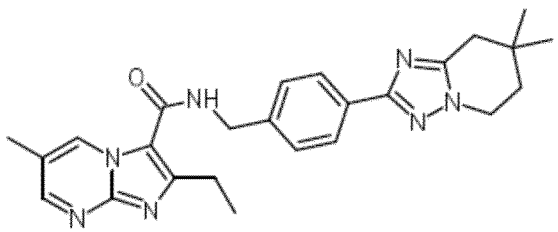
Compound **142** was synthesized from intermediates **I-151b** and **II-17a** and obtained as a white solid (60.7 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 8.21 (t, J = 6.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.26 (d, J = 8.2 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H), 4.16 (dd, J = 12.6, 3.3 Hz, 1H), 4.02 – 3.92 (m, 3H), 3.13 – 3.03 (m, 2H), 2.77 (dd, J = 17.5, 12.6 Hz, 1H), 2.70 (t, J = 6.3 Hz, 2H), 2.63 (q, J = 7.5 Hz, 2H), 2.27 – 2.19 (m, 1H), 2.01 – 1.89 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.74 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **143**



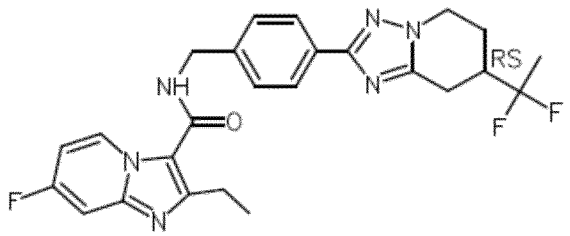
Compound **143** was synthesized from intermediates **I-124** and **II-3a** and obtained as a white solid (122.6 mg, 66%). **^{1}H NMR** (400 MHz, DMSO) δ 9.20 – 9.15 (m, 1H), 8.55 – 8.48 (m, 2H), 7.94 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 9.7 Hz, 2H), 4.57 (s, 2H), 4.31 – 4.19 (m, 1H), 4.15 – 4.03 (m, 1H), 3.41 – 3.36 (m, 2H), 3.32 (s, 3H), 3.03 (q, J = 7.5 Hz, 2H), 3.00 – 2.88 (m, 1H), 2.60 – 2.54 (m, 1H), 2.36 – 2.31 (m, 3H), 2.31 – 2.25 (m, 1H), 2.17 – 2.09 (m, 1H), 1.86 – 1.73 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **144**



Compound **144** was synthesized from intermediates **I-116** and **II-3a** and obtained as a white solid (155.8 mg, 64%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (dd, J = 2.3, 1.1 Hz, 1H), 8.51 (t, J = 5.0 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 6.3 Hz, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.67 (s, 2H), 2.34 (s, 3H), 1.86 (t, J = 6.3 Hz, 2H), 1.30 – 1.25 (t, J = 7.5 Hz, 3H), 1.04 (s, 6H).

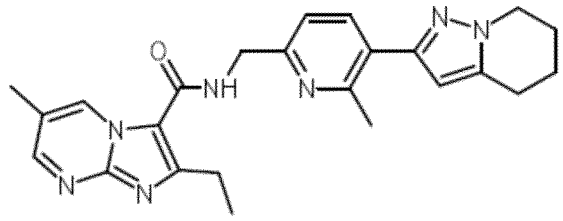
Synthesis of Compound **145**



Compound **145** was synthesized from intermediates **I-73a** and **I-160** and obtained as a beige solid (146.1 mg, 73%). **^{1}H NMR** (400 MHz, DMSO) δ 9.04 (dd, J = 7.4, 6.2 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.50 (dd, J = 9.8, 2.6 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.07 (td, J = 7.6, 2.7 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 4.35 – 4.27 (m, 1H), 4.12 (td, J = 12.1, 4.6 Hz, 1H), 3.10 (dd, J = 16.6, 4.1 Hz, 1H), 3.00 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 16.5,

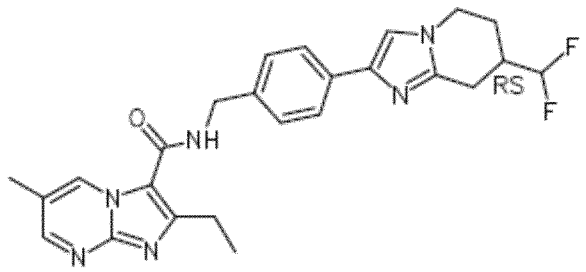
11.4 Hz, 1H), 2.71 – 2.57 (m, 1H), 2.26 (dd, J = 13.4, 2.2 Hz, 1H), 1.96 (qd, J = 11.8, 5.7 Hz, 1H), 1.72 (t, J = 19.5 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **146**



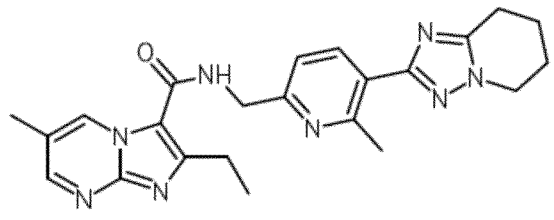
Compound **146** was synthesized from intermediates **I-149** and **II-3a** and obtained as a beige solid (15.1 mg, 7%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (s, 1H), 8.52 (t, J = 3.9 Hz, 1H), 8.49 (t, J = 5.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 6.33 (s, 1H), 4.62 (d, J = 5.6 Hz, 2H), 4.11 (t, J = 6.1 Hz, 2H), 3.09 (q, J = 7.5 Hz, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.66 (s, 3H), 2.34 (s, 3H), 1.99 (d, J = 5.3 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.33 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **147**



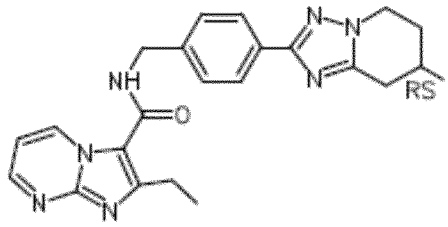
Compound **147** was synthesized from intermediates **I-137** and **II-3a** and obtained as a white solid (68 mg, 31%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (s, 1H), 8.51 (d, J = 2.3 Hz, 1H), 8.47 (t, J = 5.8 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 6.15 (td, J = 56.1, 4.1 Hz, 1H), 4.52 (d, J = 5.8 Hz, 2H), 4.18 – 4.09 (m, 1H), 4.00 – 3.87 (m, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.94 (dd, J = 16.5, 4.5 Hz, 1H), 2.66 (dd, J = 10.4, 5.7 Hz, 2H), 2.34 (s, 3H), 2.14 – 2.07 (m, 1H), 1.88 – 1.74 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **148**



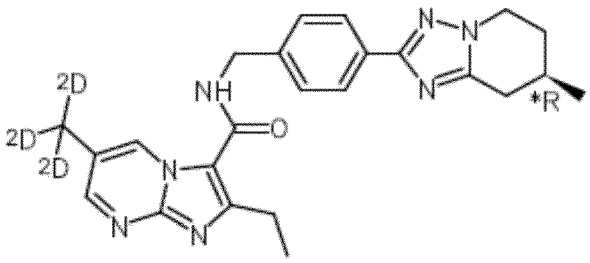
Compound **148** was synthesized from intermediates **I-150** and **II-3a** and obtained as a white solid (86.6 mg, 46%). **^{1}H NMR** (400 MHz, DMSO) δ 9.21 (s, 1H), 8.54 – 8.45 (m, 2H), 8.22 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 4.65 (d, J = 5.6 Hz, 2H), 4.17 (t, J = 5.9 Hz, 2H), 3.09 (q, J = 7.4 Hz, 2H), 2.88 (t, J = 6.2 Hz, 2H), 2.80 (s, 3H), 2.34 (s, 3H), 2.09 – 1.97 (m, 2H), 1.92 (dd, J = 11.1, 5.4 Hz, 2H), 1.37 – 1.28 (m, 3H).

Synthesis of Compound **149**



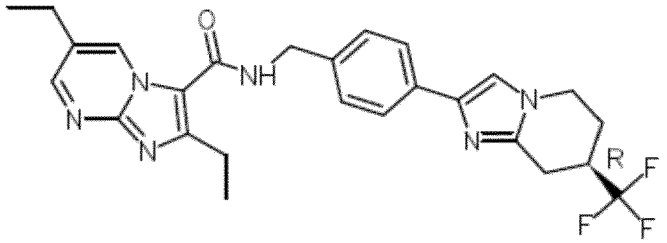
Compound **149** was synthesized from intermediates **I-16** and **II-102** and obtained as a white solid (52 mg, 21%). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (s, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.22 (ddd, J = 12.6, 5.6, 2.9 Hz, 1H), 4.16 – 4.00 (m, 1H), 3.04 (q, J = 7.5 Hz, 2H), 2.98 (dd, J = 17.2, 5.4 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.18 – 2.00 (m, 2H), 1.82 – 1.67 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **150**



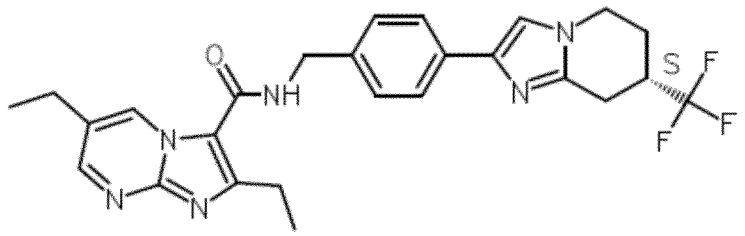
Compound **150** was synthesized from intermediates **I-153** and **II-98** and obtained as an off-white solid (136 mg, 75%). **^{1}H NMR** (400 MHz, DMSO) δ 9.16 (d, J = 2.4 Hz, 1H), 8.50 (t, J = 5.3 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.4 Hz, 2H), 4.22 (ddd, J = 12.5, 5.5, 2.8 Hz, 1H), 4.13 – 4.04 (m, 1H), 3.06 – 2.94 (m, 3H), 2.47 – 2.39 (m, 1H), 2.13 – 2.00 (m, 2H), 1.80 – 1.68 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **151**



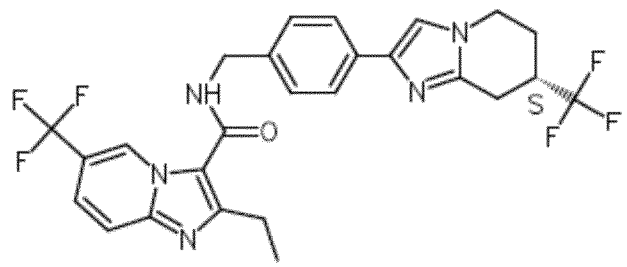
Compound **151** was synthesized from intermediates **I-151a** and **II-3a** and obtained as a beige solid (63.8 mg, 35%). **^{1}H NMR** (400 MHz, DMSO) δ 9.15 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 2.5 Hz, 1H), 8.49 (t, J = 5.9 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 4.53 (d, J = 5.9 Hz, 2H), 4.21 – 4.13 (m, 1H), 3.99 (td, J = 12.1, 4.5 Hz, 1H), 3.12 – 3.06 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.83 – 2.66 (m, 3H), 2.28 – 2.19 (m, 1H), 2.02 – 1.90 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **152**



Compound **152** was synthesized from intermediates **I-151b** and **II-104** and obtained as a white solid (68.8 mg, 38%). **^{1}H NMR** (400 MHz, DMSO) δ 9.14 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 2.5 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.16 (dd, J = 12.8, 3.4 Hz, 1H), 3.98 (td, J = 12.2, 4.7 Hz, 1H), 3.13 – 2.96 (m, 4H), 2.84 – 2.64 (m, 3H), 2.23 (d, J = 11.1 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H).

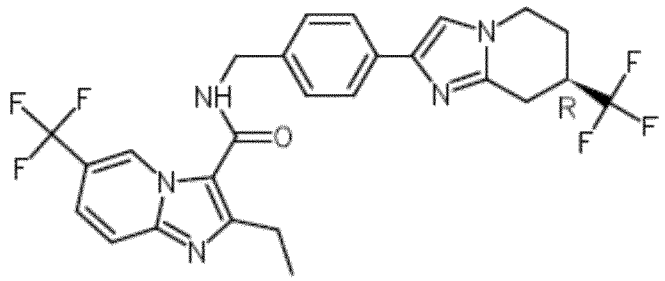
Synthesis of Compound **153**



Compound **153** was synthesized from intermediates **I-151b** and **II-19** and obtained as an off white solid (110.9 mg, 50%).**^{1}H NMR** (400 MHz, DMSO) δ 9.42 (s, 1H), 8.61 (s, 1H), 7.82 (d, J = 9.4 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.53 (s, 1H), 7.35 (d, J

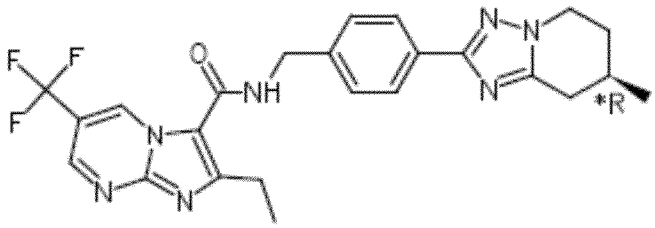
= 8.1 Hz, 2H), 4.54 (s, 2H), 4.22 – 4.11 (m, 1H), 3.98 (td, J = 12.1, 4.3 Hz, 1H), 3.15 – 2.99 (m, 4H), 2.78 (dd, J = 17.3, 12.6 Hz, 1H), 2.23 (d, J = 11.6 Hz, 1H), 2.03 – 1.88 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **154**



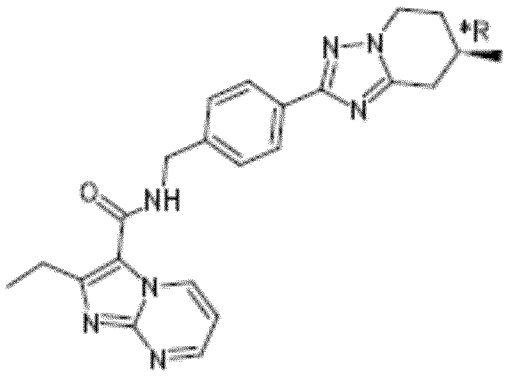
Compound **154** was synthesized from intermediates **I-151a** and **II-19** and obtained as an off white solid (70.5 mg, 32%). **^{1}H NMR** (400 MHz, DMSO) δ 9.43 (s, 1H), 8.62 (t, J = 6.0 Hz, 1H), 7.83 (d, J = 9.4 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.65 (dd, J = 9.4, 1.9 Hz, 1H), 7.61 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 4.55 (d, J = 5.8 Hz, 2H), 4.19 (d, J = 13.4 Hz, 1H), 4.01 (td, J = 12.5, 4.8 Hz, 1H), 3.15 – 3.09 (m, 2H), 3.05 (q, J = 7.5 Hz, 2H), 2.89 – 2.78 (m, 1H), 2.30 – 2.19 (m, 1H), 1.99 (dt, J = 18.6, 6.4 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **155**



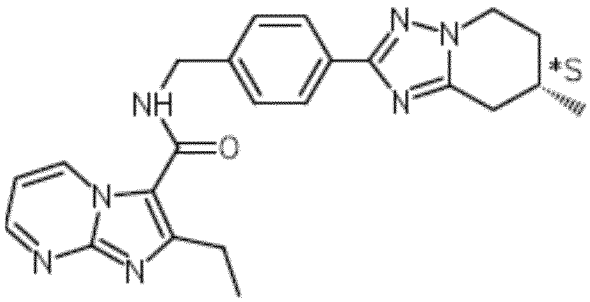
Compound **155** was synthesized from intermediates **I-153** and **II-19** and obtained as a white solid (15 mg, 10%). **^{1}H NMR** (400 MHz, DMSO) δ 9.68 (s, 1H), 8.97 (d, J = 2.4 Hz, 1H), 8.73 (t, J = 5.7 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.22 (ddd, J = 12.7, 5.3, 2.6 Hz, 1H), 4.14 – 4.03 (m, 1H), 3.09 (q, J = 7.5 Hz, 2H), 2.98 (dd, J = 16.7, 4.6 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.16 – 1.97 (m, 2H), 1.83 – 1.67 (m, 1H), 1.31 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **156**



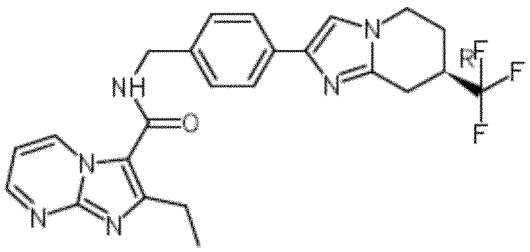
Compound **156** was synthesized from intermediates **I-153** and **II-102** and obtained as a white solid (139.5 mg, 59%). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.56 (t, J = 5.9 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 6.9, 4.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.24 – 4.17 (m, 1H), 4.13 – 4.03 (m, 1H), 3.04 (q, J = 7.5 Hz, 2H), 3.01 – 2.94 (m, 1H), 2.46 – 2.40 (m, 1H), 2.15 – 2.00 (m, 2H), 1.81 – 1.68 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **157**



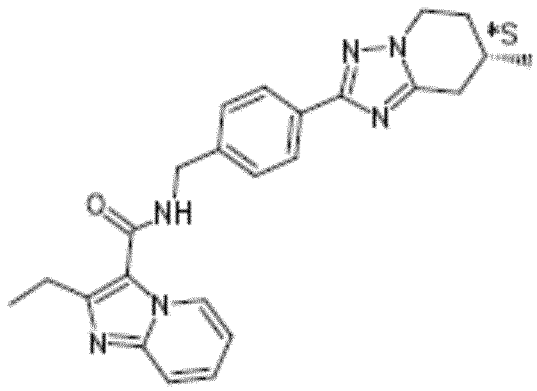
Compound **157** was synthesized from intermediates **I-154** and **II-102** and obtained as a white solid (153.5 mg, 71%). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.55 (t, J = 5.9 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.22 (ddd, J = 12.6, 5.5, 2.8 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.04 (q, J = 7.5 Hz, 2H), 3.01 – 2.94 (m, 1H), 2.48 – 2.39 (m, 1H), 2.09 (d, J = 7.7 Hz, 1H), 2.05 (dd, J = 14.3, 3.6 Hz, 1H), 1.74 (dtd, J = 13.4, 10.8, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **158**



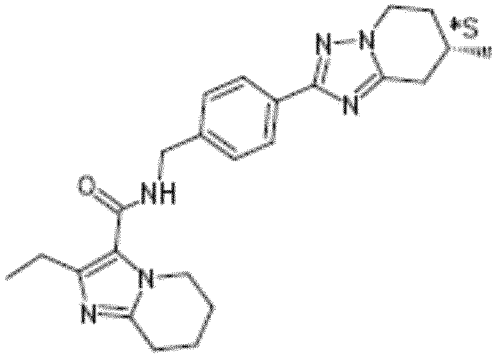
Compound **158** was synthesized from intermediates **I-151a** and **II-102** and obtained as a white solid (64 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 9.32 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.51 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.52 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.16 (dd, J = 6.9, 4.2 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.16 (dd, J = 12.5, 3.3 Hz, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.13 – 3.05 (m, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.78 (dd, J = 17.3, 12.6 Hz, 1H), 2.29 – 2.16 (m, 1H), 2.04 – 1.89 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **159**



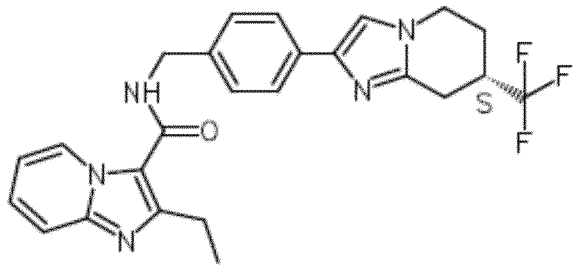
Compound **159** was synthesized from intermediates **I-154** and **II-102** and obtained as a white solid (41.5 mg, 21%). **^{1}H NMR** (400 MHz, DMSO) δ 8.98 (d, J = 6.9 Hz, 1H), 8.44 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.60 (dd, J = 9.0, 1.0 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.26 – 4.18 (m, 1H), 4.12 – 4.04 (m, 1H), 3.00 (q, J = 7.5 Hz, 2H), 2.97 – 2.94 (m, 1H), 2.46 – 2.40 (m, 1H), 2.15 – 2.00 (m, 2H), 1.81 – 1.68 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **160**



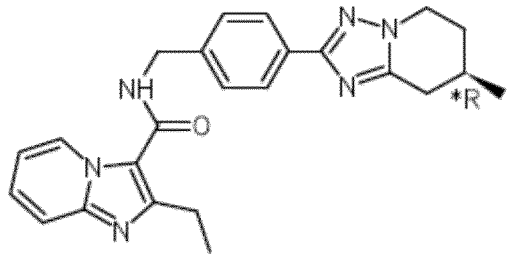
Compound **160** was synthesized from intermediates **II-17a** and **I-154** and obtained as a white solid (126.8 mg, 53%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 4.26 – 4.19 (m, 1H), 4.14 – 4.04 (m, 1H), 4.00 (t, J = 5.8 Hz, 2H), 3.03 – 2.94 (m, 1H), 2.72 (t, J = 6.3 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.48 – 2.40 (m, 1H), 2.17 – 2.03 (m, 2H), 1.89 – 1.66 (m, 5H), 1.11 (t, J = 7.5 Hz, 3H), 1.12-1.10 (m, 3H).

Synthesis of Compound **161**



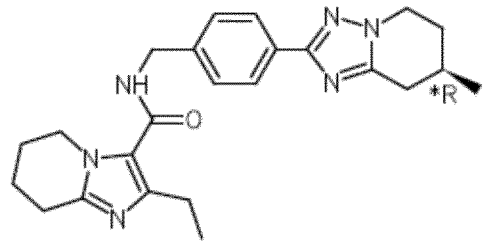
Compound **161** was synthesized from intermediates **II-102** and **I-151b** and obtained as a white solid (112.1 mg, 58%). **^{1}H NMR** (400 MHz, DMSO) δ 8.99 – 8.90 (m, 1H), 8.40 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.52 (s, 1H), 7.40 – 7.36 (m, 1H), 7.34 (dd, J = 6.8, 4.8 Hz, 2H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.20 – 4.12 (m, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.12 – 3.03 (m, 2H), 2.99 (q, J = 7.5 Hz, 2H), 2.78 (dd, J = 17.4, 12.7 Hz, 1H), 2.23 (dd, J = 13.2, 2.2 Hz, 1H), 2.04 – 1.88 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **162**



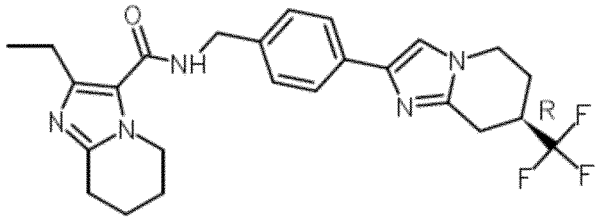
Compound **162** was synthesized from intermediates **II-102** and **I-153** and obtained as a white solid (78.9 mg, 46%). **^{1}H NMR** (400 MHz, DMSO) δ 9.01 – 8.95 (m, 1H), 8.44 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.41 – 7.34 (m, 1H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.27 – 4.17 (m, 1H), 4.13 – 4.01 (m, 1H), 3.04 – 2.94 (m, 3H), 2.46 – 2.40 (m, 1H), 2.15 – 2.00 (m, 2H), 1.82 – 1.68 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **163**



Compound **163** was synthesized from intermediates **II-17a** and **I-153** and obtained as a white solid (50.6 mg, 29%). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.25 – 4.17 (m, 1H), 4.13 – 4.03 (m, 1H), 3.99 (t, J = 5.8 Hz, 2H), 2.98 (dd, J = 17.0, 5.2 Hz, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.48 – 2.40 (m, 1H), 2.17 – 2.00 (m, 2H), 1.91 – 1.69 (m, 5H), 1.13 – 1.07 (m, 6H).

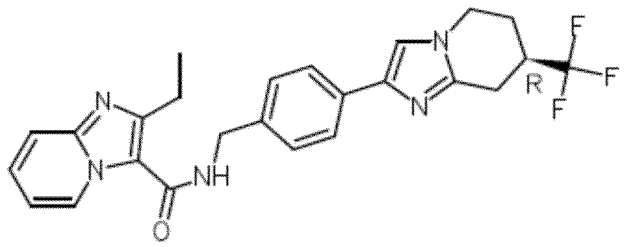
Synthesis of Compound **164**



Compound **164** was synthesized from intermediates **II-17a** and **I-151a** and obtained as a white solid (114.8 mg, 61%). **^{1}H NMR** (400 MHz, DMSO) δ 8.21 (t, J = 6.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.26 (d, J = 8.2 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H), 4.19 – 4.12

(m, 1H), 4.03 – 3.92 (m, 3H), 3.16 – 3.00 (m, 2H), 2.77 (dd, J = 17.4, 12.6 Hz, 1H), 2.70 (t, J = 6.3 Hz, 2H), 2.63 (q, J = 7.5 Hz, 2H), 2.28 – 2.18 (m, 1H), 2.02 – 1.89 (m, 1H), 1.88 – 1.73 (m, 4H), 1.10 (t, J = 7.5 Hz, 3H).

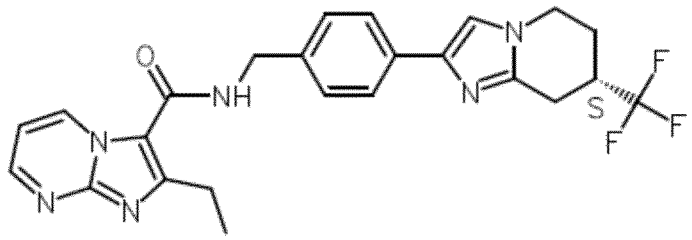
Synthesis of Compound **165**



Compound **165** was synthesized from intermediates **II-102** and **I-151a** and obtained as a white solid (91.6 mg, 38%).

^{1}H NMR (400 MHz, DMSO) δ 8.97 (d, J = 6.9 Hz, 1H), 8.40 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.52 (s, 1H), 7.39 – 7.35 (m, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.01 (td, J = 6.9, 1.2 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.21 – 4.12 (m, 1H), 3.98 (td, J = 12.1, 4.7 Hz, 1H), 3.13 – 3.03 (m, 2H), 2.99 (q, J = 7.5 Hz, 2H), 2.78 (dd, J = 17.3, 12.5 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.01 – 1.89 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H).

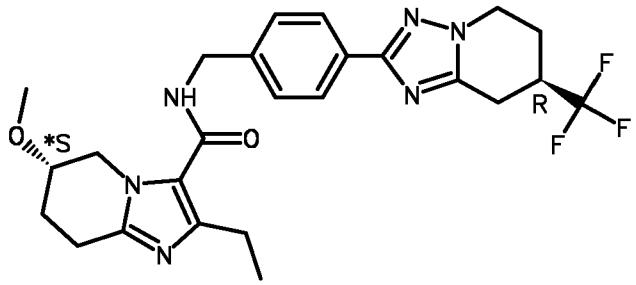
Synthesis of Compound **166**



Compound **166** was synthesized from intermediates **II-83** and **I-151b** and obtained as a white solid (155.9 mg, 61%).

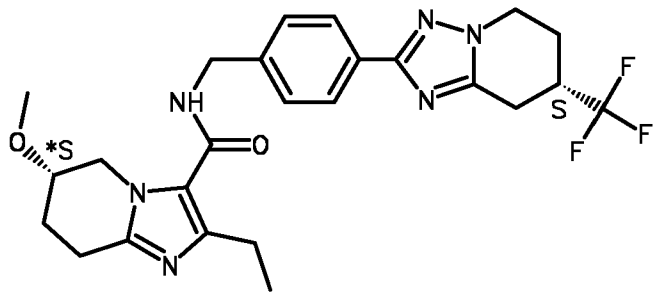
^{1}H NMR (400 MHz, DMSO) δ 9.32 (dd, J = 6.9, 2.0 Hz, 1H), 8.61 (dd, J = 4.2, 2.0 Hz, 1H), 8.51 (t, J = 5.8 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.16 (dd, J = 6.9, 4.2 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.20 – 4.11 (m, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.14 – 2.98 (m, 4H), 2.77 (dd, J = 17.4, 12.7 Hz, 1H), 2.23 (dd, J = 13.2, 2.1 Hz, 1H), 2.03 – 1.86 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **167**



Compound **167** was synthesized from intermediates **II-74** and **I-88** and obtained as a white solid (78.4 mg, 47%). **^{1}H NMR** (400 MHz, DMSO) δ 8.26 (t, *J* = 5.9 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.36 – 4.28 (m, 1H), 4.22 – 4.09 (m, 2H), 4.04 (dd, *J* = 13.8, 3.5 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.29 (s, 3H), 3.23 – 3.13 (m, 2H), 2.92 (dd, *J* = 17.8, 12.3 Hz, 1H), 2.71 (dd, *J* = 7.9, 4.9 Hz, 2H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.37 – 2.27 (m, 1H), 2.18 – 2.02 (m, 2H), 1.95 – 1.85 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H).

Synthesis of Compound **168**



Compound 168 was synthesized from intermediates **II-74** and **I-87** obtained as a white solid (132.3 mg, 83%). **^{1}H NMR** (400 MHz, DMSO) δ 8.33 (t, *J* = 5.6 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.36 – 4.27 (m, 1H), 4.22 – 4.10 (m, 2H), 4.05 (dd, *J* = 13.8, 3.5 Hz, 1H), 3.84 (dd, *J* = 5.5, 2.0 Hz, 1H), 3.29 (s, 3H), 3.25 – 3.14 (m, 2H), 2.92 (dd, *J* = 17.6, 12.1 Hz, 1H), 2.74 (dd, *J* = 8.2, 5.1 Hz, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 2.37 – 2.27 (m, 1H), 2.18 – 2.02 (m, 2H), 1.96 – 1.85 (m, 1H), 1.12 (t, *J* = 7.5 Hz, 3H).

METHOD B: Coupling reaction between acyl chloride derivatives and amine derivatives

General procedure

Method A: In a round bottom flask, amine derivative (1 eq.) was added to a solution of acyl chloride derivative (1.6 eq.) in anhydrous dioxane at room temperature under nitrogen atmosphere. The mixture was stirred for 10 min and DIPEA (1.6 eq.) was added. The reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with a solution of $NaHCO_3$ (sat., aq.) and water.

Method B: In a round bottom flask, DIPEA (3 to 6 eq.) was added to a solution of amine derivative (1 eq.) in anhydrous dioxane. The reaction mixture was stirred for 10 min and the mixture was added to a solution of acyl chloride derivative (1.7 to 3 eq.) in anhydrous dioxane. The reaction mixture was stirred at room temperature for 16 hours.

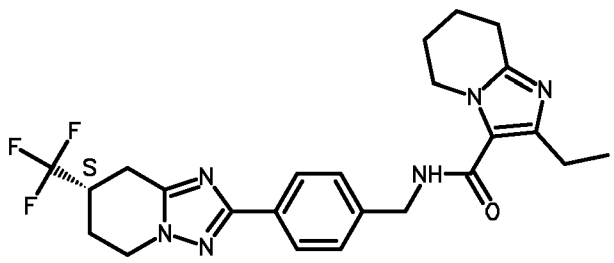
The mixture was worked up by dilution of the reaction mixture with a solution of $NaHCO_3$ (sat., aq.) and water, and extracted with DCM. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo.

In an alternative, after dilution, the mixture was filtered and the solid was washed before being dried under vacuum.

The crude product may be purified by flash column chromatography (silica) and/or triturated with DIPE, Et_2O, DCM/MeOH (9:1).

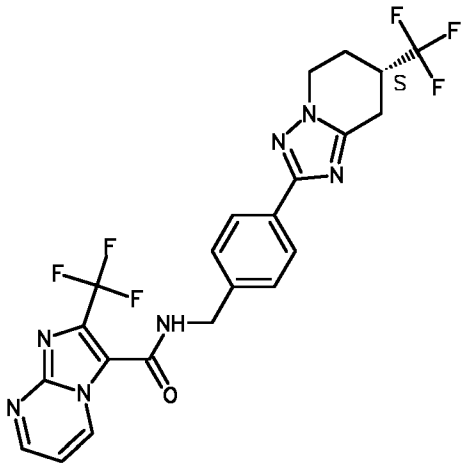
The following compounds were obtained through Method B:

Synthesis of Compound **169**



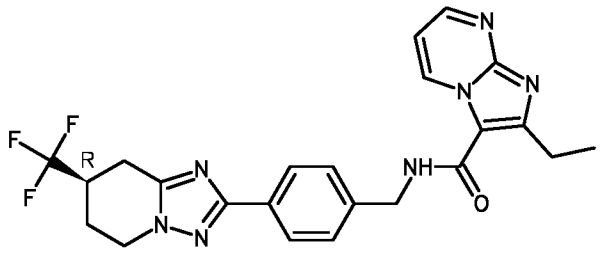
Compound **169** was synthesized from intermediates **II-52** and **I-88** and obtained as a white solid (117.7 mg, 72%). **^{1}H NMR** (400 MHz, DMSO) δ 8.24 (t, J = 5.9 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.45 (d, J = 5.9 Hz, 2H), 4.32 (dd, J = 12.8, 3.6 Hz, 1H), 4.17 (td, J = 12.0, 4.8 Hz, 1H), 3.99 (t, J = 5.7 Hz, 2H), 3.25 – 3.12 (m, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.71 (t, J = 6.2 Hz, 2H), 2.64 (dd, J = 15.0, 7.5 Hz, 2H), 2.36 – 2.28 (m, 1H), 2.19 – 2.04 (m, 1H), 1.90 – 1.72 (m, 4H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **170**



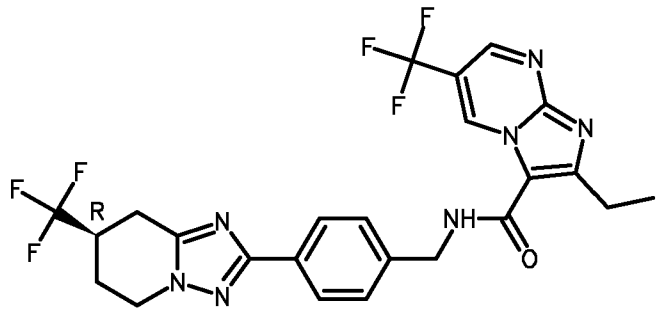
Compound **170** was synthesized from intermediates **II-108** and **I-87** and obtained as a pale brown solid (146.7 mg, 70%). **^{1}H NMR** (400 MHz, DMSO) δ 9.00 (dd, J = 6.9, 1.8 Hz, 1H), 8.90 (s, 1H), 8.81 (dd, J = 3.9, 1.9 Hz, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 6.9, 4.1 Hz, 1H), 4.62 (d, J = 5.7 Hz, 2H), 4.40 – 4.12 (m, 2H), 3.31 – 3.10 (m, 2H), 2.91 (s, 1H), 2.42 – 2.29 (m, 1H), 2.25 – 2.05 (m, 1H).

Synthesis of Compound **171**



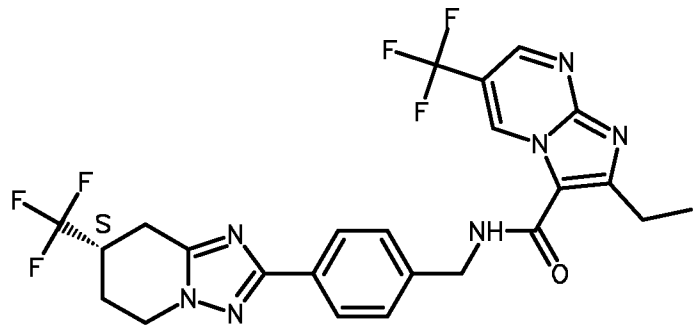
Compound **171** was synthesized from intermediates **II-55** and **I-88** and obtained as a beige solid (12.1 g, 94%). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 1.9 Hz, 1H), 8.62 (dd, J = 4.1, 2.0 Hz, 1H), 8.55 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.9, 3.6 Hz, 1H), 4.17 (td, J = 12.1, 4.9 Hz, 1H), 3.25 – 3.14 (m, 2H), 3.04 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.11 (qd, J = 11.6, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **172**



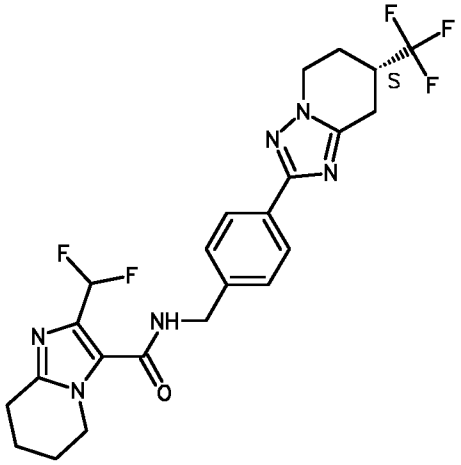
Compound **172** was synthesized from intermediates **II-54** and **I-88** obtained as a white solid (121.4 mg, 63%). **^{1}H NMR** (400 MHz, DMSO) δ 9.69 (dd, J = 2.4, 1.1 Hz, 1H), 8.97 (d, J = 2.6 Hz, 1H), 8.73 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 4.60 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.8, 3.7 Hz, 1H), 4.17 (td, J = 12.2, 4.9 Hz, 1H), 3.25 – 3.15 (m, 2H), 3.09 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.7, 12.2 Hz, 1H), 2.32 (dd, J = 10.8, 2.2 Hz, 1H), 2.11 (qd, J = 11.4, 5.9 Hz, 1H), 1.31 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **173**



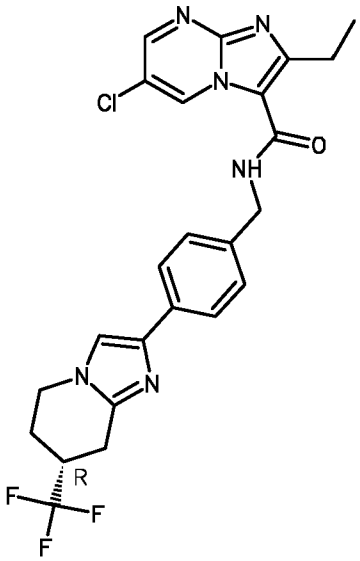
Compound **173** was synthesized from intermediates **II-54** and **I-87** obtained as a light beige solid (66 mg, 33%). **^{1}H NMR** (400 MHz, DMSO) δ 9.70 – 9.68 (m, 1H), 8.97 (d, J = 2.5 Hz, 1H), 8.73 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 4.60 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.9, 3.7 Hz, 1H), 4.17 (td, J = 12.0, 4.7 Hz, 1H), 3.23 – 3.15 (m, 2H), 3.09 (q, J = 7.5 Hz, 2H), 2.93 (dd, J = 17.6, 12.2 Hz, 1H), 2.35 – 2.29 (m, 1H), 2.17 – 2.05 (m, 1H), 1.31 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **174**



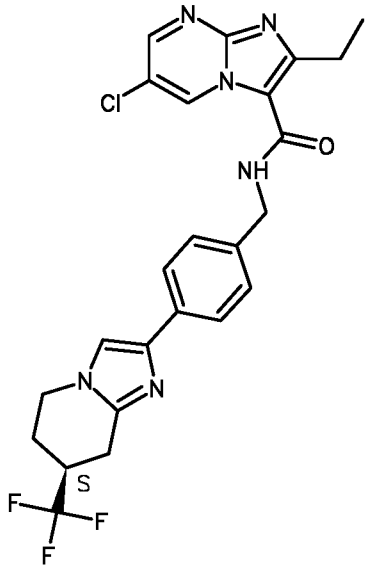
Compound **174** was synthesized from intermediates **II-107** and **I-87** obtained as a beige solid (66.8 mg, 34.2%). **^{1}H NMR** (400 MHz, DMSO) δ 8.83 (t, J = 5.9 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.95 (t, J = 54.3 Hz, 1H), 4.48 (d, J = 5.8 Hz, 2H), 4.37 – 4.29 (m, 1H), 4.17 (td, J = 12.0, 4.9 Hz, 1H), 4.04 (t, J = 5.7 Hz, 2H), 3.24 – 3.13 (m, 2H), 2.93 (dd, J = 17.6, 12.1 Hz, 1H), 2.79 (t, J = 6.3 Hz, 2H), 2.37 – 2.27 (m, 1H), 2.21 – 2.05 (m, 1H), 1.96 – 1.78 (m, 4H).

Synthesis of Compound **175**



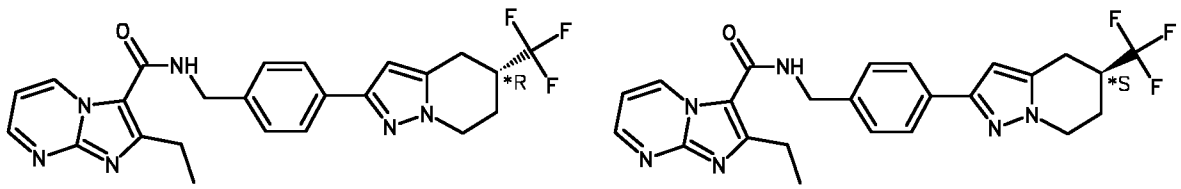
Compound **175** was synthesized from intermediates **II-106** and **I-151a** obtained as a pale orange solid (45.4 mg, 29%). **^{1}H NMR** (400 MHz, DMSO) δ 9.41 (d, J = 2.6 Hz, 1H), 8.68 (d, J = 2.6 Hz, 1H), 8.59 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.53 (d, J = 5.9 Hz, 2H), 4.16 (dd, J = 12.7, 3.5 Hz, 1H), 3.98 (td, J = 12.1, 4.5 Hz, 1H), 3.12 – 3.08 (m, 2H), 3.07 – 3.00 (m, 2H), 2.78 (dd, J = 17.4, 12.7 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.03 – 1.87 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **176**



Compound **176** was synthesized from intermediates **II-106** and **I-151b** obtained as a yellow solid (85.3 mg, 30%). **^{1}H NMR** (400 MHz, DMSO) δ 9.41 (d, J = 2.6 Hz, 1H), 8.68 (d, J = 2.6 Hz, 1H), 8.59 (t, J = 5.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 4.53 (d, J = 5.8 Hz, 2H), 4.16 (dd, J = 12.5, 3.4 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.04 (dd, J = 15.0, 7.5 Hz, 4H), 2.78 (dd, J = 17.5, 12.7 Hz, 1H), 2.23 (dd, J = 13.2, 2.1 Hz, 1H), 1.95 (dq, J = 11.6, 5.3 Hz, 1H), 1.28 (t, J = 7.5 Hz, 3H).

Synthesis of Compounds **177** and **178**



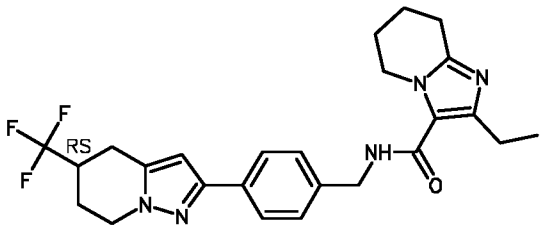
Isomers **177** and **178** were synthesized from intermediates **II-55** and **I-47,** after SFC separation (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars), to yield **177** (386.1 mg, 48% yield) and **178** (335.8 mg, 42% yield) as white solids.

177: **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.17 (dt, J = 12.4, 6.2 Hz, 1H), 6.53 (s, 1H), 4.55 (d, J = 5.9 Hz, 2H), 4.31 (dd, J = 12.9, 3.5 Hz, 1H), 4.12

(td, J = 12.2, 4.8 Hz, 1H), 3.14 (dd, J = 15.8, 3.8 Hz, 1H), 3.04 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 15.8, 11.f1 Hz, 1H), 2.28 (dd, J = 13.3, 2.3 Hz, 1H), 2.04 (ddd, J = 25.0, 11.9, 5.8 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H).

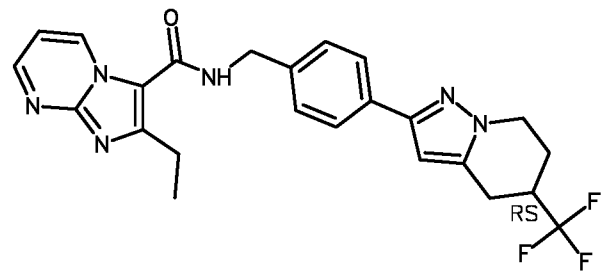
178: **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 6.53 (s, 1H), 4.55 (d, J = 5.9 Hz, 2H), 4.31 (dd, J = 12.7, 3.4 Hz, 1H), 4.12 (td, J = 12.3, 4.8 Hz, 1H), 3.13 (dt, J = 16.0, 7.9 Hz, 1H), 3.04 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 15.8, 11.2 Hz, 1H), 2.28 (dd, J = 13.4, 2.3 Hz, 1H), 2.04 (ddd, J = 24.9, 11.8, 5.7 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **179**



Compound **179** was synthesized from intermediates **II-52** and **I-27** and obtained as a white solid (49.4 mg, yield: 51 %). **^{1}H NMR** (400 MHz, DMSO) δ 8.23 (t, J = 6.0 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.52 (s, 1H), 4.42 (d, J = 5.9 Hz, 2H), 4.30 (dd, J = 12.9, 3.5 Hz, 1H), 4.11 (td, J = 12.3, 4.8 Hz, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.13 (dd, J = 15.9, 3.6 Hz, 1H), 3.07 – 2.93 (m, 1H), 2.78 (dd, 1H), 2.70 (t, J = 6.3 Hz, 2H), 2.64 (q, 2H), 2.28 (dd, J = 13.4, 2.3 Hz, 1H), 2.04 (qd, J = 11.8, 5.7 Hz, 1H), 1.92 – 1.81 (m, J = 7.8 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H).

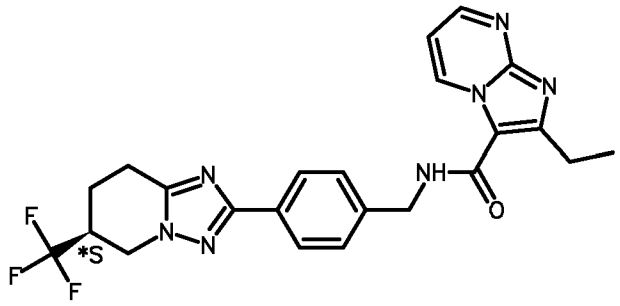
Synthesis of Compound **180**



Compound **180** was synthesized from intermediates **II-55** and **I-10** and obtained as a pale orange solid (54.5 mg, yield: 49 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz,

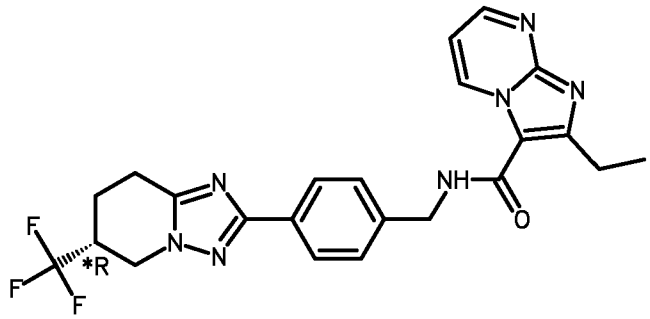
1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 6.53 (s, 1H), 4.55 (d, J = 5.9 Hz, 2H), 4.31 (dd, J = 12.6, 3.6 Hz, 1H), 4.12 (td, J = 12.4, 4.8 Hz, 1H), 3.24 – 3.08 (m, 1H), 3.04 (q, J = 7.5 Hz, 3H), 2.95 – 2.68 (m, 1H), 2.42 – 2.20 (m, 1H), 2.04 (qd, J = 11.8, 5.7 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **181**



Compound **181** was synthesized from intermediates **II-55** and **I-47**. Isomers were separated by SFC (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) to yield a pale orange solid (35 mg, yield: 23 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.56 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 6.9, 4.2 Hz, 1H), 4.59 (d, J = 5.9 Hz, 2H), 4.47 (dd, J = 12.4, 5.6 Hz, 1H), 4.24 – 4.16 (m, 1H), 3.30 (s, 1H), 3.05 (q, J = 7.5 Hz, 2H), 2.99 – 2.88 (m, 1H), 2.29 – 2.19 (m, 1H), 2.09 – 1.92 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

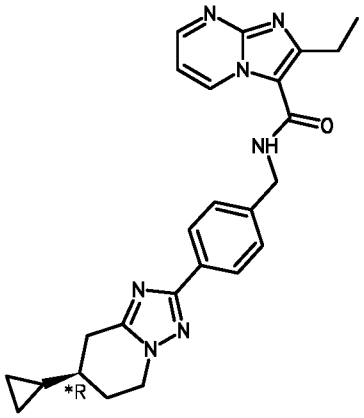
Synthesis of Compound **182**



Compound **182** was synthesized from intermediates **II-55** and **I-47**. Isomers were separated by SFC (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle

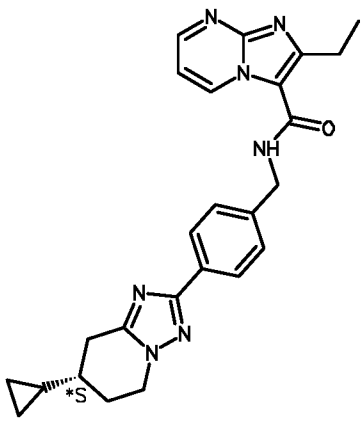
size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) to yield a pale orange solid (30.5 mg, yield: 20 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.56 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.3 Hz,2H), 7.46 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 6.9, 4.2 Hz, 1H), 4.59 (d, J = 5.9 Hz, 2H), 4.47 (dd, J = 12.4, 5.6 Hz, 1H), 4.25 – 4.15 (m,1H), 3.30 (s, 1H), 3.05 (q, J = 7.5 Hz, 2H), 2.94 (ddd, J = 17.1, 10.5, 6.2 Hz, 1H), 2.25 (dd, J = 8.6, 5.0 Hz, 1H), 2.10 – 1.95 (m, 1H),1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **183**



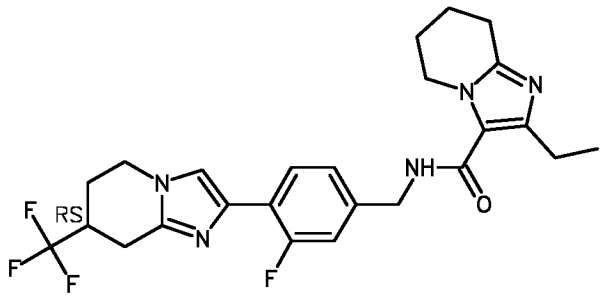
Compound **183** was synthesized from intermediates **II-55** and **I-60**. Isomers were separated by SFC (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) to yield as a pale white solid (45 mg, yield: 14 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.55 (t, J = 5.9 Hz, 1H), 7.96 – 7.91 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.25 (ddd, J = 12.7, 5.7, 3.3 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.07 – 2.97 (m, 3H), 2.68 – 2.60 (m, 1H), 2.17 – 2.10 (m, 1H), 1.96 – 1.85 (m, 1H), 1.29 (t, J = 7.5 Hz, 4H), 0.81 – 0.71 (m, 1H), 0.50 – 0.43 (m, 2H), 0.27 – 0.18 (m, 2H).

Synthesis of Compound **184**



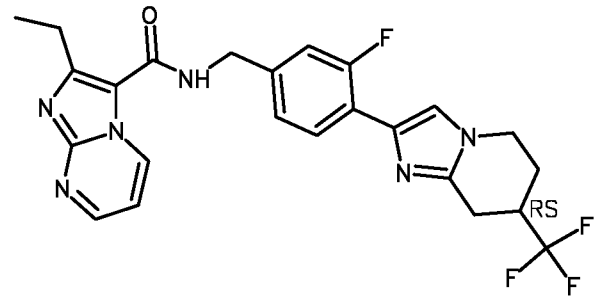
Compound **184** was synthesized from intermediates **II-55** and **I-60**. Isomers were separated by SFC (Jasco SFC prep system, i-cellulose column (Phenomenex) 250*30mm, 5mm particle size, isocratic mode at 100 ml/min of CO_2 (40%) / MeOH (60%) / diethylamine (0.1%) at 30 °C, 120 bars) to yield a pale white solid (61 mg, yield: 19 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.33 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.55 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.25 (ddd, J = 12.6, 5.6, 3.4 Hz, 1H), 4.10 – 4.00 (m, 1H), 3.08 – 2.97 (m, 3H), 2.64 (dd, J = 16.9, 10.0 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.96 – 1.85 (m, 1H), 1.29 (t, J = 7.5 Hz, 4H), 0.81 – 0.71 (m, 1H), 0.49 – 0.44 (m, 2H), 0.26 – 0.18 (m, 2H).

Synthesis of Compound **185**



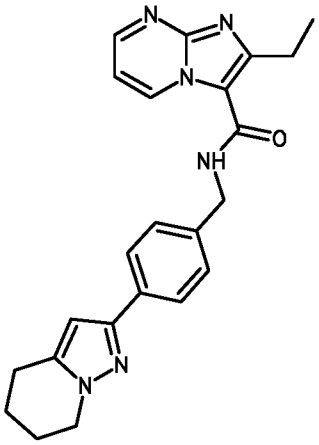
Compound **185** was synthesized from intermediates **II-52** and **I-130** and obtained as a white solid (87 mg, yield: 68 %). **^{1}H NMR** (400 MHz, DMSO) δ 8.24 (t, J = 5.9 Hz, 1H), 7.96 (t, J = 8.1 Hz, 1H), 7.43 (d, J = 4.2 Hz, 1H), 7.14 (t, J = 9.9 Hz, 2H), 4.42 (d, J = 5.9 Hz, 2H), 4.21 (dd, J = 12.7, 3.3 Hz, 1H), 4.03 – 3.93 (m, 3H), 3.14 – 3.05 (m, 2H), 2.80 (dd, J = 17.3, 12.6 Hz, 1H), 2.71 (t, J = 6.1 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.24 (d, J = 13.2 Hz, 1H), 1.95 (qd, J = 11.9, 5.6 Hz, 1H), 1.85 (d, J = 4.2 Hz, 2H), 1.78 (d, J = 5.0 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **186**



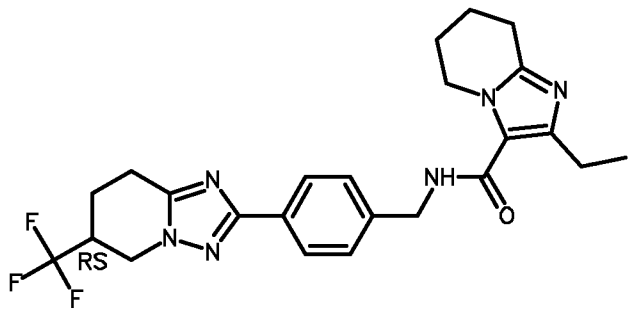
Compound **186** was synthesized from intermediates **II-55** and **I-130** and obtained as a white solid (43 mg, yield: 34 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.63 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 6.0 Hz, 1H), 7.98 (t, J = 8.1 Hz, 1H), 7.44 (d, J = 4.3 Hz, 1H), 7.24 (s, 1H), 7.21 (d, J = 4.7 Hz, 1H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.55 (d, J = 5.8 Hz, 2H), 4.29 – 4.13 (m, 1H), 3.99 (td, J = 12.3, 4.7 Hz, 1H), 3.14 – 3.09 (m, 1H), 3.05 (q, J = 7.5 Hz, 2H), 2.80 (dd, J = 17.4, 12.5 Hz, 1H), 2.25 (d, J = 11.1 Hz, 1H), 1.96 (qd, J = 12.0, 5.4 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **187**



Compound **187** was synthesized from intermediates **II-55** and **I-86** and obtained as a yellowish solid (62 mg, yield: 71 %). **^{1}H NMR** (400 MHz, DMSO) δ 9.32 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.51 (t, J = 5.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.16 (dd, J = 6.9, 4.2 Hz, 1H), 6.40 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 4.08 (t, J = 6.1 Hz, 2H), 3.03 (q, J = 7.5 Hz, 2H), 2.77 (t, J = 6.3 Hz, 2H), 2.02 – 1.94 (m, 2H), 1.83 – 1.75 (m, 2H), 1.29 (t, J = 7.5 Hz, 3H).

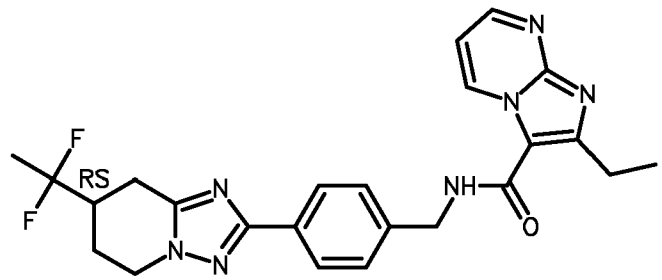
Synthesis of Compound **188**



Compound **188** was synthesized from intermediates **II-52** and **I-47** and obtained as a yellowish solid (51 mg, yield: 53 %). **^{1}H NMR** (400 MHz, DMSO) δ 8.25 (t, J = 6.0 Hz, 1H),

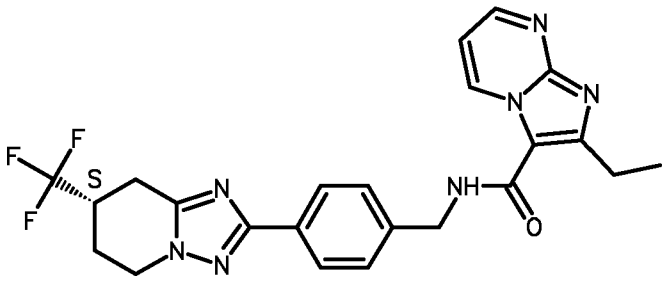
7.93 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.46 (t, J = 7.2 Hz, 3H), 4.23 – 4.16 (m, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.29 (s, 1H), 3.06 – 2.98 (m, 1H), 2.95 (dt, J = 12.8, 6.3 Hz, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.28 – 2.20 (m, 1H), 2.02 (dtd, J = 13.2, 10.8, 6.0 Hz, 1H), 1.87 – 1.76 (m, 4H), 1.10 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **189**



Compound **189** was synthesized from intermediates **II-55** and **I-160** and obtained as a palid beige solid (66.9 mg, yield: 74 %). **^{1}H NMR** (400 MHz, DMSO) δ 8.55 (dd, J = 6.9, 1.9 Hz, 1H), 7.83 (dd, J = 4.2, 1.9 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 8.1 Hz, 2H), 6.35 (dd, J = 6.9, 4.2 Hz, 1H), 3.87 (s, 2H), 3.77 (s, 1H), 3.58 (dd, J = 12.7, 3.4 Hz, 1H), 3.36 (td, J = 12.3, 5.1 Hz, 1H), 2.39 (dd, J = 16.5, 4.8 Hz, 1H), 2.26 (q, J = 7.6 Hz, 2H), 2.08 (dd, J = 16.9, 11.3 Hz, 1H), 1.82 (s, 1H), 1.59 (d, J = 13.8 Hz, 1H), 1.34 – 1.22 (m, 1H), 0.92 (t, J = 19.1 Hz, 3H), 0.54 (t, J = 7.6 Hz, 3H).

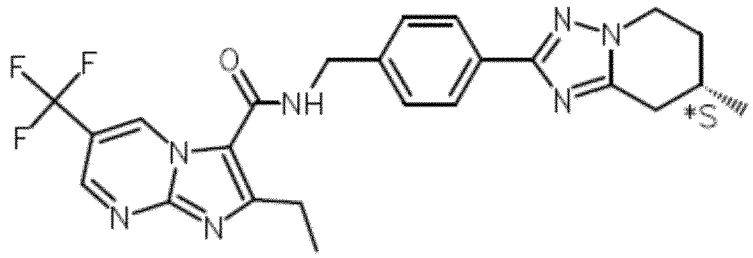
Synthesis of Compound **190**



Compound **190** was synthesized from intermediates **II-55** and **I-87** and obtained as a beige solid (13.2 g, 98%). **^{1}H NMR** (400 MHz, DMSO) δ 9.34 (dd, J = 6.9, 2.0 Hz, 1H), 8.62 (dd, J = 4.2, 2.0 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 6.9, 4.2 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 4.33 (dd, J = 12.9, 3.4 Hz, 1H), 4.17

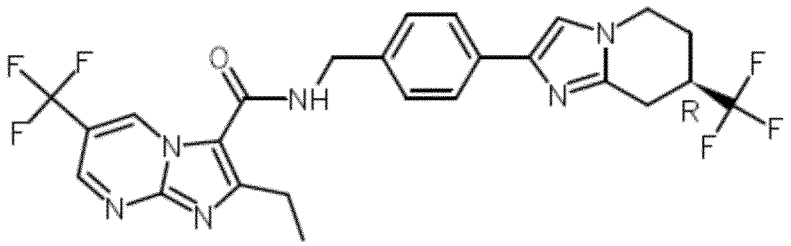
(td, J = 12.2, 4.9 Hz, 1H), 3.23 – 3.14 (m, 2H), 3.04 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.11 (qd, J = 11.4, 5.8 Hz, 1H), 1.29 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **191**



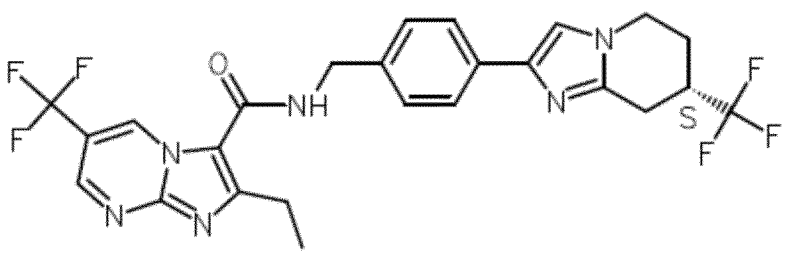
Compound **191** was synthesized from intermediates **II-54** and **I-154** and obtained as a beige solid (45.8 mg, 23%). **^{1}H NMR** (400 MHz, DMSO) δ 9.68 (d, J = 1.3 Hz, 1H), 8.97 (d, J = 2.5 Hz, 1H), 8.73 (t, J = 5.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.22 (ddd, J = 12.6, 5.5, 2.8 Hz, 1H), 4.12 – 4.03 (m, 1H), 3.09 (q, J = 7.5 Hz, 2H), 2.98 (dd, J = 17.1, 5.3 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.14 – 2.01 (m, 2H), 1.74 (dtd, J = 13.3, 10.8, 5.7 Hz, 1H), 1.31 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

Synthesis of Compound **192**



Compound **192** was synthesized from intermediates **II-54** and **I-151a** and obtained as a light beige solid (41.1 mg, 25%). **^{1}H NMR** (400 MHz, DMSO) δ 9.67 (d, J = 1.3 Hz, 1H), 8.96 (d, J = 2.5 Hz, 1H), 8.69 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 4.54 (d, J = 5.8 Hz, 2H), 4.16 (dd, J = 12.5, 3.4 Hz, 1H), 3.98 (td, J = 12.1, 4.5 Hz, 1H), 3.08 (dd, J = 15.0, 7.4 Hz, 4H), 2.77 (dd, J = 17.4, 12.6 Hz, 1H), 2.23 (d, J = 11.3 Hz, 1H), 1.95 (qd, J = 11.8, 5.4 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **193**



Compound **193** was synthesized from intermediates **II-54** and **I-151b** and obtained as a pale orange solid (17.8 mg, 11%). **^{1}H NMR** (400 MHz, DMSO) δ 9.67 (d, J = 1.4 Hz, 1H), 8.96 (d, J = 2.6 Hz, 1H), 8.69 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 4.54 (d, J = 5.8 Hz, 2H), 4.16 (dd, J = 12.6, 3.4 Hz, 1H), 3.98 (td, J = 12.1, 4.6 Hz, 1H), 3.12 – 3.01 (m, 4H), 2.77 (dd, J = 17.4, 12.7 Hz, 1H), 2.23 (d, J = 11.0 Hz, 1H), 2.02 – 1.87 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

METHOD C: Coupling reaction followed by protecting group cleavage

General procedure

a) Coupling reaction

In a round bottom flask, carboxylic acid derivative (1.1 to 1.3 eq.) was added to a solution of amine derivative (1 eq.) in DMF. DIPEA (7 eq.) and HATU [CAS 148893-10-1] (1.5 eq.) were added and the reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with a solution of $NaHCO_3$ (sat., aq.) and extracted with DCM. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica, gradient: DCM/MeOH (9:1) in DCM). The desried fractions were collected and concentrated in vacuo to afford the desired intermediate XX.

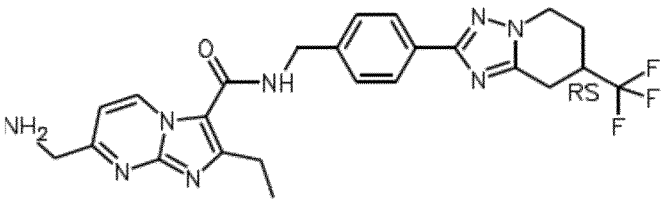
b) Protecting group cleavage

Method CA: HCl in dioxane (4M, 6 eq.) was added to a solution of the obtained product from step a) (1 eq.) in DCM in a round bottom flask at room temperature. The reaction mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo. An extraction step prior to the concentration may be used. The crude product was then purified by flash column chromatography (silica) and/or trituration (with DIPE, DCM) to afford the desired compound.

Method CB**:** TFA was added to a solution of the obtained product from step a) (1 eq.) in a round bottom flask at 0 °C. The reaction mixture was stirred at room temperature for 1 hours. The mixture was neutralised with a solution of $NaHCO_3$ (sat., aq.) and extracted with an appropriate solvent. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography, reverse phase or triturated (DCM) to afford the desired compound.

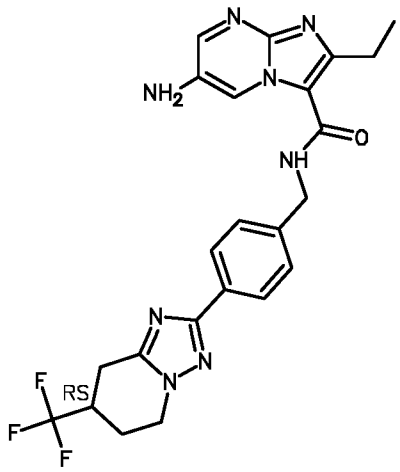
The following compounds were obtained through Method C:

Synthesis of Compound **138**



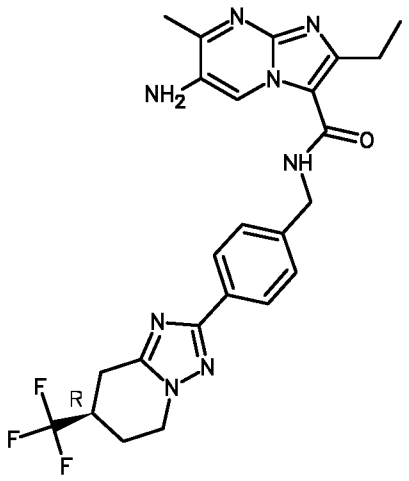
The coupling reaction (step a) between intermediates **II-22** and **I-6** delivered a yellow solid (200 mg, 80%, 85% purity).
Treatment with HCl in an analogous procedure to the one described for method A afforded compound **138** as a yellow solid (33 mg, 16%). **^{1}H NMR** (400 MHz, DMSO) δ 9.26 (d, J = 7.1 Hz, 1H), 8.46 (t, J = 5.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.1 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 4.32 (dd, J = 12.5, 3.7 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.86 (s, 1H), 3.19 (d, J = 13.1 Hz, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.92 (dd, J = 17.7, 12.2 Hz, 1H), 2.69 (d, J = 13.7 Hz, 1H), 2.32 (d, J = 8.4 Hz, 2H), 2.17 – 2.03 (m, 2H), 1.27 (dd, J = 15.9, 8.4 Hz, 3H).

Synthesis of Compound **194**



The coupling reaction (step a) was performed between intermediates **II-91** and **I-6**.
Treatment with HCl in an analogous procedure to the one described for method A afforded compound **194** as a beige solid (158 mg, 72%). **^{1}H NMR** (400 MHz, DMSO) δ 9.78 (d, J = 10.7 Hz, 2H), 8.53 (d, J = 2.7 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 4.33 (dd, J = 12.9, 3.9 Hz, 1H), 4.17 (td, J = 12.1, 4.7 Hz, 1H), 3.19 (d, J = 12.6 Hz, 1H), 3.02 (q, J = 7.5 Hz, 2H), 2.96 – 2.86 (m, 2H), 2.36 – 2.27 (m, 1H), 2.11 (qd, J = 11.5, 5.8 Hz, 1H), 1.49 (s, 9H), 1.27 (t, J = 7.5 Hz, 3H).

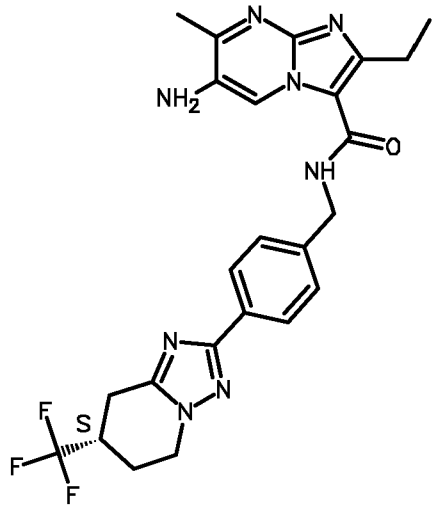
Synthesis of Compound **195**



The coupling reaction (step a) between intermediates **II-15** and **I-88** delivered a beige solid (191 mg, 68%).

Treatment with TFA in an analogous procedure to the one described for method B afforded compound **195** (45.8 mg, 37%). **^{1}H NMR** (400 MHz, DMSO) δ 8.97 (d, J = 27.8 Hz, 1H), 8.45 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.11 (s, 1H), 6.42 (d, J = 8.2 Hz, 2H), 4.69 – 4.58 (m, 2H), 4.55 (d, J = 5.8 Hz, 2H), 4.37 – 4.27 (m, 1H), 4.17 (td, J = 12.2, 4.9 Hz, 1H), 3.69 (s, 3H), 3.47 (d, J = 21.5 Hz, 3H), 3.26 – 3.13 (m, 2H), 3.05 – 2.97 (m, 2H), 2.93 (dd, J = 17.9, 12.5 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.23 (s, 3H), 2.17 – 2.05 (m, 1H), 1.56 – 1.21 (m, 12H).

Synthesis of Compound **196**

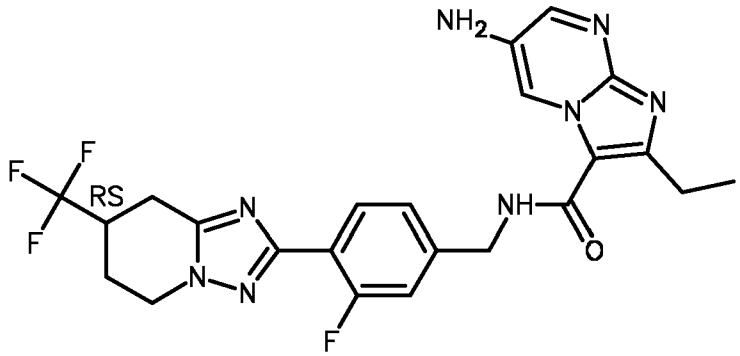


The coupling reaction (step a) between intermediates **II-15** and **I-87** delivered a beige solid (203 mg, 73%).

Treatment with TFA in an analogous procedure to the one described for method B afforded compound **196** (19.1 mg, 14%). **^{1}H NMR** (300 MHz, DMSO) δ 8.94 (s, 1H), 8.46 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.11 (s, 1H), 6.42 (d, J = 8.2 Hz, 2H), 4.64

(s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.31 (dd, J = 12.5, 8.1 Hz, 1H), 4.17 (td, J = 11.8, 4.7 Hz, 1H), 3.69 (s, 3H), 3.44 (s, 3H), 3.25 – 3.12 (m, 2H), 3.07 – 2.98 (m, 2H), 2.98 – 2.85 (m, 1H), 2.37 – 2.26 (m, 1H), 2.22 (s, 3H), 2.18 – 2.02 (m, 1H), 1.56 – 1.19 (m, 12H).

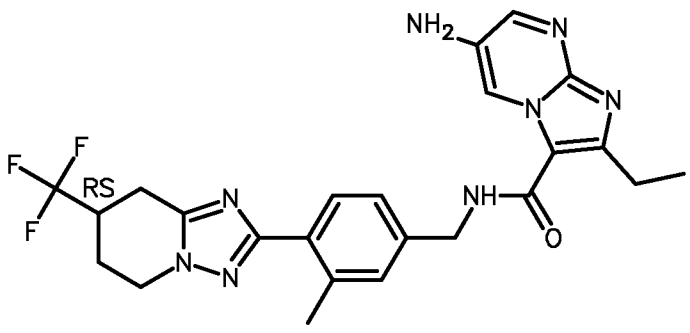
Synthesis of Compound **197**



The coupling reaction (step a) between intermediates **II-91** and **I-150b** delivered a brown solid (186 mg, 73%).

Treatment with HCl in an analogous procedure to the one described for method A afforded compound **197** (126 mg, 80%). **^{1}H NMR** (400 MHz, DMSO) δ 8.74 (d, J = 2.8 Hz, 1H), 8.31 (t, J = 6.0 Hz, 1H), 8.24 (d, J = 2.9 Hz, 1H), 7.94 (t, J = 7.9 Hz, 1H), 7.29 (s, 1H), 7.27 (d, J = 1.9 Hz, 1H), 5.28 (d, J = 8.2 Hz, 2H), 4.55 (d, J = 5.5 Hz, 2H), 4.41 – 4.29 (m, 1H), 4.18 (td, J = 12.1, 4.8 Hz, 1H), 3.26 – 3.14 (m, 2H), 2.98 (q, J = 7.5 Hz, 2H), 2.95 – 2.89 (m, 1H), 2.37 – 2.28 (m, 1H), 2.21 – 2.05 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

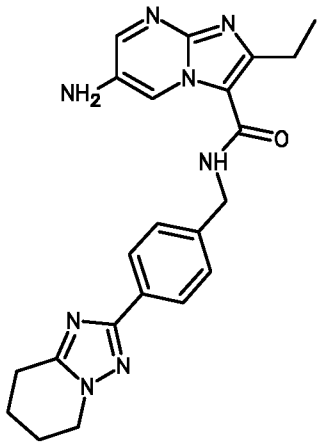
Synthesis of Compound **198**



The coupling reaction (step a) between intermediates **II-91** and **I-125** delivered a brown solid (193 mg, 74%).

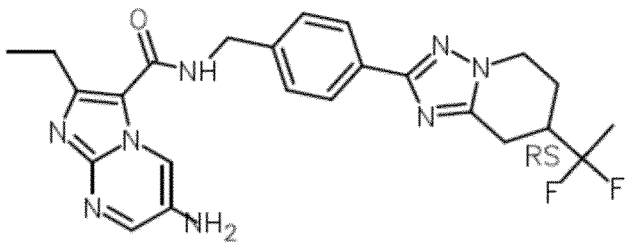
Treatment with HCl in an analogous procedure to the one described for method A afforded compound **198** as a white solid (79.4 mg, 49%). **^{1}H NMR** (400 MHz, DMSO) δ 8.73 (d, J = 2.9 Hz, 1H), 8.30 (t, J = 6.0 Hz, 1H), 8.24 (d, J = 2.9 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 5.28 (s, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.38 – 4.29 (m, 1H), 4.18 (td, J = 12.0, 4.8 Hz, 1H), 3.26 – 3.14 (m, 2H), 3.02 – 2.88 (m, 3H), 2.57 (s, 3H), 2.36 – 2.28 (m, 1H), 2.20 – 2.06 (m, 1H), 1.26 (t, J = 7.5 Hz, 3H).

Synthesis of Compound **199**



The coupling reaction (step a) between intermediates **II-91** and **I-72a** delivered a brown solid (193 mg, 74%).
Treatment with HCl in an analogous procedure to the one described for method A afforded compound **199** as a white solid (187 mg, 77%). **^{1}H NMR** (400 MHz, DMSO) δ 8.74 (d, J = 2.9 Hz, 1H), 8.27-8.33 (m, 1H), 8.22-8.25 (m, 1H), 7.90-7.96 (m, 2H), 7.40-7.44 (m, 2H), 5.23-5.31 (m, 2H), 4.51-4.57 (m, 2H), 4.10-4.16 (m, 2H), 2.93-3.00 (m, 2H), 2.85 (t, J = 6.3 Hz, 2H), 1.98-2.05 (m, 2H), 1.86-1.94 (m, 2H), 1.25 ppm (t, J = 7.5 Hz, 3H).

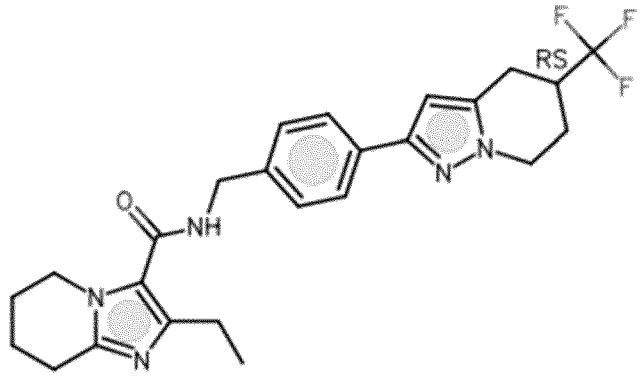
Synthesis of Compound **200**

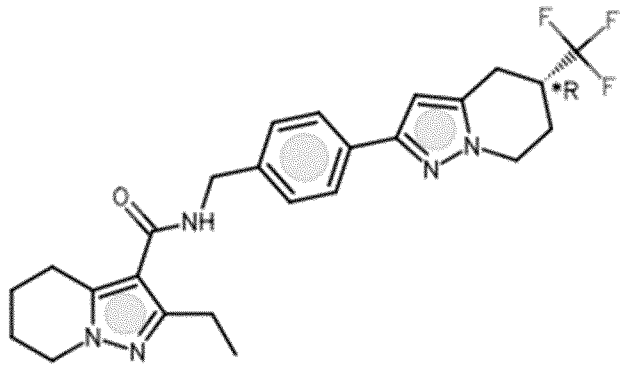


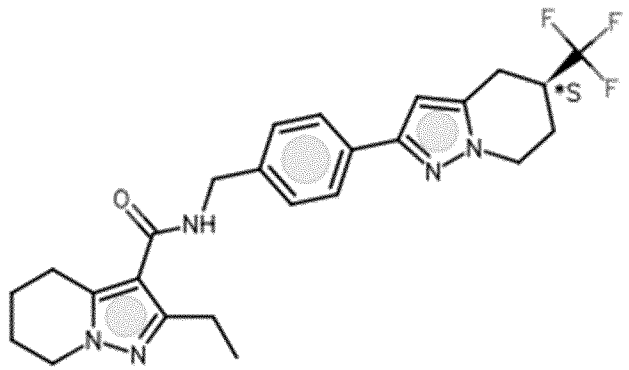
The coupling reaction (step a) between intermediates **II-91** and **I-160** delivered a yellow solid (200 mg, 81%).
Treatment with HCl in an analogous procedure to the one described for method A afforded compound **200** as a beige solid (121.4 mg, 72%).

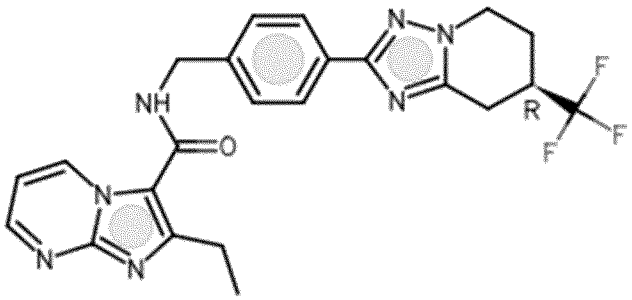
^{1}H NMR (400 MHz, DMSO) δ 8.74 (d, J = 2.8 Hz, 1H), 8.30 (t, J = 6.0 Hz, 1H), 8.24 (d, J = 2.9 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 5.27 (d, J = 8.2 Hz, 2H), 4.55 (d, J = 5.8 Hz, 2H), 4.37 – 4.25 (m, 1H), 4.11 (td, J = 12.2, 4.9 Hz, 1H), 3.09 (dd, J = 16.5, 4.3 Hz, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.79 (dd, J = 16.5, 11.4 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.29 – 2.20 (m, 1H), 2.04 – 1.88 (m, 1H), 1.71 (t, J = 19.5 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H).

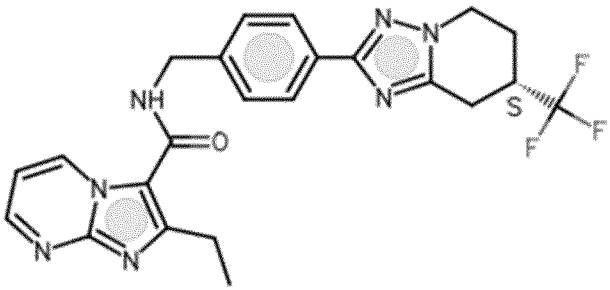
The following compounds were also prepared in accordance with the procedures disclosed herein:

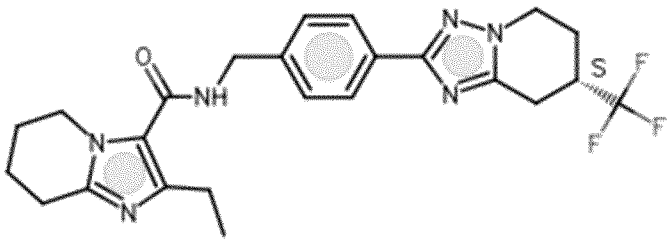


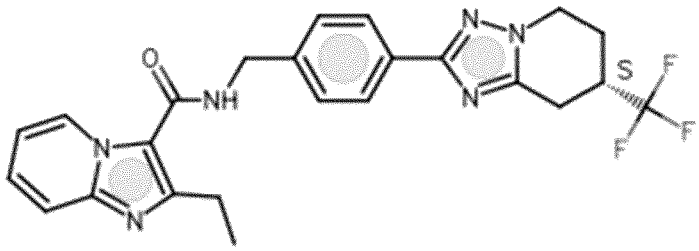


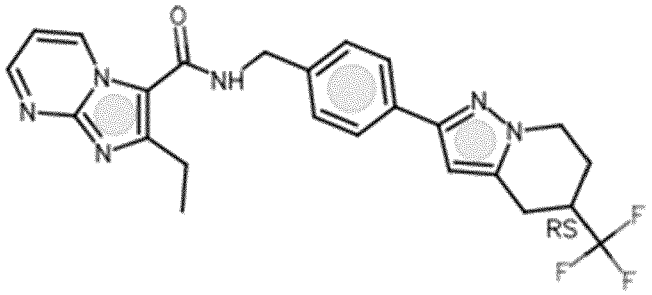


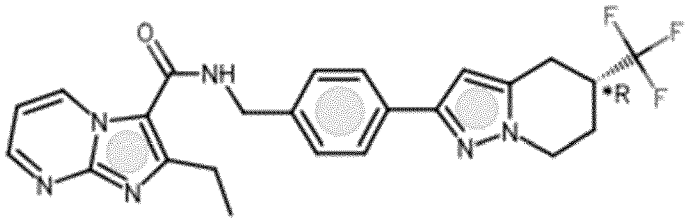


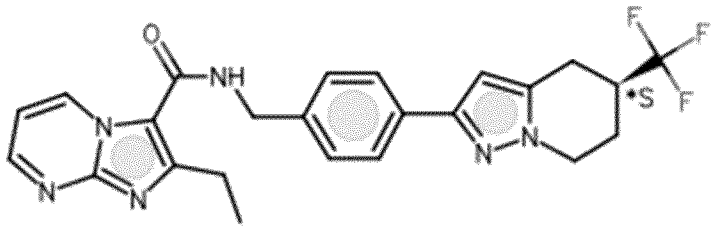












3- ANALYTICAL DATA:

HPLC- LCMS

The mass of some compounds was recorded with LCMS (liquid chromatography mass spectrometry). The methods used are described below.

General procedure LCMS Methods

The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below). Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time…) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (Rt) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the [M+H]+ (protonated molecule) and/or [M-H]- (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. [M+NH4]+, [M+HCOO]-, etc…). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector, "MSD" Mass Selective Detector.

TABLE 1: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow / Column T	Run time
A	Agilent 1100 HPLC DAD LC/MS G1956A	YMC-pack ODS-AQ C18 (50 x 4.6 mm, 3 µm)	A: 0.1% HCOOH in H_2O B: CH_3CN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min.	2.6 / 35	6.2
B	Agilent 1290 Infinity II HPLC DAD LC/MSD iQ G6160A	Phenomenex Kinetex C18 (50 x 2.1 mm, 1.7 µm)	A: 0.1% HCOOH in H_2O B: CH_3CN	From 90% A to 10% A in 1.6 min, held for 0.4 min, to 90% A in 0.2 min.	1.2 / 60	2.2
C	Agilent 1260 Infinity DAD TOF-LC/MS G6224A	YMC-pack ODS-AQ C18 (50 x 4.6 mm, 3 µm)	A: 0.1% HCOOH in H_2O B: CH_3CN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min.	2.6 / 35	6.8
D	Agilent 1290 Infinity DAD LC/MS 6120 (G1948B)	Thermo Scientific Accucore C18 (50 x 2.1 mm, 2.6 µm)	A: 0.1% HCOOH in H2O B: CH3CN	From 95% A to 5% A in 1.3 min, held for 0.5 min, to 95% A in 0.1 min.	1.5 / 35	2.0

TABLE 2: Characterizing data of the compounds. Rt means retention time (in minutes), MW means the molecular weight of the compound, [M+H]+ means the protonated mass of the compound, method refers to the method used for LCMS analysis of compounds.

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
1ab	N.D.	2.57	99	483.5	484.2	A
1a	255.1 (MT)	2.57	99	483.5	484.2	A
1b	263.1 (MT)	2.57	99	483.5	484.2	A
2ab	213.3 (MT)	3.09	98	508.4	509.1.	A
2a	226.1 (DSC)	3.08	99	508.4	509.1	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
2b	226.5 (DSC)	3.08	99	508.4	509.1	A
3ab	220.0 (MT)	1.86	99	482.5	483.2	A
3a	223.3 (MT)	1.82	99	482.5	483.2	A
3b	224.7 (MT)	1.83	98	482.5	483.2	A
4ab	236.7 (MT)	2.37	97	429.5	430.2	A
5ab	255.0 (MT)	2.43	99	483.5	484.2	A
5a	nd	0.78	99	483.5	484.2	B
5b	nd	0.78	99	483.5	484.2	B
6ab	224.9 (MT)	2.64	99	499.5	500.2	A
7ab	228.3 (MT)	2.44	99	486.5	487.1	A
8ab	271.8 (MT)	2.81	99	495.5	496.2	A
9ab	256.8 (MT)	2.50	99	497.5	498.2	A
10ab	229.9 (MT)	3.02	97	503.9	504.1	A
10a	nd	2.86	99	503.9	504.1	A
10b	nd	2.99	99	503.9	504.1	A
11ab	271.1 (MT)	2.53	98	513.5	514.2	A
12ab	272.5 (MT)	2.24	99	498.5	499.2	A
13ab	181.9 (MT)	2.17	99	472.5	473.2	A
14ab	206.9 (MT)	3.10	99	490.4	491.2	A
15ab	226.8 (MT)	2.29	99	482.5	483.2	A
16ab	172.9 (MP)	1.81	96	498.5	499.2	A
17ab	251.1 (MT)	2.34	99	469.5	470.1	A
18ab	183.1 (MT)	2.85	99	507.4	508.2	C
19ab	252.4 (MT)	1.92	99	496.5	497.2	A
20ab	225 (MT)	3.05	99	482.5	483.2	A
21ab	236.7 (MT)	3.18	99	496.5	497.2	A
22ab	251.7 (MT)	2.56	99	501.5	502.2	A
23ab	211.6 (MT)	2.73	99	497.5	498.2	A
24ab	257.4 (MT)	2.63	99	483.5	484.2	A
25ab	246.7 (MT)	2.35	99	465.5	466.2	A
26ab	216.7 (MP)	2.18	99	445.5	446.2	A
27ab	221.7 (MP)	2.70	99	455.6	456.2	A
28ab	213.3 (MP)	2.90	99	457.6	458.3	A
29ab	274.2 (DSC)	1.82	99	431.5	432.2	A
30ab	137.9 (DSC)	2.3	97	489.6	491.2	A
31ab	252.1 (MT)	2.06	99	415.5	416.2	A
32ab	243.9 (DSC)	1.99	99	433.5	434.2	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
33ab	226.6 (MT)	2.63	99	499.5	500.2	A
34ab	265.6 (DSC)	1.68	99	482.5	483.3	A
35ab	235.2 (MT)	2.16	98	432.5	433.2	A
36ab	210.4 (MT)	1.94	99	508.5	509.1	A
37	245.0 (MT)	2.32	98	498.5	499.1	A
38	233.3 (MT)	2.37	99	498.5	499.2	A
39	225.68 (DSC)	2.17	99	484.5	485.1	A
138	193.44 (DSC)	1.90	95	498.5	499.2	A
40	216.31 (DSC)	2.31	99	501.5	502.2	A
41	226.6 (MT)	1.97	97	485.5	486.2	A
42	265.23 (DSC)	2.71	98	409.4	409.7	A
45	242.15 (DSC)	2.23	99	502.5	503.1	A
43	247.11 (DSC)	2.16	99	484.5	485.2	A
44	180.31 (DSC)	2.67	99	515.5	516.2	A
194	N.D.	0.75	93	584.6	585.2	D
46	233.39 (DSC)	2.17	99	498.5	499.2	A
47	223.3 (MT)	2.77	99	527.4	528.0	A
195	N.D.	3.86	97	748.9	749.3	A
196	N.D.	0.919	96	748.8	749.4	D
197	263.38 (DSC)	2.12	99	502.5	503.1	A
198	222.92 (DSC)	2.252	99	498.5	499.1	A
48	223.58 (DSC)	2.693	99	499.5	500.2	A
49	221.73 (DSC)	2.686	99	499.5	500.2	A
50	220.16 (DSC)	2.627	99	486.5	486.9	A
51	247.37 (DSC)	2.621	99	486.5	487.2	A
52	223.56 (DSC)	2.676	99	486.5	487.1	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
61	203.08 (DSC)	3.063	99	490.4	491.1	A
53	237.89 (DSC)	2.932	98	509.4	510.1	A
54	260.2 (DSC)	3.039	97	512.5	513.2	A
55	219.18 (DSC)	2.200	99	468.5	469.1	A
56	194.23 (DSC)	2.121	98	472.5	473.2	A
57	217.2 (DSC)	2.206	98	468.5	469.1	A
58	258.9 (DSC)	3.00	99	512.5	513.1	A
169	195.66 (DSC)	2.09	98	472.5	473.2	A
170	235.43 (DSC)	2.93	96	509.4	510.1	A
59	227.07 (DSC)	2.820	99	497.5	498.2	A
60	201.06 (DSC)	3.063	99	490.4	491.1	A
62	224.33 (DSC)	2.819	98	497.5	498.2	A
63	199.74 (DSC)	3.472	98	536.5	537.0	A
64	202.03 (DSC)	3.470	97	536.5	537.1	A
171	246.61 (DSC)	2.553	99	469.5	470.1	A
190	244.92 (DSC)	2.573	99	469.5	470.1	A
172	182.0 (DSC)	3.338	99	537.5	538.1	A
173	180.1 (DSC)	3.330	99	537.5	538.1	A
65	194.29 (DSC)	2.257	98	486.5	487.2	A
66	228.63 (DSC)	2.241	99	486.5	487.2	A
67	232.0 (DSC)	2.251	99	486.5	487.0	A
68	229.4 (DSC)	2.251	98	486.5	487.0	A
69	192.78 (DSC)	2.269	99	486.5	487.2	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
70	226 (DSC)	2.236	97	486.5	487.2	A
71	192.7 (DSC)	2.259	99	486.5	487.2	A
72	180.1 (DSC)	2.263	99	486.5	487.2	A
74	279.11 (DSC)	2.545	98	487.5	488.1	A
73	267.75 (DSC)	2.544	98	487.5	488.1	A
174	249.75 (DSC)	2.793	99	494.5	495.1	A
75	196.7 (DSC)	3.110	99	486.5	487.1	A
76	237.55 (DSC)	2.124	99	490.5	491.0	A
77	238.17 (DSC)	2.113	99	490.5	491.0	A
78	214.5 (DSC)	2.203	99	486.5	487.0	A
79	214.9 (DSC)	2.192	99	486.5	487.1	A
80	249.79 (DSC)	2.793	99	494.5	495.0	A
81	172.36 (DSC)	3.111	98	486.5	487.2	A
82	172.03 (DSC)	3.113	99	486.5	487.2	A
83	189.73 (DSC)	3.114	99	486.5	487.1	A
84	230.9 (DSC)	3.373	98	553.5	554.1	A
85	224.8 (DSC)	3.369	99	553.5	554.1	A
86	184.93 (DSC)	2.708	99	483.5	484.1	A
87	202.06 (DSC)	2.707	98	483.5	484.1	A
88	N.D.	1.630	95	414.5	415.1	A
103	>300 (MT)	2.533	99	479.5	480.1	A
89	231.05 (DSC)	1.65	99	428.5	429.2	A
90	N.D.	2.073	99	516.9	517.1	A
91	232.55 (DSC)	1.59	99	428.5	429.3	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
93	235.98 (DSC)	2.18	99	429.5	430.2	A
94	235.34 (DSC)	2.33	99	429.5	430.2	A
92	235.39 (DSC)	2.11	99	429.5	430.2	A
95	228.81 (DSC)	2.52	99	414.5	415.2	A
96	244.49 (DSC)	2.02	99	433.5	434.2	A
97	229.91 (DSC)	2.255	99	447.5	448.2	A
98	198.05 (DSC)	2.14	99	459.5	460.2	A
99	236.12 (DSC)	2.227	99	465.5	466.3	A
100	202.36 (DSC)	1.849	98	496.5	497.2	A
101	232.4 (DSC)	2.076	98	526.4	527.1	A
102	197.52 (DSC)	2.224	96	459.5	460.2	A
104	223.22 (DSC)	2.563	99	479.5	480.2	A
105	223.57 (DSC)	2.557	99	479.5	480.2	A
106	217.83 (DSC)	2.562	97	497.5	498.2	A
107	202.43 (DSC)	2.107	99	463.5	464.2	A
108	202.18 (DSC)	1.797	98	478.5	479.2	A
109	190.70 (DSC)	1.839	96	442.6	443.2	A
110	227.98 (DSC)	2.676	96	497.5	498.1	A
111	232.63 (DSC)	1.816	98	498.5	499.2	A
112	220.51 (DSC)	1.827	98	498.5	499.1	A
113	181.84 (DSC)	1.682	97	485.5	486.1	A
114	183.44 (DSC)	1.687	98	485.5	486.2	A
115	151.4 (MT)	2.45	97	473.6	474.2	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
116	240.81 (DSC)	1.803	98	482.5	483.2	A
176	252.23 (DSC)	2.075	98	502.9	503.1	A
117	260.7 (DSC)	1.919	99	500.5	501.1	A
175	258.12 (DSC)	2.076	99	502.9	503.1	A
143	230.41 (DSC)	2.229	99	477.5	478.2	A
118	184.47 (DSC)	1.698	99	458.6	459.2	A
119	238.18 (DSC)	2.209	99	431.5	432.2	A
120	2.055 (DSC)	2.055	99	418.5	419.2	A
121	200.95 (DSC)	1.851	98	496.5	497.2	A
122	N.D.	1.681	99	497.5	498.2	A
123	205.16 (DSC)	1.753	99	497.5	498.2	A
199	267.18 (DSC)	1.754	99	416.5	417.0	A
124	222.36 (DSC)	1.950	99	512.5	513.2	A
144	206.86 (DSC)	2.537	97	443.5	444.2	A
200	252.02 (DSC)	2.111	98	480.5	481.2	A
145	216.15 (DSC)	2.445	96	482.5	483.2	A
146	220.44 (DSC)	2.084	99	429.5	430.2	A
125	230.42 (DSC)	2.384	98	429.5	430.2	A
147	179.96 (DSC)	1.673	98	464.5	465.1	A
148	221.24 (DSC)	1.892	99	430.5	431.0	A
149	219.76 (DSC)	2.302	99	415.5	416.0	A
150	235.14 (DSC)	2.38	98	432.5	433.2	A
151	248.67 (DSC)	1.966	98	496.5	497.1	A
152	247.79	1.978	98	496.5	497.2	A

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
	(DSC)					
153	188.18 (DSC)	2.464	98	535.5	536.1	A
154	191.6 (DSC)	2.48	98	535.5	536.1	A
155	203.8 (DSC)	3.142	98	483.5	484.2	A
156	216.42 (DSC)	2.334	97	415.5	416.1	A
157	219.59 (DSC)	2.342	98	415.5	416.2	A
191	212.4 (DSC)	3.145	99	483.5	484.2	A
158	206.97 (DSC)	1.768	98	468.5	469.2	A
159	222.55 (DSC)	2.05	99	414.5	415.2	A
160	214.62 (DSC)	1.970	99	418.5	419.2	A
161	202.04 (DSC)	1.550	99	467.5	468.1	A
162	224.44 (DSC)	2.055	99	414.5	415.2	A
163	214.18 (DSC)	1.988	99	418.5	419.2	A
192	176.9 (DSC)	2.360	98	536.5	537.1	A
164	216.09 (DSC)	1.469	99	471.5	472.2	A
165	201.39 (DSC)	1.564	99	467.5	468.0	A
166	210.32 (DSC)	1.75	98	468.5	469.1	A
193	177.52 (DSC)	2.348	96	536.5	537.1	A
142	219.04 (DSC)	1.456	99	471.5	472.2	A
129	258.41 (DSC)	2.01	99	488.5	489.2	C
178	220.99 (DSC)	2.96	99	468.5	469.2	C
177	219.28 (DSC)	2.99	98	468.5	469.2	C
181	241.83 (DSC)	2.57	99	469.5	470.2	C
182	243.26	2.51	99	469.5	470.2	C

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
	(DSC)					
130	216.8 (MT)	2.04	98	488.5	489.2	C
131	192.55 (DSC)	1.99	98	488.5	489.2	A
183	191.5 (DSC)	2.59	98	441.5	442.2	C
184	192.0 (DSC)	2.72	98	441.5	442.2	C
185	224 (DSC)	1.66	99	489.5	490.2	C
132	221.6 (MT)	1.97	98	488.5	489.2	A
179	197 (DSC)	2.51	99	471.5	472.3	C
186	238.11 (DSC)	1.97	99	486.5	487.2	C
187	190.8 (DSC)	2.63	99	400.5	401.2	C
180	219.4 (DSC)	2.93	99	468.5	469.2	C
188	197 (DSC)	2.26	99	472.5	473.1	A
133	205.04 (DSC)	2.26	99	464.5	465.2	C
134	204 (DSC)	2.11	99	468.5	469.1	A
135	214.62 (DSC)	2.12	99	502.5	503.2	A
189	205.21 (DSC)	2.49	99	465.5	466.1	C
136	259.3 (DSC)	2.46	99	540.5	541.2	A
137	257.94 (DSC)	2.45	98	540.5	541.2	A
139	213.23 (DSC)	2.23	98	502.5	503.2	A
140	222.6 (DSC)	2.15	99	502.5	503.2	A
141	200.7 (DSC)	2.15	99	502.5	503.1	A
167	174.94 (DSC)	2.15	99	502.5	503.2	A
168	208.74 (DSC)	2.15	99	502.5	503.2	A
126	168 (DSC)	3.18	99	471.5	472.2	C

Compound number	Melting point (°C) (DSC or MT)	R_t	UV Area (%)	MW	$[M+H]^+$	Method
127	168 (DSC)	3.18	98	471.5	472.2	C
128	181.09 (DSC)	2.17	99	472.5	473.2	A

SFCMS-METHODS

GENERAL PROCEDURE FOR SFC-MS METHODS

The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO_2) and modifier, an autosampler, a column oven, an UV detector equipped with a high-pressure flow cell standing up to 400 bars. Data acquisition was performed with appropriate software.

Table 3: Analytical SFC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; run time in minutes; backpressure (BPR) in bars.

Method	**Column**	**Mobile Phase**	**Gradient**	**Flow ------- T**	**Run time -------- BPR**
1	Phenomenex Lux Cellulose-1 150x4.6 mm, 5um	A: CO_2 B: MeOH (+ 0.1% DEA)	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
2	Phenomenex Lux i-Amylose-1 150x4.6 mm, 5um	A: CO_2 B: EtOH (+ 0.1% DEA)	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
3	Phenomenex Lux i-Amylose-1 150x4.6 mm, 5um	A: CO_2 B: iPrOH (+ 0.1% DEA)	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
4	Regis Technologies Reflect i-Cellulose-C 100x4.6 mm, 3um	A: CO_2 B: EtOH (+ 0.1% DEA)	From 5% B to 60% B in 7 min, hold 2 min. To 5% B in 1 min.	3 ------- 35	13 ------- 100

Method	Column	Mobile Phase	Gradient	Flow ------- T	Run time -------- BPR
5	Phenomenex Lux Amylose-2 150x4.6 mm, 5um	A: CO2 B: Ethanol +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
6	Phenomenex Lux Amylose-1 150x4.6 mm, 5um	A: CO2 B: iPROH +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
7	Phenomenex Lux Amylose-1 150x4.6 mm, 5um	A: CO2 B: Ethanol +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
8	Phenomenex Lux Amylose-1 150x4.6 mm, 5um	A: CO2 B: Methanol +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
9	Phenomenex Lux Cellulose-1 150x4.6 mm, 5um	A: CO2 B: Ethanol +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100
10	Regis Technologies Reflect i-Cellulose-C 100x4.6 mm, 3um	A: CO_2 B: Methanol (+ 0.1% DEA)	From 5% B to 60% B in 7 min, hold 2 min. To 5% B in 1 min.	2.5 ------- 35	13 ------- 100
11	Regis Technologies Reflect i-Amylose-A 150x4.6 mm, 5um	A: CO2 B: Ethanol +0.1% Diethylamine	From 5% B to 60% B in 10 min, hold 3 min. To 5% B in 1.9 min.	3 ------- 35	20 ------- 100

Table 4. Analytical SFC data – Rt means retention time (in minutes), MW the molecular weight of the compound, [M+H]+ means the protonated mass of the compound, method refers to the method used for (SFC)MS analysis of enantiomerically pure compounds.

Compound number	R_t	UV Area%	MW	$[M+H]^+$	Method	Isomer Elution Order
1a	8.8	99	483.5	484.2	1	A
1b	9.51	99	483.5	484.2	1	B
2a	5.41	99	508.4	509.1	2	A
2b	5.82	99	508.4	509.1	2	B
3a	7.76	99	482.5	483.2	3	A
3b	8.54	99	482.5	483.2	3	B
5a	8.30	99	483.5	484.2	4	A
5a	8.64	99	483.5	484.2	1	A
5b	9.84	99	483.5	484.2	4	B
5b	9.24	99	483.5	484.2	1	A
10a	9.18	99	503.9	504.1	1	A
10a	9.03	99	503.9	504.1	1	A
10b	9.95	99	503.9	504.1	1	B
10b	9.90	99	503.9	504.1	1	B
48	7.685	99	499.5	-	5	A
49	8.070	99	499.5	-	5	B
50	9.327	99	486.5	-	6	B
51	9.900	99	486.5	-	6	-
52	9.205	95	486.5	-	6	A
61	9.773	99	490.4	-	6	A
55	10.182	91	468.5	-	6	A
56	8.943	99	472.5	-	6	A
57	10.833	91	468.5	-	6	B
58	5.543	98	512.5	-	1	-
169	9.28	99	472.5	-	6	B
170	9.833	99	509.4	-	6	-
60	10.398	99	409.4	-	6	B
62	9.733	99	497.5	-	6	B

Compound number	R_t	UV Area%	MW	$[M+H]^+$	Method	Isomer Elution Order
63	8.058	98	536.5	-	6	A
64	8.307	99	536.5	-	6	B
171	10.122	99	469.5	-	1	B
190	8.317	99	469.5	-	1	A
172	7.843	99	537.5	-	6	A
173	8.097	99	537.5	-	6	B
65	9.927	97	486.5	-	7	-
66	10.095	99	486.5	-	6	A
67	10.378	98	486.5	-	6	B
68	10.410	98	486.5	-	6	B
69	9.103	99	486.5	-	6	B
70	10.032	99	486.5	-	6	A
71	8.880	99	486.5	-	6	A
72	8.788	99	486.5	-	6	-
74	7.883	99	487.5	-	4	A
73	8.708	99	487.5	-	4	B
174	10.888	99	494.5	-	7	-
75	6.787	99	486.5	-	8	-
76	6.678	99	490.5	-	9	B
77	6.257	99	490.5	-	9	A
78	9.628	99	486.5	-	6	A
79	9.938	99	486.5	-	6	B
80	9.917	98	494.5	-	7	-
81	8.975	99	486.5	-	6	-
82	9.480	99	486.5	-	6	-

Compound number	R_t	UV Area%	MW	$[M+H]^+$	Method	Isomer Elution Order
83	8.603	99	486.5	-	6	-
84	7.370	99	553.5	-	6	B
85	7.302	99	553.5	-	6	A
86	2.558	99	483.5	-	4	A
87	3.267	99	483.5	-	4	B
93	9.233	99	429.5	-	7	A
94	10.047	99	429.5	-	7	B
104	9.785	99	479.5	-	1	A
105	10.815	98	479.5	-	1	B
111	10.343	99	498.5	-	7	A
112	11.368	99	498.5	-	7	B
113	11.30	97	485.5	-	8	B
114	10.515	99	485.5	-	8	A
176	10.972	98	502.9	-	6	B
175	10.218	97	502.9	-	6	A
150	9.388	99	432.5	-	9	-
151	9.707	99	496.5	-	6	A
152	10.733	99	496.5	-	6	B
153	9.222	99	535.5	-	6	B
154	8.442	99	535.5	-	6	A
155	7.657	99	483.5	-	6	A
156	10.128	99	415.5	-	6	A

Compound number	R_t	UV Area%	MW	$[M+H]^+$	Method	Isomer Elution Order
157	10.465	99	415.5	-	6	B
191	7.868	99	483.5	-	6	B
158	11.477	96	468.5	-	6	A
159	10.7	99	414.5	-	6	B
160	9.387	99	418.5	-	6	B
161	11.418	99	468.5	-	6	B
162	10.582	99	414.5	-	6	A
163	9.192	99	418.5	-	6	A
192	8.455	99	536.5	-	6	A
164	10.053	99	471.5	-	7	A
165	10.678	99	467.5	-	6	A
166	12.587	99	468.5	-	6	B
193	9.040	96	536.5	-	6	B
142	11.072	99	471.5	-	7	B
129	7.52	98	488.5	-	4	-
178	11.51	98	468.5	-	6	B
177	10.78	98	468.5	-	6	A
181	9.27	99	469.6	-	10	B
182	8.12	99	469.6	-	10	A
130	5.12	96	488.5	-	11	-
131	9.26	99	488.5	-	6	B
183	8.03	99	441.5	-	1	A
184	8.47	99	441.5	-	1	B

Compound number	R_t	UV Area%	MW	$[M+H]^+$	Method	Isomer Elution Order
132	7.78	98	488.5	-	6	A
135	8.47	99	502.5	-	7	-
136	5.64	99	540.5	-	5	-
137	10.85	99	540.5	-	6	-
139	10.54	97	502.5	-	7	-
140	6.748	99	502.5	-	6	A
141	8.47	97	502.5	-	6	B
167	8.23	99	502.5	-	6	A
168	9.07	99	502.5	-	6	B
126	5.22	99	471.5	-	1	B
127	2.84	99	471.5	-	1	A

4- CHEMICAL STABILITY TESTING

HTChem stab assay was used to assess the chemical stability of the compounds. 72 h stirring at rt in a buffer pH2, pH4 and pH7 vs a reference DMSO solution. HTChem stab assay is based on the handbook of Pharmaceutical Stress Testing, Predicting Drug Degradation, second edition, authors Baertschi, Alsante, Reed ISBN 978-143980179-6.

Compounds disclosed herein may have the advantage that they are chemically more stable than other compounds (e.g. than other known compounds), for instance as tested in the chemical stability assay described below.

General procedure HTChem stab assay

Compounds were plated (1µl 10mM DMSO stock in 96 well plate (DMSO control+3 pH conditions), one plate per condition).
200 µL of respectively DMSO, Buffer/DMSO mix pH2, Buffer/DMSO mix pH4 and Buffer/DMSO mix pH7 was added.
After 72h shaking (300rpm) at room temperature the samples were analysed by LC/UV/MS.
Chromatograms of samples (stability conditions) were compared with the chromatograms of control sample (DMSO). Extra peaks were flagged and identified by mass spectrometry. Sample purity (reference included) were reported.

Buffer preparation
pH3 buffer: For 1l; weigh 4.14g NaH2PO4.H2O, add 600ml H2O, add H3PO4 to pH3, add H2O to 1000ml. Filter over 0.2µm and store at 4°C. Expires after 30 days.
pH6 buffer: For 1l; weigh 4.14g NaH2PO4.H2O, add 600ml H2O, add 1N NaOH to pH6, add H2O to 1000ml. Filter over 0.2µm and store at 4°C. Expires after 30 days.

Buffer/DMSO mixture preparation:
pH2 Buffer/DMSO (StabSolvent): mix 2 parts of HCl 0.1N with 1 part of DMSO
pH4 Buffer/DMSO (StabSolvent): mix 2 parts of buffer pH3 with 1 part of DMSO
pH7 Buffer/DMSO (StabSolvent): mix 2 parts of buffer pH6 with 1 part of DMSO
measure pH prior to use.

UPLC method HT chemical stability:
Instrument: Acquity UPLC; Column: Acquity HSS T3, 50 mm length x 2.1 mm i.d., 1.8 µm particle size. Detectors: PDA (250-350nm) and SQD2 (90-1500m/z). Mobile phase A: 0.1% Formic acid in water; Mobile phase B: 0.1% Formic acid in Acetonitrile.
Injection volume: 5µL, flow rate 0.6mL/min.
Gradient

Time(min)	%A	%B
0	100	0
0.3	95	5
1.8	0	100
2.6	0	100
2.9	100	0

Data processing including peak integration and identification was done with Waters OpenLynx software.

TABLE 5. Chemical stability data

Compound number	Vehicle			
	DMSO	Buffer pH2	Buffer pH4	Buffer pH7
1a	100	100	100	100
1ab	100	100	100	100
1b	100	99	96	96
2a	100	100	100	100
2ab	100	100	100	98
2b	100	100	100	100

Compound number	Vehicle			
3a	100	100	100	100
3b	98	93	99	93
4ab	98	98	98	98
5a	100	100	100	100
5ab	94	95	96	96
5b	100	100	100	100
6ab	93	100	100	100
7ab	100	100	100	100
8ab	100	100	100	100
9ab	100	100	100	100
10a	100	84	76	97
10ab	90	72	64	90
10b	96	81	71	92
12ab	99	100	100	100
13ab	100	100	100	100
14ab	100	100	100	100
15ab	98	98	100	99
16ab	77	74	74	80
17ab	100	100	97	100
18ab	98	98	100	100
19ab	98	98	98	98
20ab	100	100	100	100
21ab	100	100	100	100
22ab	98	97	97	98
23ab	100	100	100	100
24ab	100	100	100	100
25ab	100	100	100	100
26ab	95	95	95	95
27ab	100	100	100	100
28ab	100	100	100	100
29ab	100	100	100	100
30ab	98	98	98	98
31ab	100	100	100	100
32ab	100	100	100	100
33ab	100	64	100	100
34ab	94	94	95	93
35ab	100	100	99	98
36ab	100	100	100	100

These chemical stability data % depend on the purity of the compounds, their solubility and the solubility of their potential degradation products. Nevertheless, this showed that, under the tested conditions, the compounds were stable, and mostly not susceptible to unwanted degradation in acidic media.

5- BIOLOGICAL ASSAYS / PHARMACOLOGICAL EXAMPLES

MIC determination for testing compounds against *M. tuberculosis*.

TEST 1

Test compounds and reference compounds are dissolved in DMSO and 1 µl of solution is spotted per well in 96 well plates at 200x the final concentration. Column 1 and column 12 are left compound-free, and from column 2 to 11 compound concentration is diluted 3-fold. Frozen stocks of *Mycobacterium tuberculosis* strain EH4.0 expressing green-fluorescent protein (GFP) are previously prepared and titrated. To prepare the inoculum, 1 vial of frozen bacterial stock is thawed to room temperature and diluted to 5x10 exp5 colony forming units per ml in 7H9 broth. 200 µl of inoculum, which corresponds to 1x10 exp5 colony forming units, are transferred per well to the whole plate, except column 12. 200µl 7H9 broth are transferred to wells of column 12. Plates are incubated at 37°C in plastic bags to prevent evaporation. After 7 days, fluorescence is measured on a Gemini EM Microplate Reader with 485 excitation and 538 nm emission wavelengths and IC_{50} and/or pIC_{50} values (or the like, e.g. IC_{50}, IC_{90}, pIC_{90}, etc) are (or may be) calculated.

TEST 2

Appropriate solutions of experimental/test and reference compounds were made in 96 well plates with 7H9 medium. Samples of *Mycobacterium tuberculosis* strain H37Rv were taken from cultures in logarithmic growth phase. These were first diluted to obtain an optical density of 0.3 at 600 nm wavelength and then diluted 1/100, resulting in an inoculum of approximately 5x10 exp5 colony forming units per ml. 100µl of inoculum, which corresponds to 5x10 exp4 colony forming units, were transferred per well to the whole plate, except column 12. Plates were incubated at 37°C in plastic bags to prevent evaporation. After 7 days, resazurin was added to all wells. Two days later, fluorescence was measured on a Gemini EM Microplate Reader with 543 excitation and 590 nm emission wavelengths and MIC_{50} and/or pIC_{50} values (or the like, e.g. IC_{50}, IC_{90}, pIC_{90}, etc) were (or may be) calculated.

TEST 3: Time kill assays

Bactericidal or bacteriostatic activity of the compounds can be determined in a time kill kinetic assay using the broth dilution method. In this assay, the starting inoculum of *M.*

tuberculosis (strain H37Rv and H37Ra) is 10^6 CFU / ml in Middlebrook (1x) 7H9 broth. The test compounds are tested alone or in combination with another compound (e.g. a compound with a different mode of action, such as with a cytochrome bd inhibitor) at a concentration ranging from 10-30μM to 0.9-0.3μM respectively. Tubes receiving no antibacterial agent constitute the culture growth control. The tubes containing the microorganism and the test compounds are incubated at 37 °C. After 0, 1, 4, 7, 14 and 21 days of incubation samples are removed for determination of viable counts by serial dilution (10^0 to 10^{-6}) in Middlebrook 7H9 medium and plating (100 μl) on Middlebrook 7H11 agar. The plates are incubated at 37 °C for 21 days and the number of colonies are determined. Killing curves can be constructed by plotting the $\log_{10}$CFU per ml versus time. A bactericidal effect of a test compound (either alone or in combination) is commonly defined as 2-$\log_{10}$ decrease (decrease in CFU per ml) compared to Day 0. The potential carryover effect of the drugs is limited by using 0.4% charcoal in the agar plates, and by serial dilutions and counting the colonies at highest dilution possible used for plating.

Results

Compounds of the invention/examples, for example when tested in Test 2 described above, may typically have a $pMIC_{50}$ from 3 to 10 (e.g. from 4.0 to 9.0, such as from 5.0 to 8.5)

Further Data

The compounds of the invention/examples may have advantages associated with *in vitro* potency, kill kinetics (i.e. bactericidal effect) *in vitro*, PK properties, food effect, safety/toxicity (including liver toxicity, coagulation, 5-LO oxygenase), metabolic stability, Ames II negativity, MNT negativity, aqueous based solubility (and ability to formulate) and/or cardiovascular effect e.g. on animals (e.g. anesthetized guinea pig). The data below that was generated/calculated may be obtained using standard methods/assays, for instance that are available in the literature or which may be performed by a supplier (e.g. Microsomal Stability Assay – Cyprotex, Mitochondrial toxicity (Glu/Gal) assay – Cyprotex, as well as literature CYP cocktail inhibition assays).

METABOLIC STABILITY IN LIVER MICROSOMES

The test compound was incubated under the generic condition (0.5 mg/ml microsomal protein, 1 mM NADPH, 1 mM MgCl2, and 0.1 M phosphate buffer, pH 7.4, 37°C) at a defined substrate concentration (typically 1 μM) in liver microsomes of selected species across a time course (typically 0, 5, 10, 20, 40 and 60 minutes) at Cyprotex (Cheshire, UK). The liver microsomes, buffer and test compound will be pre-incubated for 5 minutes. The addition of the co-factor NADPH will initiate the reaction and the reaction was terminated by

addition of acetonitrile. The samples were centrifuged prior to analysis by LC-MS/MS analysis. The relative amount of parent compound remaining in the active incubations vs. the control incubations (t=0 mins) for each compound was measured by peak area comparison. The in vitro metabolic half-life ($t_{1/2}$) was calculated using the slope of the log-linear regression from the percentage parent compound remaining versus time relationship (κ), The in vitro intrinsic clearance (Cl_{int}) (µl/min/mg microsomal protein) was calculated using the in vitro metabolic half-life, incubation volume and the weight of microsomal protein in the incubation.

GENOTOXICITY ASSAY (AmesIIb mutagenicity test)

The aim is to evaluate compounds (and/or their metabolites) for their ability to induce reverse mutations in a gene of histidine-requiring Salmonella typhimurium strains to produce histidine-independent strains of these bacteria, in the absence and in the presence of a mammalian metabolic activation system.

Point mutations were made in the histidine (*His*) operon in *Salmonella typhimurium*, rendering the bacteria incapable of producing histidine. These single base substitutions are positioned at strategic points within the *His* gene, resulting in *his*-organisms that cannot grow unless histidine is supplied. When a mutagenic event occurs, base substitutions within the *His* gene then cause the reversion of the *his*-Ames II™ strains to *His*.

A chemical's mutagenic potential is assessed by exposing these *his*-organisms to varying concentrations of chemical and selecting for the reversion event. Medium lacking histidine is used for this selection which allows only those cells that have undergone the *his*- to *His* reversion to survive and grow.

The assay may be performed using a kit and instructions from Xenometric. The two strains provided in the Xenometric kit are the Ames II™ Mixed Strains and TA98. The Ames II™ Mixed Strains contains an equimolar mixture of the Ames II™ TA7001-TA7006 strains. Individually, these strains are designed to revert by only one specific base-pair substitution out of six possible changes. Thus, when mixed, all six base substitution mutations can be represented in one culture. This kit also contains TA98 for the detection of frameshift mutations. For the avoidance of doubt, an AmesIIb score of 1 shows no genotoxicity signals.

Biological Results

Compounds of the examples were tested for bacterial activity (Test 2 described above in section "MIC determination for testing compounds against *M. tuberculosis*.") and Metabolic Stability in liver microsome; the results presented in Table 6 were obtained:

TABLE 6. Biological data table

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
1ab	8,020	0,028	<7.7	>180	<7.7	>180	1
1a	8,505	0,009	<7.7	>180	<7.7	>180	
1b	8,576	0,007	7,8	178	7,81	178	
2ab	7,627	0,089	10,7	129	<7.7	>180	1
2a	7,648	0,086	11,4	121	<7.7	>180	1
2b	7,502	0,098	12,3	112	<7.7	>180	1
3ab	8,450	0,009	13,6	102	15	92,5	
3a	8,532	0,008	7,78	178	13,4	103	1
3b	8,483	0,010	23,8	58,3	26,1	53,2	1
4ab	8,152	0,017	8,38	165			1
5ab	8,082	0,023	<7.7	>180			1
5a	7,665	0,060	<7.7	>180			1
5b	7,873	0,044	<7.7	>180			1
6ab	8,459	0,007	14,2	97,4			1
7ab	8,362	0,014	20,5	67,7			
8ab	8,148	0,018					1
9ab	8,306	0,011	13,9	99,7			1
10ab	8,260	0,016	<7.7	>180			1
10a	<6.301		<7.7	>180			1
10b	8,207	0,021	11,1	125			1
11ab							
12ab	7,631	0,064	<7.7	>180	<7.7	>180	1
13ab	8,067	0,024	15,5	89,4			1
14ab	7,877	0,036	<7.7	>180			1
15ab	8,512	0,006					1
16ab	<6.301						
17ab	7,526	0,105	<7.7	>180			1
18ab	7,431	0,142	11,1	125			1
19ab	7,940	0,047					
20ab	9,031	0,003	21,3	65	36,3	38,2	1
21ab	8,457	0,011					

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
22ab	8,641	0,007	13	107			1
23ab	8,081	0,022	14,6	94,9			1
24ab	8,471	0,008	<7.7	>180			1
25ab	8,127	0,014	9,97	139			1
26ab	7,306	0,143	10,9	127			1
27ab	8,336	0,014					
28ab	8,436	0,011					
29ab	<6.301	3,188	<7.7	>180	<7.7	>180	1
30ab	6,964	0,332	9,08	153			1
31ab	7,797	0,052	<7.7	>180			1
32ab	7,098	0,248					
33ab	7,895	0,039					
34ab	7,024	0,387	<7.7	>180			1
35ab	7,873	0,041	46,4	29,9			1
36ab	<6.301						
37	7.9	0,0035	<7.7	>168			1
38	7.77	0,052	<7.7	>180			1
39	7.31	0,16	<7.7	>180			1
138	<6.3	>0.5					
40	7.47	0,11	<7.7	>180			1
41	<6.3	>0.5					
42	<6.3	>0.5					
45	6.61	1,05					
43	6,81	0,37					
44	7.34	0,21					
194	7,43	0,1	<7.7	>180	<7.7	>180	1
46	<6.3	>0.5					
47	<6.3	>0.5					
196	7.56	0,067	<7.7	>180			1
197	7.16	0,21					
198	7,34	0,15					
48	8,08	0,026					
49	8,11	0,023	12,9	108			
50	7,55	0,11	11,7	118			1
51	8,5	0,008	<7.7	>180			1
52	7.38	0.16					
61	7,96	0,036					

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
53	7,96	0,036					
54	7,14	0,22					
55	8,53	0,0086					
57	8,16	0,022					
58	7,02	0,39					
170	<6.56	>0.45					
59	7,75	0,061	59,4	23,4	347	4	1
60	7,76	0,067					
62	7,96	0,033	57,8	24	294	4,7	1
63	<6.65	>0,46					
64	<6,3	>0,5					
171	7,33	0,18					
190	7,32	0,19					
172	<6,53	>0,46					
173	<6,49	>0,47					
65	7,87	0,039					
66	7,29	0,24					
67	7,39	0,18					
68	7,32	0,23					
69	7,95	0,031					
70	7,25	0,23					
71	8,02	0,024					
72	7,86	0,042					
74	6,94	>0,5	<7,7	>180			
73	7,18	0,35	<7,7	>180			
174	7,17	0,25	17,3	80,3			
75	7,48	0,086					
76	7,55	0,09					
77	7,6	0,098	26,1	53,1			
78	8,08	0,028					
79	7,99	0,035					
80	7,25	0,2	16,3	84,9			
81	7,24	0,19					
82	7,51	0,087					
83	7,2	0,23					
84	<7,03	>0,38					
85	<6,3	>0,5					

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
86	6,98	0,44					
87	6,97	0,47					
88	7,43	0,099					
103	8,12	0,02	<7,7	>180	119	11,6	
89	7,85	0,046	<7,7	>180			1
90	7,22	0,15					
91	6,72	0,48	<7,7	>180			1
94	7,86	0,039					
92	7,21	0,2					
95	8,44	0,011	0,012	58,7	<0,0012	>560	1
96	7,47	0,094					
97	7,72	0,057					
98	7.56	0,11					
99	7,15	0,22					
100	7,21	0,2					
101	5,7	3,95					
102	7,59	0,058	<7,7	>180			1
104	8,25	0,015					
105	8,24	0,014					
106	7,92	0,03	12,1	115			1
107	6,87	0,33					
108	8,12	0,018					
109	8,04	0,024					
110	8,23	0,016					
111	8,33	0,012					
112	8,07	0,027					
113	7,89	0,034					
114	8,12	0,032					
115	7,61	0,096					
116	8,34	0,0097					
176	7,9	0,039					
117	8,51	0,077					
175	7,66	0,059					
143	7,48	0,092					
118	7,48	0,083					
119	7,72	0,052					
120	7,84	0,042	14,4	96,6			1

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
121	8.06	0,035					
122	7,36	0,21					
123	<6,3	>0,5					
199	<6,3	>0,5					
144	7,9	0,05	<7,7	>180			1
200	7,21	0,22					
145	7,94	0,041					
146	7,37	0,15					
125	7,95	0,04					
147	7,82	0,05					
148	6,48	>0,5					
149	6,64	>0,5					
150	8	0,03					
151	7,74	0,054	62,5	22,2	326	4,3	1
152	7,63	0,088	129	10,7	>347	<4	1
153	<6,3	>0,5					
154	<6,3	>0,5					
155	<6,3	>0,5					
156	6,72	>0,5					
157	6,9	0,41					
191	<6,3	>0,5					
158	7,12	0,29					
159	7,96	0,037					
160	7,45	0,088					
161	7,73	0,056					
162	7,95	0,044					
163	7,18	0,17					
192	5,81	>5					
164	7,77	0,058					
165	7,79	0,055					
166	6,84	>0,5					
193	<6,3	>0,5					
142	7,64	0,097					
178	7,66	0,11	<7,7	>180			1
177	7,85	0,056	15,8	87,8			1
181	7,24	0,22					
182	7,28	0,2					

Compound number	Bacterial activity		Metabolic Stability (liver microsome intrinsic clearance)				GeneTox
	$pMIC_{50}$	MIC_{90} (in µM)	Clearance (mouse, µl/min./mg protein)	Half life (mouse, min.)	Clearance (human, µl/min./mg protein)	Half life (human, min.)	AmesIIb Score
131	<6,3	>0,5					
183	6,19	0,48	10,1	137			1
184	6,78	0,43	<7,7	>180			1
185	8,01	0,034					
132	<6,57	>0,45					
179	8,48	0,0097	53,5	25,9			1
186	7,39	0,19	<7,7	>180			
187	6,82	>0,5					
180	7,7	0,12	9,9	141			
188	7,64	0,23					
133	7,93	0,051					
134	7,59	0,12					
135	<6,65	>0,44					
189	7,06	0,33					
136	<6,3	>0,5					
137	<6,3	>0,5					
139	<6,74	>0,45					
140	6,94	0,33					
141	6,78	>0,5					
167	6,88	0,45					
168	6,76	0,5					
126	7,62	0,12	47,6	29,1			1
127	7,29	0,28	39,7	34,9			1

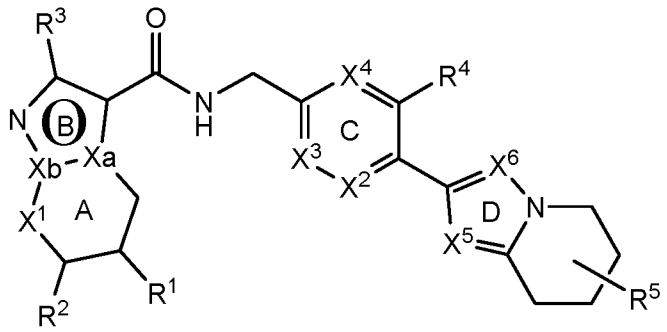
Compounds disclosed herein:

- Are active using the test methods described above, and may have other potency advantages depending on the setting
- May have the advantage that they are chemically more stable that other compounds (for instance in the tests described herein); this may have the advantage that they do not form degradants (e.g. that are undesired or may elicit unwanted side-effects)
- May display better stability, for instance compared to compounds known in the prior art, e.g. in the stability tests described herein (including the metabolic stability in liver microsomes test described herein)

- May have advantages in relation to toxicity, for instance as displayed/measured using the genotoxicity assay/mutagenicity test described, or another test described herein, for instance displaying the CVS results or due to the Glu/Gal assay results)

CLAIMS

1. A compound of formula (IA)



(IA)

wherein

A is a 6-membered ring, which may be aromatic or non-aromatic,

B is a 5-membered aromatic ring;

one of X_a and X_b represents N and the other represents C;

X^1 represents =N-, $-CH_2-$ or $=C(R^{10a})-$;

X^2, X^3, X^4, X^5 and X^6 each independently represent =N- or $=C(R^{10b})-$;

R^1 and R^2 each independently represent a substituent selected from hydrogen, halo, $-R^{6c}$, $-O-R^{6d}$, $-C(=O)-R^{6e}$, $-C(=O)-N(R^6)(R^7)$, -CN and $-N(R^{6a})R^{6b}$;

R^3 represents a substituent selected from H, halo (e.g. Cl, F), and $-C_{1-3}$ alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. F) and $-O-C_{1-3}$ alkyl;

R^4 represents a substituent selected from H, F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl;

R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, and $-N(R^{11a})R^{11b}$;

R^6 and R^7 are independently selected from H and $-C_{1-3}$ alkyl;

R^{6a} and R^{6b} independently represent H, C_{1-6} alkyl or R^{6a} and R^{6b} are linked together to form a 3- to 6-membered ring;

R^{6c} and R^{6d} independently represent hydrogen or -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F), -O-CH_3, phenyl, -N(R^{6a})R^{6b};

R^{6e} is -C_{1-3} alkyl;

R^{8a} represents -CN, - C_{1-4} alkyl (linear, branched or cyclic; which alkyl group is optionally substituted by one or more substituents selected from halo, so forming e.g. -CF_3, -CHF_2, -CF_2CH_3), or, -OC_{1-3} alkyl (optionally substituted by one or more substituents selected from halo and -O-CH_3);

R^{8b} is hydrogen or -C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

R^9 represents -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F) and -O-CH_3;

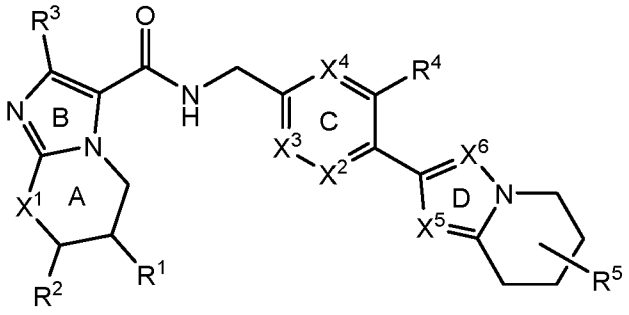
R^{10a} and R^{10b} independently represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, -R^{12a}, -OR^{12b}, -N(R^{12c})R^{12d} and/or -C(O)N(R^{12e})R^{12f}) or -O-C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -R^{12g}, -OR^{12h} and/or -N(R^{12i})R^{12j});

R^{11a} and R^{11b}, independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or -$S(O)_2R^{6c}$ (where R^{6c} is defined above);

R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i} and R^{12j} independently represent hydrogen or C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula (I)



(I)

wherein

A is a 6-membered ring, which may be aromatic or non-aromatic,

X^1 represents =N- , $-CH_2-$ or $=C(R^{10a})-$;
X^2, X^3, X^4, X^5 and X^6 each independently represent =N- or $=C(R^{10b})-$;

R^1 and R^2 each independently represent a substituent selected from hydrogen, halo (e.g. Cl, F), $-R^{6c}$, $-O-R^{6d}$, $-C(=O)-R^{6e}$, $-C(=O)-N(R^6)(R^7)$, -CN and $-N(R^{6a})R^{6b}$;

R^3 represents a substituent selected from H, halo (e.g. Cl, F), and $-C_{1-3}$ alkyl (linear, branched or cyclic) optionally substituted by one or more substituents selected from halo (e.g. F) and $-O-C_{1-3}$ alkyl;
R^4 represents a substituent selected from H, F, $-C_{1-3}$ alkyl and $-O-C_{1-3}$ alkyl;
R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, and $-N(R^{11a})R^{11b}$;

R^6 and R^7 are independently selected from H and $-C_{1-3}$ alkyl;
R^{6a} and R^{6b} independently represent H, C_{1-6} alkyl or R^{6a} and R^{6b} are linked together to form a 3- to 6-membered ring;
R^{6c} and R^{6d} independently represent hydrogen or $-C_{1-4}$ alkyl optionally substituted by one or more substituents selected from halo (e.g. F), $-O-CH_3$, phenyl, $-N(R^{6a})R^{6b}$;
R^{6e} is $-C_{1-3}$ alkyl;

R^{8a} represents -CN, $-C_{1-4}$ alkyl (linear, branched or cyclic; where the alkyl is optionally substituted by one or more substituents selected from halo, so forming e.g. $-CF_3$, $-CHF_2$, $-CF_2CH_3$) or $-OC_{1-3}$ alkyl (optionally substituted by one or more substituents selected from halo and $-O-CH_3$);
R^{8b} is hydrogen or $-C_{1-3}$ alkyl (optionally substituted by one or more fluoro atoms);

R^9 represents -C_{1-4} alkyl optionally substituted by one or more substituents selected from halo (e.g. F) and -O-CH_3;

R^{10a} and R^{10b} independently represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, -R^{12a}, -OR^{12b}, -$N(R^{12c})R^{12d}$ and/or -$C(O)N(R^{12e})R^{12f}$) or -O-C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -R^{12g}, -OR^{12h} and/or -$N(R^{12i})R^{12j}$);

R^{11a} and R^{11b}, independently represent hydrogen, C_{1-3} alkyl (optionally substituted by one or more fluoro atoms) or -$S(O)_2R^{6c}$ (where R^{6c} is defined above);

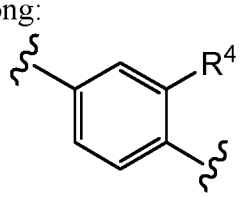
R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, R^{12f}, R^{12g}, R^{12h}, R^{12i} and R^{12j} independently represent hydrogen or C_{1-3} alkyl (optionally substituted by one or more fluoro atoms);

or a pharmaceutically-acceptable salt thereof.

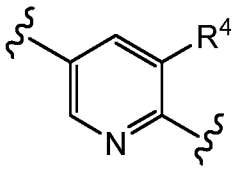
3. A compound according to claim 1 or Claim 2, wherein:
Ring A is aromatic and
X^1 represents =N-, or =CH-,
R^1 and R^2 each independently represent a substituent selected from hydrogen, -CH_3, -F, -Cl, -OCH_3, -NH_2, - CH_2NH_2.

4. A compound according to claim 1, 2 or 3, wherein:
R_3 represents a substituent selected from H, -CF_3, -CHF_2, -CH_3, -CH_2CH_3, or cyclopropyl.

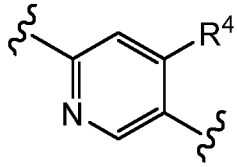
5. A compound according to any of the preceding claims, wherein ring C is selected among:



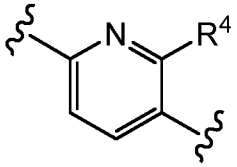
(II)



(III)



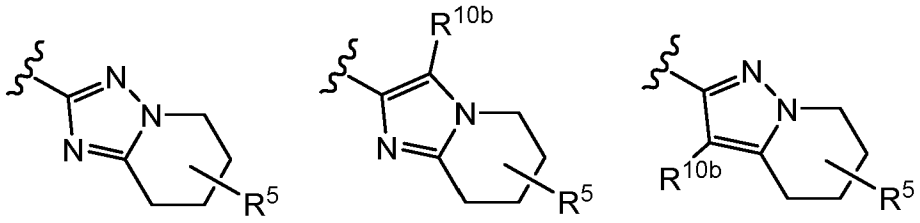
(IV)



(V)

and wherein R^4 represents, a substituent selected from H, F, -C_{1-3} alkyl and -O-C_{1-3} alkyl.

6. A compound according to any of the preceding claims, wherein ring D is selected among:



(VI) (VII) (VIII)

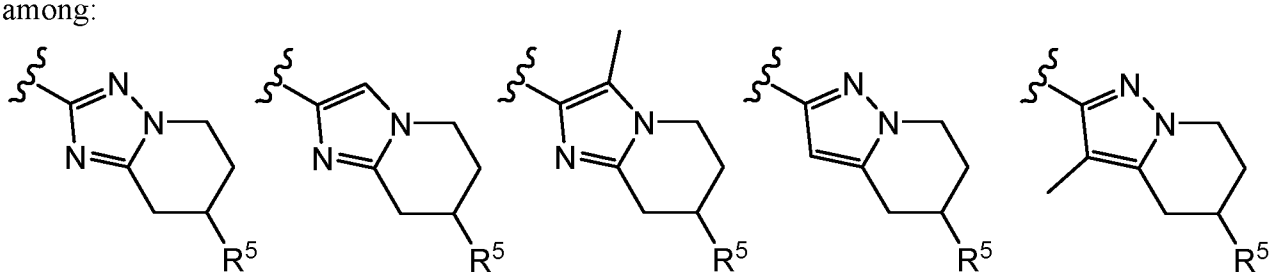
wherein:

R^5 represents one or more substituents selected from H, -OH, $-R^{8a}$, $-C(=O)-R^{8b}$, $-SO_2-R^9$, or $-N(R^{11a})R^{11b}$;

R^{10b} represent H, halo, C_{1-4} alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, -CN, $-R^{12a}$, $-OR^{12b}$, $-N(R^{12c})R^{12d}$ and/or $-C(O)N(R^{12e})R^{12f}$) or $-O-C_{1-4}$ alkyl (itself optionally substituted by one or more, e.g. one, substituent(s) selected from fluoro, $-R^{12g}$, $-OR^{12h}$ and/or $-N(R^{12i})R^{12j}$);

7. A compound according to any of the preceding claims, wherein R^5 represents H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, -OH, $-OCH_3$, $-OCF_3$, $-OCH_2CH_2OCH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-NH_2$, $-NH(SO_2)CF_3$, $-N(CH_3)(SO_2)CF_3$, and $-SO_2CF_3$.

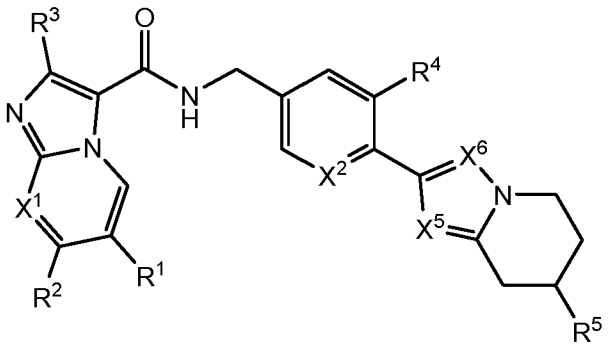
8. A compound according to any of the preceding claims, wherein ring D is selected among:



(VI') (VIIa') (VIIb') (VIIIa') (VIIIb')

and wherein R^5 represents H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, -OH, $-OCH_3$, $-OCF_3$, $-OCH_2CH_2OCH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-NH_2$, $-NH(SO_2)CF_3$, $-N(CH_3)(SO_2)CF_3$, or $-SO_2CF_3$.

9. A compound according to any of the preceding claims, of formula (IX)



(IX)

wherein

X^1 represents =N- or =CH-;

X^2, X^5 and X^6 each independently represent =N-, =CH- or $=C(CH_3)$-;

R^1 and R^2 each independently represent a substituent selected from hydrogen, $-CH_3$, -F, -Cl, $-OCH_3$, $-NH_2$, - CH_2NH_2,

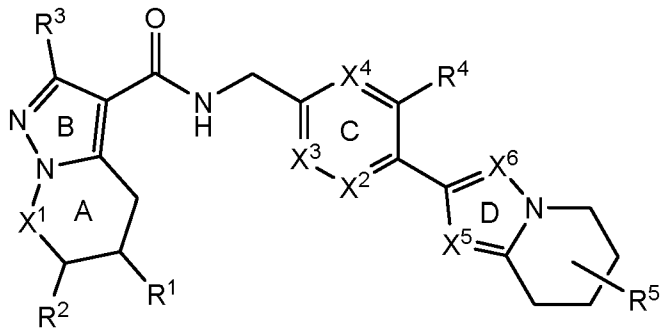
R^3 represents a substituent selected from H, $-CF_3$, $-CHF_2$, $-CH_3$, $-CH_2CH_3$, and cyclopropyl,

R^4 represents a substituent selected from H, F and $-CH_3$,

R^5 represents H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, cyclopropyl, -OH, $-OCH_3$, $-OCF_3$, $-OCH_2CH_2OCH_3$, $-CF_3$, $-CHF_2$, $-CF_2CH_3$, $-NH_2$, $-NH(SO_2)CF_3$, $-N(CH_3)(SO_2)CF_3$, or $-SO_2CF_3$,

or a pharmaceutically-acceptable salt thereof.

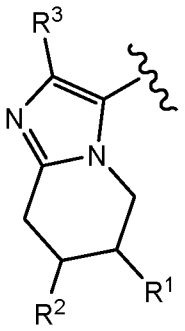
10. A compound of formula (IB),

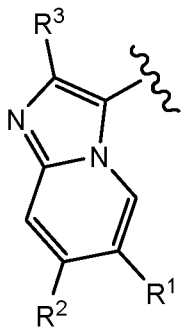


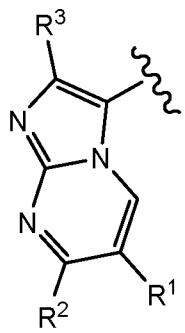
(IB)

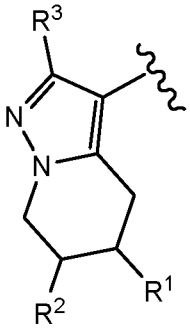
wherein all the integers are as defined in Claim 1 (or as defined in any of Claims 2 to 9).

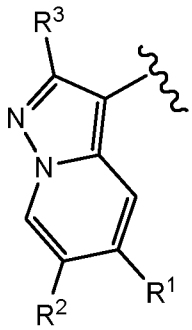
11. A compound as claimed in Claim 10, wherein the bicycle containing rings A and B represents any one of the following:


(XX)


(XXII)


(XXIV)

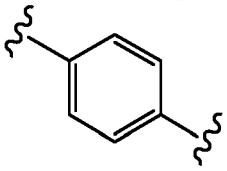

(XXI)


(XXIII)

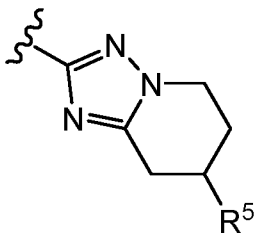
12. A compound as claimed in Claim 10 or Claim 11 wherein R^1 and R^2 both represent hydrogen.

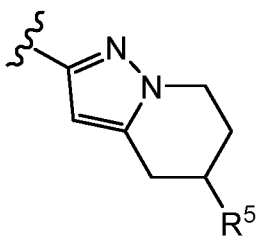
13. A compound as claimed in any of Claims 10 to 12, wherein R^3 represents C_{1-3} alkyl, such as ethyl.

14. A compound as claimed in any of Claims 10 to 13, wherein the C ring represents unsubstituted phenyl, i.e. of the formula (XXX):


(XXX)

15. A compound as claimed in any of Claims 10 to 14, wherein the D ring represents the formula (XXXI) or the formula (XXXII):


(XXXI)


(XXXII)

16. A compound as claimed in any of Claims 10 to 15, wherein R^5 represents C_{1-3} alkyl optionally substituted by one or more fluoro atoms (e.g. CF_3).

17. A compound as claimed in any one of claims 1 to 16, for use as a pharmaceutical.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of Claims 1 to 16.

19. A compound as claimed in any one of claims 1 to 16 for use in the treatment of a mycobacterial infection (e.g. tuberculosis).

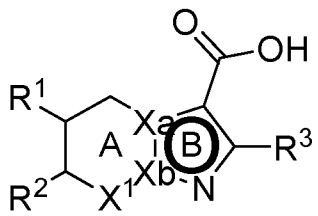
20. Use of a compound as claimed in any one of claims 1 to 16 for the manufacture of a medicament for the treatment of a mycobacterial infection (e.g. tuberculosis).

21. A method of treatment of a mycobacterial infection (e.g. tuberculosis), which method comprises administration of a therapeutically effective amount of a compound as claimed in any one of Claim 1 to 16.

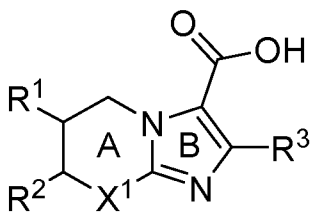
22. A combination of (a) a compound as claimed in any one of claims 1 to 16, and (b) one or more other anti-mycobacterial (e.g. anti-tuberculosis) agent.

23. A product containing (a) a compound as claimed in any one of claims 1 to 16, and (b) one or more other anti-mycobacterial (e.g. anti-tuberculosis) agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.

24. A process for the preparation of a compound of formula (IA) as claimed in Claim 1 or a compound of formula (I) as claimed in Claim 2, which process comprises:
(i) reaction of a compound of formula (XL) or (X),

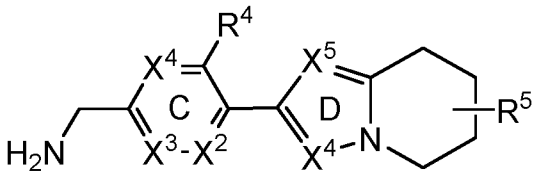


(XL)



(X)

in which the integers are defined in Claim 1, with a compound of formula (XI),

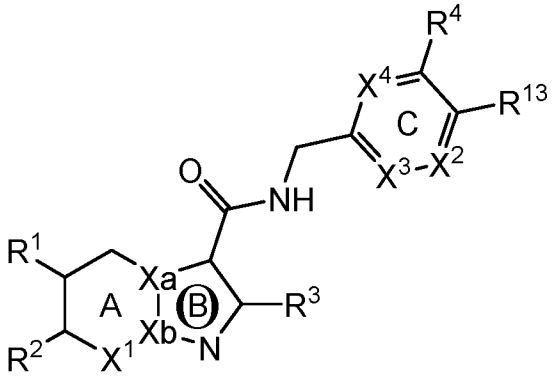


(XI)

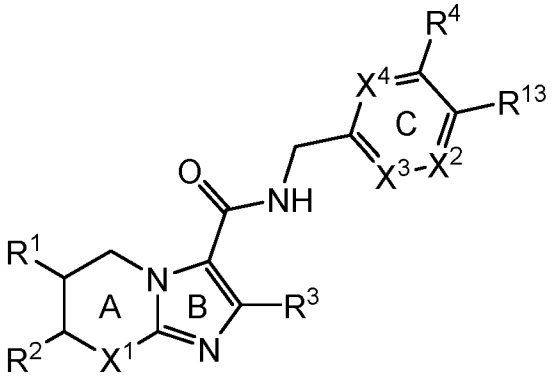
wherein the integers are as defined in Claim 1;

or

(ii) coupling of a compound of formula (XLI) or (XII),



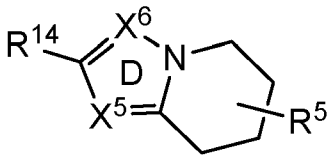
(XLI)



(XII)

wherein the integers are as defined in Claim 1, and R^{13} represents a suitable group, e.g. a suitable leaving group,

with a compound of formula (XIII),



(XIII)

wherein R^4 is as defined in Claim 1, and R^{14} represents a suitable group, e.g. a suitable leaving group.