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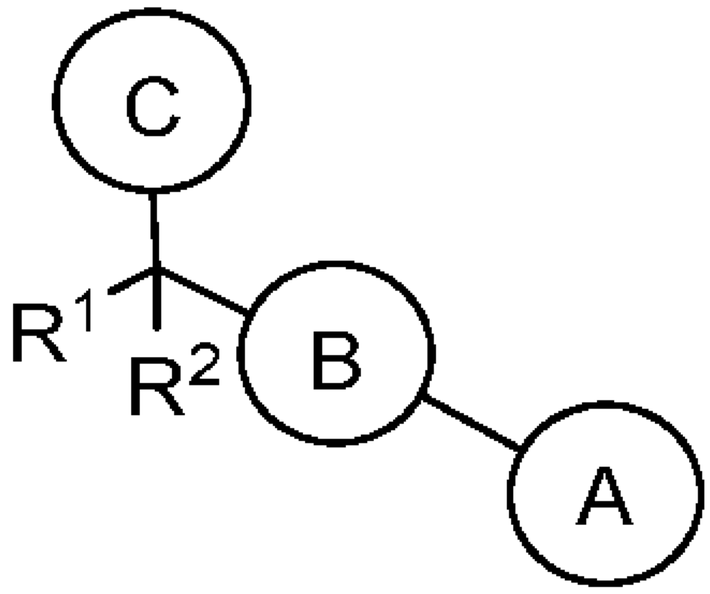

(I)

(57) Abrégé/Abstract:
The present invention provides compounds of Formula (I): wherein all variables are as defined in the specification, and compositions comprising any of such novel compounds. These compounds are biased agonists, or ß-Arrestin agonists of the angiotensin II receptor, which may be used as medicaments.

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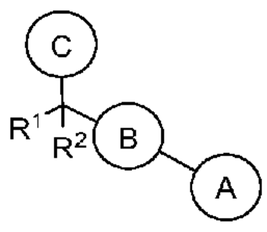

(I)

(57) Abstract: The present invention provides compounds of Formula (I): wherein all variables are as defined in the specification, and compositions comprising any of such novel compounds. These compounds are biased agonists, or β-Arrestin agonists of the angiotensin II receptor, which may be used as medicaments.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 445

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 445

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Biarylmethyl Heterocycles

FIELD OF THE INVENTION

The present invention provides substituted biaryl compounds and their analogues thereof, acting as biased agonists at the Angiotensin II receptor, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of cardiovascular diseases, such as chronic heart failure or chronic hypertensive conditions.

BACKGROUND OF THE INVENTION

Cardiovascular disease and mortality continue to represent the leading cause of death in developed countries despite significant advances in understanding of disease progression and the availability of new treatments. Within this context, heart failure continues to be a growing healthcare problem with millions of new cases occurring worldwide annually. Morbidity and mortality of those patients presenting in hospital for decompensation is high with approximately 35% of these patients dying or requiring re-hospitalization within 3 months of discharge (Bhatia, Tu et al. 2006, Fonarow, Stough et al. 2007, Gheorghiade, Vaduganathan et al. 2013); 50% of heart failure patients die within 5 years of diagnosis (Go, Mozaffarian et al. 2013, Mozaffarian, Benjamin et al. 2015). As a result, heart failure represents a significant burden to human health and the efficient administration of healthcare services (Desai and Stevenson 2012, Go, Mozaffarian et al. 2013, Mozaffarian, Benjamin et al. 2015).

There are currently two forms of heart failure recognized and classified based upon their etiology and pathogenesis (Satomura, Wada et al.). Heart failure with reduced ejection fraction (HFrEF, systolic heart failure) typically follows ischemic insult such as myocardial infarction, coronary artery disease or underlying cardiomyopathies and is characterized by significant cardiac scarring, fibrosis, thinning of the left ventricular wall, left ventricular dilation and a concomitant reduction in left ventricular ejection fraction. Heart failure with preserved ejection fraction (HFpEF, diastolic heart failure) is generally a result of chronic increased cardiac load associated with chronic hypertension resulting in cardiac remodeling, thickening of the left ventricular wall, fibrosis and reduced left ventricular volume. In the early stages of HFpEF, tissue remodeling and thickening of the ventricular wall can compensate for the increased load and maintain ejection fraction.

However, as the disease progresses continued maladaptive remodeling leads to failure of ventricular function. The impact of heart failure on the health of the patient can be assessed by the myriad of symptoms associated with the disease including dyspnea, exercise intolerance, pulmonary and peripheral edema and chronic fatigue. Current effective therapies exist for HFrEF but not HFpEF.

Among the clinically accepted standard of care for HFrEF are diuretics that reduce volume overload and dyspnea associated with reduced perfusion, as well as angiotensin-converting enzyme (ACE) inhibitors (ACEi) and angiotensin receptor blockers (ARBs) (Yancy, Jessup et al. 2013). Drugs such as ACEi and ARBs target the renin-angiotensin aldosterone system (RAAS). The RAAS system is a physiologically important endocrine/paracrine pathway through its actions to maintain homeostatic blood pressure and cardiac output. The RAAS pathway is generally activated during conditions such as renal dysfunction and heart failure due to reduced kidney function that induces release of renin by the kidneys. Renin is a circulating enzyme that converts angiotensinogen to angiotensin I. In turn, angiotensin I is converted to the vasoactive hormone angiotensin II (AII) by angiotensin-converting enzyme (ACE) in the lung and other tissues. AII exerts its effects on target tissues through binding to specific receptors on these cells, the AT1R and AT2R receptors.

AT1R is thought to be the predominant AII receptor based upon expression level. The AT1R works primarily through activation of the Gq signaling pathway within cells. However, AT1R has also been shown to activate other signaling pathways including non-G-protein- mediated pathways such as β-arrestin (Wei, Ahn et al. 2003, Aplin, Christensen et al. 2007).

Therapeutically, ACEi block AII production through inhibition of the conversion of angiotensin I to AII (Brown and Vaughan 1998), while ARBs specifically block AII action via competitive antagonism of the AII receptor, AT1R (Gring and Francis 2004). The resultant blockade of AII activity results in lowering of blood pressure and cardiac load. ARBs have the added benefit of improving kidney function through maintenance of glomerular filtration and therefore improved diuresis and natriuresis. Recently, combination therapy containing an ARB + neprilysin inhibitor has shown improved benefit in tolerant HFrEF patients over ARB alone (McMurray, Packer et al. 2014). Furthermore, AT1R biased agonist peptides have also shown the ability to improve renal

function in preclinical models of heart failure (Boerrigter, Soergel et al. 2012) and in humans (Soergel, Subach et al. 2013, Felker, Butler et al. 2015).

Despite their differences in mechanism, ACEi and ARBs continue to be mainstays of therapeutic intervention in heart failure patients (Yancy, Jessup et al. 2013). However, it is now appreciated that, in addition to the detrimental effects of AII action on the cardio-renal system, AII can also have some beneficial effects through activation of non-Gq signaling pathways, most notably β-arrestin . Indeed, peptidergic analogs of AII (e.g. SII) have been found to be biased agonists of AT1R. For example, the SII peptide has been found to bind AT1R and activate β-arrestin signaling but not Gq signaling (Rajagopal, Whalen et al. 2006, Kendall, Strungs et al. 2011). This peptide has been shown to stimulate cardiomyocyte contractility and prevent apoptosis (Rajagopal, Whalen et al. 2006). Biased agonist peptides to AT1R, have also been shown to lower blood pressure and improve cardiac function in animal models of heart failure (Violin, DeWire et al. 2010, Kim, Abraham et al. 2012) and in human clinical trials (Soergel, Subach et al. 2013, Felker, Butler et al. 2015).

In addition to being recognized as key treatments for HFrEF, blockade of AT1R signaling has been used extensively in the clinic to treat hypertension. Hypertension is a recognized risk factor for microvascular and macrovascular diseases and there is significant literature supporting the beneficial effects of reducing blood pressure in improving these risks (Staessen, Li et al. 2005, Farsang 2011). AII blockade is a first line therapy for the treatment of clinical hypertension (James, Oparil et al. 2014) and has been shown to decrease the relative risk for both heart failure (Ong, Ong et al. 2013) and stroke (Ravenni, Jabre et al. 2011) in susceptible patients. Furthermore, chronic hypertension is a key determinant for HFpEF (Kitzman, Little et al. 2002, Owan and Redfield 2005). In addition to increasing blood pressure via activation of Gq signaling pathways in smooth muscle cells, AII also is a pro-inflammatory stimulus for the vascular endothelium through its regulation of key anti-inflammatory genes (Luft 2002, Dandona, Dhindsa et al. 2006). ARBs have been shown to inhibit the pro-inflammatory effects of AII in endothelial cells at least partially through blocking Gq- dependent negative regulation of endothelial nitric oxide synthase (eNOS) (Main 2005, Mason, Jacob et al. 2012). Interestingly, the impact of AT1R activation to affect endothelial function does not require AII but can also be impacted by mechanical forces imposed on the cell (Mederos

y Schnitzler, Storch et al. 2011, Tang, Strachan et al. 2014). In one instance, the impact of mechanical force on AT1R has been shown to allosterically promote β-arrestin signaling by an AT1R biased agonist (Tang, Strachan et al. 2014). Activation of AT1R by mechanical stretch has also been noted in cardiomyocytes (Mederos y Schnitzler, Storch et al. 2011).

These data suggest that biased agonism (preferential activation of some signaling pathways (including β-arrestin) over the Gq signaling pathway) of the AT1R could have long term benefit in heart failure patients by altering AII signaling via AT1R in several cell types. Biasing of AT1R signaling could prove a significant improvement on ARBs that block all the signaling outputs of the AT1R. Unfortunately, peptide-based therapies have limitations in dosing that restrict their ability to be used as a chronic therapy and in less advanced heart failure. Therefore, development of safe and efficacious synthetic biased agonists or modulators of AT1R could significantly improve treatment of HFrEF and HFpEF patients through not only unloading the heart but also through activation of beneficial signaling pathways directly in cardiomyocytes. Similarly, anti-fibrotic activities combined with antihypertensive effects associated with AT1R biased agonism further suggests potential for this mechanism in treatment of HFpEF.

Recently, a series of peptidic compounds have been disclosed in WO10077339 demonstrating the possible therapeutic effects of preferentially agonizing β-Arrestin recruitment while minimizing Gq signaling at the AT1 receptor. These peptides have exhibited the potential for cardiovascular benefits in an acute clinical setting following intravenous administration (Soergel, Subach et al. 2013, Felker, Butler et al. 2015, Pang, Butler et al. 2017). However, study of an AT1R biased agonist peptide in acute decompensated heart failure patients using a 48-96 h infusion did not meet its composite primary end point (Pang, Butler et al. 2017). Interestingly, acute treatment of stable, chronic heart failure patients with an infusion of this biased agonist peptide did show significant improvement in left ventricular filling pressure and arterial pressure, especially those with elevated RAAS (Soergel, R. A. Subach et al. 2013). Furthermore, preclinical data in mouse models of heart failure using this peptide or close analogs have found that they have direct cardiac effects to improve cardiac function not seen with ARBs (Abraham, Davis et al. 2016). Taken together, these data suggest it is possible that this mechanism does not lend itself to acute/sub-acute treatment but perhaps is better

suited as a chronic therapy alone or in combination with other heart failure medicines, such as ACEi. In light of this potential, the discovery of an orally bioavailable biased modulator of the AT1 receptor remains an important research goal.

In this application we describe the invention of a series of non-peptide, β-arrestin biased modulators of the AT1 receptor intended for the chronic treatment of cardiovascular disease. Though non-peptide agonists of the AT1 receptor have been previously described in U.S. Pat. No. 5,444,067 and in several academic publications (Perlman, Schambye et al. 1995, Perlman, Costa-Neto et al. 1997, Miura, Kiya et al. 2012), the agonist activity observed in these documents was correlated to an increased stimulus in phosphoinositide hydrolysis, which is a known biomarker for increased Gq signaling. Thus, when a representative agonist from these works was examined *in vivo* it was found to cause increased vascular resistance in a manner analogous to the native AII ligand (De Witt, Garrison et al. 2000). The desire for, or identification of, a non-peptide biased agonist preferentially agonizing the β-arrestin signaling pathway via AT1R is not contemplated in any of these documents. The present invention describes the identification of non-peptide small molecule AT1R biased agonists that selectively agonize β-arresting signaling in preference to Gq signaling.

SUMMARY OF THE INVENTION

The present invention provides substituted biaryl compounds, and analogues thereof, which are useful as Angiotensin II biased agonists, or β-Arrestin agonists of the Angiotensin II Receptor, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of diseases or disorder associated with biased agonism of the Angiotensin II Receptor

(defined as preferential activation of some AT1R-dependent signaling pathways (including β-arrestin) over AT1R-dependent Gq signaling), such as heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and renal disease.

In addition to the effects as biased agonists of AT1R, as selective ligands to the AT1R, the compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with the AT1R, such as heart failure, coronary artery disease, cardiomyopathy, fibrosis, atrial fibrillation, diabetes and related conditions including but not limited to acute coronary syndrome, myocardial ischemia, hypertension, atherosclerosis, pulmonary hypertension, peripheral arterial disease, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, angina, renal disease, obesity, metabolic syndrome and insulin resistance.

The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with AT1R- mediated recruitment of β-arrestin and/or other non-Gq mediated signaling, such as HFpEF, HFrEF, and renal disease.

The compounds of the invention may be used in therapy.

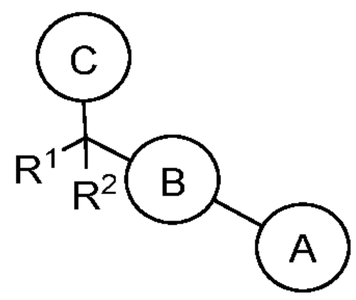
The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with AT1R- mediated recruitment of β-arrestin and/or other non-Gq mediated signaling.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

Other features and advantages of the invention will be apparent from the following detailed description and claims.

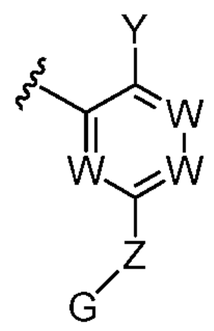
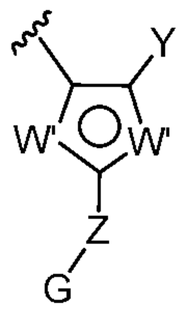
DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present disclosure provides, *inter alia*, a compound of Formula (X):



(X)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring A is  or  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16}, wherein at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

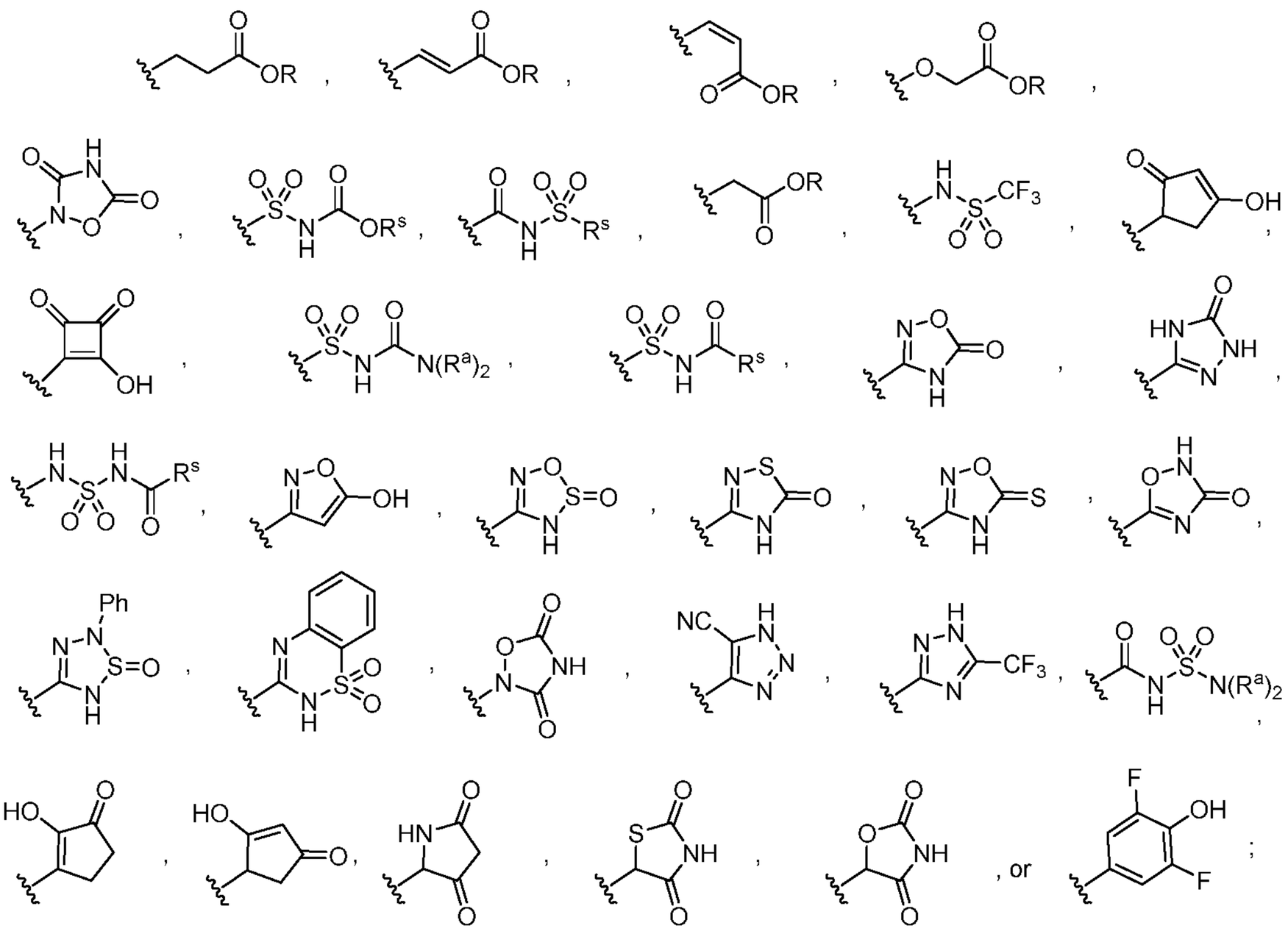
alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4 to 6 membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H , PO_3H_2, COOR,



R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_{6-10}-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_3 alkyl, C_{6-10} aryl, C_{6-10}-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl is a 5-10 membered group and the heterocycle is a 4-10 membered each having 1-3 heteroatoms selected from N, O, or S;

Z, at each occurrence, is independently selected from a bond, O, S, $N(R^z)$, $C(R^z)_2$, C=O, $C(=O)N(R^z)$, $N(R^z)C(=O)$, $C(R^z)_2C(R^z)_2$, $OC(R^z)_2$, $SC(R^z)_2$, $N(R^z)C(R^z)_2$, $C(R^z)_2O$, $C(R^z)_2S$, $C(R^z)_2N(R^z)$;

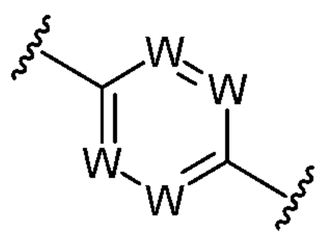
R^z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxyalkyl, C_1-C_4-haloalkyl, C_3-C_{10}-cycloalkyl, 5-10-membered heterocycle-C_1-C_6-alkyl, 5-10-membered heterocycle, C_3-C_{10}- cycloalkyl-C_1-C_6-

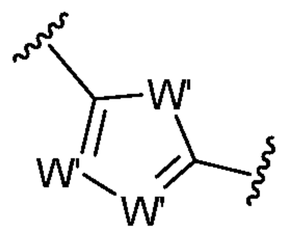
alkyl, 4 to 7 membered heterocyclyl having 1-2 heteroatoms selected from N, O, or S, or, alternatively, two R^z groups either on the same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, CH_2-phenyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ hydroxyalkyl, phenyl, CH_2-phenyl;

ring B is



or


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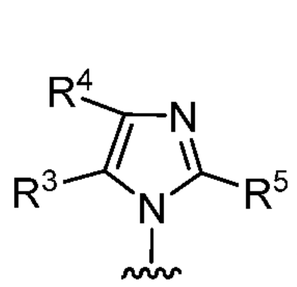
Group C is



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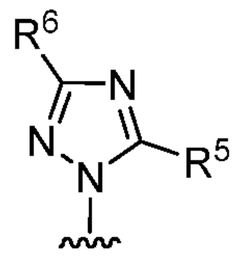

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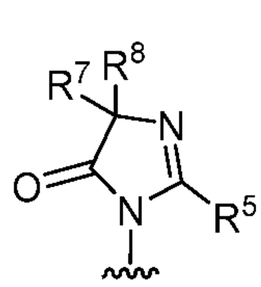

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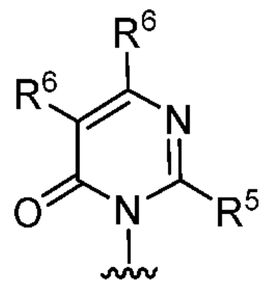


ID,

IG,

IH ,
or

IJ

R^3 is $C_{1\text{-}4}$ hydroxyalkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}6}$–hydroxycycloalkyl, $C_{1\text{-}6}$–halocycloalkyl,

COOR, $CON(R^z)_2$, 5-6 membered heteroaryl or ;

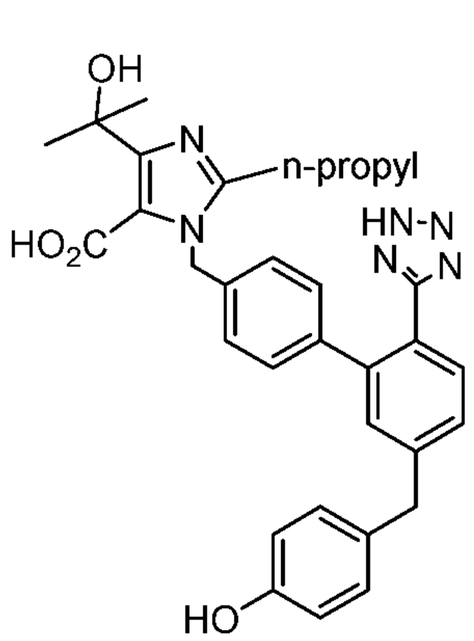
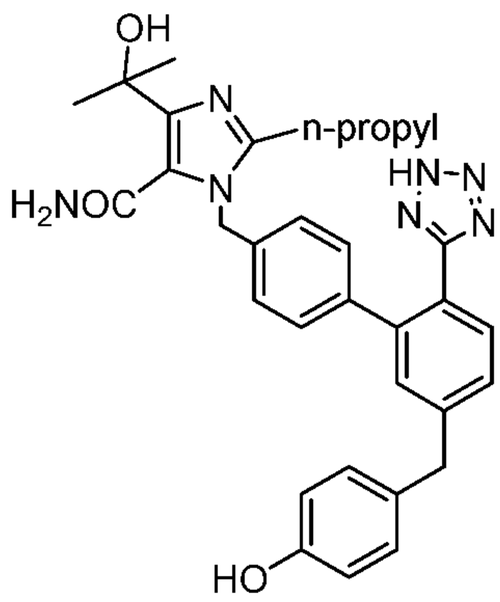
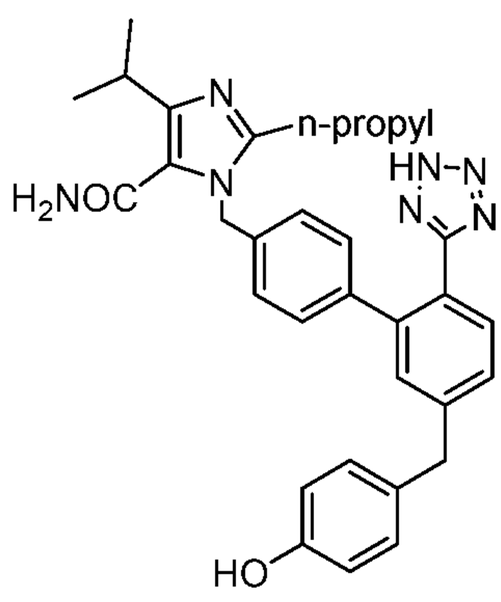
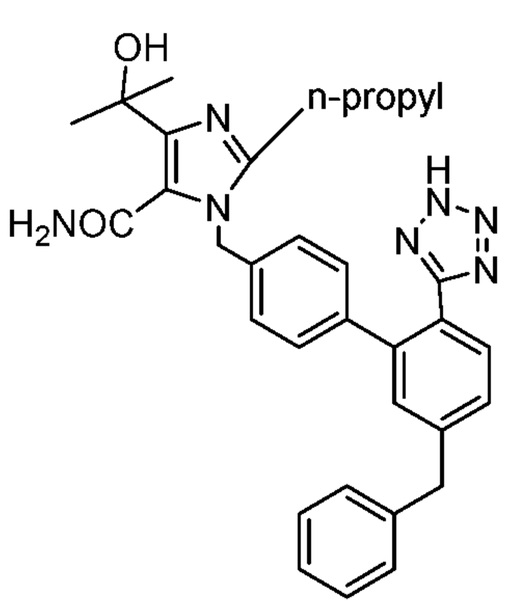
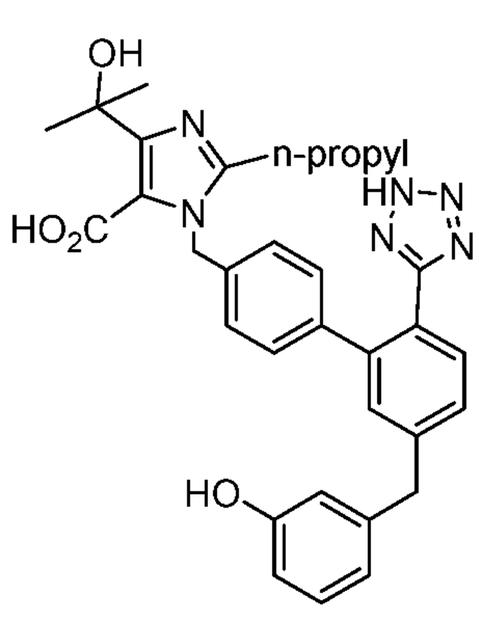
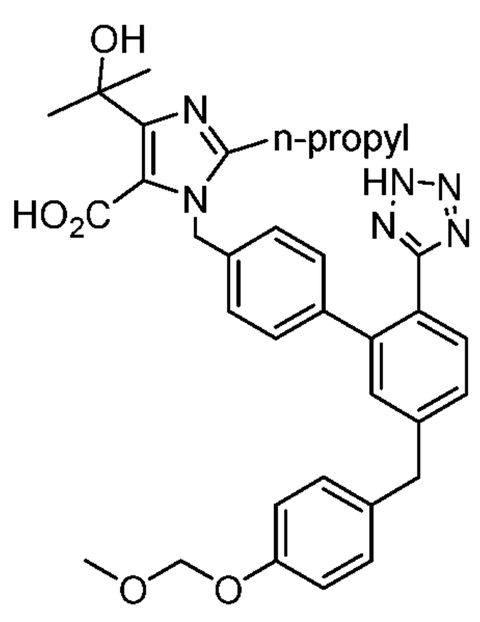
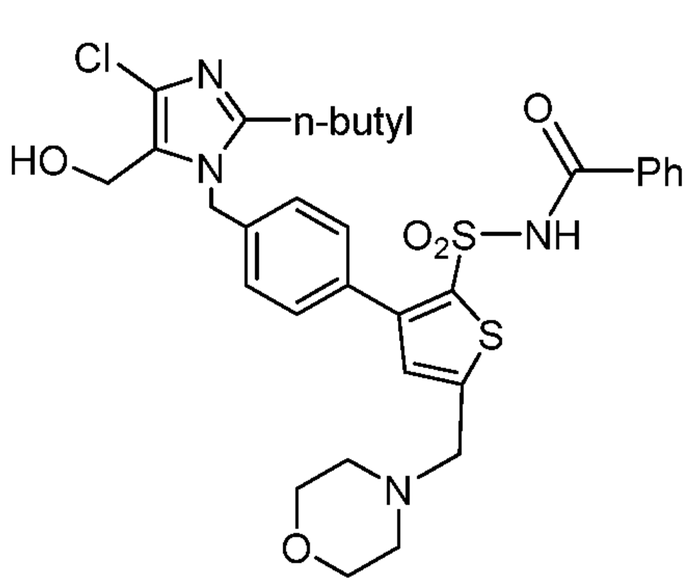
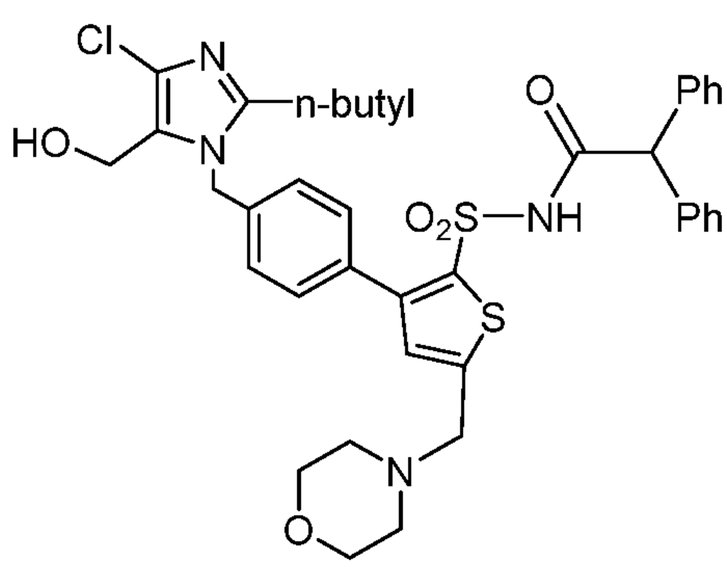
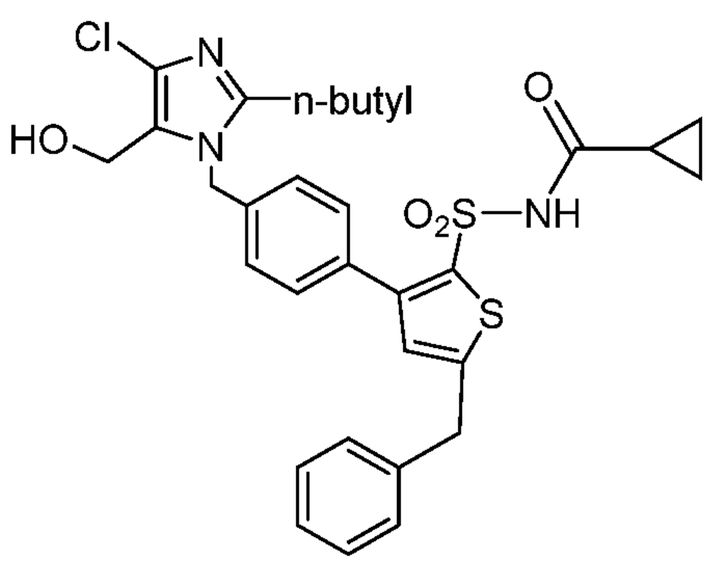
R^4 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$,C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{3-6}–cycloalkyl, C_{3-6}–halocycloalkyl, C_{3-6}–alkoxycycloalkyl, C_3-C_6-cycloalkyl-C_1-C_6-alkyl, or C_{3-6}–hydroxycycloalkyl;

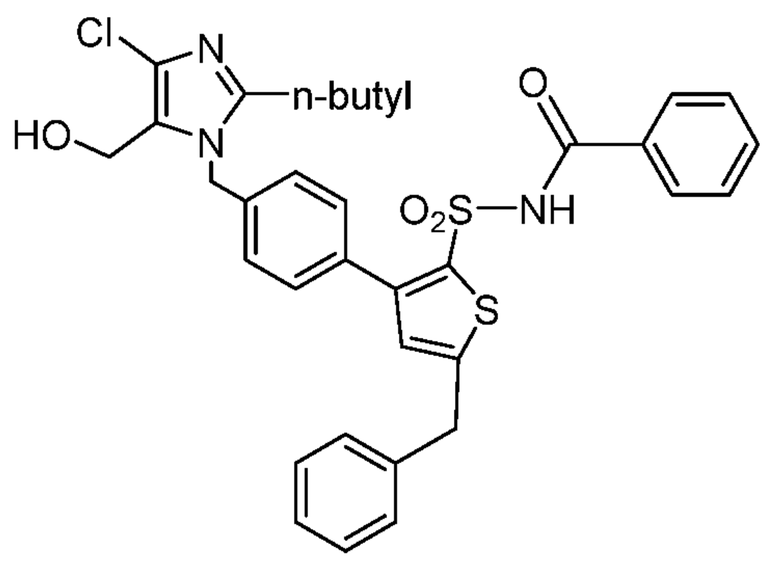
R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl; C_{1-6} alkoxyalkyl, C_{3-6}–cycloalkyl-C_{0-4}–alkyl which may be substituted with 1-3 halogens or a C_{1-3}-alkoxy group;

R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, C_{1-4}-alkyl, C_{1-4}-haloalkyl, C_{1-4}-alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{3-6}–cycloalkyl, C_{3-6}–halocycloalkyl, C_{1-6}–alkoxy-C~~3~~-C_6-cycloalkyl, or C_{3-6}–hydroxycycloalkyl; and

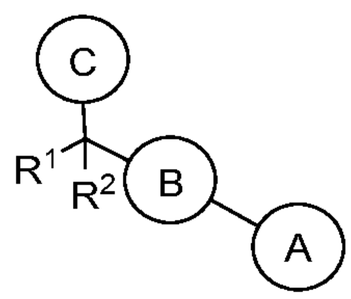
R^7 and R^8, are independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, R^7 and R^8, along with the atom to which they are attached, can join to form a C_3-C_9 cycloalkyl, a C_3-C_9-halocycloalkyl, a C_3-C_9-hydroxycycloalkyl or a 4 to 7 membered heterocycle having 1-2 heteroatoms selected from N, O, or S each of said cycloalkyl and heterocycle being optionally substituted with 1-4 F, OH, C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, or C_{1-4} hydroxyalkyl, and may be fused with a 6-membered aryl or 5-6 membered heteroaryl ring,

provided the compounds of Formula (X) are not

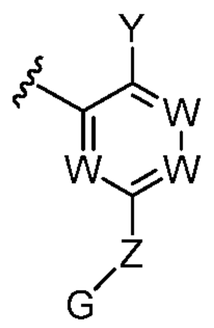
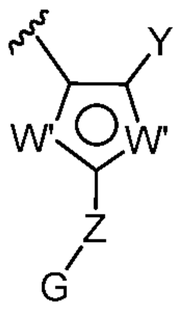


In another aspect, the present disclosure provides, *inter alia*, a compound of Formula (I):



(I)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring A is  or  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16}, wherein at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

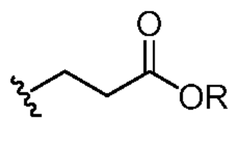
alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4 to 6 membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H , PO_3H_2, COOR,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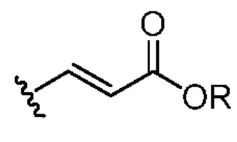
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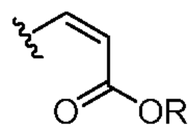
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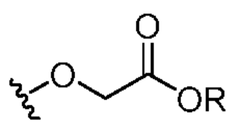
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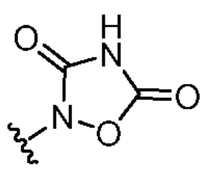
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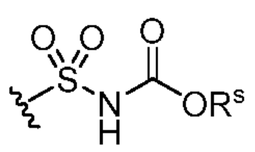
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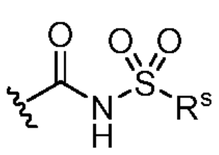
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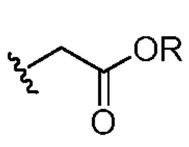
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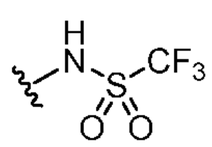
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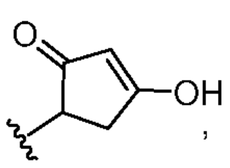
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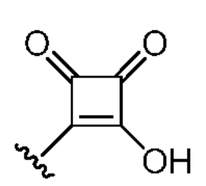
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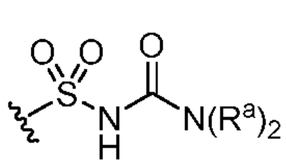
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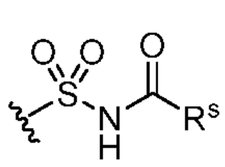
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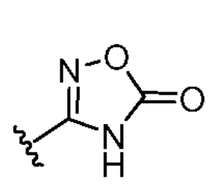
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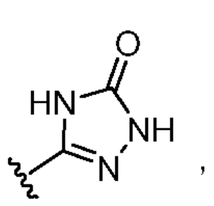
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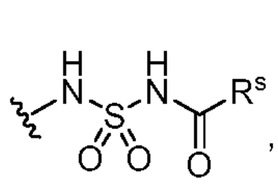
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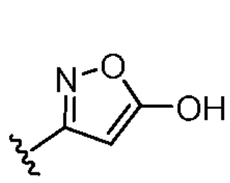
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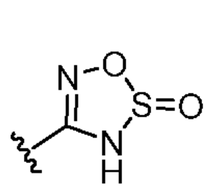
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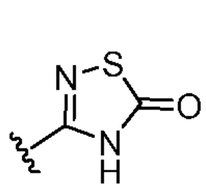
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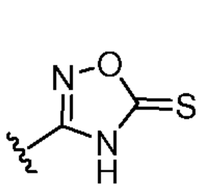
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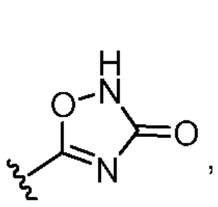
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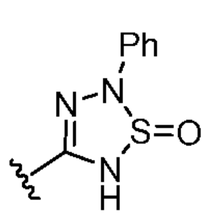
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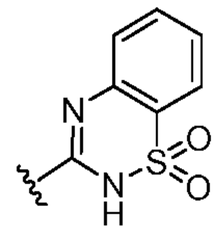
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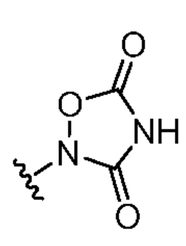
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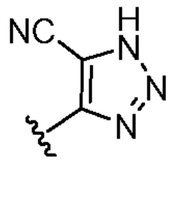
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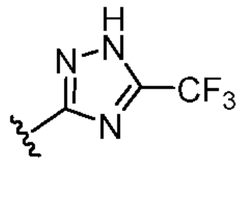
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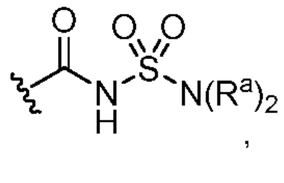
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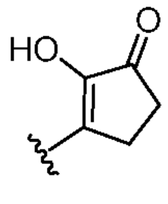
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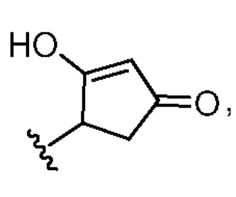
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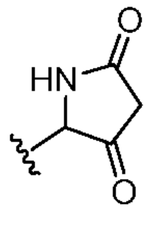
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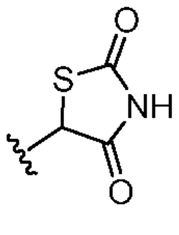
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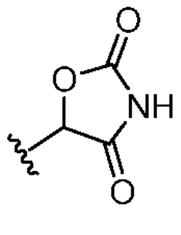
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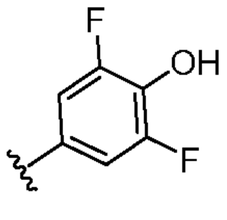

;

R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, $C_{6\text{-}10}$-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_3 alkyl, $C_{6\text{-}10}$ aryl, $C_{6\text{-}10}$-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl is a 5-10 membered group and the

heterocycle is a 4-10 membered each having 1-3 heteroatoms selected from N, O, or S;

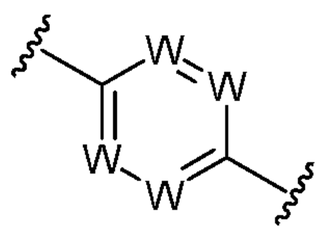
Z, at each occurrence, is independently selected from a bond, O, S, $N(R^Z)$, $C(R^Z)_2$, C=O, $C(=O)N(R^Z)$, $N(R^Z)C(=O)$, $C(R^Z)_2C(R^Z)_2$, $OC(R^Z)_2$, $SC(R^Z)_2$, $N(R^Z)C(R^Z)_2$, $C(R^Z)_2O$, $C(R^Z)_2S$, $C(R^Z)_2N(R^Z)$;

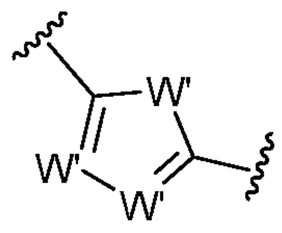
R^Z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, two R^Z groups either on the same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ hydroxyalkyl, phenyl, CH_2-phenyl;

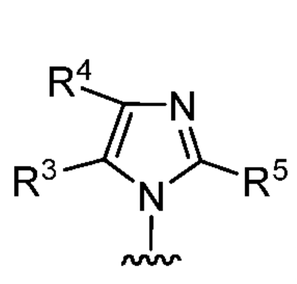
ring B is



or


;

Group C is



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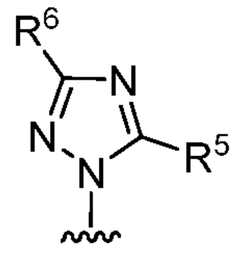
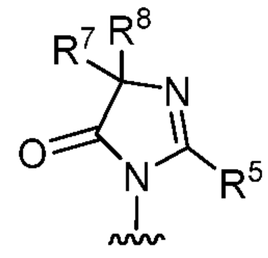
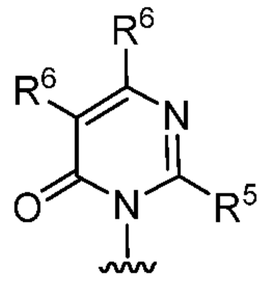
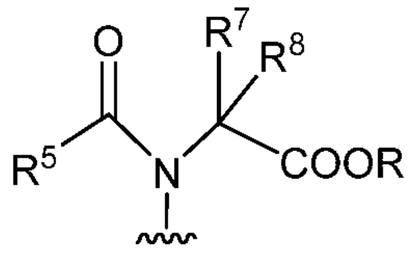


IB,


IC,


ID,


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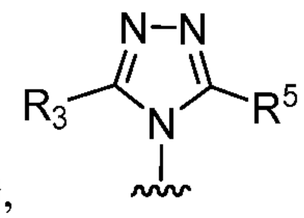
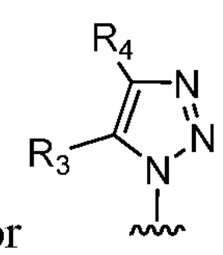
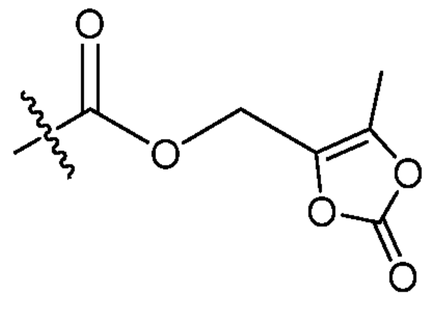


IH ,
or


IJ

R^3 is C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{1-6}–hydroxycycloalkyl, C_{1-6}–halocycloalkyl,

COOR, $CON(R^z)_2$, or  ;

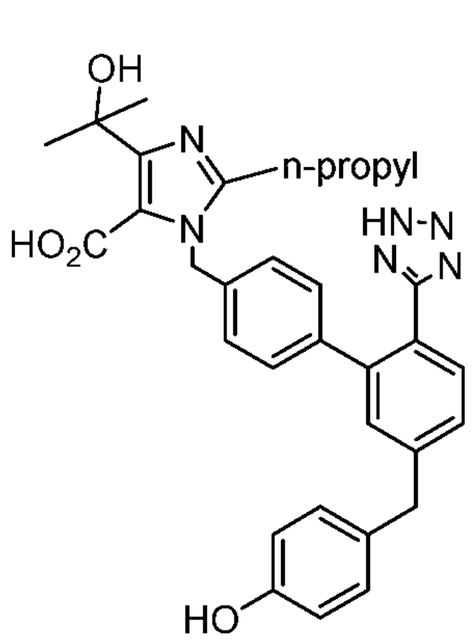
R^4 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$,C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{1-6}–cycloalkyl, C_{1-6}–halocycloalkyl, C_{1-6}–alkoxycycloalkyl, or C_{1-6}–hydroxycycloalkyl;

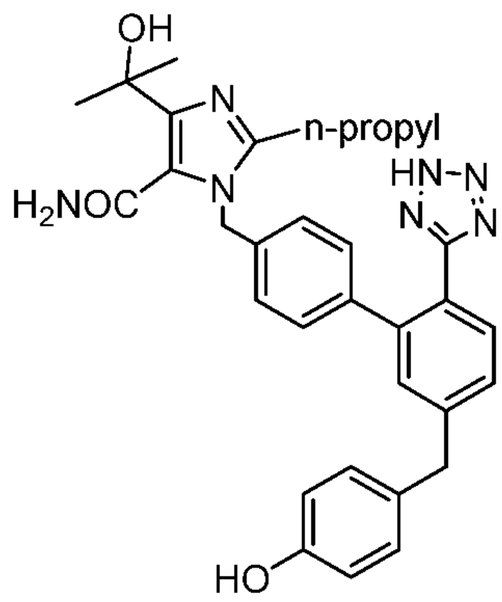
R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl; C_{1-6} alkoxyalkyl, C_{1-6}–cycloalkyl-C_{0-4}–alkyl which may be substituted with 1-3 halogens or a C_{1-3}-alkoxy group;

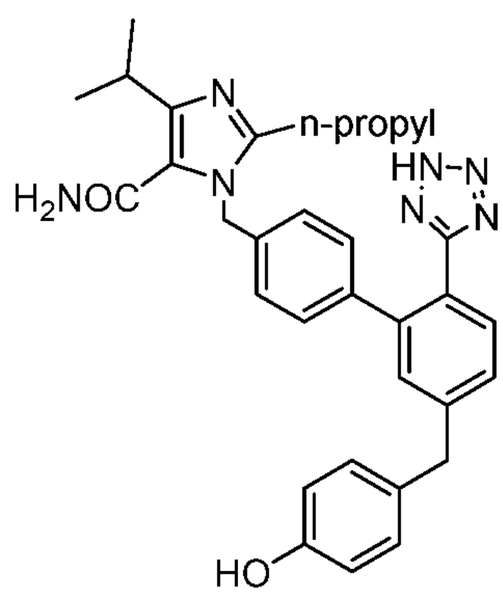
R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, C_{1-4}-alkyl, C_{1-4}-haloalkyl, C_{1-4}-alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{1-6}–cycloalkyl, C_{1-6}–halocycloalkyl, C_{1-6}–alkoxycycloalkyl, or C_{1-6}–hydroxycycloalkyl; and

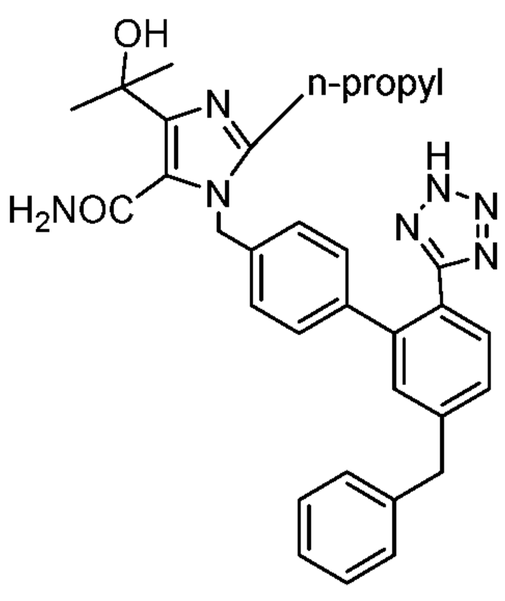
R^7 and R^8, are independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, R^7 and R^8, along with the atom to which they are attached, can join to form a C_3-C_6-cycloalkyl, a C_3-C_6-halocycloalkyl, a C_3-C_6-hydroxycycloalkyl or a 4 to 7 membered heterocycle having 1-2 heteroatoms selected from N, O, or S and the potential for further substitution with 1-4 F, OH, C_{1-4}-alkyl, C_{1-4}-haloalkyl C_{1-4}-alkoxyalkyl, C_{1-4}-hydroxyalkyl,

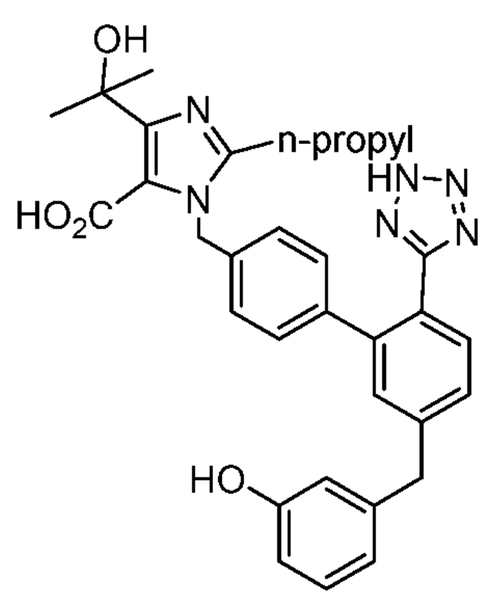
provided the compounds of Formula (I) are not

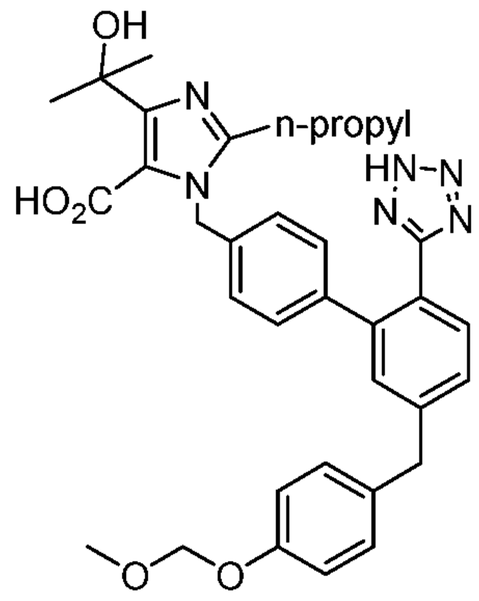

OH
N
n-propyl
HO2C
N
HN-N
N
N
HO

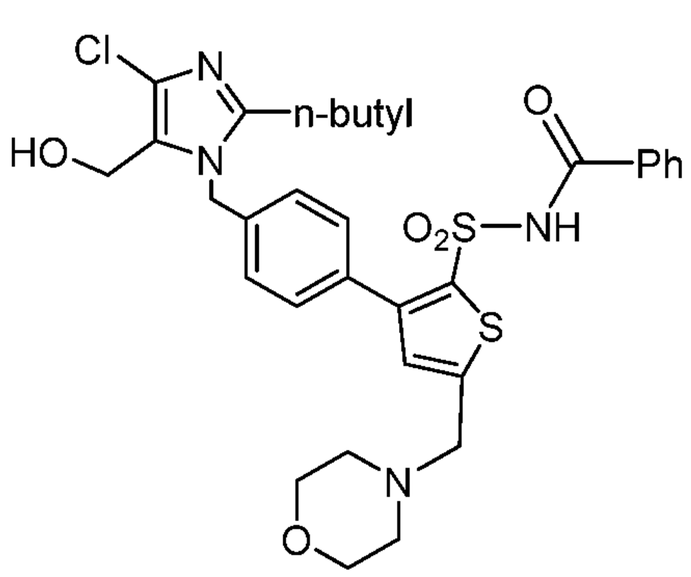

OH
N
n-propyl
H2NOC
N
HN-N
N
N
HO

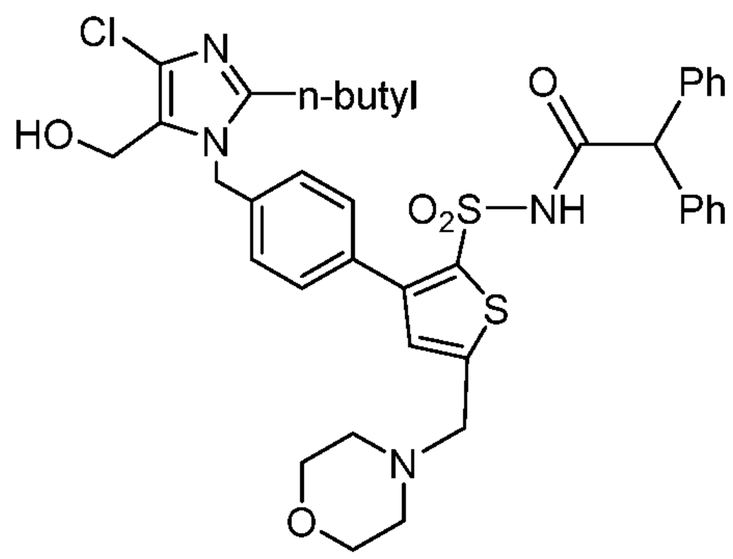

N
n-propyl
H2NOC
N
HN-N
N
N
HO

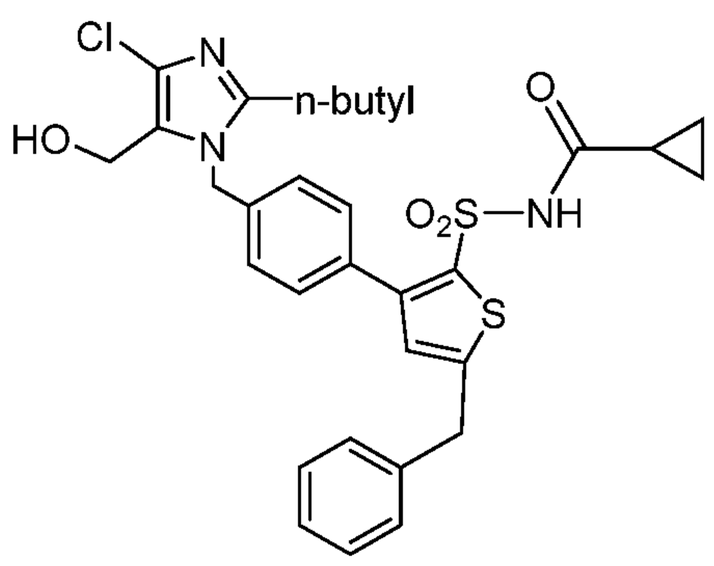

OH
N
n-propyl
H2NOC
N
H
N-N
N
N
HO

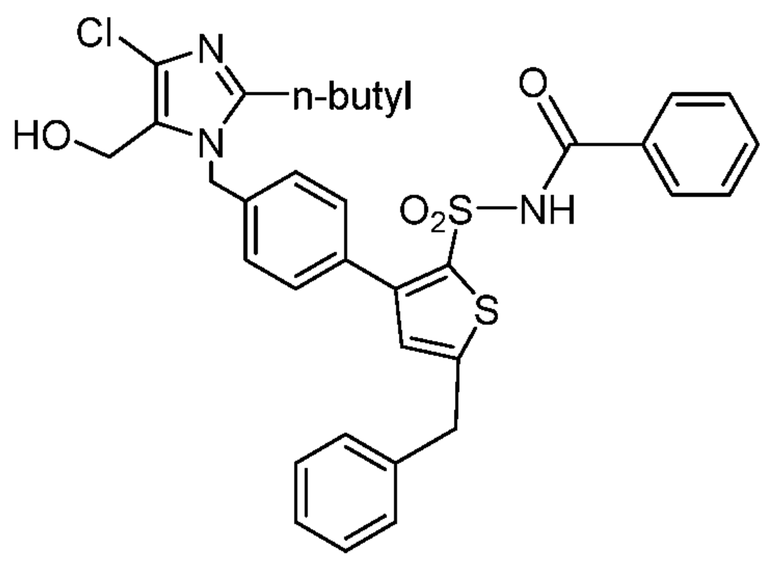

OH
N
n-propyl
HO2C
N
HN-N
N
N
HO


OH
N
n-propyl
HO2C
N
HN-N
N
N
O
O


Cl
N
n-butyl
HO
N
O
Ph
O2S
NH
S
N
O


Cl
N
n-butyl
HO
N
O
Ph
Ph
O2S
NH
S
N
O

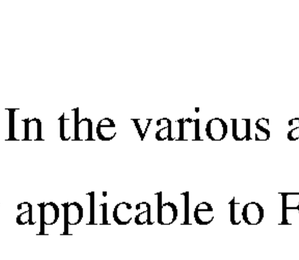
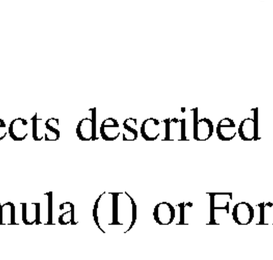
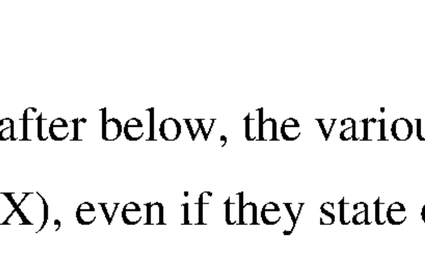

Cl
N
n-butyl
HO
N
O
O2S
NH
S



In the various aspects described hereinafter below, the various embodiments are equally applicable to Formula (I) or Formula (X), even if they state only one of Formula (I) and Formula (X).

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

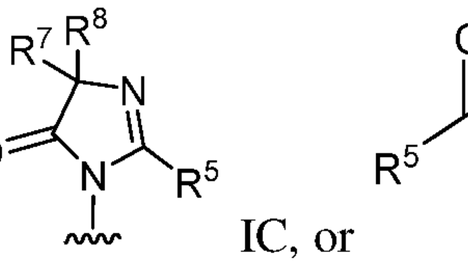
Group C is

 IA,  IC, or  IG.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

R^1 and R^2 are H;

R^3 is H, C_{1-2} hydroxyalkyl, CO_2H, CO_2-C_{1-6} –alkyl, $CONH_2$, $CONH(C_{1-6}$ –alkyl) ,



$CON(C_{1-6}$-alkyl$)_2$, or ;

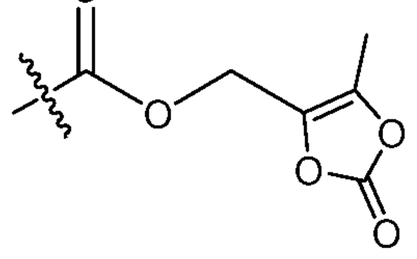
R^4 is H, F, Cl, Br, CF_3, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-2} hydroxyalkyl;-

R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl or $O(C_{1-6}$ alkyl);

R^6 is hydrogen, or C_{1-4} alkyl;

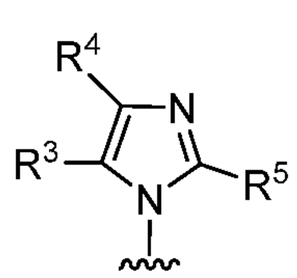
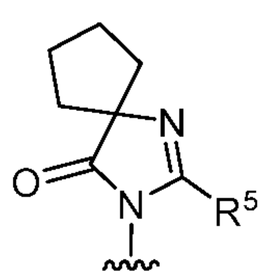
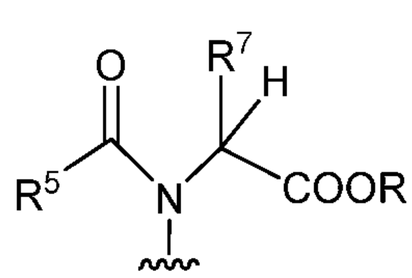
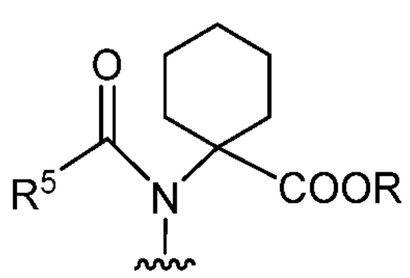
R^7 and R^8 are H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-3} hydroxyalkyl

alternatively, R^7 and R^8, along with the atom to which they are attached, join to form a C_3-C_6-cycloalkyl or a C_4-C_7-heterocycle; and

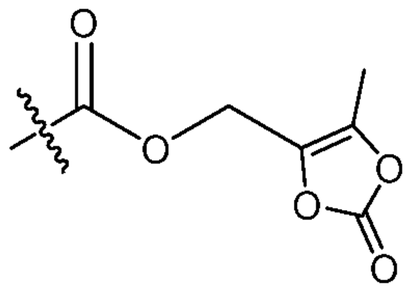
R is H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, or  ;

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Group C is

 ,  ,  , or  ;

R^1 and R^2 are H;



R^3 is hydroxyalkyl, CO_2H, or ;

R^4 is C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-3} hydroxyalkyl; and

R^5 is ethyl, n-propyl, or n-butyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

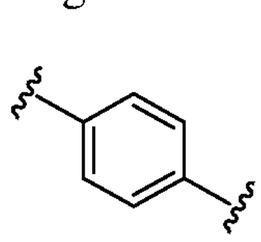
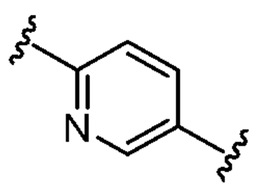
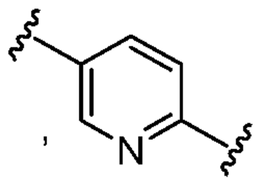
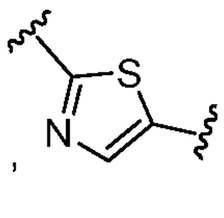
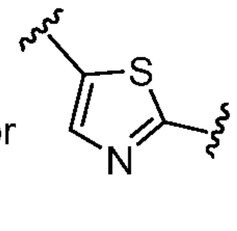
G is selected from a 5 to 10 membered heterocycle having 1-3 atoms selected from N, O, and S, phenyl or a C_6-C_{10}-heteroaryl having 1-3 atoms selected from N, O, and S; wherein the heterocycle, phenyl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkylthio, C_1-C_6-hydroxyalkyl,

OH, OR^X, $N(R^X)_2$, $CO(R^X)$, $CON(R^X)_2$, CO_2R^X, $N(R^X)CO_2(R^X)$, $N(R^X)CO(R^X)$, $N(R^X)CON(R^X)_2$, $S(O)_2(R^X)$, $S(O)_2R^X$, $S(O)_2N(R^X)_2$, $N(R^X)S(O)_2(R^X)$, or $N(R^X)S(O)_2R^X$;

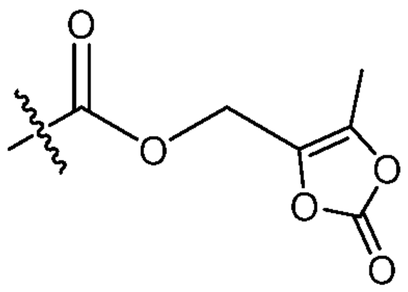
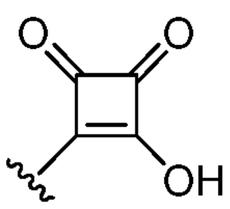
R^X is H, $C_{1\text{-}6}$ alkyl, CF_3, phenyl, CH_2-phenyl.

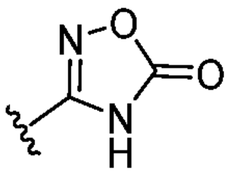
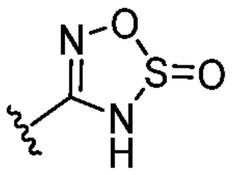
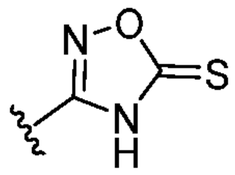
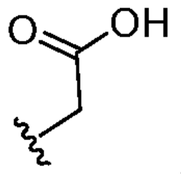
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is

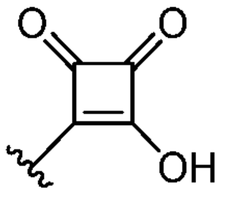
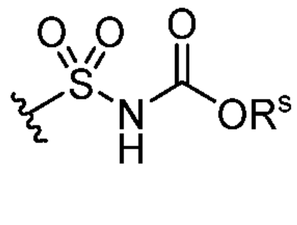
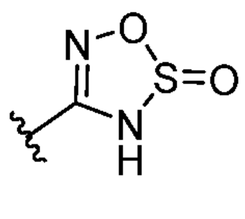
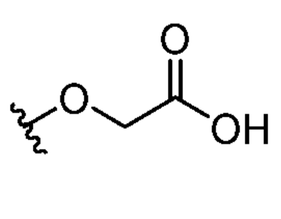
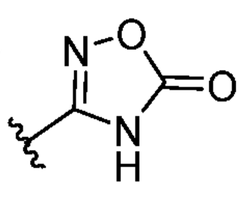
any of which are optionally substituted with 0-2 F,

Y is COOH, COOMe, COOEt,  , 5-tetrazolyl, SO_3H,  ,

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

wherein Y is COOH, 5-tetrazolyl, SO_3H,

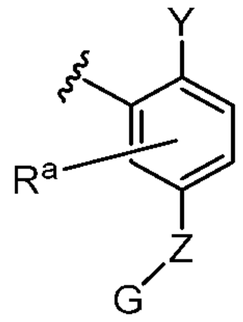






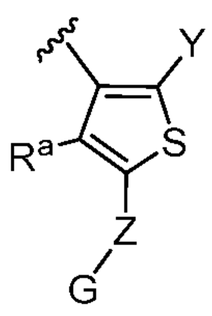
; and

R^S is $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$-aryl-C_1-C_6-alkyl , or (CH_2Ph).

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring A is



or


; and

R^a is H or F.

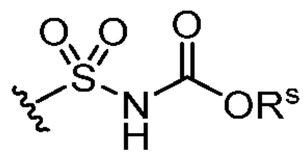
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

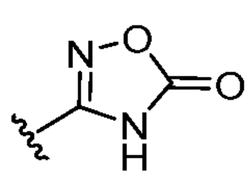
G is selected from a phenyl, thiophenyl, quinolinyl, isoquinolinyl, indolyl, pyrazolyl, pyrrolyl, pyridinyl, isoindolinyl, pyrrolidinyl; any of which are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2R^x$; and

R^x is H, C_{1-3} alkyl, CF_3, phenyl, CH_2-phenyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Y is COOH, 5-tetrazolyl,

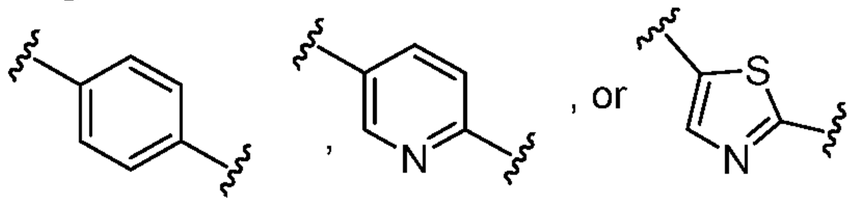


or


; and

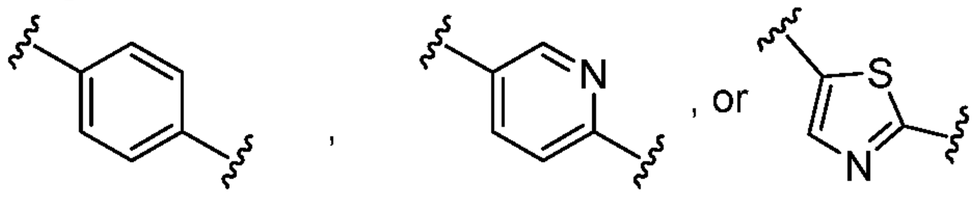
R^s is C_{1-6} alkyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

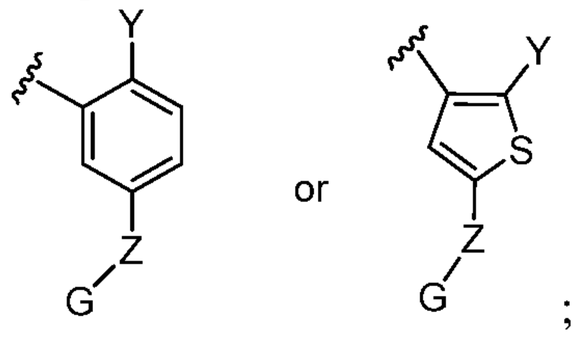
Ring B is 

, any of which are substituted with 0-2 F.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is 

any of which are substituted with 0-2 F;

Ring A is 

;

Z is a bond or NR^a;

G is isoindolinyl-1,3-dione, pyrrolidine-2,5-dione, phenyl, thiazolyl, pyridinyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, any of which may be substituted with 0-3 substituents selected from =O, C_{1-4} alkyl, -O-R^x, C_{1-4} haloalkyl, -C(O)NR^x, -$N(R^x)_2$, and F;

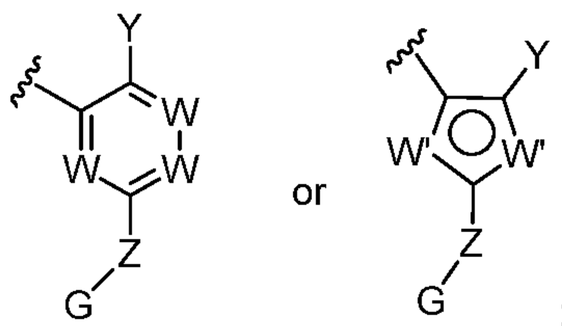
R^5 is C_{3-4} alkyl;

R^6 is C_{3-4} alkyl;

R^a is hydrogen, C_{1-4}-alkyl, and C_{1-2}-haloalkyl; and

Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

ring A is  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16} where at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

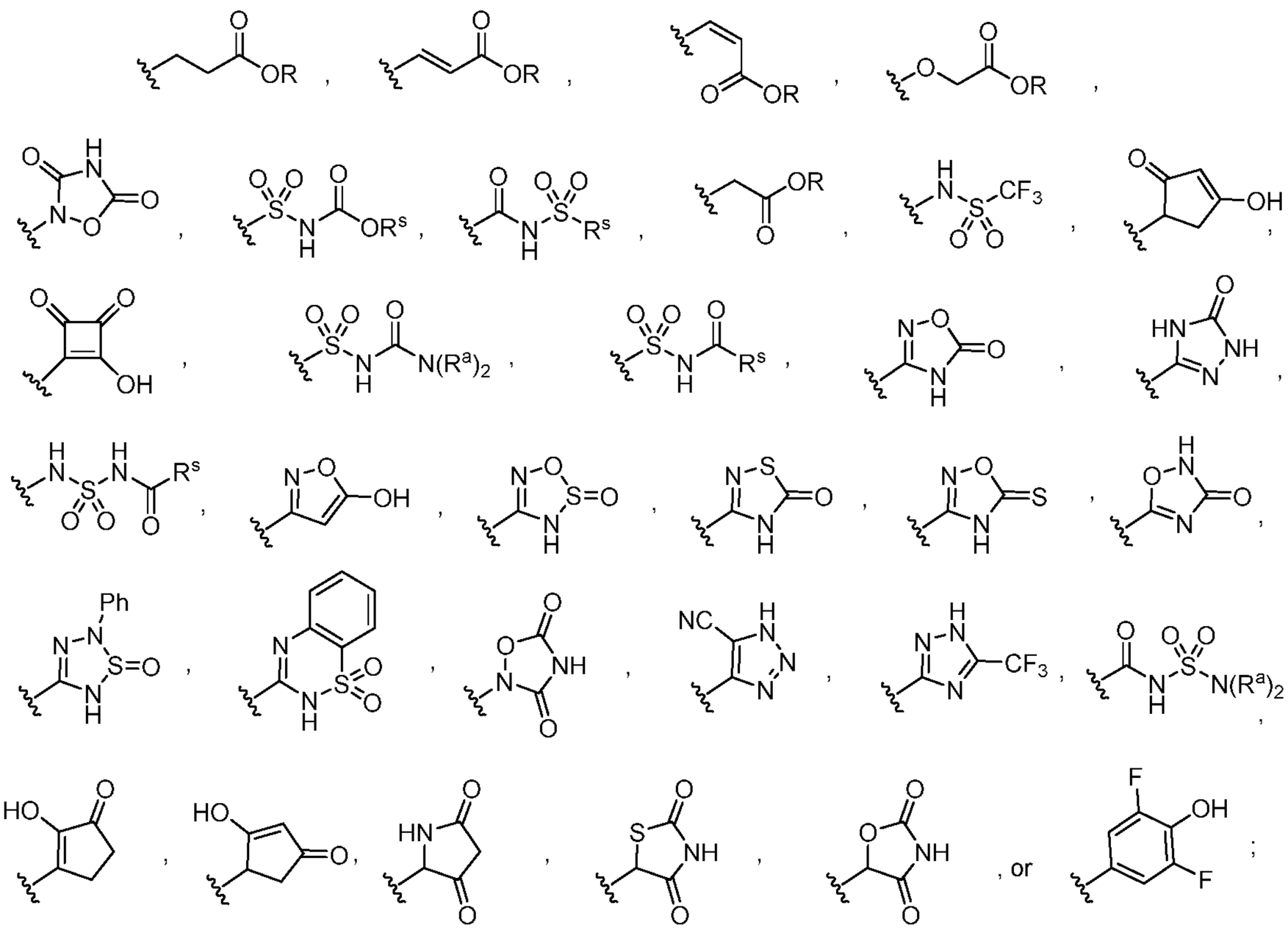
alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4- to 6-membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl;

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H, PO_3H_2, COOR,



R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_{6-10}-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl-C_1-C_3 alkyl, C_{6-10} aryl, C_{6-10}-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl and heterocycle are each a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S;

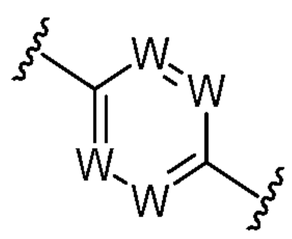
Z, at each occurrence, is independently selected from a bond, O, S, $N(R^z)$, $C(R^z)_2$, C=O, $C(=O)N(R^z)$, $N(R^z)C(=O)$, $C(R^z)_2C(R^z)_2$, $OC(R^z)_2$, $SC(R^z)_2$, $N(R^z)C(R^z)_2$, $C(R^z)_2O$, $C(R^z)_2S$, $C(R^z)_2N(R^z)$;

R^z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, two R^z groups either on the same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ hydroxyalkyl, phenyl, CH_2-phenyl;

ring B is



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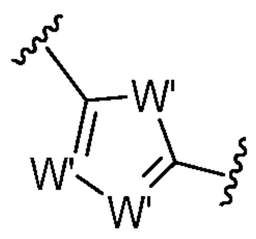
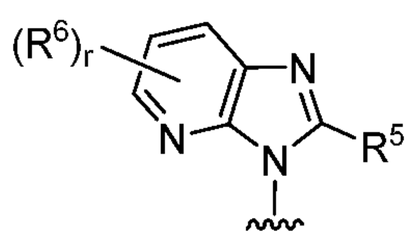
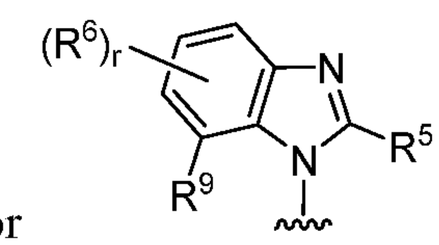


;

Group C is



IE, or



IF;

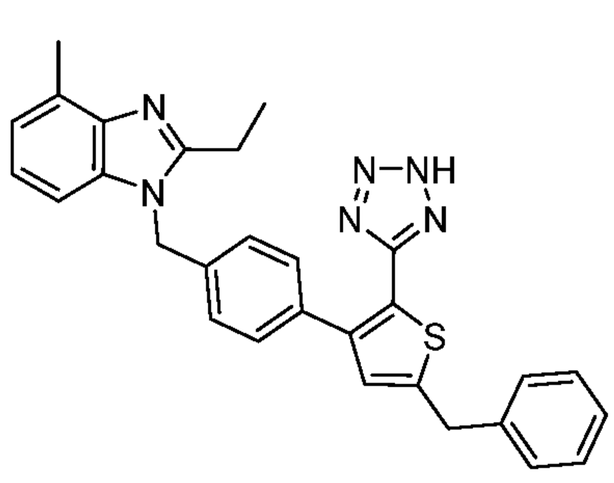
R^5 is $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl $C_{1\text{-}6}$ alkoxyalkyl, $C_{3\text{-}6}$–cycloalkyl$C_{0\text{-}4}$–alkyl which may be substituted with 1-3 halogens or a $C_{1\text{-}3}$-alkoxy group;

R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ haloalkyl $C_{1\text{-}4}$ alkoxyalkyl, $C_{1\text{-}4}$ hydroxyalkyl, $C_{3\text{-}6}$–cycloalkyl, $C_{3\text{-}6}$–halocycloalkyl, $C_{1\text{-}6}$–alkoxy-C_3-C_6-cycloalkyl, or $C_{1\text{-}6}$–hydroxycycloalkyl;

R^9 is COOR, $CON(R^z)_2$; and

r is 0 to 3;

provided that the compounds of Formula (I) are not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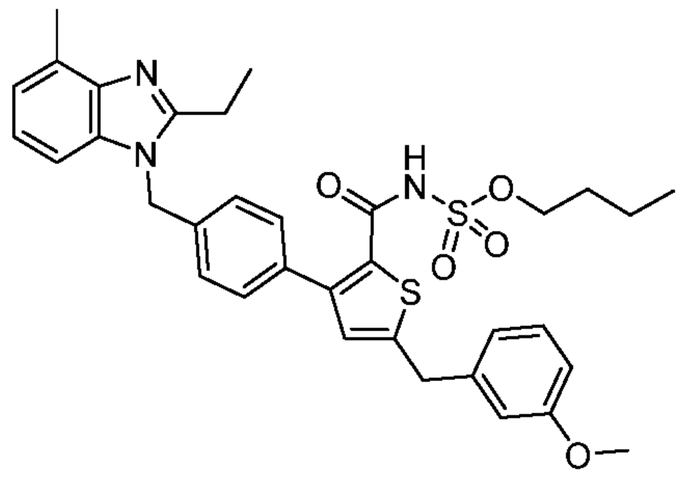
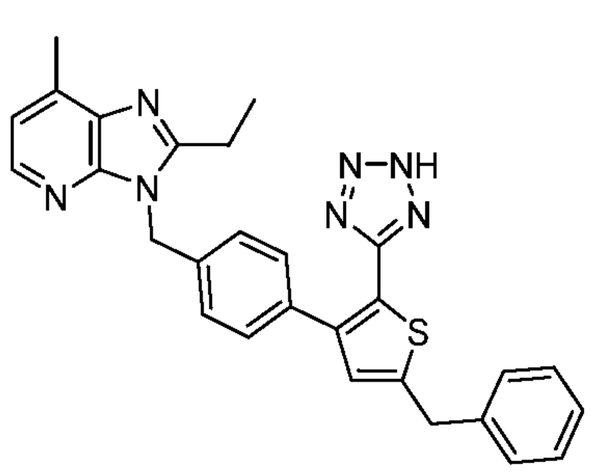
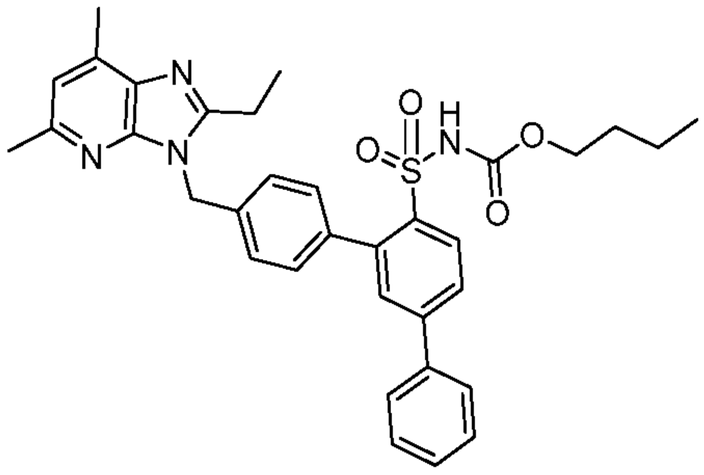
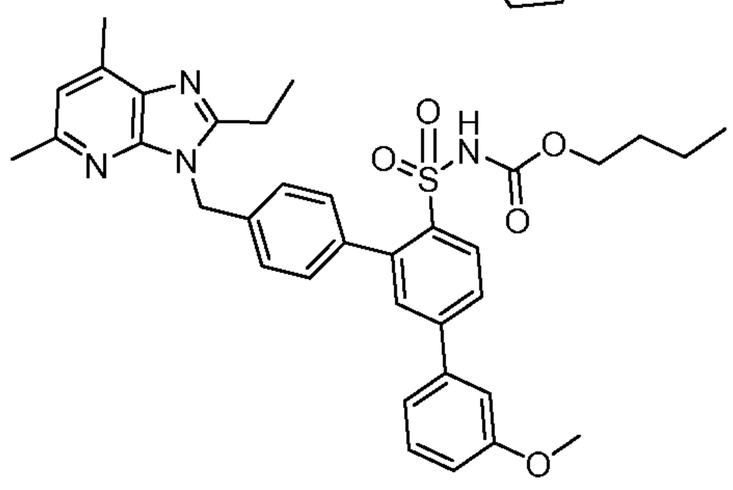
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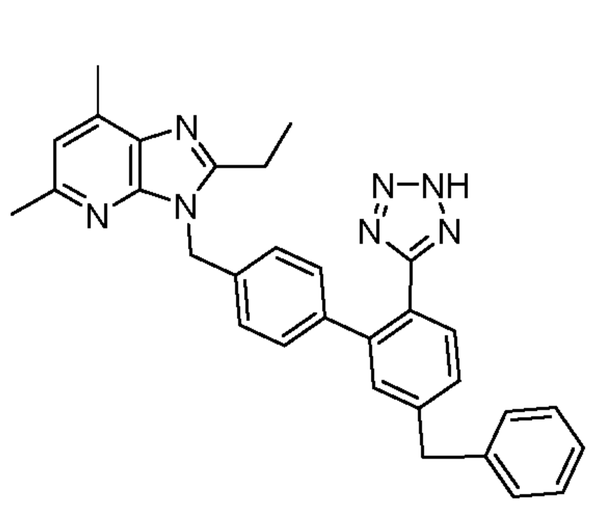
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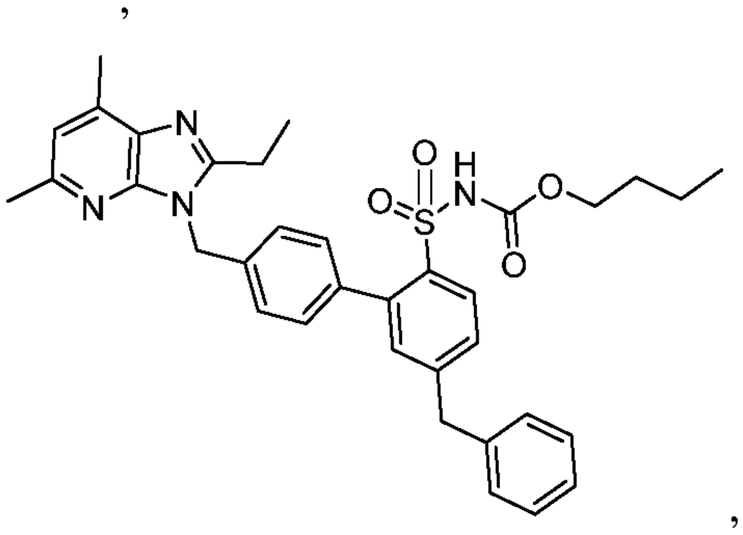
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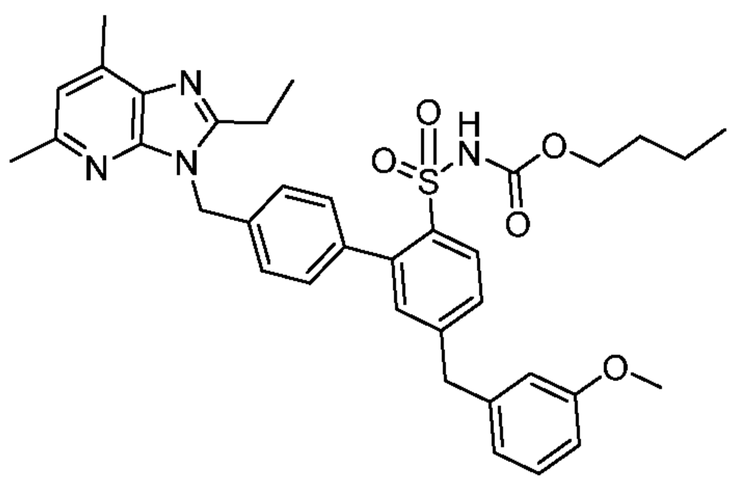
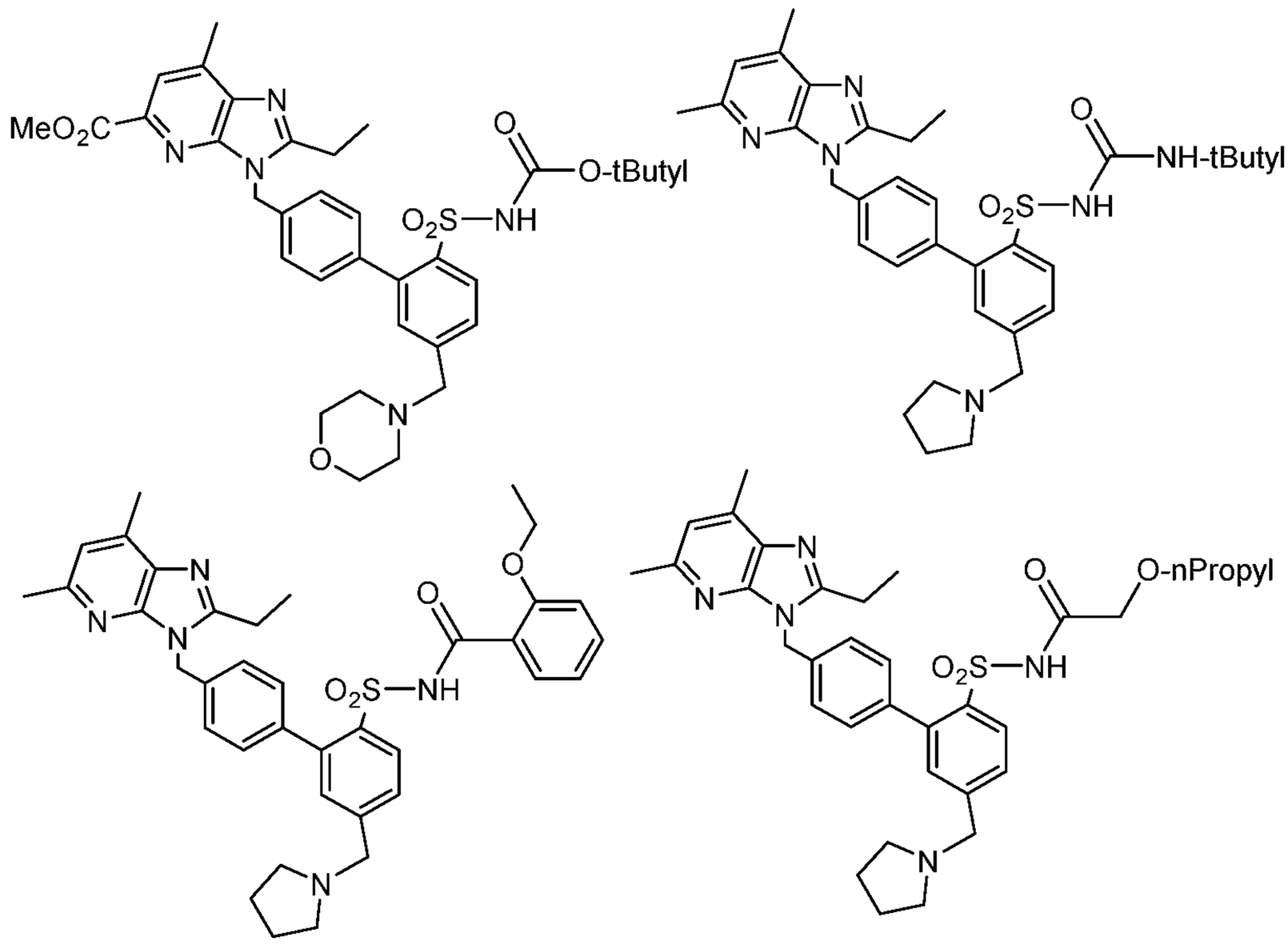
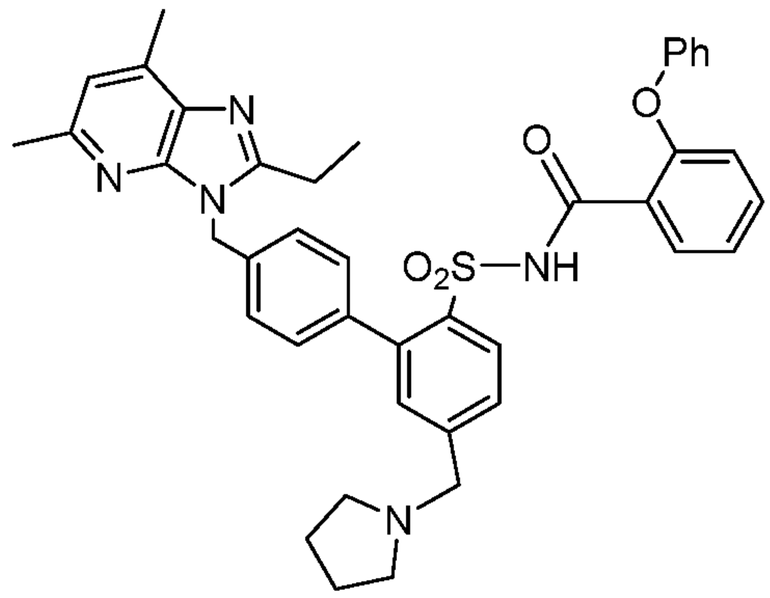
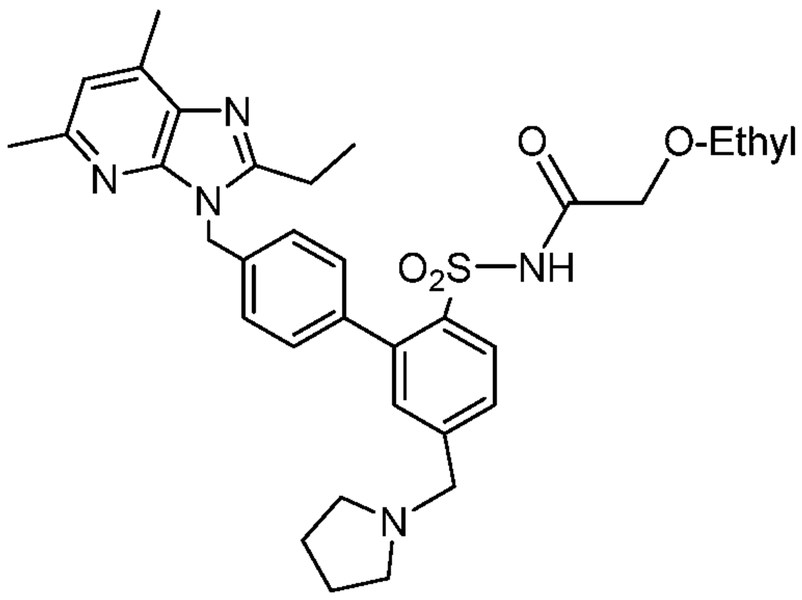
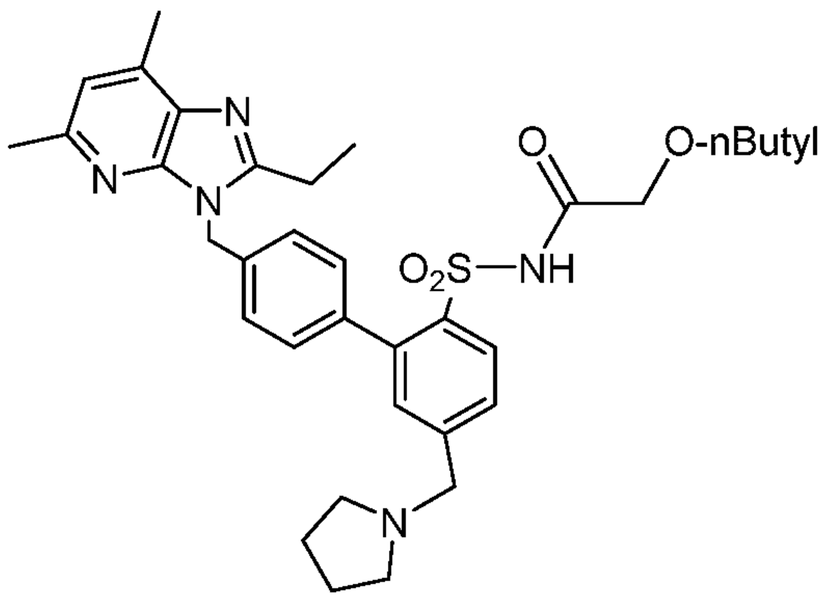
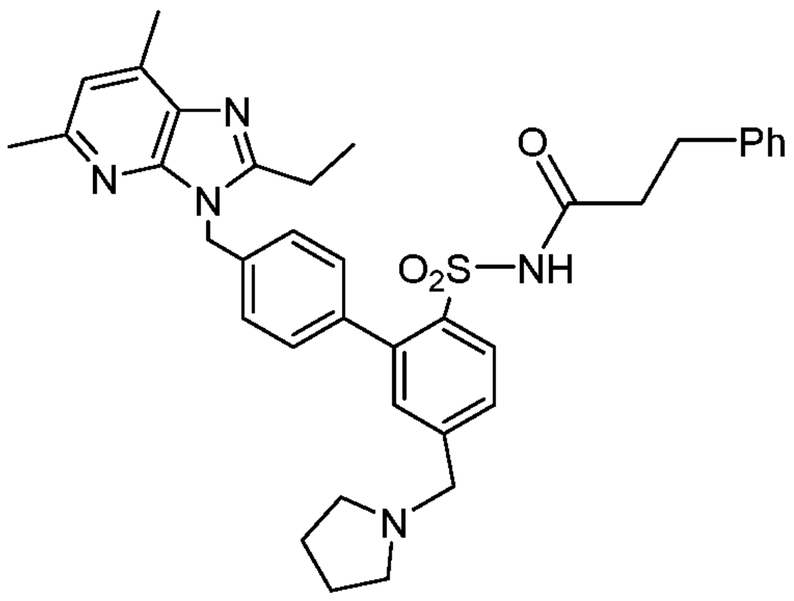


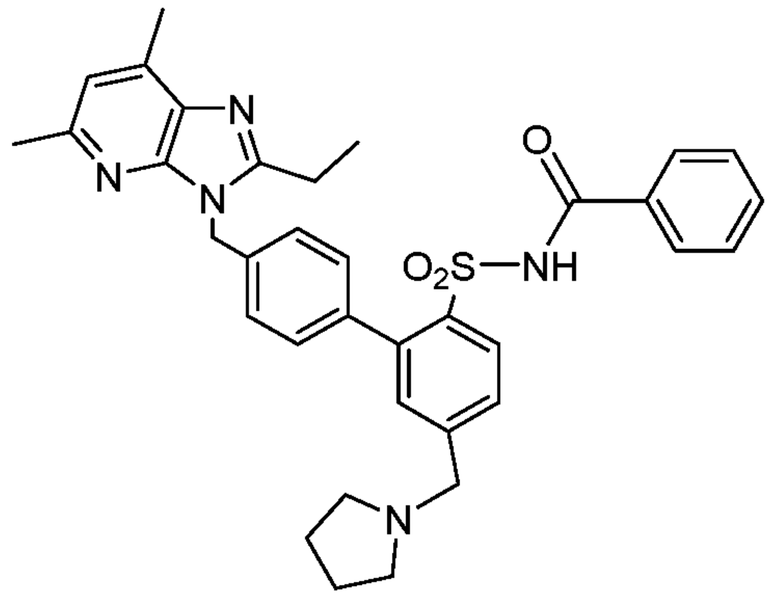

MeO2C
N
N
N
O
O-tButyl
O2S—NH
N
O
N
N
N
O
NH-tButyl
O2S—NH
N
N
N
O
O
O-nPropyl
O2S—NH
N
N
N
O
O
O2S—NH
N

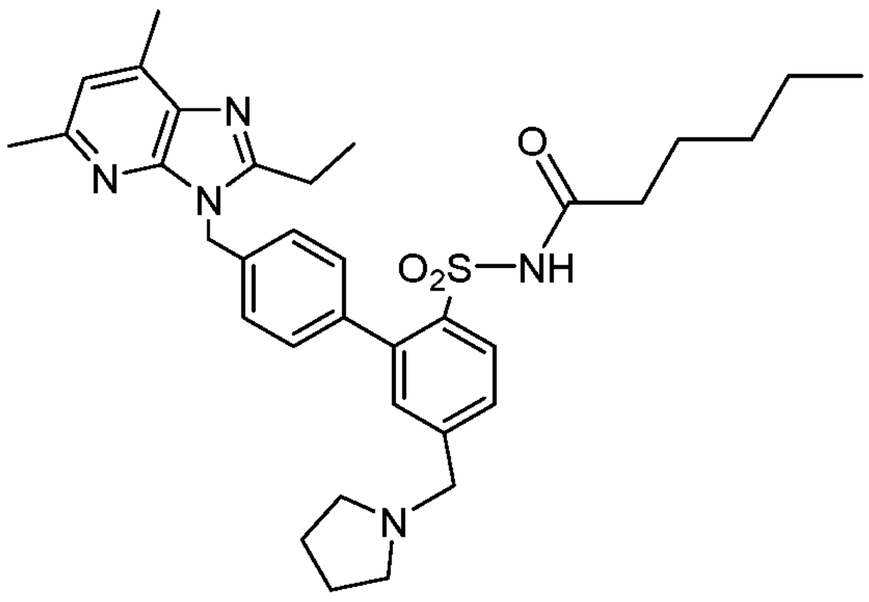

Ph
O
O
N
N
N
O_2S—NH
N

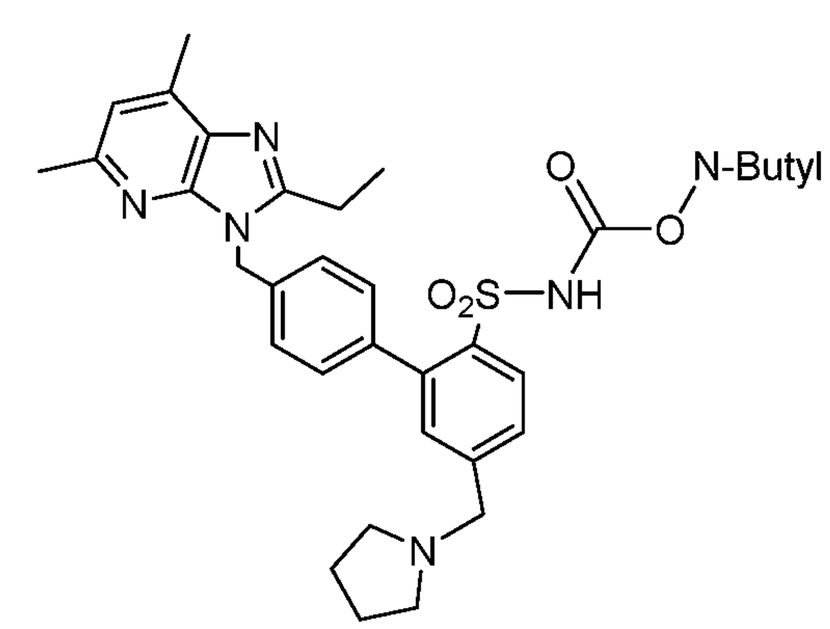

O
O-Ethyl
N
N
N
O_2S—NH
N

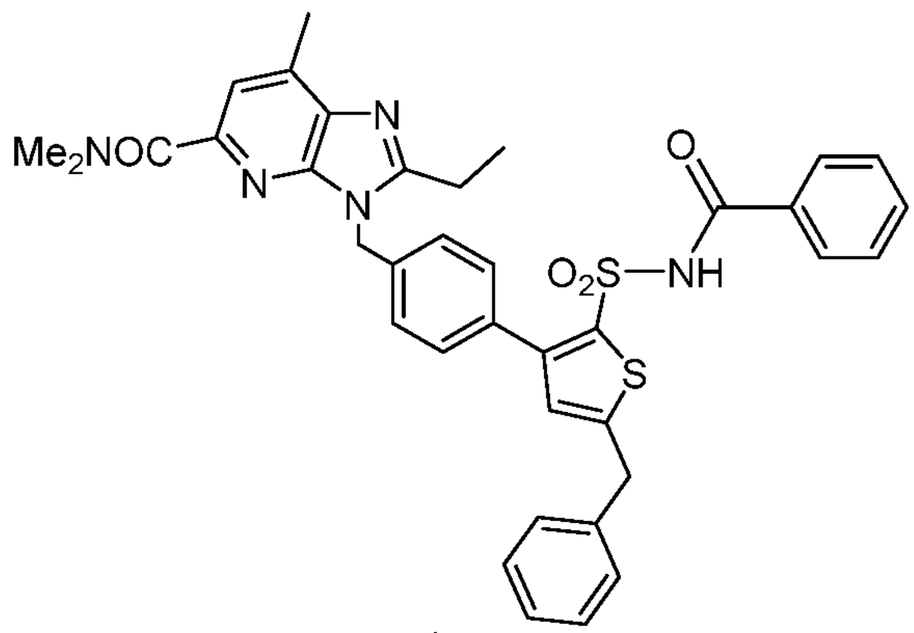

O
O-nButyl
N
N
N
O_2S—NH
N

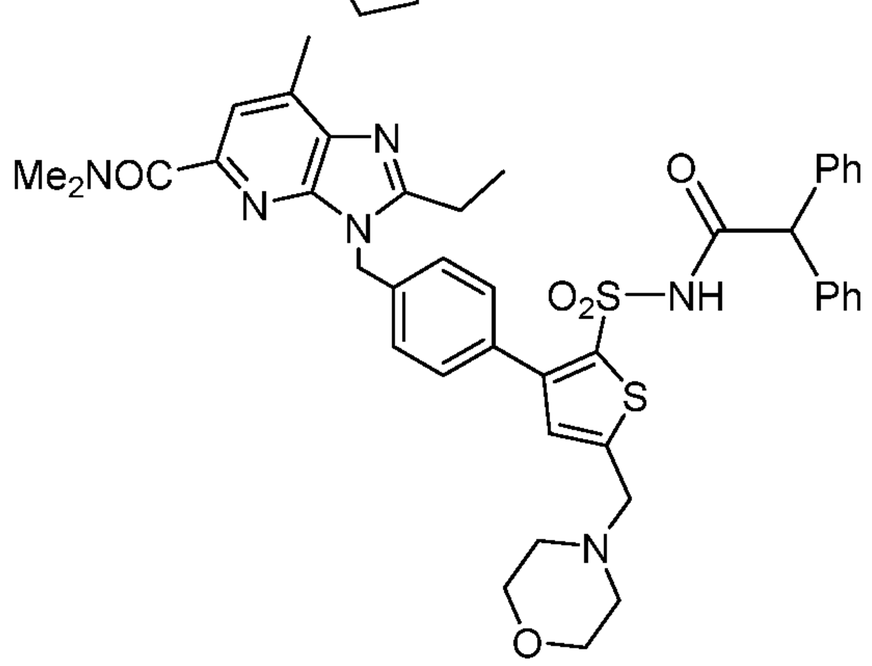

O
Ph
N
N
N
O_2S—NH
N

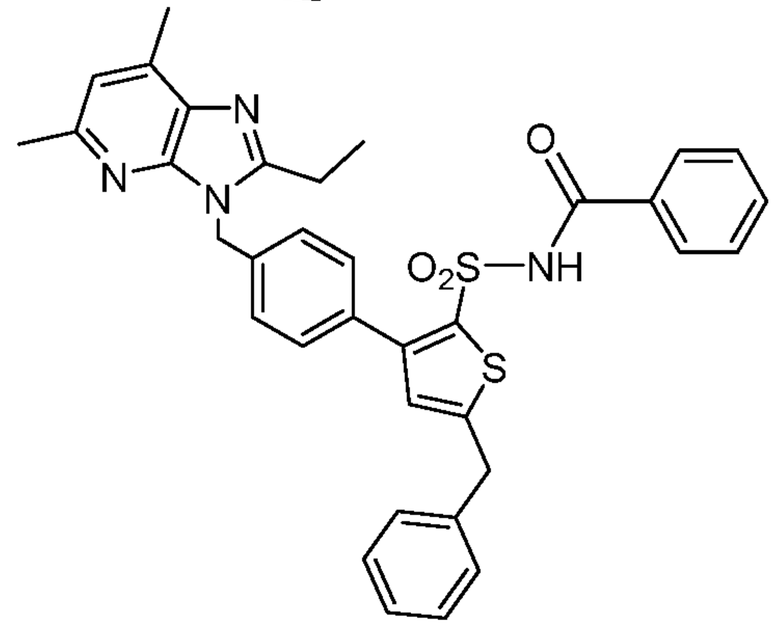

O
N
N
N
O_2S—NH
N

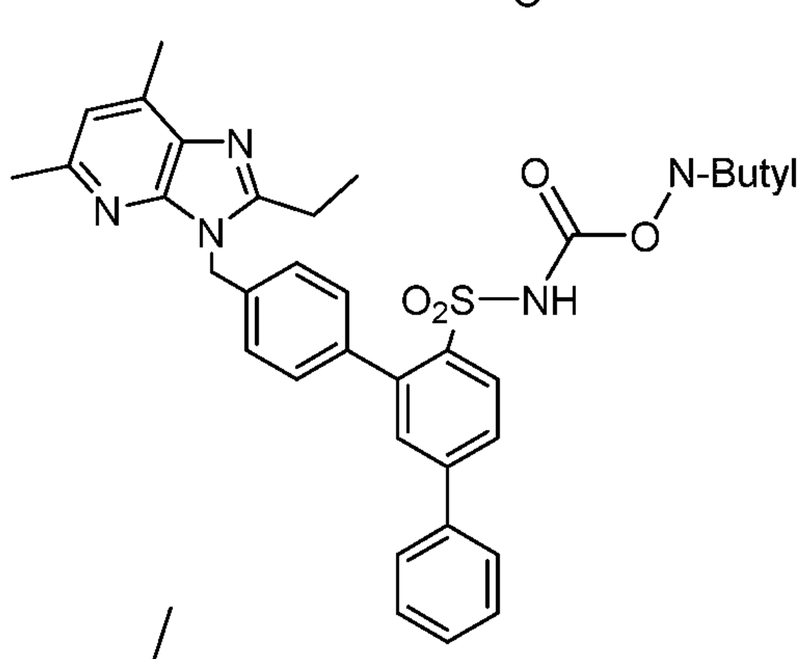

O
N
N
N
O_2S—NH
N

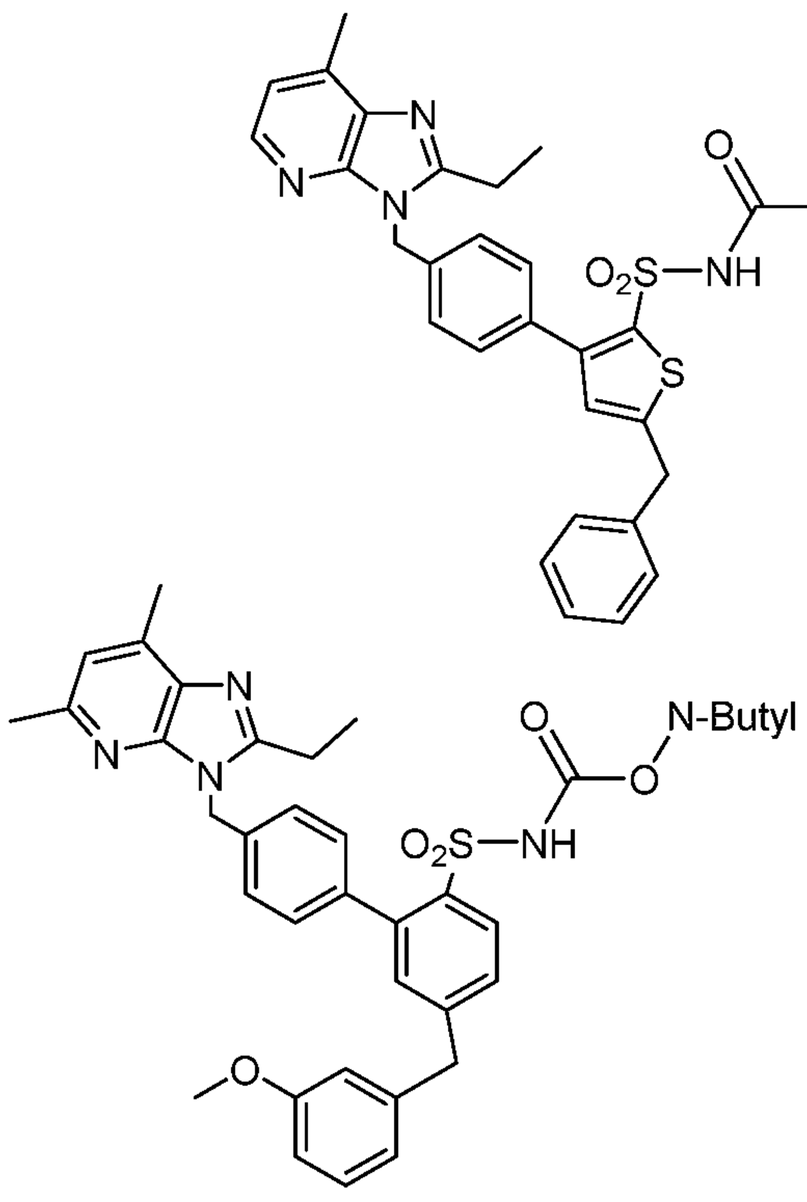


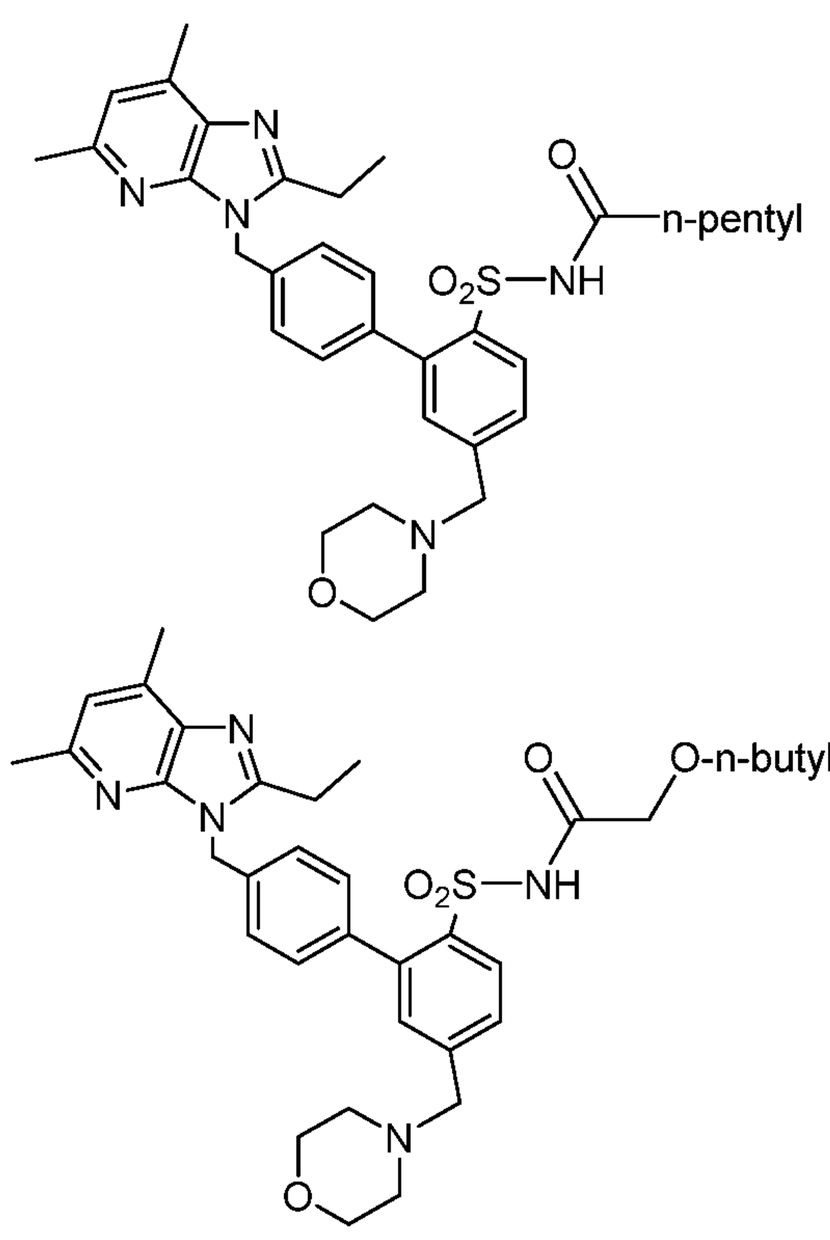


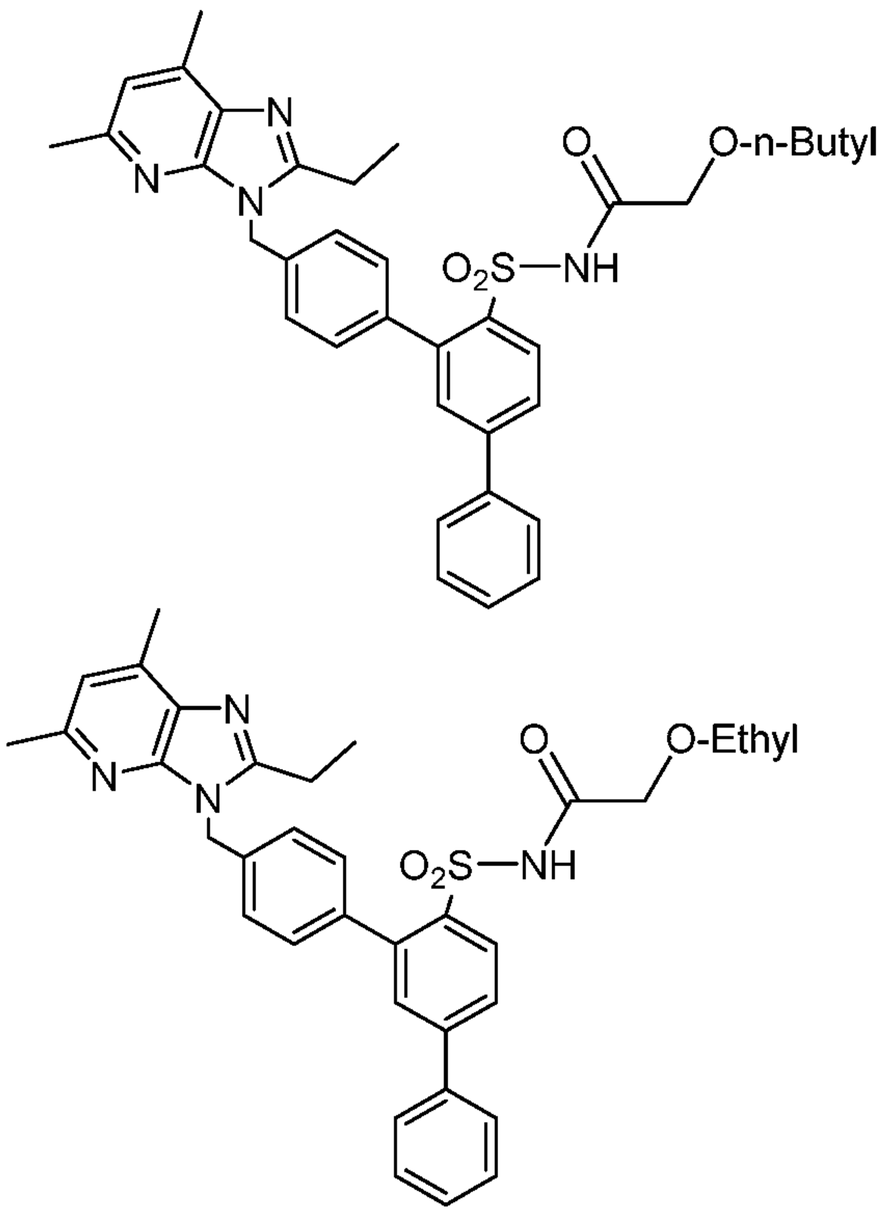


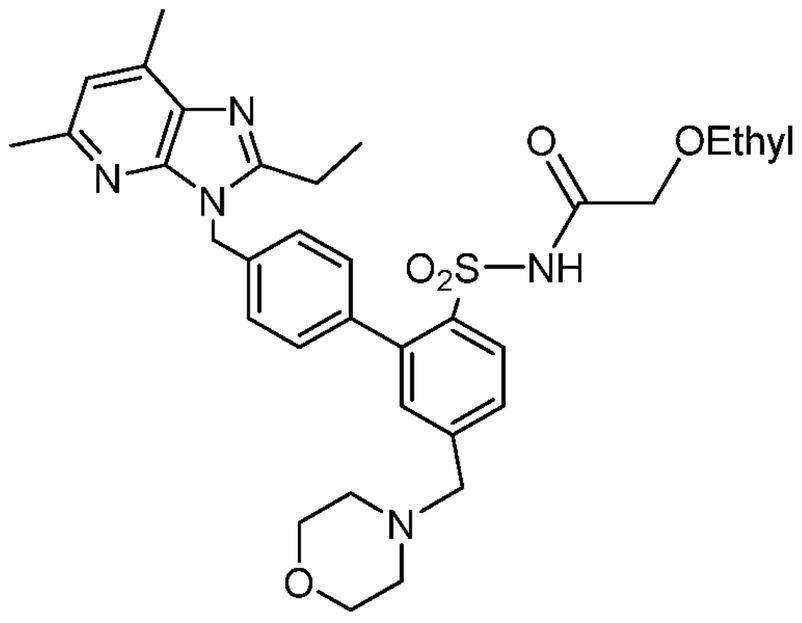


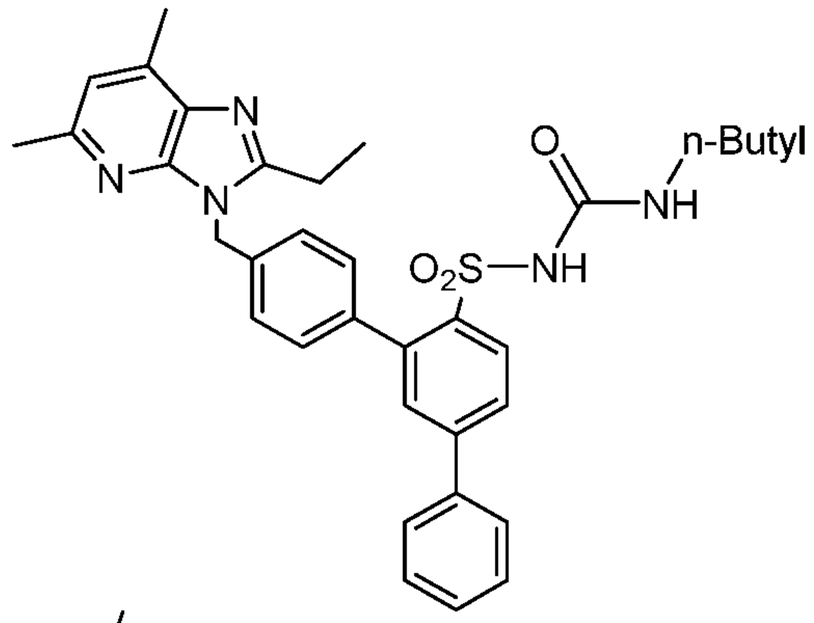


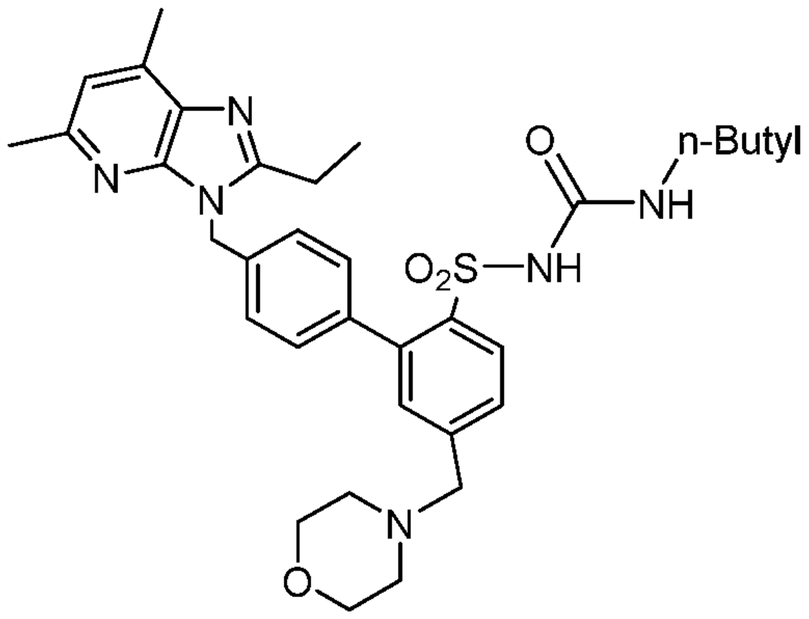


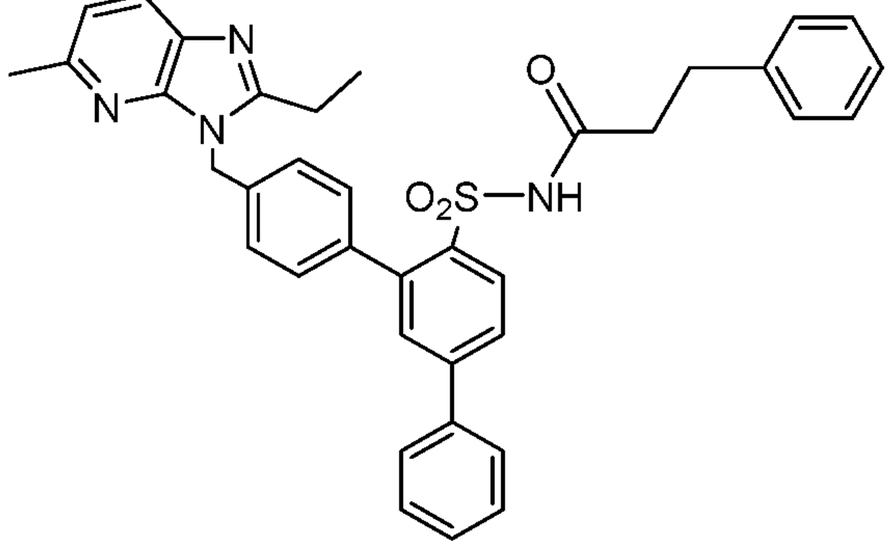

n-pentyl
O-n-butyl

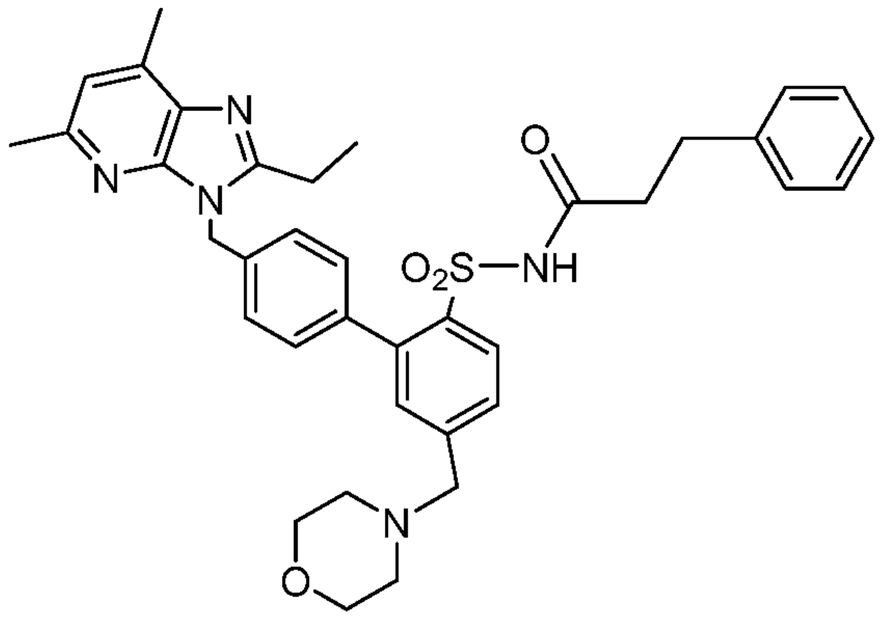

O-n-Butyl
O-Ethyl

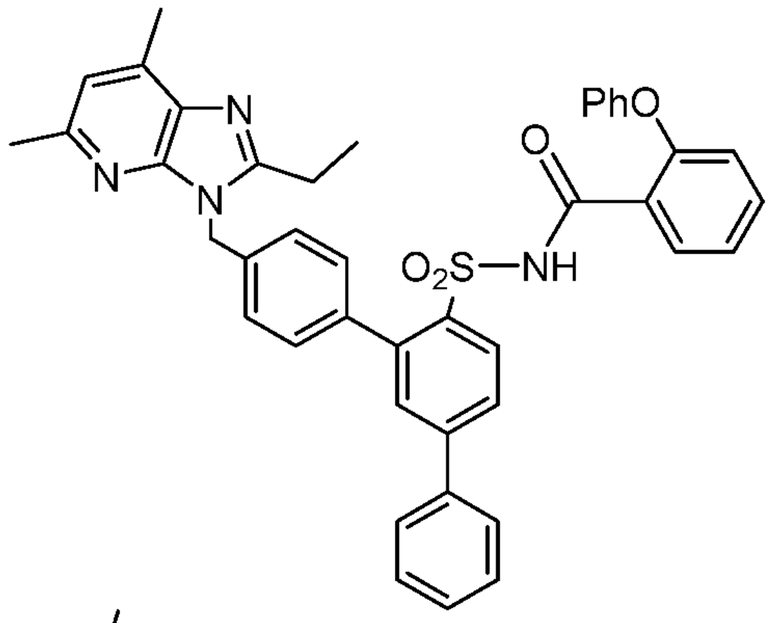


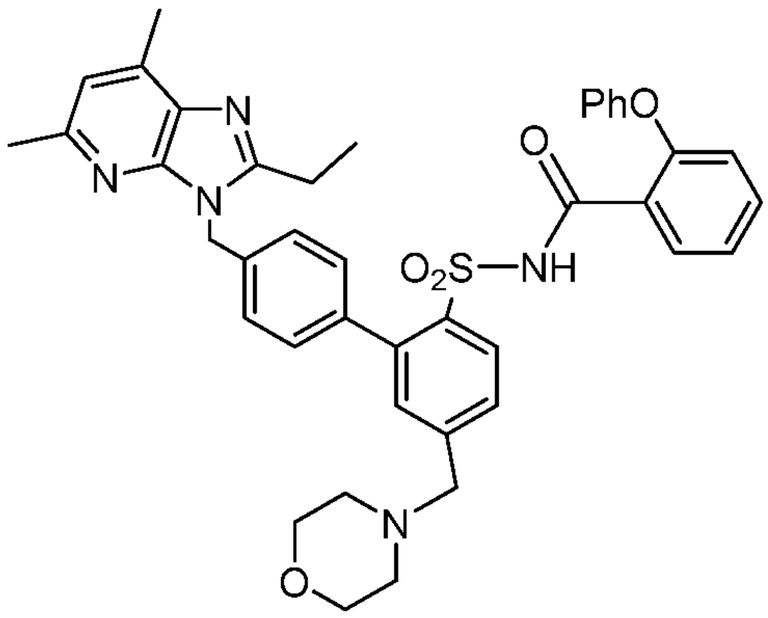


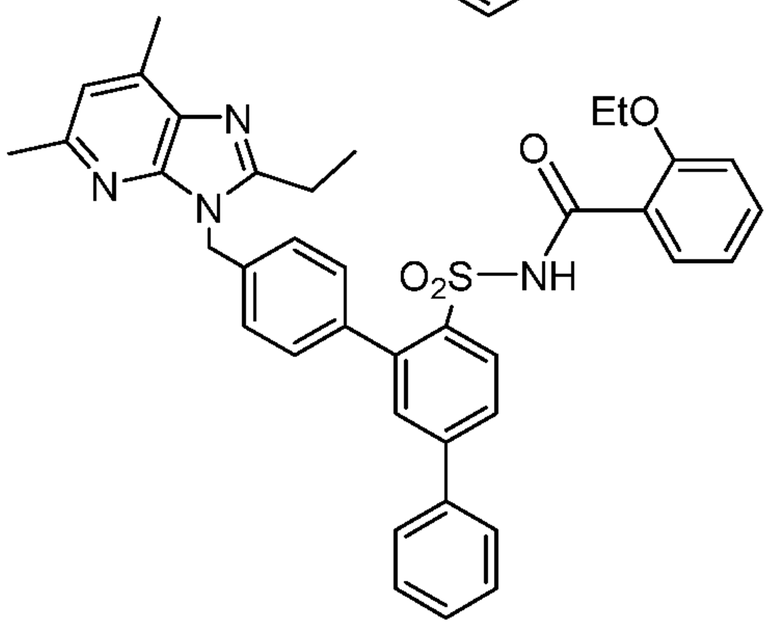


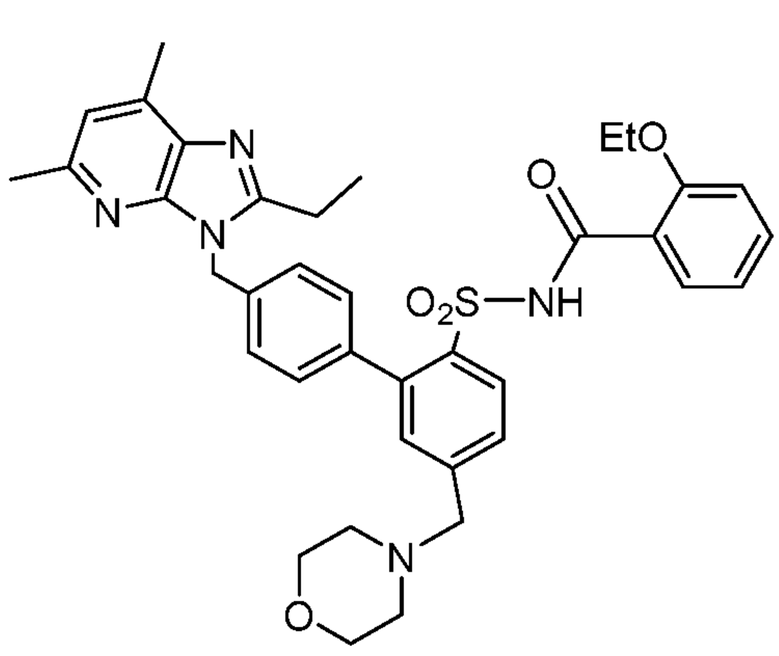


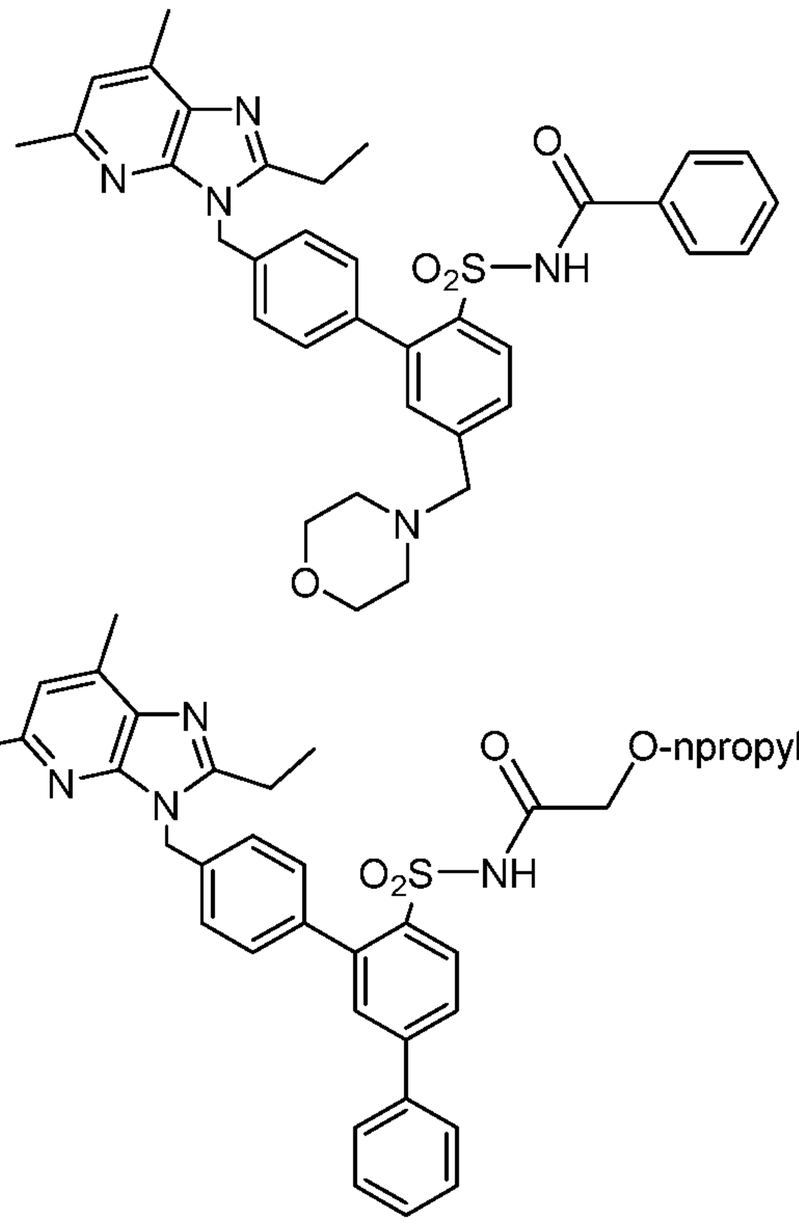


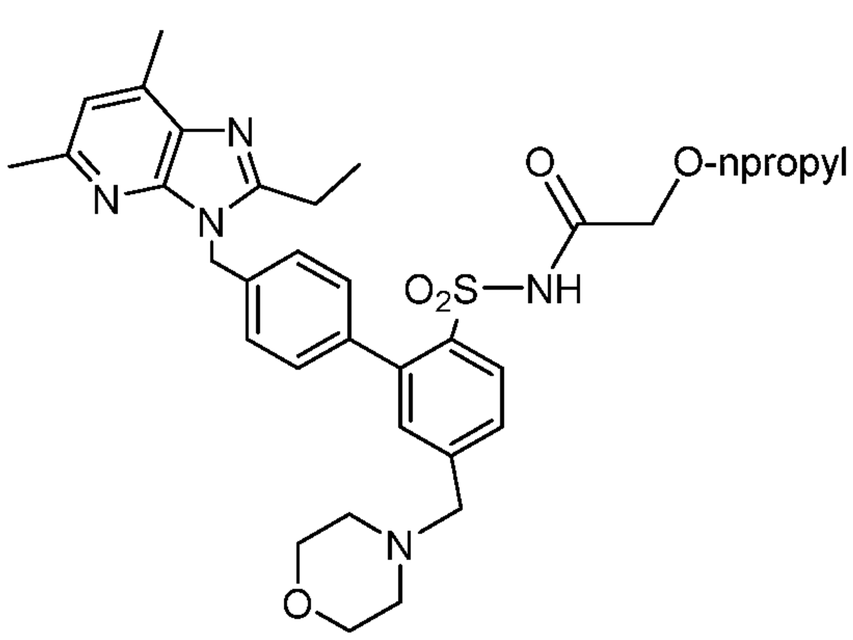


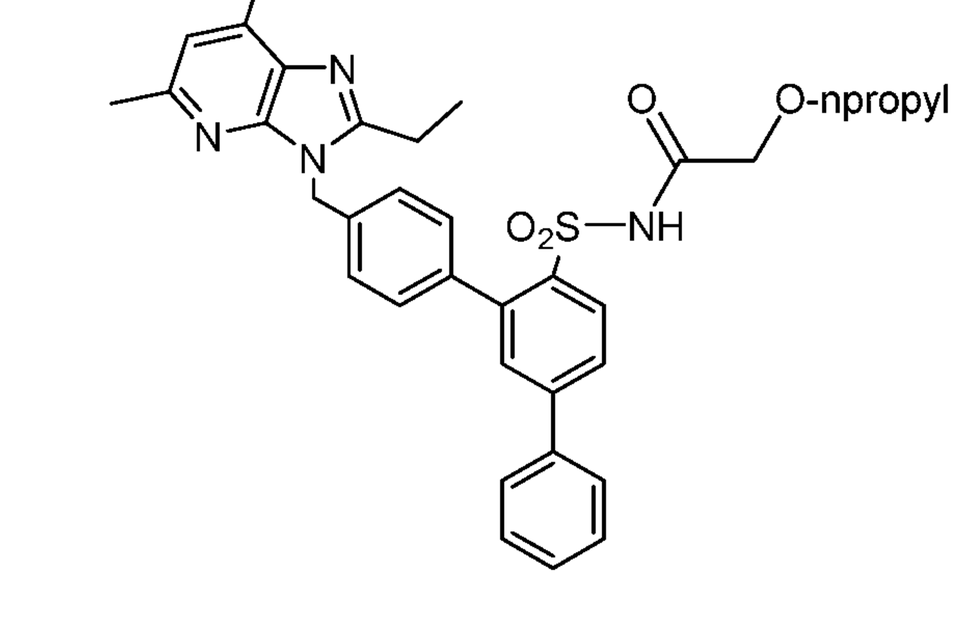


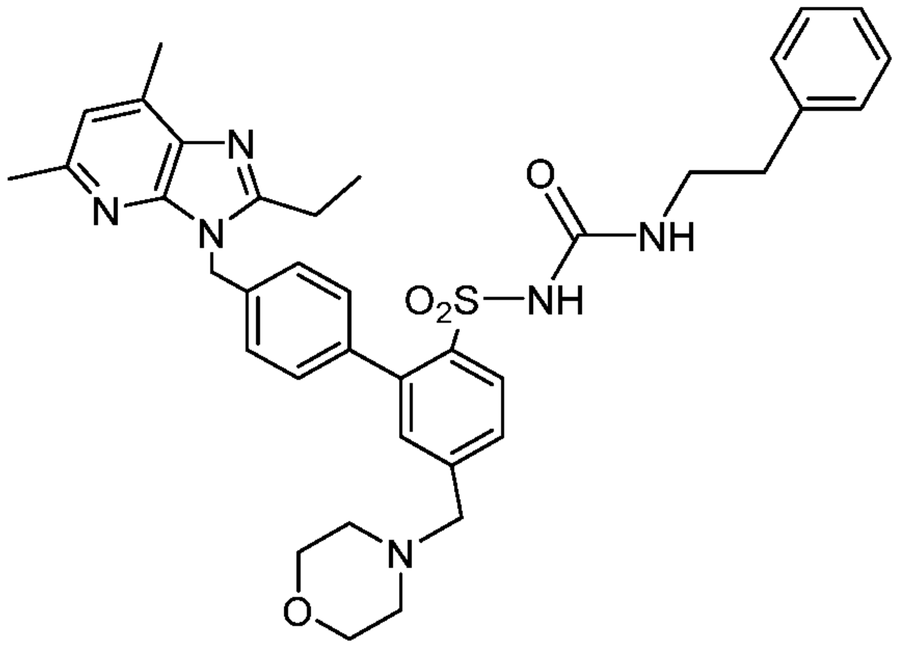


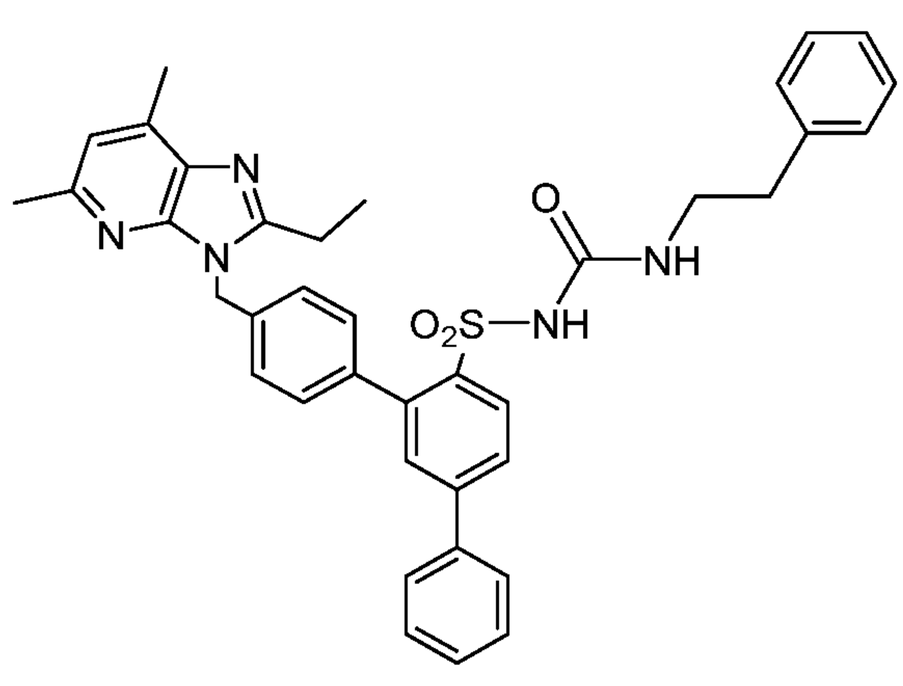

EtO
O
N
N
N
O_2S—NH

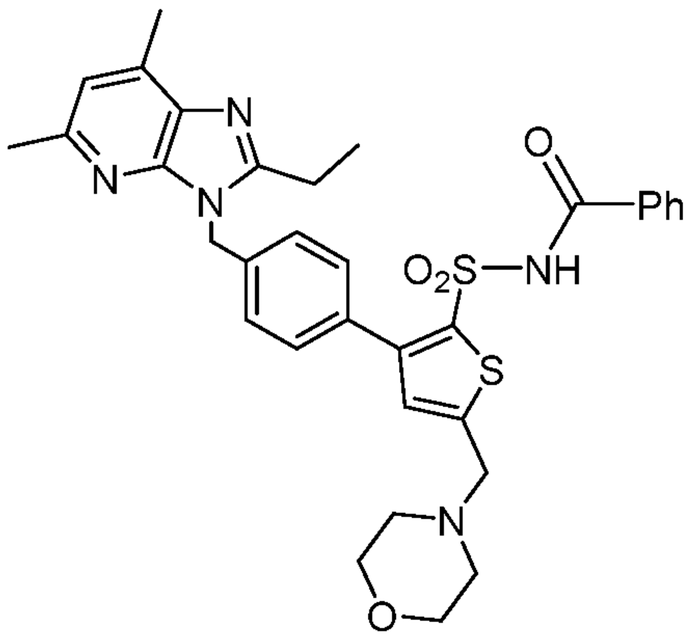

O
N
N
N
O_2S—NH

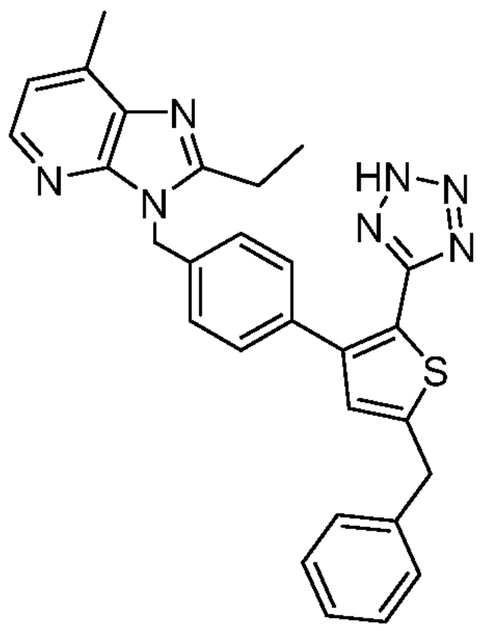

O
O-npropyl
N
N
N
O_2S—NH

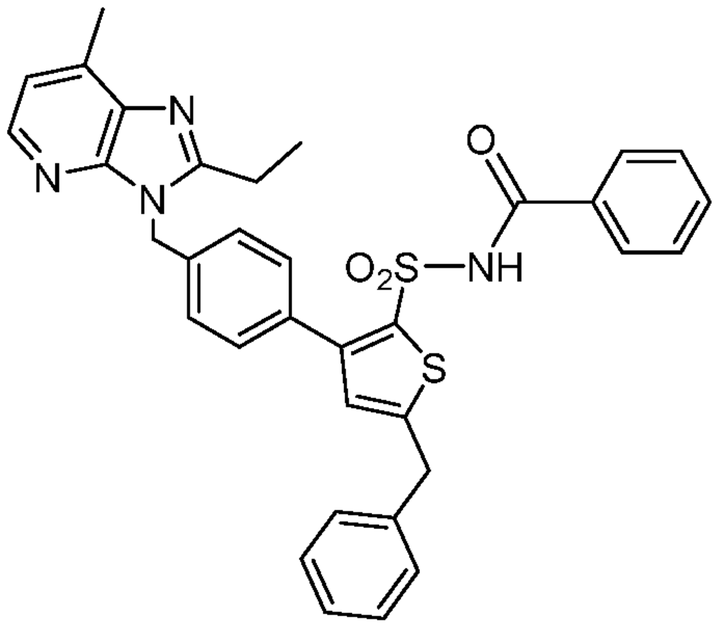

O
O-npropyl
N
N
N
O_2S—NH

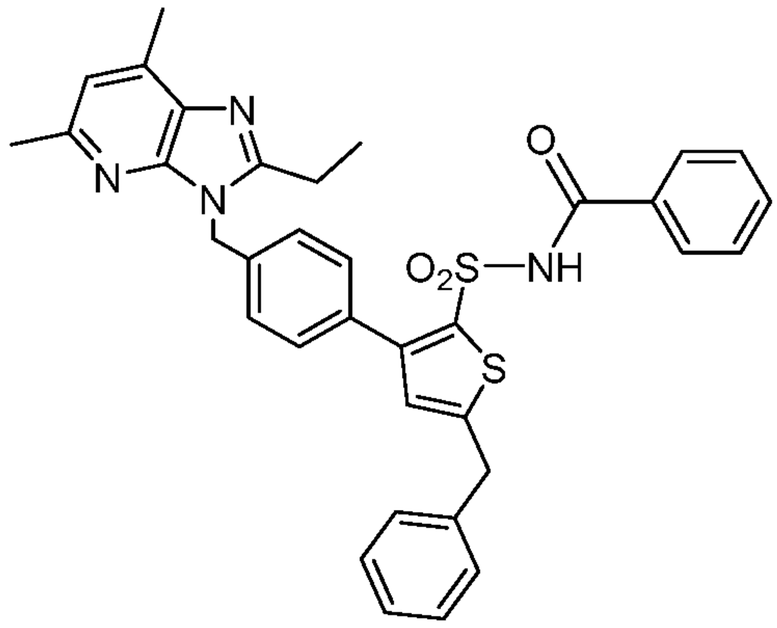

O
NH
N
N
N
O_2S—NH

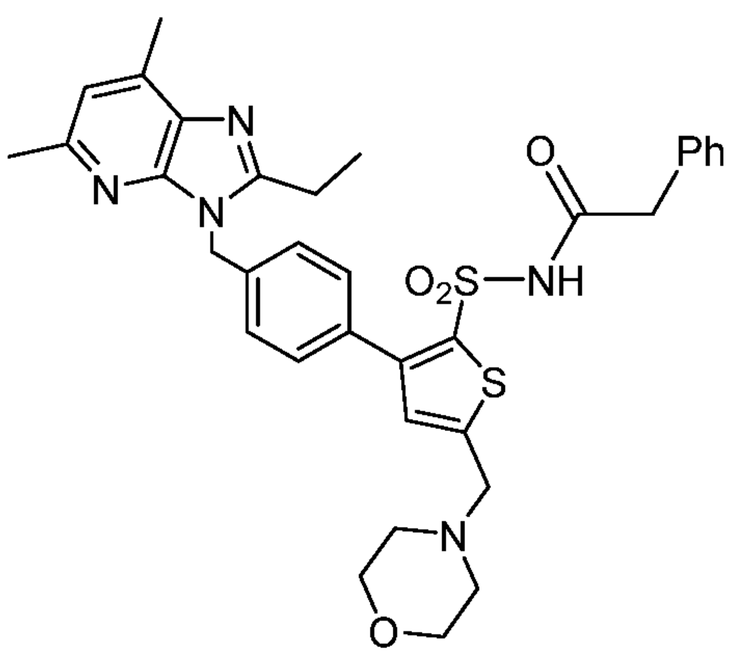

O
NH
N
N
N
O_2S—NH

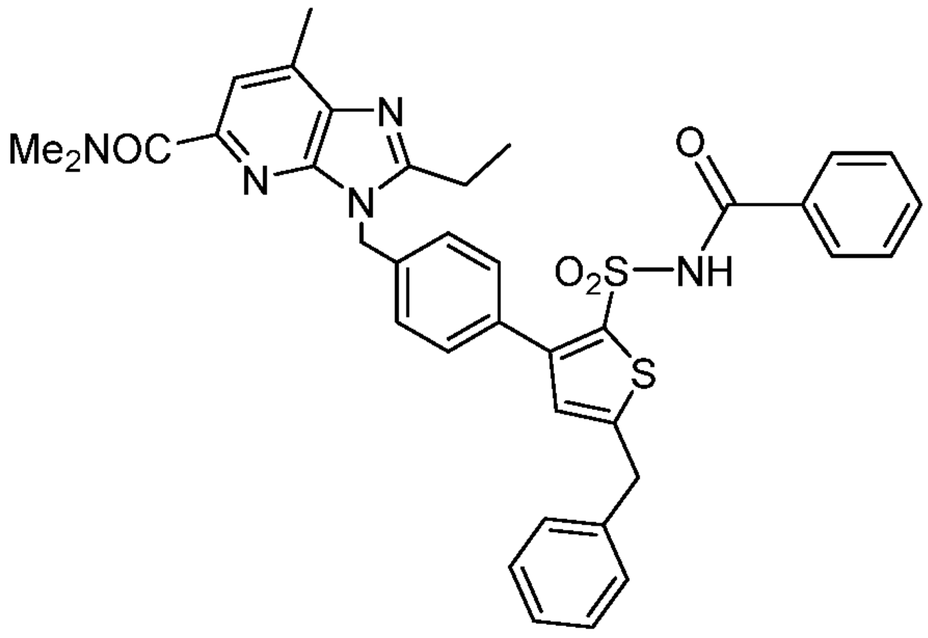


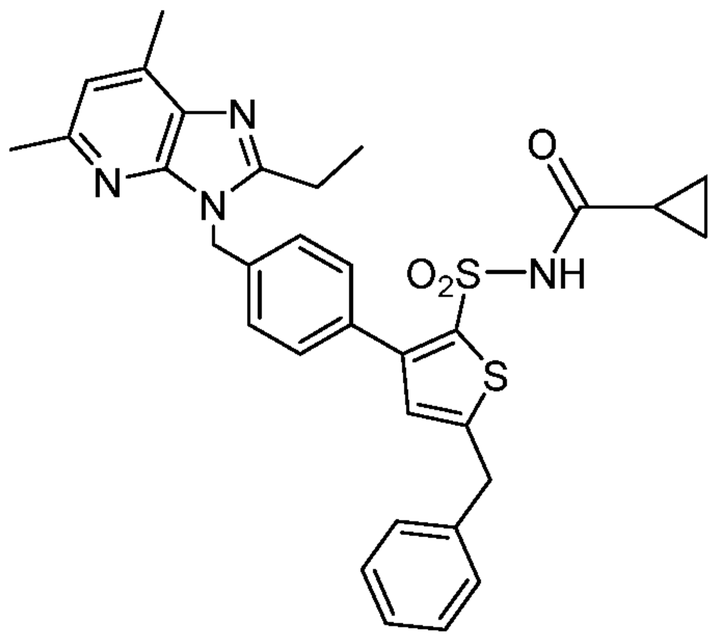


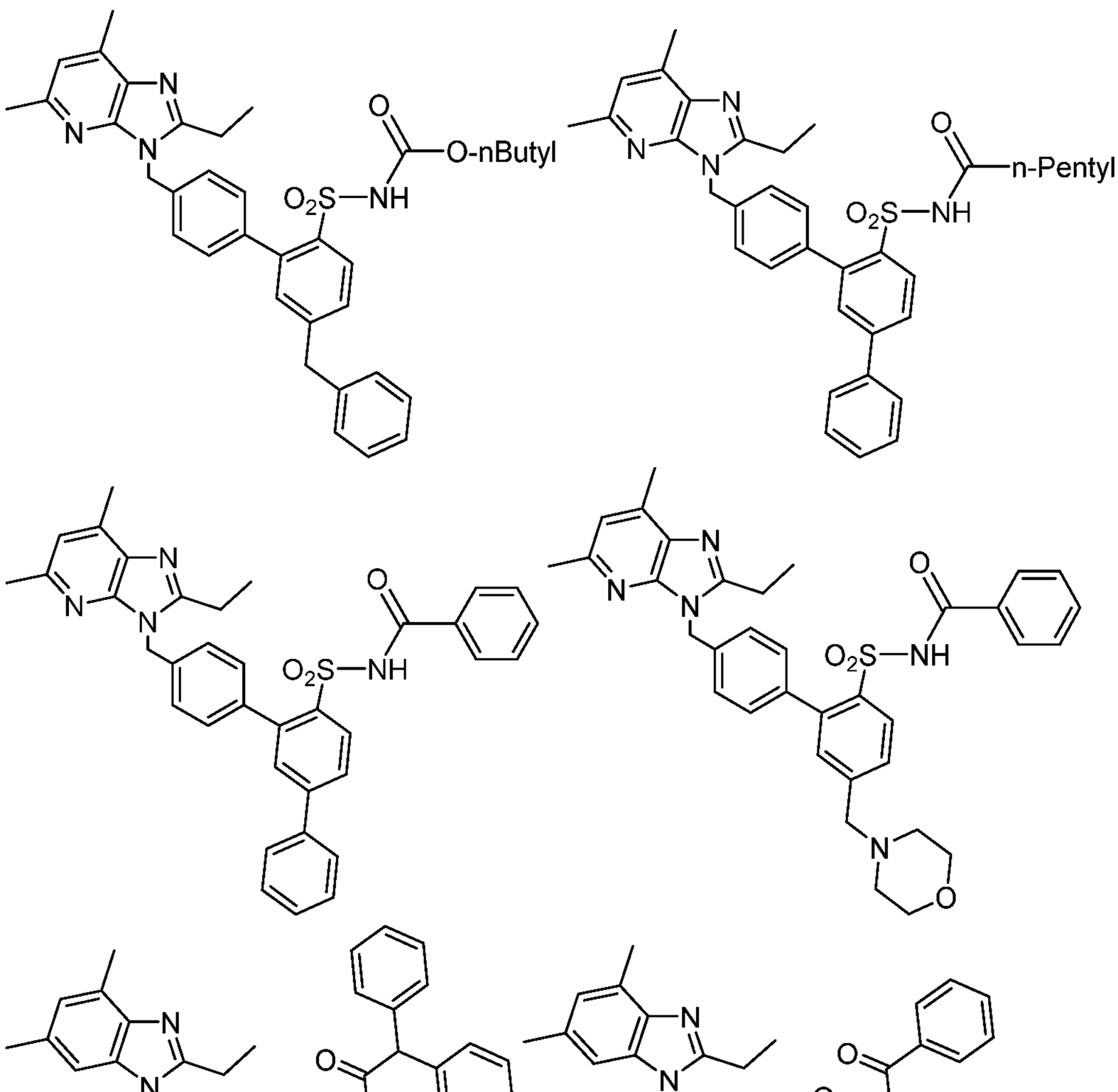




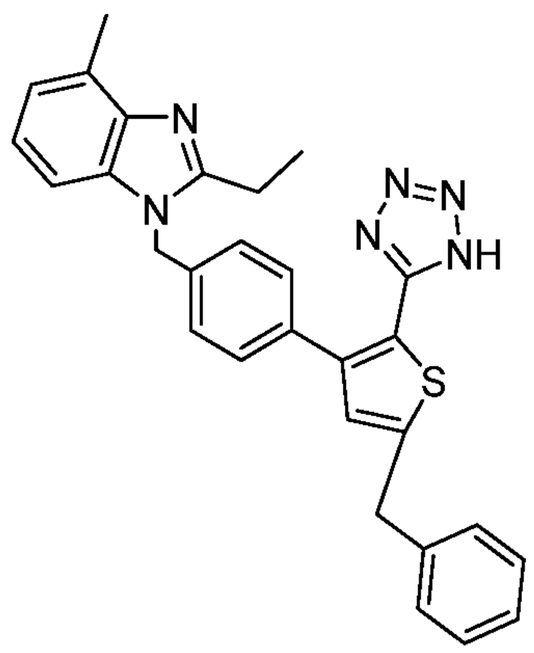








or



In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl or $O(C_{1-6}$ alkyl); and

R^6 is hydrogen, or C_{1-4} alkyl.

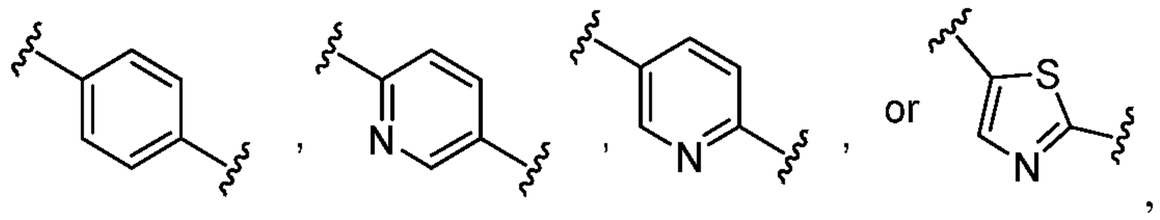
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

G is selected from a 5 to 10 membered heterocycle having 1-3 atoms selected from N, O, and S, phenyl or a C_6-C_{10}-heteroaryl having 1-3 atoms selected from N, O, and S; wherein the heterocycle, phenyl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkylthio, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2R^x$;

R^x is H, C_{1-6} alkyl, CF_3, phenyl, CH_2-phenyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is

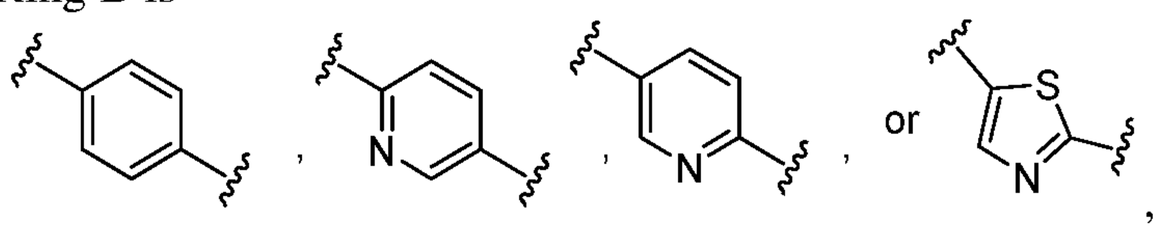


any of which are optionally substituted with 0-2 F,

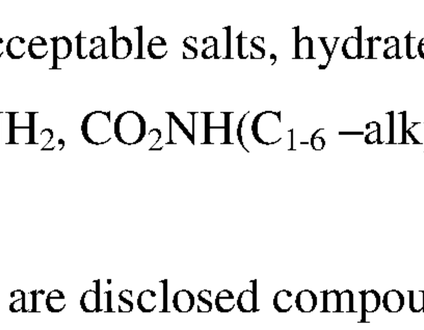
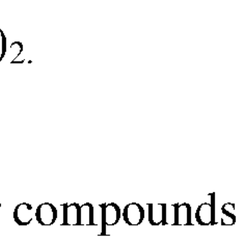
In another aspect, there are disclosed compounds of Formula (IF) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein R^9 is CO_2H, CO_2- C_{1-6} –alkyl, CO_2NH_2, $CO_2NH(C_{1-6}$ –alkyl), $CO_2N(C_{1-6}$ –alkyl)$_2$.

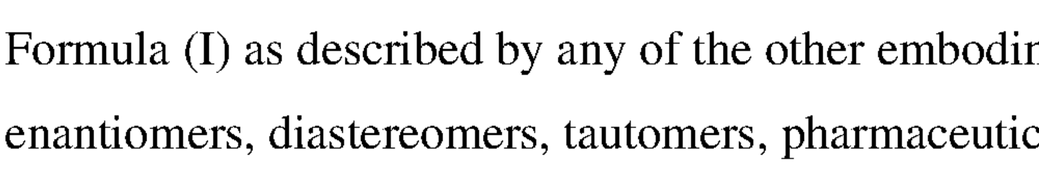
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is



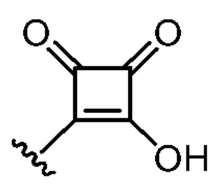
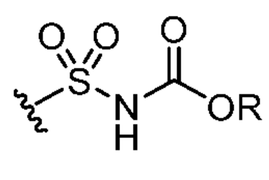
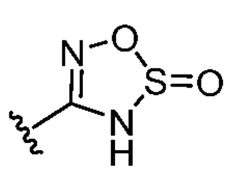
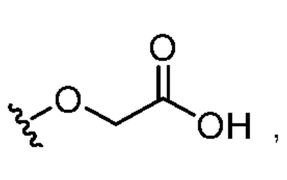
any of which are optionally substituted with 0-2 F,

Y is COOH, COOMe, COOEt,  , 5-tetrazolyl, SO_3H,  ,



In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

wherein Y is COOH, 5-tetrazolyl, SO_3H,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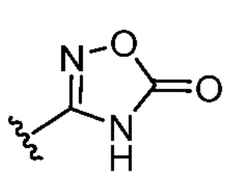
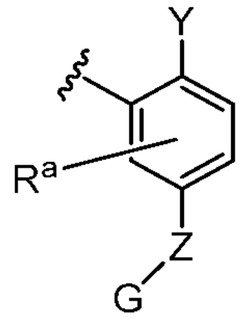
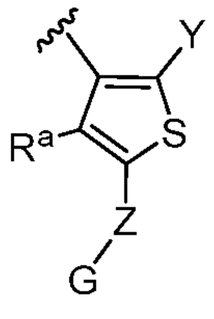

; and

R is C_{1-6} alkyl, C_{6-10}-aryl-C_1-C_6-alkyl ,, or (CH_2Ph).

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring A is


or

; and

R^a is H or F.

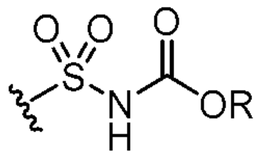
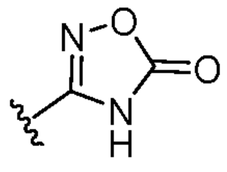
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

G is selected from a phenyl, thiophenyl, quinolinyl, isoquinolinyl, indolyl, pyrazolyl, pyrrolyl, pyridinyl, isoindolinyl, pyrrolidinyl; ; any of which are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2R^x$;

R^x is H, C_{1-3} alkyl, CF_3, phenyl, CH_2phenyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

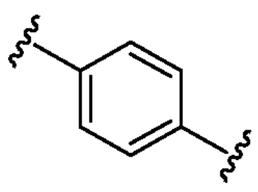
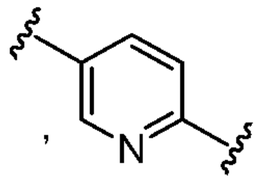
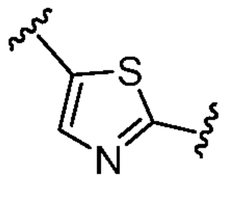
Y is carboxyl, 5-tetrazolyl,



; and

R is C_{1-6} alkyl.

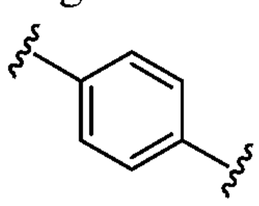
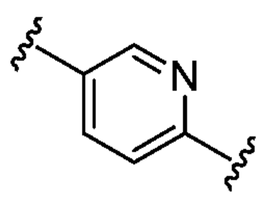
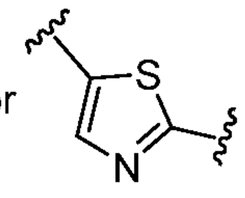
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is

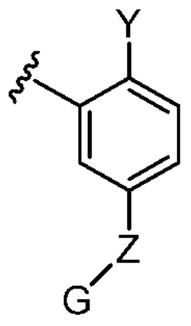
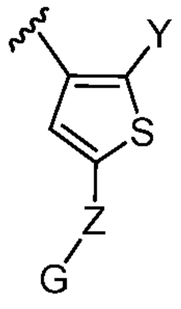

, 
, or 
, any of which are substituted with 0-2 F.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is


, 
, or 

Ring A is


or 

Z is a bond or NR^a;

G is isoindolinyl-1,3-dione, pyrrolidine-2,5-dione, phenyl, thiazolyl, pyridinyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, any of which may be substituted with 0-3 substituents selected from =O, C_{1-4} alkyl, -O-R^x, C_{1-4} haloalkyl, -C(O)NR^x, -N(R^x)$_2$, and F;

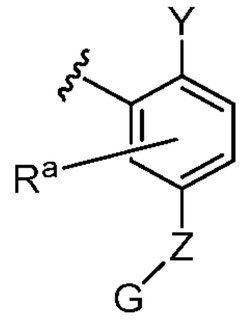
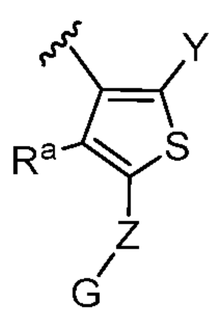
R^5 is C_{3-4} alkyl;

R^6 is C_{3-4} alkyl;

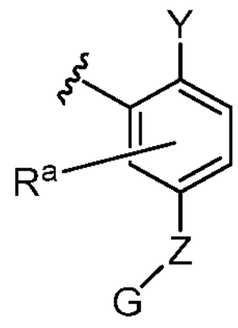
R^a is hydrogen, C_{1-4}alkyl, and C_{1-2} haloalkyl; and

Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring A is  or  .

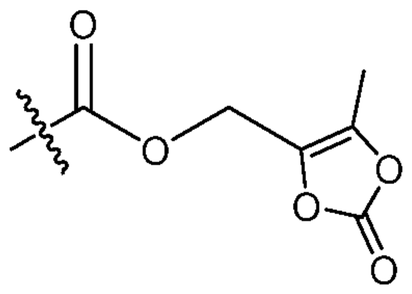
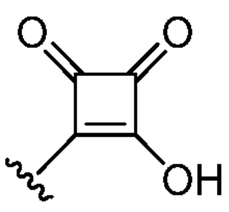
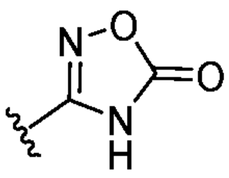
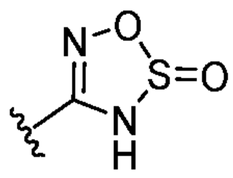
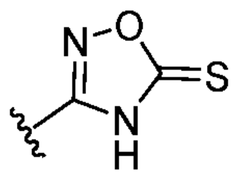
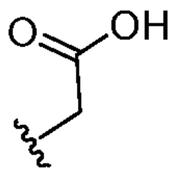
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring A is 

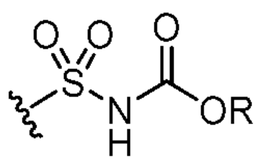
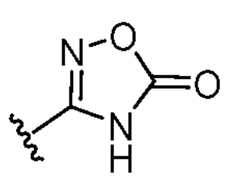
R^a is H or F,

or R^a is H.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Y is COOH, COOMe, COOEt,  , 5-tetrazolyl, SO_3H,  ,  ,  ,  , or  ;

or Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl;

or Y is carboxyl, 5-tetrazolyl,   ;

or Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Z is a bond or NR^a, where R^a is hydrogen, $C_{1\text{-}4}$alkyl, or $C_{1\text{-}2}$ haloalkyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Z is a bond.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

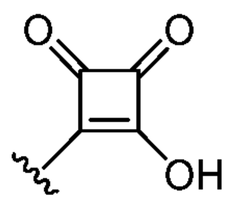
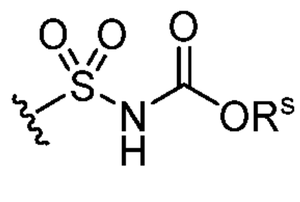
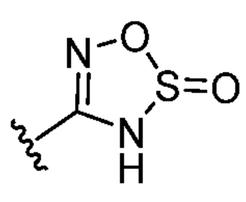
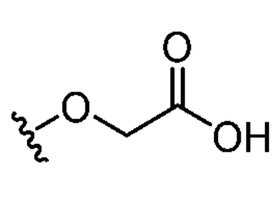
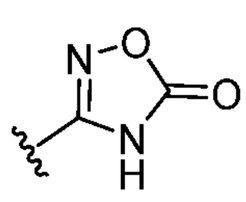
G is selected from a phenyl, thiophenyl, quinolinyl, isoquinolinyl, indolyl, pyrazolyl, pyrrolyl, pyridinyl, isoindolinyl, pyrrolidinyl; any of which are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$,

$CON(R^X)_2$, CO_2R^X, $N(R^X)CO_2(R^X)$, $N(R^X)CO(R^X)$, $N(R^X)CON(R^X)_2$, $S(O)_2(R^X)$, $S(O)_2R^X$, $S(O)_2N(R^X)_2$, $N(R^X)S(O)_2(R^X)$, or $N(R^X)S(O)_2R^X$;

or G is isoindolinyl-1,3-dione, pyrrolidine-2,5-dione, phenyl, thiazolyl, pyridinyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, any of which may be substituted with 0-3 substituents selected from =O, C_{1-4} alkyl, -O-R^X, C_{1-4} haloalkyl, $-C(O)NR^X$, $-N(R^X)_2$, and F.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

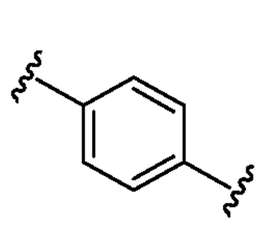
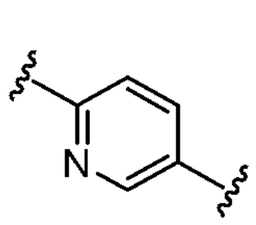
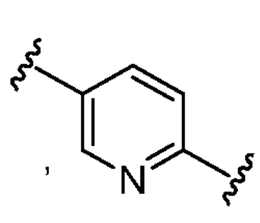
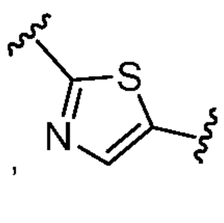
wherein Y is COOH, 5-tetrazolyl, SO_3H,






; and

R^S is C_{1-6} alkyl, or (CH_2Ph).

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

Ring B is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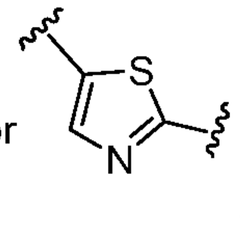
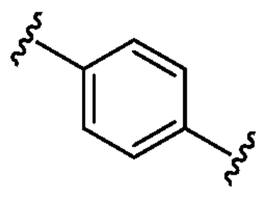
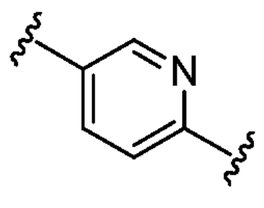

;

or Ring B is


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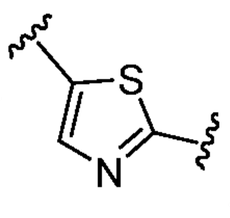
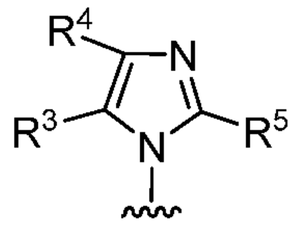
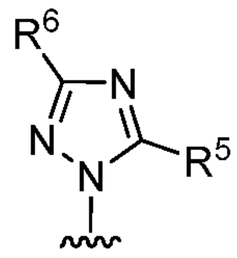
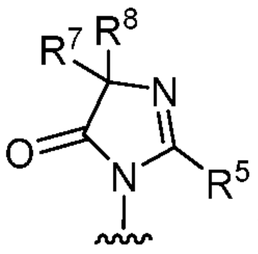
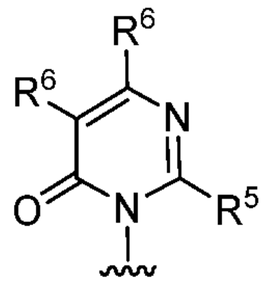

.

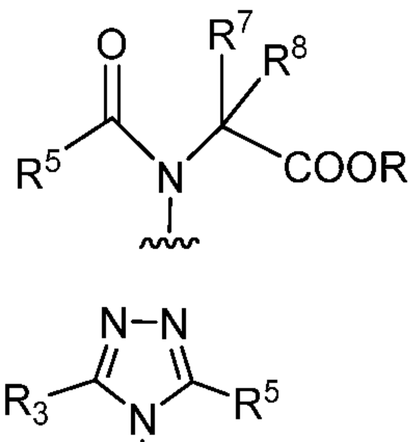
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

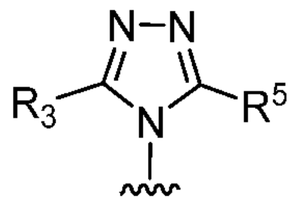
Group C is  IA,

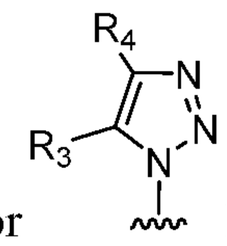
or Group C is  IB,

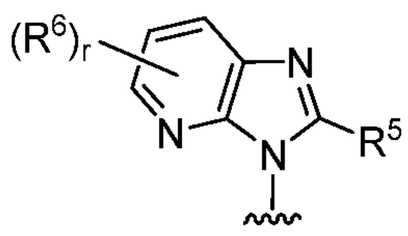
or Group C is  IC,

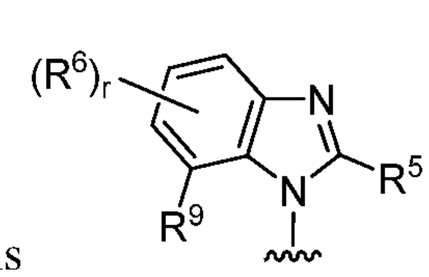
or Group C is  ID,

or Group C is  IG,

or Group C is  IH ,

or Group C is  or IJ.

or Group C is  IE,

or Group C is  IF.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

R^1 and R^2 are H.

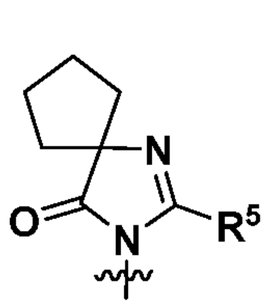
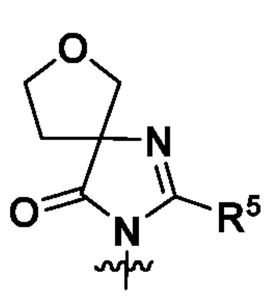
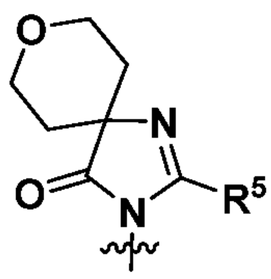
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein:

R^x is H, C_{1-6} alkyl, CH_2-phenyl; and

R^s is C_{1-6} alkyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety:

is selected from the following:

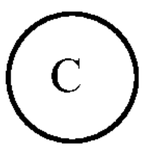




;

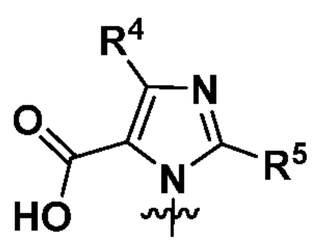
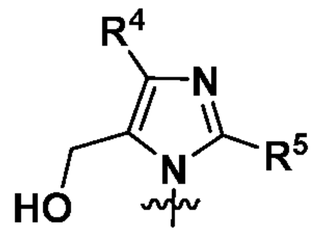
where

R^5 is C_{1-4} alkyl, methoxymethyl, ethoxymethyl or cyclopropyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety:

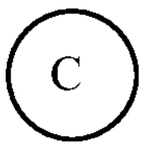


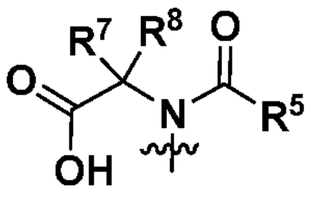
is selected from the following:



;

where R^4 is H, F, Cl, methyl or ethyl and R^5 is C_{1-4} alkyl, methoxymethyl, ethoxymethyl or cyclopropyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety:

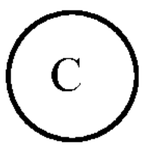

is:


, wherein

R^5 is C_{1-4} alkyl, C_{1-4} haloalkyl, or cyclopropyl

R^7 and R^8 are independently H, C_{1-3} alkyl, or taken together join to form cyclopentyl, cyclohexyl, cycloheptyl, or tetrahydropyranyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety: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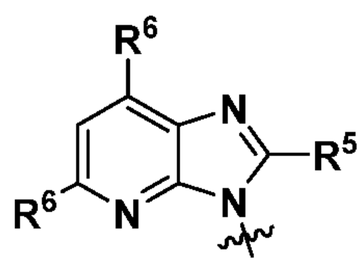
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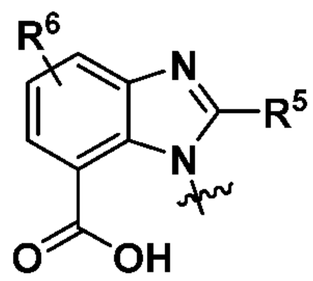
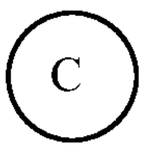


wherein R^6 is independently H or Me; and

R^5 is C_{1-2} alkyl, C_{1-2} haloalkyl, methoxymethyl, or cyclopropyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety:



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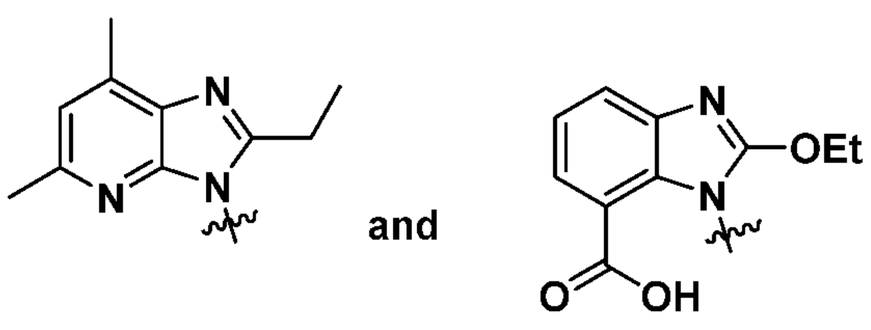

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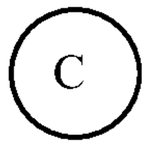
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety:



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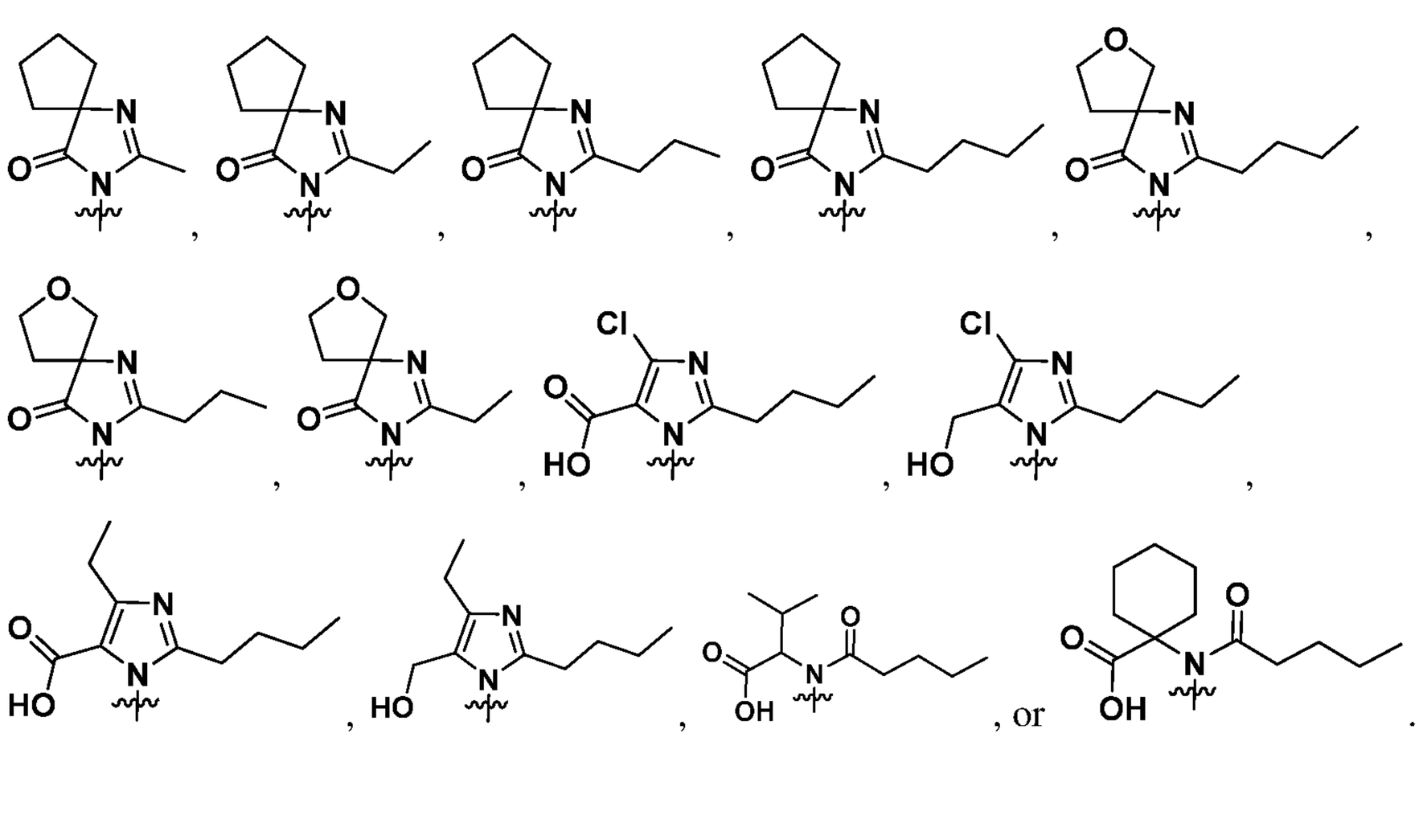

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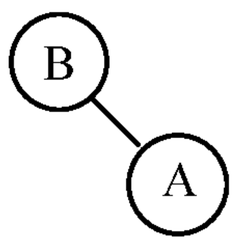
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or

solvates thereof, wherein the moiety is selected from phenyl, pyridyl, pyrimidinyl or pyrazinyl, and ring is phenyl or thiophenyl and R^{16} is as defined earlier.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety



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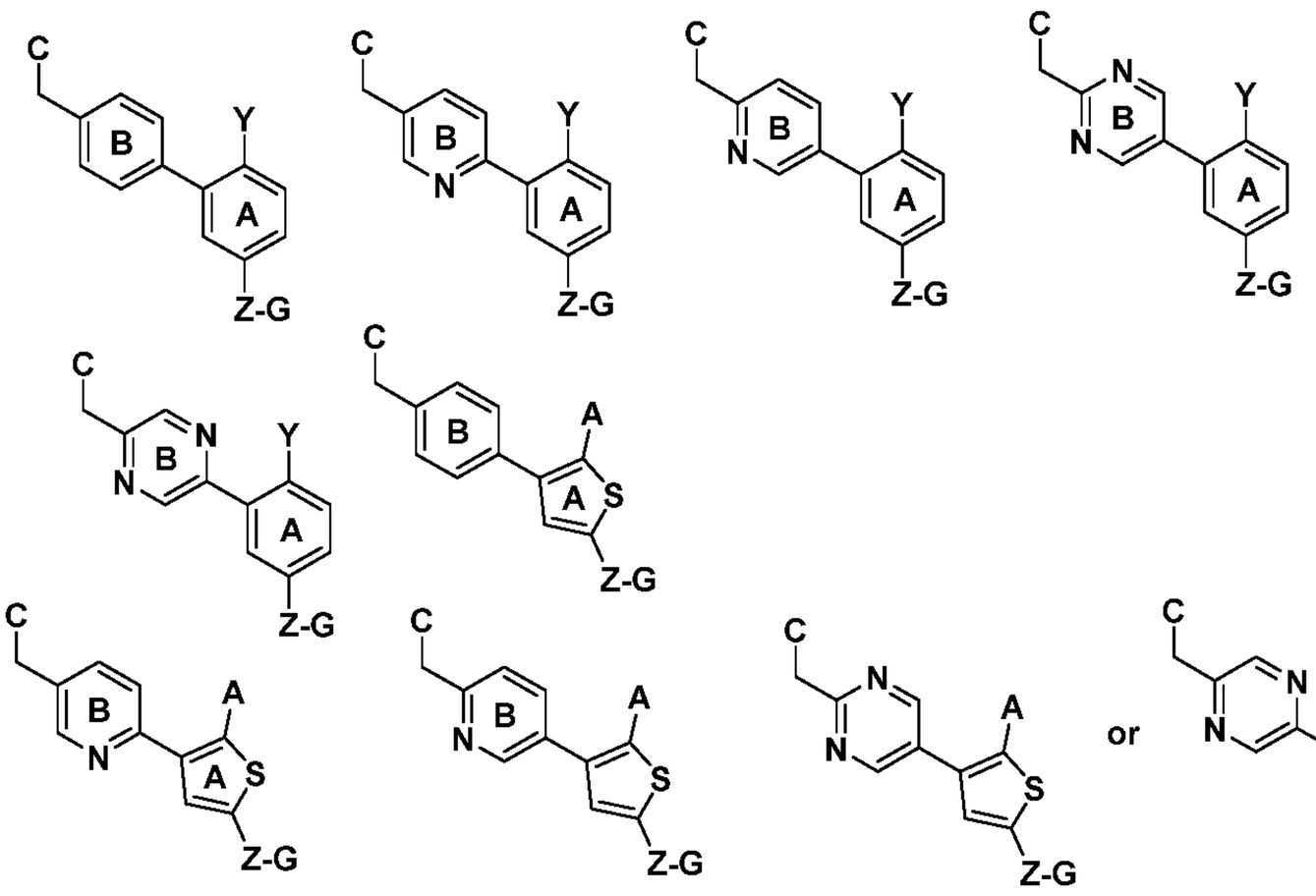
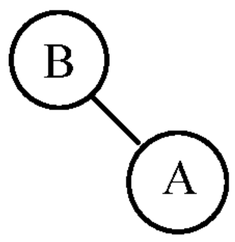


where rings B and A can be substituted with 0-4 substituents chosen independently from F, Cl, CN, methyl, ethyl, methoxy, or $OCHF_2$; and "C" indicates: .

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety



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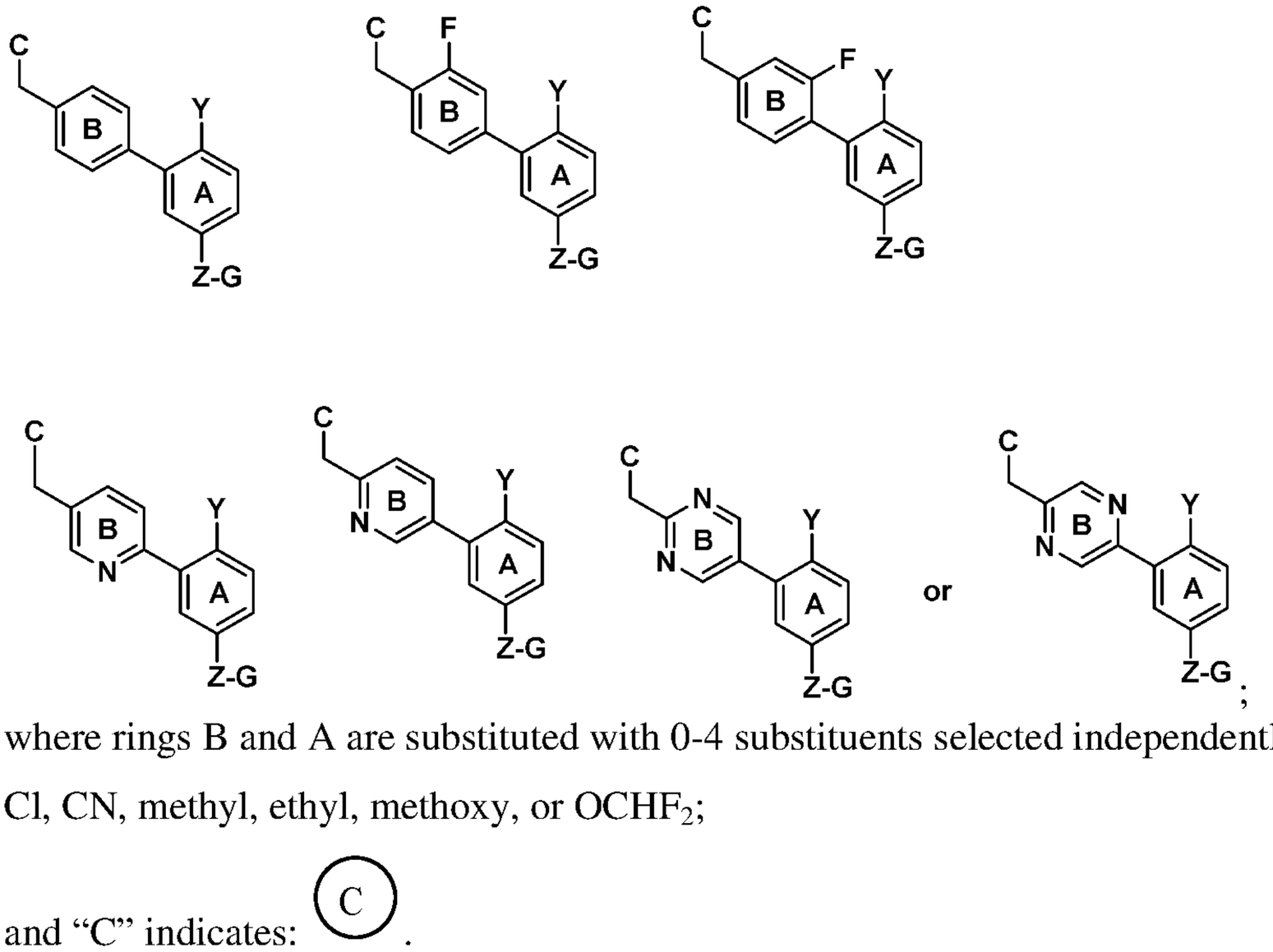
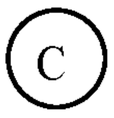


;

where rings B and A are substituted with 0-4 substituents selected independently from F, Cl, CN, methyl, ethyl, methoxy, or $OCHF_2$;

and "C" indicates: 

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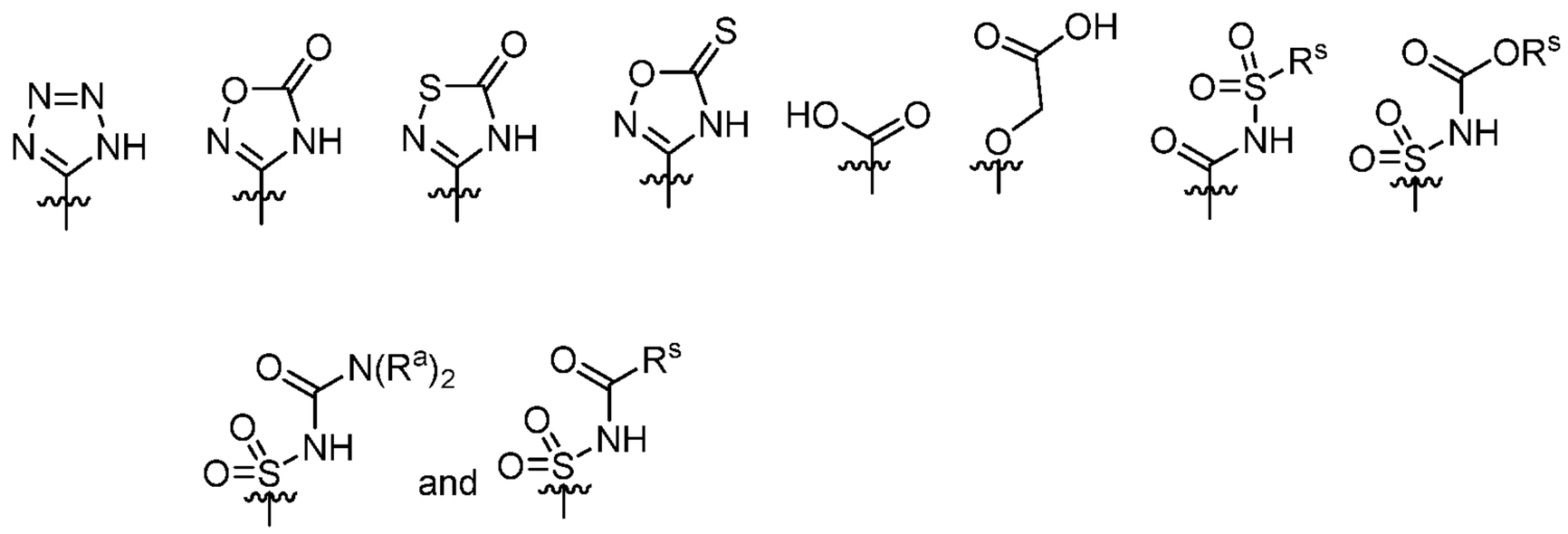
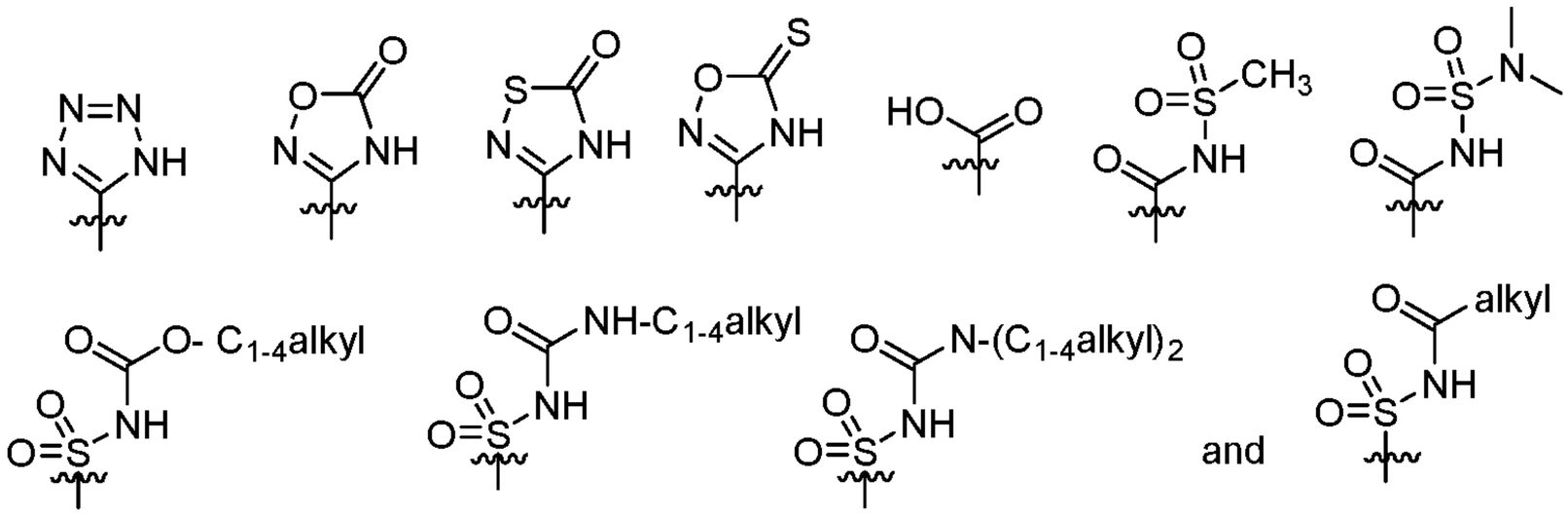
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety Y is selected from the following:



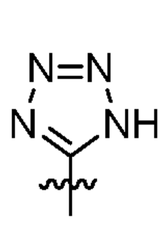
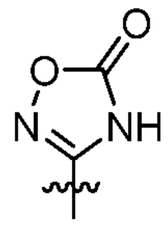
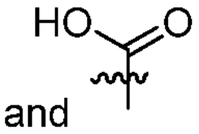
wherein R^a is, at each occurrence, independently selected from H, C1-C4-alkyl, C1-C4-haloalkyl, C1-C4-hydroxyalkyl, and C3-C6-cycloalkyl; and

R^s at each occurrence, is independently selected from H, C1-C6 alkyl, C1-C6-haloalkyl, C1-C6-hydroxyalkyl, C3-C7 cycloalkyl, C3-C7 cycloalkyl C1-C3 alkyl, C6-10 aryl, C6-10-aryl-C1-C6-alkyl , heteroaryl, heteroaryl-C1-C6-alkyl, heterocyclyl, heterocycle-C1-C6-alkyl, wherein the heteroaryl is a 5-10 membered group and the heterocycle is a 4-10 membered each having 1-3 heteroatoms selected from N, O, or S.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety Y is selected from the following:



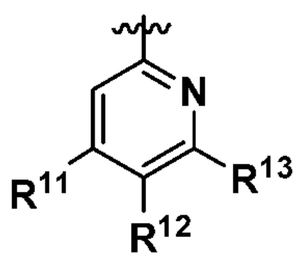
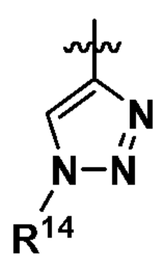
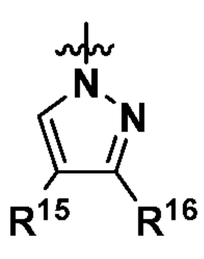
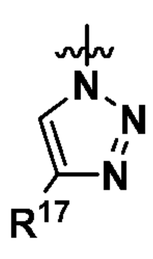
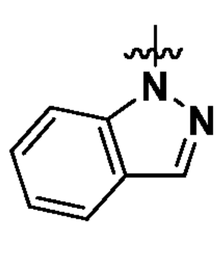
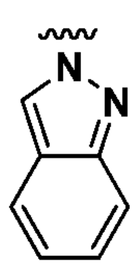
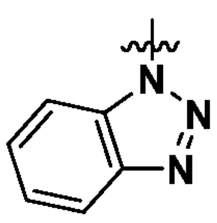
In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein the moiety Y is selected from the following:




and .

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z is a bond and the moiety Z-G is selected from the following: phenyl, pyridyl, pyrazolyl, triazolyl, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, thiazolyl, isothiazolyl and imidazolyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z is a bond and the moiety Z-G is selected from the following: phenyl, pyrid-2-yl, pyrid-3-yl, pyrazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-1-yl, indazol-1-yl, indazol-2-yl, benzotriazol-1-yl, tetrahydropyran-2-yl, tetrahydrofuran-2-yl, morpholin-2-yl, thiazol-2-yl, and isothiazol-3-yl, each said moiety being substituted with 0-3 substituents selected from F, Cl, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl, methoxyC_{1-2}alkyl, hydroxyC_{12}alkyl, and N(C_{1-2}alkyl)$_2$.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z is a bond and the moiety Z-G is selected from the following: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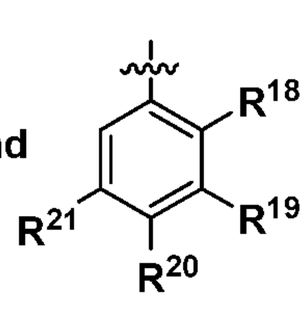

;

wherein

R^{11} is H, Cl, F, methyl, ethyl, cyclopropyl, methoxy, CHF_2, CF_3, CF_2CH_3, $OCHF_2$, $N(CH_3)_2$, or methoxymethyl;

R^{12} is H, Cl, F, methyl, methoxy, hydroxymethyl, CHF_2, or CF_3;

R^{13} is H, F, Cl, CH_3, CHF_2, CF_3, or methoxy;

R^{14} is methyl, ethyl, i-propyl, cyclopropylmethyl, cyclobutylmethyl, n-butyl, i-butyl, CH_2CH_2F, CH_2CHF_2, or hydroxyethyl;

R^{15} is H, methyl, CF_3, CHF_2, hydroxymethyl, or hydroxyethyl;

R^{16} is H, methyl, CF_3, or CHF;

R^{17} is methyl, ethyl, propyl, cyclopropyl, i-propyl or t-butyl;

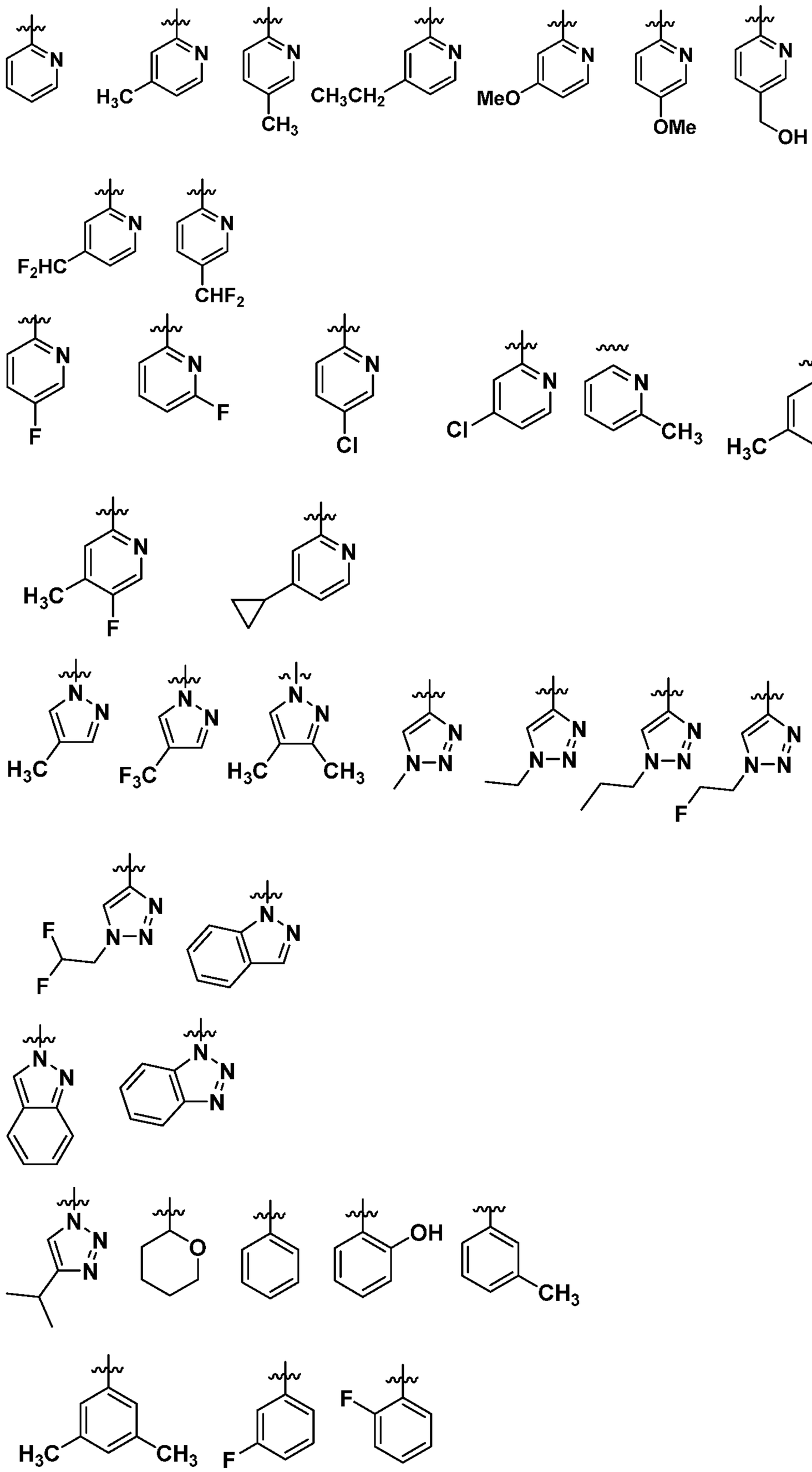
R^{18} is H, F, or OH;

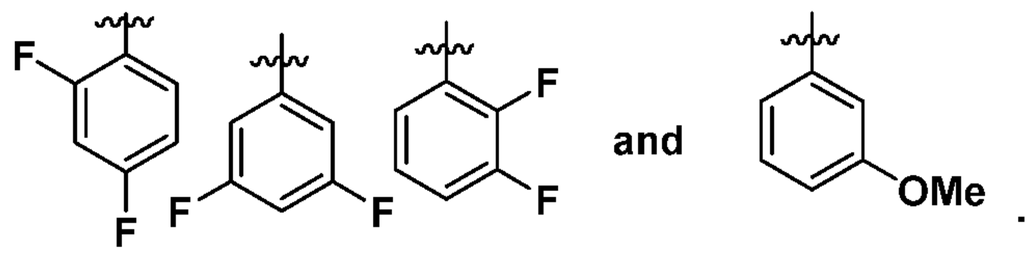
R^{19} is H, F, Cl, methyl, or methoxy;

R^{20} is H, or F; and

R^{21} is H, F, Cl, methyl, or methoxy.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z is a bond and the moiety Z-G is selected from the following:





In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein

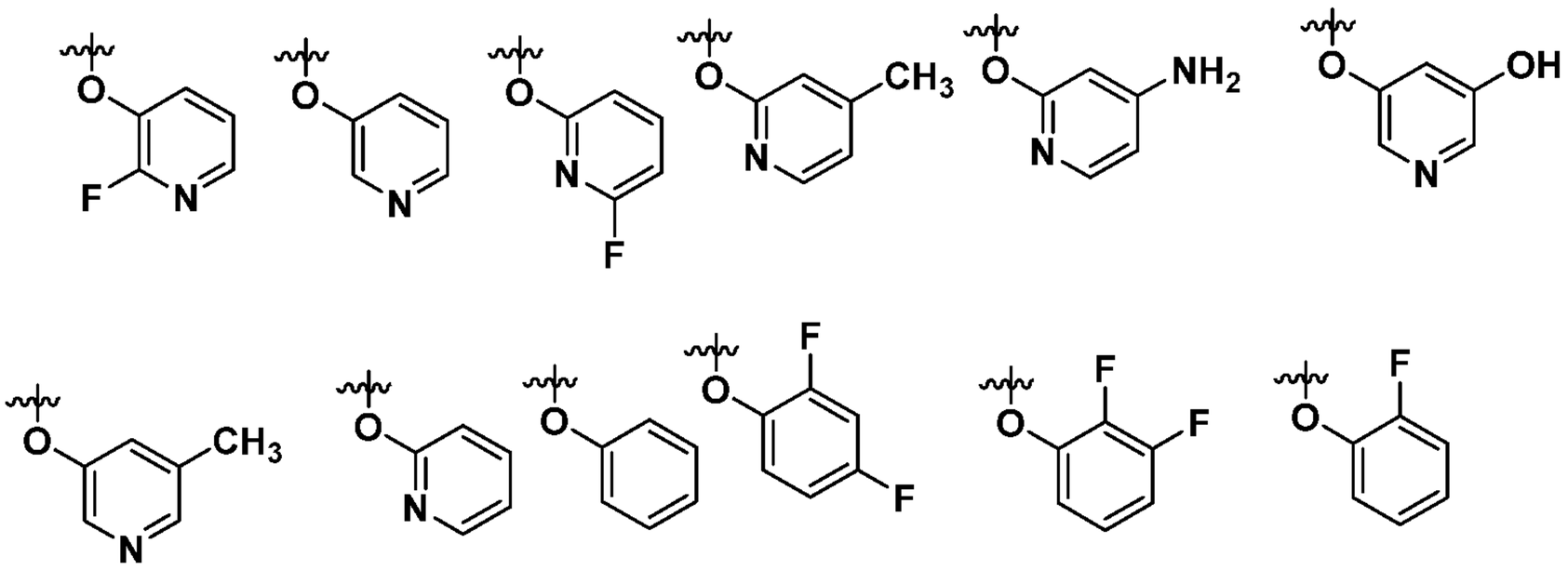
Z is O, N, or C=O;

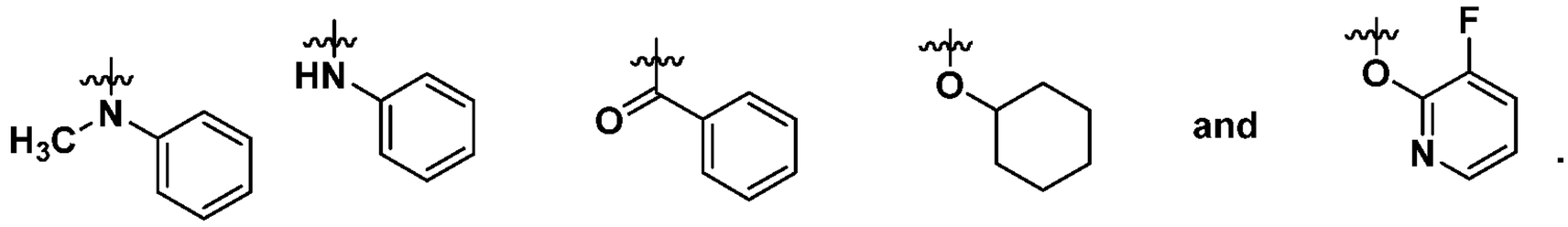
G is phenyl, pyridyl, or C_{3-7} cycloalkyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z is O, N, or C=O;

G is phenyl, pyrid-2-yl, pyrid-3-yl, cyclohexyl, cyclopentyl, each being substituted with 0-2 substituents selected from F, Cl, OH, NH_2, C_{1-3}alkyl, C_{1-3}alkoxy, and C_{1-2}fluoroalkyl.

In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein Z-G is selected from the following:





In another aspect, there are disclosed compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, including salts, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, hydrates, or solvates thereof, wherein: the compound is selected from Examples 1-462.

In another aspect, there is disclosed a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and any one or more compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, or a pharmaceutically acceptable salt thereof.

In another aspect, there is disclosed a method for the treatment or prophylaxis of one or more disease or disorder which can be modulated by biased agonism of the angiotensin II receptor, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of at least one of the compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, wherein the disease or disorder is heart failure with preserved ejection fraction, reduced ejection heart failure, and/or renal disease.

In another aspect, there is disclosed a method for the treatment or prophylaxis of one or more disease or disorder which can be modulated by biased agonism of the angiotensin II receptor, wherein the compound of any of the embodiments is administered in combination with at least one other type of therapeutic agent.

In another aspect, there is disclosed a method for the treatment or prophylaxis of multiple diseases or disorders, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of at least one of the compounds of Formula (I), or compounds of Formula (I) as described by any of the other embodiments or aspects, wherein the disease or disorder is heart failure with preserved ejection fraction, reduced ejection heart failure, and/or renal disease.

In another aspect, there is disclosed a method for the treatment or prophylaxis of diseases or disorders, wherein the compound of any of the embodiments is administered in combination with at least one other type of therapeutic agent. In another aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another aspect, the present invention provides a compound selected from any subset list of compounds within the scope of the tenth aspect.

In another embodiment, the compounds of the present invention have EC_{50} values $\leq$ 10 μM, in stimulating β-arrestin recruitment using the assays disclosed herein, preferably, EC_{50} values $\leq$ 5 μM, more preferably, EC_{50} values $\leq$ 1 μM, even more preferably, EC_{50} values $\leq$ 0.5 μM. Additionally, compounds of the present invention show efficacy in stimulating β-arrestin recruitment relative to AII of >30% Ymax, more preferably > 50 % Ymax, and even more preferably >70 % Ymax. Moreover, compounds of the present invention show activity in at least one of the three β-arrestin assays disclosed herein. Preferred compounds of the invention show activity in the BRET β-arrestin assay, and more preferred compounds of the invention show activity in the BRET β-arrestin low AT1R expression assay. Additionally, the compounds may stimulate Gq activity with efficacy (Ymax or Emax) less than 50% that of angiotensin II using the assays disclosed herein, preferably, Ymax $\leq$ 30%, more preferably Ymax $\leq$ 20%, even more preferably Ymax $\leq$10%. In addition, preferred compounds of the invention may show reduced potency (higher EC_{50}) in Gq signaling assays relative to β-arrestin assays. These compounds may also have ability to activate other AT1R-dependent G-protein signaling including: Gs isoforms, Gi isoforms, Go isoforms, G11 isoforms, G12 isoforms, G13 isoforms, and Gz isoforms.

II. OTHER EMBODIMENTS OF THE INVENTION

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

The present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent is, for example, angiotensin converting enzyme (ACE) inhibitor, β-adrenergic receptor blocker, neprilysin inhibitor, diuretic, aldosterone antagonist, Ca2+ channel blocker, nitrates and/or digitalis compound.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with angiotensin II biased agonism activity, or β-Arrestin agonism of the angiotensin II receptor, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

Examples of diseases or disorders associated with the activity of the AT1R and AII, or β-Arrestin agonists of the Angiotensin II Receptor, that can be prevented, modulated, or treated according to the present invention include, but are not limited to heart failure such as acute decompensated heart failure (ADHF), chronic heart failure, fibrosis, atrial fibrillation, coronary artery disease, peripheral vascular disease, atherosclerosis, renal disease, diabetes, obesity, metabolic syndrome, hypertension, pulmonary hypertension, cerebrovascular disorders and the sequelae thereof, cardiovascular disorders, angina, ischemia, stroke, myocardial infarction, acute coronary syndrome, reperfusion injury, angioplastic restenosis, vascular complications of diabetes and obesity.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of heart failure, coronary artery disease, cardiomyopathy, atrial fibrillation, and related conditions including but not limited to acute coronary syndrome, myocardial ischemia, hypertension, atherosclerosis, pulmonary hypertension, peripheral arterial disease, ischemia/reperfusion injury, angina, renal disease,

Examples of diseases or disorders associated with the activity of the biased agonism, or β-Arrestin agonism of the angiotensin II receptor, that can be prevented, modulated, or treated and/or prophylaxis according to the present invention include, but are not limited to HFpEF, HFrEF, and renal disease.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, and renal disease, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of renal disease, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of heart failure with preserved ejection fraction, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of reduced ejection fracton heart failure, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a compound of the present invention for use in therapy.

In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment and/or prophylaxis of multiple diseases or disorders associated with biased agonism, or β-Arrestin agonism of the angiotensin II receptor.

In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with biased agonism, or β-Arrestin agonism of the Angiotensin II Receptor.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with biased agonism, or β-Arrestin agonism of the angiotensin II receptor, comprising administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention. Preferably, the second therapeutic agent, for example ACEi (e.g. enalapril) or a selected inotropic agent such as β-adrenergic agonist (for example dobutamine) or other therapeutically relevant agent that elevates natriuretic peptide levels such as a neprilysin inhibitor (for example, sacubitril).

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with AT1R and angiotensin II.

In another embodiment compounds within the present invention may be utilized alone or in combination with additional therapeutic agents described herein for the treatment of various conditions associated with heart failure: heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, acute decompensated heart failure, fibrotic disease. Additionally the compounds presented within the present invention may be used alone or in combination with additional therapeutic agents described herein as either acute, sub-acute or chronic therapy.

Where desired, the compound of the present invention may be used in combination with one or more other types of cardiovascular agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of cardiovascular agents that may be optionally employed in combination with the biased agonist of the angiotensin II receptor of the present invention may be one, two, three or more cardiovascular agents administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

The compounds of the present invention may be employed in combination with additional therapeutic agent(s) selected from one or more, preferably one to three, of the following therapeutic agents: anti-hypertensive agents, ACE inhibitors, mineralocorticoid receptor antagonists, calcium channel blockers, β-adrenergic receptor blockers, diuretics, vasorelaxation agents such as nitrates, inotropic agents, digitalis compounds, anti-atherosclerotic agents, anti-dyslipidemic agents, anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-thrombotic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-ischemic agents, anti-obesity agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-

hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, cognition promoting agents, appetite suppressants, agents for treating heart failure, agents for treating peripheral arterial disease, agents for treating malignant tumors, and anti-inflammatory agents.

In another embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of the following therapeutic agents in treating heart failure: ACE inhibitors, β-blockers, diuretics, mineralocorticoid receptor antagonists, renin inhibitors, calcium channel blockers, nitrates, digitalis compounds, inotropic agents, APJ receptor agonists, relaxin receptor agonists, formyl peptide receptor 2 agonists/biased agonists, nitroxyl donors and neprilysin inhibitors.

The present invention may be embodied in other specific forms without parting from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or Z- and E-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by

synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For examples, "C_1 to C_{12} alkyl" or "C_{1-12} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12} alkyl groups; "C_4 to C_{18} alkyl" or "C_{4-18} alkyl" (or alkylene), is intended to include C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene),

is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

When the term "hydrocarbon chain" is used, it is intended to include "alkyl", "alkenyl" and "alkynyl", unless otherwise specified.

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

"Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy,

2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. For example, "C_3 to C_6 cycloalkyl" or "C_{3-6} cycloalkyl" is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

As used herein, "carbocycle", "carbocyclyl", or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, indanyl, and tetrahydronaphthyl. When the term "carbocycle" is used, it is intended to include "aryl." A bridged ring occurs when one or more, preferably one to three, carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two

fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

"Aryl" groups refer to monocyclic or bicyclic aromatic hydrocarbons, including, for example, phenyl, and naphthyl. Aryl moieties are well known and described, for example, in Lewis, R.J., ed., *Hawley's Condensed Chemical Dictionary*, 15th Edition, John Wiley & Sons, Inc., New York (2007). "C_{6-10} aryl" refers to phenyl and naphthyl.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl,

benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 1,3-dioxol-2-one, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1*H*-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl,

1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

Examples of 5- to 6-membered heteroaryls include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n=0-4 and m=0-4) and the like.

When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007) and *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl

(Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Compounds of the Formula (I) and/or the Examples herein may in some cases form salts which are also within the scope of this invention. Reference to a compound of the Formula (I) and/or Examples herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Allen, Jr., L.V., ed., *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

"Base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. In one aspect, inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. In another aspect, organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Acid addition salts" and "base addition salts" which are not pharmaceutically acceptable may be useful in the preparation and/or purification of the compounds.

The present invention is intended to cover the compounds in their neutral state, salts of those compounds, or mixtures of the compounds in their neutral state with one or more salt forms, or mixtures of salt forms.

In addition, compounds of Formula (I) may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of Formula

(I)) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", Krosgaard-Larsen, P. et al., eds., *A Textbook of Drug Design and Development*, pp. 113-191, Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and

f) Rautio, J., ed., *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol. 47, Wiley-VCH (2011).

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield Formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of Formula (I) include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (2nd Edition, reproduced (2006)); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and

Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, 3rd Edition, Academic Press, San Diego, CA (2008).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Deuterium has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium can be represented by symbols such as "^{2}H" or "D". The term "deuterated" herein, by itself or used to modify a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. Isotopes of carbon include ^{13}C and ^{14}C.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $S(O)_2H$, or S(O)H group.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates.

OTHER DEFINITIONS

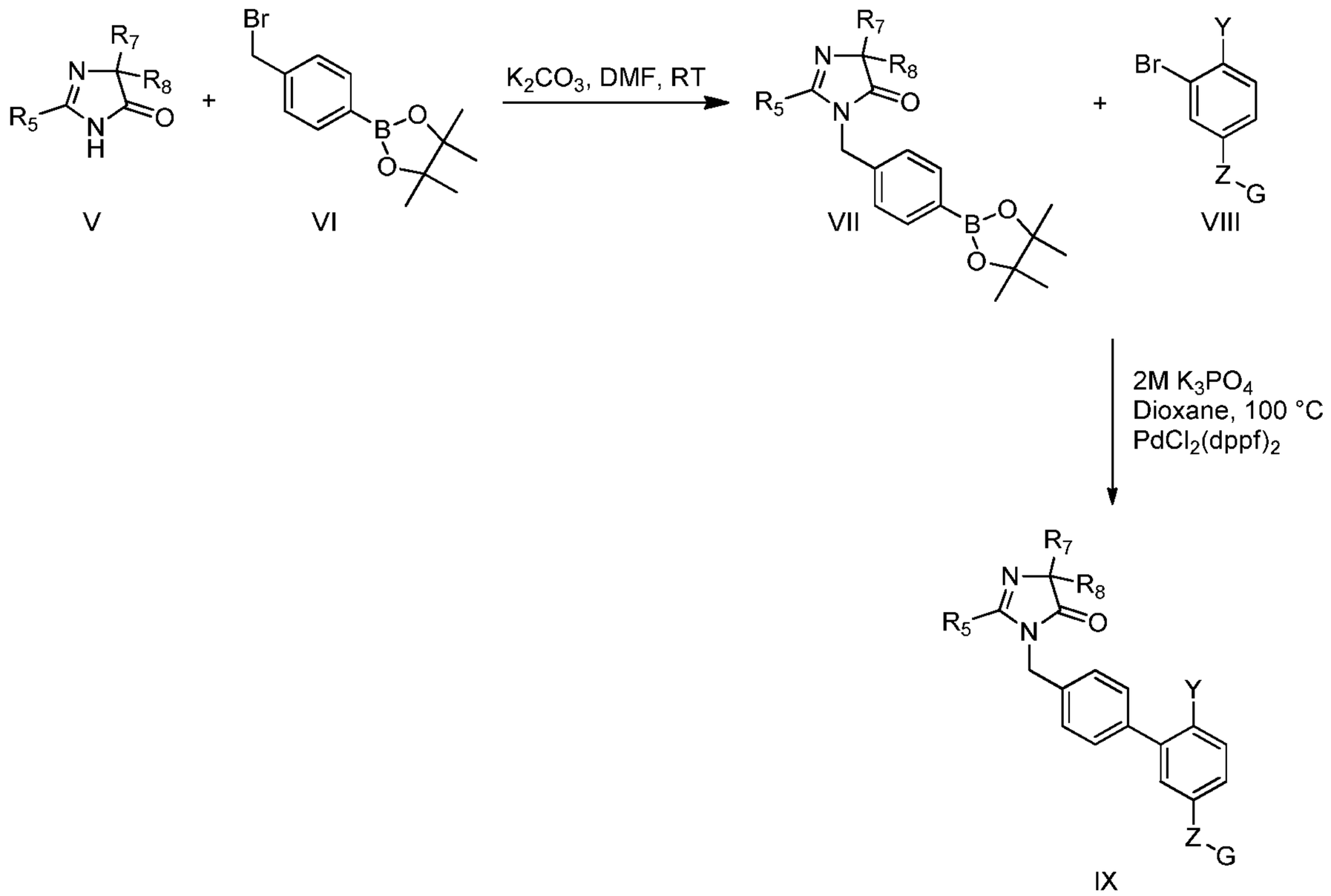
Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "ºC" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "aq" for "aqueous", "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee" are stereochemical designations familiar to one skilled in the art.

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

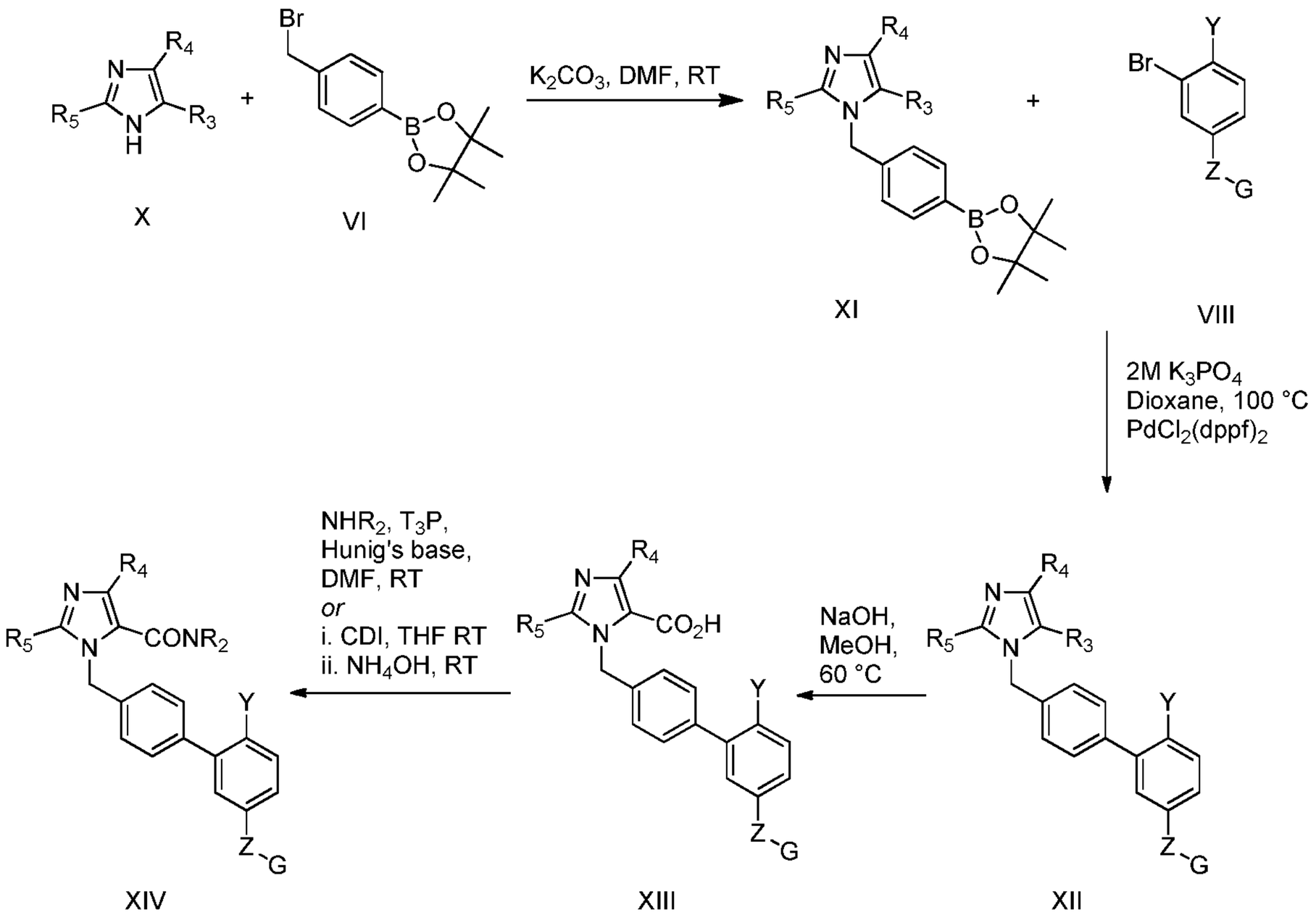
The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); Smith, M.B. et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. 6th Edition, Wiley & Sons, New York, NY (2007); Katritzky, A.R. et al, eds., *Comprehensive Organic Functional Groups Transformations II*, 2nd Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1999), and references therein.

Imidazolone biphenyl compounds with general structure IX may be prepared according to the synthetic scheme shown below. Thus, a functionalized imidazolone is alkylated with benzyl bromide VI using a base such as K_2CO_3 to form a boronate with general structure VII. Boronate VII is then reacted with a phenylbromide with general structure VIII in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form imidazolone biphenyl compounds with general structure IX.

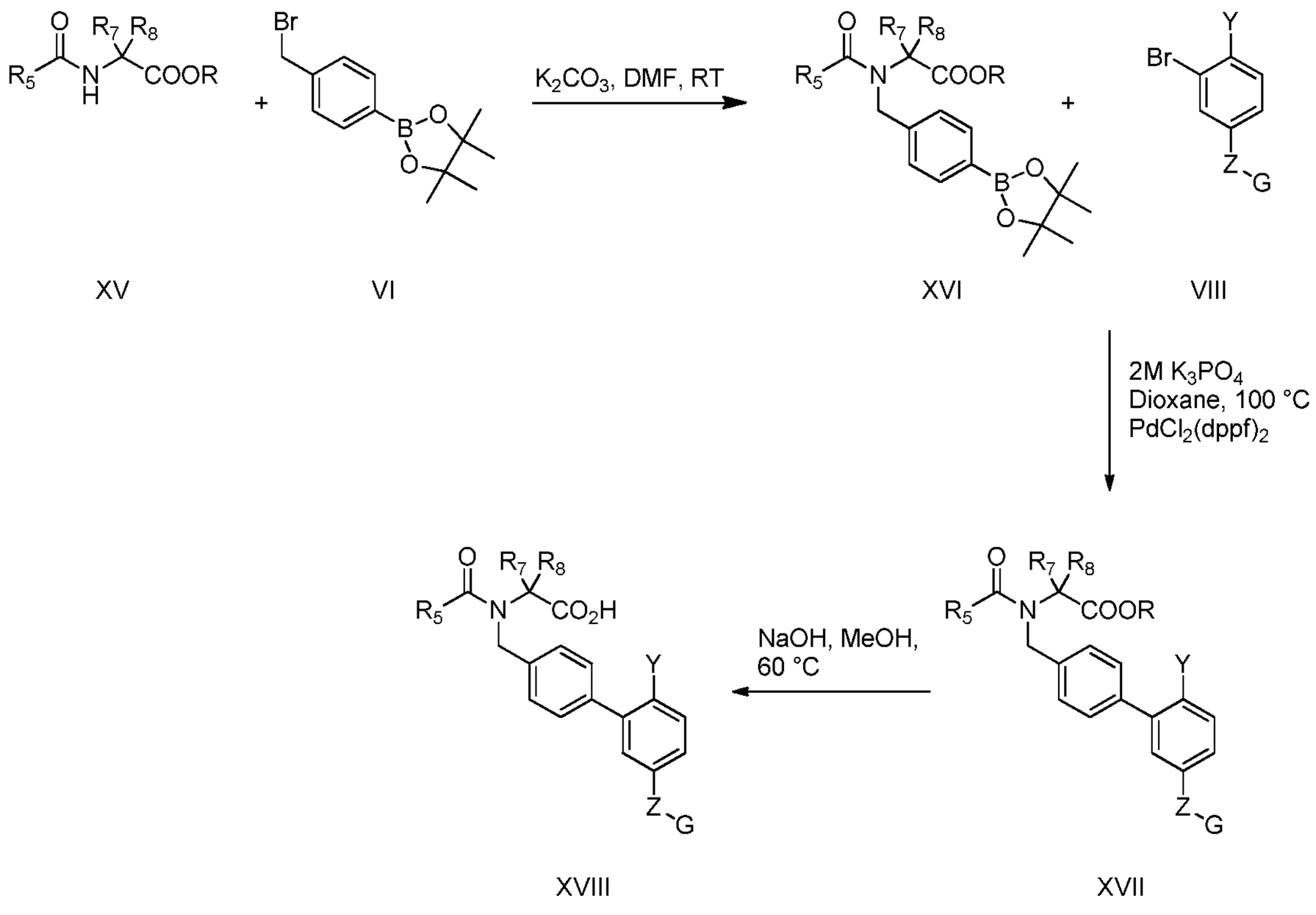


Imidazole biphenyl compounds with general structure XII, XIII and XIV may be prepared with the following scheme. Thus, a functionalized imidazole is alkylated with benzyl bromide VI using a base such as K_2CO_3 to form a boronate with general structure XI.

Boronate XI is then reacted with phenyl bromide with general structure VIII in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form biphenyl compounds with general structure XII. When R_3 is an ester, the ester may be hydrolyzed using NaOH in MeOH at 60 °C to form the free acid XIII. Free acid XIII may then be converted to an amide using T3P, Hunig's base, NHR_2 in DMF to form secondary and tertiary amides or CDI and NH_4OH to form the primary amide.



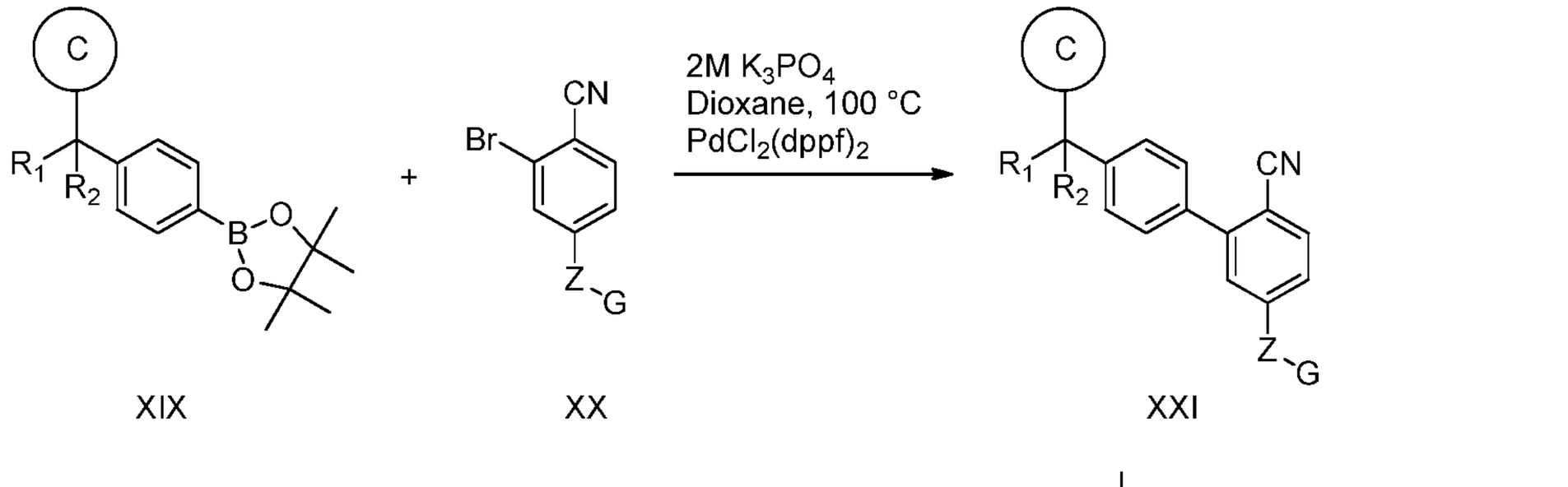
Biphenyl alpha-amido carboxylic acid with general structure XVIII may be prepared with the following scheme. Thus, a functionalized alpha-amido ester with general structure XV may be alkylated with benzyl bromide VI using a base such as K_2CO_3 to form a boronate with general structure XVI. Alkylated alpha-amido ester XVI may then be reacted with a phenylbromide with general structure VIII in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form compounds with general structure XVII. The ester may be hydrolyzed using NaOH in MeOH at 60 °C to form the free acid with general structure XVIII.



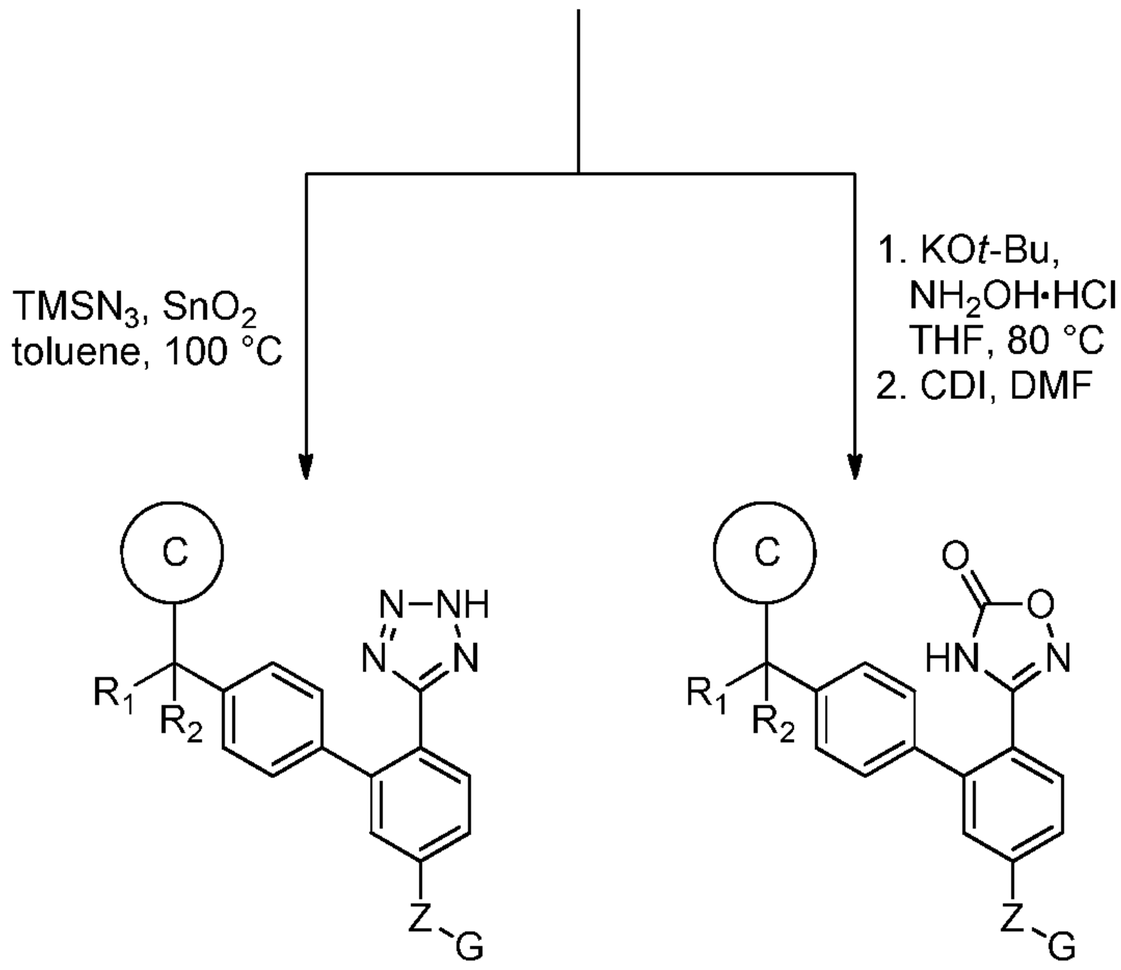
XV VI XVI VIII

XVIII XVII

Biphenyl tetrazoles with general structure XXII and biphenyl oxadiazolones with general structure XXIII may be prepared with the following scheme. Thus, boronates with general structure XIX may be reacted with a bromophenyl nitrile with general structure XX in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form biphenyl nitrile with general structure XXI. The biphenyl nitrile may then be reacted with TMS-azide, dibutyltin oxide in toluene at 100 °C to form biphenyl tetrazole with general structure XXII. The biphenyl nitrile may also be reacted with KO*t*-Bu, hydroxylamine hydrochloride in THF, followed by CDI to form biphenyl oxadiazolone with general structure XXIII.

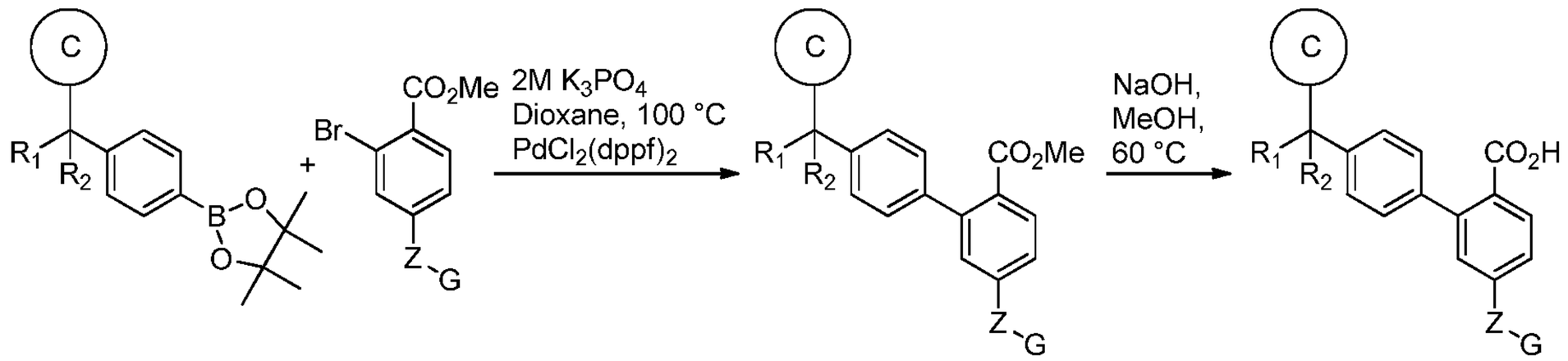


XIX XX XXI



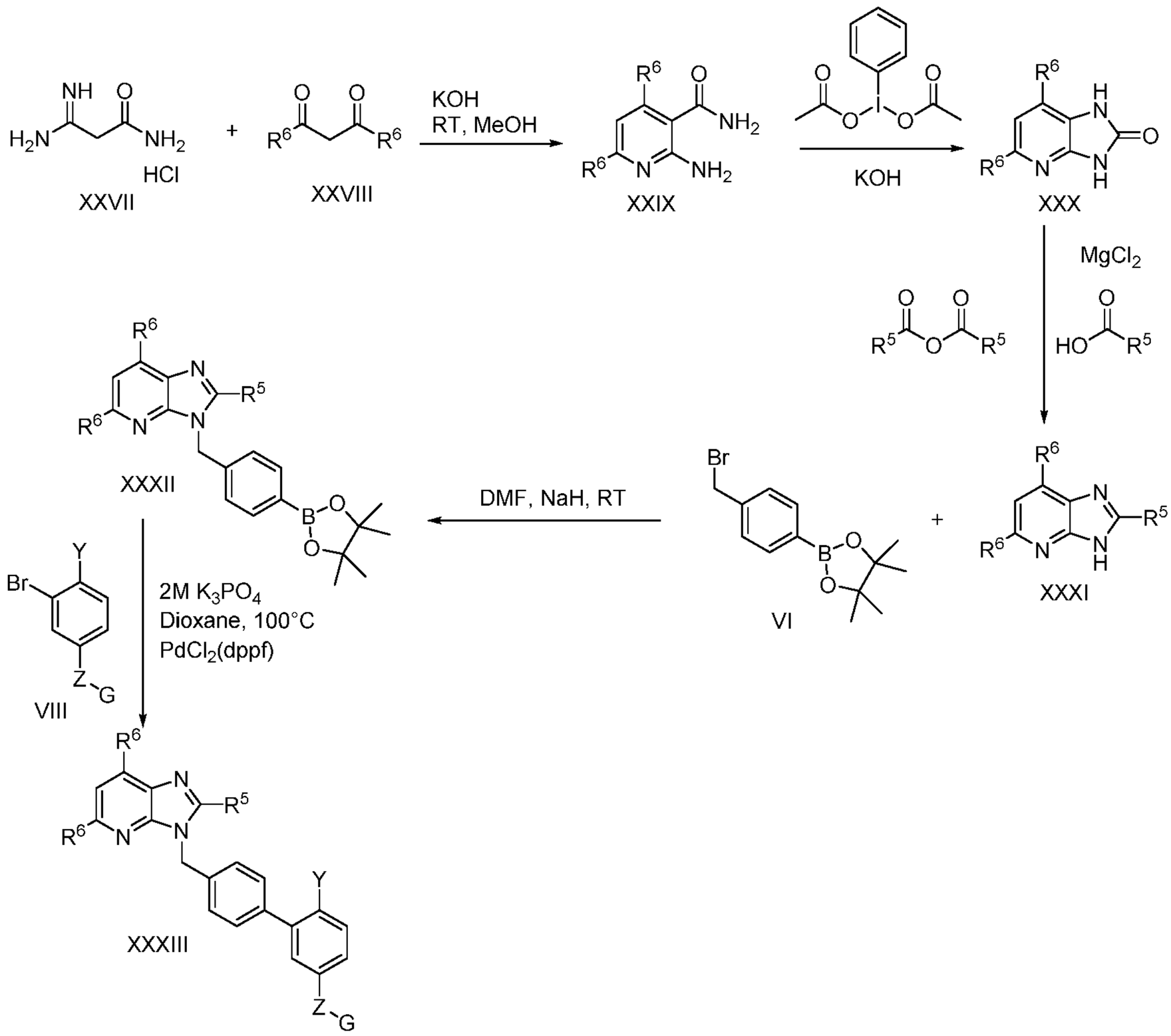
XXII XXIII

Biphenyl acids with general structure XXVII may be prepared according to the following scheme. Thus, boronates with general structure XIX may be reacted with a bromophenyl ester with general structure XXIV in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form biphenyl ester with general structure XXV. The biphenyl ester may then be hydrolyzed with NaOH in MeOH at 100 °C to form biphenyl acid with general structure XXVI.

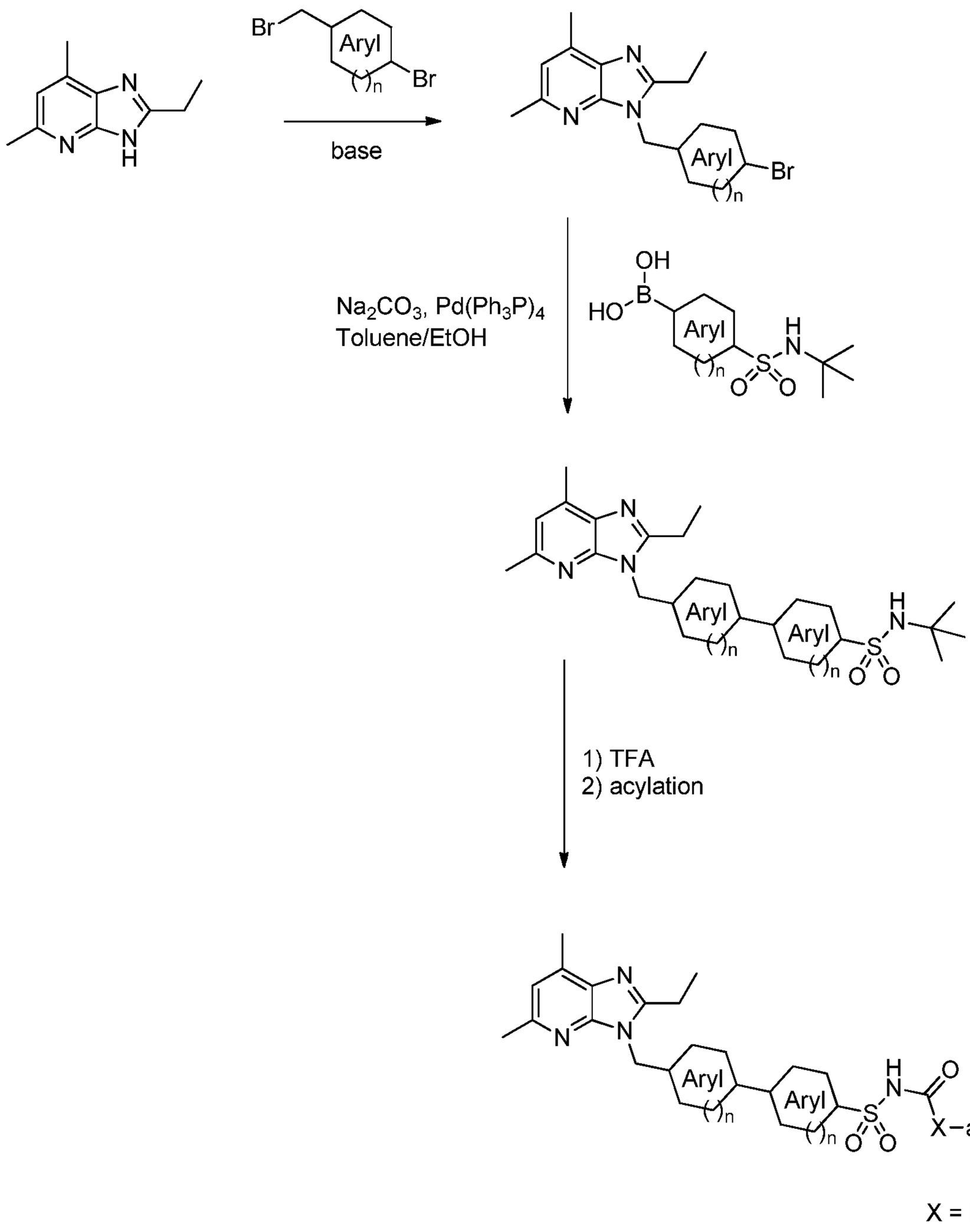


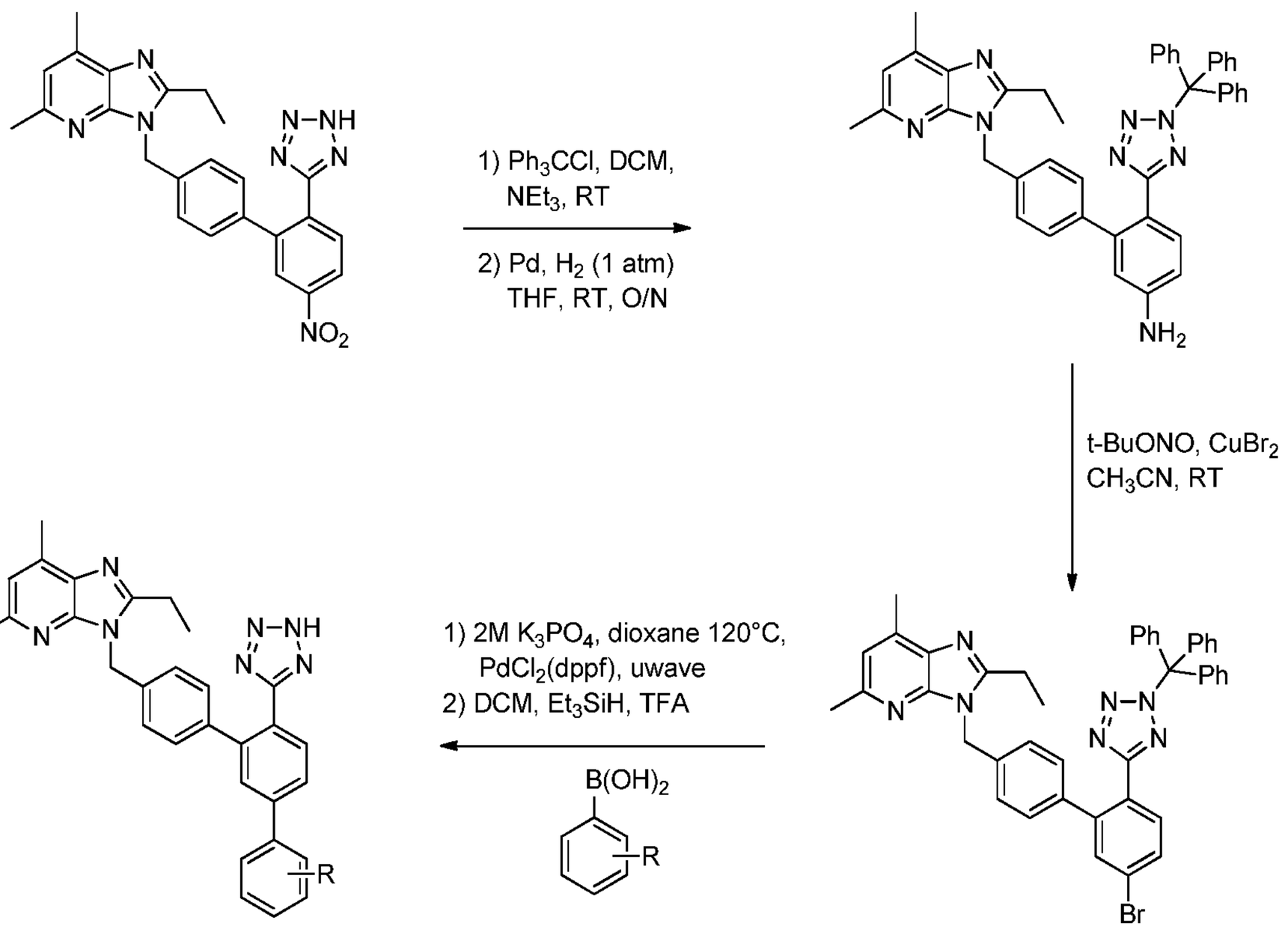
XIX XXIV XXV XXVI

Imidazopyridines may be prepared according the synthetic scheme shown below. Thus, a functionalized amidine XXVII is condensed with diketone XXVIII to afford the desired pyridine XXIX. This core then undergoes an oxidative cyclization followed by condensation with an acid derivative to furnish the imidazopyridineXXXI. This imidazopyridine is then alkylated with a boronic ester intermediate VI to give boronic ester XXXII. Subsequent Suzuki cross coupling with substituted arene VIII affords biaryl XXXIII.

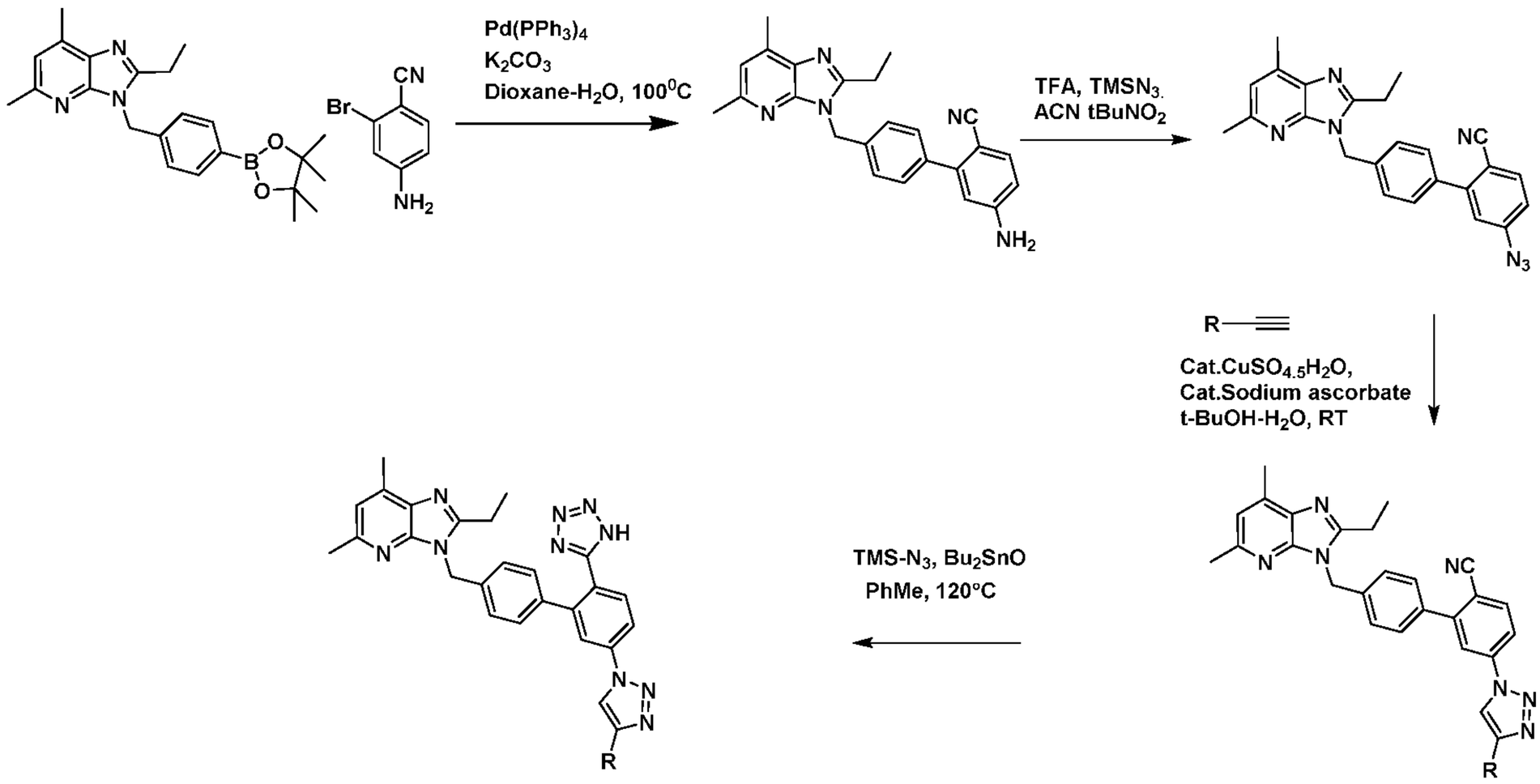


General synthetic pathway to access to the biarylacid imidazopyridine analogs: The imidazopyridine headpiece previously synthesized can also be alkylated with an aryl bromide which allows for Suzuki cross-coupling with a variety of substituted boronic acids containing a protected t-butyl-sulfonamide moiety. The t-butyl group can be subsequently removed to allow for further functionalization of the sulfonamide, thus providing the examples shown below.

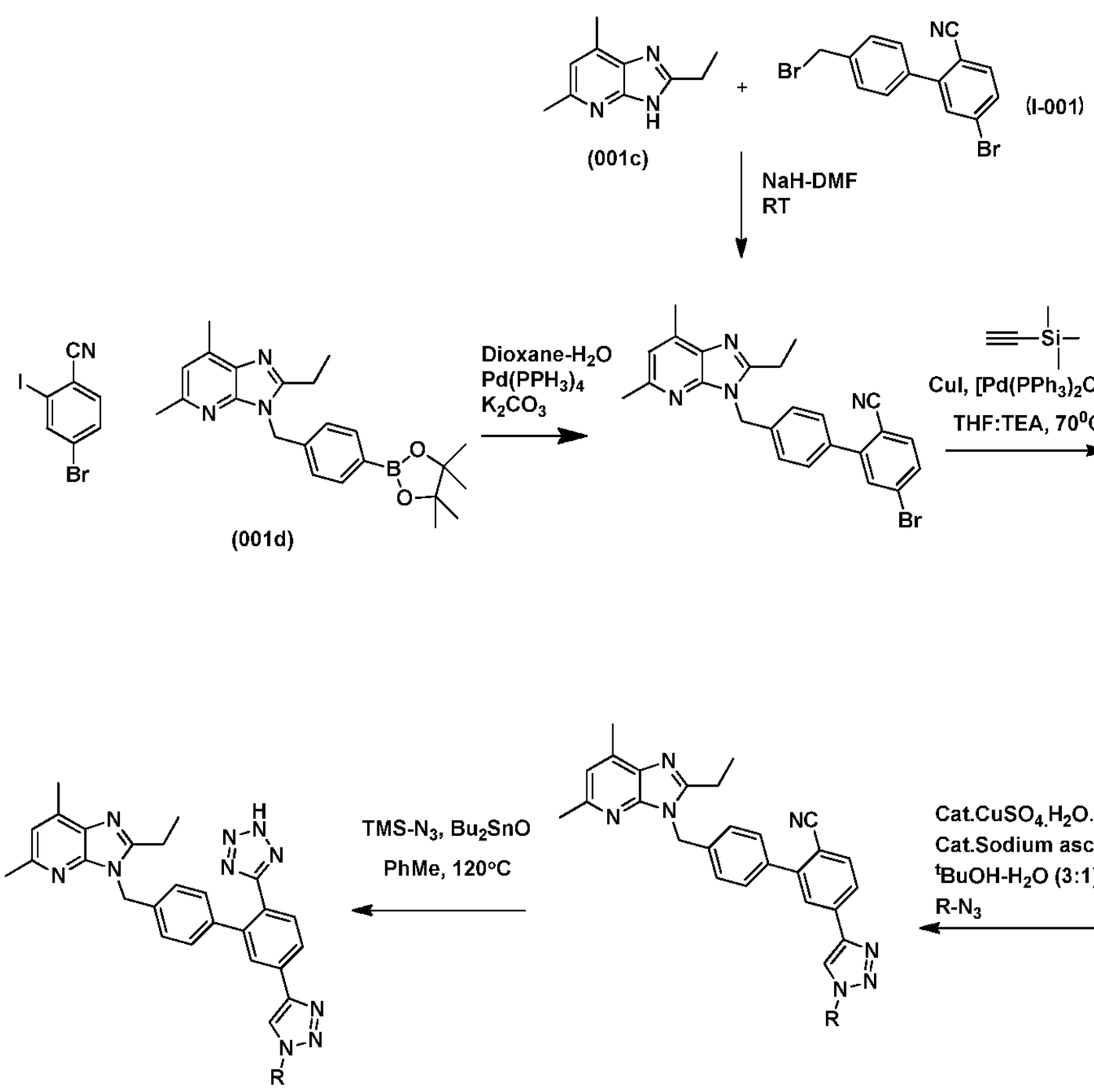

Br
Aryl
Br
base
N
N
H
N
N
Aryl
Br
Na_2CO_3, $Pd(Ph_3P)_4$
Toluene/EtOH
OH
B
HO
Aryl
H
N
S
O
O
1) TFA
2) acylation
Aryl
Aryl
X–alkyl
X = NH, O



Compounds in which the Z-G group is an N-linked 1,2,3-triazole can be synthesized using the route shown in the scheme below:



Compounds in which the Z-G group is a C-linked 1,2,3-triazole can be synthesized using the route shown in the scheme below:

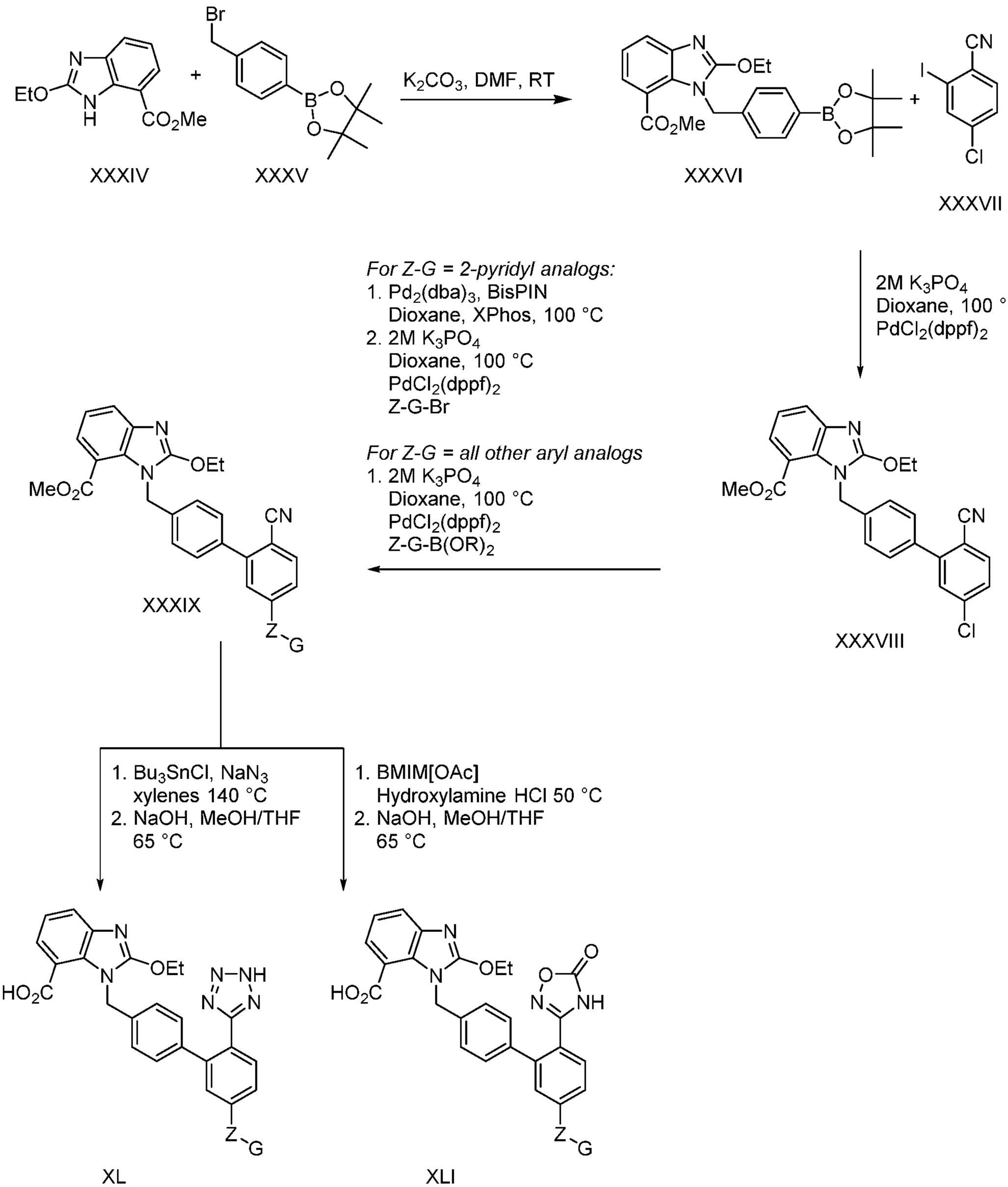


Benzimidazole compounds with general structure XL and XLI may be prepared with the following scheme. Thus, benzimidazole XXXIV is alkylated with benzyl bromide XXXV using a base such as K_2CO_3 to form a boronate XXXVI. Boronate XXXVI is then reacted with iodobenzonitrile XXXVII in a Suzuki reaction using conditions such as 2M K_3PO_4, dioxane, $PdCl_2(dppf)_2$ at 100 °C to form biphenyl compound XXXVIII.

For analogs in which Z-G is a substituted 2-pyridyl group, XXXVIII is reacted with BisPIN $Pd_2(dba)_3$ and Xphos in dioxane at 100 °C to form a boronate which is then reacted with a substituted 2-pyridyl bromide Z-G-Br using conditions such as $PdCl_2(dppf)_2$ and 2M K_3PO_4 in dioxane, at 100 °C to form nitrile XXXIX.

For analogs in which Z-G is not a substituted 2-pyridyl group, XXXVIII is reacted with a boronate or boronic acid Z-G-$B(OR)_2$ using conditions such as $PdCl_2(dppf)_2$ and 2M K_3PO_4 in dioxane, at 100 °C to form nitrile XXXIX.

Nitrile XXXIX can then be reacted with Bu_3SnCl, NaN_3 in xylenes at 140 °C followed by NaOH in MeOH/THF at 65 °C to form compounds with general structure XL. Alternatively, XXXIX can be reacted with BMIM[OAc], hydroxylamine HCl at 50 °C followed by NaOH in MeOH/THF at 65 °C to form compounds with general structure XLI.


Br
EtO
N
N
H
CO2Me
XXXIV
XXXV
K2CO3, DMF, RT
OEt
CN
I
Cl
XXXVI
XXXVII
2M K3PO4
Dioxane, 100 °
PdCl2(dppf)2
XXXVIII
For Z-G = 2-pyridyl analogs:
1. Pd2(dba)3, BisPIN
Dioxane, XPhos, 100 °C
2. 2M K3PO4
Dioxane, 100 °C
PdCl2(dppf)2
Z-G-Br
For Z-G = all other aryl analogs
1. 2M K3PO4
Dioxane, 100 °C
PdCl2(dppf)2
Z-G-B(OR)2
MeO2C
XXXIX
Z
G
1. Bu3SnCl, NaN3
xylenes 140 °C
2. NaOH, MeOH/THF
65 °C
1. BMIM[OAc]
Hydroxylamine HCl 50 °C
2. NaOH, MeOH/THF
65 °C
HO2C
N–NH
O
NH
XL
XLI

EXAMPLES

The following compounds of the invention have been prepared, isolated and characterized using the methods disclosed herein. They demonstrate a partial scope of the invention and are not meant to be limiting of the scope of the invention. In the experimental procedures, solution ratios express a volume relationship, unless stated otherwise. NMR chemical shifts (δ) are reported in parts per million (ppm). Products were purified by reverse phase preparative HPLC and analyzed by reverse phase analytical LC-MS and HPLC using the following methods:

Method A1: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 ACN:H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN:H_2O with 10 mM NH_4OAc; Temperature: 50°C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: MS and UV at 220 nm.

Method A2: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μm particles; Mobile Phase A: H_2O with 0.05% TFA; Mobile Phase B: ACN with 0.05% TFA; Gradient: 2-98% B over 1 minute, then a 0.5 minute hold at 98% B; Flow: 0.8 mL/min; Detection: MS and UV at 220 nm.

Method A3: Column: Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 ACN:H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN:H_2O with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

Method A4:Column: Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 ACN:H_2O with 0.1 % trifluoroacetic acid; Mobile Phase B: 95:5 ACN:H_2O with 0.1 % trifluoroacetic acid; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

Method A5: Column: Phenomenex Luna C18 4.6 x 50 mm: Mobile Phase A: 10:90 MeOH:H_2O with 0.1 % trifluoroacetic acid; Mobile Phase B: 90:10 MeOH:H_2O with 0.1 % trifluoroacetic acid; Gradient: 0 % B to 100 % B over 2 min, then a 1 min hold at 100 %B; Flow: 4 mL/min; Detection: MS and UV (220 nm).

Method B: Column Zorbax XDB-C18, 4.6 x 30 mm, 3.5 micron; Mobile Phase A: 5/95/0.05 MeOH/H_2O/TFA; Mobile Phase B: 95/5/0.05 MeOH/H_2O/TFA, gradient: 100% A to 100% B in 2 min then hold 100% B for 2 min, flow rate 3 mL/min, monitoring absorbance at 220 nm and 254 nm.

Method C: Column: Kinetex C18, 21.2 x 100 mm, 5 micron; Mobile Phase A: 5/95/0.05 MeOH/H_2O/TFA; Mobile Phase B: 95/5/0.05 MeOH/H_2O/TFA. Gradient: 3-minute at 30% B, then 30-100% B over 7 minutes and a 5-minute hold at 100% B; Flow: 20 mL/min; stop time at 15 minutes, monitoring absorbance at 220 nm and 254 nm.

Method D: Kinetex C18, 21 x 100 mm, 5 micron; Mobile Phase A: 5/95/0.1 MeOH/H_2O/HCO_2H; Mobile Phase B: 95/5/0.1 MeOH/H_2O/HCO_2H. Gradient: 3 minute at 30% B, then 30-100% B over 7 minutes and 5 minutes hold at 100% B; Flow: 20 mL/min; stop time 15 minutes, monitoring absorbance at 220 nm and 254 nm.

Method E: C18 Phenomenex Luna AXIA column 30 x 100 mm, 5 micron; Mobile Phase A: 10% MeOH- 90% H_2O - 0.1% TFA; Mobile Phase B: 90% MeOH- 10% H_2O - 0.1% TFA. Gradient: 20-100% B in 10 min; then 100%B in 2 min with a flow rate of 40 mL/min; stop time 12 minutes, monitoring absorbance at 220 nm and 254 nm.

Method F: Column: Kinetex C18, 21.2 x 100 mm, 5 micron; Mobile Phase A: 5/95/0.05 MeOH/H_2O/TFA *or* 5/95/0.1 MeOH/H_2O/ HCO_2H; Mobile Phase B: 95/5/0.05 MeOH/H_2O/TFA *or* 95/5/0.1 MeOH/H_2O/ HCO_2H. Gradient: 0.5 minute at 50% B, then 50-100% B over 8 minutes and a 2.5 minutes hold at 100% B; Flow: 20 mL/min; stop time at 11 minutes, monitoring absorbance at 220 nm and 254 nm.

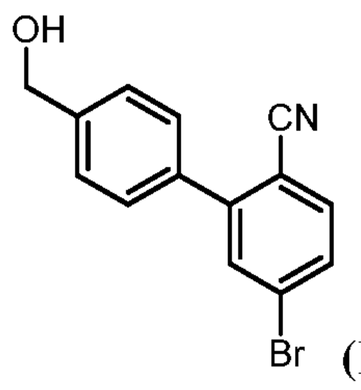
Method G: Column: XBridge C18, 19 x 200 mm, 5 micron; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 10-50% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min., monitoring absorbance at 220 nm and 254 nm.

Method H: Column Kinetex C18, 3.0 x 30 mm, 2.6 micron; Mobile Phase A: 5/95/0.1 MeOH/H_2O/AcOH; Mobile Phase B: 95/5/0.1 MeOH/H_2O/AcOH. Gradient: 100% A to 100% B over 0.5 min, then hold at 100% B for 1.5 min; Flow: 1.5 mL/min; stop time at 2 minutes, monitoring absorbance at 220 nm and 254 nm.

Method I: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 11-51% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.

Method J: Column: Kinetex-C18, 3.0 x 30 mm, 2.6 m particles; Mobile Phase A: 5:95 MeOH:H_2O with 0.1% AcOH; Mobile Phase B: 95:5 MeOH:H_2O with 0.1% AcOH; Gradient: 0-100% B over 2 minutes, flow 1.5 mL/min; Detector wavelength= 220 nm and 254 nm

Common Intermediate I-001: 5-bromo-4'-(hydroxymethyl)-[1,1'-biphenyl]-2-carbonitrile

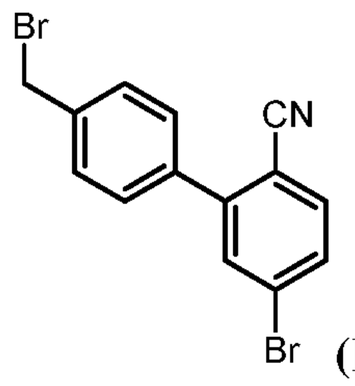


(I-001)

To a solution of (4-(hydroxymethyl)phenyl)boronic acid (400 mg, 2.6 mmol), 4-bromo-2-iodobenzonitrile (800 mg, 2.6 mmol) and $Pd(PPh_3)_4$ (66 mg, 0.057 mmol) in THF/MeOH (3 : 1, 12 ml) was added 1.5 N Na_2CO_3 (2.6 ml, 3.9 mmol). The reaction mixture was sealed, placed in a microwave reactor and heated at 120 °C for 60 min. LC-MS indicated completion of reaction. The reaction mixture was diluted with EtOAc/H_2O. The organic

layer was collected, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (2% to 60% EtOAc in hexane over 18 min using a 40 g silica gel cartridge). The desired fractions were combined and concentrated to yield **I-001** (446 mg, 1.5 mmol, 60 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=1.4 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.60 - 7.51 (m, 4H), 4.81 (d, *J*=5.5 Hz, 2H), 1.80 (br t, *J*=5.8 Hz, 1H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 148.4, 144.1, 137.1, 136.2, 134.5, 132.3, 130.0, 129.3, 128.5, 119.3, 65.1. LC-MS: Waters Aquity BEH C18 2.1x50 mm, 1.7m; A: 90% H_2O + 0.05% TFA; B: 90% ACN + 0.05% TFA; wavelength 220 nm; flow rate 0.8 mL/min; gradient time 1.0 min; 2 to 98% B. RT = 0.86 min, MS (ESI) m/z: 270.0 and 272.0 $(M-18)^+$.

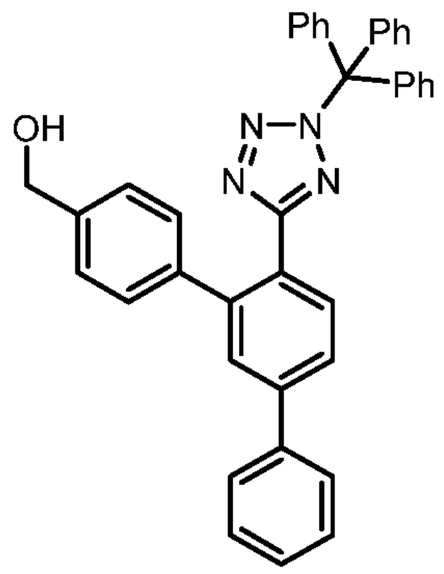
Common Intermediate I-002: 5-bromo-4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile



(I-002)

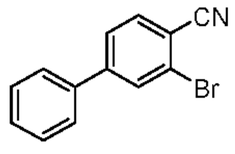
To a suspension of **I-001** (522 mg, 1.8 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added PBr_3 (0.19 ml, 2.0 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 0 °C for 15 min, and rt overnight. The mixture was diluted with CH_2Cl_2 and poured into a stirred ice-cold sat. $NaHCO_3$ solution. The organic layer was collected, washed with brine, dried over Na_2SO_4 and concentrated to yield **I-002** (574 mg, 1.6 mmol, 90 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J*=1.5, 0.7 Hz, 1H), 7.64 - 7.58 (m, 2H), 7.53 (s, 4H), 4.54 (s, 2H).

Common Intermediate I-003: (6'-(2-trityl-2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methanol



(I-003)

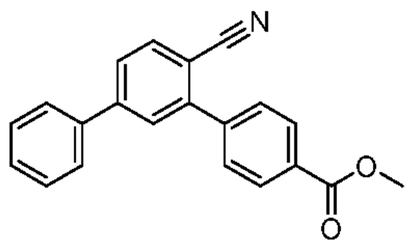
Intermediate I-003A: 3-bromo-[1,1'-biphenyl]-4-carbonitrile



(I-003A)

To a solution of 3-amino-[1,1'-biphenyl]-4-carbonitrile (22 g, 113 mmol) in ACN (250 mL) was added copper(II) bromide (0.253 g, 1.133 mmol), CSA (31.6 g, 136 mmol), tetrabutylammonium bromide (73.0 g, 227 mmol) and *tert*-butyl nitrite (17.96 mL, 136 mmol) dropwise and the reaction mixture was stirred at 60 °C overnight. On the next day, the reaction mixture was filtered over celite, washed with EtOAc (100 ml) and the filtrate was concentrated. H_2O (500 ml) was added to the crude residue, followed by extraction with EtOAc (3 x 300 ml). The combined organic layers were washed with water (400 ml), brine (300 ml), dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography and eluted with 30% EtOAc in petroleum ether. The desired fractions were concentrated to give the desired product **I-003A** (20.5 g, 74.7 mmol, 65.9 % yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) 8.20 (d, J= 1.6 Hz, 1H), 8.027 (d, J = 8 Hz, 1H), 7.92 - 7.89 (m, 1H), 7.81 - 7.79 (m, 2H), 7.55 - 7.48 (m, 3H).

Intermediate I-003B: methyl 6'-cyano-[1,1':3',1''-terphenyl]-4-carboxylate

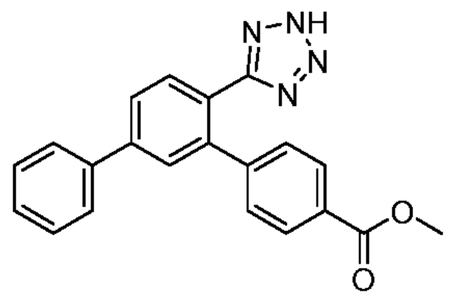


(I-003B)

In a flask charged with a stirring bar, a solution of **I-003A** (19 g, 73.6 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (15.90 g, 88 mmol) and potassium phosphate, tribasic (73.6 mL, 147 mmol) in 1,4-dioxane (250 mL) was purged with N_2 for 10 min. Then bis(triphenylphosphine)palladium(II) chloride (5.17 g, 7.36 mmol) was added, and

the mixture was again purged with N_2 for 5 min. The mixture was heated at 100 °C for 5 h. The reaction mixture was cooled to RT, filtered over celite bed, washed with EtOAc (100 ml) and concentrated to give the crude residue, to which H_2O (500 ml) was added, stirred for 15 min, filtered and dried to give the crude product. The crude product was triturated with MTBE (100 ml) and the solid obtained was stirred for 15 min, filtered and dried to get the product which was slightly black in color. The product was dissolved in THF and was treated with charcoal at 60 °C, filtered and concentrated to give the desired **I-003B** (18 g, 57.4 mmol, 78 % yield) as a yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) 8.27 - 8.15 (m, 2H), 7.93 - 7.84 (m, 1H), 7.78 - 7.70 (m, 4H), 7.68 - 7.63 (m, 2H), 7.58 - 7.43 (m, 3H), 3.99 (s, 3H).

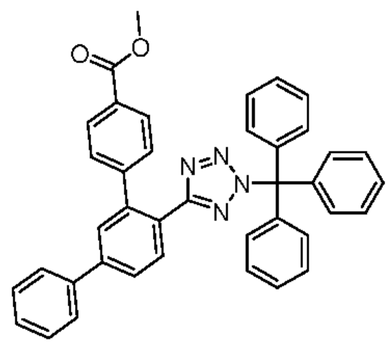
Intermediate I-003C: methyl 6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-carboxylate



(I-003C)

A solution of **I-003B** (7.5 g, 23.93 mmol), TMS-N_3 (15.88 mL, 120 mmol) and dibutyltin oxide (5.96 g, 23.93 mmol) in toluene (175 mL) was heated in a sealed tube at 100 °C overnight. Methanol (20 ml) was first added to the reaction and the resulting solution was diluted with EtOAc. To this organic phase was added ceric ammonium nitrate (75 g dissolved in 1 L of H_2O) dropwise and with swirling until bubbling ceased (N_2 gas evolution). To the mixture was added sat. NH_4Cl solution (250 ml) and then it was extracted with EtOAc (150 ml x 3). The combined organic layers were washed with H_2O (500 ml), brine (400 ml), dried over sodium sulphate, and concentrated to give the crude product. The crude product was triturated with MTBE (150 ml) and the solid obtained was stirred for 30 min, filtered, washed with MTBE (50 ml) and dried to give the **I-003C** (7.25 g, 18.43 mmol, 77% yield) as the product. ^{1}H NMR (500MHz, MeOH-d_4) δ 8.01 (d, *J*=8.3 Hz, 2H), 7.92 - 7.87 (m, 1H), 7.86 - 7.81 (m, 2H), 7.77 (d, *J*=7.7 Hz, 2H), 7.58 - 7.49 (m, 2H), 7.45 (d, *J*=7.4 Hz, 1H), 7.35 (d, *J*=8.5 Hz, 2H), 3.93 (s, 3H);); LC-MS: method A2, Rt = 0.89 min, MS (ESI) *m/z*: 357.10 $(M+H)^+$.

Intermediate I-003D: methyl 6'-(2-trityl-2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-carboxylate



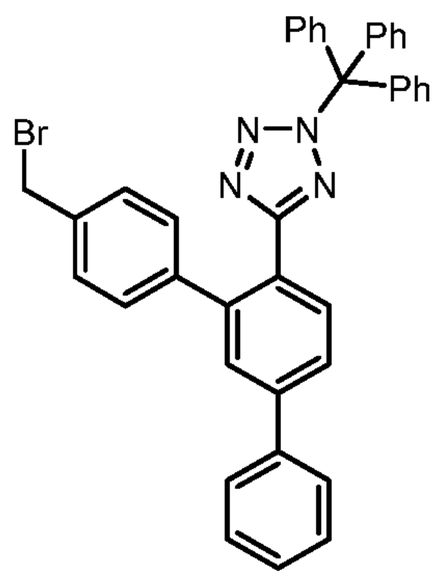
(I-003D)

To a solution of **I-003C** (14.5 g, 40.7 mmol) and TEA (11.34 mL, 81 mmol) in DCM (200 mL) was added trityl-Cl (17.01 g, 61.0 mmol) and the reaction mixture was stirred at RT overnight. To the reaction mixture H_2O (300 ml) was added and extracted with DCM (2 x 200 ml). The combined organic layers was washed with H_2O (300 ml), brine (200 ml), dried over sodium sulphate and concentrated to get the crude product. The crude product was triturated with MeOH (300 ml) and the solid obtained was stirred for 30 min, filtered, washed with MeOH (100 ml) and dried to give **I-003D** (22 g, 34.5 mmol, 85 % yield) as the product. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.14 (d, *J*=8.0 Hz, 1H), 7.84 (d, *J*=8.3 Hz, 2H), 7.76 (dd, *J*=8.1, 1.8 Hz, 1H), 7.68 (d, *J*=7.4 Hz, 2H), 7.63 (d, *J*=1.7 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.44 - 7.40 (m, 1H), 7.38 - 7.16 (m, 11H), 6.93 (d, *J*=7.7 Hz, 7H), 3.96 (s, 3H).

Common Intermediate I-003:

I-003D (1 g, 1.670 mmol) was dissolved in THF (20 mL). Methanol (0.135 mL, 3.34 mmol) was added at 0 °C followed by 2M lithium borohydride in THF (1.670 mL, 3.34 mmol). The reaction was allowed to stir at 40 °C overnight. The reaction was quenched with ~10 mL of H_2O at 0 °C and allowed to stir at RT for 3 hours. The reaction mixture was then extracted with EtOAc (3x) and the combined organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated. The residue was purified on 80 g silica gel cartridge on ISCO, which was eluted with a 30 min gradient of 0-100% EtOAc in hexane. The desired fraction was evaporated to give **Common Intermediate I-003** (0.736 g, 1.290 mmol, 77 % yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.73 - 7.68 (m, 1H), 7.64 (d, *J*=6.2 Hz, 3H), 7.46 (s, 2H), 7.40 - 7.24 (m, 10H), 7.21 - 7.16 (m, 2H), 7.14 (s, 2H), 6.94 - 6.81 (m, 6H), 4.59 (d, *J*=5.9 Hz, 2H).

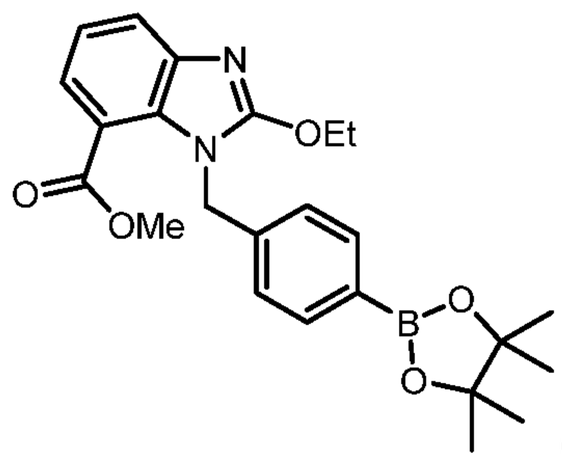
Common Intermediate I-004: 5-(4''-(bromomethyl)-[1,1':3',1''-terphenyl]-4'-yl)-2-trityl-2H-tetrazole



(I-004)

To an ice-cold mixture of (6'-(2-trityl-2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methanol (**Intermediate I-003**, 0.750 g, 1.31 mmol) in DCM (15 mL) was added triphenylphosphine (0.479 g, 1.45 mmol) and 2,6-dimethylpyridine (0.169 g, 1.58 mmol). To this mixture was added carbon tetrabromide (0.470 g, 1.45 mmol) in one portion and the reaction mixture was stirred for 15 min. The volatiles were then evaporated while maintaining a pot temperature of 0°C. The oily residue was dissolved in DCM (5 ml), a minimum volume of hexane was added and the resulting slightly turbid mixture was applied to a 40 gram ISCO-type silica gel column. Flash chromatography (0 to 30% EtOAc / hexane gradient) then afforded the title compound (0.760 g, 1.20 mmol, 91% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ ppm 8.08 (d, J = 7.8 Hz, 1H), 7.71 (dd, J = 8.0, 1.8 Hz, 1H), 7.59 - 7.68 (m, 3H), 7.42 - 7.49 (m, 2H), 7.31 - 7.41 (m, 4H), 7.23 - 7.31 (m, 6H), 7.11 - 7.18 (m, 4H), 6.88 - 6.95 (m, 6H), 4.40 (s, 2H).

Common Intermediate I-005: methyl 2-ethoxy-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-benzo[d]imidazole-7-carboxylate

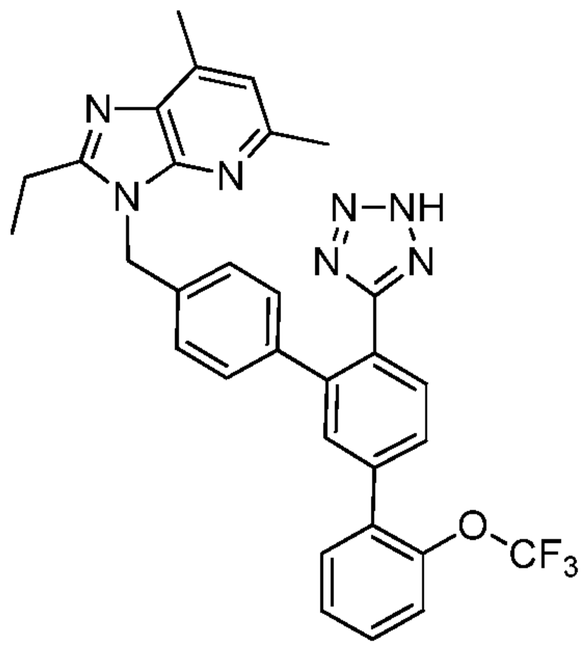


(I-005)

To a solution of methyl 2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (1.00 g, 4.54 mmol) in 2-propanol (15 ml) was added potassium carbonate (1.26 g, 9.08 mmol) and this was stirred at 30°C for 5 minutes. To this mixture were added 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.44 g, 4.77 mmol) and

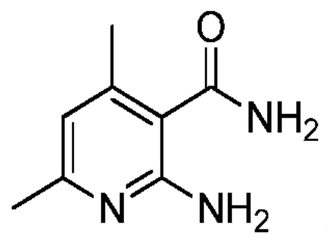
tetrabutylammonium iodide (0.084 g, 0.227 mmol) and the temperature was increased to 45°C. After stirring for 2.5 hours, another portion of 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.250 g, 0.842 mmol) was added and the reaction was stirred for an additional 18 hours. The reaction was cooled to RT and diluted with EtOAc (200 ml), and H_2O (50 ml) was added. The layers were separated and the organic layer was washed with brine (50 ml), then dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was dissolved in DCM (10 ml) and injected on a 40-gram ISCO-type silica gel column pre-equilibrated with hexane and the title compound was purified by elution using a 0 to 60% EtOAc/hexane gradient to provide the title compound as a yellow solid. (1.44 g, 3.31 mmol, 72% yield). LC-MS (Method H): 1.42 min, $[M + H]^+$= 437.2; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (dd, *J*=8.0, 1.0 Hz, 1 H) 7.67 (m, *J*=8.2 Hz, 2 H) 7.53 (dd, *J*=7.8, 1.2 Hz, 1 H) 7.16 (t, *J*=7.8 Hz, 1 H) 6.96 (m, *J*=8.2 Hz, 2 H) 5.63 (s, 2 H) 4.65 (q, *J*=7.0 Hz, 2 H) 3.72 (s, 3 H) 1.46 (t, *J*=7.0 Hz, 3 H) 1.31 (s, 12 H).

Example 001: 3-((6'-(2*H*-tetrazol-5-yl)-2''-(trifluoromethoxy)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine



(Ex. 001)

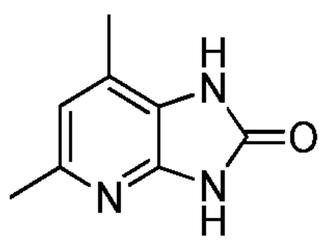
Intermediate 001a: 2-amino-4,6-dimethylnicotinamide



(001a)

The title compound was prepared from 3-amino-3-iminopropanamide hydrochloride (1.376 g, 10 mmol) and pentane-2,4-dione (1.073 mL, 10.50 mmol) according to the procedure described in *J. Med. Chem.* **2007**, *50*, 828. The crude was purified by ISCO (DCM/MeOH, 0-20%) to afford 001a (1.54 g, 9.32 mmol, 93 % yield) as a white solid. LC-MS (Method A2): 0.32 min, $[M + H]^+$= 166.0; ^{1}H NMR (400 MHz, MeOD) δ ppm 6.43 (s, 1H), 2.28 (s, 3H), 2.28 (s, 3H).

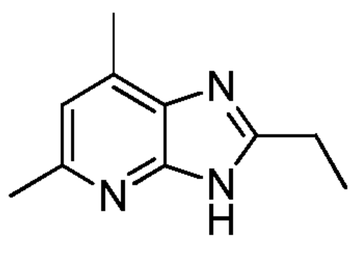
Intermediate 001b: 5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one



(001b)

A solution of 2-amino-4,6-dimethylnicotinamide (001a, 0.470 g, 2.85 mmol) in MeOH (14.2 mL) was treated with potassium hydroxide (0.559 g, 9.96 mmol) and iodobenzene diacetate (1.375 g, 4.27 mmol) as described in *J. Med. Chem.* **2011**, *54*, 4219. The crude was purified by ISCO (DCM/MeOH, 0-20%) to afford the title compound as an off-white solid (0.235 g, 1.440 mmol, 50.6 % yield). LC-MS (Method A2): 0.42 min, $[M + H]^+$= 164.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.03 (br s, 1H), 10.76 (s, 1H), 6.64 (s, 1H), 2.33 (s, 3H), 2.23 (s, 3H).

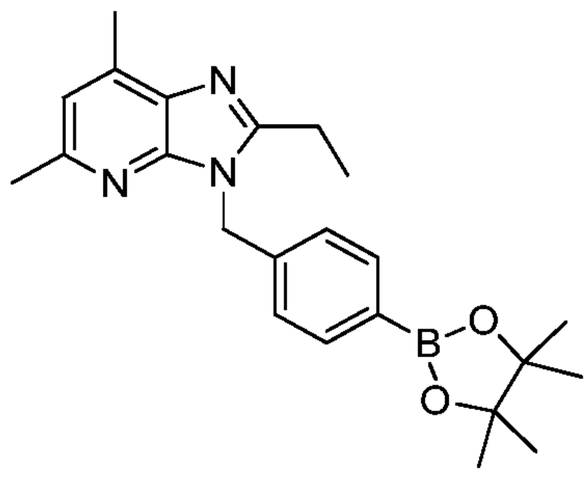
Intermediate 001c: 2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine



(001c)

Intermediate 001b (0.224 g, 1.373 mmol) was treated with propionic acid (1.95 mL, 26.1 mmol), propionic anhydride (1.94 mL, 15.10 mmol) and magnesium chloride (0.196 g, 2.059 mmol) as described in *J. Med. Chem.* **2007**, *50*, 828. The crude was purified by ISCO (DCM/MeOH, 0-20%) to yield the title compound as a brown oil (0.220 g, 1.130 mmol, 82 % yield). LC-MS (Method A2): 0.42 min, $[M + H]^+$= 176.7; ^{1}H NMR (400 MHz, MeOD) δ ppm 7.05 (s, 1H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.59 (s, 6H), 1.43 (t, *J* = 7.7 Hz, 3H).

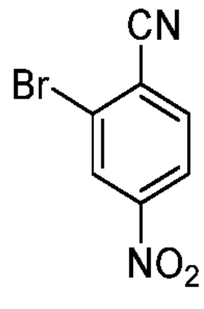
Intermediate 001d: 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3*H*-imidazo[4,5-*b*]pyridine



(001d)

To a solution of **Intermediate 001c** (1.2 g, 6.85 mmol) in DMF (41.5 mL) was added sodium hydride (0.498 g, 12.45 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.849 g, 6.23 mmol) in DMF (20.75 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (hexane/EtOAc, 0-100%) to afford the title compound (1.35 g, 3.45 mmol, 55.4 % yield) as a light yellow solid. LC-MS (Method A2): 0.81 min, $[M + H]^+$= 392.4; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.71 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 5.46 (s, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 2.57 (s, 3H), 1.31 (s, 12H), 1.27 (t, *J* = 7.6 Hz, 3H).

Intermediate 001e: 2-bromo-4-nitrobenzonitrile

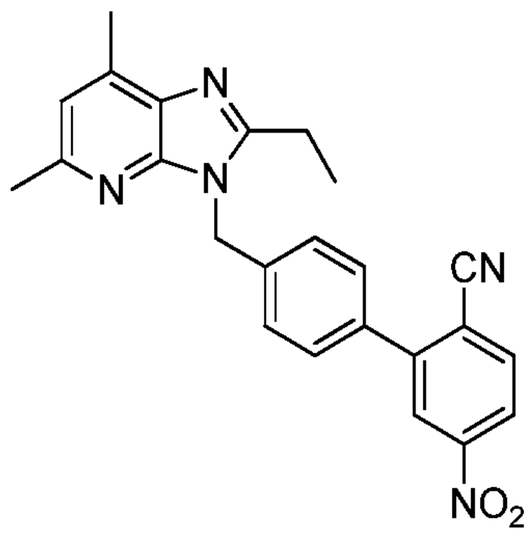


(001e)

A solution of 4-nitrobenzonitrile (1.0 g, 6.75 mmol) in DCE (27.0 mL) was treated with NBS (1.322 g, 7.43 mmol), CSA (0.784 g, 3.38 mmol) and diacetoxypalladium (0.152 g, 0.675 mmol) according to the procedure described in *JOC*, **2013**, *78*, 2786. After 16 h at 70°C, LC-MS analysis only showed about 60% conversion. Another portion of diacetoxypalladium (0.152 g, 0.675 mmol) was added along with NBS (0.5 eq., 0.600 g) and the reaction mixture was reheated at 70 °C for 7.5 h. The cooled reaction mixture was diluted with DCM, washed with 1.5 M aqueous K_2HPO_4, followed by saturated aqueous NH_4Cl. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by

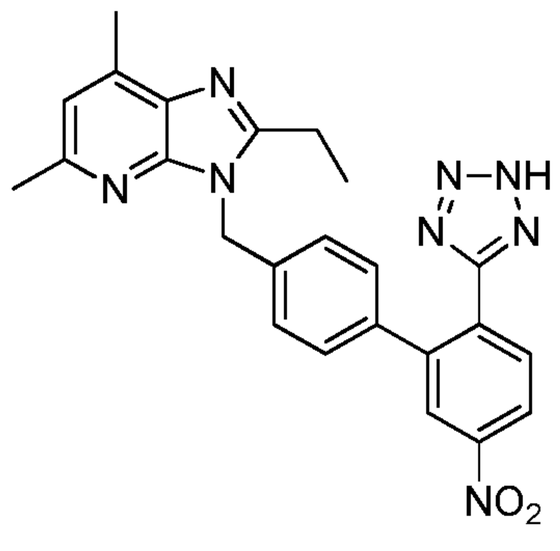
ISCO (Hexanes/EtOAc, 0-100%) to afford the title compound **Intermediate 001e**(1.01 g, 4.45 mmol, 65.9 % yield) as a white solid. LC-MS (Method A2): 0.82 min, [M+H] No ion observed; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 (d, *J* = 2.2 Hz, 1H), 8.29 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H).

Intermediate 001f: 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-5-nitro-[1,1'-biphenyl]-2-carbonitrile


(001f)

A mixture of **Intermediate 001d** (0.670 g, 1.712 mmol) and **Intermediate 001e** (0.466 g, 2.055 mmol) in dioxane (11.4 mL) was treated with K_3PO_4 (2M aq., 2.14 ml, 4.28 mmol) followed by $PdCl_2$(dppf) (0.125 g, 0.171 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and heated at 100°C overnight. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 001f,** 0.540 g, 1.312 mmol, 77 % yield) as an amber oil. LC-MS (Method A2): 0.79 min, $[M + H]^+$= 412.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.33 (d, *J* = 2.2 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.92 (s, 1H), 5.55 (s, 2H), 2.83 (q, *J* = 7.4 Hz, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 1.35 (t, *J* = 7.6 Hz, 3H).

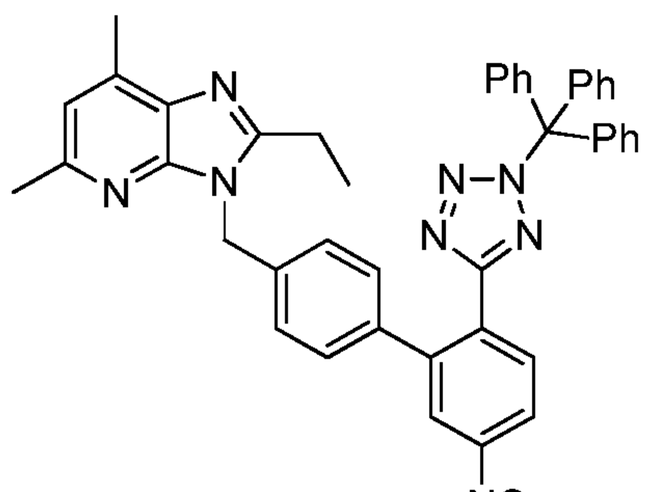
Intermediate 001g: 2-ethyl-5,7-dimethyl-3-((5'-nitro-2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3*H*-imidazo[4,5-*b*]pyridine



(001g)

To a solution of **Intermediate 001f** (0.250 g, 0.608 mmol) in toluene (6.1 mL) was added dibutyltin oxide (0.151 g, 0.608 mmol) and TMS-N_3 (0.403 mL, 3.04 mmol). Then the reaction vessel was sealed and the mixture was heated at 110 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, **1993**, *58*, 4139). After cooling, the reaction mixture was diluted with MeOH and EtOAc and quenched by the portionwise addition of a 10% aqueous solution of CAN (16.700 g, 3.05 mmol) until bubbling ceased. The resulting mixture was stirred at RT for 30 min, then partitioned with saturated aqueous NH_4Cl and EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated to give a yellow foam which was purified by ISCO (DCM/MeOH, 0-20%) to afford the title compound as a light yellow foam (0.250 g, 0.550 mmol, 91 % yield). LC-MS (Method A2): 0.71 min, $[M + H]^+$= 455.3; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 - 8.19 (m, 2H), 8.08 (br. s., 1H), 7.18 - 7.10 (m, 2H), 7.08 - 7.02 (m, 2H), 6.97 (s, 1H), 5.50 (s, 2H), 2.77 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 2.48 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H).

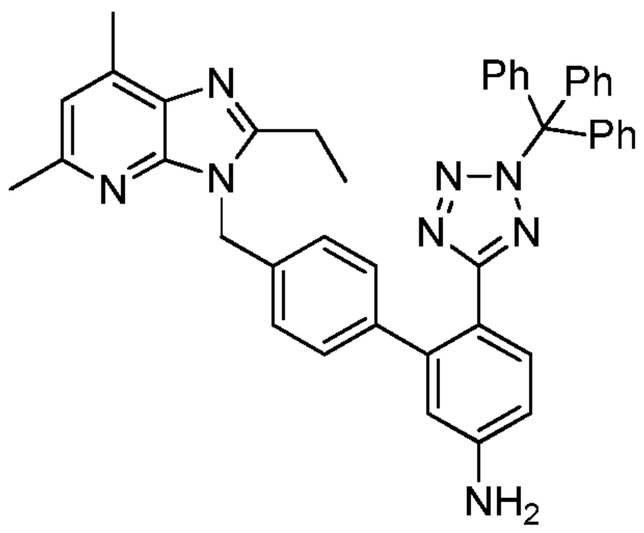
Intermediate 001h: 2-ethyl-5,7-dimethyl-3-((5'-nitro-2'-(2-trityl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3*H*-imidazo[4,5-*b*]pyridine



(001h)

To a solution of **Intermediate 001g** (1.6 g, 3.52 mmol) in DCM (17.6 mL) at RT was added triethylamine (0.638 mL, 4.58 mmol) followed by trityl chloride (1.030 g, 3.70 mmol). After 20 min, the reaction mixture was quenched with few drops of MeOH, diluted with DCM and washed with 1 M aqueous K_2HPO_4. The organic phase was dried over $MgSO_4$, filtered and concentrated. A quantitative yield was assumed and the product was taken to the subsequent reduction step without further purification. LC-MS (Method A2): 1.06 min, $[M + H]^+$= 697.1.

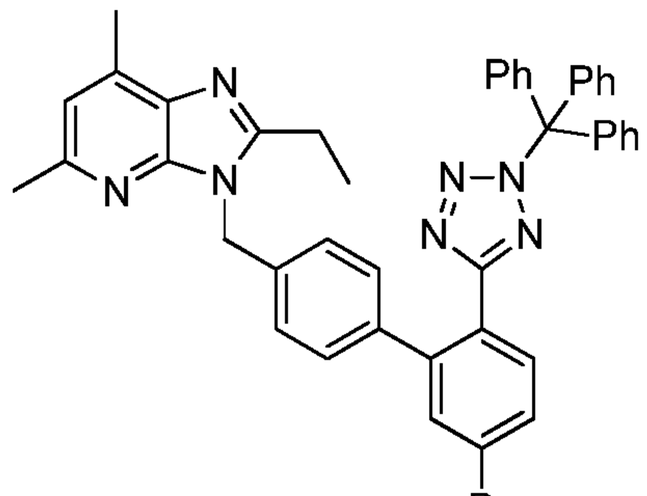
Intermediate 001i: 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-6-(2-trityl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



(001i)

Intermediate 001h (2.15 g, 3.09 mmol) was diluted in THF (61.7 mL) and treated with Pd-C (Degussa) (0.328 g, 0.309 mmol). The resulting suspension was purged with H_2 (3x flask volume, approximatively 1.5 L) and allowed to stir under a balloon atmosphere of H_2 overnight. The reaction mixture was then diluted with EtOAc, filtered over Celite and concentrated. The crude residue was used as such in the next step. LC-MS (Method A2): 0.98 min, $[M + H]^+$= 667.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 8.4 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.34 - 7.27 (m, 4H), 7.25 - 7.17 (m, 6H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.90 (dd, *J* = 7.4, 1.7 Hz, 5H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.72 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 5.33 (s, 2H), 3.86 (s, 2H), 2.70 - 2.63 (m, 5H), 2.58 (s, 3H), 1.26 - 1.21 (m, 3H).

Intermediate 001j: 3-((5'-bromo-2'-(2-trityl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine



(001j)

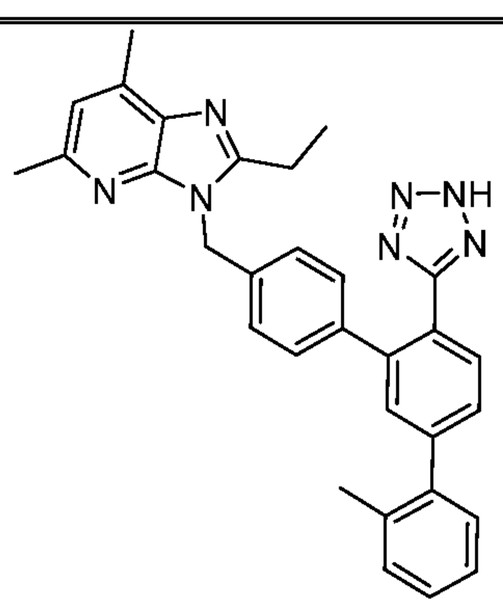
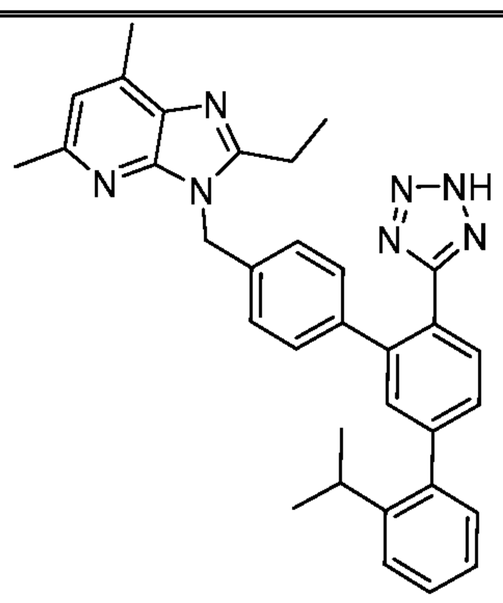
To a suspension of **Intermediate 001i** (1.15 g, 1.725 mmol) in ACN (17.3 mL) was added copper (II) bromide (0.501 g, 2.242 mmol) followed by t-butyl nitrite (0.456 mL, 3.45 mmol). The reaction was stirred at RT for 45 min then diluted with EtOAc (100 mL). The organic phase was then washed with 1 M aqueous HCl rapidly followed by 1 M aqueous K_2HPO_4 to re-basify the organic phase. The organic phase was then dried over $MgSO_4$, filtered, concentrated and purified by ISCO (Hexanes/EtOAc, 0-100%). The title compound was isolated as a viscous, pale yellow oil (**Intermediate 001j,** 0.560 g, 0.766 mmol, 44.4 % yield over the three-step sequence). LC-MS (Method A2): 1.10 min, $[M + H]^+$= 732.3; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.81 (d, *J* = 8.1 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.37 - 7.27 (m, 4H), 7.26 - 7.19 (m, 5H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.96 - 6.82 (m, 9H), 5.35 (s, 2H), 2.71 - 2.61 (m, 5H), 2.57 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H).

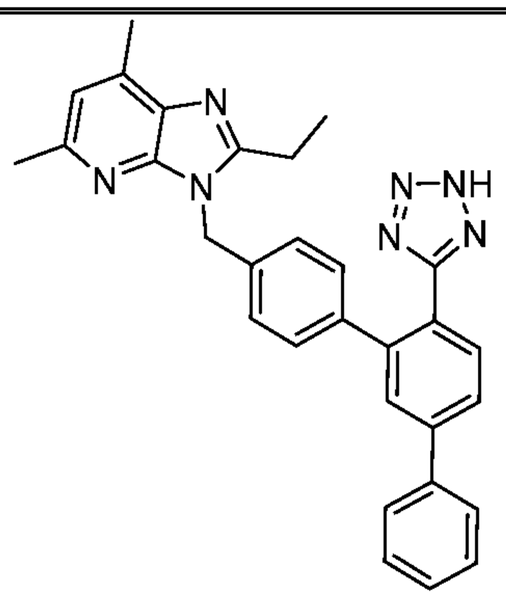
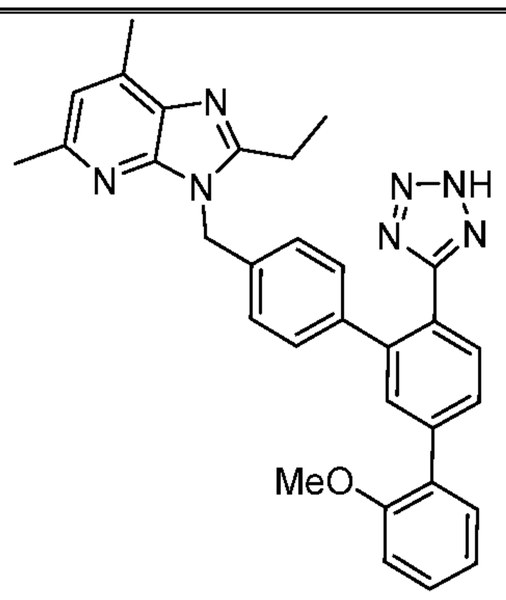
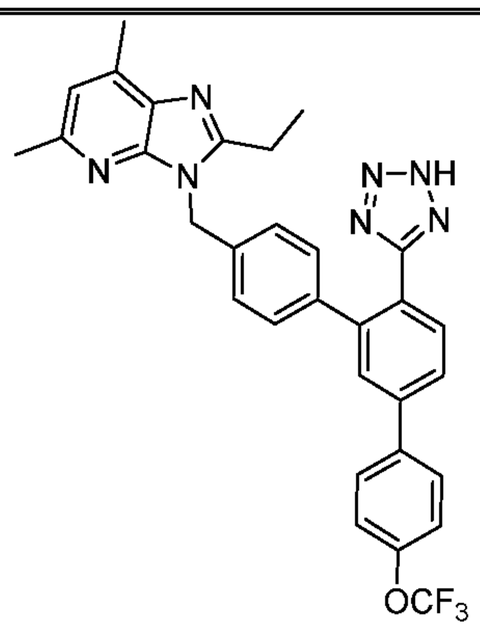
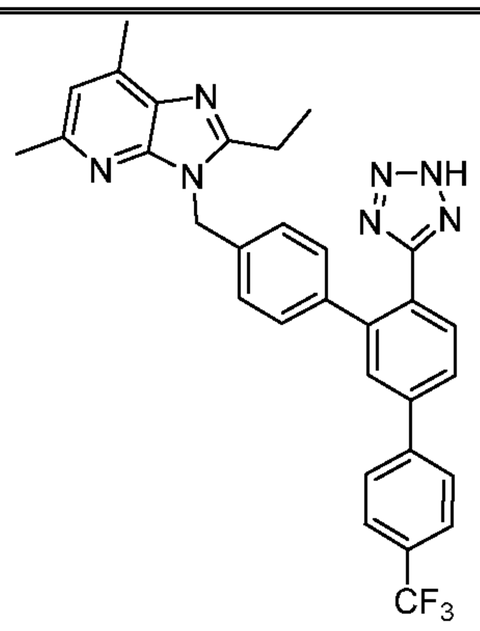
Example 001: 3-((6'-(2*H*-tetrazol-5-yl)-2''-(trifluoromethoxy)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

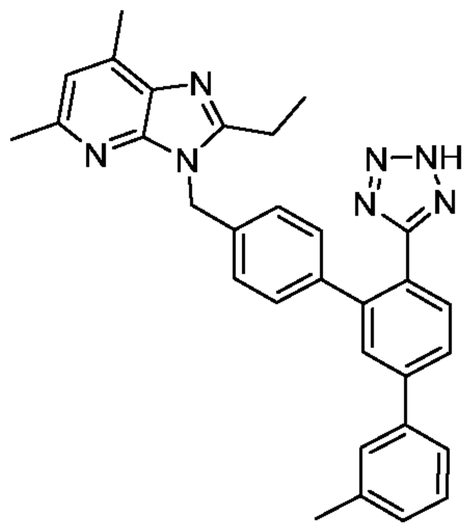
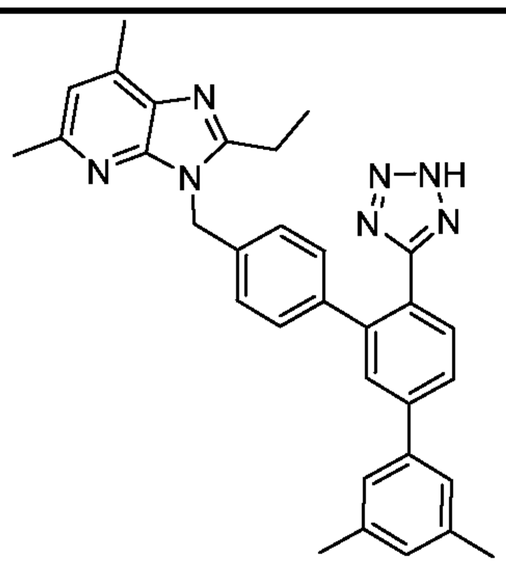
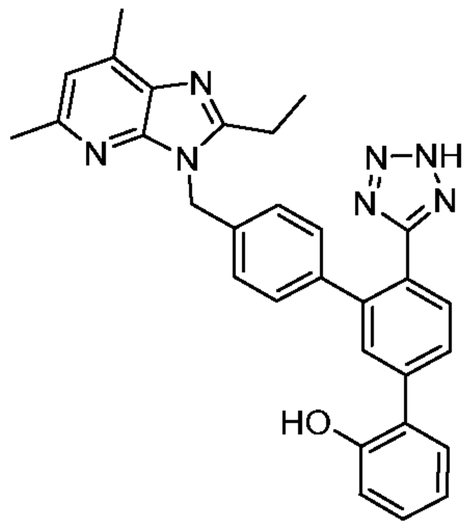
To a solution of **Intermediate 001j** (0.020 g, 0.027 mmol) and (2-(trifluoromethoxy) phenyl)boronic acid (0.028 g, 0.137 mmol) in dioxane (2 mL) was added 2M aqueous K_3PO_4 (0.068 mL, 0.137 mmol) followed by $PdCl_2$(dppf) (0.002 g, 2.74 μmol). The resulting mixture was sparged with N_2 for 2 min before the reaction vessel was sealed and heated at 120°C for 30 min under microwave irradiation. The reaction mixture was cooled to RT, diluted with EtOAc and filtered over a pad of Celite/$MgSO_4$. The filtrate was concentrated to a brown residue which was dissolved in DCM (2 mL) and treated with triethylsilane (0.022 mL, 0.137 mmol) followed by TFA (0.105 mL, 1.369 mmol) for 10 min. The reaction mixture was then concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN:

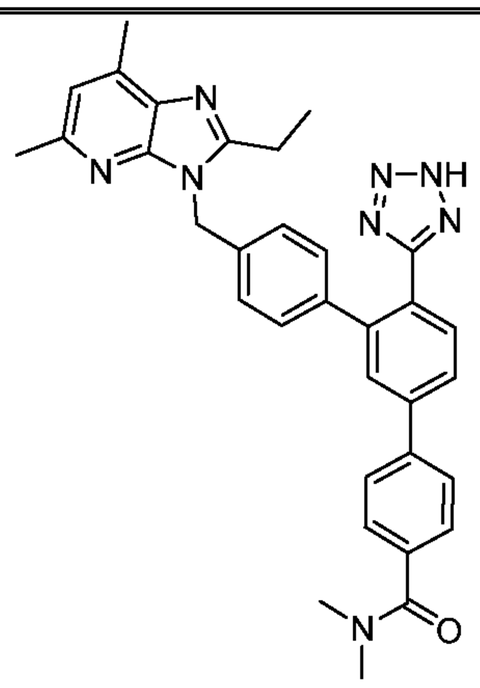
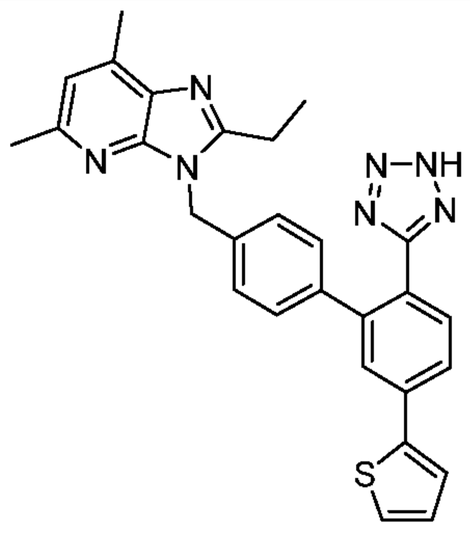
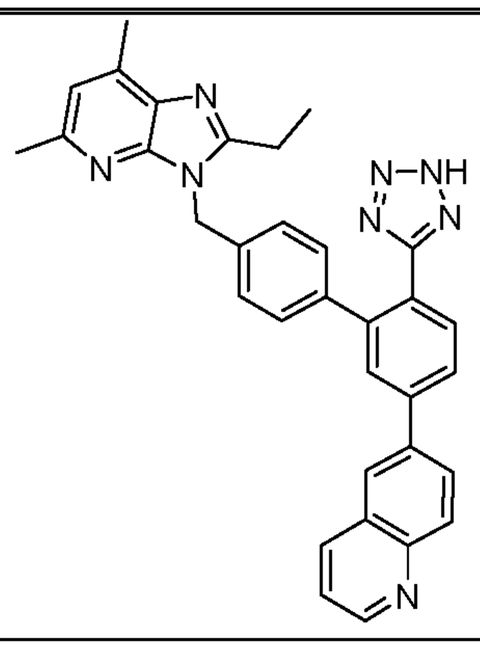
H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 0.0065 g (0.011 mmol, 40% yield) of the title compound **Example 001**. LC-MS (Method A2): 0.86 min, $[M + H]^+$= 570.1; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 7.76 - 7.52 (m, 5H), 7.51 (br s, 2H), 7.13 - 6.99 (m, 4H), 6.95 (s, 1H), 5.44 (s, 2H), 2.75 (q, J = 7.4 Hz, 2H), 2.50 - 2.47 (m, 6H), 1.19 (t, J = 7.4 Hz, 3H).

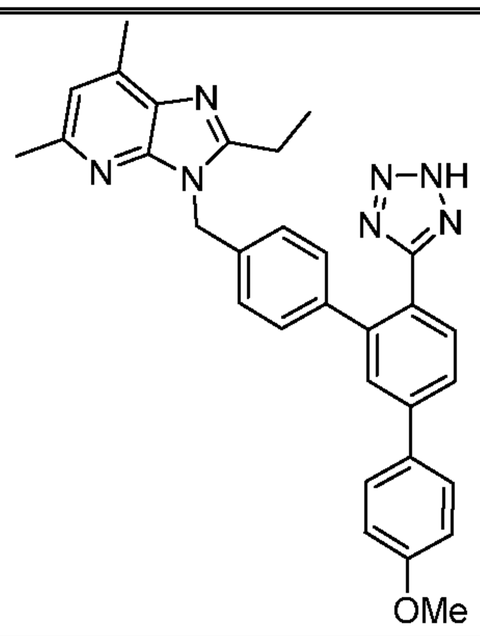
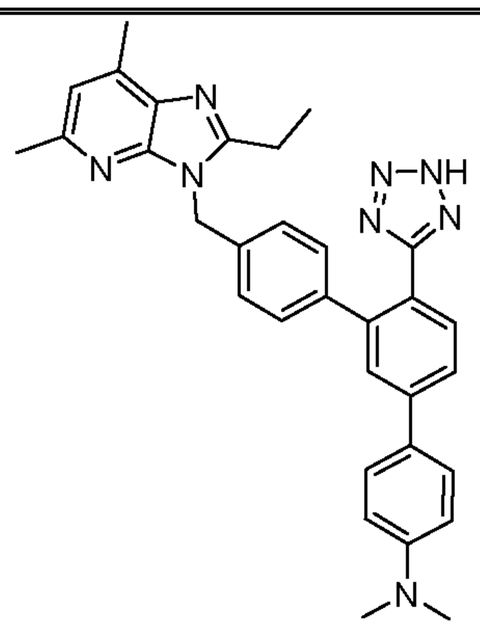
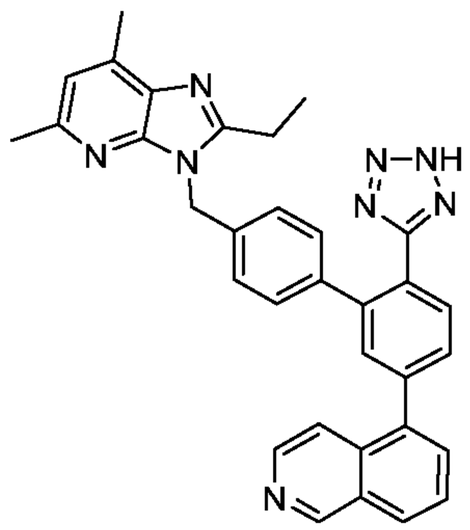
The following examples have been similarly prepared from **Intermediate 001j** as described above for the synthesis of **Example 001**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A1 or Method A2.

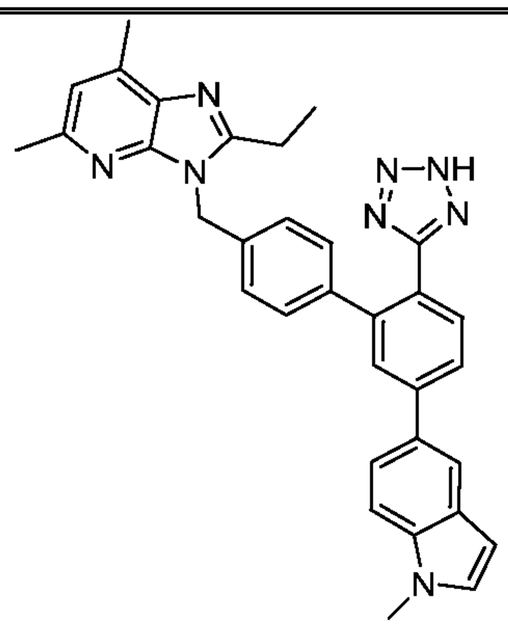
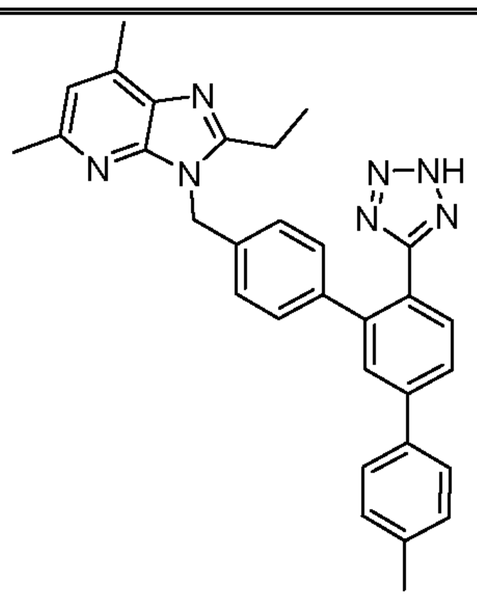
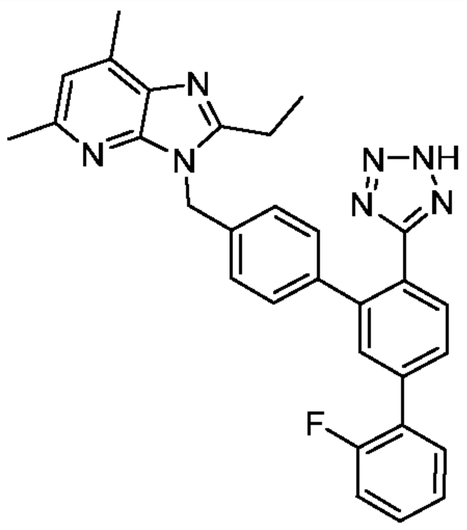
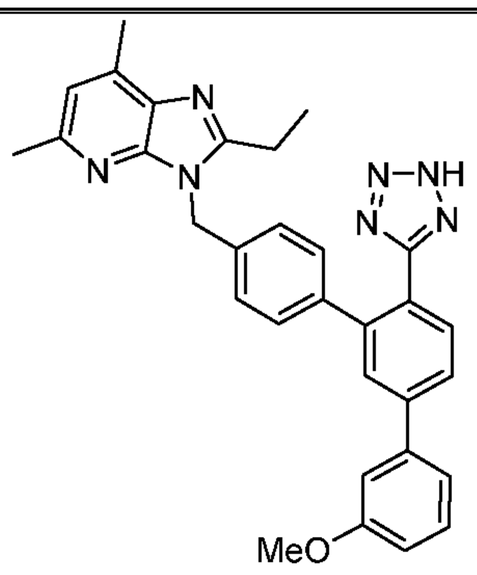
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^1H NMR (500MHz, DMSO-d_6) δ ppm
002		499.61	500.10; 0.83 min (Method A2)	7.70 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.36 - 7.25 (m, 4H), 7.13 - 7.07 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.79 - 2.71 (m, 3H), 2.55 (s, 6H), 2.30 (s, 3H), 1.21 (t, J = 7.4 Hz, 3H)
003		527.66	528.30; 0.90 min (Method A2)	7.72 (d, J = 7.8 Hz, 1H), 7.53 - 7.44 (m, 2H), 7.43 - 7.34 (m, 2H), 7.30 - 7.21 (m, 3H), 7.17 (s, 1H), 7.14 - 7.08 (m, 2H), 7.07 (s, 1H), 5.53 (s, 2H), 3.02 (dt, J = 13.4, 6.8 Hz, 1H), 2.93 - 2.84 (m, 2H), 2.54 (d, J = 2.7 Hz, 6H), 1.20 (t, J = 7.5 Hz, 3H), 1.14 (d, J = 6.7 Hz, 6H)

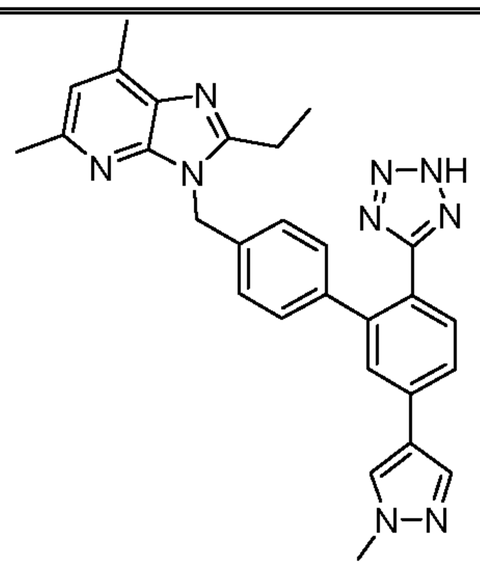
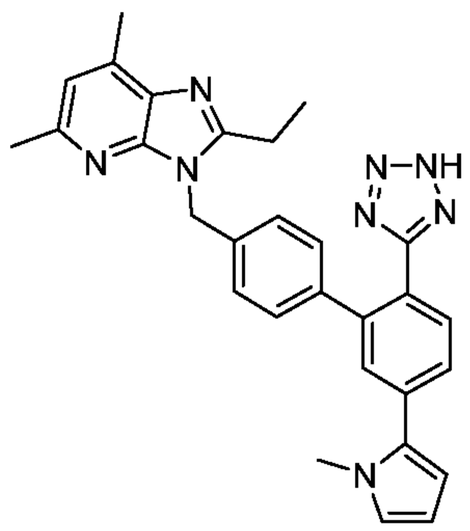
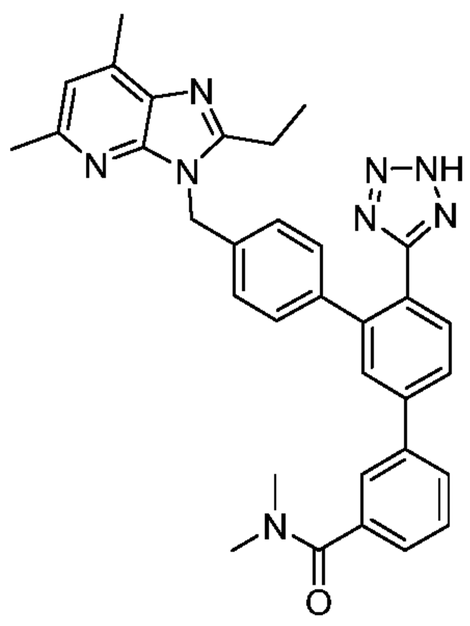
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
004		485.58	486.10; 0.81 min (Method A2)	7.83 - 7.74 (m, 3H), 7.73 - 7.64 (m, 2H), 7.53 - 7.45 (m, 2H), 7.44 - 7.36 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.77 (d, *J* = 7.3 Hz, 2H), 2.55 (s, 6H), 1.22 (t, *J* = 7.5 Hz, 3H)
005		515.61	516.10; 0.81 min (Method A2)	
006		569.58	570.20; 0.88 min (Method A2)	7.90 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.10 (br s, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.95 (s, 1H), 5.44 (s, 2H), 2.80 - 2.74 (m, 2H), 2.50 (d, *J* = 2.9 Hz, 6H), 1.20 (t, *J* = 7.4 Hz, 3H)
007		553.58	554.20; 0.88 min (Method A2)	8.02 (d, *J* = 7.9 Hz, 2H), 7.91 - 7.72 (m, 5H), 7.21 - 7.01 (m, 4H), 6.95 (s, 1H), 5.46 (s, 2H), 2.78 (q, *J* = 7.3 Hz, 2H), 2.51 (br. s., 6H), 1.23 (d, *J* = 3.1 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
008		499.61	500.10; 1.800 min (Method A1)	7.79 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.78 (q, *J* = 7.5 Hz, 2H), 2.55 (s, 6H), 2.38 (s, 3H), 1.27 - 1.19 (m, 3H)
009		513.64	514.30; 1.970 min (Method A1)	7.79 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.68 (s, 1H), 7.39 (s, 2H), 7.15 - 7.10 (m, 2H), 7.08 - 7.01 (m, 3H), 6.95 (s, 1H), 5.46 (s, 2H), 2.77 (q, *J* = 7.5 Hz, 2H), 2.55 (s, 6H), 2.33 (s, 6H), 1.25 - 1.21 (m, 5H)
010		501.58	502.30; 1.500 min (Method A1)	7.77 - 7.72 (m, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.64 (s, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.26 (s, 1H), 7.24 - 7.18 (m, 1H), 7.15 (s, 1H), 7.13 - 7.08 (m, 4H), 7.05 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 5.53 (s, 2H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.54 - 2.52 (m, 6H), 1.23 - 1.20 (m, 3H)

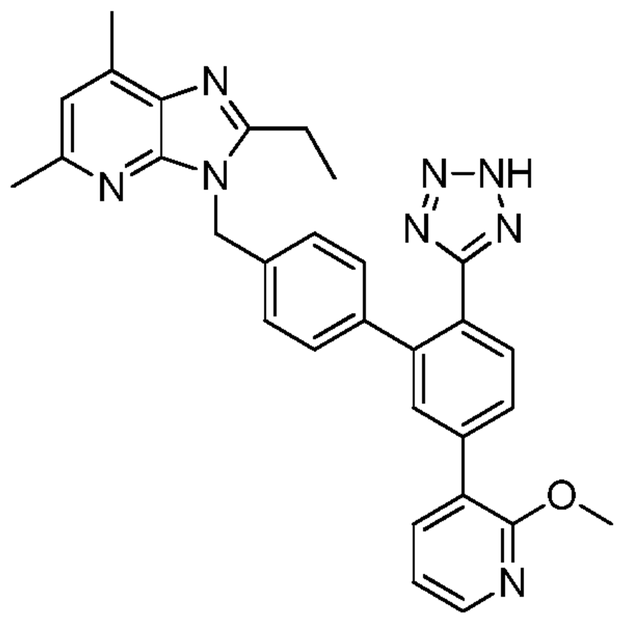
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
011		556.66	557.00; 1.380 min (Method A1)	7.90 - 7.82 (m, 3H), 7.78 - 7.73 (m, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.96 (s, 1H), 5.46 (s, 2H), 3.00 (br s, 3H), 2.95 (br s, 3H), 2.77 (q, *J* = 7.4 Hz, 2H), 2.55 (s, 6H), 1.26 - 1.19 (m, 3H)
012		491.61	492.40; 1.600 min (Method A1)	7.79 (d, *J* = 7.6 Hz, 1H), 7.68 (br s, 3H), 7.62 (d, *J* = 4.9 Hz, 1H), 7.20 - 7.15 (m, 1H), 7.13 - 7.08 (m, 2H), 7.08 - 7.03 (m, 2H), 6.96 (s, 1H), 5.46 (s, 2H), 2.81 - 2.74 (m, 2H), 2.55 (s, 6H), 1.26 - 1.19 (m, 3H)
013		536.63	537.20; 1.140 min (Method A1)	8.97 (d, *J* = 2.8 Hz, 1H), 8.55 - 8.48 (m, 2H), 8.28 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.27 - 7.02 (m, 5H), 5.56 (s, 2H), 2.90 (q, *J* = 7.2 Hz, 2H), 2.51 (br. s., 6H), 1.25 (t, *J* = 7.4 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
014		515.61	516.30; 1.640 min (Method A1)	7.82 (d, *J* = 7.3 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.71 (br s, 2H), 7.18 - 7.07 (m, 3H), 7.07 - 6.97 (m, 3H), 5.49 (s, 2H), 3.81 (s, 3H), 2.81 (q, *J* = 6.8 Hz, 2H), 2.55 (s, 3H), 2.53 (br. s., 3H), 1.24 (t, *J* = 7.3 Hz, 3H)
015		528.65	529.20; 1.700 min (Method A1)	7.65 - 7.54 (m, 4H), 7.50 (s, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.95 (s, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 2H), 2.93 (s, 6H), 2.78 (q, *J* = 7.5 Hz, 2H), 2.55 (s, 6H), 1.24 (t, *J* = 7.5 Hz, 3H)
016		536.63	536.90; 1.470 min (Method A1)	9.40 (br s, 1H), 8.51 (br s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 3H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.47 (br s, 1H), 7.15 (br s, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.93 (s, 1H), 5.43 (s, 2H), 2.77 (q, *J* = 7.3 Hz, 2H), 2.55 (s, 6H), 1.22 (t, *J* = 7.4 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
017		538.64	539.00; 1.650 min (Method A1)	
018		499.61	500.30; 1.750 min (Method A1)	
019		503.57	504.10; 0.81 min (Method A2)	7.79 - 7.69 (m, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.60 (s, 1H), 7.51 - 7.43 (m, 1H), 7.40 - 7.29 (m, 2H), 7.15 - 7.08 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.81 - 2.70 (m, 2H), 2.55 (s, 6H), 1.22 (t, *J* = 7.4 Hz, 3H)
020		515.61	516.10; 0.81 min (Method A2)	7.79 (d, *J* = 7.7 Hz, 1H), 7.73 - 7.64 (m, 2H), 7.43 - 7.36 (m, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.28 (br s, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.00 - 6.92 (m, 2H), 5.45 (s, 2H), 3.82 (s, 3H), 2.78 (q, *J* = 7.3 Hz, 2H), 2.55 (s, 6H), 1.23 (t, *J* = 7.4 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
021		489.57	490.10; 0.66 min (Method A2)	8.26 (s, 1H), 7.96 (s, 1H), 7.68 - 7.62 (m, 1H), 7.60 - 7.55 (m, 2H), 7.12 - 7.06 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 3.85 (s, 3H), 2.78 (q, *J* = 7.3 Hz, 2H), 2.55 (s, 6H), 1.25 (t, *J* = 7.4 Hz, 3H)
022		488.59	489.10; 0.77 min (Method A2)	7.95 (s, 1H), 7.72 - 7.67 (m, 1H), 7.66 - 7.62 (m, 1H), 7.52 (s, 1H), 7.25 (s, 1H), 7.15 (s, 1H), 7.05 (s, 2H), 6.92 (s, 1H), 6.37 (br s, 1H), 6.11 (d, *J* = 2.7 Hz, 1H), 5.51 (s, 2H), 3.74 (s, 3H), 2.85 (q, *J* = 7.4 Hz, 2H), 2.53 (s, 6H), 1.23 (t, *J* = 7.5 Hz, 3H)
023		556.66	557.1; 0.72 min (Method A2)	7.82 (d, *J* = 7.9 Hz, 1H), 7.76 - 7.71 (m, 2H), 7.70 - 7.66 (m, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.95 (s, 1H), 5.44 (s, 2H), 3.00 (br. s., 3H), 2.93 (br. s., 3H), 2.79 (q, *J* = 7.5 Hz, 2H), 2.55 (s, 3H), 2.51 (s, 3H), 1.25 (t, *J* = 7.4 Hz, 3H)

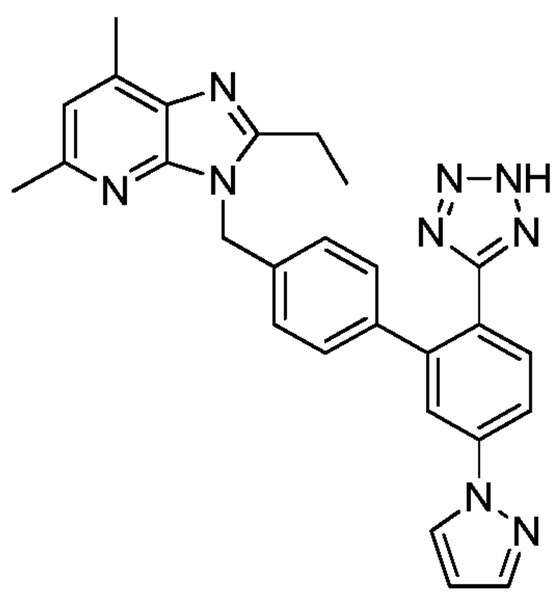
Example 024: 2-ethyl-3-((5'-(2-methoxypyridin-3-yl)-2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine



(Ex. 024)

A solution of **Intermediate 001j** (0.030 g, 0.041 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.029 g, 0.123 mmol) in dioxane (3 mL) was treated with 2M aqueous K_3PO_4 (0.103 mL, 0.205 mmol) and $PdCl_2$(dppf) (0.003 g, 4.11 μmol) and reacted as described in **Ex. 001**. The crude residue was purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford (0.0099 g, 0.019 mmol, 47%) of the title compound **Example 024**. LC-MS (Method A2): 0.77 min, $[M + H]^+$= 517.1; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.20 (d, J = 4.8 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.67 (s, 2H), 7.56 (s, 1H), 7.16 - 7.06 (m, 3H), 7.02 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 5.44 (s, 2H), 3.89 (s, 3H), 2.77 (q, J = 7.4 Hz, 2H), 2.55 (s, 6H), 1.23 (t, J = 7.4 Hz, 3H).

Example 025: 3-((5'-(1*H*-pyrazol-1-yl)-2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

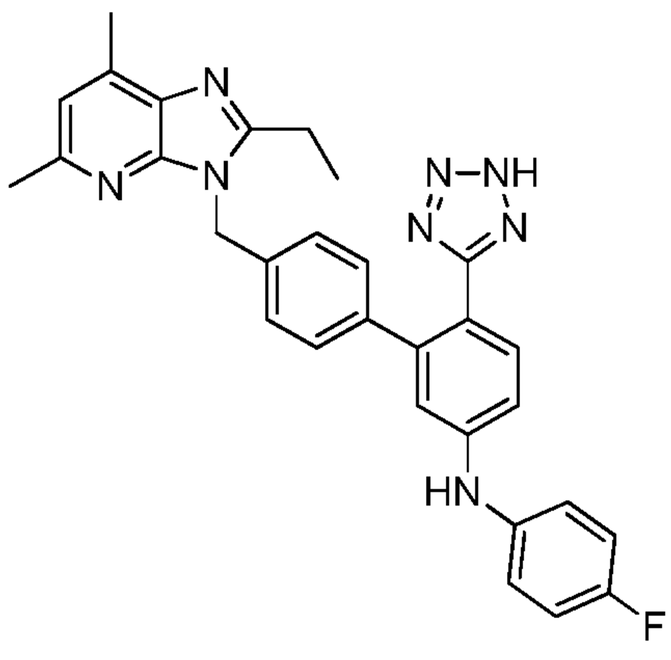


(Ex. 025)

To a vial charged with **Intermediate 001j** (0.030 g, 0.041 mmol), 1*H*-pyrazole (0.0084 g, 0.123 mmol), copper(I) iodide (0.0039 g, 0.021 mmol), potassium carbonate (0.028 g,

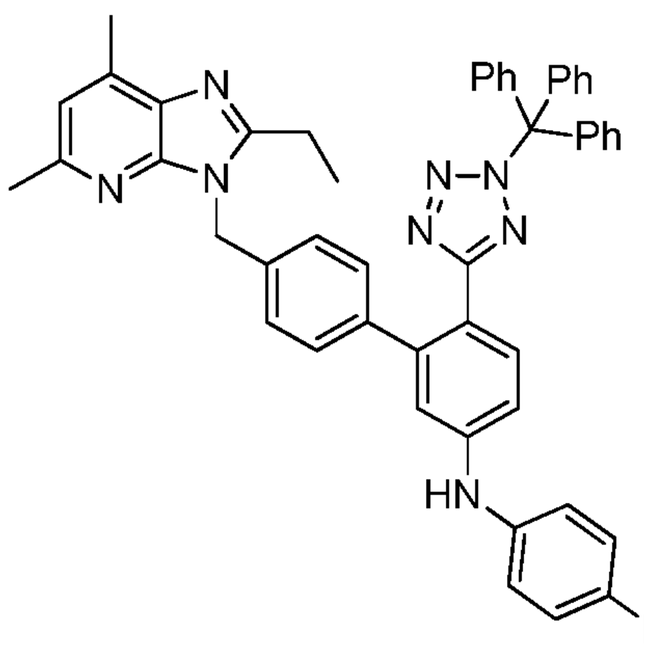
0.205 mmol) and L-proline (0.0047 g, 0.041 mmol) was added DMSO (0.821 mL). The mixture was heated at 100 °C for 24 h and at 150 °C for an additional 24 h. The reaction mixture was allowed to cool to RT and filtered through a microfilter. The residue was rinsed with DMSO and the filtrate purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min) to afford the title compound (**Example 025**, 0.0051 g, 0.011 mmol, 27%). LC-MS (Method A2): 0.69 min, $[M + H]^+$= 476.1; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.58 (d, J = 2.1 Hz, 1H), 7.88 (dd, J = 8.4, 2.0 Hz, 1H), 7.82 - 7.73 (m, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 6.95 (s, 1H), 6.55 (s, 1H), 5.45 (s, 2H), 2.79 (q, J = 7.3 Hz, 2H), 1.91 (s, 6H), 1.25 (t, J = 7.5 Hz, 3H).

Example 026: 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-N-(4-fluorophenyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



(Ex. 026)

Intermediate 026a: 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-N-(4-fluorophenyl)-6-(2-trityl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



(026a)

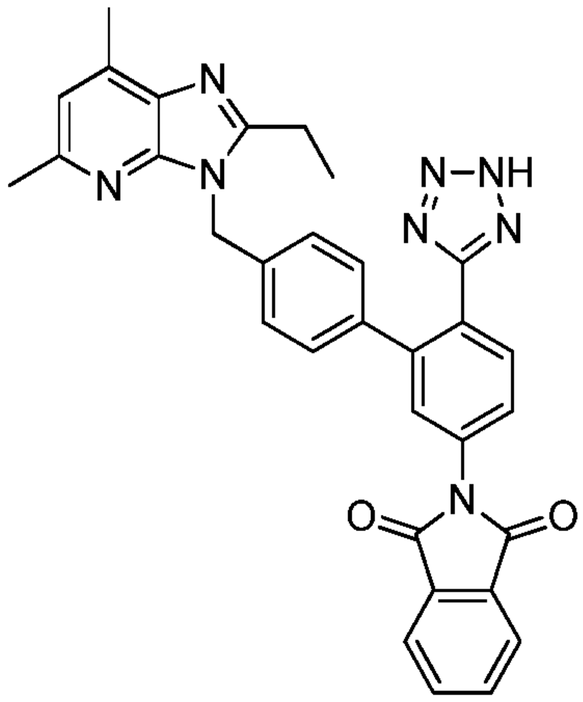
To a solution of **Intermediate 001i** (0.040 g, 0.060 mmol) in DCE (2 mL) containing 4A molecular sieves (previously heated at 110 °C under vacuum for 1 h prior to use) was added triethylamine (0.017 mL, 0.120 mmol), pyridine (0.0097 mL, 0.120 mmol) and (4-fluorophenyl)boronic acid (0.025 g, 0.180 mmol). The reaction mixture was stirred for 15 min, then copper (II) acetate (0.011 mg, 0.060 mmol) was added. The reaction vial was sealed under an air atmosphere and allowed to stir at RT overnight. After 16 h, the reaction mixture was filtered over Celite, washed with DCM and concentrated to afford a green residue (**Intermediate 026a**) which was used as such in the next step. LC-MS (Method A2): 1.07 min, $[M + H]^+$= 761.5.

Example 026: 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-N-(4-fluorophenyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine

A solution of **Intermediate 026a** (0.040 g, 0.053 mmol) in DCM (2 mL) was treated with triethylsilane (0.084 mL, 0.526 mmol) followed by TFA (0.203 mL, 2.63 mmol). The reaction was stirred at RT for 10 min, then concentrated to dryness. The residue was taken up in DMF, the mixture was neutralized with a few drops of triethylamine, filtered and purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min). A further purification by preparative LC-MS was performed on the resulting sample (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% TFA; Mobile Phase B: 95:5 ACN: H_2O with 0.1% TFA; Gradient: 20-60% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20

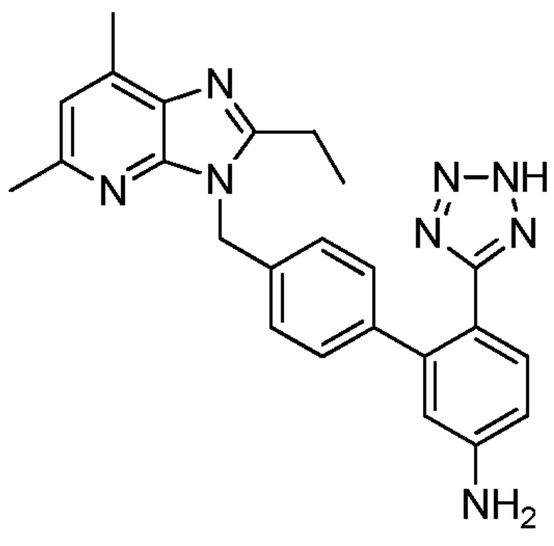
mL/min) to afford the title compound (**Example 026,** 0.0021 g, 0.004 mmol, 8%). LC-MS (Method A2): 0.78 min, $[M + H]^+$= 519.1; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.94 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.23 - 7.00 (m, 9H), 6.95 (d, J = 1.8 Hz, 1H), 5.55 (s, 2H), 2.96 - 2.90 (m, 2H), 2.51 (br s, 6H), 1.21 (t, J = 7.5 Hz, 3H).

Example 027: 2-(4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione



(Ex. 027)

Intermediate 027a 4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



(027a)

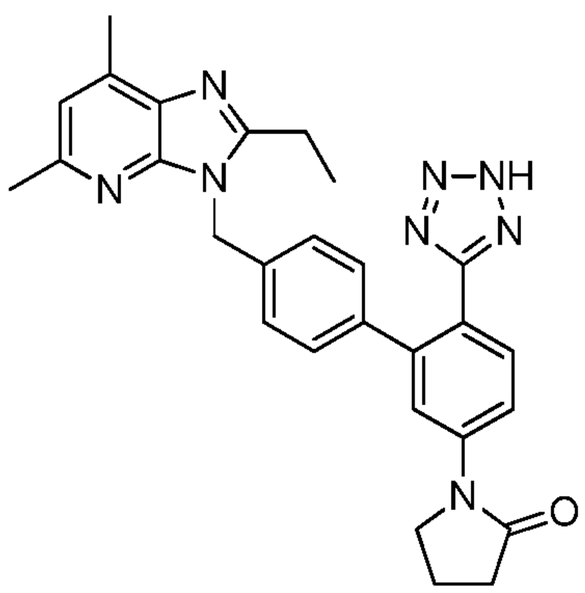
To a solution of **Intermediate 001g** (0.270 g, 0.594 mmol) in MeOH (30 mL) was added zinc powder (0.777 g, 11.88 mmol) followed by ammonium chloride (0.953 g, 17.82 mmol) and the mixture was heated at reflux at 70 °C overnight. Then the reaction mixture was partially concentrated under reduced pressure and the residue was partitioned between EtOAc (30 mL) and saturated aqueous NH_4Cl (30 mL). The corresponding mixture was stirred vigorously for 2 h and filtered. The filtrate was further diluted with EtOAc and the aqueous phase was separated and again extracted with EtOAc (2x). The

combined organic phase was dried over $MgSO_4$, filtered and concentrated to afford the title compound (**Intermediate 027a**, 0.148 g, 0.349 mmol, 59%). LC-MS (Method A2): 0.59 min, $[M + H]^+$= 425.3; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.26 (d, J = 8.3 Hz, 1H), 7.03 - 6.92 (m, 5H), 6.66 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 5.43 (s, 2H), 2.74 (q, J = 7.3 Hz, 2H), 2.55 (s, 6H), 1.18 (t, J = 7.5 Hz, 3H).

Example 027: 2-(4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)isoindoline-1,3-dione

A solution of **Intermediate 027a** (0.010 g, 0.024 mmol) in AcOH (0.5 mL) was treated with phthalic anhydride (0.035 g, 0.236 mmol). The reaction vial was sealed and heated atat 100°C for 16 h. The mixture was concentrated, dissolved in DMF, filtered and purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% TFA; Mobile Phase B: 95:5 ACN: H_2O with 0.1% TFA; Gradient: 15-55% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford the title compound (**Example 027,** 0.0081 g, 0.015 mmol, 62%). LC-MS (Method A2): 0.74 min, $[M + H]^+$= 555.4; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (br. s., 2H), 7.94 (br s, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.71 - 7.62 (m, 2H), 7.18 - 7.05 (m, 5H), 5.55 (s, 2H), 2.90 (q, J = 7.4 Hz, 2H), 2.54 (br s, 6H), 1.21 (t, J = 7.4 Hz, 3H).

Example 028: 1-(4'-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-6-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)pyrrolidin-2-one

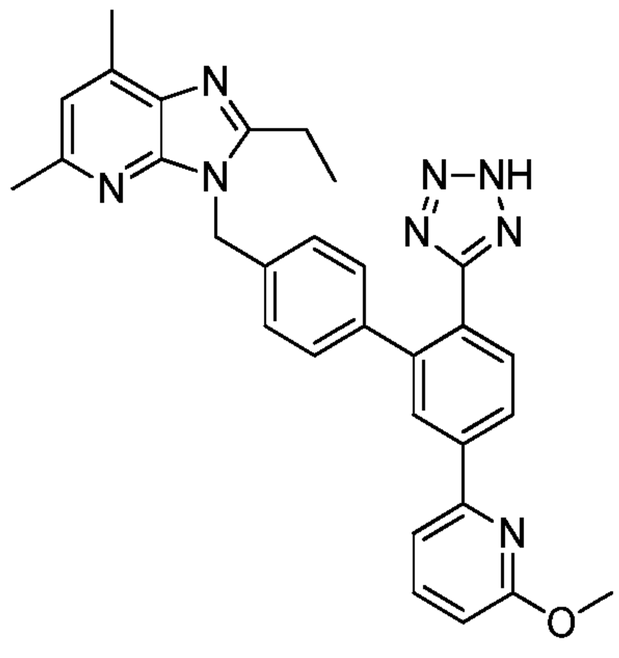


(Ex. 028)

A suspension of **Intermediate 027a** (0.009 g, 0.021 mmol) in DMF (1 mL) was treated with 4-chlorobutanoyl chloride (7.13 μL, 0.064 mmol) and NaH (0.0025 g, 0.064 mmol). The corresponding reaction mixture was allowed to stir at RT overnight. The reaction was quenched with a few drops of H_2O, filtered and purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10

mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min). The material was further purified via a second preparative LC-MS (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford the title compound (**Example 028,** 0.008 g, 0.020 mmol, 95%). LC-MS (Method A2): 0.66 min, $[M + H]^+$= 493.3; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 7.65 - 7.60 (m, 1H), 7.59 - 7.51 (m, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 9.2 Hz, 3H), 5.42 (s, 2H), 3.88 (t, J = 6.9 Hz, 2H), 2.79 (q, J = 7.5 Hz, 2H), 2.52 - 2.48 (m, 8H), 2.12 - 2.00 (m, 2H), 1.26 (t, J = 7.4 Hz, 3H).

Example 029: 2-Ethyl-3-((5'-(6-methoxypyridin-2-yl)-2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

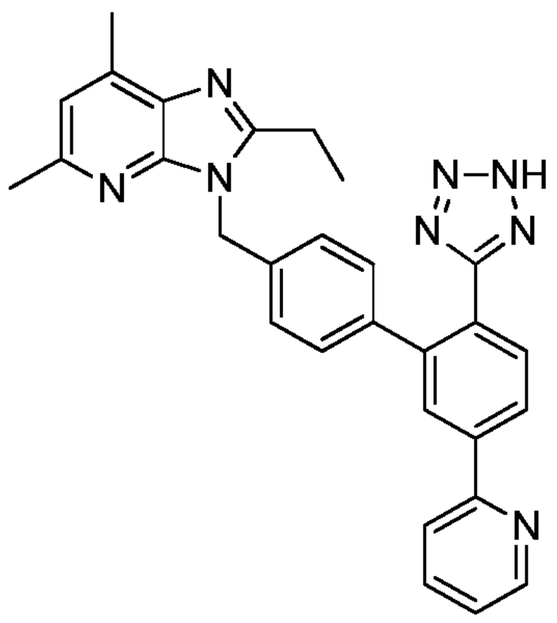


(Ex. 029)

To a vial containing (**Intermediate 001j** (0.030 g, 0.041 mmol), $Pd(Ph_3P)_4$ (4.74 mg, 4.11 μmol) and 2-methoxy-6-(tributylstannyl)pyridine (0.033 g, 0.082 mmol) was added toluene (1 mL). The mixture was sparged with N_2 for 2 min before the reaction vessel was sealed and heated at 110 °C for 3 h. The reaction mixture was cooled to RT and concentrated. The crude residue was taken up in DCM (1 mL) and treated with triethylsilane (0.033 mL, 0.205 mmol) followed by TFA (0.127 mL, 1.642 mmol). The resulting reaction mixture was stirred for 10 min before being concentrated, taken up in DMF and purified via preparative HPLC with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-57% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min. Fractions containing

the desired product were combined and dried via centrifugal evaporation to afford the title compound (**Example 029,** 0.008 g, 0.015 mmol, 36%). LC-MS (Method A2): 0.83 min, $[M + H]^+$= 517.0; ^{1}H NMR (600MHz, DMSO-d_6) δ ppm 8.13 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.95 (s, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 5.45 (s, 2H), 3.93 (s, 3H), 2.79 (q, *J* = 7.5 Hz, 2H), 2.55 (s, 9H), 1.25 (t, *J* = 7.5 Hz, 3H).

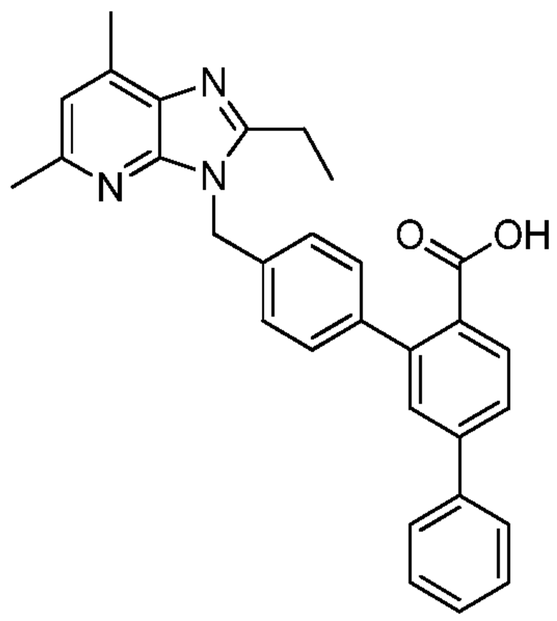
Example 030: 2-Ethyl-5,7-dimethyl-3-((5'-(pyridin-2-yl)-2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3*H*-imidazo[4,5-*b*]pyridine



(Ex. 030)

A mixture of **Intermediate 001j**(0.030 g, 0.041 mmol), $Pd(Ph_3P)_4$ (0.005 mg, 4.11 µmol), 2-(tributylstannyl)pyridine (0.030 g, 0.082 mmol) and toluene (1 mL) was treated as described in **Example 29**. After cooling at RT, the reaction mixture was concentrated, retaken in DCM (1 mL) and treated with triethylsilane (0.033 mL, 0.205 mmol) followed by TFA (0.127 mL, 1.642 mmol) for 20 min. Then the reaction mixture was concentrated, the crude was taken up in DMF and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-52% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound **Example 030** (0.014 g, 0.027 mmol, 67%). LC-MS (Method A2): 0.64 min, $[M + H]^+$= 487.0; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.68 (d, *J* = 4.0 Hz, 1H), 8.17 (d, *J* = 5.2 Hz, 1H), 8.13 - 8.03 (m, 2H), 7.90 (t, *J* = 7.6 Hz, 1H), 7.75 (br. s., 1H), 7.40 (dd, *J* = 7.2, 4.9 Hz, 1H), 7.12 (br. s., 2H), 7.03 (d, *J* = 6.3 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.77 (q, *J* = 7.3 Hz, 2H), 2.55 (s, 6H), 1.23 (t, *J* = 7.4 Hz, 3H).

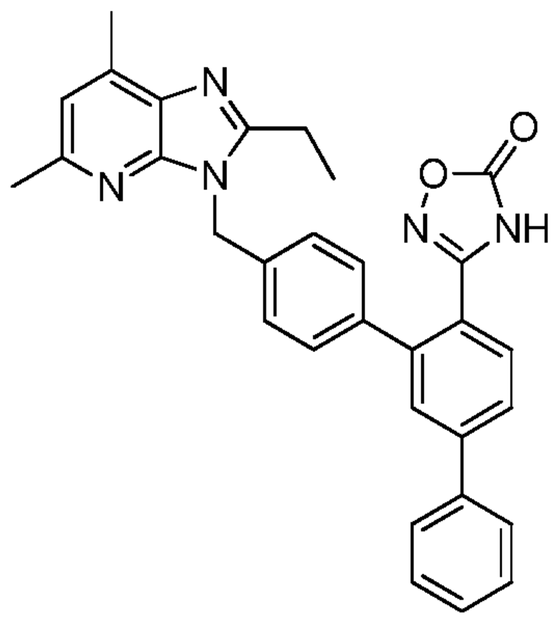
Example 031: 4''-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylic acid



(Ex. 031)

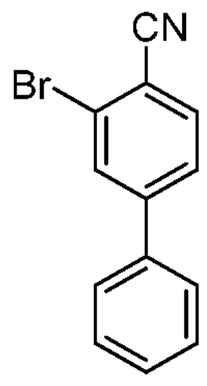
A solution of **Intermediate 001d**(0.035 g, 0.089 mmol) and 3-chloro-[1,1'-biphenyl]-4-carboxylic acid (0.031 g, 0.134 mmol) in dioxane (2.5 mL) was was treated with 2M aqueous K_3PO_4 (0.224 mL, 0.447 mmol) followed by $PdCl_2$(dppf) (0.0065 g, 8.94 µmol) as described in **Example 001**. LC-MS showed only traces of the desired compound. More $PdCl_2$(dppf) was added (0.0065 g, 8.94 µmol) and the reaction mixture was heated at 100°C overnight. The reaction mixture was cooled to RT, filtered over a pad of Celite/$MgSO_4$ and concentrated. The resulting residue was dissolved in DMF, filtered and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. to afford the title compound **Example 031** (0.005 g, 0.011 mmol, 12%). LC-MS (Method A2): 0.87 min, $[M + H]^+$= 462.0. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.81 - 7.66 (m, 4H), 7.56 (s, 1H), 7.51 - 7.44 (m, 2H), 7.43 - 7.36 (m, 3H), 7.16 (d, J = 8.1 Hz, 2H), 6.96 (s, 1H), 5.51 (s, 2H), 2.83 (q, J = 7.5 Hz, 2H), 2.53 (s, 6H), 1.27 (t, J = 7.5 Hz, 3H).

Example 032: 3-(4''-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4*H*)-one



(Ex. 032)

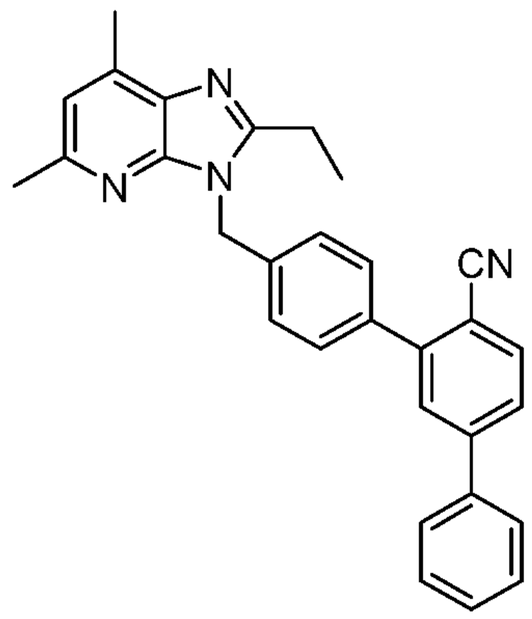
Intermediate 032a: 3-bromo-[1,1'-biphenyl]-4-carbonitrile



(032a)

To a vial charged with [1,1'-biphenyl]-4-carbonitrile (500 mg, 2.79 mmol), NBS (447 mg, 2.51 mmol) (recrystallized), CSA (324 mg, 1.395 mmol) and diacetoxypalladium (62.6 mg, 0.279 mmol) was added DCE (11.2 mL). The reaction mixture was sealed and heated at 80 °C for 15 h (*J. Org. Chem*, **2013**, *78*, 2786). The reaction mixture was diluted with EtOAc and concentrated directly onto Celite® for ISCO purification (0-50% EtOAc/Hex) to afford the title compound **Intermediate 032a** (400 mg, 1.550 mmol, 55.5 % yield) as a white solid. LC-MS (Method A2): 1.07 min, [M+H] No ion observed; ^{1}H NMR (400MHz, DMSO-d_6) 8.20 (d, J= 1.6 Hz, 1H), 8.027 (d, *J* = 8 Hz, 1H), 7.92 - 7.89 (m, 1H), 7.81 - 7.79 (m, 2H), 7.55 - 7.48 (m, 3H).

Intermediate 032b: 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(032b)

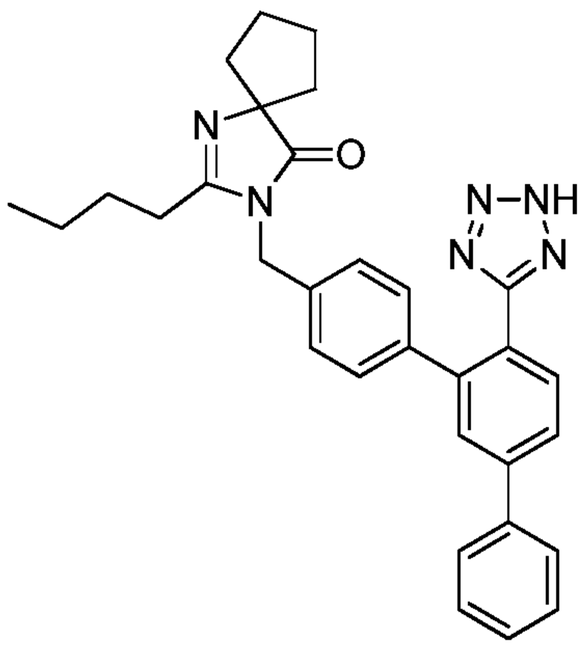
To a solution of **Intermediate 001d**(150 mg, 0.383 mmol) and **I-003A** (189 mg, 0.498 mmol) in dioxane (3 mL) was added K_3PO_4 (2 M, aq) (0.575 mL, 1.150 mmol) followed by PdCl2(dppf) (28.0 mg, 0.038 mmol). The resulting mixture was sparged with N_2 for 2 min before the vessel was sealed and heated at 120 °C for 45 min in the microwave. The crude reaction was diluted with EtOAc and filtered through celite. The filtrate was concentrated and the residue was dissolved in a small amount of methylene chloride and charged to a 40 g silica gel cartridge which was eluted with a 30 min gradient ofof 0-100% EtOAc in hexane to afford the title compound (**Intermediate 032b**, 133 mg, 0.301 mmol, 78 % yield), as a white solid. LC-MS (Method A2): 0.92 min, $[M + H]^+ = 443.1$; ^1H NMR (500MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 - 7.65 (m, 2H), 7.64 - 7.61 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.53 - 7.47 (m, 2H), 7.47 - 7.42 (m, 1H), 7.31 - 7.26 (m, 3H), 6.94 (s, 1H), 5.56 (s, 2H), 2.90 - 2.83 (m, 2H), 2.67 (s, 3H), 2.63 (s, 3H), 1.37 (t, *J* = 7.6 Hz, 3H).

Example 032: 3-(4''-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4*H*)-one

Hydroxylamine hydrochloride (70.7 mg, 1.017 mmol) was dissolved in DMSO (1 mL). TEA (0.142 mL, 1.017 mmol) was added and the reaction was allowed to stir at RT for 5 minutes. The mixture was then diluted with THF (1 mL) and filtered. The THF was then concentrated from the filtrate under reduced pressure and the resulting DMSO solution was added to a solution of **Intermediate 032b** (15 mg, 0.034 mmol) in 0.5 mL of DMSO. The mixture was heated at 80 °C for 15 hours. The reaction was diluted with 4 mL of H_2O and the precipitate was filtered off. This precipitate was redissolved in DMF (2 mL) and DBU (0.026 mL, 0.169 mmol) was added. CDI (55.0 mg, 0.339 mmol) was then added and the reaction mixture was allowed to stir at RT for 10 minutes before being

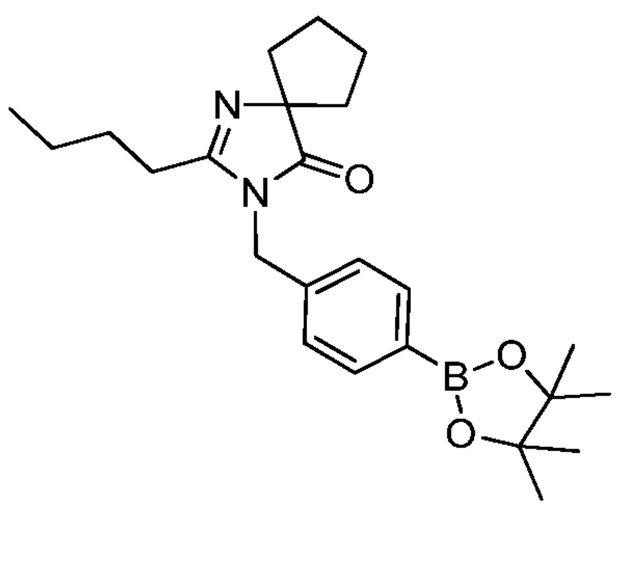
filtered and purified by preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (**Example 032**, 1.9 mg, 0.004 mmol, 11% yield). LC-MS (Method A2): 0.84 min, $[M + H]^+ = 502.1$; ^1H NMR (500MHz, $CDCl_3$) δ 7.80 - 7.71 (m, 1H), 7.69 - 7.58 (m, 1H), 7.51 - 7.44 (m, 1H), 7.42 - 7.37 (m, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.96 (s, 1H), 5.49 (s, 2H), 2.80 (q, *J* = 7.4 Hz, 2H), 2.55 (s, 6H), 1.23 (t, *J* = 7.5 Hz, 3H).

Example 033: 3-((6'-(2*H*-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 033)

Intermediate 033a: 2-butyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,3-diazaspiro[4.4] non-1-en-4-one

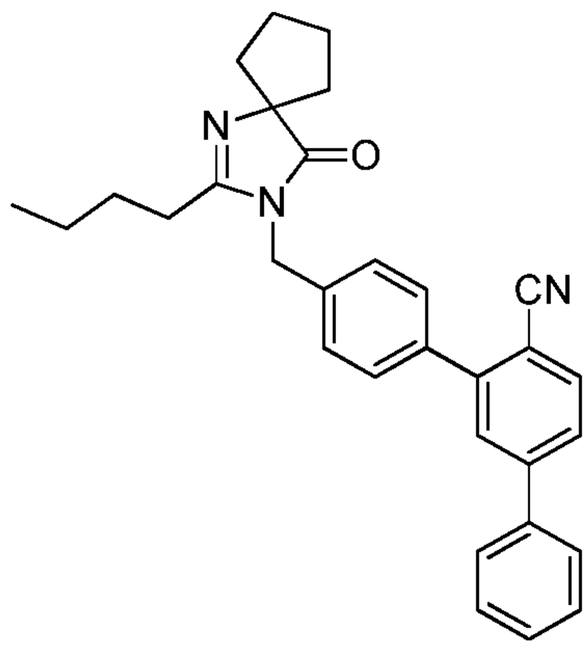


(033a)

A suspension of 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one, HCl (0.150 g, 0.650 mmol) and 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.232 g, 0.780 mmol) in DMF (3.25 mL) was treated with potassium carbonate (0.270 g, 1.950 mmol)

according to the procedure described in *Synth. Commun.*, **2005**, 35, 1979. After 20 h of stirring, the reaction mixture was diluted with EtOAc and filtered over Celite®. The organic phase was washed with brine, dried over $MgSO_4$, re-filtered over Celite®, concentrated and purified by ISCO (EtOAc/Hexanes, 0-100%) to afford the title compound (**Intermediate 033a**, 0.200 g, 0.487 mmol, 75.0 % yield) as a viscous oil. LC-MS (Method A2): 0.89 min, $[M + H]^+$= 411.2; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.68 (s, 2H), 2.29 - 2.21 (m, 2H), 2.03 - 1.87 (m, 6H), 1.86 - 1.74 (m, 2H), 1.59 - 1.49 (m, 2H), 1.38 - 1.21 (m, 14H), 0.85 (t, *J* = 7.4 Hz, 3H).

Intermediate 033b: 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



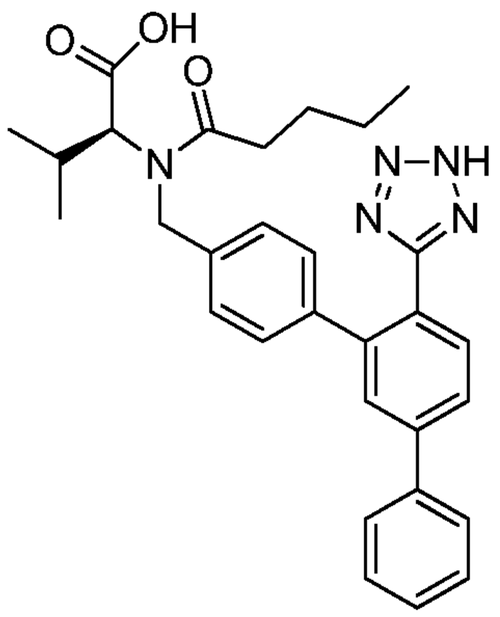
(033b)

To a solution of **Intermediate 033a** (0.050 g, 0.122 mmol) and **Intermediate 032a** (0.047 g, 0.183 mmol) in dioxane (3 mL) was added K_3PO_4 (2 M, aq., 0.183 mL, 0.366 mmol) followed by $PdCl_2(dppf)$ (0.009 g, 0.012 mmol). The resulting mixture was sparged with N_2 for 2 min before the vessel was sealed and heated at 120 °C for 45 min under microwave irradiation. The reaction mixture was cooled to RT, diluted with EtOAc and filtered over a pad of Celite®/$MgSO_4$. The filtrate was concentrated to a brown residue which was purified by ISCO (EtOAc/Hexanes, 0-100%) to afford the title compound (**Intermediate 033b,** 0.053 g, 0.115 mmol, 94 % yield) as a viscous oil. LC-MS (Method A2): 0.96 min, $[M + H]^+$= 462.2; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 7.9 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.64 - 7.57 (m, 4H), 7.53 - 7.40 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.76 (s, 2H), 2.39 - 2.33 (m, 2H), 2.04 - 1.90 (m, 6H), 1.90 - 1.80 (m, 2H), 1.61 (dt, *J* = 15.5, 7.6 Hz, 2H), 1.42 - 1.30 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

Example 033: 3-((6'-(2*H*-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4] non-1-en-4-one

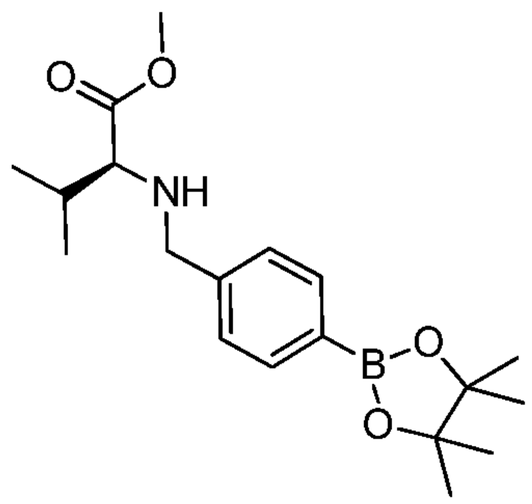
A vial containing **Intermediate 033b** (0.053 g, 0.115 mmol) and dibutyltin oxide (0.057 g, 0.230 mmol) in toluene (1.15 mL) was treated with TMS-N_3 (0.152 mL, 1.148 mmol) according to the procedure described for **Intermediate 001g**. After cooling, the reaction mixture was diluted with MeOH and EtOAc and quenched by the portionwise addition of a 10% aqueous solution of CAN (6.30 g, 1.148 mmol) until bubbling ceased. Then the organic phase was washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered over Celite® and concentrated. The crude residue was taken up in DMF, filtered and purified via preparative LC-MS (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-100% B over 25 minutes, then a 10-minute hold at 100% B; Flow: 20 mL/min) to afford 0.0055 g (0.011 mmol, 10%) of the title compound **Example 033**. LC-MS (Method A2): 0.85 min, $[M + H]^+$= 505.1; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 7.88 - 7.78 (m, 3H), 7.77 - 7.70 (m, 2H), 7.55 - 7.47 (m, 2H), 7.46 - 7.39 (m, 1H), 7.19 (d, J = 7.7 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 4.69 (s, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.92 - 1.76 (m, 6H), 1.67 (d, J = 6.6 Hz, 2H), 1.48 (quint, J = 7.4 Hz, 2H), 1.27 (sext, J = 7.4 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H).

Example 034: (S)-2-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoic acid



(Ex. 034)

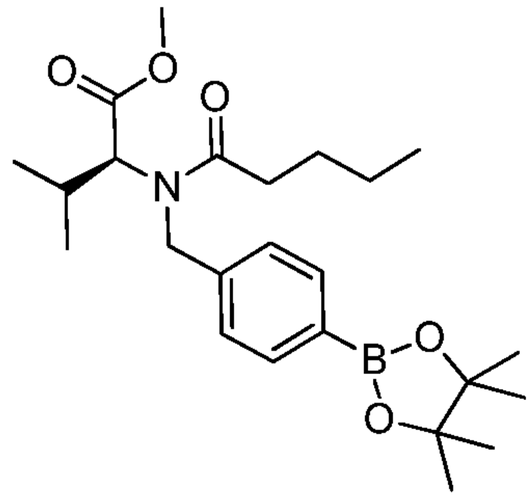
Intermediate 034a: (S)-Methyl 3-methyl-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl) amino)butanoate



(034a)

To a suspension containing (*S*)-methyl 2-amino-3-methylbutanoate, HCl (0.169 g, 1.010 mmol) and 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.250 g, 0.842 mmol) in ACN (2.81 mL) was added potassium carbonate (0.465 g, 3.37 mmol). The reaction vessel was sealed and the mixture was heated at 70 °C for 5 h. The cooled reaction mixture was diluted with EtOAc and filtered over Celite®. The resulting mixture was concentrated to afford the crude product, which was used as such in the next step. LC-MS (Method A2): 0.75 min, $[M + H]^+$= 348.1.

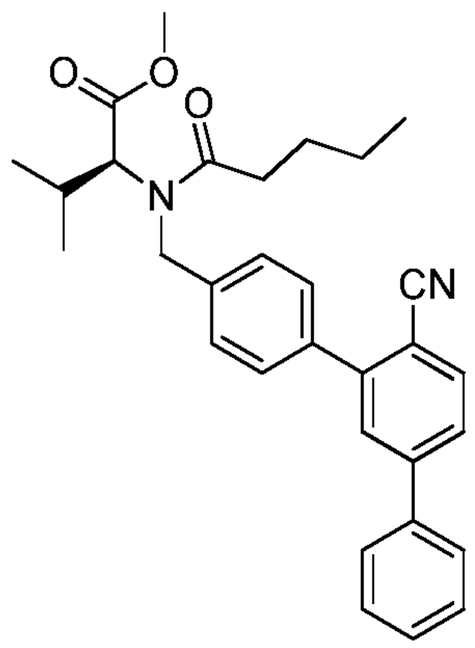
Intermediate 034b: (S)-Methyl 3-methyl-2-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl) pentanamido)butanoate



(034b)

To a solution of crude **Intermediate 034a** (0.250 g, 0.720 mmol) in DCM (7.2 mL) was added Hünig's base (0.63 mL, 3.60 mmol) followed by valeryl chloride (0.17 mL, 1.440 mmol). After 15 min of stirring, the reaction mixture was concentrated and purified by ISCO (EtOAc/Hexanes, 0-50%) to afford the title compound (**Intermediate 034b,** 0.250 g, 0.406 mmol, 56.4 % yield) as a yellow oil. LC-MS (Method A2): 1.18 min, $[M + H]^+$= 432.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.98 (d, *J* = 10.6 Hz, 1H), 4.63 (s, 2H), 3.44 (s, 3H), 2.32 - 2.23 (m, 2H), 2.21 - 2.12 (m, 1H), 1.67 - 1.52 (m, 2H), 1.35 - 1.31 (m, 12H), 1.29 - 1.15 (m, 2H), 1.00 - 0.93 (m, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 - 0.77 (m, 3H).

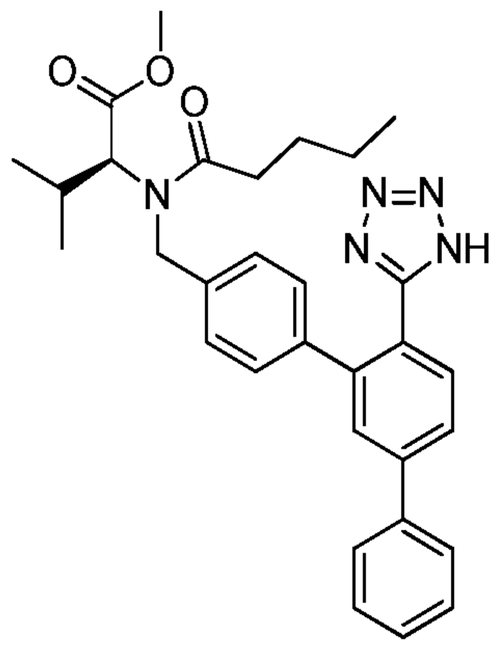
Intermediate 034c: (S)-Methyl 2-(N-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-3-methylbutanoate



(034c)

To a solution of **Intermediate 034b** (0.060 g, 0.139 mmol) and **Intermediate 032a** (0.054 g, 0.209 mmol) in dioxane (3 mL) was added K_3PO_4 (2M aq, 0.209 mL, 0.417 mmol) followed by $PdCl_2(dppf)$ (0.011 g, 0.014 mmol) and the resulting mixture was reacted as described in **Example 033b**. The cooled reaction mixture was diluted with EtOAc and filtered over a pad of Celite®/$MgSO_4$. The filtrate was concentrated to a brown residue which was purified by ISCO (EtOAc/Hexanes, 0-100%) to afford the title compound (**Intermediate 034c,** 0.064 g, 0.080 mmol, 57.2 %) as a yellow oil. LC-MS (Method A2): 1.21 min, $[M + H]^+$= 483.1; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 - 7.78 (m, 1H), 7.72 - 7.66 (m, 1H), 7.65 - 7.56 (m, 4H), 7.54 - 7.39 (m, 4H), 7.36 - 7.28 (m, 2H), 4.97 (d, *J* = 10.3 Hz, 1H), 4.70 (s, 2H), 3.47 (s, 3H), 2.53 - 2.34 (m, 3H), 1.70 - 1.56 (m, 2H), 1.36 - 1.28 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 6H), 0.93 - 0.89 (m, 3H).

Intermediate 034d: (S)-Methyl 2-(N-((6'-(1H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoate

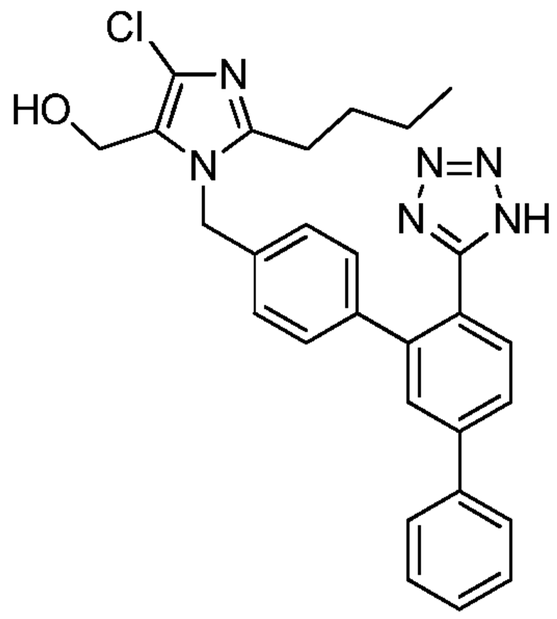


(034d)

To a vial containing **Intermediate 034c** (0.060 g, 0.124 mmol) was added dibutyltin oxide (0.031 g, 0.124 mmol) and toluene (2 mL) followed by TMS-N_3 (0.083 mL, 0.622 mmol). The reaction vial was sealed and the mixture heated at 100 °C overnight. After 14 h of heating, LC-MS showed 70% conversion to the desired tetrazole. Another aliquot of TMS-N_3 (0.083 mL, 0.622 mmol) was added and heating was continued for another 6 h. The cooled reaction mixture was then diluted with EtOAc and a small amount of MeOH was added to fully solubilize the tetrazole product. To this organic phase was added CAN (10% aqueous) (6.82 g, 1.244 mmol) and the residue was vigorously stirred until bubbling ceased. The organic phase was separated, concentrated and used as such in the next step (quantitative yield of **Intermediate 034d** was assumed). LC-MS (Method A2): 1.07 min, $[M + H]^+$= 526.1.

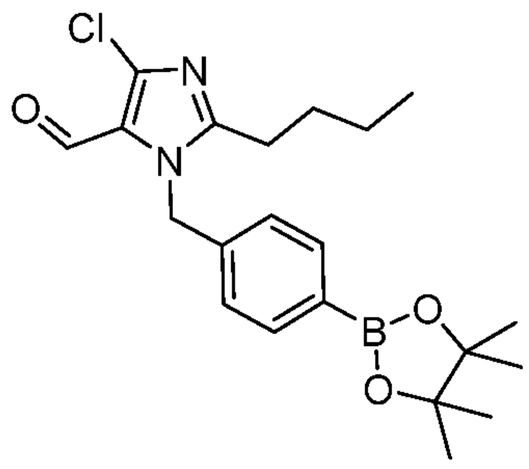
Example 034: (S)-2-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoic acid To a solution of crude **Intermediate 034d** (0.050 g, 0.095 mmol) in THF (1 mL) was added H_2O (1 mL) followed by LiOH monohydrate (0.040 g, 0.951 mmol). The resulting emulsion was sonicated and vigorously stirred for 20 min before being heated at 65°C overnight. After cooling to RT, the mixture was diluted with EtOAc and washed with 1 M HCl. The cloudy organic phase was concentrated to a crude yellow oil, which was taken up in DMF, filtered and purified via preparative LC-MS (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 0.012 g (0.024 mmol, 25%) of the title compound **Example 034**. LC-MS (Method A2): 1.01 min, $[M + H]^+$= 512.1; ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C) δ ppm 7.79 - 7.67 (m, 4H), 7.62 - 7.58 (m, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.43 - 7.36 (m, J = 7.7 Hz, 1H), 7.26 - 7.11 (m, 4H), 4.70 - 4.47 (m, 2H), 3.58 - 3.50 (m, 1H), 2.40 - 2.15 (m, 3H), 1.61 - 1.43 (m, 2H), 1.36 - 1.21 (m, 2H), 0.98 (d, J = 6.3 Hz, 3H), 0.81 (d, J = 6.9 Hz, 6H). [Note: VT NMR used to coalesce rotomer peaks].

Example 035: (1-((6'-(1H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methanol



(Ex. 035)

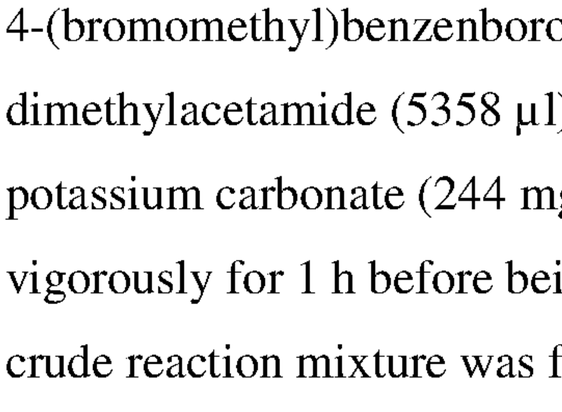
Intermediate 035a: 2-Butyl-4-chloro-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-imidazole-5-carbaldehyde



(035a)

A solution of 2-butyl-4-chloro-1H-imidazole-5-carbaldehyde (300 mg, 1.607 mmol) and 4-(bromomethyl)benzenboronic acid pinacol ester (501 mg, 1.688 mmol) in N,N-dimethylacetamide (5358 µl) was cooled to -10 °C. To this cooled solution was added potassium carbonate (244 mg, 1.768 mmol) (9:15 am) and the mixture was stirred vigorously for 1 h before being allowed to warm to RT and stir for an additional 3 h. The crude reaction mixture was filtered over Celite® and rinsed with a 3 mL of DMA. This solution containing the title compound (**Intermediate 035a**) was taken directly into the subsequent sodium borohydride reduction without further purification. LC-MS (Method A2): 1.19 min, $[M + H]^+$= 403.1, 405.1.

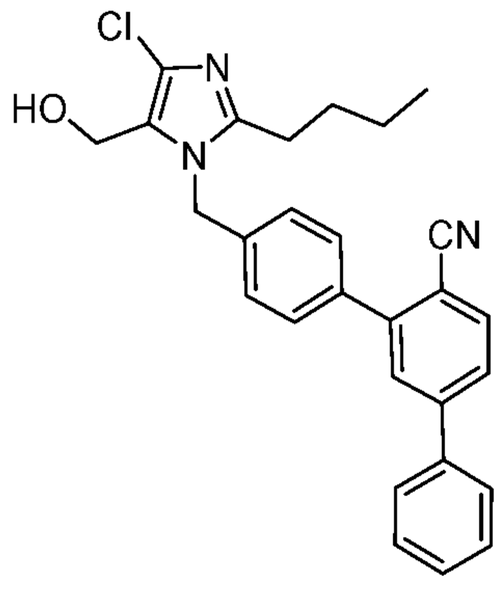
Intermediate 035b: (2-Butyl-4-chloro-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-imidazol-5-yl)methanol



(035b)

To the crude solution of **Intermediate 035a** (483 mg, 1.200 mmol) in DMA (9 mL) was added MeOH (9 mL) followed by sodium borohydride (113 mg, 3.00 mmol). After 2 h of stirring, 2 mL of AcOH was added to quench the reaction, and the resulting reaction mixture was concentrated to a crude residue. This residue was purified by ISCO (0-100% EtOAc/Hex) to afford the title compound (**Intermediate 035b,** 380 mg, 0.939 mmol, 78 % yield over the two-step process) as an amorphous white solid. LC-MS (Method A2): 0.91 min, $[M + H]^+$= 405.1, 407.1. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 5.23 (s, 2H), 4.46 (s, 2H), 2.57 - 2.50 (m, 2H), 1.70 - 1.57 (m, 2H), 1.38 - 1.29 (m, 14H), 0.86 (t, *J* = 7.4 Hz, 3H).

Intermediate 035c: 4''-((2-Butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



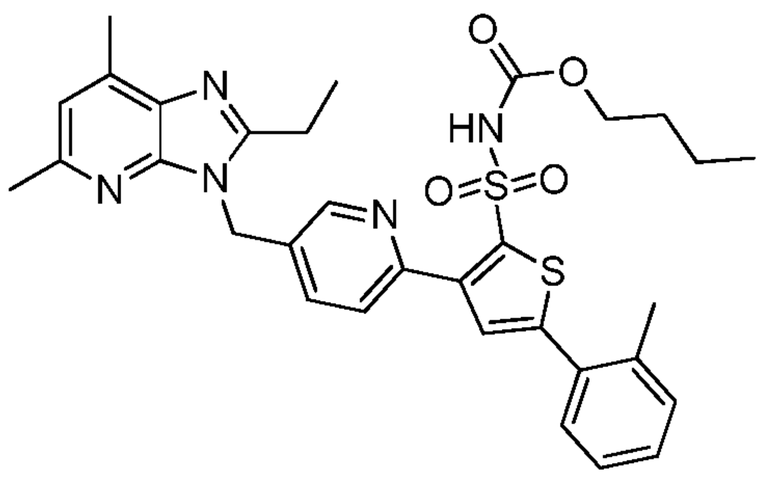
(035c)

To a solution of **Intermediate 035b** (90 mg, 0.222 mmol) and **Intermediate 032a** (86 mg, 0.334 mmol) in dioxane (3 mL) was added K_3PO_4 (2 M, aq) (0.222 mL, 0.445 mmol) followed by $PdCl_2$(dppf) (16.27 mg, 0.022 mmol). The resulting mixture was sparged with N_2 for 2 min before being sealed and heated at 120 °C for 45 min in the microwave. The reaction mixture was cooled to RT, diluted with EtOAc and filtered over a pad of Celite®/MgSO4. The filtrate was concentrated to a brown residue which was purified by ISCO (0-100% EtOAc/Hex) to afford the title compound (**Intermediate 035c**, 65 mg, 0.143 mmol, 64.1 % yield) as a light brown oil. LC-MS (Method A2): 0.97 min, $[M + H]^+$= 456.0, 458.0. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 - 7.80 (m, 1H), 7.70 - 7.65 (m, 2H), 7.64 - 7.56 (m, 4H), 7.53 - 7.42 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.30 (s, 2H), 4.54 (d, *J* = 5.3 Hz, 2H), 2.65 - 2.57 (m, 2H), 1.75 - 1.64 (m, 2H), 1.43 - 1.31 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

Example 035: (1-((6'-(1H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methanol

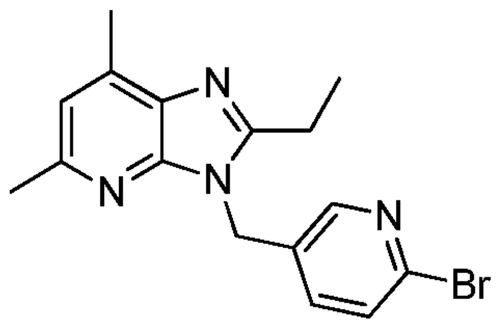
To a vial containing **Intermediate 035c** (65 mg, 0.143 mmol) was added dibutyltin oxide (35.5 mg, 0.143 mmol) and toluene (1.5 mL) followed by TMS-N_3 (0.095 mL, 0.713 mmol). The reaction mixture was sealed and heated at 100 °C behind a blast shield. After 16 h of heating, the reaction mixture was diluted with EtOAc and a small amount of MeOH was added to fully solubilize the tetrazole product. To this organic phase was added CAN (10% aqueous) and the residue was vigorously stirred until bubbling ceased. The organic phase was separated, concentrated, retaken in DMF, filtered and purified via preparative LC-MS with the following conditions: Column: XBridge Phenyl, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (**Example 035,** 0.001 g, 0.001 mmol, 1%). LC-MS (Method A2): 0.87 min, $[M + H]^+$= 499.0; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 7.6 Hz, 1H), 7.68 (br. s., 1H), 7.54 (s, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.41 - 7.34 (m, 1H), 7.19 (br. s., 2H), 6.94 (d, J = 7.3 Hz, 2H), 5.23 (s, 2H), 4.32 (s., 2H), 2.51 - 2.45 (m, 2H), 1.49 (quin, J = 7.4 Hz, 2H), 1.32 - 1.21 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H).

Example 039: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl) methyl) pyridin-2-yl)-5-(o-tolyl)thiophen-2-yl)sulfonylcarbamate



(Ex. 039)

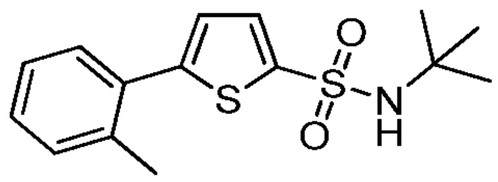
Intermediate 039a: 3-((6-Bromopyridin-3-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine



(039a)

To a solution of **Intermediate 001c** (0.491 g, 2.800 mmol) in NMP (15 mL) was added freshly pulverized NaOH (0.230 g, 5.74 mmol). The resulting mixture was stirred at RT under N_2 for 1 h and then it was cooled at 0°C and a solution of 2-bromo-5-(bromomethyl)pyridine (0.738 g, 2.94 mmol) in NMP (3 mL) was added over 5 min. The cooling bath was subsequently removed and the reaction mixture was stirred at RT for 48 h. The resulting mixture was cooled at 0°C and H_2O (40 mL) was added dropwise over *ca.* 15 min. The cooling bath was then removed and the resulting solution was stirred at RT for several hours. The resulting homogenous mixture was extracted with EtOAc (x2) and the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give an amber solid which was purified by ISCO (0-100%, EtOAc-DCM) to afford the pure product as a white solid (**Intermediate 039a,** 0.757 g, 78%). LC (Method B): 1.586 min; HRMS (ESI): Calcd. for $C_{16}H_{18}BrN_4$ $[M + H]^+$ *m/z* 345.0719; found 345.0715; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, *J* = 2.35 Hz, 1H), 7.57 (d, *J* = 8.22 Hz, 1H), 7.44 (dd, *J* = 8.22, 2.35 Hz, 1H), 6.94 (s, 1H), 5.45 (s, 2H), 2.81 (q, *J* = 7.43 Hz, 2H), 2.50 (s, 6H *under DMSO*), 1.22 (t, *J* = 7.43 Hz, 3H).

Intermediate 039b: N-(tert-Butyl)-5-(o-tolyl)thiophene-2-sulfonamide

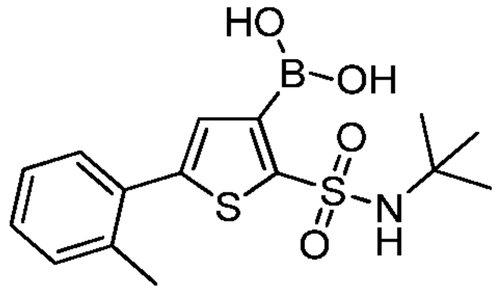


(039b)

A mixture of 5-bromo-N-(tert-butyl)thiophene-2-sulfonamide (0.596 g, 2.000 mmol) and o-tolylboronic acid (0.408 g, 3.00 mmol) in toluene-ethanol (9:1, 10 mL) was purged with a stream of N_2 for 20 min in a sealable vial. To this mixture was added $Pd(Ph_3P)_4$ (0.231 g, 0.200 mmol) and 2 M aqueous Na_2CO_3 (3.00 mL, 6.00 mmol), the vial was sealed and the mixture was stirred at 95°C overnight. The cooled mixture was filtered and the residue was washed with EtOAc. The filtrate was washed (sat. aq. $NaHCO_3$), dried (Na_2SO_4) and evaporated to give a dark brown gum. This material was purified by ISCO (0-50%, EtOAc-hexane) to give the title compound (**Intermediate 039b,** 0.490 g, 79 % yield) as a white solid. LC (Method B): 2.124 min; HRMS (ESI): Calcd. for $C_{15}H_{20}NO_2S_2$

$[M + H]^+$ *m/z* 310.0935; found: 310.0923; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 (s, 1H), 7.56 (d, *J* = 3.91 Hz, 1H), 7.40 (d, *J* = 7.83 Hz, 1H), 7.32 - 7.36 (m, 2H), 7.28 (d, *J* = 7.43 Hz, 1H), 7.18 (d, *J* = 3.91 Hz, 1H), 2.37 (s, 3H), 1.18 (s, 9H).

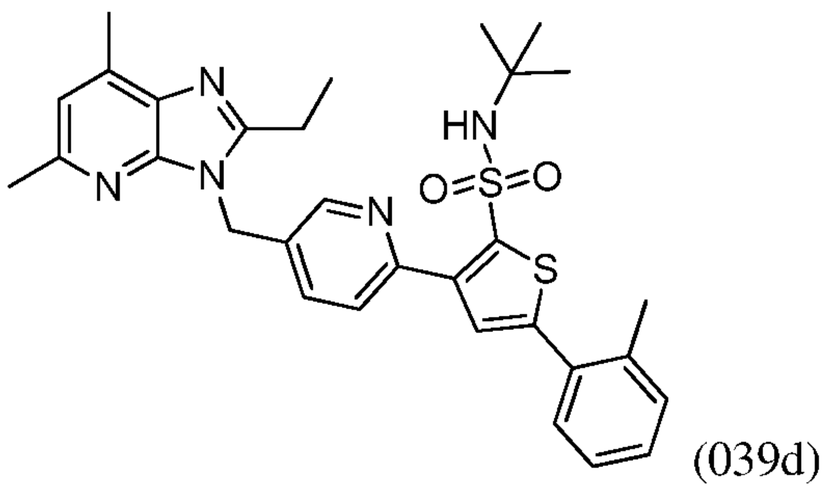
Intermediate 039c: (2-(N-(tert-Butyl)sulfamoyl)-5-(o-tolyl)thiophen-3-yl)boronic acid



(039c)

A solution of **Intermediate 039b** (0.409 g, 1.322 mmol) in dry THF (15 mL) was cooled at -78°C under N_2 and a solution of 1.6 M n-BuLi in hexanes (2.065 mL, 3.30 mmol) was added dropwise over 5 min. The mixture was stirred for 30 min and then the temperature was raised to about -20°C (-10°C to -18°C using ice-MeOH) and stirring was continued at that temperature for 3 h. The resulting light yellow solution was recooled at -78°C and triisopropyl borate (0.460 mL, 1.983 mmol) was added dropwise. Stirring was continued as the cooling bath discharged overnight. The resulting turbid mixture was quenched with 2M HCl (9.91 mL, 19.83 mmol) and the mixture was stirred for 30 min. This mixture was then partitioned with EtOAc-H_2O and the organic phase was separated, washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give a gum. This gum was purified by flash chromatography (ISCO 0-100%, EtOAc-hex) to afford the title compound (**Intermediate 039c,** 0.192 g, 41%). LC-MS (APCI): Calcd. for $C_{15}H_{19}BNO_4S_2$ $[M-H]^-$ *m/z* 352.0849; found: 352.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (s, 1H), 7.39 (d, *J* = 7.83 Hz, 1H), 7.23 - 7.33 (m, 4H), 2.38 (s, 3H), 1.18 (s, 9H).

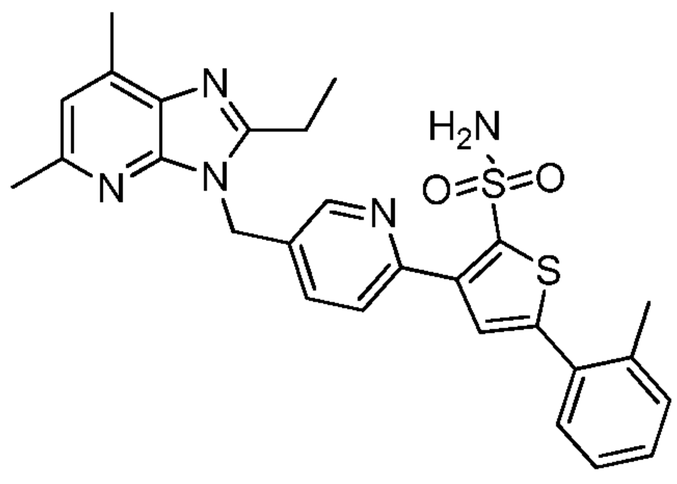
Intermediate 039d: N-(tert-Butyl)-3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(o-tolyl)thiophene-2-sulfonamide



(039d)

A mixture of **Intermediate 039a** (0.086 g, 0.250 mmol), **Intermediate 039c** (0.132 g, 0.375 mmol), 2 M aqueous Na_2CO_3 (0.50 mL, 1.00 mmol) and $Pd(Ph_3P)_4$ (0.029 g, 0.025 mmol) in toluene-ethanol (9:1, 10 mL) was treated as described in **Example 039b**. The cooled mixture was diluted with EtOAc and the organic phase was separated, dried (Na_2SO_4) and evaporated to give an amber gum. This material was taken up in DMF and purified by preparative LC (Method C) to give the title compound (**Intermediate 039d,** 0.163 g, 81 % yield) as a colourless gum which was used as such in the next step. LC (Method B): 2.169 min; HRMS (ESI): Calcd. for $C_{31}H_{36}N_5O_2S_2$ $[M + H]^+$ *m/z* 574.2310; found: 574.2332; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 7.84 - 7.93 (m, 2H), 7.68 (d, *J* = 7.83 Hz, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 7.43 Hz, 1H), 7.34 (dd, *J* = 3.72, 2.15 Hz, 2H), 7.24 - 7.32 (m, 1H), 7.08 (br s, 1H), 5.62 (br s, 2H), 2.97 (d, *J* = 7.04 Hz, 2H), 2.53 (d, *J* = 2.74 Hz, 6H), 2.40 (s, 3H), 1.28 (t, *J* = 7.43 Hz, 3H), 1.13 (s, 9H).

Intermediate 039e: 3-(5-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)pyridin-2-yl)-5-(o-tolyl)thiophene-2-sulfonamide



(039e)

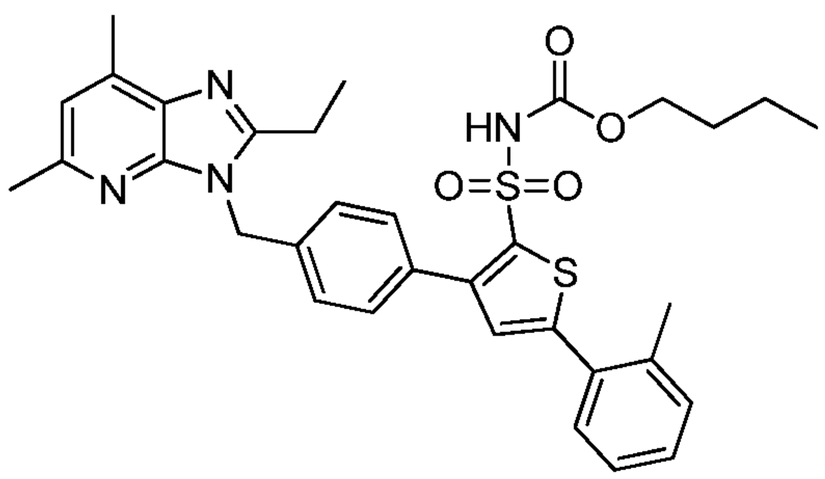
To a mixture of **Intermediate 039d** (0.144 g, 0.180 mmol) in DCM (3 mL) and anisole (0.196 mL, 1.796 mmol) was added TFA (5 mL) and the mixture was stirred at RT in a sealed flask overnight. The volatiles were removed under reduced pressure and the residue was evaporated from ACN solution (x2) to give a colourless gum. Quantitative yield of **Intermediate 039e** was assumed and this material was used as such in the next step without further purification. LC-MS (APCI): Calcd. for $C_{27}H_{28}N_5O_2S_2$ $[M + H]^+$ *m/z* 518.1684; found: 518.1.

Example 039: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)pyridin-2-yl)-5-(o-tolyl)thiophen-2-yl)sulfonylcarbamate

A solution of **Intermediate 039e** (0.045 g, 0.060 mmol) in pyridine (1 mL) was treated with triethylamine (0.063 mL, 0.450 mmol), 4-(pyrrolidin-1-yl)pyridine (0.027 g, 0.180 mmol) and butyl carbonochloridate (0.024 mL, 0.180 mmol) and the reaction mixture was

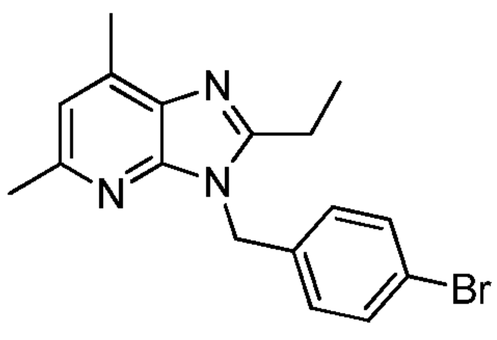
stirred at RT overnight. The reaction mixture was subsequently evaporated to dryness to give a solid residue. The residue was taken up in DMF, the mixture was acidified with AcOH and the solution was submitted to preparative LC purification (Method D) to give the title compound (**Example 039,** 0.023 g, 0.037 mmol, 62 % yield) as a white solid. LC (Method B): 2.125 min; HRMS (ESI): Calcd. for $C_{32}H_{36}N_5O_4S_2$ $[M + H]^+$ *m/z* 618.2209; found 618.2224; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.52 - 8.56 (m, 1H), 7.83 (d, *J* = 7.83 Hz, 1H), 7.65 (dd, *J* = 8.41, 2.15 Hz, 1H), 7.56 (s, 1H), 7.47 (d, *J* = 7.43 Hz, 1H), 7.34 - 7.38 (m, 2H), 7.27 - 7.33 (m, 1H), 6.98 (s, 1H), 5.56 (s, 2H), 3.96 (t, *J* = 6.46 Hz, 2H), 2.85 (q, *J* = 7.43 Hz, 2H), 2.51 - 2.52 (m, 6H), 2.39 - 2.44, (m, 3H), 1.36 - 1.45 (m, 2H), 1.26 (t, *J* = 7.43 Hz, 3H), 1.15 - 1.20 (m, 3H), 0.76 (t, *J* = 7.43 Hz, 3H).

Example 040: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(o-tolyl) thiophen-2-yl)sulfonylcarbamate



(Ex. 040)

Intermediate 040a: 3-(4-Bromobenzyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-*b*]pyridine

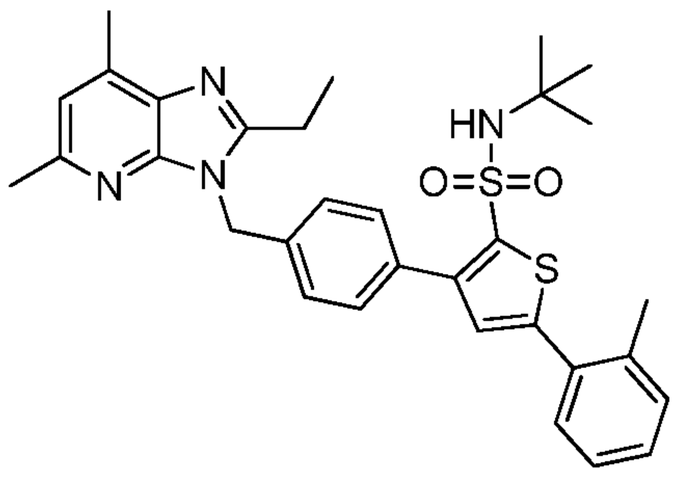


(040a)

A solution of **Intermediate 001c** (0.491 g, 2.800 mmol) in NMP (10 mL) was treated with a solution of NaOH (0.230 g, 5.74 mmol) in NMP (2 mL) followed with a solution of 1-bromo-4-(bromomethyl)benzene (0.735 g, 2.94 mmol) in NMP (2 mL) as described in **Example 039a**. The cooling bath was then removed and the reaction mixture was stirred at RT for 1.5 h. The mixture was cooled at 0°C and H_2O (40 mL) was added dropwise over *ca.*15 min. The cooling bath was then removed and the resulting slurry was stirred at RT for 1 h. The mixture was then filtered and the filter cake was washed with NMP-H_2O (1:3, 10 mL) and then H_2O (2 x 20 mL). The resulting solid was dried in

vacuo in a dessicator to give the title compound (**Intermediate 040a,** 0.637 g, 66.1 % yield) as a beige solid. This material was used as such in the next step. LC (Method B): 1.815 min; HRMS (ESI): Calcd. for $C_{17}H_{19}BrN_3$ $[M + H]^+$ *m/z* 344.0762; found 344.0756; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.47 - 7.53 (m, 2H), 7.02 - 7.08 (m, 2H), 6.93 (s, 1H), 5.41 (s, 2H), 2.74 (q, J = 7.4 Hz, 2H), 2.50 (s, 6H, *under DMSO*), 1.20 (t, J = 7.6 Hz, 3H).

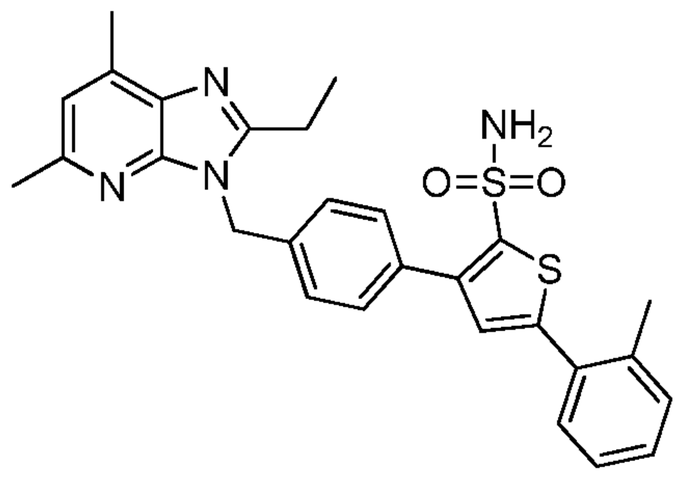
Intermediate 040b: N-(tert-Butyl)-3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(o-tolyl)thiophene-2-sulfonamide



(040b)

A mixture of **Intermediate 040a** (0.070 g, 0.203 mmol) and **Intermediate 039c** (0.090 g, 0.254 mmol), 2 M aqueous Na_2CO_3 (0.434 mL, 0.869 mmol) and $Pd(Ph_3P)_4$ (0.023 g, 0.020 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039b**. The cooled mixture was diluted with EtOAc, filtered through Na_2SO_4 and evaporated to give an amber gum. This material was purified by ISCO (0-100% EtOAc-DCM) to give the product (117 mg) as a gum. This material was taken up in DMF and was repurified by preparative LC (Method C) to give the title compound (**Intermediate 040b**, 0.082 g, 58.7 % yield) as a colourless gum which was used as such in the next step. LC (Method B): 2.211 min; HRMS (ESI): Calcd. for $C_{32}H_{37}N_4O_2S_2$ $[M + H]^+$ *m/z* 573.2358; found: 573.2377; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.60 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.42 (s, 1H), 7.19 - 7.36 (m, 6H), 7.08 (br. s., 1H), 5.57 (br. s., 2H), 2.88 (d, J = 7.0 Hz, 2H), 2.53 (s, 6H), 2.41 (s, 3H), 1.25 (t, J = 7.4 Hz, 3H), 0.96 (s, 9H).

Intermediate 040c: 3-(4-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)phenyl)-5-(o-tolyl) thiophene-2-sulfonamide



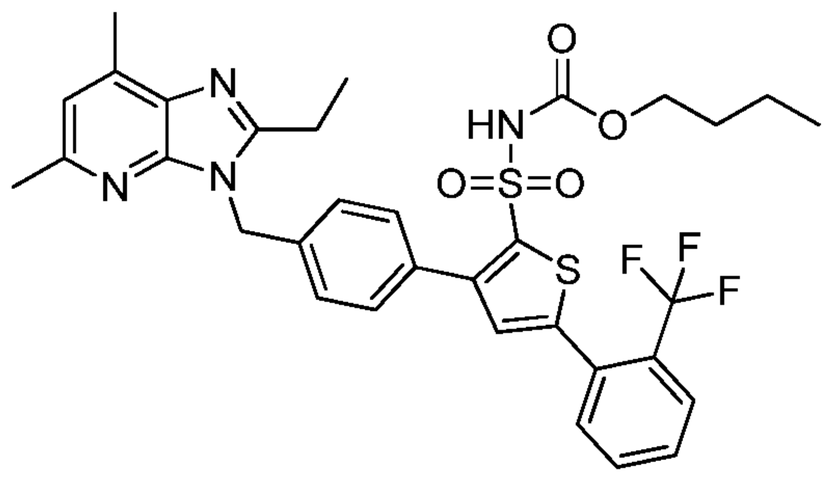
(040c)

To a solution of **Intermediate 040b** (0.074 g, 0.108 mmol) in DCM (3 mL) was added anisole (0.118 mL, 1.077 mmol) and then TFA (5 mL). The mixture was stirred at RT in a sealed flask for two days and then the volatiles were removed under reduced pressure and the residue was evaporated from ACN solution (x2) to give a nearly colourless gum. Quantitative yield was assumed and this material **Intermediate 040c** was used as such in the next step without further purification. LC-MS (APCI): Calcd. for $C_{28}H_{29}N_4O_2S_2$ [M + H]$^+$ *m/z* 517.1732; found: 517.2.

Example 040: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(o-tolyl) thiophen-2-yl)sulfonylcarbamate

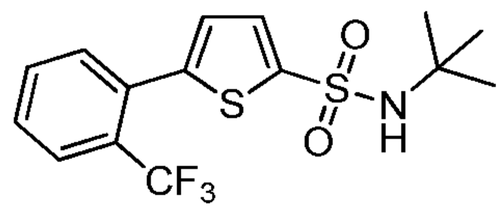
A solution of **Intermediate 040c** (0.034 g, 0.054 mmol) in pyridine (1 mL) was treated with triethylamine (0.056 mL, 0.405 mmol), 4-(pyrrolidin-1-yl)pyridine (0.024 g, 0.162 mmol) and butyl carbonochloridate (0.021 mL, 0.162 mmol) and the reaction mixture was stirred at RT overnight. The reaction mixture was subsequently evaporated to dryness to give a solid residue. The residue was taken up in DMF, the mixture was acidified with AcOH and the solution was submitted to preparative LC purification (Method C) to give the title compound (**Example 040,** 0.034 g, 86 % yield) as a white solid. LC (Method B): 2.202 min; HRMS (ESI): Calcd. for $C_{33}H_{37}N_4O_4S_2$ [M + H]$^+$ *m/z* 617.2256; found 617.2274; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.62 (m, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.4 Hz, 1H), 7.27 - 7.36 (m, 4H), 7.21 - 7.25 (m, 2H), 7.07 (br s, 1H), 5.57 (br s, 2H), 3.95 (t, J = 6.5 Hz, 2H), 2.89 (m, 2H), 2.53 (s, 6H), 2.42 (s, 3H), 1.36 - 1.42 (m, 2H), 1.26 (t, J = 7.4 Hz, 3H), 1.15 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H).

Example 045: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-(trifluoromethyl)phenyl)thiophen-2-yl)sulfonylcarbamate



(Ex. 045)

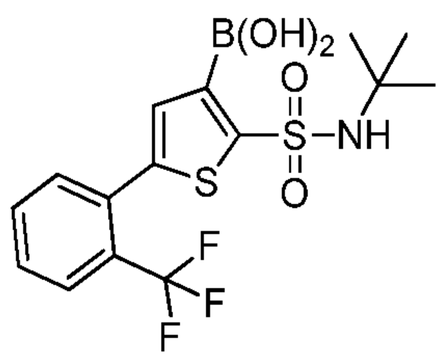
Intermediate 045a: N-(tert-Butyl)-5-(2-(trifluoromethyl)phenyl)thiophene-2-sulfonamide



(045a)

A vial charged with 5-bromo-N-(tert-butyl)thiophene-2-sulfonamide (1.00 g, 3.35 mmol), (2-(trifluoromethyl)phenyl)boronic acid (0.955 g, 5.03 mmol), 2M aqueous Na_2CO_3 (4.50 mL, 10.06 mmol) and $Pd(Ph_3P)_4$ (0.194 g, 0.168 mmol) in a mixture of toluene-ethanol (9:1, 20 mL) was reacted as described in Example 039b. The crude material was pre-adsorbed on 10 g of silica gel and purified by flash chromatography (ISCO 10-40%, EtOAc-hexane) to give the title compound (**Intermediate 045a,** 1.141 g, 3.14 mmol, 94%) as a white solid. LC-MS (Method H): 1.300 min, Calcd. for $C_{15}H_{15}F_3NO_2S_2$ $[M-H]^-$ *m/z* 362.1; found 362.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 (d, J = 7.4 Hz, 1H), 7.82 (s, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 3.9 Hz, 1H), 7.13 (d, J = 3.9 Hz, 1H), 1.16 (s, 9H).

Intermediate 045b: (2-(N-(tert-Butyl)sulfamoyl)-5-(2-(trifluoromethyl)phenyl)thiophen-3-yl)boronic acid

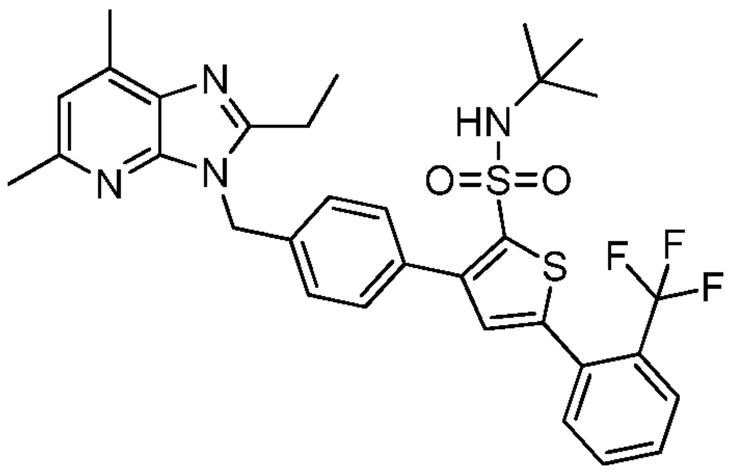


(045b)

A solution of **Intermediate 045a** (1.12 g, 3.08 mmol) in dry THF (25 mL) was treated with a solution of 1.2 M n-BuLi in hexanes (6.42 mL, 7.70 mmol) and triisopropyl borate (2.13 mL, 9.25 mmol) as described in **Example 039c**. The resulting turbid mixture was quenched with 2M aqueous HCl (9.91 mL, 19.83 mmol), then partitioned with EtOAc-H_2O and the organic phase was separated, washed with H_2O and brine, dried over Na_2SO_4

and evaporated. The resulting residue was purified by ISCO (10-40%, EtOAc/Hexane) to afford the desired compound as a pale yellow foam (**Intermediate 045b,** 0.717 g, 1.761 mmol, 57%). LC-MS (Method H): 1.296 min, Calcd. for $C_{15}H_{17}BF_3NO_4S_2$ $[M-H]^-$ *m/z* 406.1; found 406.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (s, 2H), 7.89 (d, J = 7.0 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.29 - 7.34 (m, 1H), 7.25 (s, 1H), 1.19 (s, 9H).

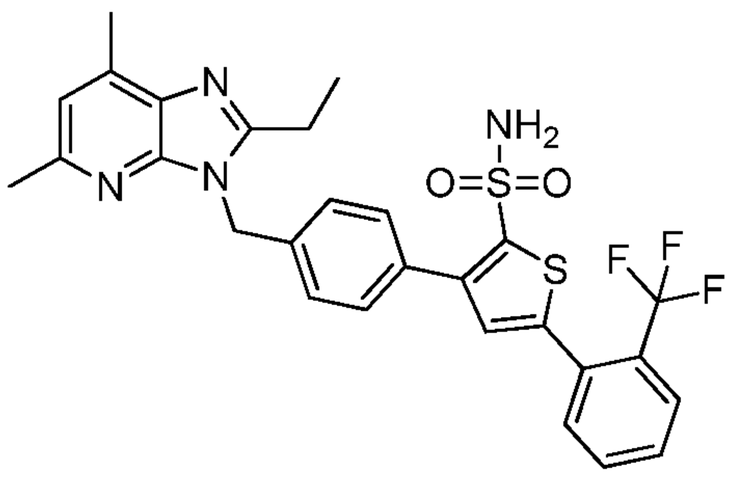
Intermediate 045c: N-(tert-Butyl)-3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-(trifluoromethyl)phenyl)thiophene-2-sulfonamide



(045c)

A mixture of **Intermediate 045b** (0.059 g, 0.145 mmol) and **Intermediate 040a** (0.050 g, 0.145 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039b**. The volatiles were then evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F, with 0.1% HCO_2H as modifier) to give the title compound (**Intermediate 045c,** 0.052 g, 0.083 mmol, 57%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{32}H_{34}F_3N_4O_2S_2$ $[M + H]^+$ *m/z* 627.2070; found: 627.2090.

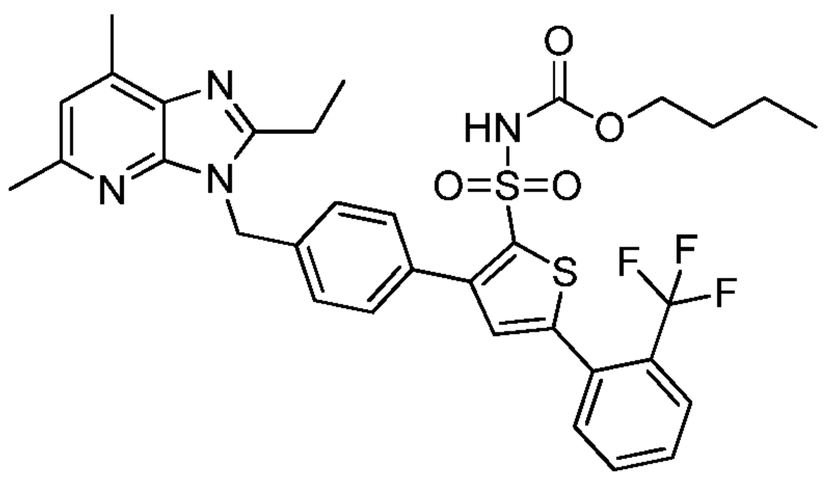
Intermediate 045d: 3-(4-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)phenyl)-5-(2-(trifluoromethyl)phenyl)thiophene-2-sulfonamide



(045d)

A solution of **Intermediate 045c** (0.052 g, 0.083 mmol) in DCM (3 mL) was treated with anisole (0.091 mL, 0.830 mmol) and TFA (5 mL) as described in **Example 040c** to afford the title compound **Intermediate 045d** quantitatively as a TFA salt. LC-MS (Method H): 1.340 min, Calcd. for $C_{28}H_{26}F_3N_4O_2S_2$ $[M + H]^+$ *m/z* 571.1 ; found 571.1.

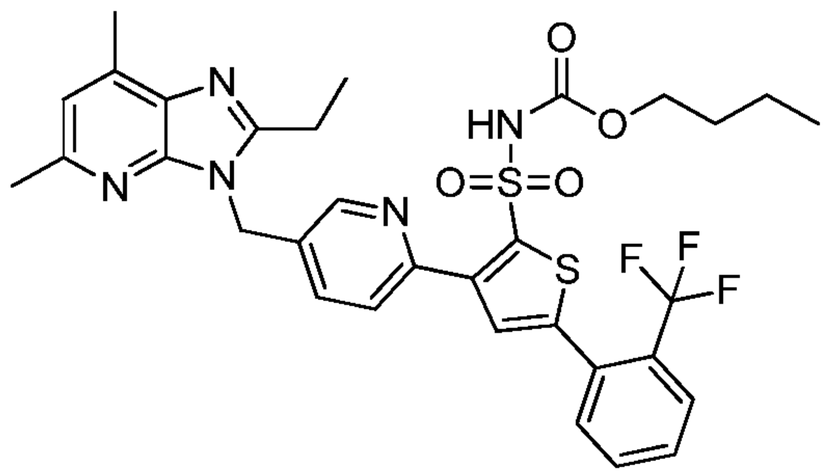
Example 045: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-(trifluoromethyl)phenyl)thiophen-2-yl)sulfonylcarbamate



(Ex. 045)

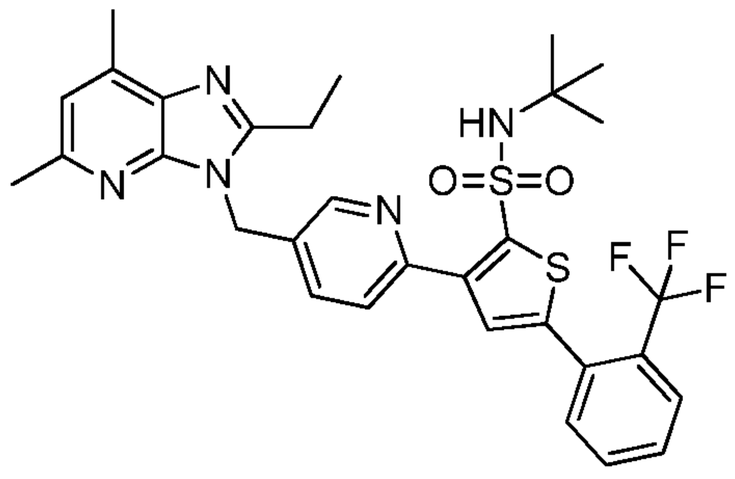
A solution of **Intermediate 045d** (0.030 g, 0.044 mmol) in pyridine (1 mL) was treated with triethylamine (0.046 mL, 0.329 mmol), 4-(pyrrolidin-1-yl)pyridine (0.0195 g, 0.131 mmol) and butyl carbonochloridate (0.017 mL, 0.131 mmol) as described in **Example 040**. The reaction mixture was then evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F, with 0.1% of HCO_2H as modifier) to give the title compound (**Example 045,** 0.021 g, 0.031 mmol, 72%) as a white solid. LC (Method B): 1.989 min; HRMS (ESI): Calcd for $C_{33}H_{34}F_3N_4O_4S_2$ $[M + H]^+$ *m/z* 671.1968; found 671.1907; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 (d, J = 7.4 Hz, 1H), 7.64 - 7.80 (m, 4H), 7.50 (d, J = 8.2 Hz, 2H), 7.23 (s, 1H), 7.18 (d, J = 8.2 Hz, 2H), 6.96 (s, 1H), 5.51 (s, 2H), 3.93 (t, J = 6.5 Hz, 2H), 2.79 (q, J = 7.7 Hz, 2H), 2.51 (s, 6H), 1.34 - 1.43 (m, 2H), 1.24 (t, J = 7.4 Hz, 3H), 1.16 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H).

Example 046: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-(trifluoromethyl)phenyl)thiophen-2-yl)sulfonylcarbamate



(Ex. 046)

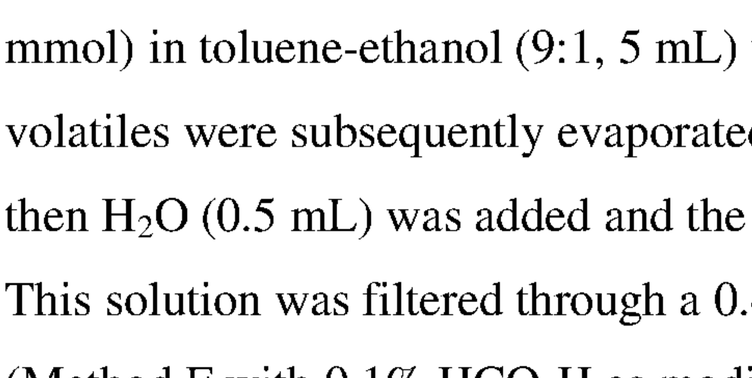
Intermediate 046a: N-(tert-Butyl)-3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-(trifluoromethyl)phenyl)thiophene-2-sulfonamide



(046a)

A mixture of **Intermediate 045b** (0.059 g, 0.145 mmol), **Intermediate 039a** (0.050 g, 0.145 mmol), 2M aq. Na_2CO_3 (0.22 mL, 0.434 mmol) and $Pd(Ph_3P)_4$ (0.017 g, 0.014 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in Example 039b. The volatiles were subsequently evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F with 0.1% HCO_2H as modifier) to give the title compound (**Intermediate 046a,** 0.076 g, 0.121 mmol, 84%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{31}H_{33}F_3N_5O_2S_2$ $[M + H]^+$ *m/z* 628.2022; found: 628.2066.

Intermediate 046b: 3-(5-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)pyridin-2-yl)-5-(2-(trifluoromethyl)phenyl)thiophene-2-sulfonamide



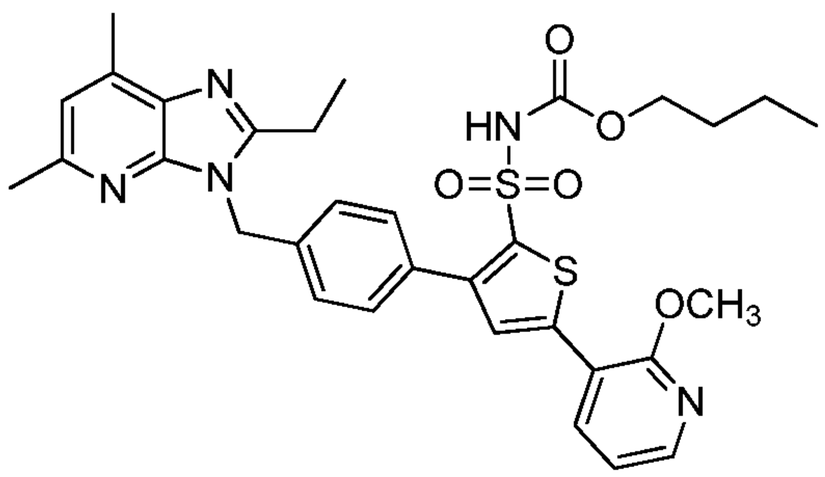
(046b)

A solution of **Intermediate 046a** (0.076 g, 0.121 mmol) in DCM (3 mL) was treated with anisole (0.132 mL, 1.211 mmol) and TFA (5 mL) as described in Example 40c to afford the title compound **Intermediate 046b** quantitatively as a TFA salt. LC-MS (Method H): 1.300 min, Calcd. for $C_{27}H_{25}F_3N_5O_2S_2$ $[M + H]^+$ *m/z* 572.14; found 572.1.

Example 046: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-(trifluoromethyl)phenyl)thiophen-2-yl)sulfonylcarbamate

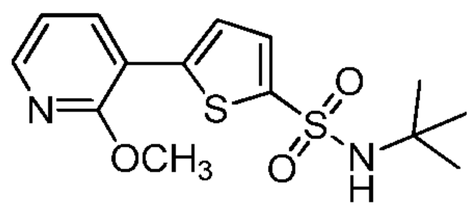
A solution of **Intermediate 046b** (0.030 g, 0.044 mmol) in pyridine (1 mL) was treated with triethylamine (0.046 mL, 0.329 mmol), 4-(pyrrolidin-1-yl)pyridine (0.0195 g, 0.131 mmol) and butyl carbonochloridate (0.017 mL, 0.131 mmol) as described in **Example 040**. The reaction mixture was then evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F with 0.1% of HCO_2H as modifier) to give the title compound (**Example 046,** 0.021 g, 0.031 mmol, 71%) as a white solid. LC (Method B): 1.949 min; HRMS (ESI): Calcd for $C_{32}H_{33}F_3N_5O_4S_2$ $[M + H]^+$ *m/z* 672.1921; found 672.1870; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.0 Hz, 1H), 7.61 - 7.75 (m, 4H), 7.52 (s, 1H), 6.98 (s, 1H), 5.56 (s, 2H), 3.94 (t, J = 6.7 Hz, 2H), 2.84 (q, J = 7.4 Hz, 2H), 2.50 - 2.54 (m, 6H), 1.36 - 1.45 (m, 2H), 1.25 (t, J = 7.4 Hz, 3H), 1.13 - 1.22 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H).

Example 047: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-methoxypyridin-3-yl)thiophen-2-yl)sulfonylcarbamate



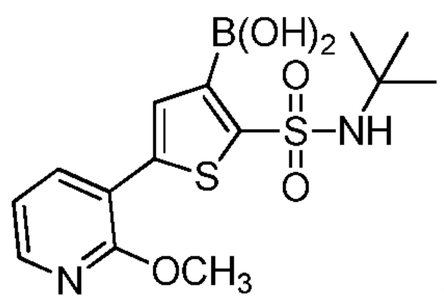
(Ex. 047)

Intermediate 047a: N-(tert-butyl)-5-(2-Methoxypyridin-3-yl)thiophene-2-sulfonamide



(047a)A vial charged with 5-bromo-N-(tert-butyl)thiophene-2-sulfonamide (1.00 g, 3.35 mmol), (2-methoxypyridin-3-yl)boronic acid (0.769 g, 5.03 mmol), 2M aqueous Na_2CO_3 (5.03 mL, 10.06 mmol) and $Pd(Ph_3P)_4$ (0.194 g, 0.168 mmol) in a mixture of toluene-ethanol (9:1, 20 mL) was treated as described in Example 039b. After cooling, the reaction mixture was diluted with EtOAc (100 mL) and H_2O (50 mL). The organic phase was separated, washed with sat. aq. $NaHCO_3$ and brine, then dried over Na_2SO_4, filtered and evaporated to give a dark brown gum. This material was pre-adsorbed on 10 g of silica gel and purified by flash chromatography (ISCO 10-50%, EtOAc-hexane) to give the title compound (**Intermediate 047a,** 1.050 g, 3.22 mmol, 96%) as a white solid. LC-MS (Method H): 1.250 min, Calcd. for $C_{14}H_{17}N_2O_3S_2$ $[M-H]^-$ *m/z* 325.07; found 325.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.29 (dd, J = 7.6, 1.8 Hz, 1H), 8.21 (dd, J = 4.9, 1.8 Hz, 1H), 7.71 - 7.77 (m, 2H), 7.57 (d, J = 3.9 Hz, 1H), 7.11 - 7.17 (m, 1H), 4.05 (s, 3H), 1.17 (s, 9H).

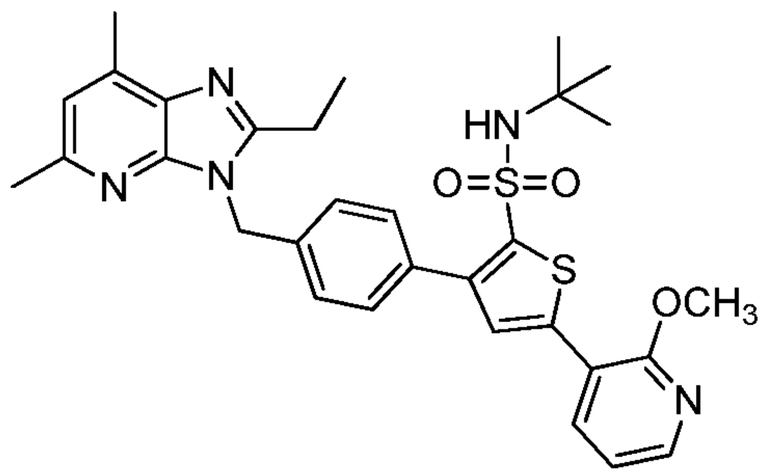
Intermediate 047b: (2-(N-(tert-Butyl)sulfamoyl)-5-(2-methoxypyridin-3-yl)thiophen-3-yl)boronic acid



(047b)

A solution of **Intermediate 047a** (1.03 g, 3.16 mmol) in dry THF (25 mL) was treated with a solution of 1.2 M n-BuLi in hexanes (6.57 mL, 7.89 mmol) and triisopropyl borate (2.18 mL, 9.47 mmol) as described in **Example 039c**. The resulting turbid mixture was quenched with 2M aqueous HCl (9.91 mL, 19.83 mmol), then partitioned with EtOAc-H_2O and the organic phase was separated, washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The resulting residue was purified by ISCO (20-70%, EtOAc/Hexane) to afford the desired compound as a dark red solid (**Intermediate 047b,** 0.275 g, 0.743 mmol, 24%). LC-MS (Method H): 1.248 min, Calcd. for $C_{14}H_{18}BN_2O_5S_2$ $[M-H]^-$ *m/z* 369.1; found 369.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.62 (s, 2H), 8.25 (dd, J = 7.6, 1.8 Hz, 1H), 8.20 (dd, J = 4.9, 1.8 Hz, 1H), 7.86 (s, 1H), 7.23 (s, 1H), 7.14 (dd, J = 7.6, 4.9 Hz, 1H), 4.04 (s, 3H), 1.18 (s, 9H).

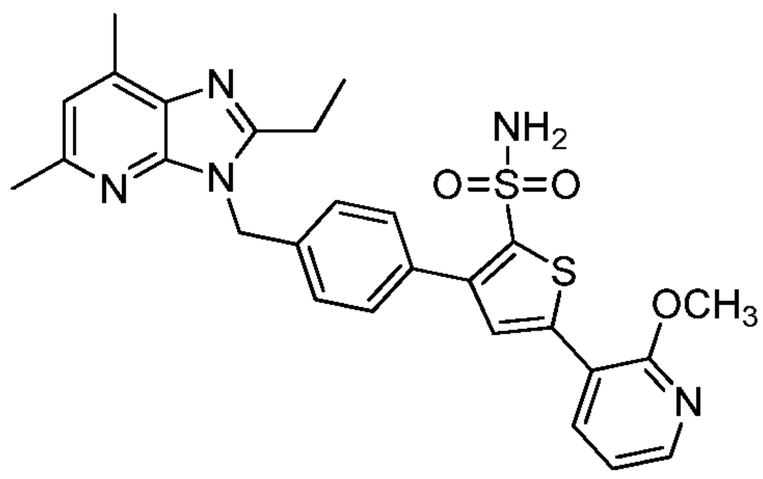
Intermediate 047c: N-(tert-Butyl)-3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-methoxypyridin-3-yl)thiophene-2-sulfonamide



(047c)

A mixture of **Intermediate 047b** (0.054 g, 0.145 mmol), **Intermediate 040a** (0.050 g, 0.145 mmol), 2M aq. Na_2CO_3 (0.22 mL, 0.436 mmol) and $Pd(Ph_3P)_4$ (0.017 g, 0.015 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039b**. The volatiles were subsequently evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F with 0.1% HCO_2H as modifier) to give the title compound (0.054 g, 0.092 mmol, 63%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{31}H_{36}N_5O_3S_2$ $[M + H]^+$ *m/z* 590.2254; found: 590.2281.

Intermediate 047d: 3-(4-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)phenyl)-5-(2-methoxypyridin-3-yl)thiophene-2-sulfonamide



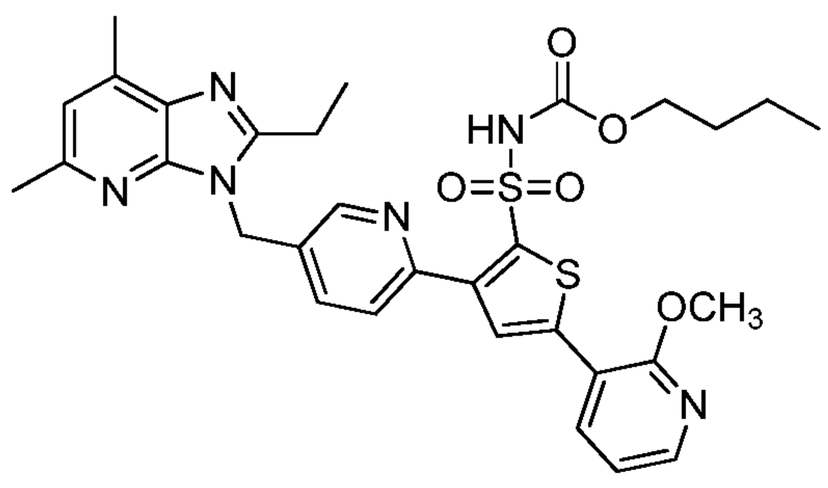
(047d)

A solution of **Intermediate 047c** (0.054 g, 0.092 mmol) in DCM (3 mL) was treated with anisole (0.100 mL, 0.916 mmol) and TFA (5 mL) as described in **Example 040c** to afford the title compound **Intermediate 047d** quantitatively as a TFA salt. LC-MS (Method H): 1.290 min, Calcd. for $C_{27}H_{28}N_5O_3S_2$ $[M + H]^+$ *m/z* 534.2; found 534.1.

Example 047: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-(2-methoxypyridin-3-yl)thiophen-2-yl)sulfonylcarbamate

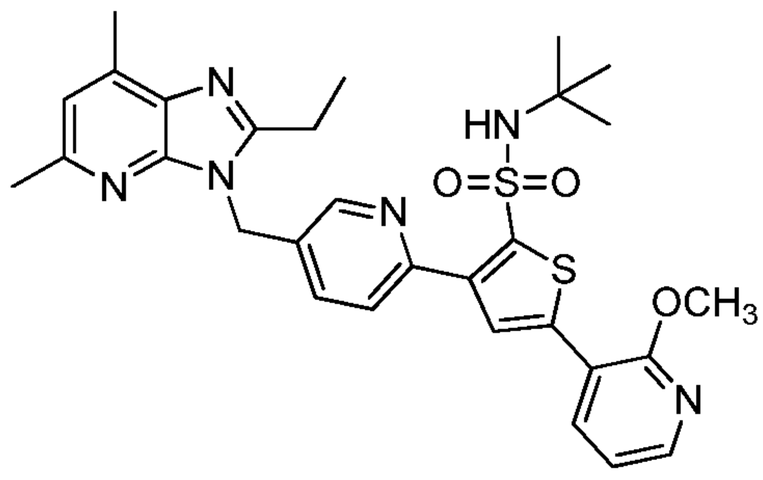
A solution of **Intermediate 047d** (0.030 g, 0.046 mmol) in pyridine (1 mL) was treated with triethylamine (0.048 mL, 0.347 mmol), 4-(pyrrolidin-1-yl)pyridine (0.021 g, 0.139 mmol) and butyl carbonochloridate (0.018 mL, 0.139 mmol) as described in Example 040. The reaction mixture was then evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F with 0.1% of HCO_2H as modifier) to give the title compound (**Example 047,** 0.018 g, 0.028 mmol, 61%) as a white solid. LC (Method B): 1.927 min; HRMS (ESI): Calcd for $C_{32}H_{36}N_5O_5S_2$ $[M + H]^+$ *m/z* 634.2152; found 634.2088; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.37 (dd, J = 7.4, 1.6 Hz, 1H), 8.22 (dd, J = 5.1, 1.6 Hz, 1H), 7.82 (s, 1H), 7.47 - 7.54 (m, J = 8.2 Hz, 2H), 7.15 - 7.21 (m, J = 8.2 Hz, 2H), 7.13 (dd, J = 7.6, 4.9 Hz, 1H), 6.96 (s, 1H), 5.51 (s, 2H), 4.05 (s, 3H), 3.90 (t, J = 6.5 Hz, 2H), 2.79 (q, J = 7.4 Hz, 2H), 2.51 (s, 6H), 1.32 - 1.40 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H), 1.08 - 1.17 (m, 2H), 0.74 (t, J = 7.4 Hz, 3H).

Example 048: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-methoxypyridin-3-yl)thiophen-2-yl)sulfonylcarbamate



(Ex. 048)

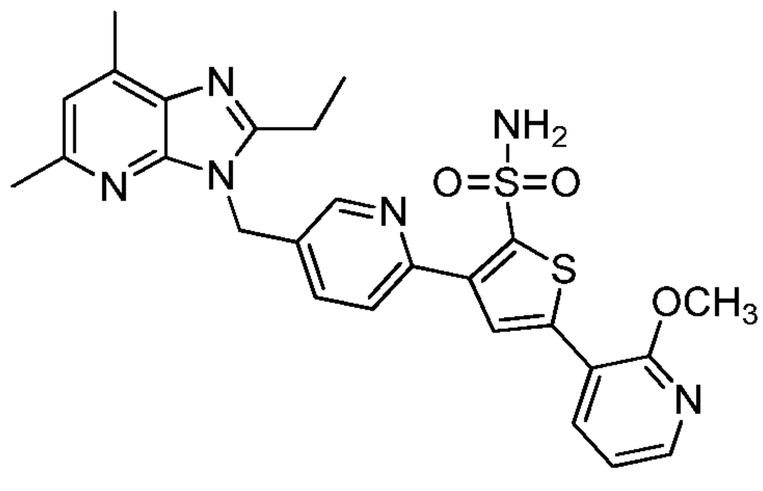
Intermediate 048a: N-(tert-Butyl)-3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-methoxypyridin-3-yl)thiophene-2-sulfonamide



(048a)

A mixture of **Intermediate 047b** (0.054 g, 0.145 mmol), **Intermediate 039a** (0.050 g, 0.145 mmol), 2M aq. Na_2CO_3 (0.22 mL, 0.434 mmol) and $Pd(Ph_3P)_4$ (0.017 g, 0.015 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039c**. The volatiles were then evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F with 0.1% HCO_2H as modifier) to give the title compound (**Intermediate 048a,** 0.060 g, 0.102 mmol, 70%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{30}H_{35}N_6O_3S_2$ $[M + H]^+$ *m/z* 591.2207; found: 591.2230.

Intermediate 048b: 3-(5-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)pyridin-2-yl)-5-(2-methoxypyridin-3-yl)thiophene-2-sulfonamide



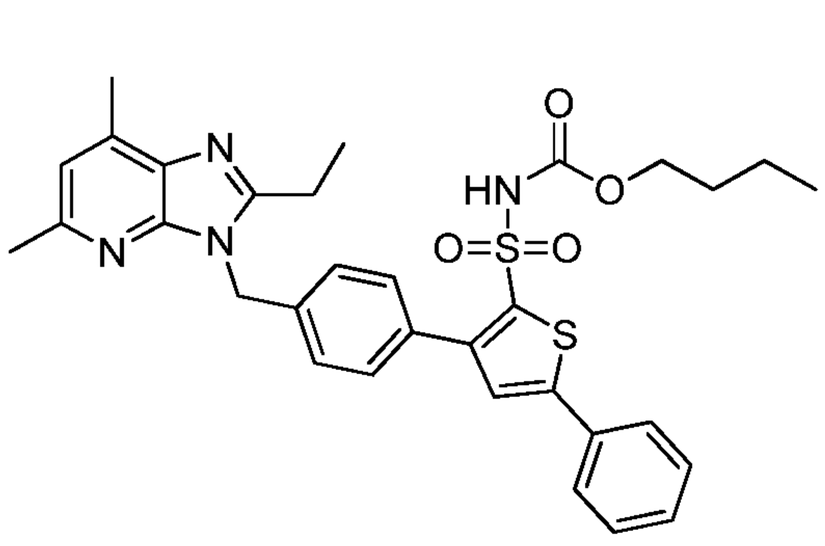
(048b)

A solution of **Intermediate 048a** (0.060 g, 0.102 mmol) in DCM (3 mL) was treated with anisole (0.111 mL, 1.016 mmol) and TFA (5 mL) as described in Example 040c to afford the title compound **Intermediate 048b** quantitatively as a TFA salt. LC-MS (Method H): 1.258 min, Calcd. for $C_{26}H_{27}N_6O_3S_2$ $[M + H]^+$ *m/z* 535.16; found 535.1.

Example 048: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-(2-methoxypyridin-3-yl)thiophen-2-yl)sulfonylcarbamate

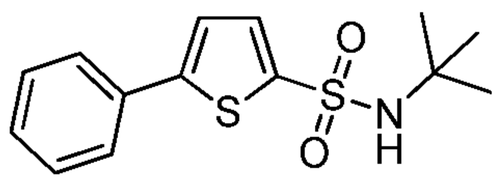
A solution of **Intermediate 048b** (0.030 g, 0.046 mmol) in pyridine (1 mL) was treated with triethylamine (0.048 mL, 0.347 mmol), 4-(pyrrolidin-1-yl)pyridine (0.021 g, 0.139 mmol) and butyl carbonochloridate (0.018 mL, 0.139 mmol) as described in Example 040. The reaction mixture was then evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F with 0.1% of HCO_2H as modifier) to give the title compound (**Example 048,** 0.017 g, 0.027 mmol, 58%) as a white solid. LC (Method B): 1.907 min; HRMS (ESI): Calcd for $C_{31}H_{35}N_6O_5S_2$ $[M + H]^+$ *m/z* 635.2105; found 635.2051; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 7.6, 1.8 Hz, 1H), 8.23 (dd, J = 4.7, 1.6 Hz, 1H), 8.08 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.66 (dd, J = 8.2, 2.3 Hz, 1H), 7.14 (dd, J = 7.6, 4.9 Hz, 1H), 6.97 (s, 1H), 5.56 (s, 2H), 4.06 (s, 3H), 3.92 (t, J = 6.5 Hz, 2H), 2.84 (q, J = 7.4 Hz, 2H), 2.51 (d, J = 2.0 Hz, 6H), 1.34 - 1.42 (m, 2H), 1.26 (t, J = 7.4 Hz, 3H), 1.09 - 1.20 (m, 2H), 0.73 (t, J = 7.4 Hz, 3H).

Example 049: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-phenylthiophen-2-yl)sulfonylcarbamate



(Ex. 049)

Intermediate 049a N-(tert-Butyl)-5-phenylthiophene-2-sulfonamide

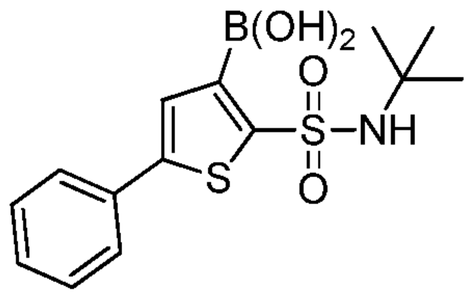


(049a)

A vial charged with 5-bromo-N-(tert-butyl)thiophene-2-sulfonamide (1.00 g, 3.35 mmol), phenylboronic acid (0.825 g, 5.03 mmol), 2M aqueous Na_2CO_3 (5.03 mL, 10.06 mmol) and $Pd(Ph_3P)_4$ (0.194 g, 0.168 mmol) in a mixture of toluene-ethanol (9:1, 20 mL)

was treated as described in **Example 39b**. After cooling, the reaction mixture was diluted with EtOAc (100 mL) and H_2O (50 mL). The organic phase was separated, washed with sat. aq. $NaHCO_3$ and brine, then dried over Na_2SO_4, filtered and evaporated to give a dark brown gum. This material was pre-adsorbed on 10 g of silica gel and purified by flash chromatography (ISCO 10-40%, EtOAc-hexane) to give the title compound (**Intermediate 049a,** 0.977 g, 3.31 mmol, 99%) as a white solid. LC-MS (Method H): 1.280 min, Calcd. for $C_{14}H_{16}NO_2S_2$ $[M-H]^-$ *m/z* 294.06; found 294.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (s, 1H), 7.69 - 7.75 (m, 2H), 7.54 - 7.57 (m, 1H), 7.51 - 7.54 (m, 1H), 7.43 - 7.50 (m, 2H), 7.37 - 7.43 (m, 1H), 1.19 (s, 9H).

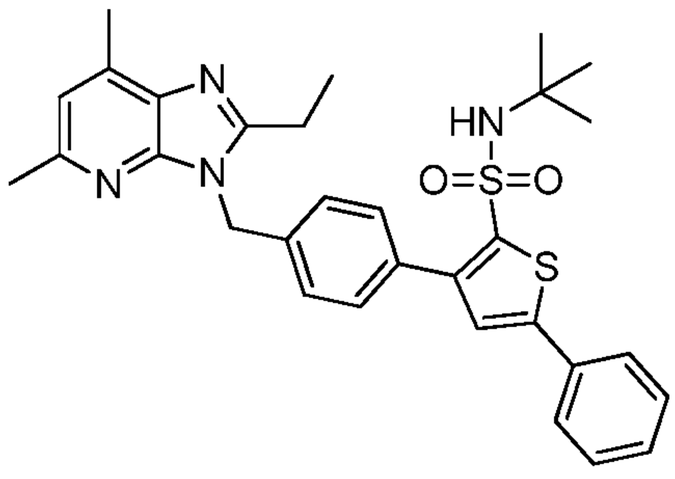
Intermediate 049b: (2-(N-(tert-Butyl)sulfamoyl)-5-phenylthiophen-3-yl)boronic acid



(049b)

A solution of **Intermediate 049a** (0.950 g, 3.22 mmol) in dry THF (25 mL) was treated with a solution of 1.2 M n-BuLi in hexanes (6.70 mL, 8.04 mmol) and triisopropyl borate (2.23 mL, 9.65 mmol) as described in **Example 039c**. The resulting turbid mixture was quenched with 2M aqueous HCl (9.91 mL, 19.83 mmol) then partitioned with EtOAc-H_2O and the organic phase was separated, washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue was purified by ISCO (20-60%, EtOAc/Hexane) to afford the title compound as a pale yellow solid (**Intermediate 049b,** 0.681 g, 2.007 mmol, 62%). LC-MS (Method H): 1.281 min, Calcd. for $C_{14}H_{17}BNO_4S_2$ $[M-H]^-$ *m/z* 338.07; found 338.0; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.62 (s, 2H), 7.67 - 7.72 (m, 2H), 7.63 (s, 1H), 7.42 - 7.49 (m, 2H), 7.33 - 7.42 (m, 1H), 7.25 (s, 1H), 1.20 (s, 9H).

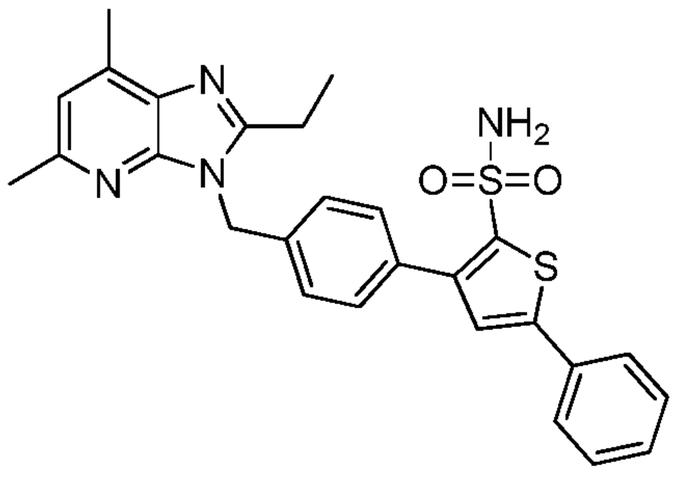
Intermediate 049c: N-(tert-Butyl)-3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl) methyl)phenyl)-5-phenylthiophene-2-sulfonamide



(049c)

A mixture of **Intermediate 049b** (0.049 g, 0.145 mmol), **Intermediate 040a** (0.050 g, 0.145 mmol), 2M aq. Na_2CO_3 (0.22 mL, 0.436 mmol) and $Pd(Ph_3P)_4$ (0.017 g, 0.015 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039b**. The volatiles were then evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F with 0.1% HCO_2H as modifier) to give the title compound (**Intermediate 049c,** 0.059 g, 0.106 mmol, 73%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{31}H_{35}N_4O_2S_2$ $[M + H]^+$ *m/z* 559.2196; found: 559.2227.

Intermediate 049d: 3-(4-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)phenyl)-5-phenylthiophene-2-sulfonamide

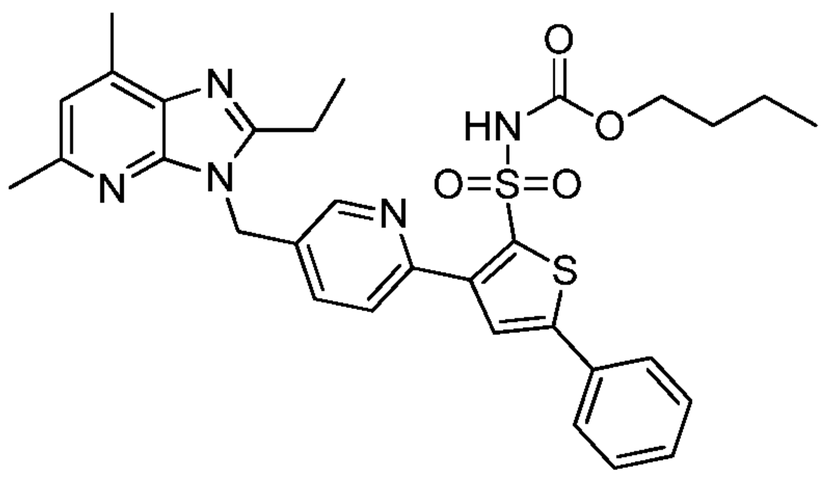


(049d)A solution of **Intermediate 049c** (0.059 g, 0.106 mmol) in DCM (3 mL) was treated with anisole (0.115 mL, 1.056 mmol) and TFA (5 mL) as described in **Example 040c** to afford the title compound **Intermediate 049d** quantitatively as a TFA salt. LC-MS (Method H): 1.323 min, Calcd. for $C_{27}H_{27}N_4O_2S_2$ $[M + H]^+$ *m/z* 503.16; found 503.1.

Example 049: Butyl (3-(4-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) phenyl)-5-phenylthiophen-2-yl)sulfonylcarbamate

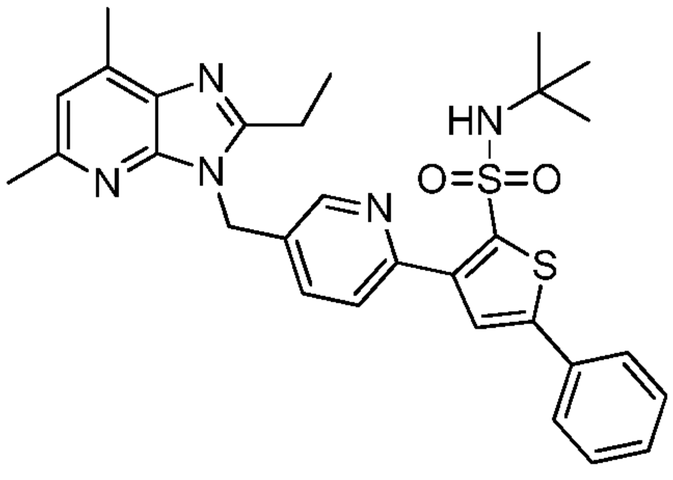
A solution of **Intermediate 049d** (0.030 g, 0.049 mmol) in pyridine (1 mL) was treated with triethylamine (0.051 mL, 0.365 mmol), 4-(pyrrolidin-1-yl)pyridine (0.022 g, 0.146 mmol) and butyl carbonochloridate (0.019 mL, 0.146 mmol) as described in **Example 040**. The reaction mixture was subsequently evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F, with 0.1% of HCO_2H as modifier) to give the title compound (**Example 049,** 0.023 g, 0.038 mmol, 78%) as a white solid. LC (Method B): 1.967 min; HRMS (ESI): Calcd for $C_{32}H_{35}N_4O_4S_2$ $[M + H]^+$ *m/z* 603.2094; found 603.2052; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 - 7.78 (m, 2H), 7.62 (s, 1H), 7.50 - 7.56 (m, 2H), 7.38 - 7.49 (m, 4H), 7.15 - 7.21 (m, 2H), 6.96 (s, 1H), 5.51 (s, 2H), 3.91 (t, J = 6.5 Hz, 2H), 2.79 (d, J = 7.4 Hz, 2H), 2.51 (s, 6H), 1.32 - 1.41 (m, 2H), 1.25 (t, J = 7.4 Hz, 3H), 1.09 - 1.16 (m, 2H), 0.75 (t, J = 7.2 Hz, 3H).

Example 050: Butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-phenylthiophen-2-yl)sulfonylcarbamate



(Ex. 050)

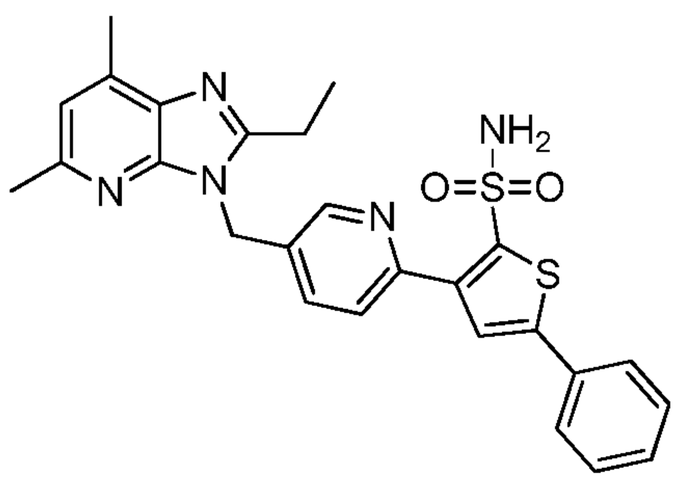
Intermediate 050a: N-(tert-Butyl)-3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-phenylthiophene-2-sulfonamide



(050a)

A mixture of **Intermediate 049b** (0.049 g, 0.145 mmol), **Intermediate 039a** (0.050 g, 0.145 mmol), 2M aq. Na_2CO_3 (0.22 mL, 0.434 mmol) and $Pd(Ph_3P)_4$ (0.017 g, 0.014 mmol) in toluene-ethanol (9:1, 5 mL) was treated as described in **Example 039b**. The volatiles were then evaporated and the residue was dissolved in DMSO (4.5 mL), then H_2O (0.5 mL) was added and the mixture was acidified with formic acid (0.10 mL). This solution was filtered through a 0.45 micron filter disk and purified by preparative LC (Method F with 0.1% HCO_2H as modifier) to give the title compound (**Example 050a,** 0.072 g, 0.129 mmol, 89%) as a pale yellow solid. HRMS (ESI): Calcd. for $C_{30}H_{34}N_5O_2S_2$ $[M + H]^+$ *m/z* 560.2148; found: 560.2168.

Intermediate 050b: 3-(5-((2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)pyridin-2-yl)-5-phenylthiophene-2-sulfonamide



(050b)

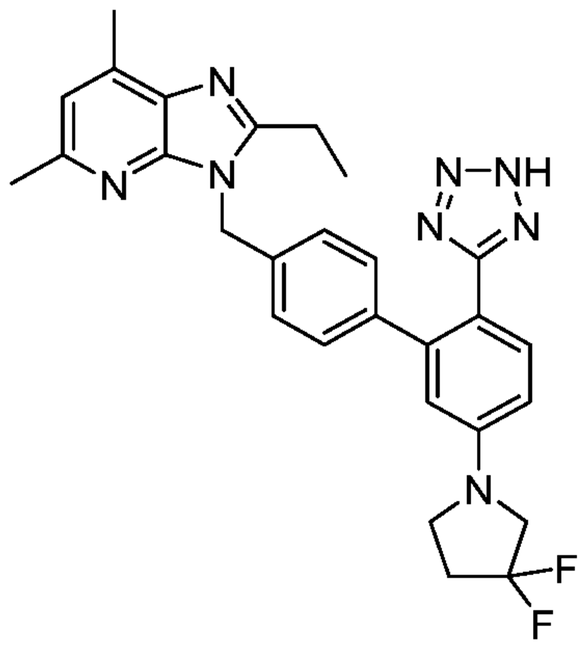
A solution of **Intermediate 050a** (0.072 g, 0.129 mmol) in DCM (3 mL) was treated with anisole (0.141 mL, 1.286 mmol) and TFA (5 mL), as described in **Example 040c** to afford the title compound **Example 050b** quantitatively as a 2.TFA salt. LC-MS (Method H): 1.288 min, Calcd. for $C_{26}H_{26}N_5O_2S_2$ $[M + H]^+$ *m/z* 504.15; found 504.0.

Example 050: butyl (3-(5-((2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl) pyridin-2-yl)-5-phenylthiophen-2-yl)sulfonylcarbamate

A solution of **Intermediate 050b** (0.030 g, 0.049 mmol) in pyridine (1 mL) was treated with triethylamine (0.051 mL, 0.364 mmol), 4-(pyrrolidin-1-yl)pyridine (0.022 g, 0.146 mmol) and butyl carbonochloridate (0.019 mL, 0.146 mmol) as described in **Example 040**. The reaction mixture was subsequently evaporated to dryness to give a solid residue which was taken up in DMSO (1.6 mL), acidified with formic acid (0.10 mL) and purified by preparative LC (Method F with 0.1% of HCO_2H as modifier) to give the title

compound (**Example 050,** 0.022 g, 0.036 mmol, 75%) as a white solid. LC (Method B): 1.930 min; HRMS (ESI): Calcd for $C_{31}H_{34}N_5O_4S_2$ $[M + H]^+$ *m/z* 604.2047; found 604.2082; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 (d, J = 1.6 Hz, 1H), 7.82 - 7.90 (m, 2H), 7.73 - 7.80 (m, 2H), 7.67 (dd, J = 8.2, 2.3 Hz, 1H), 7.37 - 7.51 (m, 4H), 6.98 (s, 1H), 5.56 (s, 2H), 3.93 (t, J = 6.5 Hz, 2H), 2.85 (q, J = 7.4 Hz, 2H), 2.51 (2s, 6H), 1.34 - 1.42 (m, 2H), 1.26 (t, J = 7.4 Hz, 3H), 1.14 (d, J = 7.4 Hz, 2H), 0.74 (t, J = 7.4 Hz, 3H).

Example 051: 3-((5'-(3,3-Difluoropyrrolidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

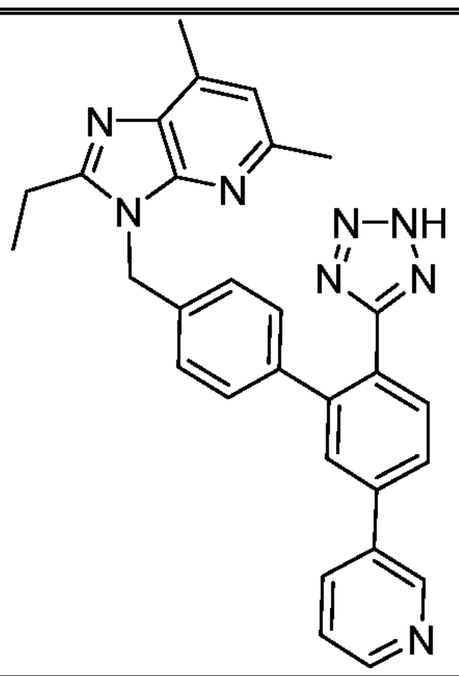
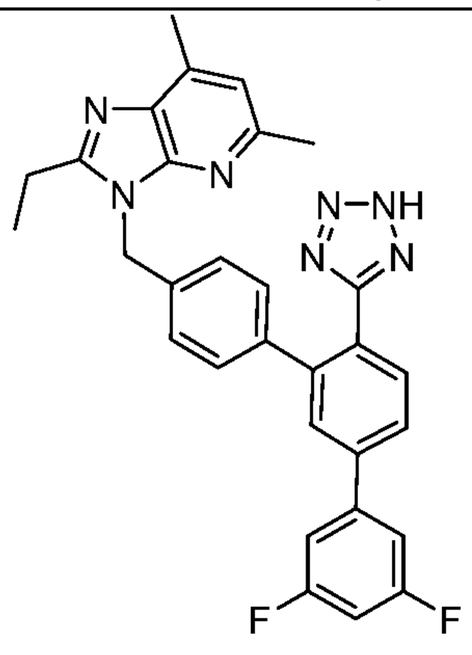


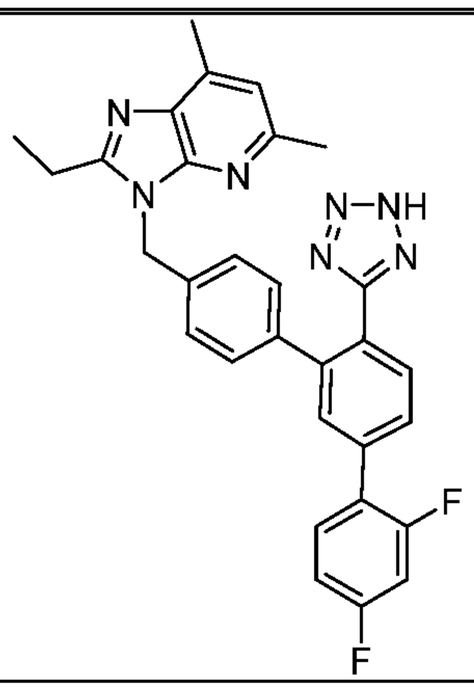
(Ex. 051)

To a vial charged with 2nd generation RuPhos precatalyst (4.78 mg, 6.16 µmol) was added **Intermediate 001j** (30 mg, 0.041 mmol) and sodium tert-butoxide (15.78 mg, 0.164 mmol). THF (1 mL) was then added followed by 3,3-difluoropyrrolidine, HCl (17.68 mg, 0.123 mmol). The reaction vial was sealed and heated at 65 °C for 1.5 h. The crude reaction mixture was then diluted with EtOAc, filtered over Celite® and concentrated to a brown residue. This crude intermediate was retaken DCM (2 mL) and subjected to triethylsilane (0.032 mL, 0.198 mmol) followed by TFA (0.092 mL, 1.189 mmol). After 10 min of stirring at RT, the reaction mixture was concentrated, retaken in DMF, filtered and purified by preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min.) to afford 7.2 mg (0.013 mmol, 34% yield) of the title compound **Example 051**. LC-MS (Method A2): 0.76 min, $[M + H]^+$= 515.0; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 7.43 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 2H),

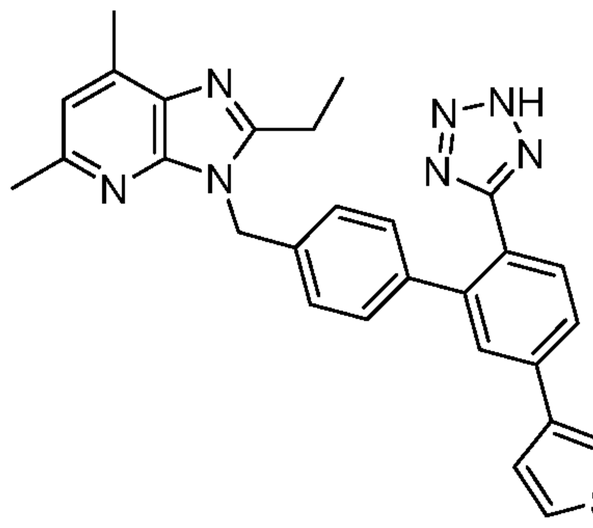
6.98 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.52 (s, 1H), 5.43 (s, 2H), 3.75 (t, *J* = 13.3 Hz, 2H), 3.53 (t, *J* = 7.2 Hz, 2H), 2.79 (q, *J* = 7.4 Hz, 2H), 2.51 (s, 6H), 1.26 (t, *J* = 7.3 Hz, 3H).

The compounds listed in the table below were synthesized using the same methods that were used to prepare Example 001.

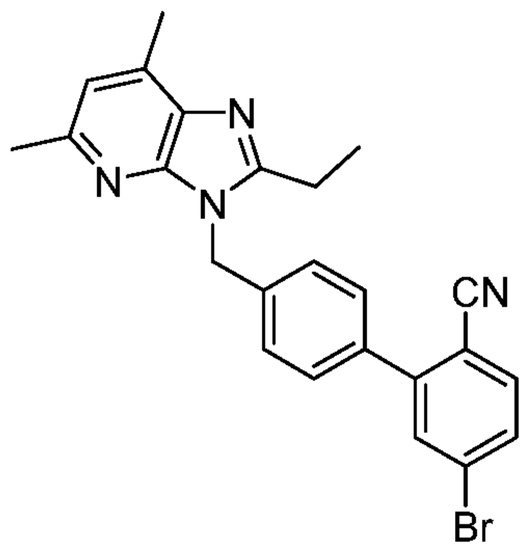
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
052		486.570	487.0; 1.31 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (br s, 1H), 8.60 (br s, 1H), 8.20 (br d, *J*=7.3 Hz, 1H), 7.85 (br d, *J*=7.3 Hz, 1H), 7.74 (br s, 2H), 7.51 (br s, 1H), 7.15 (br d, *J*=7.3 Hz, 2H), 7.04 (br d, *J*=7.6 Hz, 2H), 6.95 (s, 1H), 5.45 (s, 2H), 2.78 (q, *J*=7.5 Hz, 2H), 2.53 (d, *J*=19.5 Hz, 6H), 1.29 - 1.19 (m, 3H) (1 exchangeable proton not observed)
053		521.563	522.3; 0.85 (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=7.9 Hz, 1H), 7.77 (s, 1H), 7.73 (d, *J*=8.0 Hz, 1H), 7.60 (d, *J*=7.2 Hz, 2H), 7.27 (t, *J*=9.1 Hz, 1H), 7.15 (d, *J*=7.8 Hz, 2H), 7.04 (d, *J*=7.9 Hz, 2H), 6.95 (s, 1H), 5.46 (s, 2H), 2.78 (q, *J*=7.4 Hz, 2H), 2.55 (s, 6H), 1.24 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
054		521.563	522.0; 0.86 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.77 - 7.68 (m, 2H), 7.63 (d, *J*=7.7 Hz, 1H), 7.53 (s, 1H), 7.40 (t, *J*=10.1 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 2H), 7.02 (d, *J*=7.9 Hz, 2H), 6.94 (s, 1H), 5.45 (s, 2H), 2.77 (q, *J*=7.3 Hz, 2H), 2.55 (s, 6H), 1.24 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)

Example 055: 2-butyl-3-((4''-methyl-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



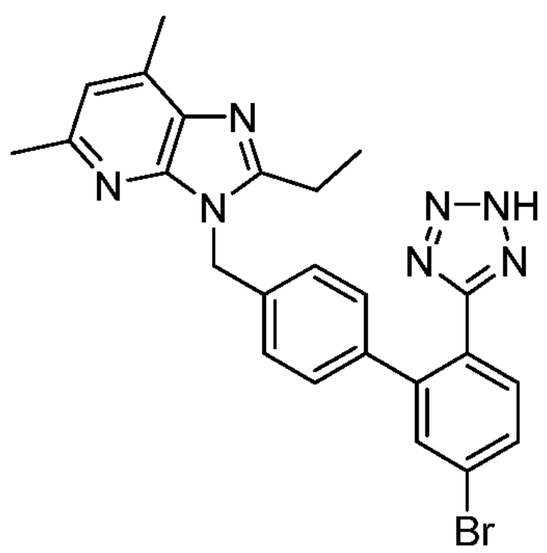
Intermediate 055a: 4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile



Intermediate 001d (1 g, 2.56 mmol), 4-bromo-2-iodobenzonitrile (0.944 g, 3.07 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 Adduct (0.209 g, 0.256 mmol) were dissolved in toluene (20.4 mL), ethanol (5.11 mL), and tripotassium phosphate (2 M aq, 2.56 mL, 5.11 mmol) and

the reaction was degassed for 15 minutes by bubbling with N_2. The reaction was sealed and heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature, filtered through celite, diluted with EtOAc, washed with saturated $NaHCO_3$, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient of 0 to 100% EtOAc in hexanes) to yield **Intermediate 055a** (0.649 g, 1.49 mmol, 57%) as a tan solid. LC-MS (Method A2) RT = 0.85 min, MS (ESI) *m/z*: 445 $(M+H)^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.66 (d, *J*=1.4 Hz, 1H), 7.64 - 7.58 (m, 2H), 7.51 - 7.47 (m, 2H), 7.27 (d, *J*=8.3 Hz, 2H), 6.94 (s, 1H), 5.55 (s, 2H), 2.84 (q, *J*=7.4 Hz, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 1.36 (t, *J*=7.6 Hz, 3H)

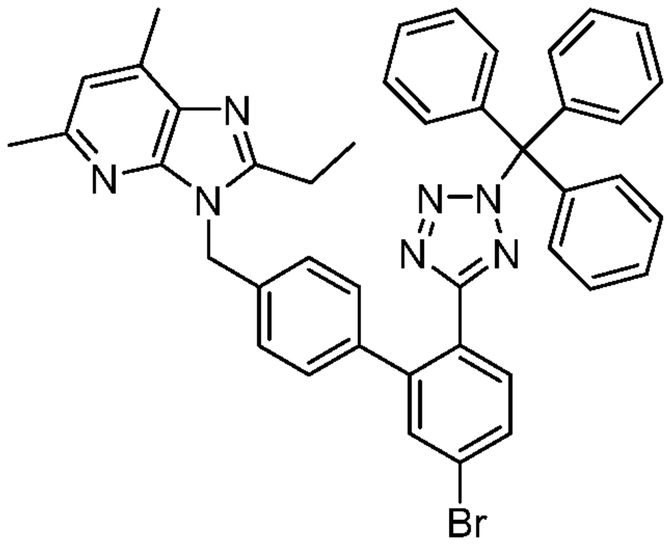
Intermediate 055b: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile



Intermediate 055a (0.649 g, 1.46 mmol) was dissolved in toluene (14.6 mL). Dibutyltin oxide (0.363 g, 1.46 mmol) and TMS-N_3 (1.94 mL, 14.6 mmol) were added and the reaction sealed in a pressure vial and heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature and diluted with EtOAc into an erlenmeyer. A 10% aqueous solution of CAN (9.60 g, 17.5 mmol) was added slowly to mild bubbling. An aliquot of the reaction was added to an aqueous 0.02 M $FeCl_3$ solution to confirm complete consumption of azide (no red color). The layers were separated and the organic layer was further washed twice with saturated NH_4Cl, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 40 g silica gel olumn, 19 minute gradient of 0 to 20% MeOH in DCM) to give **Intermediate 055b** (0.580 g, 1.19 mmol, 81%) as a tan solid. LC-MS (Method A2) RT = 0.76 min, MS (ESI) *m/z*: 486 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.4 Hz, 1H), 7.64 (dd, *J*=8.4, 2.0 Hz, 1H), 7.55 (d, *J*=1.8 Hz, 1H), 7.11 - 7.04 (m, 2H), 7.03 - 6.97

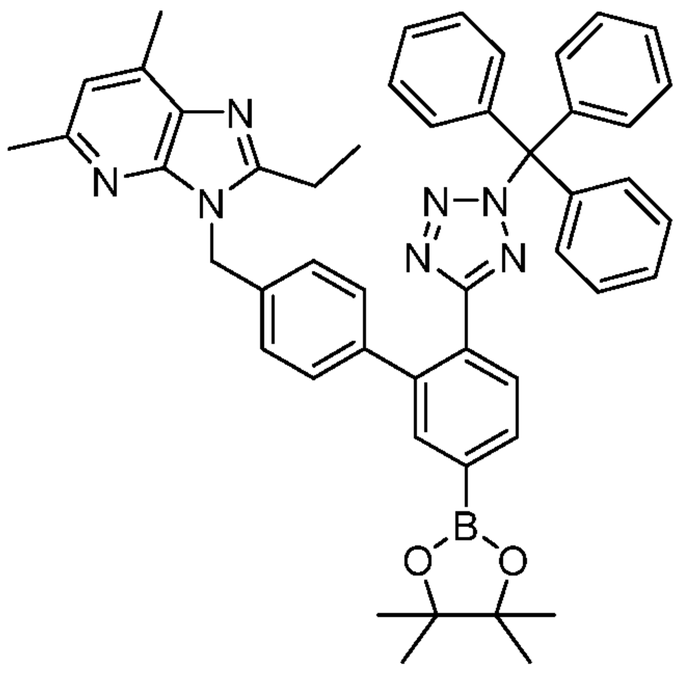
(m, 2H), 6.93 (s, 1H), 5.44 (s, 2H), 3.48 (s, 1H), 2.71 (q, *J*=7.6 Hz, 2H), 2.57 (s, 3H), 2.49 (s, 3H), 1.17 (t, *J*=7.5 Hz, 3H)

Intermediate 055c: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile



Intermediate 055b (580 mg, 1.19 mmol), TEA (215 µL, 1.54 mmol) and trityl chloride (381 mg, 1.37 mmol) were dissolved in DCM (5.94 mL). After 1 hour, the reaction was diluted with DCM and washed with 1M K_2HPO_4, then brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 055c** (707 mg, 0.97 mmol, 81%) as a clear oil. LC-MS (Method A2) RT = 1.07 min, MS (ESI) *m/z*: 731 $(M+H)^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.84 (d, *J*=8.3 Hz, 1H), 7.60 (dd, *J*=8.3, 1.9 Hz, 1H), 7.52 (d, *J*=1.9 Hz, 1H), 7.37 - 7.32 (m, 4H), 7.28 - 7.25 (m, 5H), 7.05 (d, *J*=8.3 Hz, 2H), 6.96 - 6.87 (m, 9H), 5.38 (s, 2H), 2.74 - 2.66 (m, 5H), 2.60 (s, 3H), 1.31 - 1.25 (m, 3H)

Intermediate 055d: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile

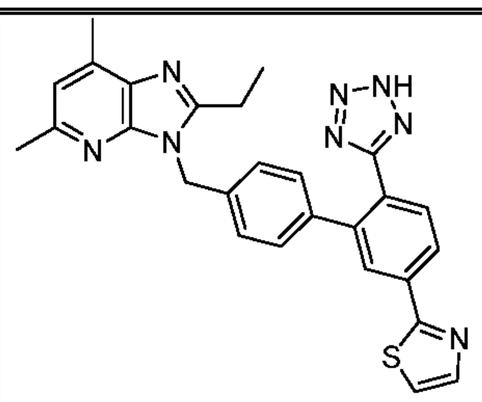


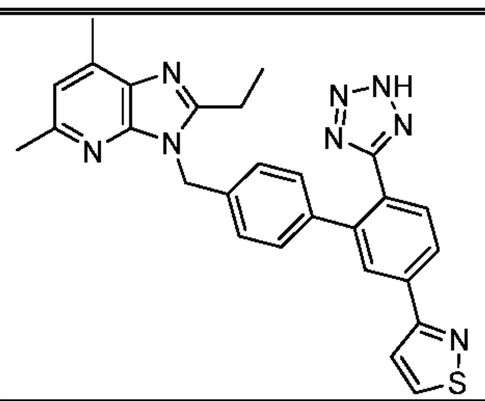
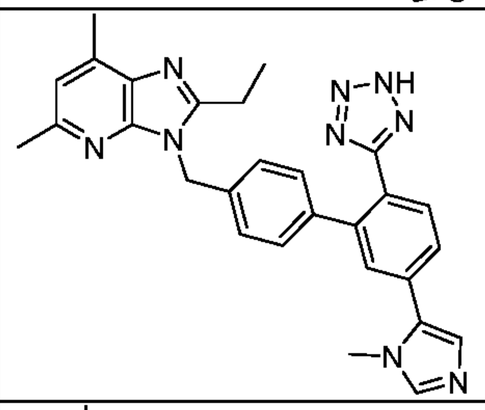
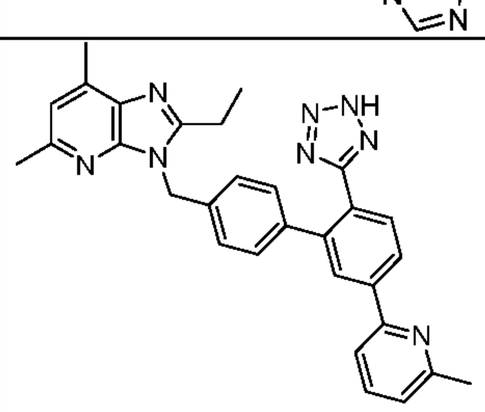
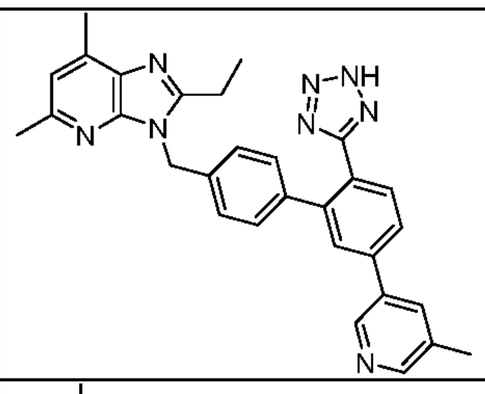
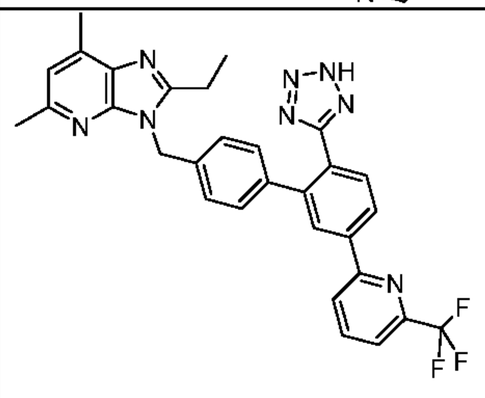
Intermediate 055c (1.46 g, 2.00 mmol), bispinacolatodiboron (760 mg, 2.99 mmol), and KOAc (492 mg, 4.99 mmol) were dissolved in 1,4-dioxane (20 mL) and degassed for 5 minutes by bubbling with Ar. $PdCl_2(dppf)$-CH_2Cl_2 adduct (130 mg, 0.159 mmol) was added and the reaction degassed for an additional 10 minutes. The reaction was heated at 130 °C in the microwave for 60 minutes. The reaction was diluted with EtOAc and washed with H_2O then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 055d** (1.03 g, 1.32 mmol, 66%) as a white solid. LC-MS (Method A2) RT = 1.11 min, MS (ESI) *m/z*: 778.7 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J*=7.4 Hz, 1H), 7.88 (dd, *J*=7.7, 1.1 Hz, 1H), 7.77 (s, 1H), 7.38 - 7.31 (m, 4H), 7.30 - 7.22 (m, 4H), 7.07 (d, *J*=8.3 Hz, 2H), 6.93 (br d, *J*=7.4 Hz, 8H), 6.87 (d, *J*=8.3 Hz, 2H), 5.37 (s, 2H), 2.74 - 2.65 (m, 5H), 2.60 (s, 3H), 1.33 - 1.24 (m, 15H)

Example 055

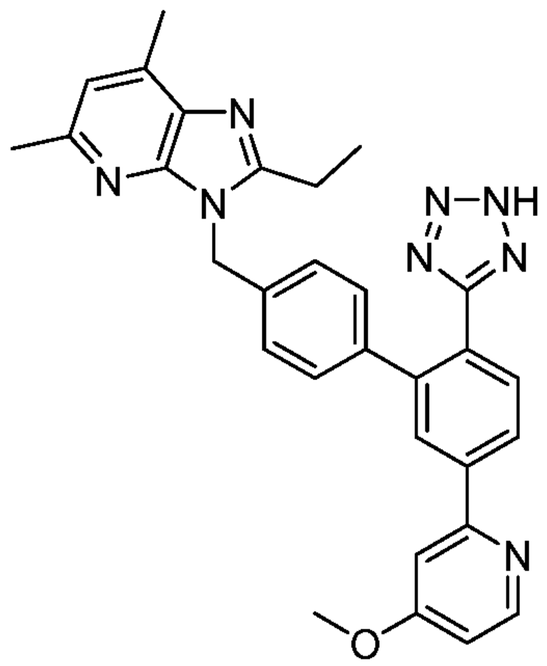
Intermediate 055d was reacted with 3-bromothiophene in a method analogous to **Example 122** to give **Example 055**. LC-MS (Method A1) RT = 1.41 min, MS (ESI) *m/z*: 492.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.78 (br d, *J*=6.7 Hz, 1H), 7.68 (s, 1H), 7.65 - 7.59 (m, 3H), 7.12 (br d, *J*=7.9 Hz, 2H), 7.02 (br d, *J*=8.2 Hz, 2H), 6.95 (s, 1H), 5.44 (s, 2H), 2.79 (q, *J*=7.6 Hz, 2H), 2.53 (d, *J*=18.6 Hz, 6H), 1.25 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed).

The compounds listed in the table below were synthesized using the same methods that were used to prepare Example 055.

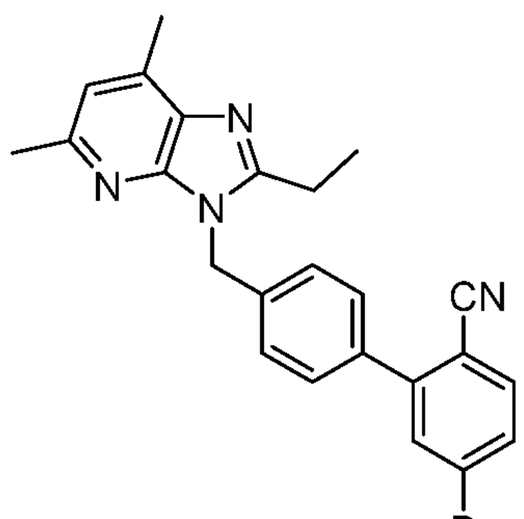
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^1H NMR
056		492.598	493.1; 1.43 min (Method A1)	^1H NMR (500 MHz, DMSO-d_6) δ 8.13 (br d, *J*=8.2 Hz, 1H), 8.01 (d, *J*=3.4 Hz, 2H), 7.89 (d, *J*=3.1 Hz, 1H), 7.82 (d, *J*=7.9 Hz, 1H), 7.16 (s, 1H), 7.16 - 7.12 (m, 2H), 7.12 - 7.08 (m, 2H), 5.49 (s, 2H), 2.79 (q, *J*=7.3 Hz, 2H), 2.57 - 2.48 (m, 6H), 1.22 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)

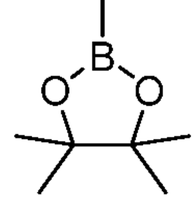
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
057		492.598	493.1; 1.46 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (br d, *J*=4.6 Hz, 1H), 8.20 (br s, 1H), 8.09 (br s, 2H), 7.95 (s, 1H), 7.23 - 7.00 (m, 4H), 6.95 (s, 1H), 5.45 (br s, 2H), 2.77 (br s, 2H), 2.53 (br d, *J*=18.9 Hz, 6H), 1.23 (br s, 3H) (1 exchangeable proton not observed)
058		489.574	490.2; 1.17 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.02 (s, 1H), 7.90 - 7.82 (m, 2H), 7.76 (s, 1H), 7.20 - 7.13 (m, 2H), 7.12 - 7.06 (m, 3H), 5.55 (s, 2H), 3.94 (s, 3H), 2.95 - 2.87 (m, 2H), 2.59 - 2.47 (m, 6H), 1.24 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
059		500.610	501.4; 1.39 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (br d, *J*=8.2 Hz, 1H), 8.09 (s, 1H), 7.87 (d, *J*=7.6 Hz, 1H), 7.78 (t, *J*=7.6 Hz, 1H), 7.74 (d, *J*=7.9 Hz, 1H), 7.26 (d, *J*=7.3 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.05 (br d, *J*=8.2 Hz, 2H), 6.95 (s, 1H), 5.46 (s, 2H), 2.78 (q, *J*=7.3 Hz, 2H), 2.59 - 2.48 (m, 9H), 1.28 - 1.19 (m, 3H) (1 exchangeable proton not observed)
060		500.610	501.2; 1.38 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (br s, 1H), 7.93 (br d, *J*=8.2 Hz, 1H), 7.83 (s, 1H), 7.78 (br d, *J*=7.9 Hz, 1H), 7.19 (s, 1H), 7.17 - 7.13 (m, 2H), 7.12 - 7.05 (m, 4H), 5.48 (s, 2H), 2.80 (q, *J*=7.6 Hz, 2H), 2.60 - 2.46 (m, 6H), 2.39 (s, 3H), 1.26 - 1.20 (m, 3H) (1 exchangeable proton not observed)
061		554.568	555.3; 1.59 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, *J*=7.9 Hz, 1H), 8.33 - 8.28 (m, 1H), 8.23 (br t, *J*=7.9 Hz, 1H), 8.20 (s, 1H), 7.93 (d, *J*=7.9 Hz, 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.20 - 7.10 (m, 5H), 5.51 (s, 2H), 2.83 (q, *J*=7.6 Hz, 2H), 2.60 - 2.46 (m, 6H), 1.23 (br t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)

Example 062: 2-Ethyl-3-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



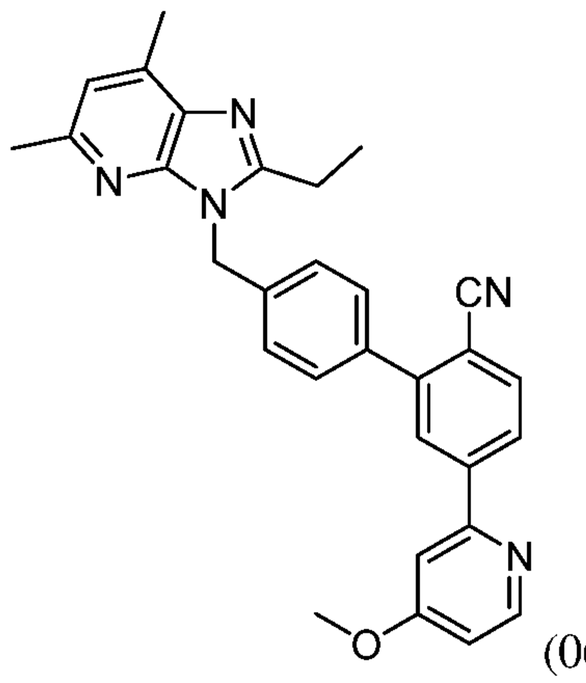
Intermediate 062a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile





Intermediate 055a (2.18 g, 4.90 mmol), bispinacolatodiboron (2.49 g, 9.80 mmol), X-PHOS (0.234 g, 0.490 mmol), $Pd_2(dba)_3$ (0.449 g, 0.490 mmol), and KOAc (2.40 g, 24.5 mmol) were dissolved in 1,4-dioxane (49.0 mL). The reaction was heated at 105 °C. After 1 hour, the reaction was cooled to ambient temperature and diluted with EtOAc, filtered through celite, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 062a** (1.49 g, 2.41 mmol, 62%) as a yellow solid. LC-MS (Method A2) RT = 0.96 min, MS (ESI) *m/z*: 493.2 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.85 (d, *J*=7.7 Hz, 1H), 7.75 (d, *J*=7.7 Hz, 1H), 7.52 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 6.93 (s, 1H), 5.55 (s, 2H), 2.85 (q, *J*=7.4 Hz, 2H), 2.67 (s, 3H), 2.63 (s, 3H), 1.39 - 1.33 (m, 15H).

Intermediate 062b: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(4-methoxypyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



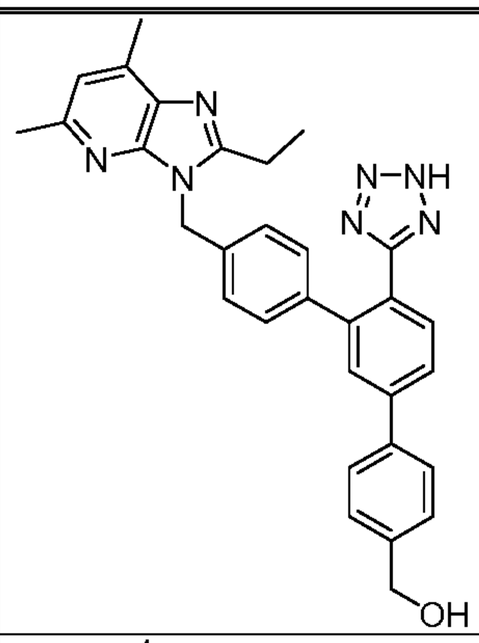
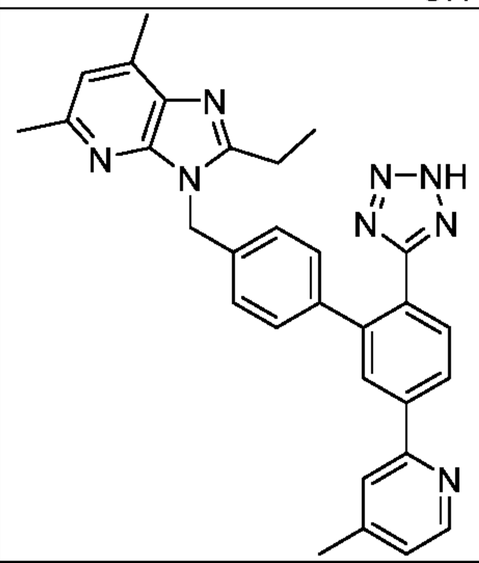
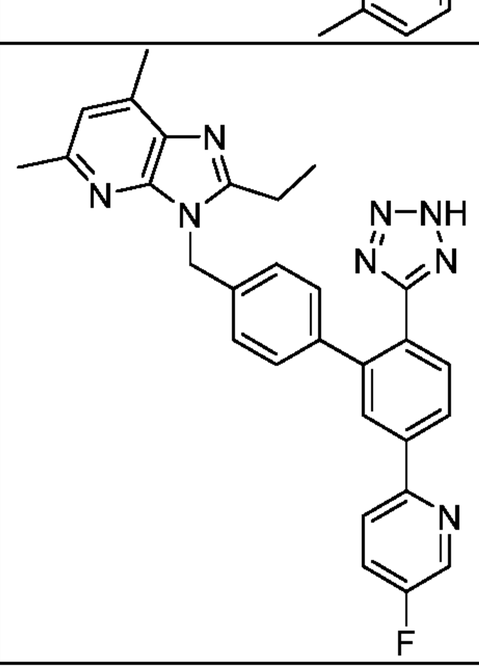
(062b)

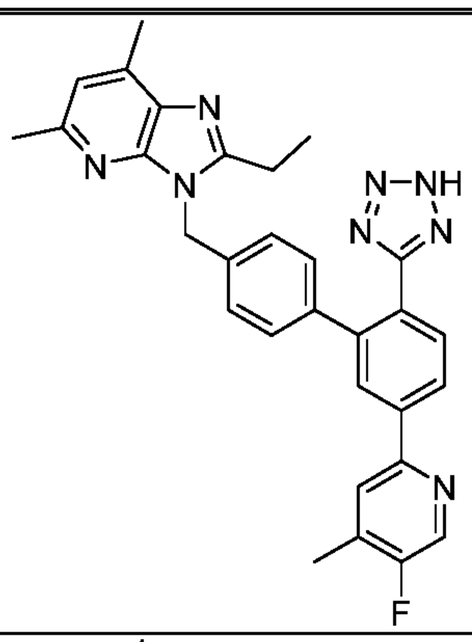
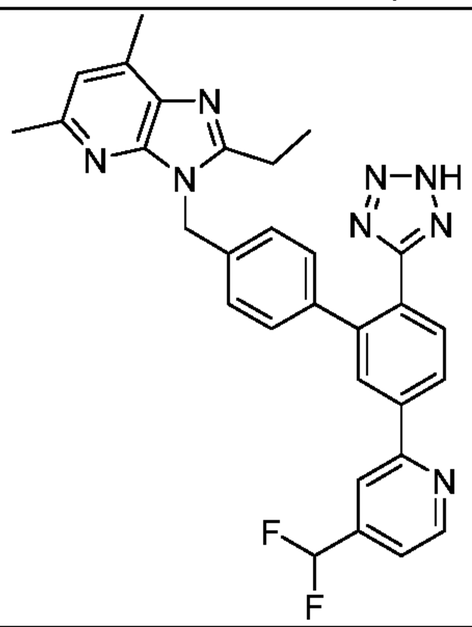
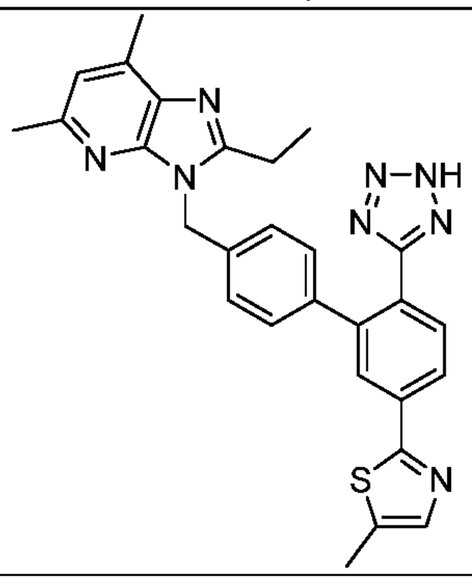
Intermediate 062a (50 mg, 0.102 mmol), 2-bromo-4-methoxypyridine (57.3 mg, 0.305 mmol), and 2nd generation XPHOS precatalyst (7.99 mg, 10.2 µmol) were dissolved in toluene (1.62mL), ethanol (406 µL), and tripotassium phosphate (2 M aq, 102 µL, 0.203 mmol). The reaction was heated at 100 °C. After 2 hours, the reaction was cooled to ambient temperature and diluted with EtOAc, filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromtography (ISCO, 24 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 062b** (17.7 mg, 0.037 mmol, 37%) as a yellow oil. LC-MS (Method A2) RT = 0.68 min, MS (ESI) *m/z*: 474.1 $(M+H)^+$.

Example 062

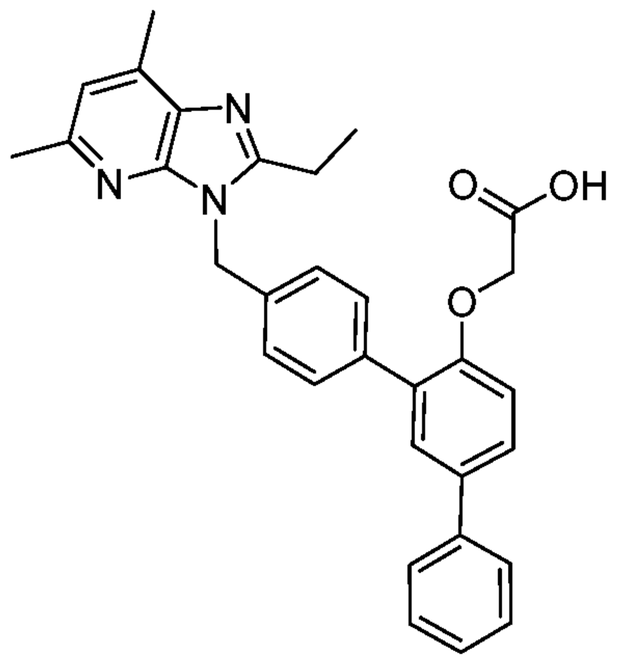
Intermediate 062b (17.7 mg, 0.038 mmol), dibutyltin oxide (18.9 mg, 0.076 mmol), and TMS-N_3 (25.2 µL, 0.190 mmol) were dissolved in toluene (760 µL) and heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature then diluted with MeOH and concentrated *in vacuo*. The crude material was purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to give **Example 062** (6.4 mg, 32%). LC-MS (Method A2) RT = 0.62 min, MS (ESI) *m/z*: 517.1 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, *J*=5.6 Hz, 1H), 8.18 (br d, *J*=8.1 Hz, 1H), 8.12 (s, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.59 (d, *J*=1.5 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 2H), 7.07 (d, *J*=8.1 Hz, 2H), 6.97 (dd, *J*=5.6, 2.3 Hz, 1H), 6.94 (s, 1H), 5.46 (s, 2H), 3.93 (s, 3H), 2.79 (q, *J*=7.5 Hz, 2H), 2.59 - 2.48 (m, 6H), 1.26 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)

The compounds listed in the table below were synthesized using the same methods that were used to prepare Example 62.

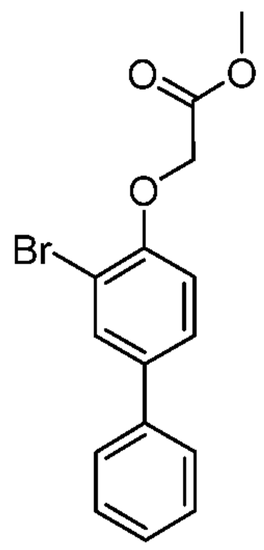
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
063		515.621	516.3; 0.72 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.83 - 7.66 (m, 5H), 7.43 (br d, *J*=7.9 Hz, 2H), 7.15 (br d, *J*=7.9 Hz, 2H), 7.06 (br d, *J*=7.9 Hz, 2H), 6.96 (s, 1H), 5.46 (s, 2H), 4.56 (s, 2H), 2.90 (s, 3H), 2.79 (q, *J*=7.5 Hz, 2H), 2.74 (s, 3H), 1.25 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)
064		500.610	501.1; 0.63 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, *J*=4.9 Hz, 1H), 8.14 (dd, *J*=8.0, 1.4 Hz, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.20 (br d, *J*=4.7 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 2H), 7.06 (d, *J*=8.0 Hz, 2H), 6.94 (s, 1H), 5.46 (s, 2H), 2.80 (q, *J*=7.4 Hz, 2H), 2.58 - 2.49 (m, 6H), 2.40 (s, 3H), 1.27 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)
065		504.573	505.1; 0.78 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (d, *J*=2.8 Hz, 1H), 8.24 - 8.15 (m, 2H), 8.12 (s, 1H), 7.83 (td, *J*=8.8, 2.9 Hz, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.20 - 7.13 (m, 2H), 7.11 - 7.04 (m, 2H), 6.95 (s, 1H), 5.47 (s, 2H), 2.78 (q, *J*=7.5 Hz, 2H), 2.61 - 2.47 (m, 6H), 1.25 (br t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
066		518.600	519.1; 1.57 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.14 - 8.05 (m, 2H), 8.01 (s, 1H), 7.75 (br d, *J*=8.3 Hz, 1H), 7.16 (br d, *J*=8.0 Hz, 2H), 7.05 (br d, *J*=8.1 Hz, 2H), 6.94 (s, 1H), 5.46 (s, 2H), 2.80 (q, *J*=7.2 Hz, 2H), 2.61 - 2.47 (m, 6H), 2.37 (s, 3H), 1.30 - 1.24 (m, 3H) (1 exchangeable proton not observed)
067		536.591	537.1; 0.80 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (d, *J*=4.9 Hz, 1H), 8.33 - 8.25 (m, 2H), 8.20 (d, *J*=1.3 Hz, 1H), 7.81 (br d, *J*=8.0 Hz, 1H), 7.59 (br d, *J*=4.8 Hz, 1H), 7.28 - 7.00 (m, 5H), 6.95 (s, 1H), 5.47 (s, 2H), 2.79 (q, *J*=7.5 Hz, 2H), 2.60 - 2.47 (m, 6H), 1.25 (br t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)
068		506.632	507.2; 0.78 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (br d, *J*=7.0 Hz, 1H), 7.79 (s, 1H), 7.71 (br d, *J*=7.9 Hz, 1H), 7.61 (s, 1H), 7.10 (br d, *J*=7.9 Hz, 2H), 7.01 (br d, *J*=7.9 Hz, 2H), 6.96 (s, 1H), 5.44 (s, 2H), 2.77 (q, *J*=7.3 Hz, 2H), 2.59 - 2.45 (m, 9H), 1.22 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)

Example 069: 2-((4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)oxy)acetic acid



Intermediate 069a: Methyl 2-((3-bromo-[1,1'-biphenyl]-4-yl)oxy)acetate



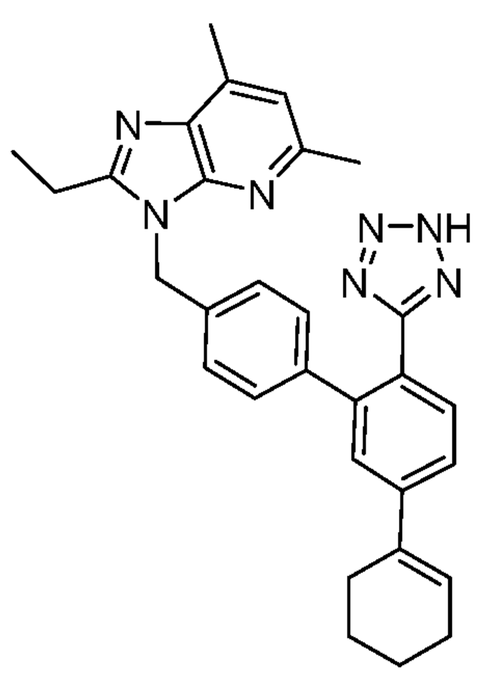
To a solution of 3-bromo[1,1'-biphenyl]-4-ol (100 mg, 0.401 mmol) in DMF (2.01mL) was added potassium carbonate (166 mg, 1.20 mmol) followed by methyl bromoacetate (41.8 µL, 0.442 mmol). The reaction was stirred vigorously at RT. After 30 min, the reaction mixture was diluted with EtOAc, filtered over celite and washed with 10% LiCl (aq). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **Intermediate 069a** (117 mg, 0.364 mmol, 91 % yield) as a white amorphous solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (d, *J*=2.2 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.46 (dd, *J*=8.5, 2.3 Hz, 1H), 7.44 - 7.39 (m, 2H), 7.36 - 7.30 (m, 1H), 6.88 (d, *J*=8.6 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H).

Example 069:

To a solution of **Intermediate 001d** (40 mg, 0.102 mmol) and **Intermediate 069a** (36.1 mg, 0.112 mmol) in dioxane (2 mL) was added tripotassium phosphate (2 M aq, 102 µL, 0.204 mmol) followed by $PdCl_2$(dppf) (7.48 mg, 10.2 µmol). The resulting mixture was sparged with N_2 for 2 min before being sealed and heated at 120 °C for 45 min in the microwave. The organic phase was diluted with EtOAc and filtered over a mixture of $MgSO_4$/Celite. The filtrate was concentrated, dissolved in a 2:1 mixture of THF (2 mL)

and LiOH (1 M aq, 1.02 mL, 1.02 mmol) and heated at 65 °C. After 30 min the reaction mixture was quenched with Sat. NH_4Cl and diluted with EtOAc. The organic phase was concentrated *in vacuo* and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% TFA; Mobile Phase B: 95:5 ACN: H_2O with 10.1% TFA; Gradient: 30-70% B over 27 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min. The material was repurified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 25-50% B over 25 minutes, then a 2-minute hold at 100% B; Flow: 20 mL/min to give **Example 69** (11 mg, 0.021 mmol, 21%). LC-MS (Method A2) RT = 0.86 min, MS (ESI) *m/z*: 492.1 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.64 (t, *J*=9.0 Hz, 4H), 7.57 (d, *J*=8.5 Hz, 1H), 7.53 (s, 1H), 7.42 (t, *J*=7.3 Hz, 2H), 7.35 - 7.27 (m, 1H), 7.17 (d, *J*=7.9 Hz, 2H), 7.04 (d, *J*=8.5 Hz, 1H), 6.96 (s, 1H), 5.51 (s, 2H), 4.68 (br. s., 2H), 2.85 (q, *J*=7.3 Hz, 2H), 2.52 (br. s., 3H), 2.51 (br. s., 3H), 1.29 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

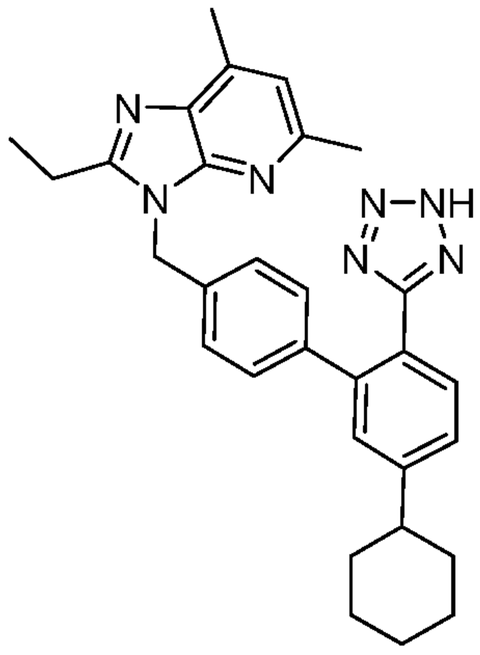
Example 070: 3-((6'-(2H-Tetrazol-5-yl)-2'',3'',4'',5''-tetrahydro-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



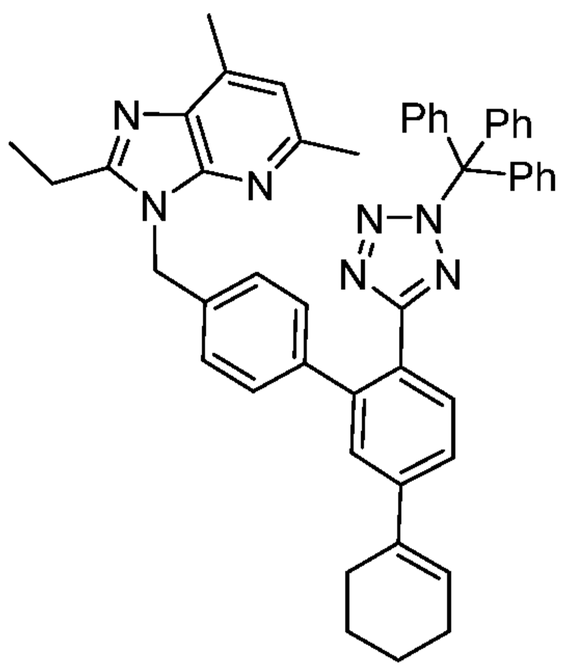
To a microwave vial containing $PdCl_2$(dppf) (2.00 mg, 2.74 μmol) and cyclohex-1-en-1-ylboronic acid (6.90 mg, 0.055 mmol) was added a solution of **Intermediate 055c** (20 mg, 0.027 mmol) in toluene (1 mL) followed by ethanol (250 μL) and tripotassium phosphate (2 M aq, 34.2 μL, 0.068 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 120 °C in the microwave for 30 min. The solution was then filtered over a pad of Celite/$MgSO_4$ then concentrated *in vacuo*. The crude residue was dissolved in DCM (2 mL), and triethylsilane (21.9 μL, 0.137

mmol) was added followed by TFA (63.3 µL, 0.821 mmol). After 5 minutes, the reaction mixture was concentrated *in vacuo* and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min to give **Example 070** (4.9 mg, 0.010 mmol, 37%). LC-MS (Method A2) RT = 0.93 min, MS (ESI) *m/z*: 490.4 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.61 - 7.49 (m, 2H), 7.42 (br. s., 1H), 7.10 - 6.99 (m, 4H), 6.95 (s, 1H), 6.33 (br. s., 1H), 5.45 (br. s., 2H), 2.77 (q, *J*=7.0 Hz, 2H), 2.55 (s, 6H), 2.41 (br. s., 2H), 2.19 (br. s., 2H), 1.73 (br. s., 2H), 1.61 (br. s., 2H), 1.23 (t, *J*=7.0 Hz, 3H.

Example 071: 3-((5'-Cyclohexyl-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



Intermediate 71a: 2-ethyl-5,7-dimethyl-3-((6'-(2-trityl-2H-tetrazol-5-yl)-2'',3'',4'',5''-tetrahydro-[1,1':3',1''-terphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

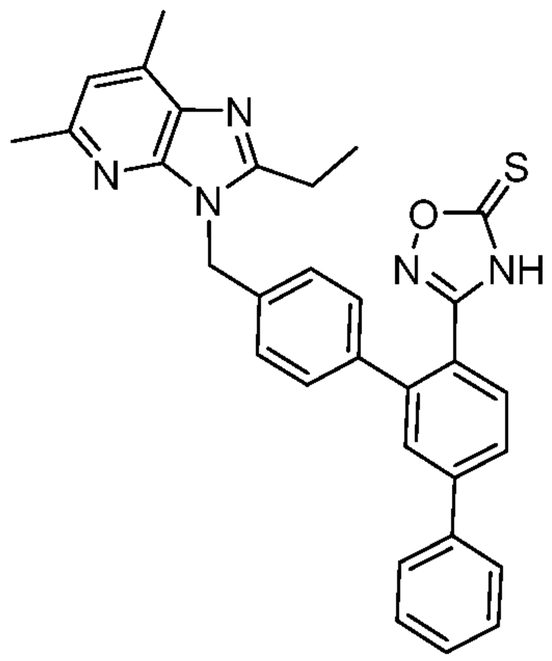


To a microwave vial containing $PdCl_2$(dppf) (3.00 mg, 4.11 μmol) and cyclohex-1-en-1-ylboronic acid (10.34 mg, 0.082 mmol) was added a solution of **Intermediate 55c** (30 mg, 0.041 mmol) in toluene (1 mL) followed by ethanol (250 μL) and tripotassium phosphate (2 M aq, 51.3 μL, 0.103 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 120 °C in the microwave for 30 min. The solution was then filtered over a pad of Celite/$MgSO_4$ before being concentrated *in vacuo*. This crude residue was purified by column chromatography (ISCO, 12g silica gel column, gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 71a** (25 mg, 0.034 mmol, 83 % yield) as an off-white solid. LC-MS (Method A2) RT = 1.22 min, MS (ESI) *m/z*: 732.3 $(M+H)^+$.

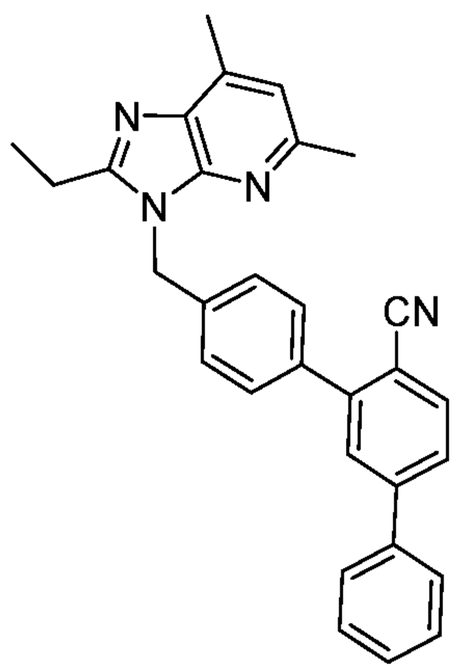
Example 71:

To a flask containing **Intermediate 71a** (25 mg, 0.034 mmol) was added THF (2 mL). Palladium on carbon (Degussa, 3.63 mg, 3.42 μmol) was added and the resulting suspension was sparged with hydrogen. The reaction mixture was stirred vigorously under a balloon atmosphere of hydrogen. After 6 h, ethanol (1 mL) was added. After 18 hours, the reaction mixture was diluted with EtOAc and filtered over Celite. The resulting solution was concentrated *in vacuo* then dissolved in DCM (2 mL). Triethylsilane (0.027 mL, 0.171 mmol) was added, followed TFA (0.079 mL, 1.02 mmol). After 5 min, the reaction mixture was concentrated *in vacuo* and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-80% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to give **Example 71** (5.7 mg, 0.012 mmol, 34%). LC-MS (Method A2) RT = 0.96 min, MS (ESI) *m/z*: 492.4 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.53 (d, *J*=7.8 Hz, 1H), 7.38 (d, *J*=7.7 Hz, 1H), 7.30 (s, 1H), 7.03 (s, 4H), 6.95 (s, 1H), 5.44 (s, 2H), 2.76 (q, *J*=7.3 Hz, 2H), 2.61 (t, *J*=11.4 Hz, 1H), 2.55 (s, 6H), 1.81 (t, *J*=14.9 Hz, 4H), 1.70 (d, *J*=11.9 Hz, 1H), 1.55 - 1.42 (m, 2H), 1.37 (q, *J*=12.4 Hz, 2H), 1.24 (m, 4H) (1 exchangeable proton not observed).

Example 72: 3-(4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazole-5(4H)-thione

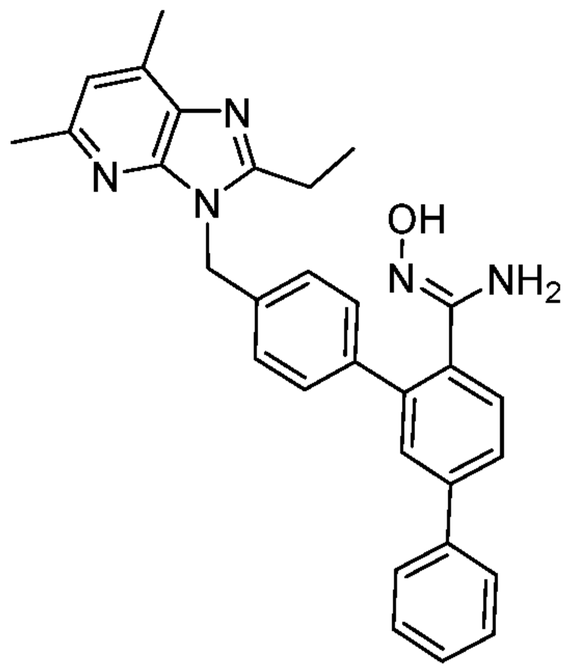


Intermediate 72a: 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



To a solution of **Intermediate 001d** (120 mg, 0.307 mmol) and 3-bromo-[1,1'-biphenyl]-4-carbonitrile (103 mg, 0.399 mmol) in 1,4-dioxane (3 mL) was added tripotassium phosphate (2 M aq, 0.460 mL, 0.920 mmol) followed by $PdCl_2$(dppf) (22.4 mg, 0.031 mmol). The resulting mixture was sparged with N_2 for 2 min before being sealed and heated at 120 °C for 45 min in the microwave. The reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 24 g silica gel column, 30 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 72a** (130 mg, 0.294 mmol, 96%). LC-MS (Method A2) RT = 0.93 min, MS (ESI) *m/z*: 443.1 $(M+H)^+$. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (d, *J*=7.9 Hz, 1H), 7.69 - 7.58 (m, 4H), 7.54 (d, *J*=8.4 Hz, 2H), 7.50 - 7.39 (m, 3H), 7.28 - 7.22 (m, 2H), 6.91 (s, 1H), 5.54 (s, 2H), 2.84 (q, *J*=7.5 Hz, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 1.37 - 1.31 (m, 3H).

Intermediate 72b: (Z)-4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide

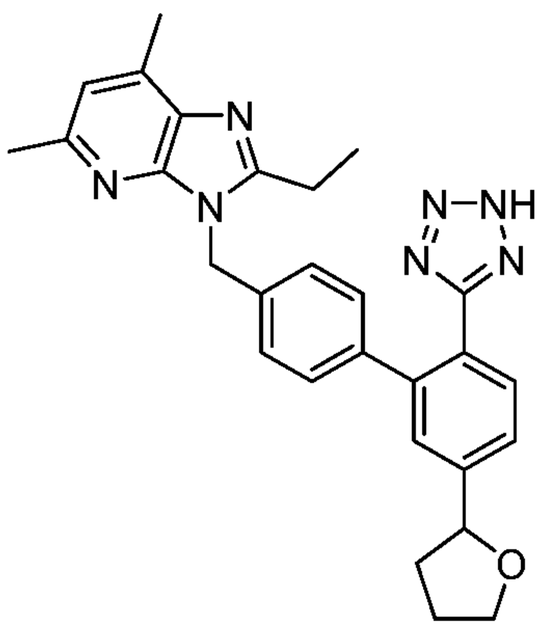


To a vial containing hydroxylamine hydrochloride (56.5 mg, 0.813 mmol) and potassium hydroxide (38.0 mg, 0.678 mmol) was added ethanol (678 µL). The mixture was stirred vigorously for 15 min, then the suspension was added directly to a vial containing **Intermediate 72a** (30 mg, 0.068 mmol) in its own solution of ethanol (678 µL). The vial was sealed and heated at 85 °C. After 16 h of heating, another 5 equiv of hydroxylamine (24 mg) was added and heating was resumed for an additional 4 h. The reaction mixture was diluted with EtOAc and washed with sat. NH_4Cl. The organic phase was dried over $MgSO_4$ and filtered over celite with an EtOAc rinse. The organic phase was concentrated *in vacuo* and was used directly in the subsequent reaction as **Intermediate 72b** (15 mg, 0.032 mmol). LC-MS (Method A2) RT = 0.72 min, MS (ESI) *m/z*: 476.1 $(M+H)^+$.

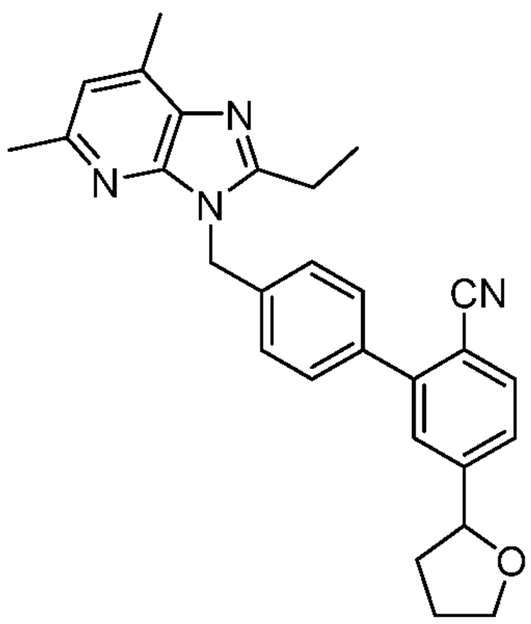
Example 72:

To a solution of **Intermediate 72b** (15 mg, 0.032 mmol) in DMF (2 mL) was added DBU (0.024 mL, 0.158 mmol) followed by 1,1'-thiocarbonyldiimidazole (28.1 mg, 0.158 mmol). After 5 min, the reaction mixture was quenched with a few drops of H_2O, filtered and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min to give **Example 72** (7.8 mg, 0.015 mmol, 46%). LC-MS (Method A2) RT = 0.95 min, MS (ESI) *m/z*: 518.3 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.80 - 7.58 (m, 4H), 7.55 - 7.35 (m, 3H), 7.33 - 6.92 (m, 6H), 5.50 (br. s., 2H), 2.82 (q, *J*=7.0 Hz, 2H), 2.55 (s, 6H), 1.26 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed).

Example 73: 2-ethyl-5,7-dimethyl-3-((5'-(tetrahydrofuran-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



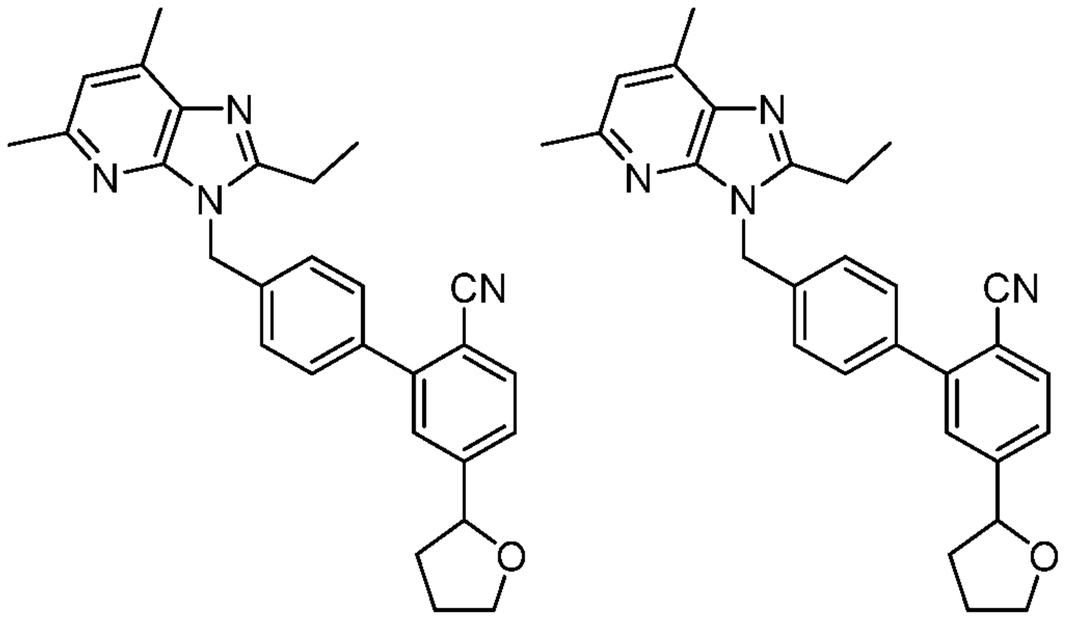
Intermediate 73a: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(tetrahydrofuran-2-yl)-[1,1'-biphenyl]-2-carbonitrile



Intermediate 55a (100 mg, 0.225 mmol), tetrahydrofuran-2-carboxylic acid (78 mg, 0.674 mmol), $[IR(DFCF_3PPY)_2(BPY)]PF_6$ (2.27 mg, 2.24 μmol), nickel(II) chloride ethylene glycol dimethyl ether complex (9.87 mg, 0.045 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (18.1 mg, 0.067 mmol), and cesium carbonate (219 mg, 0.674 mmol) were dissolved in DMF (4.49 mL). The reaction was degassed by bubbling with N_2 for 20 minutes, then irradiated with a 34 W Blue LED lamp. After 18 hours, the reaction was diluted with EtOAc and washed with saturated $NaHCO_3$, H_2O, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 40 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in DCM) to give **Intermediate 73a** (42.3 mg, 0.097 mmol, 43%). LC-MS (Method A2) RT = 0.82 min, MS (ESI) *m/z*: 437.7 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=8.3 Hz, 2H), 7.45 (s, 1H), 7.41 (dd, *J*=8.0, 1.1 Hz, 1H), 7.26 (br d, *J*=8.3 Hz, 2H), 6.93 (s, 1H), 5.55 (s, 2H), 4.97 (t, *J*=7.3 Hz, 1H), 4.23 - 4.05 (m,

J=19.5, 7.7 Hz, 1H), 4.05 - 3.95 (m, 1H), 2.90 - 2.79 (m, 2H), 2.67 (s, 3H), 2.65 - 2.61 (m, 3H), 2.45 - 2.38 (m, 1H), 2.12 - 1.99 (m, 2H), 1.79 (br dd, *J*=12.2, 7.8 Hz, 1H), 1.42 - 1.34 (m, 3H).

Intermediate 73b & Intermediate 73c: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(tetrahydrofuran-2-yl)-[1,1'-biphenyl]-2-carbonitrile

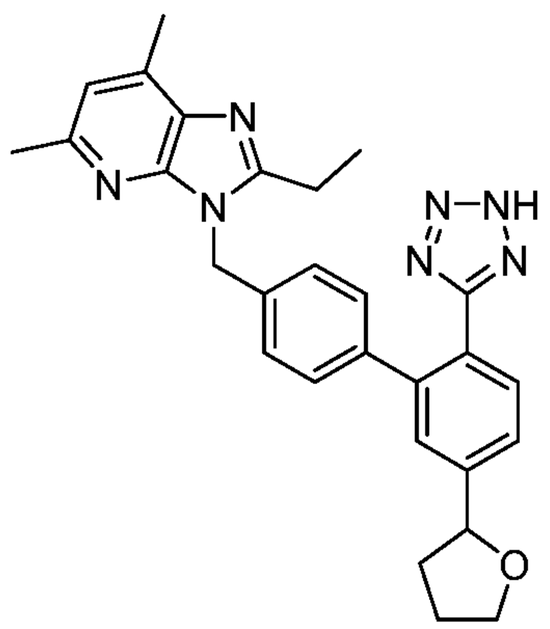


Intermediate 73a (42.3 mg, 0.097 mmol) was separated by chiral SFC (Regis Whelk-01, 21x250 mm, 5 micron column; 20% MeOH / 80% CO_2 mobile phase; 45 mL/min, 150 bar, 40 °C) to give two peaks, the first eluting of which was **Intermediate 73b** (9.2 mg, 0.021 mmol, 22%) as a clear glassy solid. The second eluting isomer was **Intermediate 73c** (11.6 mg, 0.027 mmol, 27%) as a clear glassy solid.

Example 73:

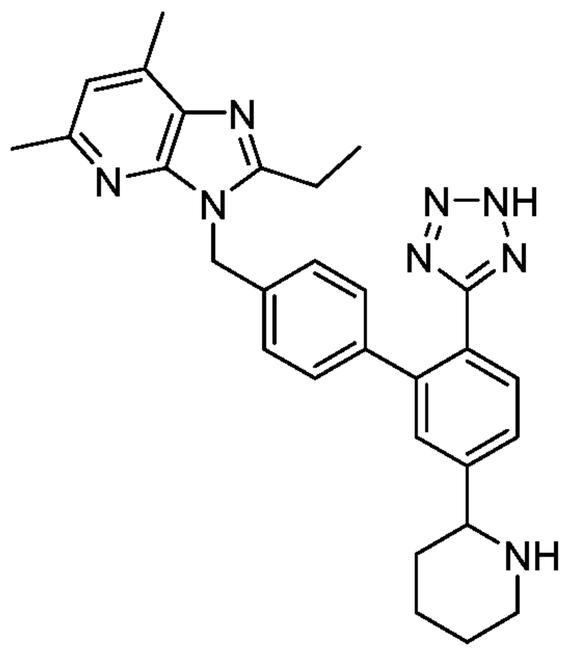
Intermediate 73b (9 mg, 0.021 mmol) was reacted with dibutyltin oxide (5.1 mg, 0.021 mmol) and TMS-N_3 (27.4 µL, 0.206 mmol) in a manner analogous to **Example 62** to give **Example 73** (1.7 mg, 0.0034 mmol, 17%). LC-MS (Method A2) RT = 0.73 min, MS (ESI) *m/z*: 480.4 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (br d, *J*=7.9 Hz, 1H), 7.44 (br d, *J*=7.3 Hz, 1H), 7.35 (s, 1H), 7.02 (s, 4H), 6.96 (s, 1H), 5.43 (s, 2H), 4.90 (br t, *J*=7.2 Hz, 1H), 3.98 (q, *J*=7.1 Hz, 1H), 2.75 (q, *J*=7.4 Hz, 2H), 2.55 (s, 6H), 2.35 (br dd, *J*=12.2, 6.4 Hz, 1H), 2.00 - 1.84 (m, 2H), 1.79 - 1.62 (m, 1H), 1.28 - 1.13 (m, 3H), 1.00 (d, *J*=6.4 Hz, 1H) (1 exchangeable proton not observed).

Example 74: 2-ethyl-5,7-dimethyl-3-((5'-(tetrahydrofuran-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

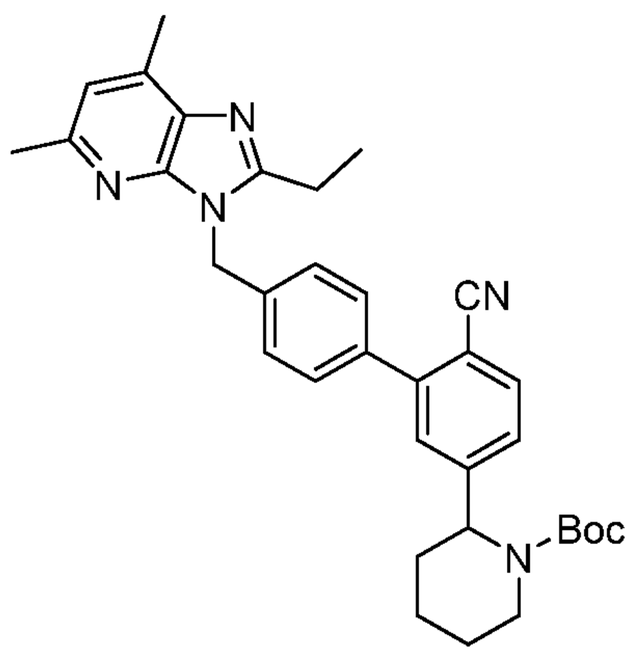


Intermediate 73c (9 mg, 0.021 mmol) was reacted with dibutyltin oxide (6.3 mg, 0.025 mmol) and TMS-N_3 (33.4 µL, 0.252 mmol) in a manner analogous to **Example 62** to give **Example 74** (5.9 mg, 0.012 mmol, 47%). LC-MS (Method A2) RT = 0.73 min, MS (ESI) *m/z*: 480.4 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (br d, *J*=7.9 Hz, 1H), 7.44 (br d, *J*=7.3 Hz, 1H), 7.35 (s, 1H), 7.02 (s, 4H), 6.96 (s, 1H), 5.43 (s, 2H), 4.90 (br t, *J*=7.2 Hz, 1H), 3.98 (q, *J*=7.1 Hz, 1H), 2.75 (q, *J*=7.4 Hz, 2H), 2.55 (s, 6H), 2.35 (br dd, *J*=12.2, 6.4 Hz, 1H), 2.00 - 1.84 (m, 2H), 1.79 - 1.62 (m, 1H), 1.28 - 1.13 (m, 3H), 1.00 (d, *J*=6.4 Hz, 1H) (1 exchangeable proton not observed).

Example 75: 2-ethyl-5,7-dimethyl-3-((5'-(piperidin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

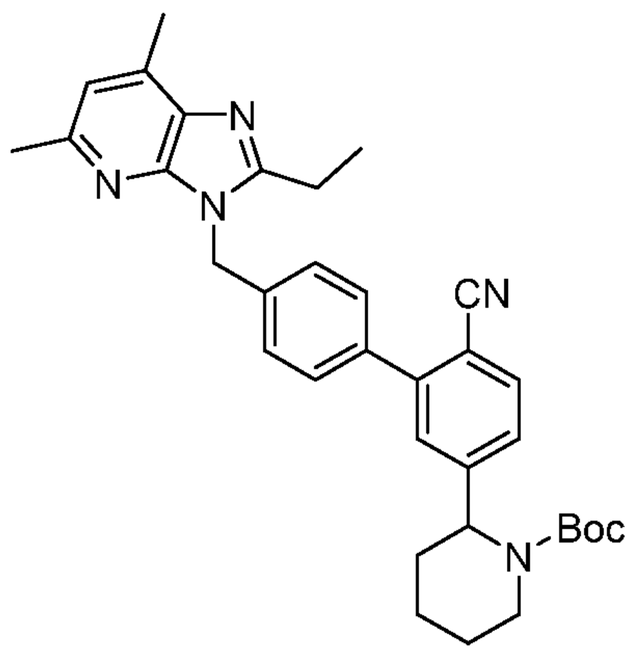


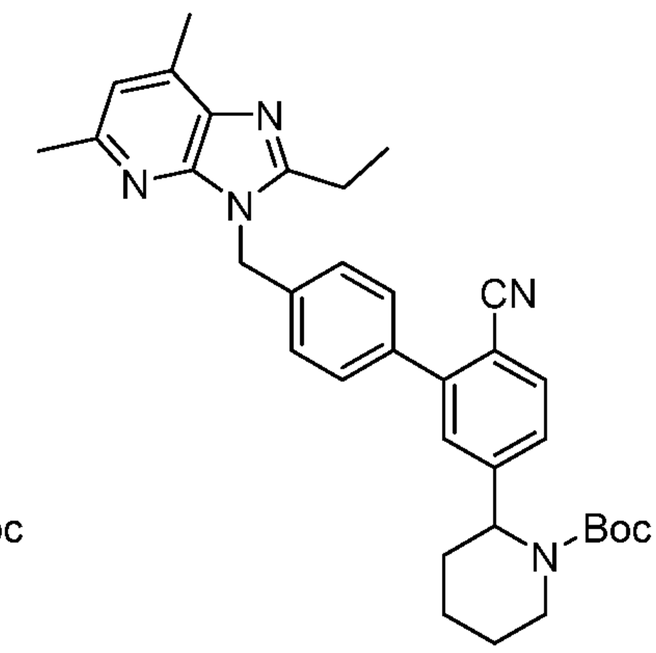
Intermediate 75a: tert-butyl 2-(6-cyano-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-yl)piperidine-1-carboxylate



Intermediate 55a (150 mg, 0.337 mmol) was reacted with Boc-L-pipecolic acid (232 mg, 1.01 mmol) in a manner analogous to **Intermediate 73a** to give **Intermediate 75a** (195.2 mg, 0.355 mmol). LC-MS (Method A2) RT = 0.94 min, MS (ESI) *m/z*: 550.8 $(M+H)^+$.

Intermediate 75b & Intermediate 75c: tert-butyl 2-(6-cyano-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-yl)piperidine-1-carboxylate

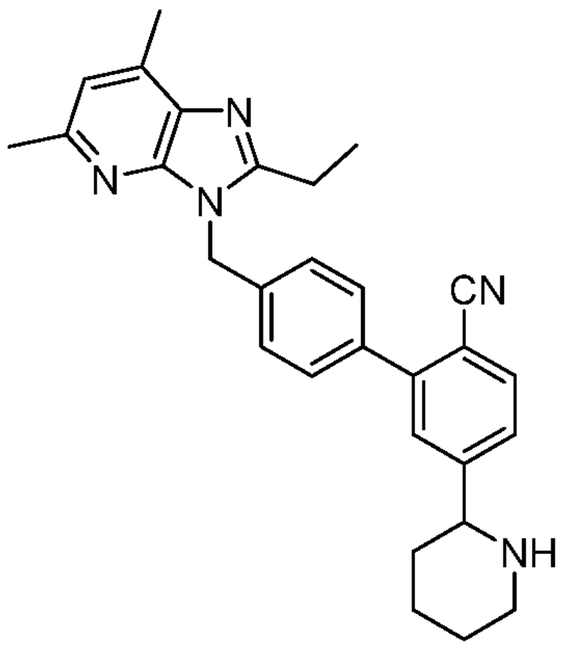




Intermediate 75a (317.4 mg, 0.577 mmol) was separated by chiral SFC (Regis Whelk-01, 30x250 mm, 5 micron column; 30% MeOH / 70% CO_2 mobile phase; 85 mL/min, 150 bar, 40 °C) to give two peaks, the first eluting of which was **Intermediate 75b** (72.4 mg, 0.132 mmol, 23%) as a clear glassy solid. The second eluting isomer was **Intermediate 75c** (80.2 mg, 0.146 mmol, 25%) as a clear glassy solid. Analytical data for both enantiomers: LC-MS (Method A2) RT = 0.94 min, MS (ESI) *m/z*: 550.8 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.5 Hz, 1H), 7.49 (d, *J*=8.3 Hz, 2H), 7.33 - 7.30 (m, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 6.93 (s, 1H), 5.55 (s, 2H), 5.45 (br d, *J*=2.2 Hz, 1H), 4.08 (br d, *J*=14.6 Hz, 1H), 2.86 (q, *J*=7.4 Hz, 2H), 2.77 (td, *J*=12.9, 3.6 Hz, 1H), 2.67 (s,

3H), 2.62 (s, 3H), 2.28 (br d, *J*=12.9 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.70 - 1.60 (m, 4H), 1.46 (s, 9H), 1.37 (t, *J*=7.4 Hz, 3H).

Intermediate 75d: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(piperidin-2-yl)-[1,1'-biphenyl]-2-carbonitrile, 2 TFA

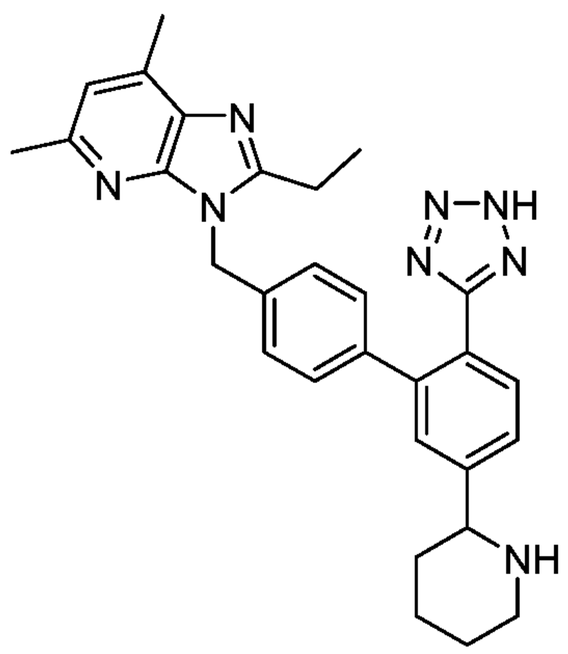


Intermediate 75b (70 mg, 0.127 mmol) was dissolved in DCM (1.27 mL) and TFA (98 µL, 1.27 mmol). After 18 hours, the reaction was concentrated *in vacuo* to give **Intermediate 75d**. LC-MS (Method A2) RT = 0.61 min, MS (ESI) *m/z*: 450.4 $(M+H)^+$.

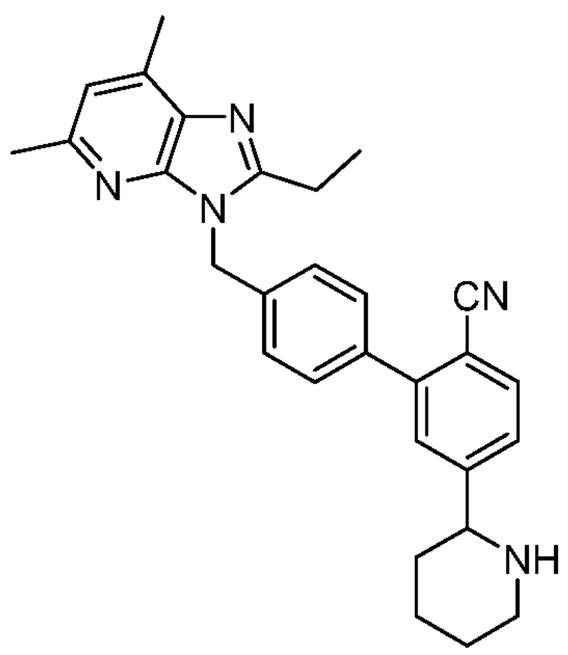
Example 75:

Intermediate 75d (10 mg, 0.022 mmol) was reacted with dibutyltin oxide (5.5 mg, 0.022 mmol) and TMS-N_3 (29.5 µL, 0.222 mmol) in a manner analogous to **Example 62** to give **Example 75** (3.6 mg, 0.007 mmol, 32%). LC-MS (Method A2) RT = 0.57 min, MS (ESI) *m/z*: 493.3 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.56 (br d, *J*=8.2 Hz, 1H), 7.40 (br s, 2H), 7.06 (br d, *J*=8.2 Hz, 2H), 7.00 - 6.91 (m, 3H), 5.43 (s, 2H), 4.18 (br d, *J*=11.9 Hz, 1H), 3.05 - 2.95 (m, 1H), 2.78 (q, *J*=7.6 Hz, 2H), 2.55 (s, 6H), 1.97 (br d, *J*=12.2 Hz, 1H), 1.89 - 1.74 (m, 3H), 1.70 - 1.55 (m, 2H), 1.25 (t, *J*=7.5 Hz, 3H) (2 exchangeable protons not observed).

Example 76: 2-ethyl-5,7-dimethyl-3-((5'-(piperidin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



Intermediate 76a: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(piperidin-2-yl)-[1,1'-biphenyl]-2-carbonitrile, 2 TFA

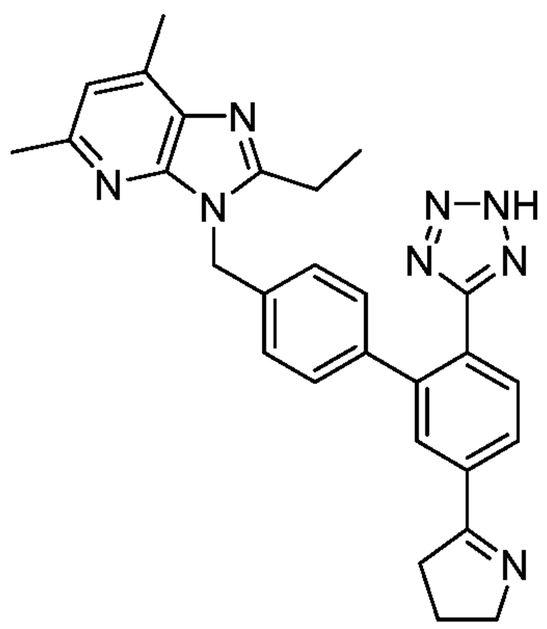


Intermediate 75c (80 mg, 0.146 mmol) was reacted in a manner analogous to **Intermediate 75d** to give **Intermediate 76a**. LC-MS (Method A2) RT = 0.61 min, MS (ESI) *m/z*: 450.4 $(M+H)^+$.

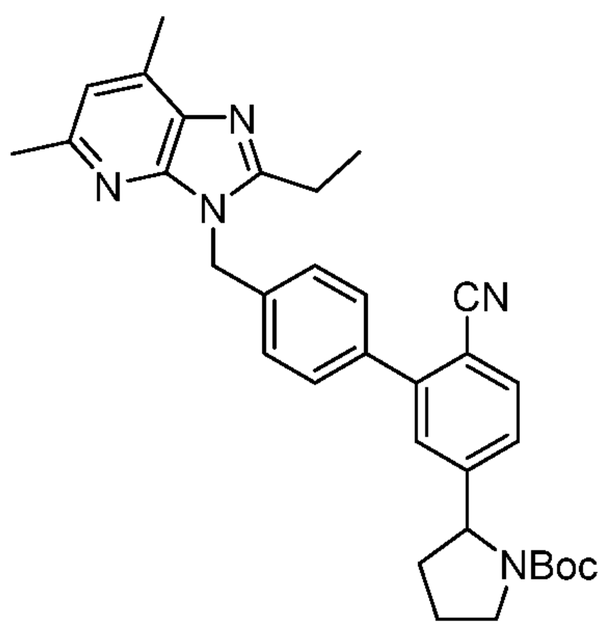
Example 76:

Intermediate 76a (10 mg, 0.022 mmol) was reacted with dibutyltin oxide (5.5 mg, 0.022 mmol) and TMS-N_3 (29.5 µL, 0.222 mmol) in a manner analogous to **Example 62** to give **Example 76** (3.6 mg, 0.007 mmol, 32%). LC-MS (Method A2) RT = 0.57 min, MS (ESI) *m/z*: 493.3 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (d, *J*=7.8 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.07 (br d, *J*=8.1 Hz, 2H), 6.99 (br d, *J*=8.2 Hz, 2H), 6.94 (s, 1H), 5.42 (s, 2H), 3.58 - 3.27 (m, 3H), 2.77 (q, *J*=7.5 Hz, 3H), 2.55 (s, 6H), 2.09 - 1.60 (m, 6H), 1.24 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed).

Example 77: 3-((5'-(3,4-dihydro-2H-pyrrol-5-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

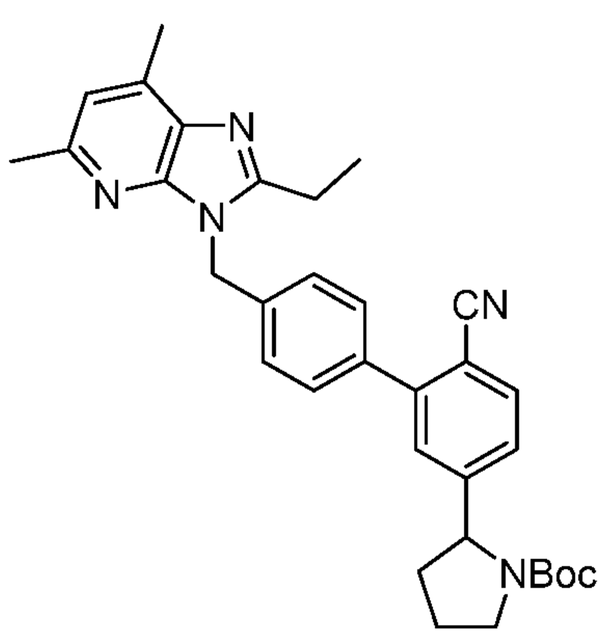


Intermediate 77a: tert-butyl 2-(6-cyano-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-yl)pyrrolidine-1-carboxylate



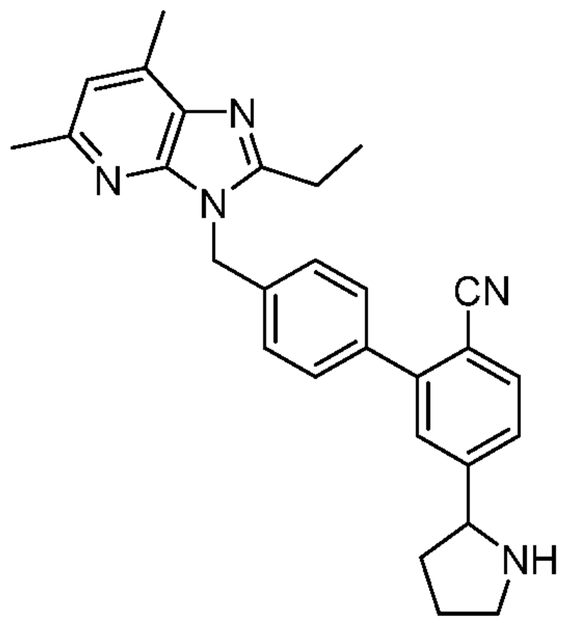
Intermediate 55a (150 mg, 0.337 mmol) was reacted with 1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (217 mg, 1.01 mmol) in a manner analogous to **Intermediate 73a** to give **Intermediate 77a** (66.3 mg, 0.124 mmol). LC-MS (Method A2) RT = 0.88 min, MS (ESI) *m/z*: 536.8 $(M+H)^+$.

Intermediate 77b: tert-butyl 2-(6-cyano-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-yl)pyrrolidine-1-carboxylate



Intermediate 77a (289.3 mg, 0.541 mmol) was separated by chiral SFC (Regis Whelk-01, 30x250 mm, 5 micron column; 30% MeOH / 70% CO_2 mobile phase; 85 mL/min, 150 bar, 40 °C) to give two peaks, the first eluting of which was **Intermediate 77b** (122.1 mg, 0.228 mmol, 42%) as a clear glassy solid. LC-MS (Method A2) RT = 0.89 min, MS (ESI) *m/z*: 536.5 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J*=8.3 Hz, 1H), 7.51 - 7.44 (m, 2H), 7.28 - 7.23 (m, 4H), 6.93 (s, 1H), 5.55 (s, 2H), 5.03 - 4.77 (m, 1H), 3.72 - 3.54 (m, 2H), 2.85 (q, *J*=7.6 Hz, 2H), 2.67 (s, 3H), 2.63 (s, 3H), 2.44 - 2.34 (m, 1H), 1.97 - 1.78 (m, 3H), 1.58 (s, 9H), 1.37 (t, *J*=7.6 Hz, 3H).

Intermediate 77c: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(pyrrolidin-2-yl)-[1,1'-biphenyl]-2-carbonitrile, 2 TFA

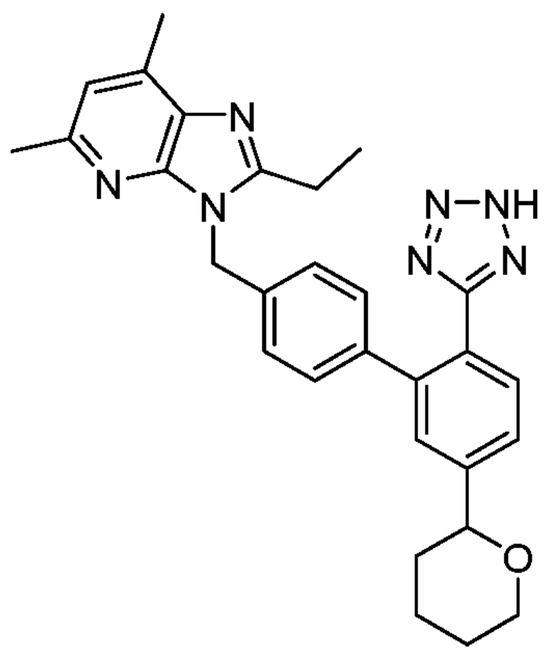


Intermediate 77b (110 mg, 0.205 mmol) was reacted in a manner analogous to **Intermediate 75d** to give **Intermediate 77c**. LC-MS (Method A2) RT = 0.59 min, MS (ESI) *m/z*: 436.3 $(M+H)^+$.

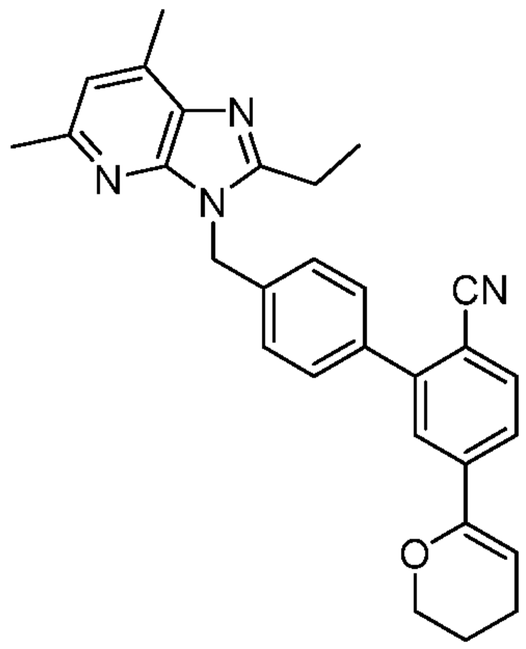
Example 77:

Intermediate 77b (13 mg, 0.030 mmol) was reacted with dibutyltin oxide (7.4 mg, 0.030 mmol) and TMS-N_3 (39.6 µL, 0.298 mmol) in a manner analogous to **Example 62** with concomitant partial oxidation to give **Example 77** (3.7 mg, 0.008 mmol, 26%). LC-MS (Method A1) RT = 1.20 min, MS (ESI) *m/z*: 477.0 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (br d, *J*=7.6 Hz, 1H), 7.83 (s, 1H), 7.72 (br d, *J*=7.6 Hz, 1H), 7.13 - 6.99 (m, 4H), 6.95 (s, 1H), 5.45 (s, 2H), 4.04 - 3.93 (m, 2H), 2.98 (br t, *J*=7.8 Hz, 2H), 2.77 (q, *J*=7.0 Hz, 2H), 2.55 (s, 6H), 2.03 - 1.93 (m, 2H), 1.23 (br t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

Example 78: 2-ethyl-5,7-dimethyl-3-((5'-(tetrahydro-2H-pyran-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

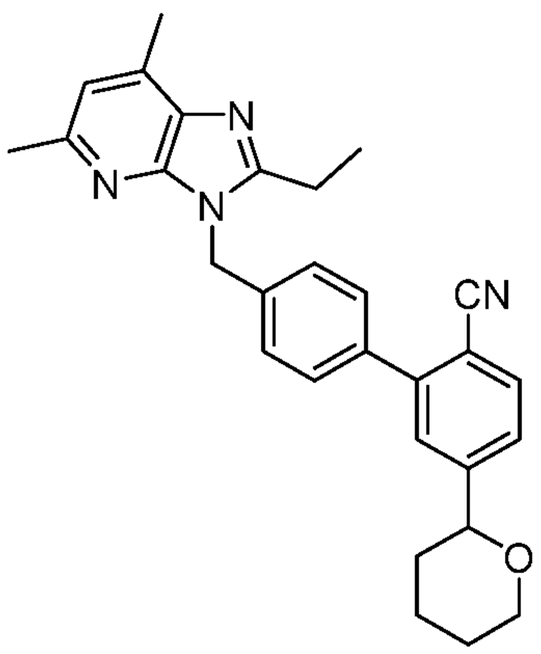


Intermediate 78a: 5-(3,4-dihydro-2H-pyran-6-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



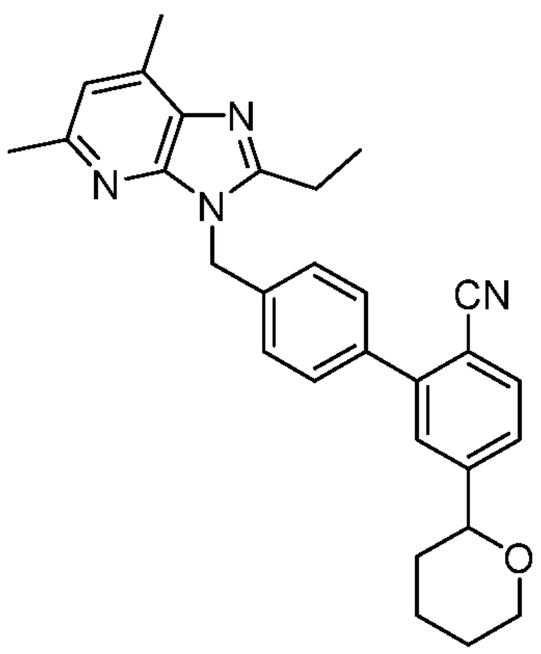
Intermediate 055a (215 mg, 0.536 mmol), 2-(3,4-dihydro-2H-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (338 mg, 1.61 mmol), and 2nd Generation XPHOS Precatalyst (42.2 mg, 0.054 mmol) were dissolved in toluene (4.29 mL), ethanol (1.07 mL), and tripotassium phosphate (536 µL, 1.07 mmol). The reaction was degassed with N_2 for 10 minutes and heated at 100 °C. After 3 hours, the reaction was diluted with EtOAc, filtered through celite/Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 40 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 78a** (182.8 mg, 0.408 mmol, 76%). LC-MS (Method A2) RT = 0.91 min, MS (ESI) *m/z*: 449.2 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 - 7.57 (m, 3H), 7.51 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 6.94 (s, 1H), 5.62 - 5.50 (m, 3H), 4.25 - 4.15 (m, 2H), 2.86 (q, *J*=7.5 Hz, 2H), 2.67 (s, 3H), 2.63 (s, 3H), 2.32 - 2.23 (m, 2H), 2.00 - 1.90 (m, 2H), 1.37 (t, *J*=7.6 Hz, 3H).

Intermediate 78b: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(tetrahydro-2H-pyran-2-yl)-[1,1'-biphenyl]-2-carbonitrile



Intermediate 78a (180 mg, 0.401 mmol) and palladium on carbon (42.7 mg, 0.040 mmol) were dissolved in MeOH (8.03 μL). The reaction was purged with hydrogen (0.809 mg, 0.401 mmol). After 1 hour, the reaction was filtered through celite and concentrated *in vacuo* to give **Intermediate 78b** (180.3 mg, 0.400 mmol, 100%). LC-MS (Method A2) RT = 0.89 min, MS (ESI) *m/z*: 451.3 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.7 Hz, 1H), 7.55 - 7.46 (m, 3H), 7.42 (d, *J*=8.0 Hz, 1H), 7.26 (br d, *J*=8.0 Hz, 2H), 6.95 (s, 1H), 5.56 (s, 2H), 4.46 - 4.37 (m, 1H), 4.22 - 4.13 (m, 1H), 3.68 - 3.58 (m, 1H), 2.94 - 2.84 (m, 2H), 2.68 (s, 3H), 2.63 (s, 3H), 1.98 (br dd, *J*=4.1, 2.2 Hz, 1H), 1.89 (br d, *J*=13.2 Hz, 1H), 1.75 - 1.64 (m, 4H), 1.37 (t, *J*=7.6 Hz, 3H).

Intermediate 78c: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(tetrahydro-2H-pyran-2-yl)-[1,1'-biphenyl]-2-carbonitrile

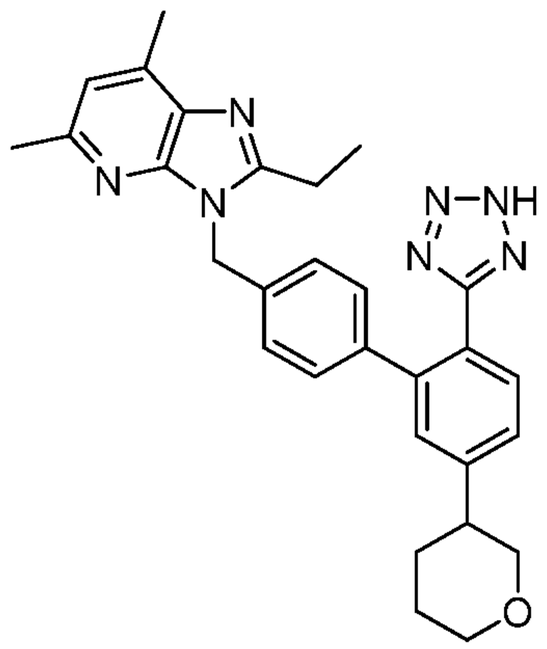


Intermediate 78b (180 mg, 0.399 mmol) was separated by chiral SFC (Chiralcel OJ-H, 21x250 mm, 5 micron column; 20% MeOH / 80% CO_2 mobile phase; 45 mL/min, 120 bar, 40 °C) to give two peaks, the first eluting of which was **Intermediate 78c** (65.9 mg, 0.146 mmol, 37%)

Example 78:

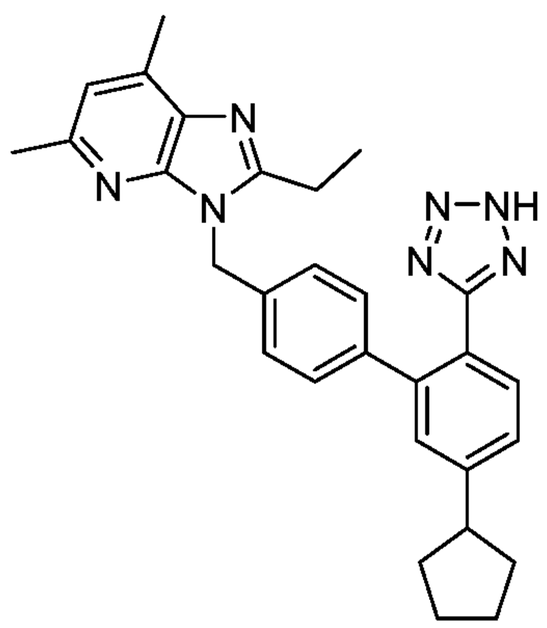
Intermediate 78c (65.9 mg, 0.146 mmol) was reacted with dibutyltin oxide (72.8 mg, 0.293 mmol) and TMS-N_3 (97 µL, 0.731 mmol) in a manner analogous to **Example 62** to give **Example 78** (63.7 mg, 0.129 mmol, 85%). LC-MS (Method A2) RT = 0.81 min, MS (ESI) *m/z*: 494.3 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (br d, *J*=7.9 Hz, 1H), 7.49 (br d, *J*=7.9 Hz, 1H), 7.42 (s, 1H), 7.04 (s, 4H), 6.96 (s, 1H), 5.45 (s, 2H), 4.45 (br d, *J*=11.1 Hz, 1H), 4.04 (br d, *J*=11.2 Hz, 1H), 3.17 (br d, *J*=3.3 Hz, 1H), 2.78 - 2.73 (m, 2H), 2.51 (s, 6H), 1.93 - 1.84 (m, 2H), 1.56 (br s, 2H), 1.50 - 1.42 (m, 1H), 1.21 (br t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed).

Example 79: 2-ethyl-5,7-dimethyl-3-((5'-(tetrahydro-2H-pyran-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

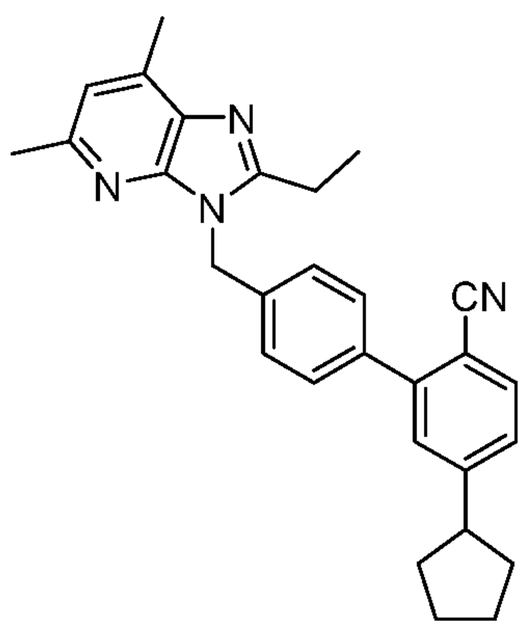


Example 79 was prepared in a manner analogous to **Example 78**. LC-MS (Method A2) RT = 0.75 min, MS (ESI) *m/z*: 494.2 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (br d, *J*=7.7 Hz, 1H), 7.34 (br d, *J*=7.6 Hz, 1H), 7.26 (s, 1H), 7.09 - 7.04 (m, 2H), 7.03 - 6.98 (m, 2H), 6.94 (s, 1H), 5.43 (s, 2H), 3.92 - 3.83 (m, 2H), 3.42 (br t, *J*=10.7 Hz, 1H), 2.87 (br t, *J*=10.9 Hz, 1H), 2.78 (q, *J*=7.4 Hz, 2H), 2.58 - 2.49 (m, 6H), 1.99 (br d, *J*=12.5 Hz, 1H), 1.85 - 1.74 (m, 1H), 1.67 (br d, *J*=3.4 Hz, 2H), 1.26 (t, *J*=7.4 Hz, 4H) (1 exchangeable proton not observed).

Example 80: 3-((5'-cyclopentyl-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



Intermediate 80a: 5-cyclopentyl-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



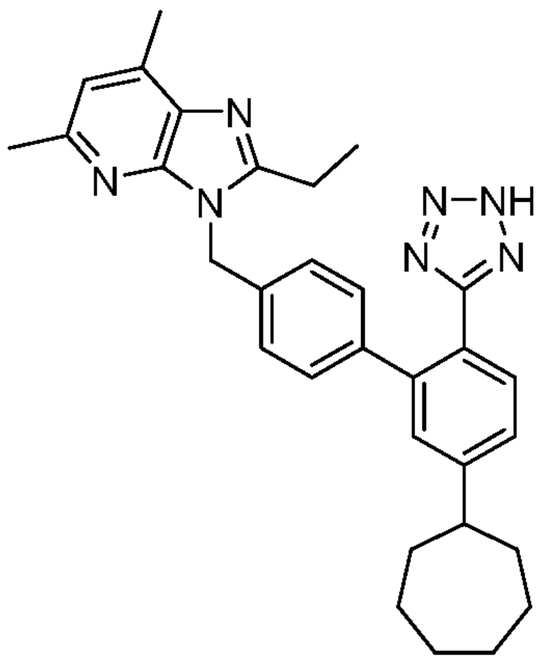
Intermediate 55a (50 mg, 0.112 mmol), bromocyclopentane (18.8 µL, 0.168 mmol), $[IR(DFCF_3PPY)_2(BPY)]PF_6$ (1.13 mg, 1.12 µmol), Tris(trimethylsilyl)silane (34.6 µL, 0.112 mmol), Na_2CO_3 (23.8 mg, 0.225 mmol), nickel chloride dimethoxyethane adduct (2.47 mg, 0.011 mmol), and 4,4'-di-tert-butyl-2,2'-dipyridyl (3.01 mg, 0.011 mmol) were dissolved in DME (2.24 mL). The solution was degassed with N_2 for 10 min. The mixture was then sealed and irradiated with a 34W Blue LED lamp. After 18 hours, the reaction was diluted with EtOAc, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 12 g silica gel column, 17 minute gradient of 0 to 100% EtOAc in DCM) to give **Intermediate 80a** (58.6 mg, 0.135 mmol), which was contaminated with des-bromo product and was used directly in the subsequent reaction. LC-MS (Method A2) RT = 0.99 min, MS (ESI) *m/z*: 435.2 $(M+H)^+$.

Example 80:

Intermediate 80a (58.6 mg, 0.135 mmol) was reacted with dibutyltin oxide (67.1 mg, 0.270 mmol) and TMS-N_3 (89 µL, 0.674 mmol) in a manner analogous to **Example 62** to give **Example 80** (8.8 mg, 0.018 mmol, 13%). LC-MS (Method A2) RT = 0.88 min, MS

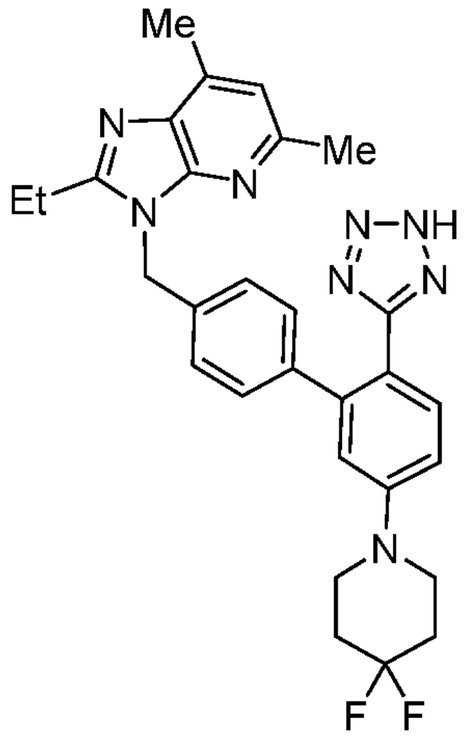
(ESI) *m/z*: 478.2 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 - 7.51 (m, 1H), 7.45 (br s, 1H), 7.35 (br s, 1H), 7.05 (br s, 4H), 6.97 (s, 1H), 5.45 (s, 2H), 3.09 (br t, *J*=8.2 Hz, 1H), 2.76 (br d, *J*=5.2 Hz, 2H), 2.62 - 2.48 (m, 6H), 2.06 (br s, 2H), 1.78 (br s, 2H), 1.71 - 1.55 (m, 4H), 1.22 (br s, 3H) (1 exchangeable proton not observed).

Example 81: 3-((5'-cycloheptyl-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

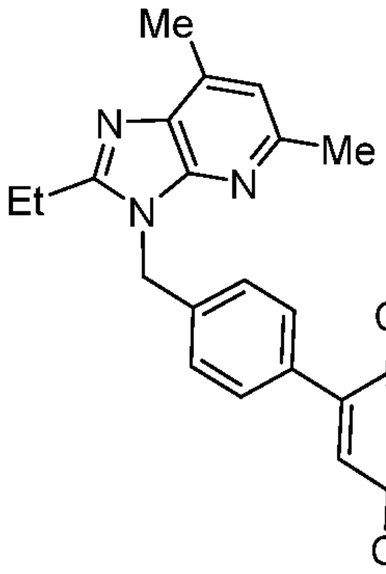


Example 81 was prepared in a manner analogous to **Example 80**. LC-MS (Method A2) RT = 0.96 min, MS (ESI) *m/z*: 506.2 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 (br d, *J*=7.9 Hz, 1H), 7.38 (br d, *J*=7.6 Hz, 1H), 7.30 (s, 1H), 7.04 (s, 4H), 6.96 (s, 1H), 5.45 (s, 2H), 2.77 (q, *J*=7.4 Hz, 3H), 2.56 (s, 6H), 1.86 (br s, 2H), 1.81 - 1.63 (m, 6H), 1.62 - 1.49 (m, 4H), 1.23 (br t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed).

Example 82: 3-((5'-(4,4-difluoropiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

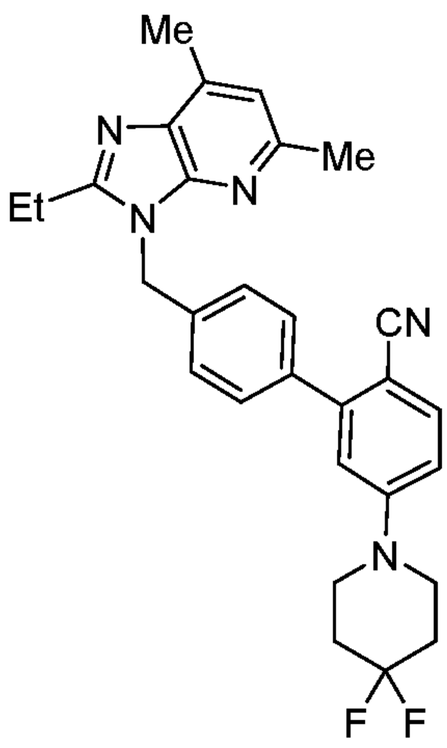


Intermediate 82a: 5-chloro-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



To a microwave vial containing $PdCl_2$(dppf) (0.224 g, 0.307 mmol), **Intermediate 001d** (1.200 g, 3.07 mmol) and 4-chloro-2-iodobenzonitrile (1.050 g, 3.99 mmol) was added toluene (12.27 ml) followed by ethanol (3.07 ml) and K_3PO_4 (2 M, aq.) (3.07 ml, 6.13 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 110 °C overnight. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic phase was concentrated and purified by ISCO (0-100% EtOAc/Hex) to afford **Intermediate 82a** (0.852 g, 2.125 mmol, 69.3 % yield) as a yellow oil. LC-MS (Method A2) RT = 0.83 min, MS (ESI) *m/z*: 401.4 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.70 (d, *J*=8.4 Hz, 1H), 7.52 - 7.42 (m, 4H), 7.26 (s, 2H), 6.93 (s, 1H), 5.55 (s, 2H), 2.84 (q, *J*=7.5 Hz, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 1.36 (t, *J*=7.5 Hz, 3H).

Intermediate 82b: 5-(4,4-difluoropiperidin-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



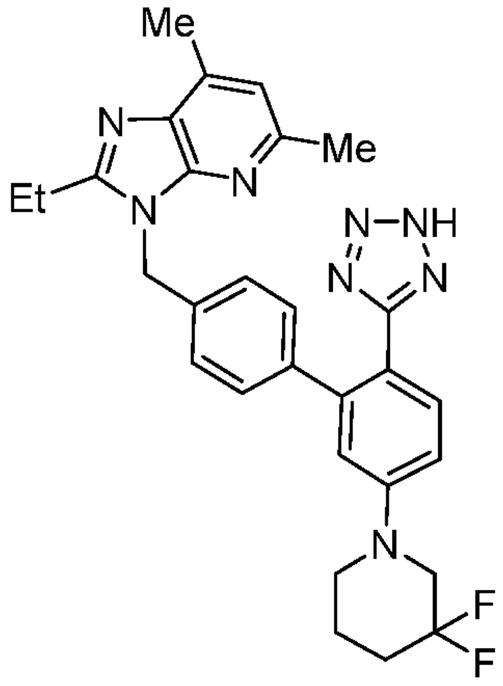
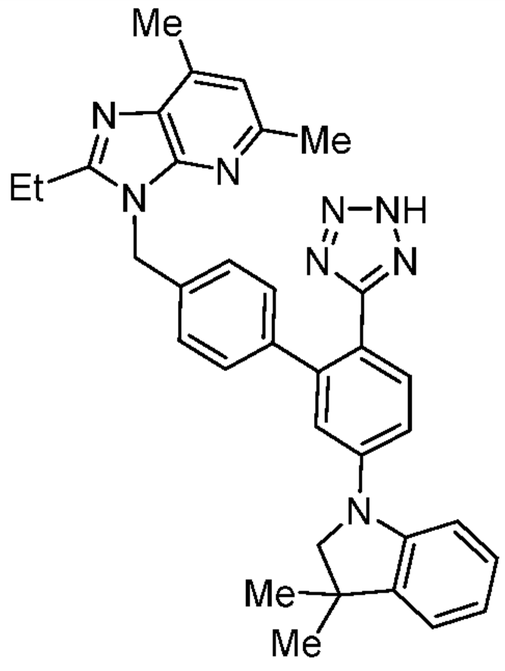
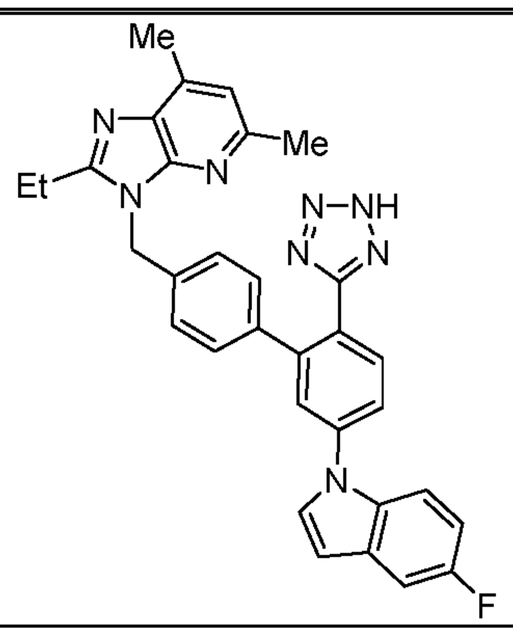
To a vial containing **Intermediate 82a** (0.050 g, 0.125 mmol) was added 2nd generation RuPhos precatalyst (9.69 mg, 0.012 mmol) followed sodium *t*-butoxide (0.072 g, 0.748 mmol). THF (3 mL) was then added followed by 4,4-difluoropiperidine (0.015 g, 0.125 mmol). The reaction vial was sealed and heated at 65 °C overnight. Reaction was concentrated and purified on ISCO using a 24 g column eluting with 0-100% EtOAc in hexanes to yield **Intermediate 82b** (0.061 g, 0.126 mmol, 100 % yield). LC-MS (Method A2) RT = 0.85 min, MS (ESI) *m/z*: 486.7 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=8.8 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=8.4 Hz, 2H), 6.93 (s, 1H), 6.91 - 6.87 (m, 1H), 6.85 (d, *J*=2.4 Hz, 1H), 5.54 (s, 2H), 3.62 - 3.47 (m, 4H), 2.85 (q, *J*=7.6 Hz, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 2.15 - 2.07 (m, 4H), 1.37 (t, *J*=7.5 Hz, 3H).

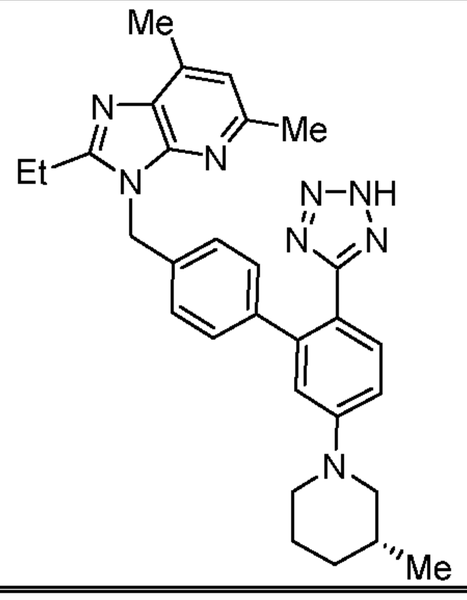
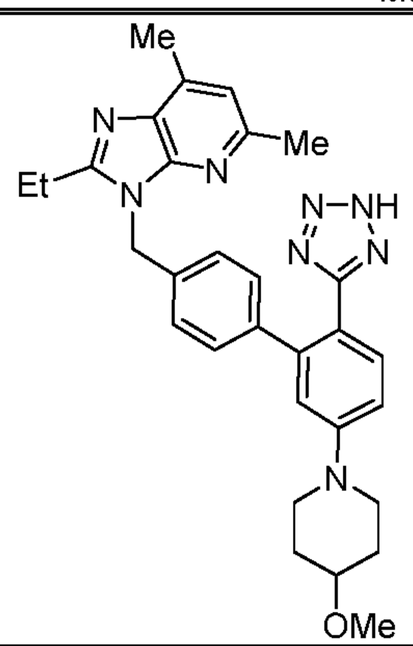
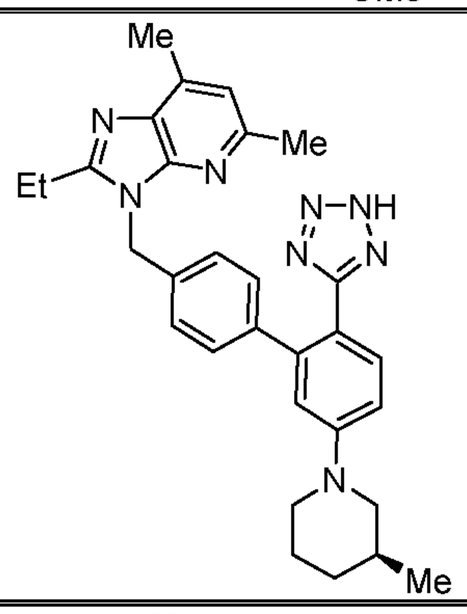
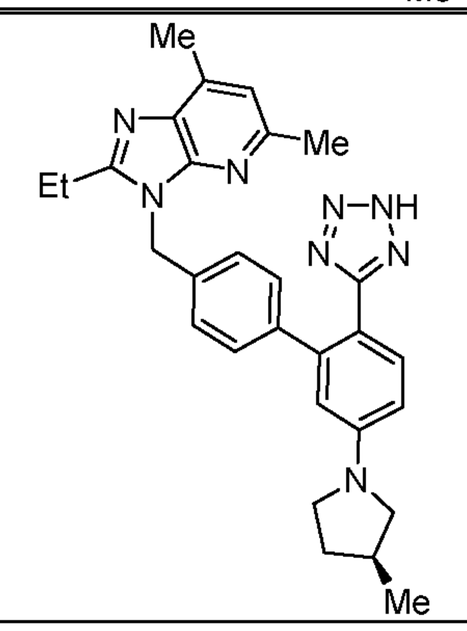
Example 82: 3-((5'-(4,4-difluoropiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

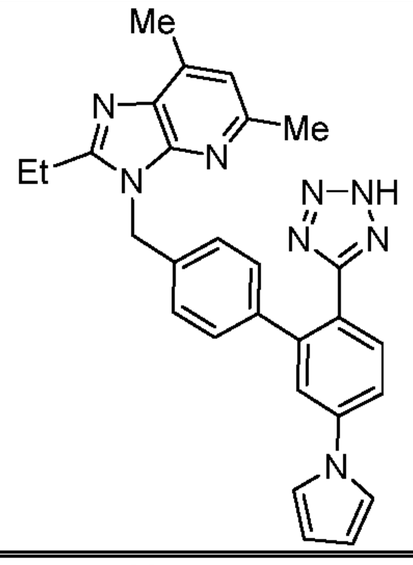
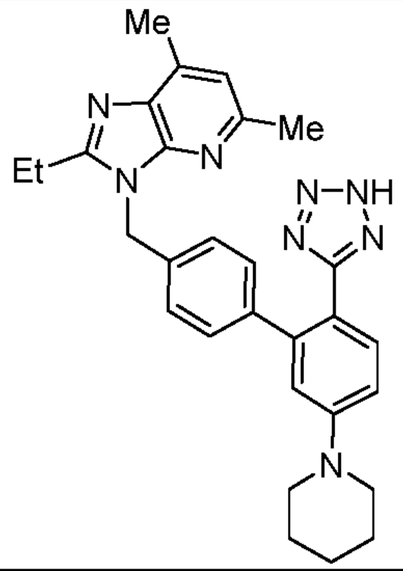
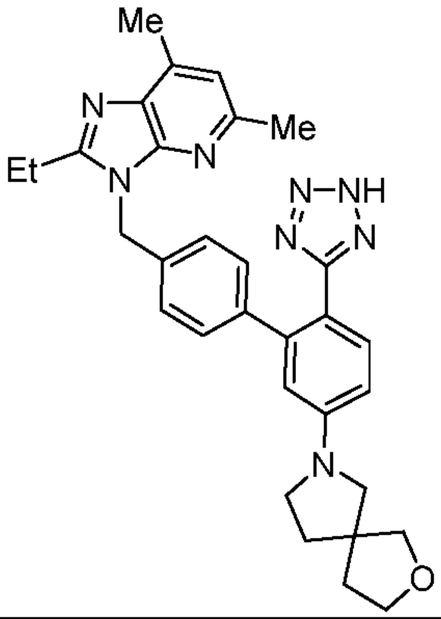
To a vial containing **Intermediate 82b** (0.061 g, 0.126 mmol) was added dibutyltin oxide (0.063 g, 0.251 mmol) and toluene (3 mL) followed by TMS-N_3 (0.083 mL, 0.628 mmol). The reaction mixture was sealed and heated at 100 °C behind a blast shield for 18 hours. Reaction was diluted with EtOAc and CAN (10% Aqueous) (0.689 g, 1.256 mmol) solution was added to quench remaining $TMSN_3$ until bubbling ceased. Layers were separated and the organic layer was washed with brine, dried with sodium sulfate, and concentrated. Purified on Preparative HPLC using Solvent A: 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B 90% MeOH / 10% H_2O / 0.1% TFA on Phenomenex AXIA C18 30 X 100 mm with a 10 min gradient and 5 min hold time with a flow rate of 40 mL/min to yield **Example 82** (13.37 mg, 0.024 mmol, 19.29 % yield). LC-MS (Method A2) RT = 0.86 min, MS (ESI) *m/z*: 529.4 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 (br d, *J*=8.9 Hz, 1H), 7.15 (br d, *J*=8.5 Hz, 1H), 7.06 (s, 4H), 6.99 (br s, 1H), 6.96 (s, 1H), 5.45 (s, 2H), 2.77 (q, *J*=7.0 Hz, 2H), 2.55 (s, 4H), 2.51 - 2.49 (m, 6H), 2.09 - 1.98 (m, 4H), 1.23 (br t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

The compounds listed in the table below were synthesized using the same methods that were used to prepare **Example 82**.

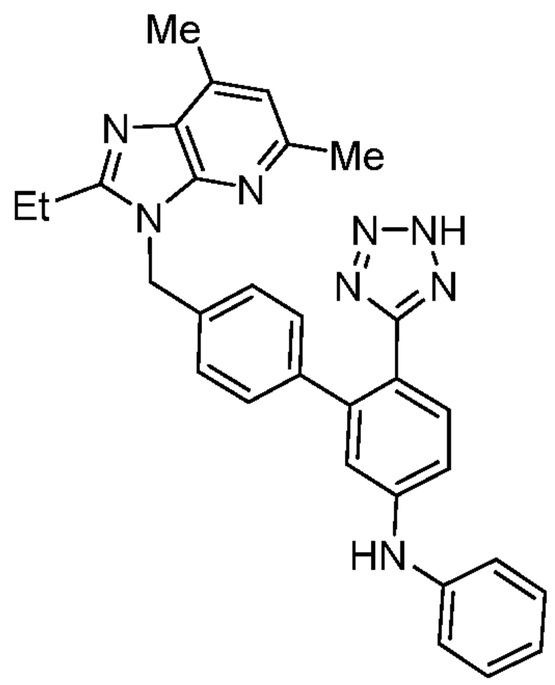
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^1H NMR

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
83		528.612	529.2; 0.78 min (Method A2)	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*=8.8 Hz, 1H), 7.19 (s, 4H), 7.02 (dd, *J*=8.8, 2.6 Hz, 1H), 6.91 (s, 1H), 6.76 (d, *J*=2.6 Hz, 1H), 5.50 (s, 2H), 3.55 (t, *J*=11.3 Hz, 2H), 3.41 - 3.34 (m, 2H), 2.87 - 2.77 (m, 2H), 2.60 (d, *J*=7.5 Hz, 6H), 2.14 - 1.96 (m, 4H), 1.36 (t, *J*=7.6 Hz, 3H) (1 exchangeable proton not observed)
84		554.291	555.6; 0.90 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.57 (br d, *J*=7.3 Hz, 1H), 7.34 (br d, *J*=8.5 Hz, 1H), 7.21 (br dd, *J*=15.7, 7.5 Hz, 2H), 7.15 - 7.07 (m, 3H), 7.02 (br d, *J*=7.6 Hz, 2H), 6.95 (s, 1H), 6.81 (br t, *J*=7.5 Hz, 1H), 5.45 (s, 2H), 3.76 (s, 2H), 2.89 (s, 3H), 2.82 - 2.75 (m, 2H), 2.74 (s, 3H), 1.31 (s, 6H), 1.24 (br t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)
85		542.609	543.9; 0.87 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (br d, *J*=2.5 Hz, 1H), 7.78 (br d, *J*=8.0 Hz, 1H), 7.72 - 7.61 (m, 2H), 7.54 (s, 1H), 7.44 (dd, *J*=9.6, 2.4 Hz, 1H), 7.16 (br d, *J*=7.7 Hz, 2H), 7.11 - 6.98 (m, 3H), 6.95 (s, 1H), 6.72 (d, *J*=3.1 Hz, 1H), 5.44 (s, 2H), 3.67 (br s, 6H), 2.76 (br d, *J*=7.4 Hz, 2H), 1.21 (br t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
86		506.645	507.3; 0.78 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 - 7.39 (m, 1H), 7.03 (br s, 5H), 6.95 (s, 1H), 6.85 (br s, 1H), 5.44 (s, 2H), 3.53 (br s, 2H), 3.33 - 3.25 (m, 2H), 2.80 - 2.74 (m, 2H), 2.55 (s, 6H), 2.18 (br t, *J*=8.1 Hz, 2H), 1.95 - 1.86 (m, 2H), 1.52 (br d, *J*=12.8 Hz, 1H), 1.23 (s, 3H), 1.00 (d, *J*=6.1 Hz, 3H) (1 exchangeable proton not observed)
87		522.644	523.6; 0.72 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44 (d, *J*=8.9 Hz, 1H), 7.09 - 7.02 (m, 5H), 6.95 (s, 1H), 6.88 (d, *J*=2.4 Hz, 1H), 5.44 (s, 2H), 3.45 - 3.34 (m, 1H), 3.25 (s, 3H), 3.04 (br s, 2H), 2.92 (q, *J*=7.2 Hz, 4H), 2.81 - 2.72 (m, 2H), 2.52 - 2.51 (m, 6H), 1.90 (br d, *J*=6.7 Hz, 2H), 1.21 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed)
88		506.645	507.3; 0.78 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (m, 1H), 7.03 (br s, 5H), 6.95 (s, 1H), 6.85 (br s, 1H), 5.44 (s, 2H), 3.53 (br s, 2H), 3.33 - 3.25 (m, 2H), 2.80 - 2.74 (m, 2H), 2.53 (s, 6H), 2.18 (br t, *J*=8.1 Hz, 2H), 1.95 - 1.86 (m, 2H), 1.52 (br d, *J*=12.8 Hz, 1H), 1.22 (s, 3H), 1.00 (d, *J*=6.1 Hz, 3H) (1 exchangeable proton not observed)
89		492.618	493.7; 0.82 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38 (d, *J*=8.5 Hz, 1H), 7.06 (d, *J*=8.1 Hz, 2H), 6.97 (br d, *J*=8.1 Hz, 2H), 6.95 (s, 1H), 6.56 (dd, *J*=8.5, 2.1 Hz, 1H), 6.39 (d, *J*=2.1 Hz, 1H), 5.43 (s, 2H), 3.91 (s, 1H), 3.28 (br d, *J*=8.5 Hz, 1H), 2.93 - 2.69 (m, 4H), 2.55 (s, 6H), 2.40 - 2.05 (m, 2H), 1.59 (br dd, *J*=11.9, 8.5 Hz, 1H), 1.26 (t, *J*=7.4 Hz, 3H), 1.08 (d, *J*=6.6 Hz, 3H) (1 exchangeable proton not observed)

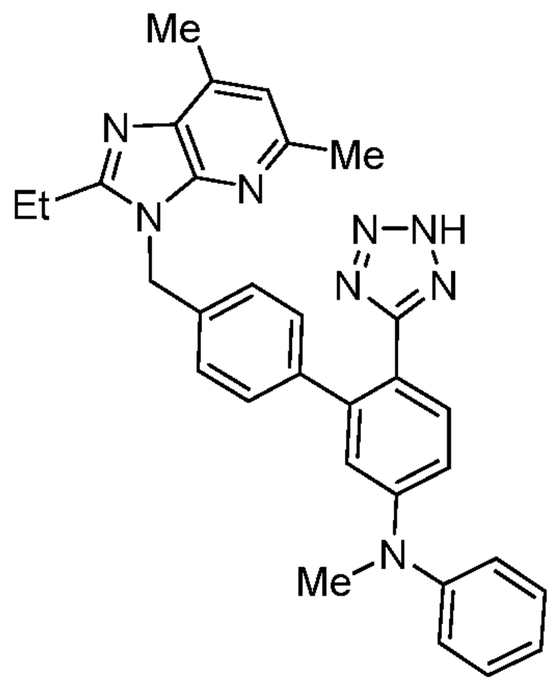
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
90		474.572	475.3; 0.77 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 - 7.68 (m, 2H), 7.64 (d, *J*=1.5 Hz, 1H), 7.54 (br s, 2H), 7.14 (br d, *J*=7.9 Hz, 2H), 7.07 (br d, *J*=7.9 Hz, 2H), 6.96 (s, 1H), 6.30 (s, 2H), 5.46 (s, 2H), 2.78 (q, *J*=7.3 Hz, 2H), 2.55 - 2.54 (m, 3H), 2.51 - 2.50 (m, 3H), 1.24 (br d, *J*=3.4 Hz, 3H) (1 exchangeable proton not observed)
91		492.631	493.2; 0.73 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (br d, *J*=5.3 Hz, 1H), 7.03 (br d, *J*=12.1 Hz, 5H), 6.95 (s, 1H), 6.84 (br s, 1H), 5.43 (s, 2H), 3.27 (br s, 2H), 2.77 (q, *J*=7.4 Hz, 2H), 2.55 (s, 3H), 2.53 - 2.52 (m, 3H), 1.91 (s, 2H), 1.57 (br s, 6H), 1.23 (br t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)
92		534.668	535.2; 0.75 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44 (d, *J*=8.5 Hz, 1H), 7.06 (s, 4H), 6.96 (s, 1H), 6.66 (br d, *J*=8.5 Hz, 1H), 6.50 (s, 1H), 5.46 (s, 2H), 3.82 (t, *J*=7.2 Hz, 2H), 3.59 (s, 2H), 2.78 (q, *J*=7.3 Hz, 2H), 2.55 (s, 6H), 2.50 - 2.47 (m, 2H), 2.05 - 1.97 (m, 2H), 1.94 - 1.87 (m, 2H), 1.25 (t, *J*=7.5 Hz, 5H) (1 exchangeable proton not observed)

Example 93: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N-phenyl-6-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



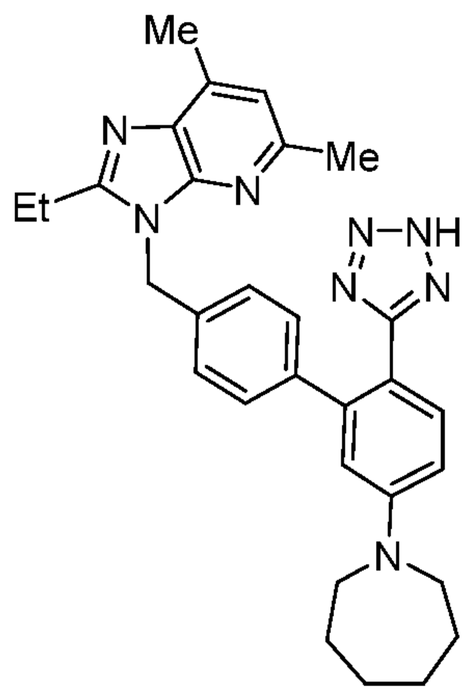
Aniline (0.012 g, 0.123 mmol), BrettPhos 3rd generation precatalyst (7.44 mg, 8.21 µmol), and sodium *t*-butoxide (15.78 mg, 0.164 mmol) were charged to a reaction flask. **Intermediate 001j** (0.030 g, 0.041 mmol) was dissolved in THF (0.8 mL) and added to the reaction. The flask was evacuated and backfilled with N_2 and stirred at 65 °C for 1 h. The crude reaction was passed through 0.45 µm syringe filters and concentrated. The crude residue was dissolved in CH_2Cl_2 (1.0 mL). Triethylsilane (0.030 mL, 0.185 mmol) and TFA (0.089 mL, 1.150 mmol) were added, and the resulting mixture stirred for 1 h. The solution was concentrated and dissolved in 1.8 mL DMF. The crude material was purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-100% B over 20 minutes, then a 2-minute hold at 100% B; Flow: 20 mL/min to yield **Example 93** (0.007 g, 0.014 mmol, 34%): LC-MS (Method A1) RT = 1.54 min, MS (ESI) *m/z*: 501.0 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.47 (br d, *J*=8.2 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.20 - 7.13 (m, 3H), 7.09 - 7.00 (m, 5H), 6.96 - 6.90 (m, 2H), 5.44 (s, 2H), 3.47 (br s, 1H), 2.76 (q, *J*=7.3 Hz, 2H), 2.51 (br s, 6H), 1.21 (br t, *J*=7.3 Hz, 3H).

Example 94: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N-methyl-N-phenyl-6-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-3-amine



Synthesized in an analogous manner to **Example 93** using **Intermediate 001j** (0.030 g, 0.041 mmol) and N-methylaniline (0.013 g, 0.123 mmol) to yield **Example 94** (0.0023 g, 0.0045 mmol, 11%): LC-MS (Method A1) RT = 1.77 min, MS (ESI) *m/z*: 515.0 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.46 - 7.36 (m, 3H), 7.23 (br d, *J*=7.6 Hz, 2H), 7.15 (br t, *J*=7.2 Hz, 1H), 6.97 (br d, *J*=17.4 Hz, 5H), 6.90 (br d, *J*=7.9 Hz, 1H), 6.77 (br s, 1H), 5.41 (br s, 2H), 3.31 (s, 3H), 2.73 (br d, *J*=7.0 Hz, 2H), 2.49 (br d, *J*=4.9 Hz, 6H), 1.18 (br t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed).

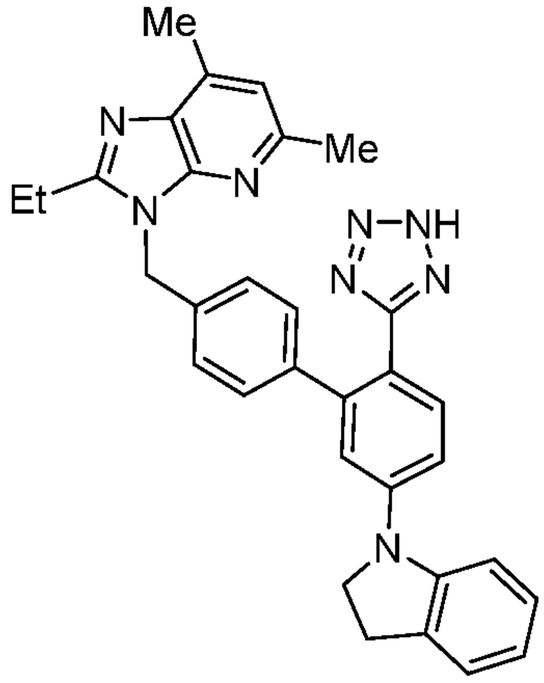
Example 95: 3-((5'-(azepan-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



Synthesized in an analogous manner to **Example 93** using **Intermediate 001j** (0.030 g, 0.041 mmol) and azepane (0.012 g, 0.123 mmol) to yield **Example 95** (0.0015 g, 0.0030 mmol, 5.9%): LC-MS (Method A1) RT = 1.74 min, MS (ESI) *m/z*: 507.0 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.40 (d, *J*=8.5 Hz, 1H), 7.29 - 7.13 (m, 1H), 7.07 - 7.04 (m, 3H), 6.97 (s, 1H), 6.81 (br d, *J*=9.2 Hz, 1H), 6.61 (s, 1H), 5.45 (s, 2H), 3.53 - 3.46 (m,

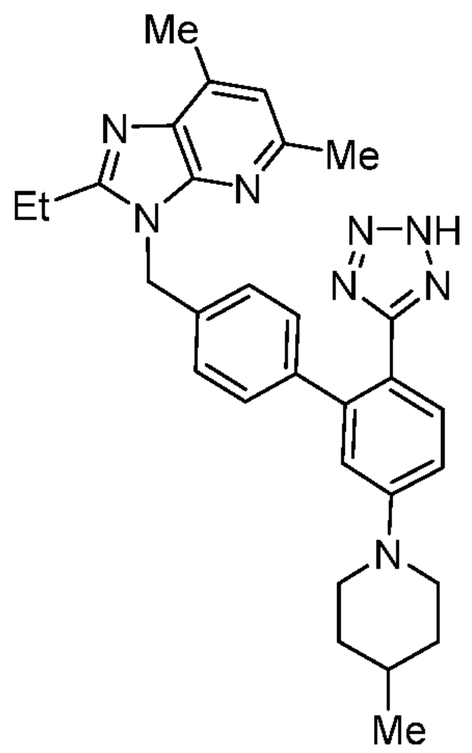
4H), 2.78 (q, *J*=7.3 Hz, 2H), 2.50 - 2.49 (m, 6H), 1.72 (br s, 4H), 1.47 (br s, 4H), 1.23 (br t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed).

Example 96: 2-ethyl-3-((5'-(indolin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



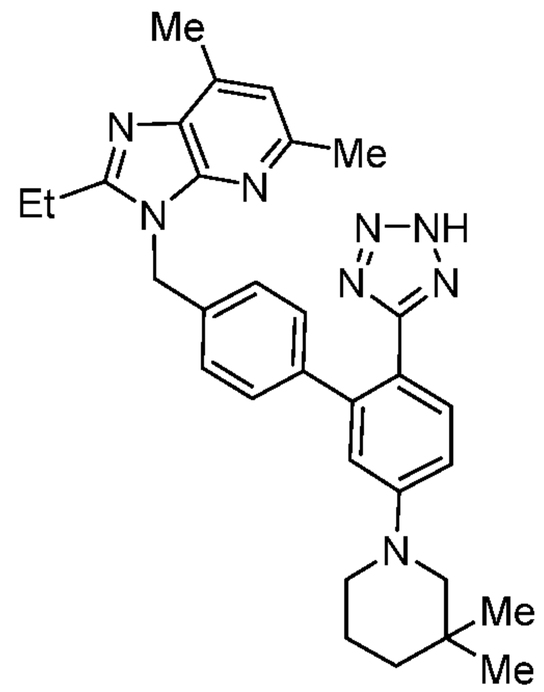
Synthesized in an analogous manner to **Example 93** using **Intermediate 001j** (0.025 g, 0.034 mmol), indoline (0.012 g, 0.103 mmol), and 2nd generation XPhos precatalyst (0.0027 g, 0.0003 mmol) to yield **Example 96** (0.009 g, 0.017 mmol, 50%): LC-MS (Method A2) RT = 0.90 min, MS (ESI) *m/z*: 527.1 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.62 (d, *J*=8.5 Hz, 1H), 7.41 (d, *J*=8.5 Hz, 1H), 7.30 - 7.18 (m, 4H), 7.18 - 7.08 (m, 4H), 7.06 (s, 1H), 6.81 (t, *J*=7.2 Hz, 1H), 5.54 (s, 2H), 4.04 (t, *J*=8.2 Hz, 2H), 3.13 (t, *J*=8.2 Hz, 2H), 2.90 (q, *J*=7.1 Hz, 2H), 2.55 (s, 6H), 1.24 (t, *J*=7.5 Hz, 3H) (1 exchangeable proton not observed).

Example 97: 2-ethyl-5,7-dimethyl-3-((5'-(4-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



Synthesized in an analogous manner to **Example 93** using **Intermediate 001j** (0.030 g, 0.041 mmol), 4-methylpiperidine (0.012 g, 0.123 mmol), and 3nd generation *t*BuXPhos precatalyst (0.0036 g, 0.0004 mmol) to yield **Example 97** (0.013 g, 0.026 mmol, 64%): LC-MS (Method A2) RT = 0.88 min, MS (ESI) *m/z*: 507.4 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.44 (d, *J*=8.8 Hz, 1H), 7.09 - 6.99 (m, 5H), 6.95 (s, 1H), 6.87 (br. s., 1H), 5.44 (s, 2H), 3.85 (d, *J*=12.6 Hz, 2H), 2.82 - 2.71 (m, 4H), 2.55 - 2.54 (m, 6H), 1.67 (d, *J*=12.5 Hz, 2H), 1.55 (br. s., 1H), 1.27 - 1.11 (m, 5H), 0.92 (d, *J*=6.3 Hz, 3H) (1 exchangeable proton not observed).

Example 98: 3-((5'-(3,3-dimethylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

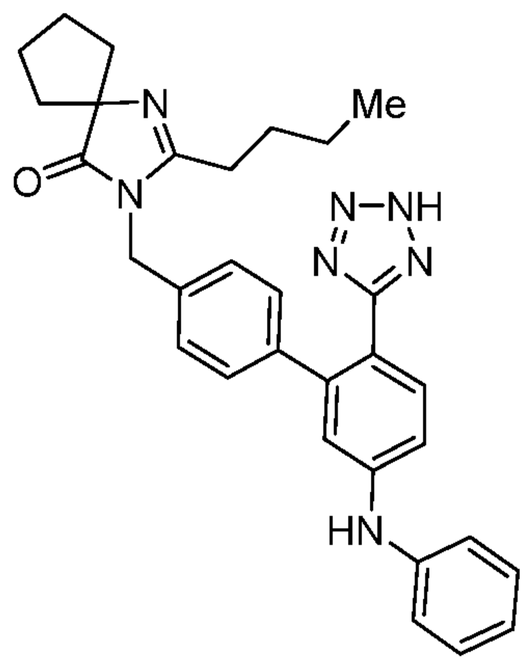


3-((5'-(3,3-dimethylpiperidin-1-yl)-2'-(2 *H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

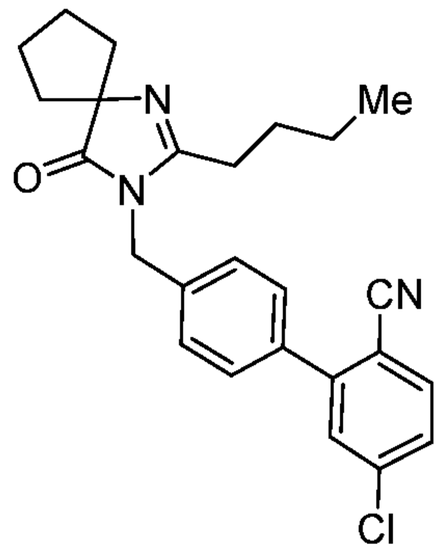
Synthesized in an analogous manner to **Example 93** using **Intermediate 001j** (0.030 g, 0.041 mmol), 3,3-dimethylpiperidine (0.009 g, 0.082 mmol), and 3nd generation

*t*BuXPhos precatalyst (0.0036 g, 0.0004 mmol) to yield **Example 98** (0.006 g, 0.001 mmol, 25%): LC-MS (Method A2) RT = 0.94 min, MS (ESI) *m/z*: 521.4 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.43 (br d, *J*=8.5 Hz, 1H), 7.26 (s, 1H), 7.17 - 7.11 (m, 2H), 7.09 - 7.03 (m, 3H), 6.85 (br s, 1H), 5.55 (br s, 2H), 3.24 (br s, 2H), 3.02 (br s, 2H), 2.94 (br d, *J*=7.3 Hz, 2H), 2.57 - 2.55 (m, 6H), 1.63 (br s, 2H), 1.37 (br s, 2H), 1.25 (br t, *J*=7.2 Hz, 3H), 0.94 (s, 6H) (1 exchangeable proton not observed).

Example 99: 2-butyl-3-((5'-(phenylamino)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



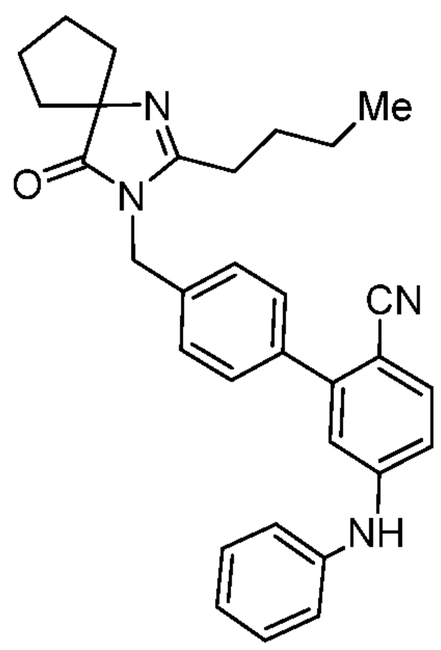
Intermediate 99a: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile



To a microwave vial containing $PdCl_2$(dppf) (0.196 g, 0.268 mmol), **Intermediate 033a** (1.1 g, 2.68 mmol) and 4-chloro-2-iodobenzonitrile (0.918 g, 3.48 mmol) was added toluene (10.72 ml) followed by ethanol (2.68 ml) and K_3PO_4 (2 M, aq.) (2.68 ml, 5.36 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 120 °C in the microwave for 30 min. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic phase was concentrated

and purified by ISCO (0-100% EtOAc in hexanes) to afford **Intermediate 99a** (0.789 g, 1.879 mmol, 70.1 % yield) as a white solid. LC-MS (Method A2) RT = 0.95 min, MS (ESI) *m/z*: 420.3 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.72 (d, *J*=8.1 Hz, 1H), 7.59 - 7.51 (m, 3H), 7.46 (dd, *J*=8.4, 2.0 Hz, 1H), 7.32 (d, *J*=8.1 Hz, 2H), 4.77 (s, 2H), 2.40 - 2.32 (m, 2H), 2.09 - 1.95 (m, 6H), 1.86 (dd, *J*=7.0, 4.6 Hz, 2H), 1.61 (d, *J*=7.7 Hz, 2H), 1.43 - 1.31 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

Intermediate 99b: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(phenylamino)-[1,1'-biphenyl]-2-carbonitrile



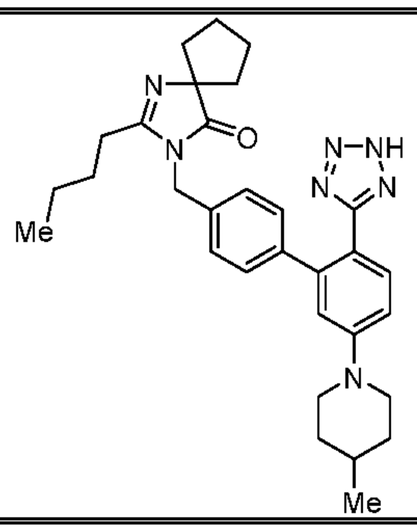
To a vial containing **Intermediate 99a** (100 mg, 0.238 mmol) was added 2nd generation RuPhos precatalyst (18.50 mg, 0.024 mmol) followed sodium *t*-butoxide (137 mg, 1.429 mmol). THF (3 mL) was then added followed by aniline (66.5 mg, 0.714 mmol). The reaction vial degassed with N_2 for 5 minutes, sealed, and heated at 65 °C for 16 hours. The reaction mixture was diluted with EtOAc, filtered over Celite, concentrated on to Celite for dry loading and purified by ISCO (0-100% EtOAc in hexanes) to afford **Intermediate 99b** (95 mg, 0.199 mmol, 84 % yield) as a colorless oil. LC-MS (Method A2) RT = 1.07 min, MS (ESI) *m/z*: 477.4. ^1H NMR (400MHz, $CDCl_3$) δ 7.62 - 7.57 (m, 1H), 7.56 - 7.50 (m, 2H), 7.43 - 7.35 (m, 2H), 7.26 (s, 2H), 7.21 (dd, *J*=8.5, 0.8 Hz, 2H), 7.15 (t, *J*=7.4 Hz, 1H), 7.00 - 6.95 (m, 2H), 6.12 (s, 1H), 4.75 (s, 2H), 2.40 - 2.32 (m, 2H), 2.06 - 1.94 (m, 6H), 1.89 - 1.81 (m, 2H), 1.62 (t, *J*=7.7 Hz, 2H), 1.37 (dd, *J*=15.0, 7.5 Hz, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

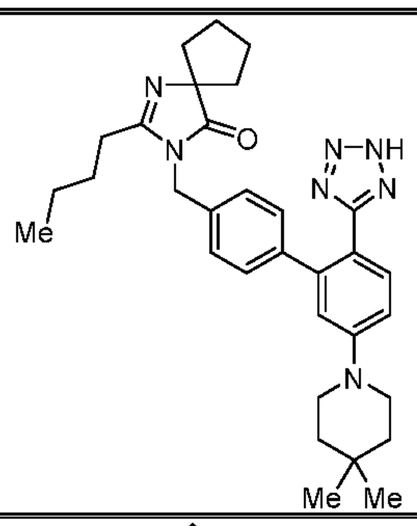
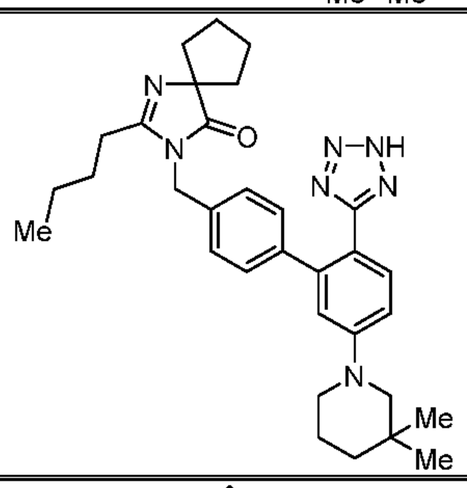
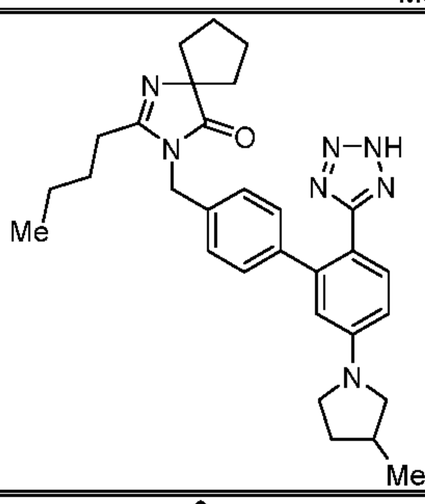
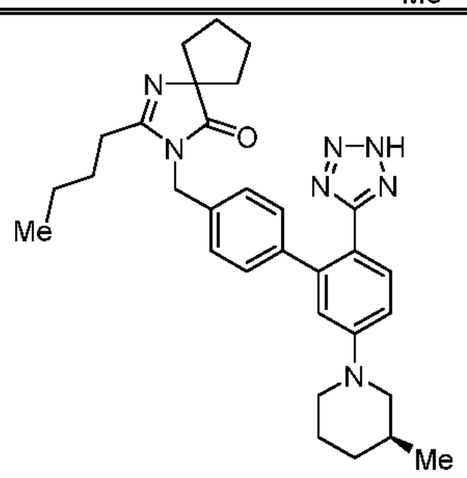
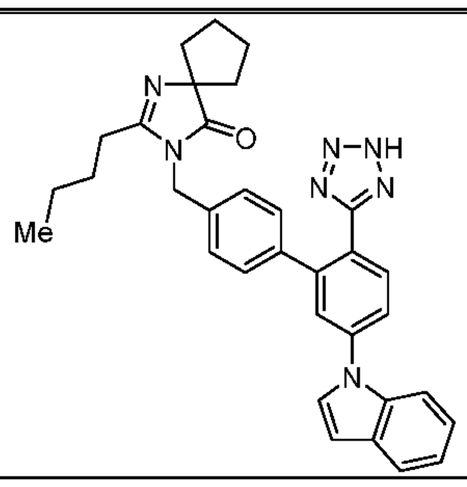
Example 99: 2-butyl-3-((5'-(phenylamino)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

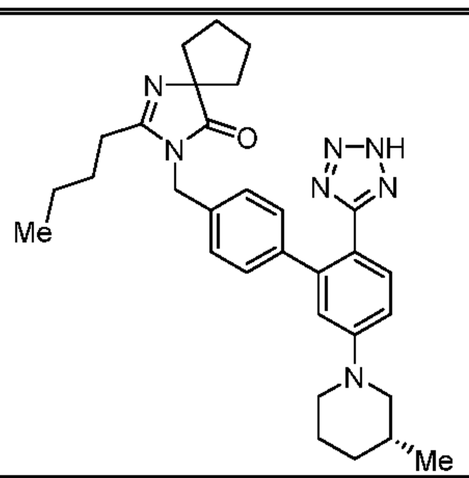
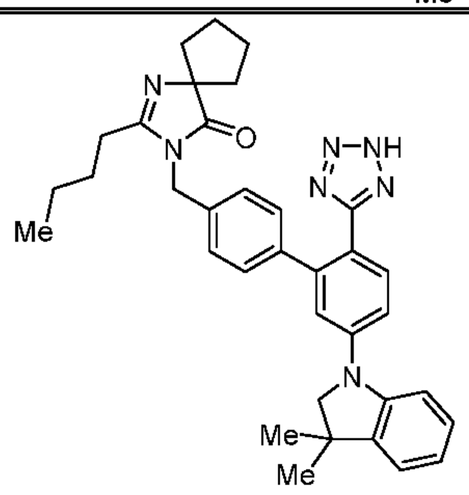
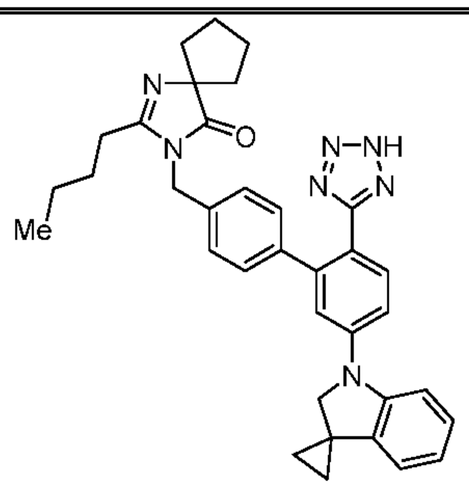
To a vial containing **Intermediate 99b** (95 mg, 0.199 mmol) was added dibutyltin oxide (99 mg, 0.399 mmol) and toluene (5 mL) followed by TMS-N_3 (0.265 mL, 1.993 mmol).

The reaction mixture was sealed and heated at 110 °C behind a blast shield. After 16 h of heating, the reaction was cooled to RT, and MeOH was added to solubilize the solution. The reaction was diluted with EtOAc and CAN (10% Aqueous) solution (1093 mg, 1.993 mmol) was added to quench remaining $TMSN_3$ until bubbling ceased. Layers were separated and the organic layer was washed with saturated aqueous ammonium chloride, washed with brine, dried with sodium sulfate, and concentrated. The residue was dissolved in DMF, and the crude material was purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 20-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 99** (5.4 mg, 10.29 µmol, 5.16 % yield): LC-MS (Method A2) RT = 0.98 min, MS (ESI) *m/z*: 520.4. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.68 (br. s., 1H), 7.48 (d, *J*=8.3 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.22 - 7.14 (m, 3H), 7.10 - 7.03 (m, 5H), 6.95 (t, *J*=7.3 Hz, 1H), 4.67 (s, 2H), 2.28 (t, *J*=7.5 Hz, 2H), 1.91 - 1.76 (m, 6H), 1.66 (d, *J*=6.9 Hz, 2H), 1.43 (d, *J*=6.9 Hz, 2H), 1.26 - 1.18 (m, 2H), 0.77 (t, *J*=7.3 Hz, 3H) One exchangeable proton not observed.

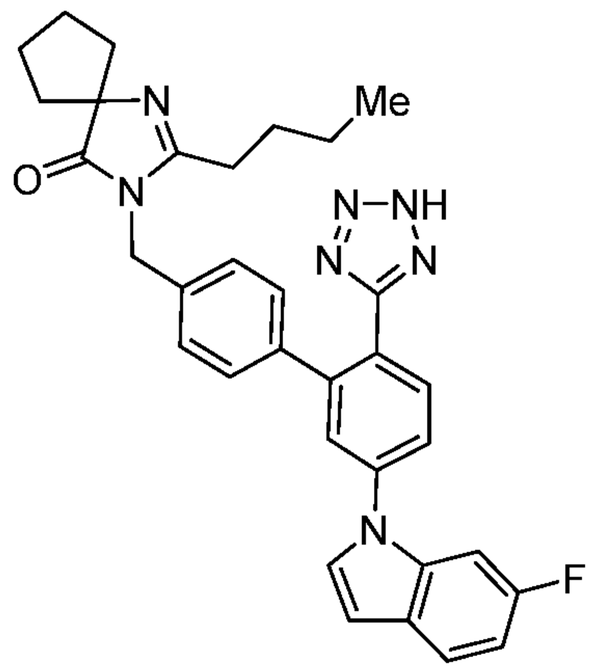
The compounds listed in the table below were synthesized using the same methods that were used to prepare **Example 99**.

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
100		525.322	526.5; 1.08 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.42 (d, *J*=8.5 Hz, 1H), 7.12 - 7.08 (m, 2H), 7.02 (d, *J*=7.9 Hz, 3H), 6.84 (s, 1H), 4.66 (s, 2H), 3.81 (d, *J*=12.2 Hz, 2H), 2.75 (d, *J*=12.8 Hz, 2H), 2.30 (t, *J*=7.5 Hz, 2H), 1.88 - 1.78 (m, 6H), 1.72 - 1.63 (m, 4H), 1.55 (br. s., 1H), 1.51 - 1.43 (m, 2H), 1.31 - 1.16 (m, 4H), 0.93 (d, *J*=6.7 Hz, 3H), 0.80 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
101		539.714	540.5; 1.07 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.41 (d, *J*=8.5 Hz, 1H), 7.08 (d, *J*=7.6 Hz, 2H), 7.01 (d, *J*=7.9 Hz, 3H), 6.84 (s, 1H), 4.65 (s, 2H), 3.26 (br. s., 4H), 2.29 (t, *J*=7.5 Hz, 2H), 1.88 - 1.77 (m, 6H), 1.66 (d, *J*=7.0 Hz, 2H), 1.50 - 1.44 (m, 2H), 1.42 (br. s., 4H), 1.31 - 1.21 (m, 2H), 0.95 (s, 6H), 0.78 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
102		539.714	540.5; 1.17 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (br s, 1H), 7.05 (br d, *J*=15.7 Hz, 5H), 6.85 (br s, 1H), 4.66 (br s, 2H), 3.56 (br s, 4H), 3.23 (br s, 2H), 2.29 (br t, *J*=7.5 Hz, 2H), 1.89 - 1.77 (m, 8H), 1.64 (br s, 4H), 1.48 - 1.42 (m, 2H), 0.95 (s, 6H), 0.79 (br t, *J*=7.3 Hz, 3H) (1 exchangeable protons not observed)
103		511.661	512.5; 0.86 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.45 (d, *J*=8.7 Hz, 1H), 7.24 (s, 2H), 7.03 (s, 2H), 6.66 (dd, *J*=8.63 Hz, 2.23 Hz, 1H), 6.48 (s, 1H), 4.78 (s, 2H), 3.37 - 2.63 (m, 3H), 2.42 - 2.05 (m, 3H), 1.87 (d, *J*=7.0 Hz, 9H), 1.56 - 1.46 (m, 3H), 1.35 - 1.23 (m, 3H), 1.09 (d, *J*=6.6 Hz, 3H), 0.82 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)
104		525.688	526.5; 0.85 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.42 (d, *J*=8.7 Hz, 1H), 7.09 - 7.06 (m, 2H), 7.02 (d, *J*=8.1 Hz, 3H), 6.84 (s, 1H), 4.65 (s, 2H), 3.90 - 3.72 (m, 4H), 2.77 - 2.67 (m, 1H), 2.42 (t, *J*=11.5 Hz, 1H), 2.29 (t, *J*=7.5 Hz, 2H), 1.88 - 1.77 (m, 6H), 1.66 (d, *J*=7.4 Hz, 4H), 1.47 - 1.40 (m, 2H), 1.27 - 1.20 (m, 2H), 1.07 (d, *J*=11.9 Hz, 1H), 0.90 (d, *J*=6.5 Hz, 3H), 0.78 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
105		543.677	544.3; 1.86 min (Method A1)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.79 - 7.73 (m, 2H), 7.70 - 7.63 (m, 2H), 7.49 (s, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 7.15 (d, *J*=4.9 Hz, 1H), 7.03 (d, *J*=7.9 Hz, 2H), 6.73 (d, *J*=2.7 Hz, 1H), 4.66 (s, 2H), 3.82 - 3.61 (m, 4H), 2.30 (t, *J*=6.4 Hz, 2H), 1.90 - 1.74 (m, 6H), 1.65 (br. s., 2H), 1.45 (br. s., 2H), 1.30 - 1.19 (m, 2H), 0.77 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)

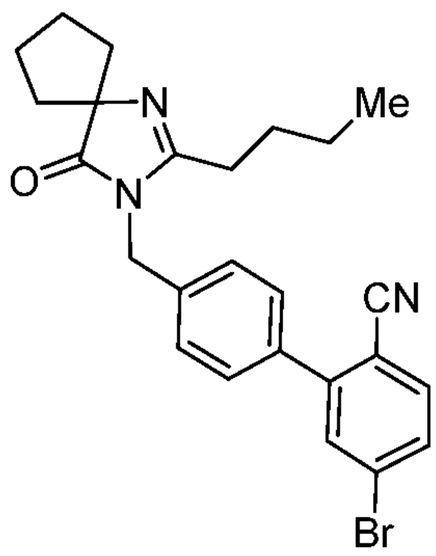
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
106		525.688	526.6; 0.85 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.44 (d, *J*=8.7 Hz, 1H), 7.06 (q, *J*=8.0 Hz, 5H), 6.88 (s, 1H), 4.66 (s, 2H), 2.29 (t, *J*=7.5 Hz, 2H), 1.88 - 1.78 (m, 6H), 1.66 (d, *J*=7.6 Hz, 4H), 1.47 - 1.41 (m, 2H), 1.25 (td, *J*=14.6, 7.0 Hz, 8H), 1.15 (t, *J*=7.3 Hz, 1H), 0.85 (br. s., 3H), 0.78 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
107		573.730	574.7; 0.94 min (Method A2)	^{1}H NMR (500MHz, DMSO-d_6) δ 7.62 (d, *J*=8.5 Hz, 1H), 7.42 (d, *J*=8.5 Hz, 1H), 7.29 (d, *J*=7.9 Hz, 1H), 7.23 (d, *J*=7.3 Hz, 1H), 7.18 (d, *J*=11.9 Hz, 2H), 7.16 - 7.11 (m, 2H), 7.09 (d, *J*=8.0 Hz, 2H), 6.86 (t, *J*=7.4 Hz, 1H), 4.69 (s, 2H), 2.30 (t, *J*=7.5 Hz, 2H), 1.92 - 1.77 (m, 6H), 1.66 (br. s., 2H), 1.45 (d, *J*=7.3 Hz, 2H), 1.36 - 1.18 (m, 10H), 0.86 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
108		571.306	572.3; 0.96 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (br d, *J*=8.2 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.20 - 7.13 (m, 3H), 7.10 - 7.02 (m, 2H), 6.99 (br d, *J*=7.9 Hz, 2H), 6.82 - 6.66 (m, 2H), 4.66 (s, 2H), 4.05 (s, 2H), 2.33 (br t, *J*=7.5 Hz, 2H), 1.84 (br d, *J*=8.5 Hz, 6H), 1.68 (br d, *J*=6.7 Hz, 2H), 1.54 - 1.44 (m, 2H), 1.28 (br d, *J*=7.6 Hz, 2H), 1.09 (br s, 1H), 1.04 (br s, 1H), 1.01 (d, *J*=6.1 Hz, 2H), 0.81 (br t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)

Example 109: 2-butyl-3-((5'-(6-fluoro-1H-indol-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



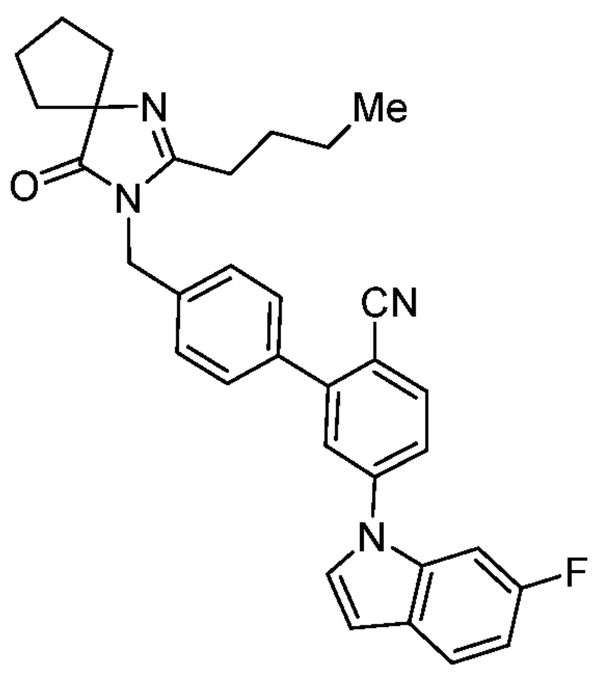
5

Intermediate 109a: 5-bromo-4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



To a microwave vial containing $PdCl_2(dppf)$ (0.196 g, 0.268 mmol), **Intermediate 033a** (1.00 g, 2.44 mmol) and 4-bromo-2-iodobenzonitrile (0.975 g, 3.17 mmol) was added toluene (9.75 ml) followed by ethanol (2.44 ml) and K_3PO_4 (2 M, aq.) (2.44 ml, 4.87 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 120 °C in the microwave for 30 min. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic phase was concentrated and purified by ISCO (0-100% EtOAc in hexanes) to afford **Intermediate 109a** (0.906 g, 1.95 mmol, 80 % yield) as a white solid. LC-MS (Method A2) RT = 0.87 min, MS (ESI) *m/z*: 464.6 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.68 (m, 1H), 7.65 - 7.61 (m, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 4.77 (s, 2H), 2.40 - 2.32 (m, 2H), 2.02 (br d, *J*=4.6 Hz, 6H), 1.86 (br s, 2H), 1.67 - 1.58 (m, 2H), 1.44 - 1.31 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

Intermediate 109b: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(6-fluoro-1H-indol-1-yl)-[1,1'-biphenyl]-2-carbonitrile

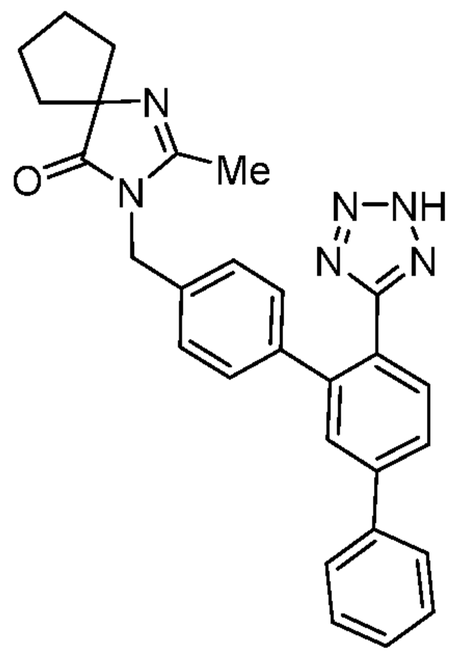


To a vial charged with **Intermediate 109a** (0.050 g, 0.108 mmol), 6-fluoro-1H-indole (0.044 g, 0.323 mmol), copper(I) iodide (10.25 mg, 0.054 mmol), potassium carbonate (0.074 g, 0.538 mmol) and L-proline (0.012 g, 0.108 mmol) was added DMSO (2.153 ml). The mixture was and heated at 120 ° C for 16 hours. The reaction was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O x3, washed with brine, and dried over sodium sulfate. The reaction was purified on ISCO using 24 g column eluting with 0-100% EtOAc in hexanes to yield **Intermediate 109b** (0.031 g, 0.060 mmol, 55.5 % yield). LC-MS (Method A2) RT = 0.96 min, MS (ESI) *m/z*: 519.8 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.68 - 7.50 (m, 5H), 7.40 - 7.29 (m, 4H), 7.06 - 6.96 (m, 1H), 6.76 (dd, *J*=3.4, 0.8 Hz, 1H), 4.79 (s, 2H), 2.45 - 2.29 (m, 2H), 2.07 - 1.95 (m, 6H), 1.87 (td, *J*=4.3, 1.3 Hz, 2H), 1.71 - 1.59 (m, 2H), 1.44 - 1.34 (m, 2H), 0.94 - 0.88 (m, 3H).

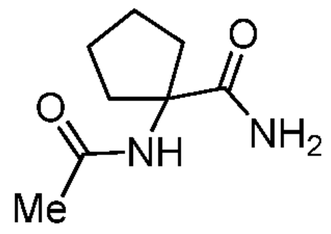
Example 109: 2-butyl-3-((5'-(phenylamino)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

Synthesized in an analogous manner to **Example 99** using **Intermediate 109b** (0.031 g, 0.060 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 30-70% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 109** (13.1 mg, 0.023 mmol, 39.0 % yield): LC-MS (Method A2) RT = 0.87 min, MS (ESI) *m/z*: 562.8 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, *J*=9.7 Hz, 3H), 7.73 - 7.61 (m, 2H), 7.47 (br d, *J*=9.5 Hz, 1H), 7.20 (br d, *J*=7.8 Hz, 2H), 7.09 (br d, *J*=7.8 Hz, 2H), 7.04 (br t, *J*=9.0 Hz, 1H), 6.78 (br d, *J*=3.0 Hz, 1H), 4.68 (s, 2H), 2.29 (br t, *J*=7.4 Hz, 2H), 1.82 (br d, *J*=10.0 Hz, 6H), 1.67 (br d, *J*=7.6 Hz, 2H), 1.52 (br d, *J*=6.9 Hz, 2H), 1.24 - 1.18 (m, 2H), 0.75 (br t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed).

Example 110: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-methyl-1,3-diazaspiro[4.4]non-1-en-4-one

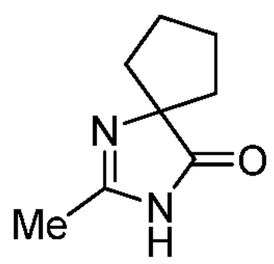


Intermediate 110a: 1-acetamidocyclopentane-1-carboxamide



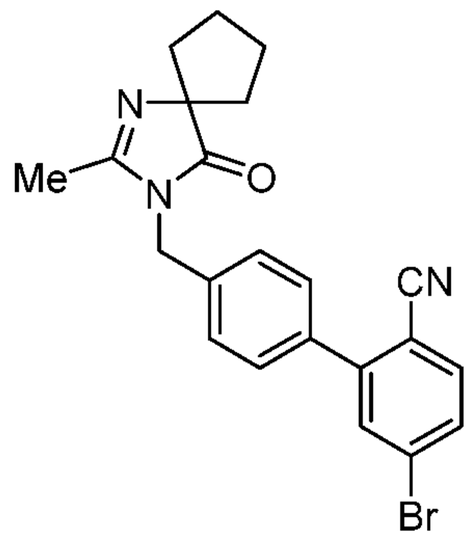
To a solution of 1-aminocyclopentane-1-carboxamide (1.15 g, 8.97 mmol) and DCM (32 mL) was added acetic anhydride (1.191 g, 11.66 mmol). The reaction mixture was stirred at RT for 18 hours. Reaction was concentrated and used without further purification in the next step. **Intermediate 110a** (1.53 g, 8.99 mmol, 100 % yield). LC-MS (Method A2) RT = 0.43 min, MS (ESI) *m/z*: 171.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 - 6.89 (m, 1H), 5.72 (br s, 1H), 5.38 - 5.19 (m, 1H), 2.40 - 2.30 (m, 2H), 2.07 - 1.98 (m, 5H), 1.86 - 1.75 (m, 4H)

Intermediate 110b: 2-methyl-1,3-diazaspiro[4.4]non-1-en-4-one



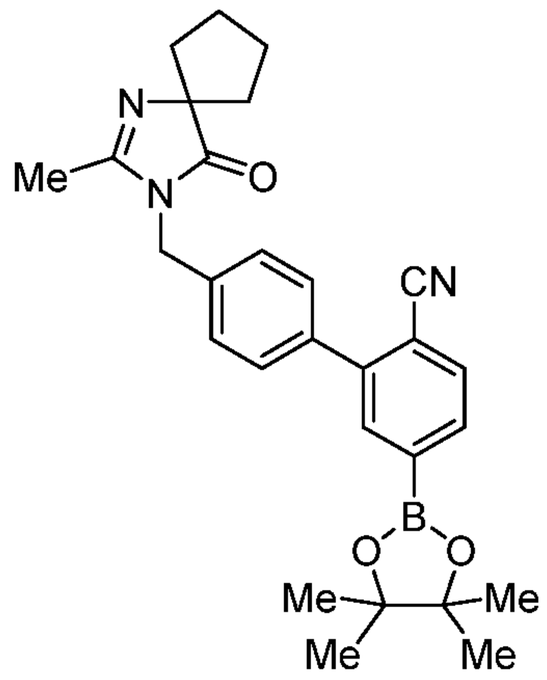
To a solution of **Intermediate 110a** (1.53 g, 8.99 mmol) in MeOH (20 mL) was added 3.0 N NaOH (23.97 mL, 71.9 mmol). The reaction mixture was heated at 50 °C for 5 hours. The reaction was cooled to RT, and the mixture was acidified with 1.0 N HCl to pH 6-7 and extracted with DCM. The organic layer was dried over sodium sulfate and concentrated to give crude **Intermediate 110b** (0.162 g, 1.064 mmol, 11.84 % yield). This was used for the next step without purification. LC-MS (Method A2) RT = 0.44 min, MS (ESI) *m/z*: 153.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.08 (s, 1H), 2.02 - 1.92 (m, 6H), 1.86 - 1.80 (m, 2H).

Intermediate 110c: 5-bromo-4'-((2-methyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



Intermediate 110b (0.162 g, 1.064 mmol) was dissolved in DMF (2.129 ml). NaH (0.106 g, 2.66 mmol) was added and allowed to stir for 15 min. **Intermediate I-002** (0.448 g, 1.277 mmol) was added. The reaction was stirred for 30 min and was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The material was purified by column chromatography (ISCO, 80 g silica gel column, 36 minute gradient of 0 to 100% EtOAc in hexanes) to yield **Intermediate 110c** (0.310 g, 0.734 mmol, 69.0 % yield). LC-MS (Method A2) RT =0.84 min, MS (ESI) *m/z*: 422.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.59 (m, 1H), 7.54 (dd, *J*=2.8, 1.2 Hz, 2H), 7.48 - 7.44 (m, 2H), 7.24 (d, *J*=8.4 Hz, 2H), 4.68 (s, 2H), 2.05 (s, 3H), 1.99 - 1.87 (m, 6H), 1.76 (br dd, *J*=7.3, 5.3 Hz, 2H).

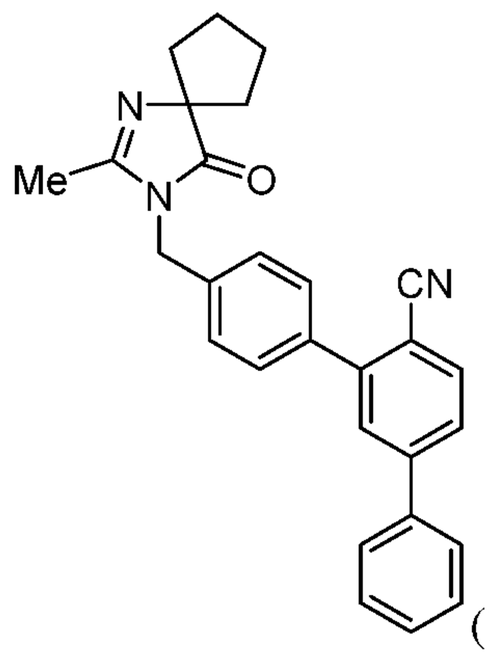
Intermediate 110d: 4'-((2-methyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



Intermediate 110c (0.315 g, 0.834 mmol), bis(pinacolato)diboron (0.423 g, 1.667 mmol), XPhos (0.040 g, 0.083 mmol), $Pd_2(dba)_3$ (0.076 g, 0.083 mmol), and KOAc (0.409 g, 4.17 mmol) were dissolved in dioxane (8.34 ml). The reaction was heated at 100 °C for 2

hours. The reaction was cooled to ambient temperature, diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 24 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in DCM) to yield **Intermediate 110d** (0.300 g, 0.639 mmol, 77%). LC-MS (Method A2) RT = 0.68 min, MS (ESI) *m/z*: 388.1 $(M+H)^+$ for boronic acid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.89 - 7.85 (m, 1H), 7.77 (d, *J*=7.7 Hz, 1H), 7.59 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 5.32 (s, 2H), 2.14 (s, 3H), 2.04 - 1.97 (m, 6H), 1.84 (br d, *J*=4.0 Hz, 2H), 1.29 (s, 12H).

Intermediate 110e: 4''-((2-methyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(110d)

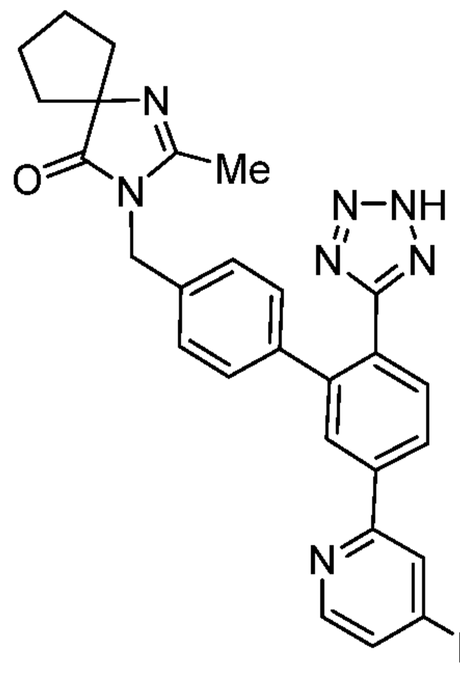
Intermediate 110d (40 mg, 0.085 mmol), bromobenzene (40.1 mg, 0.256 mmol), and 2nd generation XPhos precatalyst (6.70 mg, 8.52 µmol) were dissolved in toluene (1363 µl), EtOH (341 µl), and 2M tripotassium phosphate (85 µl, 0.170 mmol) was added. The reaction was heated at 100 °C for one hour. The reaction was diluted with EtOAc, filtered through Celite and concentrated *in vacuo*. The crude material will be used as-is without further purification for the subsequent reaction. **Intermediate 110e** (36 mg, 0.086 mmol, 101 % yield): LC-MS (Method A2) RT = 0.92 min, MS (ESI) *m/z*: 420.1 $(M+H)^+$.

Example 110: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-methyl-1,3-diazaspiro[4.4]non-1-en-4-one

Synthesized in an analogous manner to **Example 99** using **Intermediate 110e** (0.040 g, 0.095 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10

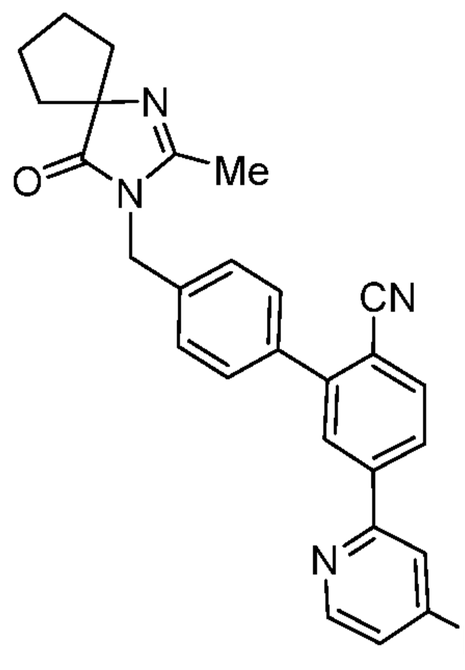
mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 12-56% B over 23 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min. **Example 110** (1.2 mg, 2.491 µmol, 2.61 % yield): LC-MS (Method A2) RT = 0.83 min, MS (ESI) *m/z*: 463.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.78 (br d, *J*=7.3 Hz, 2H), 7.75 - 7.69 (m, 2H), 7.63 (s, 1H), 7.49 (t, *J*=7.6 Hz, 2H), 7.42 - 7.38 (m, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 7.06 (br d, *J*=8.2 Hz, 2H), 4.68 (s, 2H), 2.05 (s, 3H), 1.88 - 1.79 (m, 6H), 1.69 (br d, *J*=7.3 Hz, 2H) (1 exchangeable proton not observed).

Example 111: 2-methyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 111)

Intermediate 111a: 4'-((2-methyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



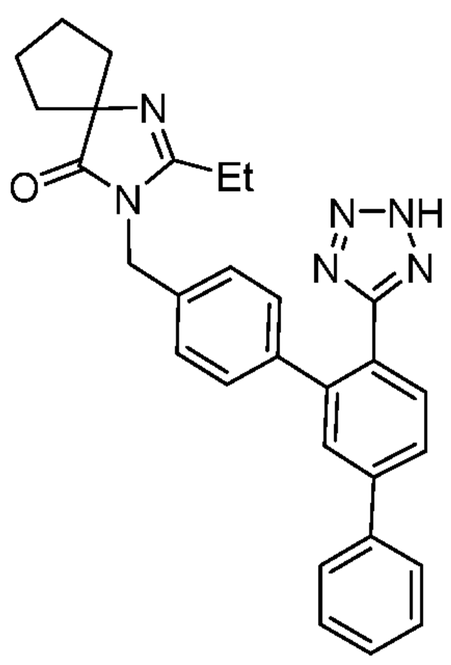
(111a)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 110d** (0.040 g, 0.085 mmol) and 2-bromo-4-methylpyridine (0.044 g, 0.256 mmol) to yield **Intermediate 111a** (0.037 g, 0.085 mmol, 100%). LC-MS (Method A2) RT = 0.72 min, MS (ESI) *m/z*: 435.2 $(M+H)^+$.

Example 111: 2-methyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

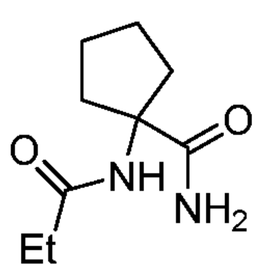
Synthesized in an analogous manner to **Example 99** using **Intermediate 111a** (0.040 g, 0.092 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 2-42% B over 23 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min. **Example 111:** LC-MS (Method A2) RT = 0.61 min, MS (ESI) *m/z*: 478.3 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, *J*=4.9 Hz, 1H), 8.19 (br d, *J*=8.2 Hz, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.77 (d, *J*=8.2 Hz, 1H), 7.24 (br d, *J*=4.9 Hz, 1H), 7.20 (d, *J*=7.9 Hz, 2H), 7.10 (br d, *J*=7.9 Hz, 2H), 4.70 (s, 2H), 2.42 (s, 3H), 2.05 (s, 3H), 1.90 - 1.81 (m, 6H), 1.68 (br s, 2H) (1 exchangeable proton not observed).

Example 112: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-1,3-diazaspiro[4.4]non-1-en-4-one



(ex.112)

Intermediate 112a: 1-propionamidocyclopentane-1-carboxamide

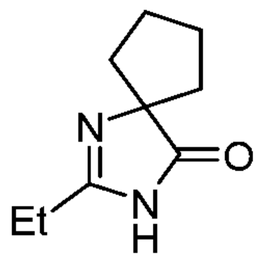


(112a)

To a solution of 1-aminocyclopentane-1-carboxamide (1.00 g, 7.80 mmol) in DCM (16 mL) was added TEA (2.72 mL, 19.50 mmol). The mixture was cooled to 0 °C with an ice bath. Propionyl chloride (1.011 g, 10.92 mmol) in DCM (4 mL) was added dropwise to the stirred solution, and the reaction mixture was at RT for 18 hours. The reaction was diluted with H_2O and DCM. The organic phase was collected. The aqueous phase was

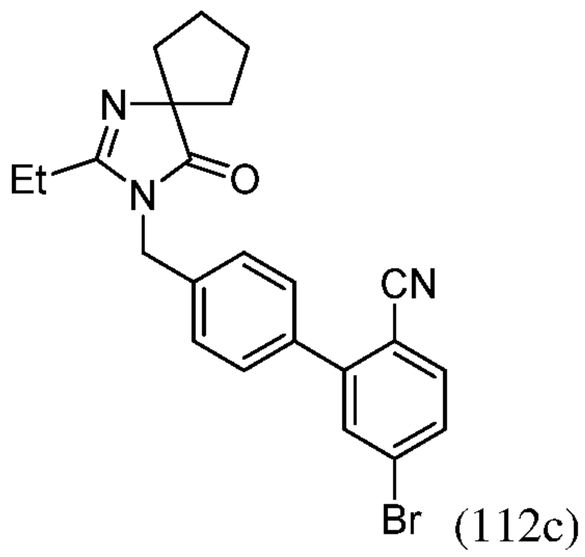
extracted (2X) with DCM. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated to give **Intermediate 112a** (0.586 g, 3.18 mmol, 40.8 % yield) as a solid. LC-MS (Method A2) RT =0.46 min, MS (ESI) *m/z*: 185.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 - 9.15 (m, 2H), 8.71 (br d, *J*=0.9 Hz, 1H), 2.42 (q, *J*=7.4 Hz, 2H), 2.39 - 2.29 (m, 2H), 1.85 - 1.68 (m, 4H), 1.67 - 1.58 (m, 2H), 1.14 - 1.10 (m, 3H).

Intermediate 112b: 2-ethyl-1,3-diazaspiro[4.4]non-1-en-4-one


(112b)

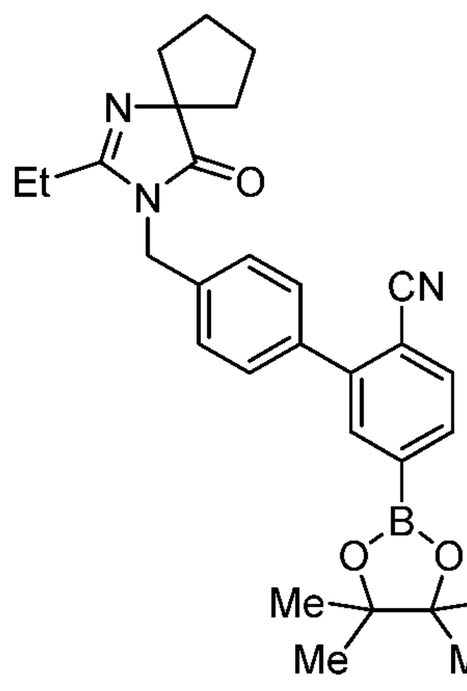
Synthesized in an analogous manner to **Example 110b** using **Intermediate 112a** (0.586 g, 3.18 mmol) to yield **Intermediate 112b** (0.445 g, 2.68 mmol, 84%). LC-MS (Method A2) RT = 0.46 min, MS (ESI) *m/z*: 167.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 2.42 (q, *J*=7.7 Hz, 2H), 1.82 (br d, *J*=3.7 Hz, 2H), 1.77 - 1.70 (m, 6H), 1.18 (t, *J*=7.6 Hz, 3H).

Intermediate 112c: 5-bromo-4'-((2-ethyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile


(112c)

Synthesized in an analogous manner to **Example 110c** using **Intermediate 112b** (0.176 g, 1.059 mmol) and **Intermediate I-002** (0.446 g, 1.271 mmol) to yield **Intermediate 112c** (0.232 g, 0.532 mmol, 50%). LC-MS (Method A2) RT = 0.87 min, MS (ESI) *m/z*: 436.0 $[M + H]^+$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.68 (m, 1H), 7.65 - 7.62 (m, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.32 (d, *J*=8.6 Hz, 2H), 5.32 (s, 2H), 2.43 - 2.36 (m, 2H), 2.06 - 1.95 (m, 6H), 1.90 - 1.85 (m, 2H), 1.22 (t, *J*=7.5 Hz, 3H).

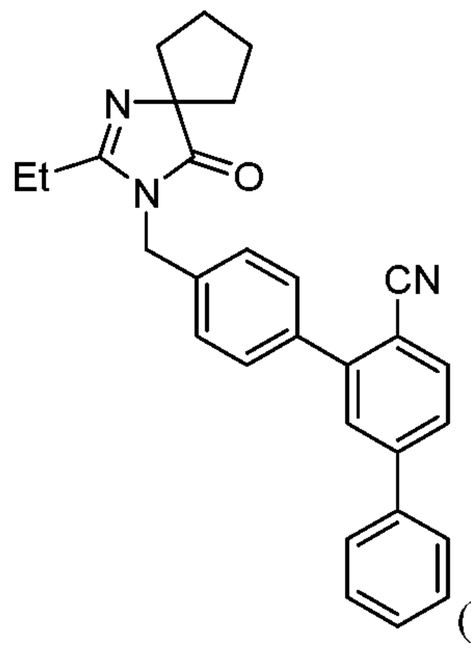
Intermediate 112d: 4'-((2-ethyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(112d)

Synthesized in an analogous manner to **Example 110d** using **Intermediate 112c** (0.232 g, 0.532 mmol) to yield **Intermediate 112d** (0.257 g, 0.455 mmol, 86%). LC-MS (Method A2) RT = 0.67 min, MS (ESI) *m/z*: 402.1 $(M+H)^+$ for boronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.85 (dd, *J*=7.7, 1.1 Hz, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.56 (d, *J*=8.1 Hz, 2H), 7.30 - 7.26 (m, 2H), 4.74 (s, 2H), 2.42 - 2.30 (m, 2H), 2.07 - 1.94 (m, 6H), 1.90 - 1.79 (m, 2H), 1.37 - 1.26 (m, 12H), 1.19 (t, *J*=7.4 Hz, 3H).

Intermediate 112e: 4''-((2-ethyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(112e)

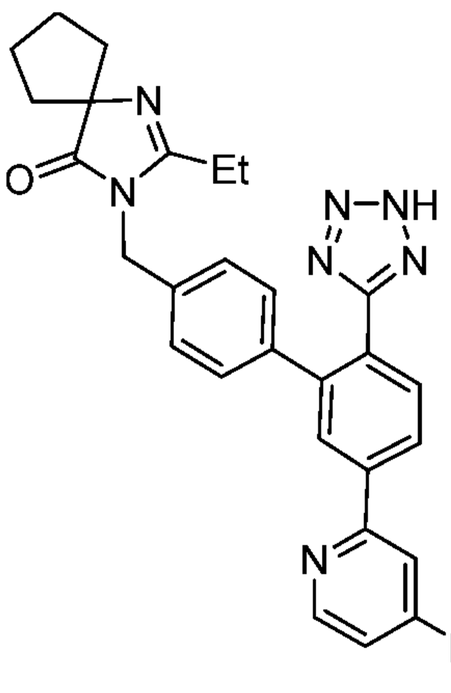
Synthesized in an analogous manner to **Example 110e** using **Intermediate 112d** (0.030 g, 0.069 mmol) and bromobenzene (0.029 g, 0.186 mmol) to yield **Intermediate 112e** (0.030 g, 0.062 mmol, 100%). LC-MS (Method A2) RT = 0.90 min, MS (ESI) *m/z*: 434.1 $(M+H)^+$.

Example 112: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-1,3-diazaspiro[4.4]non-1-en-4-one

Synthesized in an analogous manner to **Example 99** using **Intermediate 112e** (0.030 g, 0.062 mmol). Purified using preparative LC-MS with the following conditions: Column:

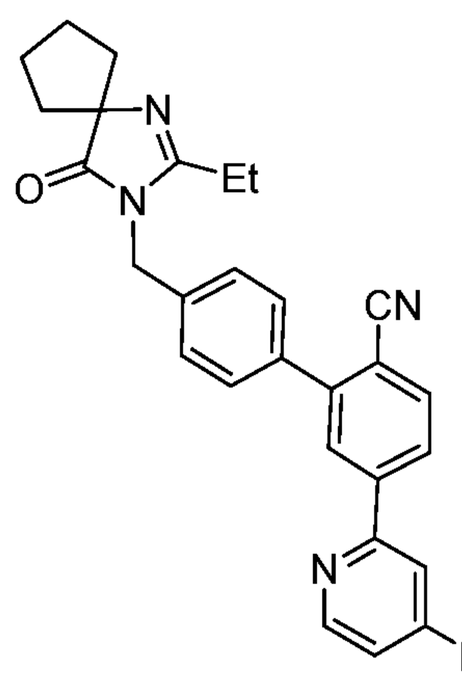
XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. **Example 112** (0.0015 g, 0.00308 mmol, 3.11%)**:** LC-MS (Method A2) RT = 0.81 min, MS (ESI) *m/z*: 477.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.90 - 7.87 (m, 1H), 7.83 (br d, *J*=7.3 Hz, 2H), 7.80 - 7.76 (m, 2H), 7.52 (br t, *J*=7.6 Hz, 2H), 7.46 (br d, *J*=7.3 Hz, 1H), 7.20 (br d, *J*=7.6 Hz, 2H), 7.12 (br d, *J*=7.6 Hz, 2H), 4.70 (s, 2H), 2.34 (br d, *J*=7.3 Hz, 2H), 2.06 - 1.74 (m, 6H), 1.70 (br d, *J*=5.8 Hz, 2H), 1.05 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

Example 113: 2-ethyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(ex. 113)

Intermediate 113a: 5-(4-methypyridin-2-yl)-4'-((4-oxo-2-ethyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(113a)

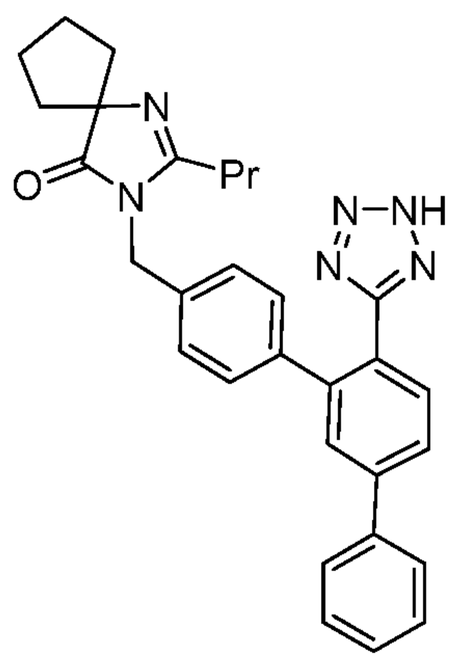
Synthesized in an analogous manner to **Example 110e** using **Intermediate 112d** (0.030 g, 0.069 mmol) and 2-bromo-4-methylpyridine (0.032 g, 0.186 mmol) to yield

Intermediate 113a (0.030 g, 0.067 mmol, 100%). LC-MS (Method A2) RT = 0.75 min, MS (ESI) *m/z*: 449.0 $(M+H)^+$.

Example 113: 2-ethyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

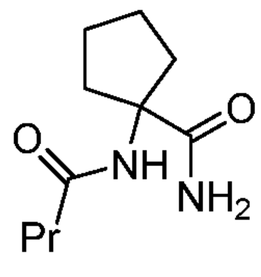
Synthesized in an analogous manner to **Example 99** using **Intermediate 113a** (0.030 g, 0.067 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 13-53% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. **Example 113** (0.0041 g, 0.00782 mmol, 8.3%)**:** LC-MS (Method A2) RT = 0.65 min, MS (ESI) *m/z*: 492.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, *J*=5.0 Hz, 1H), 8.27 (br d, *J*=7.9 Hz, 1H), 8.22 (s, 1H), 8.00 (s, 1H), 7.80 (d, *J*=8.0 Hz, 1H), 7.27 (br d, *J*=4.8 Hz, 1H), 7.22 - 7.19 (m, 2H), 7.19 - 7.14 (m, 2H), 4.74 (s, 2H), 2.47 - 2.40 (m, 5H), 1.89 (br d, *J*=7.3 Hz, 6H), 1.81 - 1.69 (m, 2H), 1.09 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed).

Example 114: (R)-3-((5'-(3-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 114)

Intermediate 114a: 1-butyramidocyclopentane-1-carboxamide

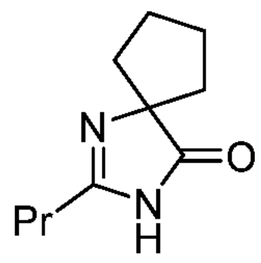


(114a)

To a solution of 1-aminocyclopentane-1-carboxamide (0.500 g, 3.90 mmol) in DCM (16 mL) was added TEA (1.359 mL, 9.75 mmol). The mixture was cooled with an ice bath.

Butyryl chloride (0.572 mL, 5.46 mmol) in DCM (4 mL) was added dropwise to the stirred solution, and the reaction mixture was at RT for 18 hours. The reaction was diluted with H_2O and DCM. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to give **Intermediate 114a** (0.300 g, 1.513 mmol, 38.8 % yield) as a solid. LC-MS (Method A2) RT =0.54 min, MS (ESI) *m/z*: 199.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 - 6.86 (m, 2H), 5.38 - 5.27 (m, 1H), 2.28 - 2.18 (m, 2H), 2.14 - 2.07 (m, 2H), 1.98 - 1.89 (m, 2H), 1.75 - 1.65 (m, 4H), 1.62 - 1.56 (m, 2H), 0.90 - 0.87 (m, 3H).

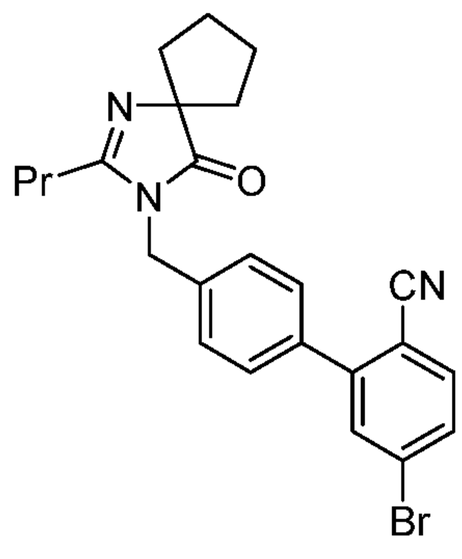
Intermediate 114b: 2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one



(114b)

Synthesized in an analogous manner to **Example 110b** using **Intermediate 114a** (0.307 g, 1.548 mmol) to yield **Intermediate 114b** (0.110 g, 0.610 mmol, 39%). LC-MS (Method A2) RT = 0.48 min, MS (ESI) *m/z*: 181.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 - 5.45 (m, 1H), 2.36 (t, *J*=7.4 Hz, 2H), 2.20 (t, *J*=7.5 Hz, 2H), 2.13 - 1.96 (m, 2H), 1.92 - 1.78 (m, 2H), 1.76 - 1.65 (m, 4H), 1.02 - 0.98 (m, 3H)

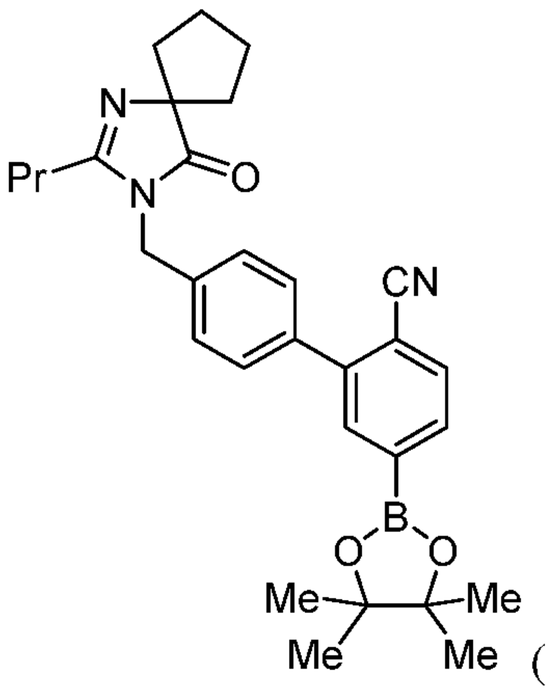
Intermediate 114c: 5-bromo-4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(114c)

Synthesized in an analogous manner to **Example 110c** using **Intermediate 114b** (0.555 g, 3.08 mmol) and **Intermediate I-002** (1.297 g, 3.69 mmol) to yield **Intermediate 114c** (0.668 g, 1.483 mmol, 48%). LC-MS (Method A2) RT = 0.87 min, MS (ESI) *m/z*: 436.0 $[M + H]^+$

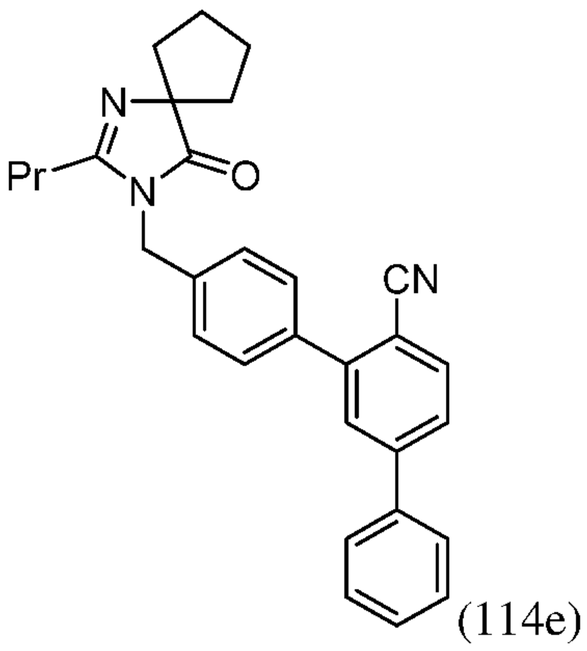
Intermediate 114d: 4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(114d)

Synthesized in an analogous manner to **Example 110d** using **Intermediate 114c** (0.450 g, 0.999 mmol) to yield **Intermediate 114d** (0.442 g, 0.889 mmol, 89%). LC-MS (Method A2) RT = 0.96 min, MS (ESI) *m/z*: 498.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.84 (d, *J*=1.1 Hz, 1H), 7.77 - 7.73 (m, 1H), 7.56 (d, *J*=8.4 Hz, 2H), 7.28 (s, 2H), 4.74 (s, 2H), 2.38 - 2.26 (m, 2H), 2.04 - 1.94 (m, 6H), 1.84 (td, *J*=4.8, 2.8 Hz, 2H), 1.70 - 1.62 (m, 2H), 1.35 (s, 12H), 0.95 (t, *J*=7.4 Hz, 3H).

Intermediate 114e: 4''-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



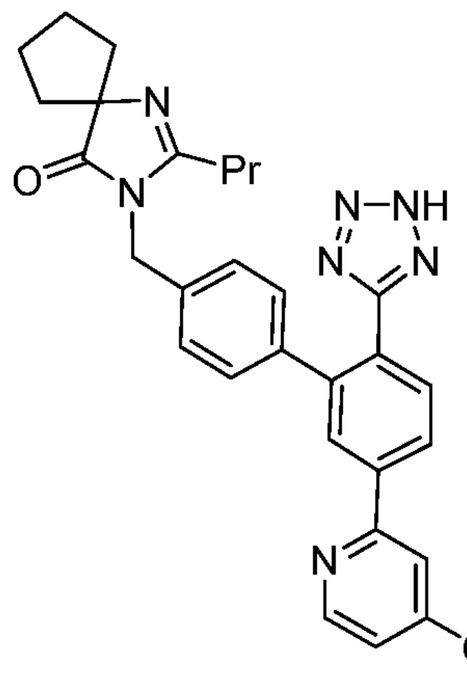
(114e)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 114d** (0.030 g, 0.060 mmol) and bromobenzene (0.028 g, 0.181 mmol) to yield **Intermediate 114e** (0.030 g, 0.067 mmol, 100%). LC-MS (Method A2) RT = 0.93 min, MS (ESI) *m/z*: 448.2 $(M+H)^+$.

Example 114: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one

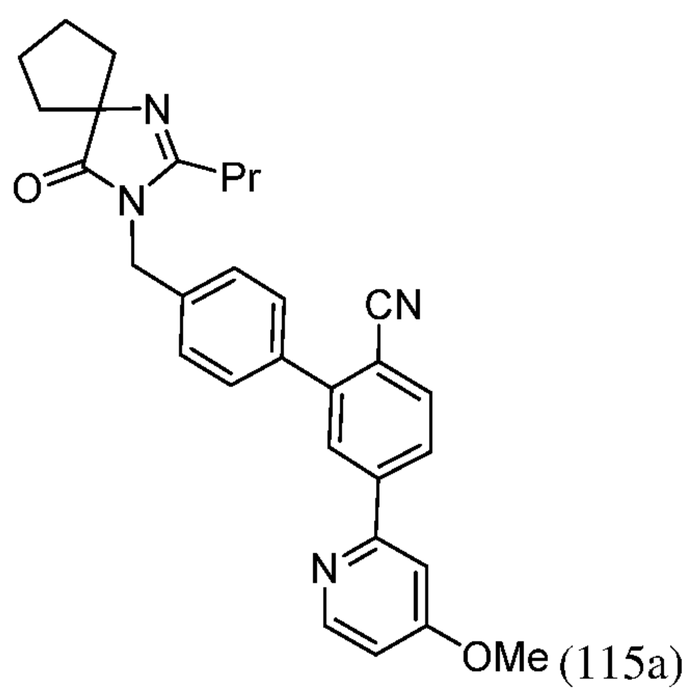
Synthesized in an analogous manner to **Example 99** using **Intermediate 114e** (0.030 g, 0.060 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 17-57% B over 25 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min. **Example 114** (0.0112 g, 0.022 mmol, 23%)**:** LC-MS (Method A2) RT = 0.83 min, MS (ESI) *m/z*: 491.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.81 - 7.76 (m, 3H), 7.74 - 7.70 (m, 1H), 7.67 (s, 1H), 7.50 (t, *J*=7.6 Hz, 2H), 7.44 - 7.39 (m, 1H), 7.19 (br d, *J*=7.9 Hz, 2H), 7.06 (br d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.30 (t, *J*=7.3 Hz, 2H), 1.90 - 1.79 (m, 6H), 1.68 (br d, *J*=7.6 Hz, 2H), 1.58 - 1.50 (m, 2H), 0.86 (t, *J*=7.3 Hz, 3H). (1 exchangeable proton not observed).

Example 115: 3-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 115)

Intermediate 115a: 5-(4-methoxypyridin-2-yl)-4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



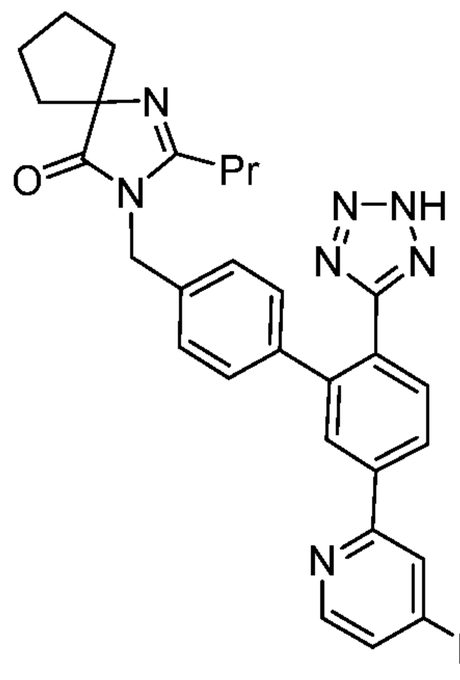
(115a)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 114d** (0.030 g, 0.060 mmol) and 2-bromo-4-methoxylpyridine (0.034 g, 0.181 mmol) to yield **Intermediate 115a** (0.030 g, 0.060 mmol, 100%). LC-MS (Method A2) RT = 0.67 min, MS (ESI) *m/z*: 479.2 $(M+H)^+$.

Example 115: 3-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one

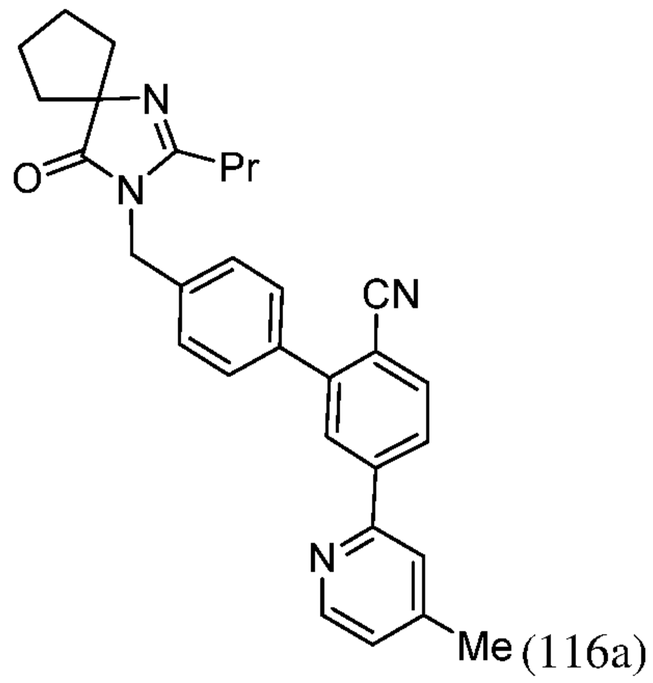
Synthesized in an analogous manner to **Example 99** using **Intermediate 115a** (0.030 g, 0.060 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 8-48% B over 25 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min. **Example 115** (0.0083 g, 0.016 mmol, 17.4%)**:** LC-MS (Method A2) RT = 0.59 min, MS (ESI) *m/z*: 522.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, *J*=5.6 Hz, 1H), 8.13 (dd, *J*=8.0, 1.6 Hz, 1H), 8.09 (d, *J*=1.4 Hz, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=2.1 Hz, 1H), 7.21 (d, *J*=8.1 Hz, 2H), 7.07 (d, *J*=8.1 Hz, 2H), 6.96 (dd, *J*=5.6, 2.3 Hz, 1H), 4.68 (s, 2H), 3.94 (s, 3H), 2.32 (t, *J*=7.3 Hz, 2H), 1.90 - 1.81 (m, 6H), 1.70 (br d, *J*=7.2 Hz, 2H), 1.63 - 1.53 (m, 2H), 0.89 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed).

Example 116: 3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one



(ex. 116)

Intermediate 116a: 5-(4-methylpyridin-2-yl)-4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



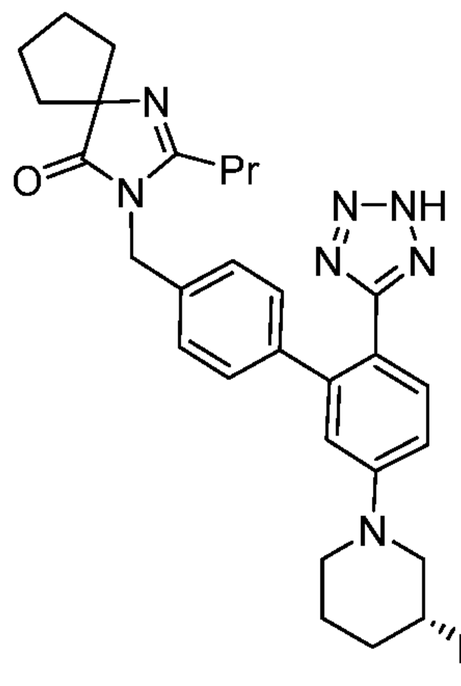
(116a)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 114d** (0.030 g, 0.060 mmol) and 2-bromo-4-methylpyridine (0.031 g, 0.181 mmol) to yield **Intermediate 116a** (0.030 g, 0.060 mmol, 100%). LC-MS (Method A2) RT = 0.75 min, MS (ESI) *m/z*: 463.2 $(M+H)^+$.

Example 116: 3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one

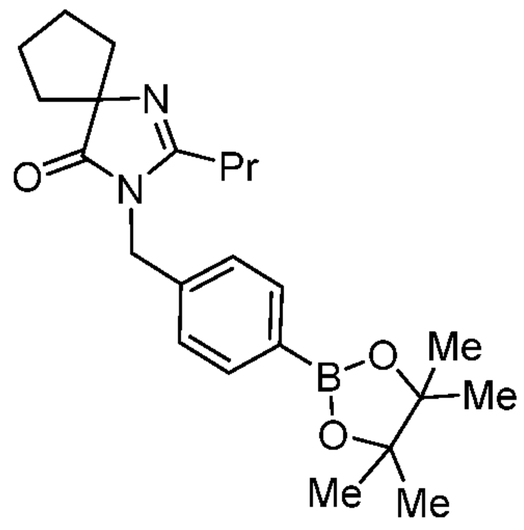
Synthesized in an analogous manner to **Example 99** using **Intermediate 116a** (0.030 g, 0.060 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 12-52% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. **Example 116** (0.018 g, 0.035 mmol, 38%)**:** LC-MS (Method A2) RT = 1.21 min, MS (ESI) *m/z*: 506.3 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, *J*=4.9 Hz, 1H), 8.13 - 8.08 (m, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.25 - 7.17 (m, 3H), 7.05 (d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.41 (s, 3H), 2.33 (t, *J*=7.3 Hz, 2H), 1.92 - 1.83 (m, 6H), 1.70 (br d, *J*=6.9 Hz, 2H), 1.59 (sxt, *J*=7.3 Hz, 2H), 0.90 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed).

Example 117: (R)-3-((5'-(3-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 117)

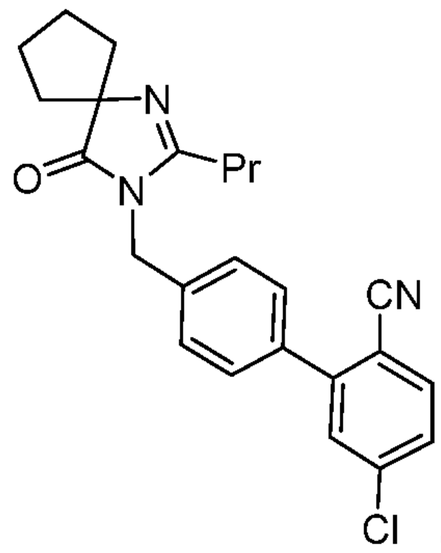
Intermediate 117a: 2-propyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(117a)

Synthesized in an analogous manner to **Example 110c** using **Intermediate 114b** (0.555 g, 3.08 mmol) and 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.463 g, 1.558 mmol) to yield **Intermediate 117a** (0.214 g, 0.540 mmol, 42%). LC-MS (Method A2) RT = 0.85 min, MS (ESI) *m/z*: 397.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.1 Hz, 2H), 7.17 (d, *J*=8.1 Hz, 2H), 4.71 (s, 2H), 2.30 - 2.22 (m, 2H), 2.08 - 1.93 (m, 6H), 1.87 - 1.79 (m, 2H), 1.65 - 1.59 (m, 2H), 1.36 (s, 12H), 0.93 (t, *J*=7.4 Hz, 3H).

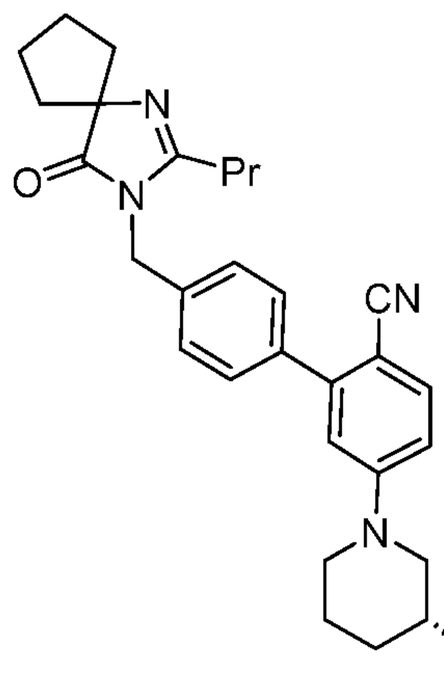
Intermediate 117b: 5-chloro-4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(117b)

To a microwave vial containing $PdCl_2$(dppf) (0.036 g, 0.049 mmol), **Intermediate 117a** (0.194 g, 0.489 mmol) and 4-chloro-2-iodobenzonitrile (0.168 g, 0.636 mmol) was added toluene (1.958 ml) followed by ethanol (0.489 ml) and K_3PO_4 (2 M, aq.) (0.489 ml, 0.979 mmol). N_2 was sparged through the reaction mixture for 5 min before the vial was sealed and heated at 110 °C for 18 hours. The reaction mixture was diluted with EtOAc and washed with sat. $NaHCO_3$. The organic phase was concentrated and purified by ISCO (0-100% EtOAc in hexanes) to afford **Intermediate 117b** (0.181 g, 0.446 mmol, 91 % yield) as a yellow oil. LC-MS (Method A2) RT = 0.80 min, MS (ESI) *m/z*: 406.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.1 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=1.8 Hz, 1H), 7.46 (dd, *J*=8.4, 2.2 Hz, 1H), 7.32 (d, *J*=8.6 Hz, 2H), 4.77 (s, 2H), 2.37 - 2.32 (m, 2H), 2.10 - 1.97 (m, 6H), 1.90 - 1.83 (m, 2H), 1.72 - 1.63 (m, 2H), 0.97 (t, *J*=7.5 Hz, 3H).

Intermediate 117c: (R)-5-(3-methylpiperidin-1-yl)-4'-((4-oxo-2-propyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(117c)

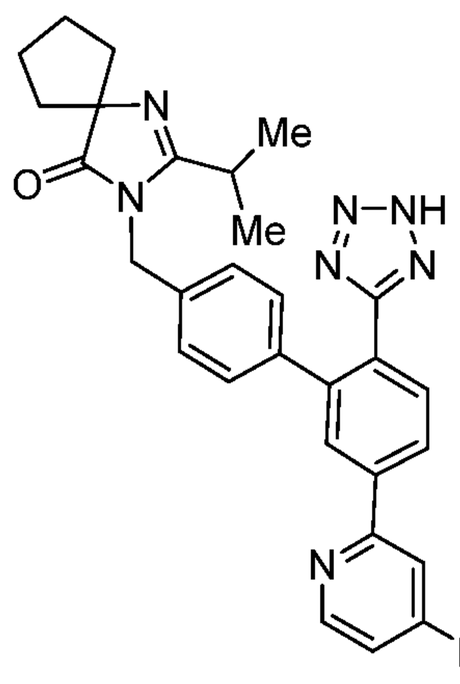
Synthesized in an analogous manner to **Intermediate 99b** using **Intermediate 117b** (0.040 g, 0.099 mmol) and (*R*)-3-methylpiperidine (0.0097 g, 0.099 mmol) to yield **Intermediate 117c** (0.032 g, 0.069 mmol, 70%). LC-MS (Method A2) RT = 1.01 min,

MS (ESI) *m/z*: 469.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.8 Hz, 1H), 7.54 (d, *J*=8.4 Hz, 2H), 7.26 (s, 2H), 6.88 - 6.82 (m, 2H), 4.75 (s, 2H), 3.90 - 3.70 (m, 2H), 2.87 (td, *J*=12.3, 3.1 Hz, 1H), 2.56 (dd, *J*=12.7, 10.7 Hz, 1H), 2.36 (dd, *J*=8.3, 7.2 Hz, 2H), 2.11 - 1.93 (m, 7H), 1.89 - 1.81 (m, 3H), 1.81 - 1.62 (m, 4H), 1.23 - 1.11 (m, 1H), 1.03 - 0.91 (m, 6H).

Example 117: (R)-3-((5'-(3-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one

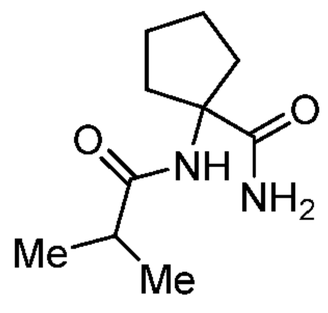
Synthesized in an analogous manner to **Example 99** using **Intermediate 117c** (0.032 g, 0.069 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 33-58% B over 25 minutes, then a 2-minute hold at 100% B; Flow: 20 mL/min. **Example 117** (0.0049 g, 0.0093 mmol, 13%)**:** LC-MS (Method A2) RT = 0.81 min, MS (ESI) *m/z*: 512.3 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.43 (br s, 1H), 7.10 (br s, 2H), 7.02 (br d, *J*=6.9 Hz, 3H), 6.85 (br s, 1H), 4.65 (s, 2H), 3.72 (br t, *J*=12.0 Hz, 2H), 2.29 (br t, *J*=7.2 Hz, 2H), 1.94 - 1.77 (m, 10H), 1.74 - 1.64 (m, 4H), 1.56 (dt, *J*=14.6, 7.3 Hz, 2H), 1.09 (br dd, *J*=11.5, 2.9 Hz, 1H), 0.93 (d, *J*=6.5 Hz, 3H), 0.88 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

Example 118: 2-isopropyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 118)

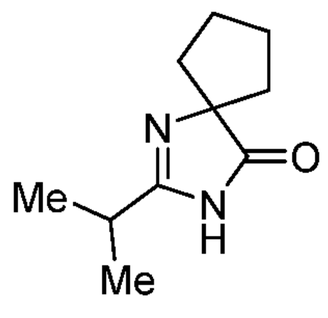
Intermediate 118a: 1-isobutyramidocyclopentane-1-carboxamide



(118a)

To a solution of 1-aminocyclopentane-1-carboxamide (1.00 g, 7.80 mmol) in DCM (16 mL) was added TEA (2.72 mL, 19.50 mmol). The mixture was cooled with an ice bath. Isobutyryl chloride (1.164 g, 10.92 mmol) in DCM (4 mL) was added dropwise to the stirred solution, and the reaction mixture was at RT for 18 hours. The reaction was diluted with H_2O and DCM. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to give **Intermediate 118a** (998 mg, 5.03 mmol, 64.5 % yield) as a solid. RT =0.52 min, MS (ESI) *m/z*: 199.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (br s, 1H), 5.55 (br s, 2H), 2.47 - 2.29 (m, 4H), 2.08 - 2.00 (m, 2H), 1.92 - 1.83 (m, 2H), 1.78 - 1.75 (m, 1H), 1.17 (d, *J*=6.8 Hz, 6H).

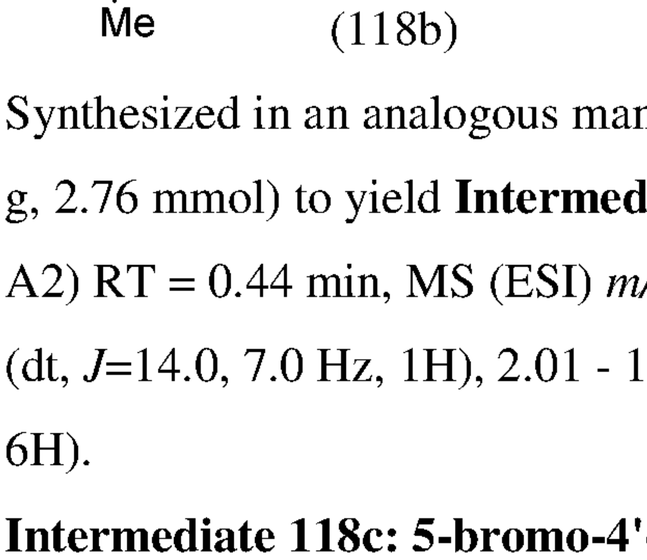
Intermediate 118b: 2-isopropyl-1,3-diazaspiro[4.4]non-1-en-4-one



(118b)

Synthesized in an analogous manner to **Example 110b** using **Intermediate 118a** (0.548 g, 2.76 mmol) to yield **Intermediate 118b** (0.448 g, 2.485 mmol, 90%). LC-MS (Method A2) RT = 0.44 min, MS (ESI) *m/z*: 181.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.76 (dt, *J*=14.0, 7.0 Hz, 1H), 2.01 - 1.88 (m, 6H), 1.83 (br d, *J*=2.4 Hz, 2H), 1.25 (d, *J*=7 Hz, 6H).

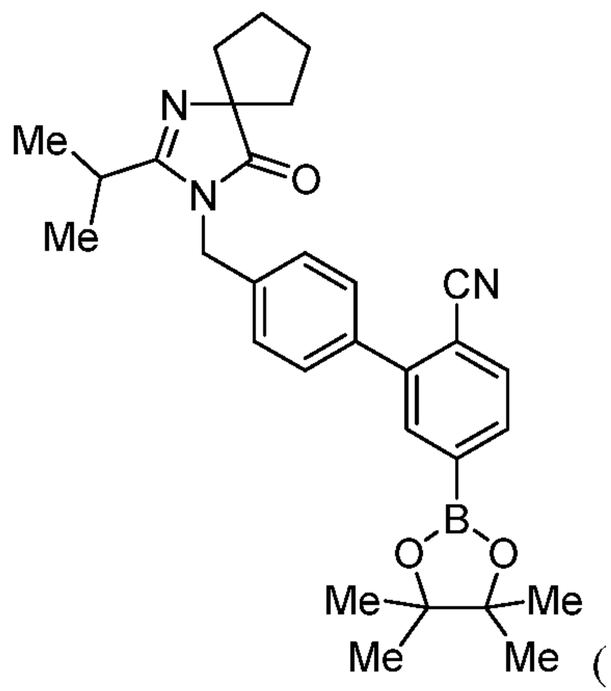
Intermediate 118c: 5-bromo-4'-((2-isopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(118c)

Synthesized in an analogous manner to **Example 110c** using **Intermediate 118b** (0.536 g, 2.97 mmol) and **Intermediate I-002** (1.253 g, 3.57 mmol) to yield **Intermediate 118c** (0.899 g, 1.996 mmol, 67%). LC-MS (Method A2) RT = 0.85 min, MS (ESI) *m/z*: 450.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=1.1 Hz, 1H), 7.62 - 7.59 (m, 2H), 7.52 (d, *J*=8.1 Hz, 2H), 7.28 (s, 2H), 4.77 (s, 2H), 2.59 (dt, *J*=13.6, 6.7 Hz, 1H), 2.04 - 1.92 (m, 6H), 1.89 - 1.81 (m, 2H), 1.17 (d, *J*=6.8 Hz, 6H).

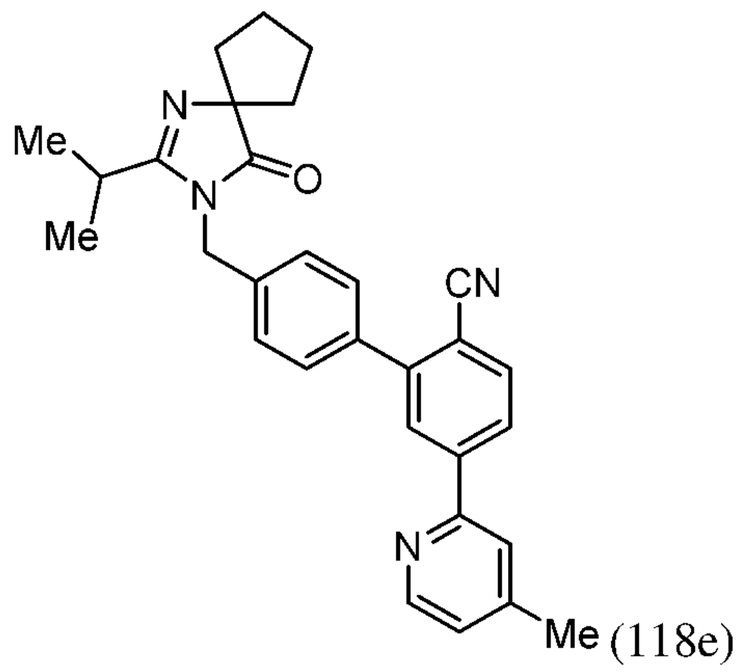
Intermediate 118d 4'-((2-isopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(118d)

Synthesized in an analogous manner to **Example 110d** using **Intermediate 118c** (0.400 g, 1.776 mmol) to yield **Intermediate 118d** (0.398 g, 0.800 mmol, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.84 (dd, *J*=7.7, 1.1 Hz, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.24 (s, 2H), 4.77 (s, 2H), 2.65 - 2.55 (m, 1H), 2.05 - 1.93 (m, 6H), 1.88 - 1.80 (m, 2H), 1.26 - 1.24 (m, 12H), 1.17 (d, *J*=6.8 Hz, 6H).

Intermediate 118e: 4'-((2-isopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



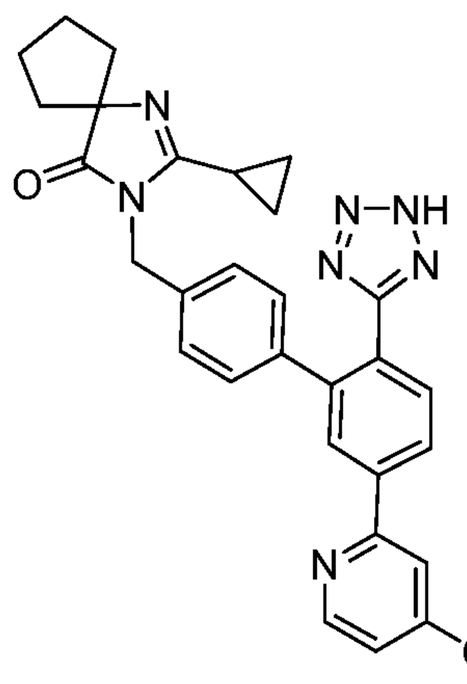
(118e)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 118d** (0.050 g, 0.101 mmol) and 2-bromo-4-methylpyridine (0.052 g, 0.302 mmol) to yield **Intermediate 118e** (0.040 g, 0.086 mmol, 86%). LC-MS (Method A2) RT = 0.75 min, MS (ESI) *m/z*: 463.1 $(M+H)^+$.

Example 118: 2-isopropyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

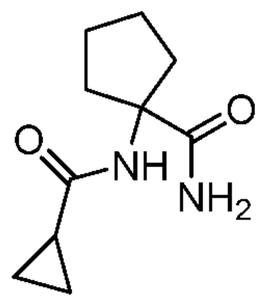
Synthesized in an analogous manner to **Example 99** using **Intermediate 118e** (0.040 g, 0.086 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 12-52% B over 22 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. **Example 118** (0.0078 g, 0.015 mmol, 16%)**:** LC-MS (Method A2) RT = 0.68 min, MS (ESI) *m/z*: 506.2 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, *J*=4.9 Hz, 1H), 8.17 (br d, *J*=8.1 Hz, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 7.31 - 7.16 (m, 3H), 7.08 (d, *J*=8.1 Hz, 2H), 4.72 (s, 2H), 2.67 (dt, *J*=13.6, 6.6 Hz, 1H), 2.42 (s, 3H), 1.93 - 1.78 (m, 6H), 1.69 (br d, *J*=7.6 Hz, 2H), 1.06 (d, *J*=6.7 Hz, 6H) (1 exchangeable proton not observed).

Example 119: 2-cyclopropyl-3-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 119)

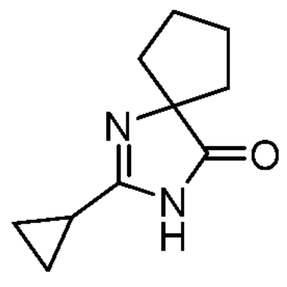
Intermediate 119a: 1-(cyclopropanecarboxamido)cyclopentane-1-carboxamide



(119a)

To a solution of 1-aminocyclopentane-1-carboxamide (1.00 g, 7.80 mmol) in DCM (16 mL) was added TEA (2.72 mL, 19.50 mmol). The mixture was cooled with an ice bath. Cyclopropanecarbonyl chloride (1.142 g, 10.92 mmol) in DCM (4 mL) was added dropwise to the stirred solution, and the reaction mixture was at RT for 18 hours. The reaction was diluted with H_2O and DCM. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to give **Intermediate 119a** (0.889g, 4.53 mmol, 58.1 % yield) as a solid. RT =0.49 min, MS (ESI) *m/z*: 197.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (br s, 2H), 5.76 - 5.57 (m, 1H), 2.49 - 2.25 (m, 1H), 2.07 (br d, *J*=16.7 Hz, 1H), 1.93 - 1.74 (m, 2H), 1.67 - 1.28 (m, 2H), 1.28 - 1.19 (m, 2H), 1.03 - 0.97 (m, 2H), 0.90 - 0.82 (m, 2H), 0.81 - 0.74 (m, 1H).

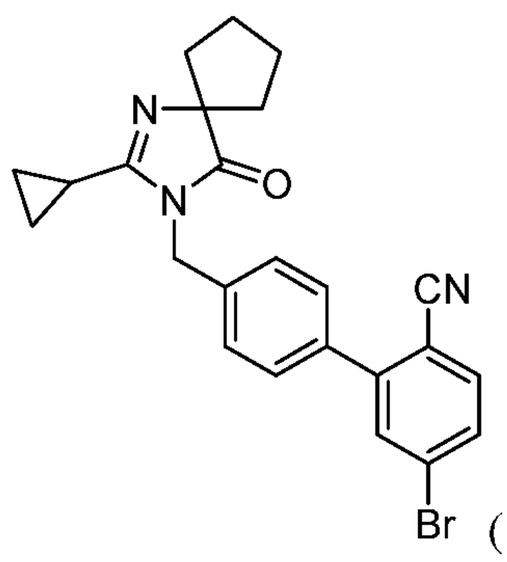
Intermediate 119b: 2-cyclopropyl-1,3-diazaspiro[4.4]non-1-en-4-one



(119b)

Synthesized in an analogous manner to **Example 110b** using **Intermediate 119a** (0.599 g, 3.06 mmol) to yield **Intermediate 119b** (0.258 g, 0.1.448 mmol, 47%). LC-MS (Method A2) RT = 0.43 min, MS (ESI) *m/z*: 178.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 - 1.86 (m, 3H), 1.85 - 1.72 (m, 2H), 1.30 - 1.22 (m, 1H), 1.08 - 1.01 (m, 3H), 0.97 - 0.89 (m, 1H).

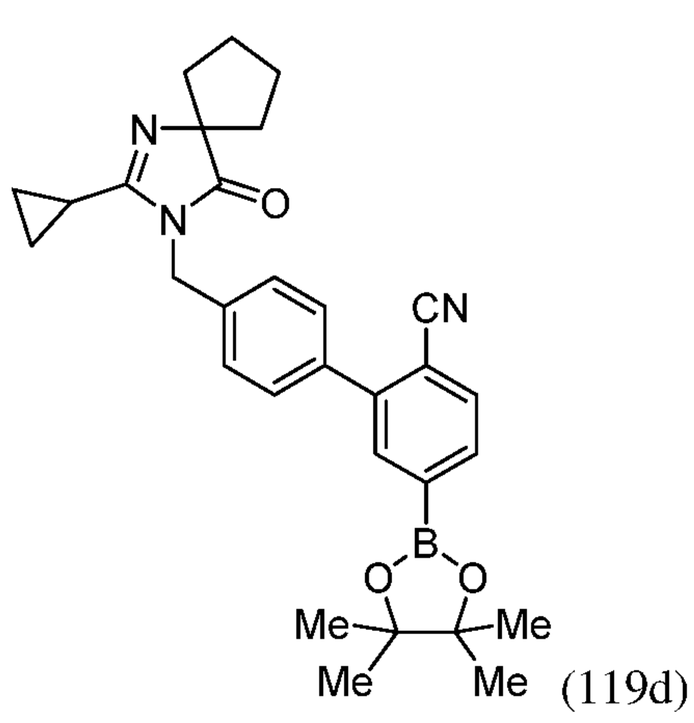
Intermediate 119c: 5-bromo-4'-((2-cyclopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(119c)

Synthesized in an analogous manner to **Example 110c** using **Intermediate 119b** (0.473 g, 2.65 mmol) and **Intermediate I-002** (1.12 g, 3.19 mmol) to yield **Intermediate 119c** (0.510 g, 1.14 mmol, 43%). LC-MS (Method A2) RT = 0.84 min, MS (ESI) *m/z*: 449.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J*=1.8, 0.7 Hz, 1H), 7.62 - 7.60 (m, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.4 Hz, 2H), 4.87 (s, 2H), 2.01 - 1.89 (m, 6H), 1.80 - 1.72 (m, 2H), 1.49 (tt, *J*=8.2, 5.0 Hz, 1H), 1.00 - 0.94 (m, 2H), 0.89 - 0.82 (m, 2H).

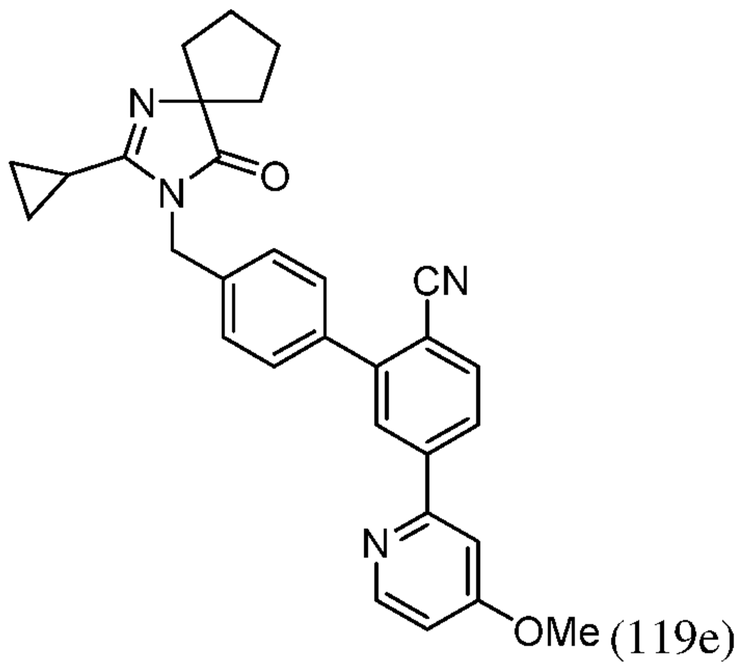
Intermediate 119d: 4'-((2-cyclopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(119d)

Synthesized in an analogous manner to **Example 110d** using **Intermediate 119c** (0.510 g, 1.137 mmol) to yield **Intermediate 119d** (0.448 g, 0.904 mmol, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.85 (dd, *J*=7.7, 1.1 Hz, 1H), 7.77 - 7.71 (m, 1H), 7.58 - 7.53 (m, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 4.86 (s, 2H), 2.02 - 1.91 (m, 6H), 1.80 - 1.74 (m, 2H), 1.53 - 1.47 (m, 1H), 1.26 (d, *J*=3.3 Hz, 12H), 1.00 - 0.94 (m, 2H), 0.89 - 0.82 (m, 2H).

Intermediate 119e: 4'-((2-cyclopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4-methoxypyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



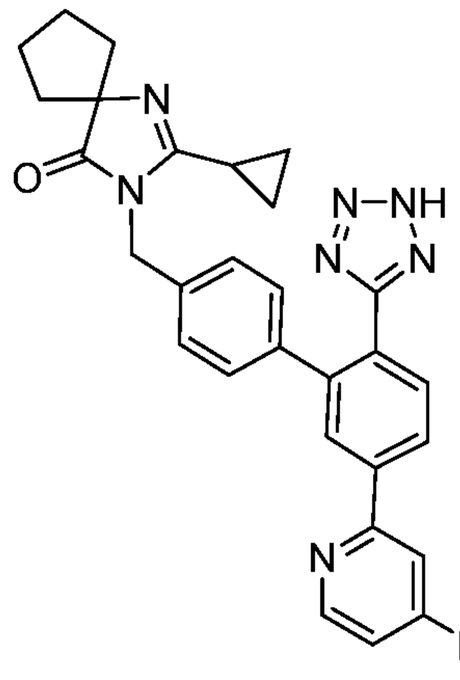
(119e)

Synthesized in an analogous manner to **Example 110e** using **Intermediate 119d** (0.051 g, 0.272 mmol) and 2-bromo-4-methoxy-pyridine (0.052 g, 0.272 mmol) to yield **Intermediate 119e** (0.040 g, 0.084 mmol, 92%). LC-MS (Method A2) RT = 0.66 min, MS (ESI) *m/z*: 477.1 $(M+H)^+$.

Example 119: 2-cyclopropyl-3-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

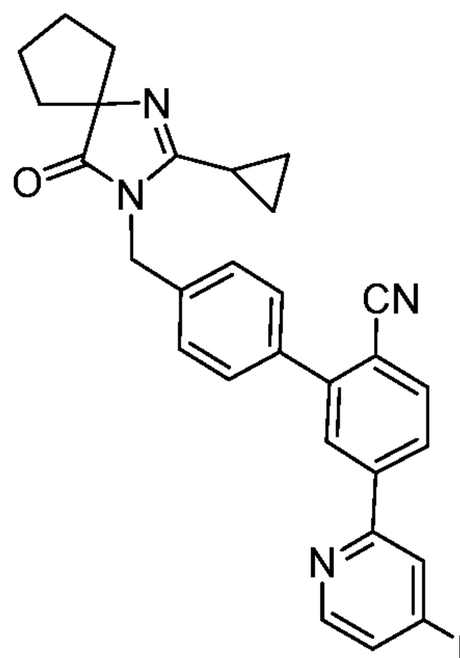
Synthesized in an analogous manner to **Example 99** using **Intermediate 119e** (0.040 g, 0.084 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 0-40% B over 22 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. **Example 119** (0.0025 g, 0.0048 mmol, 5%)**:** LC-MS (Method A2) RT = 0.58 min, MS (ESI) *m/z*: 520.1 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J*=5.5 Hz, 1H), 8.20 (br d, *J*=7.9 Hz, 1H), 8.16 (s, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.64 (d, *J*=1.8 Hz, 1H), 7.22 - 7.17 (m, 2H), 7.16 - 7.11 (m, 2H), 6.99 (dd, *J*=5.5, 2.1 Hz, 1H), 4.81 (s, 2H), 3.94 (s, 3H), 1.86 - 1.78 (m, 6H), 1.72 (br t, *J*=5.3 Hz, 1H), 1.62 (br d, *J*=7.0 Hz, 2H), 0.86 - 0.76 (m, 4H) (1 exchangeable proton not observed).

Example 120: 2-cyclopropyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(ex. 120)

Intermediate 120a: 4'-((2-cyclopropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(120a)

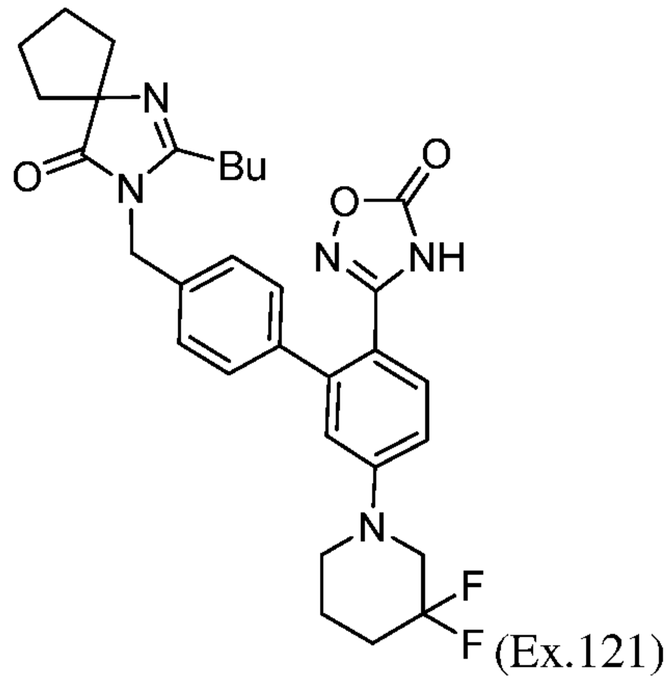
Synthesized in an analogous manner to **Example 110e** using **Intermediate 119d** (0.045 g, 0.091 mmol) and 2-bromo-4-methylpyridine (0.047 g, 0.272 mmol) to yield **Intermediate 120a** (0.040 g, 0.087 mmol, 96%). LC-MS (Method A2) RT = 0.74 min, MS (ESI) *m/z*: 461.1 $(M+H)^+$.

Example 120: 2-cyclopropyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

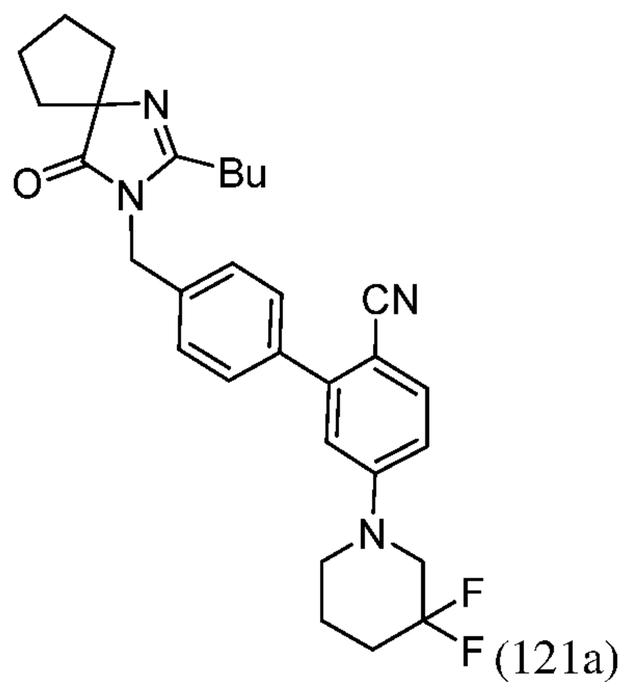
Synthesized in an analogous manner to **Example 99** using **Intermediate 120a** (0.040 g, 0.087 mmol). Purified using preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. **Example 120** (0.0022 g, 0.00384 mmol, 3.9%)**:** LC-MS (Method A2) RT = 0.62 min, MS (ESI) *m/z*: 504.1 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.54 (br d, *J*=4.6 Hz, 1H), 8.19 (br s, 1H), 8.13 (br s, 1H), 7.97 (br s, 1H), 7.76 (br s, 1H), 7.23 (br d, *J*=4.6 Hz, 1H), 7.17 (br

s, 2H), 7.13 (br s, 2H), 4.80 (s, 2H), 2.41 (s, 3H), 1.86 - 1.78 (m, 6H), 1.75 - 1.66 (m, 2H), 1.61 (br s, 2H), 0.84 - 0.79 (m, 3H). (1 exchangeable proton not observed).

Example 121: 3-(4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(3,3-difluoropiperidin-1-yl)-[1,1'-biphenyl]-2-yl)-1,2,4-oxadiazol-5(4H)-one

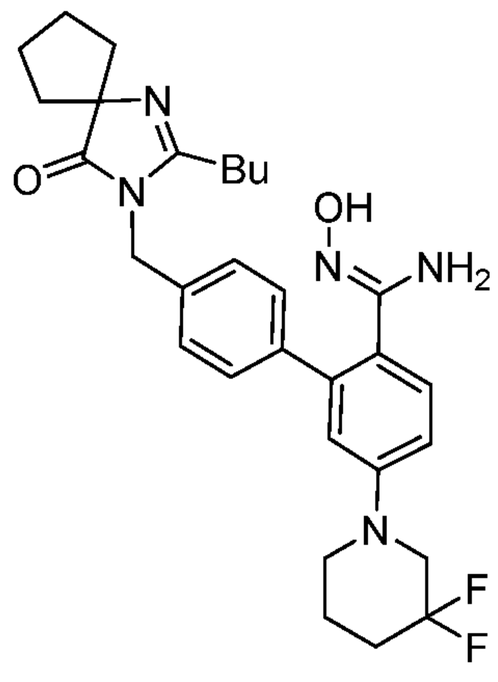

(Ex.121)

Intermediate 121a: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(3,3-difluoropiperidin-1-yl)-[1,1'-biphenyl]-2-carbonitrile


(121a)

Synthesized in an analogous manner to **Intermediate 99b** using **Intermediate 99a** (0.135 g, 0.321 mmol) and 3,3-difluoropiperidine hydrochloride (0.025 g, 0.032 mmol) to yield **Intermediate 121a** (0.100 g, 0.198 mmol, 62%). LC-MS (Method A2) RT = 0.94 min, MS (ESI) *m/z*: 505.1 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.59 (d, *J*=8.6 Hz, 1H), 7.52 (d, *J*=8.1 Hz, 2H), 7.26 (d, *J*=7.9 Hz, 2H), 6.91 - 6.83 (m, 2H), 4.74 (s, 2H), 3.59 (t, *J*=11.4 Hz, 2H), 3.45 - 3.38 (m, 2H), 2.39 - 2.31 (m, 2H), 2.16 - 1.80 (m, 12H), 1.61 (dt, *J*=15.5, 7.6 Hz, 2H), 1.35 (dq, *J*=15.0, 7.4 Hz, 2H), 0.88 (t, *J*=7.3 Hz, 3H).

Intermediate 121b: (Z)-4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(3,3-difluoropiperidin-1-yl)-N'-hydroxy-[1,1'-biphenyl]-2-carboximidamide



(121b)

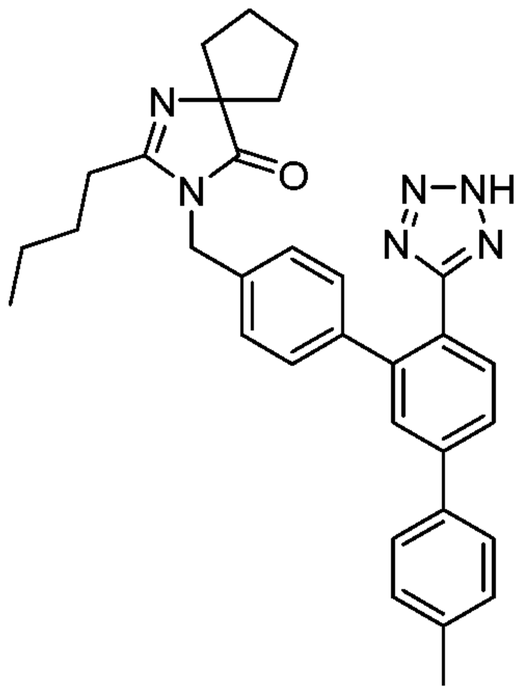
To a vial containing hydroxylamine hydrochloride (174 mg, 2.497 mmol) and potassium *t*-butoxide (233 mg, 2.081 mmol) was added ethanol (2081 µl). The mixture was stirred vigorously at RT for 1 min before being pipetted into a vial containing **Intermediate 121a** (105 mg, 0.208 mmol). The reaction was heated at 85 °C for 48 hours. The reaction mixture was diluted with DCM and washed with H_2O. The organic phase was concentrated and azeotroped with toluene to yield **Intermediate 121b** (0.015 g, 0.028 mmol, 13%) which was used without further purification in the next step. LC-MS (Method A2) RT = 0.79 min, MS (ESI) *m/z*: 538.1 $(M+H)^+$.

Example 121: 3-(4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(3,3-difluoropiperidin-1-yl)-[1,1'-biphenyl]-2-yl)-1,2,4-oxadiazol-5(4H)-one

To a vial charged with **Intermediate 121b** (15 mg, 0.028 mmol) was added DMF (2 mL) followed by DBU (0.021 mL, 0.139 mmol) and CDI (22.62 mg, 0.139 mmol). The reaction was allowed to stir at RT for 18 hours. The reaction was filtered and concentrated. The crude reaction mixture was dissolved in 2 mL of DMF. The crude material was purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 20-65% B over 30 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min to yield **Example 121** (0.005 g, 0.0085 mmol, 31%): LC-MS (Method A2) RT = 0.92 min, MS (ESI) *m/z*: 564.1 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.44 (d, *J*=8.5 Hz, 1H), 7.30 (d, *J*=7.6 Hz, 2H), 7.16 (d, *J*=7.9 Hz, 2H), 7.10 (d, *J*=8.5 Hz, 1H), 6.92 (br. s., 1H), 4.72 (s, 2H), 3.69 (t, *J*=11.6 Hz, 2H), 3.51 (d, *J*=7.9 Hz, 1H), 3.42 (br. s., 1H), 2.33 (t, *J*=7.3 Hz, 2H), 2.07 (br. s., 2H), 1.90 - 1.81 (m, 6H), 1.77 (br. s., 2H), 1.68 (br. s., 2H),

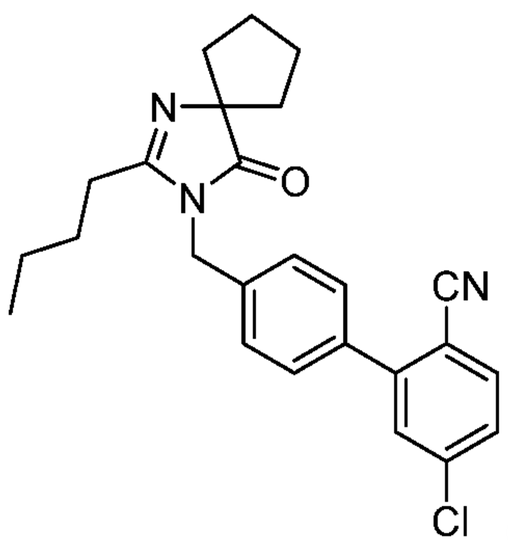
1.56 - 1.41 (m, 2H), 1.34 - 1.24 (m, 2H), 0.80 (t, *J*=7.3 Hz, 3H) (one exchangeable proton not observed).

Example 122: 2-butyl-3-((4''-methyl-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(ex. 122)

Intermediate 122a: 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carbonitrile

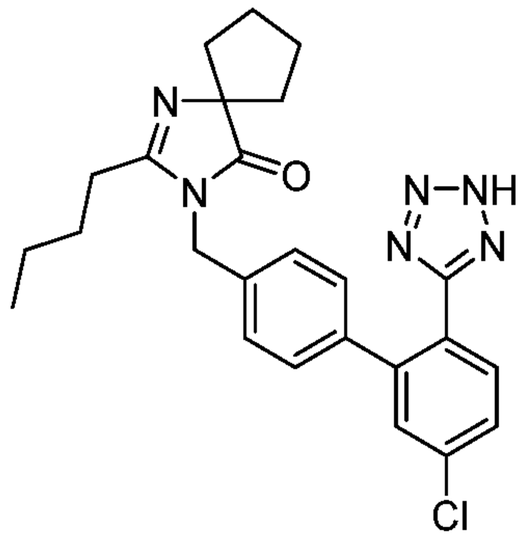


(122a)

Intermediate 033a (1.21 g, 2.95 mmol), 4-chloro-2-iodobenzonitrile (0.932 g, 3.54 mmol), and $PdCl_2$(dppf)-CH_2Cl_2Adduct (0.241 g, 0.295 mmol) were dissolved in toluene (23.6 mL), ethanol (5.90 mL), and tripotassium phosphate (2 M aq, 2.95 mL, 5.90 mmol) and the reaction was degassed for 15 minutes by bubbling with Ar. The reaction was sealed and heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature, filtered through celite, diluted with EtOAc, washed with saturated $NaHCO_3$, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 122a** (1.03 g, 2.45 mmol, 83%). LC-MS (Method A2) RT = 1.00 min, MS (ESI) *m/z*: 420.3 $(M+H)^+$. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.72 (d, *J*=8.3 Hz, 1H), 7.58 - 7.54 (m, 2H), 7.52 (d, *J*=2.2 Hz, 1H), 7.46 (dd,

J=8.4, 2.1 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 2H), 4.77 (s, 2H), 2.40 - 2.33 (m, 2H), 2.06 - 1.94 (m, 6H), 1.90 - 1.83 (m, 2H), 1.67 - 1.60 (m, 2H), 1.42 - 1.33 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

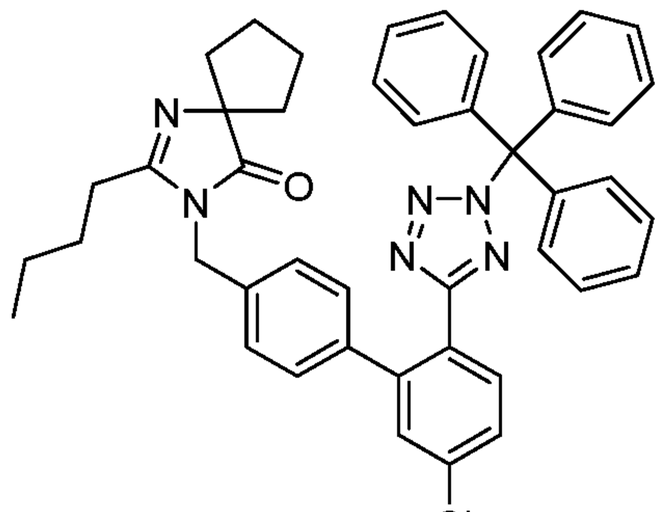
Intermediate 122b: 2-butyl-3-((5'-chloro-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(122b)

Intermediate 122a (1.03 g, 2.45 mmol) was dissolved in toluene (24.5 mL). Dibutyltin oxide (0.611 g, 2.45 mmol) and TMS-N_3 (1.63 mL, 12.3 mmol) were added. The reaction was sealed in a pressure vial and heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature and diluted with EtOAc into a large erlenmeyer. A 10% aqueous solution of ceric ammonium nitrate (6.72 g, 12.3 mmol) was added slowly to mild bubbling. An aliquot of the reaction was added to an aqueous 0.02 M iron trichloride solution to confirm complete consumption of azide (no red color). The layers were separated and the organic layer was further washed twice with saturated NH_4Cl, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 40 g silica gel olumn, 19 minute gradient of 0 to 20% MeOH in DCM) to give **Intermediate 122b** (0.946 g, 2.04 mmol, 83%) as a tan solid. LC-MS (Method A2) RT = 0.93 min, MS (ESI) *m/z*: 463.3 $(M+H)^+$. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.03 (d, *J*=8.5 Hz, 1H), 7.56 (dd, *J*=8.3, 2.2 Hz, 1H), 7.47 (d, *J*=2.2 Hz, 1H), 7.25 - 7.17 (m, 4H), 4.73 (s, 2H), 2.33 - 2.27 (m, 2H), 2.06 (d, *J*=6.6 Hz, 1H), 1.99 - 1.93 (m, 2H), 1.93 - 1.86 (m, 4H), 1.80 (dd, *J*=11.6, 5.0 Hz, 3H), 1.58 (dt, *J*=15.3, 7.6 Hz, 2H), 1.39 - 1.30 (m, 2H), 0.88 (t, *J*=7.3 Hz, 3H)

Intermediate 122c: 2-butyl-3-((5'-chloro-2'-(2-trityl-2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(122c)

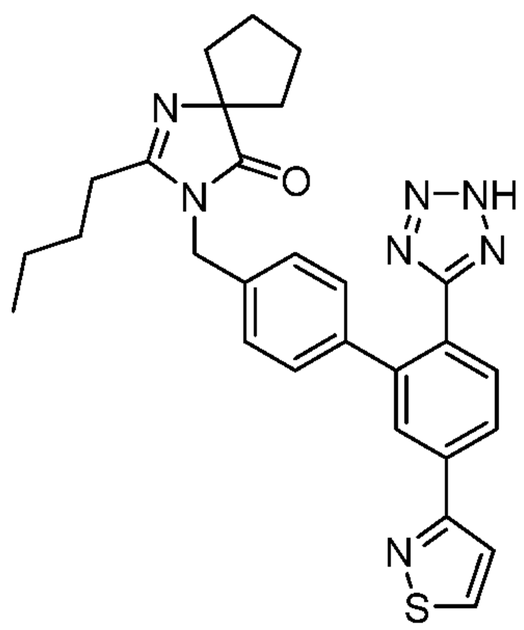
Intermediate 122b (0.900 g, 1.94 mmol), TEA (0.352 mL, 2.53 mmol) and tritylchloride (0.623 g, 2.24 mmol) were dissolved in DCM (9.72 mL). After stirring for 3 hours, the reaction was diluted with DCM and washed with 1M K_2HPO_4, then brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 122c** (0.879 g, 1.25 mmol, 63%) as a white solid. LC-MS (Method A2) RT = 1.26 min, MS (ESI) *m/z*: 705.5 $(M+H)^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.92 (d, *J*=8.5 Hz, 1H), 7.46 (dd, *J*=8.3, 2.2 Hz, 1H), 7.41 - 7.35 (m, 4H), 7.32 - 7.27 (m, 6H), 7.11 (d, *J*=8.0 Hz, 2H), 6.97 - 6.90 (m, 8H), 2.25 (t, *J*=7.8 Hz, 2H), 2.06 - 1.95 (m, 6H), 1.84 (br. s., 2H), 1.61 - 1.52 (m, 2H), 1.34 - 1.26 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H).

Example 122: 2-butyl-3-((4''-methyl-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

Intermediate 122c (20 mg, 0.028 mmol), p-tolylboronic acid (11.6 mg, 0.085 mmol), and 2nd Generation XPHOS Precatalyst (2.23 mg, 2.84 µmol) were dissolved in toluene (1.13 mL), EtOH (284 µL), and tripotassium phosphate (2 M aq, 28.4 µL, 0.057 mmol). The reaction was heated at 100 °C for 18 hours. The reaction was cooled to ambient temperature then diluted with EtOAc, filtered through celite/Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in DCM (1.42 mL). Triethylsilane (22.6 µL, 0.142 mmol) and TFA (109 µL, 1.42 mmol) were added. After 30 minutes, the reaction was concentrated *in vacuo*. The crude material was purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 40-80% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to give **Example 122** (3.9 mg, 7.14 µmol, 25%). LC-MS

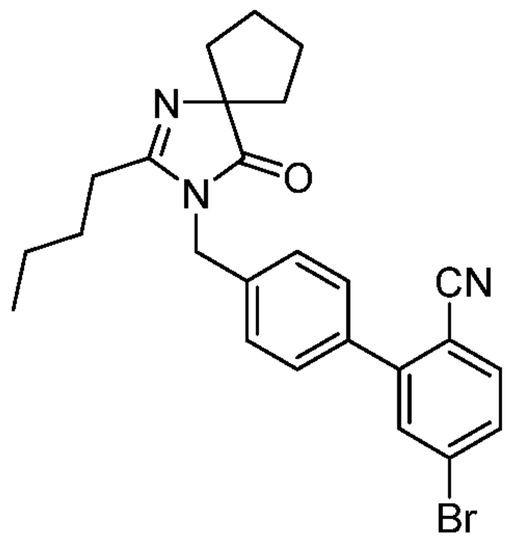
(Method A2) RT = 1.14 min, MS (ESI) *m/z*: 519.5 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.81 (d, *J*=7.3 Hz, 1H), 7.74 - 7.64 (m, 4H), 7.31 (d, *J*=7.9 Hz, 2H), 7.16 (d, *J*=7.3 Hz, 2H), 7.07 (d, *J*=7.6 Hz, 2H), 4.67 (s, 2H), 2.35 (s, 3H), 2.29 (t, *J*=7.5 Hz, 2H), 1.89 - 1.77 (m, 6H), 1.67 (d, *J*=6.4 Hz, 2H), 1.45 (quin, *J*=7.4 Hz, 2H), 1.24 (dq, *J*=14.6, 7.1 Hz, 2H), 0.78 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

Example 123: 2-butyl-3-((5'-(isothiazol-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



(ex. 123)

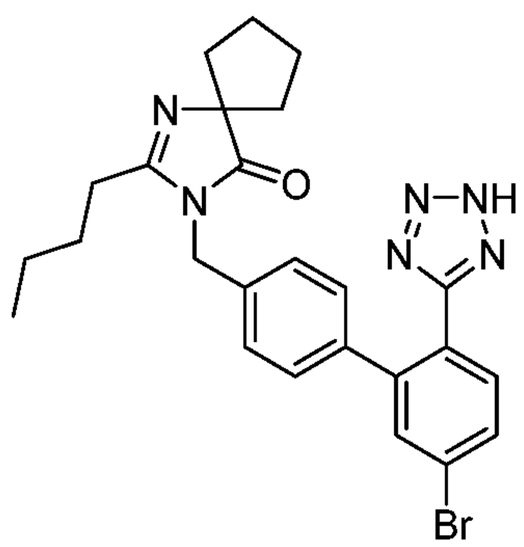
Intermediate 123a: 5-bromo-4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(123a)

Intermediate 033a was reacted with 4-bromo-2-iodobenzonitrile in a method analogous to **Intermediate 122a** to give **Intermediate 123a**. LC-MS (Method A2) RT = 0.89 min, MS (ESI) *m/z*: 464 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=1.4 Hz, 1H), 7.66 - 7.59 (m, 2H), 7.55 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.3 Hz, 2H), 4.77 (s, 2H), 2.40 - 2.33 (m, 2H), 2.06 - 1.94 (m, 5H), 1.91 - 1.82 (m, 2H), 1.63 (dt, *J*=15.4, 7.7 Hz, 3H), 1.42 - 1.32 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H).

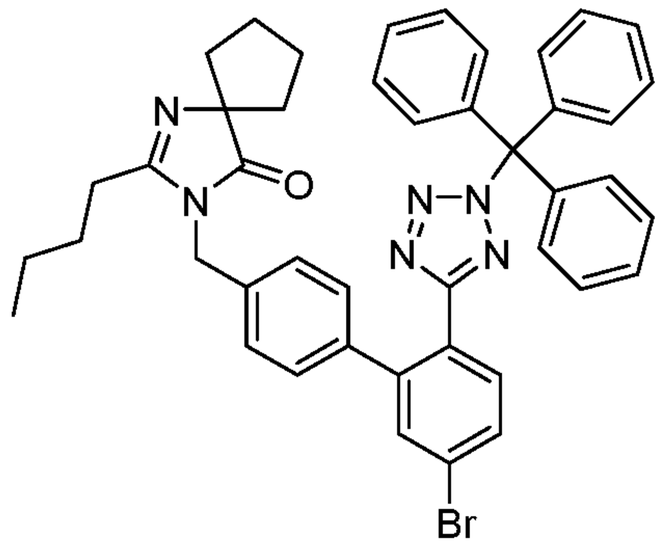
Intermediate 123b: 3-((5'-bromo-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one



(123b)

Intermediate 123a was reacted in a method analogous to **Intermediate 122b** to give **Intermediate 123b**. LC-MS (Method A2) RT = 0.79 min, MS (ESI) *m/z*: 507 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J*=8.3 Hz, 1H), 7.71 (dd, *J*=8.3, 1.9 Hz, 1H), 7.63 (d, *J*=1.9 Hz, 1H), 7.25 - 7.20 (m, 2H), 7.18 - 7.13 (m, 2H), 4.72 (s, 2H), 2.34 - 2.26 (m, 2H), 1.99 - 1.87 (m, 6H), 1.85 - 1.74 (m, 3H), 1.58 (dt, *J*=15.3, 7.6 Hz, 2H), 1.37 - 1.32 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H).

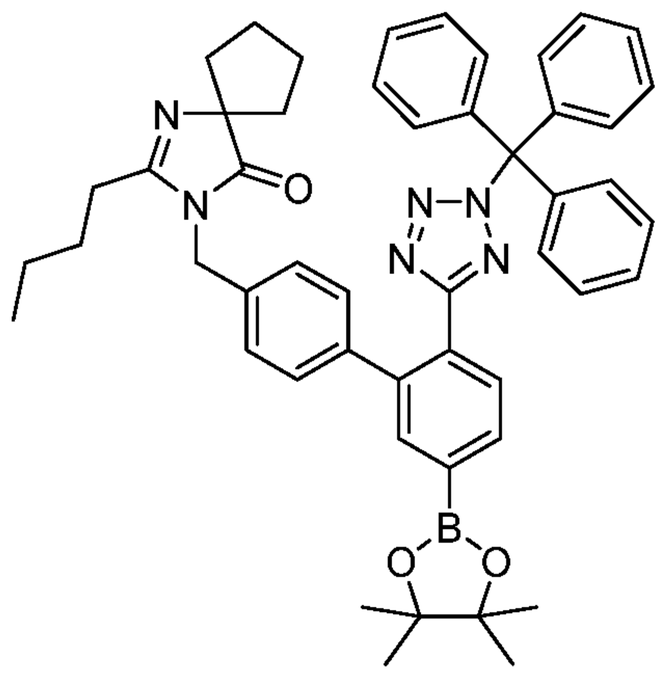
Intermediate 123c: 3-((5'-bromo-2'-(2-trityl-2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one



(123c)

Intermediate 123b was reacted in a method analogous to **Intermediate 122c** to give **Intermediate 123c**. LC-MS (Method A2) RT = 1.09 min, MS (ESI) *m/z*: 750 $(M+H)^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.85 (d, *J*=8.3 Hz, 1H), 7.62 (dd, *J*=8.3, 1.9 Hz, 1H), 7.55 (d, *J*=2.2 Hz, 1H), 7.40 - 7.35 (m, 3H), 7.32 - 7.26 (m, 7H), 7.11 (d, *J*=8.0 Hz, 2H), 6.96 - 6.91 (m, 7H), 4.59 (s, 2H), 2.28 - 2.23 (m, 2H), 2.05 - 1.97 (m, 6H), 1.84 (d, *J*=5.8 Hz, 2H), 1.33 - 1.27 (m, 4H), 0.87 (t, *J*=7.3 Hz, 3H).

Intermediate 123d: 2-butyl-3-((5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2'-(2-trityl-2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one



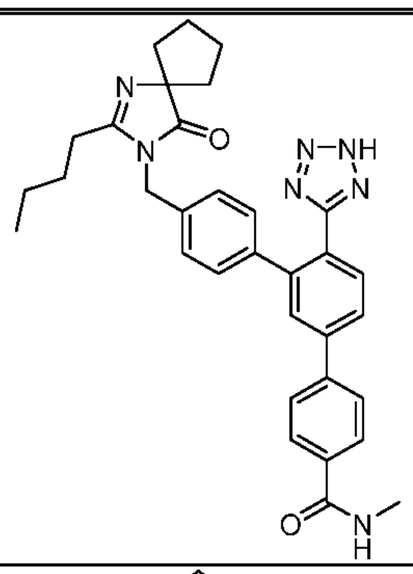
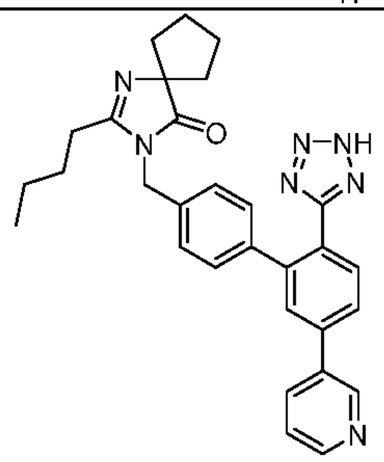
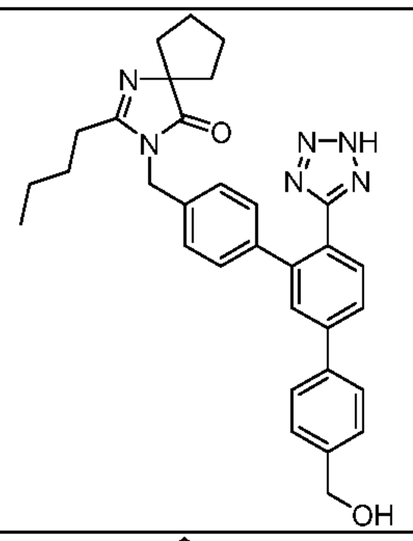
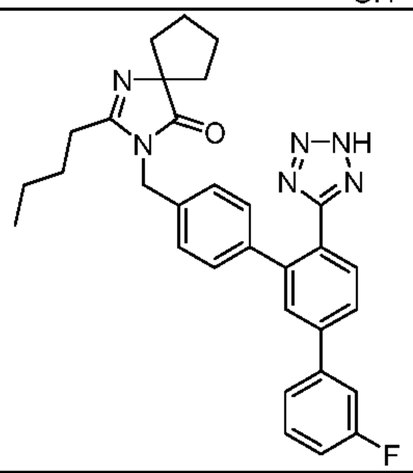
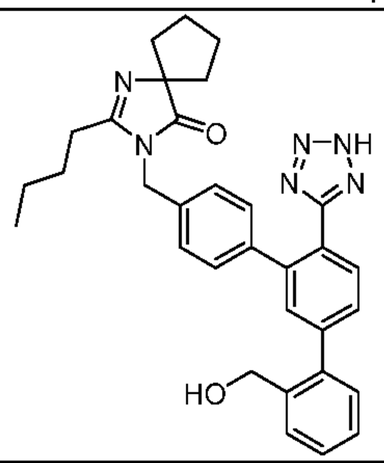
(123d)

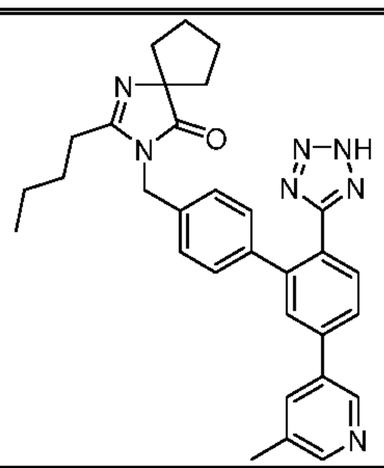
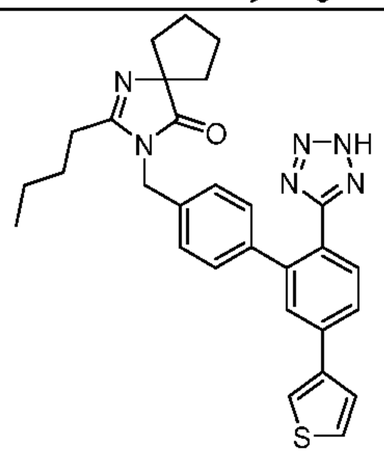
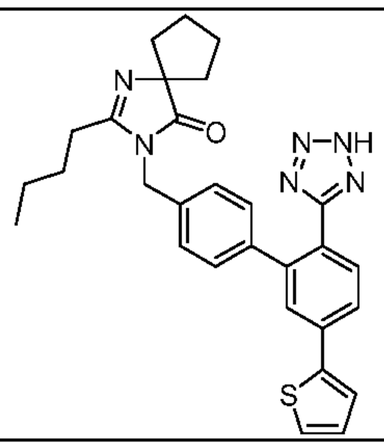
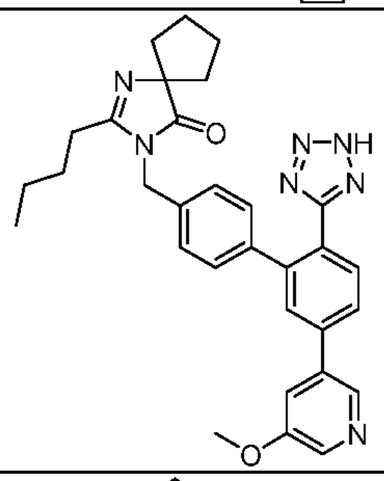
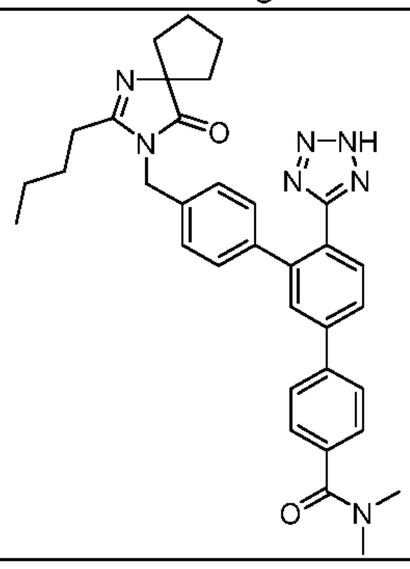
Intermediate 123c (540 mg, 0.720 mmol), bispinacolatodiboron (274 mg, 1.08 mmol), and KOAc (177 mg, 1.80 mmol) were dissolved in 1,4-dioxane (7.20 mL) and degassed for 5 minutes by bubbling with Ar. $PdCl_2$(dppf)-CH_2Cl_2 Adduct (47.1 mg, 0.058 mmol) was added and the reaction degassed for an additional 10 minutes. The reaction was heated at 130 °C in the microwave for 60 minutes. The reaction was diluted with EtOAc and washed with H_2O then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 40 g silica gel column, 19 minute gradient of 0 to 100% EtOAc in hexanes) to give **Intermediate 123d** (350 mg, 0.439 mmol, 61%) as a white solid. LC-MS (Method A2) RT = 1.12 min, MS (ESI) *m/z*: 798 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=7.7 Hz, 1H), 7.90 (d, *J*=6.9 Hz, 1H), 7.80 (s, 1H), 7.41 - 7.34 (m, 5H), 7.31 - 7.26 (m, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 6.97 - 6.90 (m, 10H), 4.59 (s, 2H), 2.28 - 2.21 (m, 2H), 2.09 - 1.97 (m, 6H), 1.88 - 1.81 (m, 2H), 1.37 (s, 12H), 1.35 - 1.30 (m, 4H), 0.89 (t, *J*=7.3 Hz, 3H).

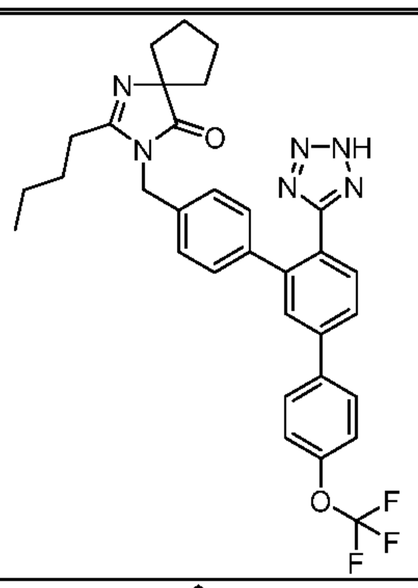
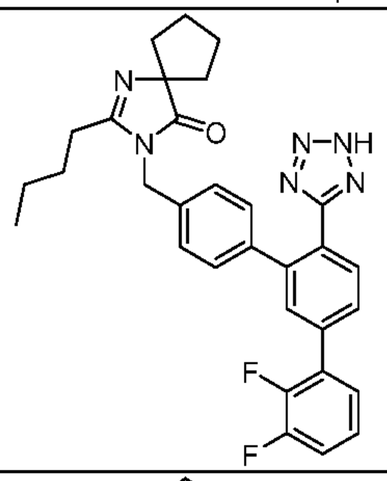
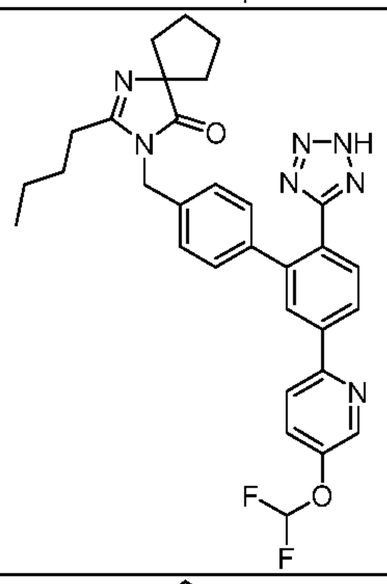
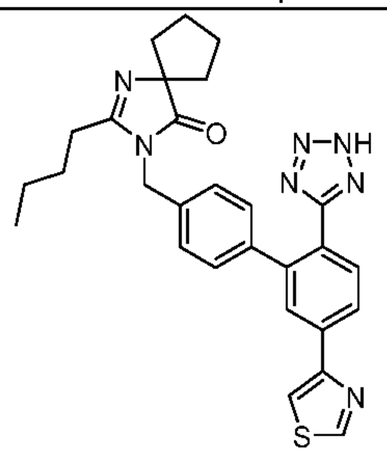
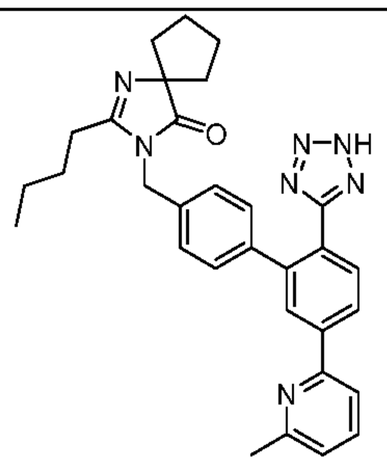
Example 123: 2-butyl-3-((5'-(isothiazol-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one

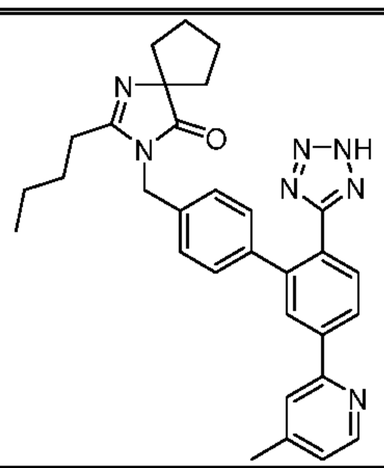
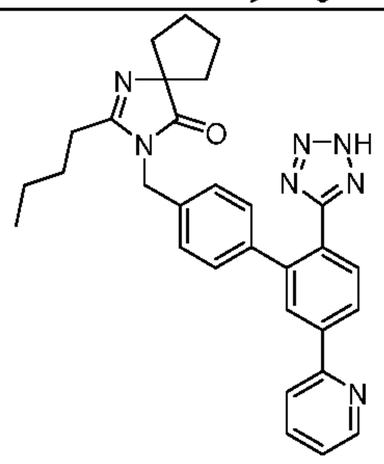
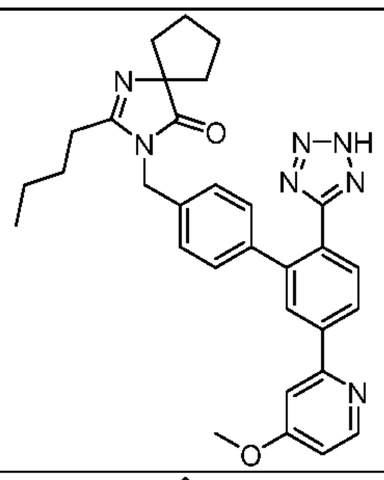
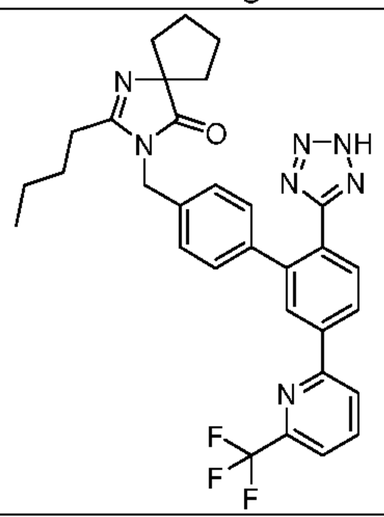
Intermediate 123d was reacted with 3-bromoisothiazole in a method analogous to **Example 122** to give **Example 123** (5.9 mg, 11.5 μmol, 46%). LC-MS (Method A1) RT = 1.39 min, MS (ESI) *m/z*: 512.4 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 9.18 (d, *J*=4.6 Hz, 1H), 8.12 (br d, *J*=7.9 Hz, 1H), 8.09 - 8.01 (m, 2H), 7.75 (br d, *J*=7.9 Hz, 1H), 7.17 (br d, *J*=7.9 Hz, 2H), 7.07 (br d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.32 (t, *J*=7.6 Hz, 2H), 1.90 - 1.77 (m, 6H), 1.67 (br d, *J*=6.7 Hz, 2H), 1.49 (quin, *J*=7.5 Hz, 2H), 1.27 (dq, *J*=14.9, 7.4 Hz, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed).

The compounds listed in the table below were synthesized using the same methods that were used to prepare Example 122 and Example 123.

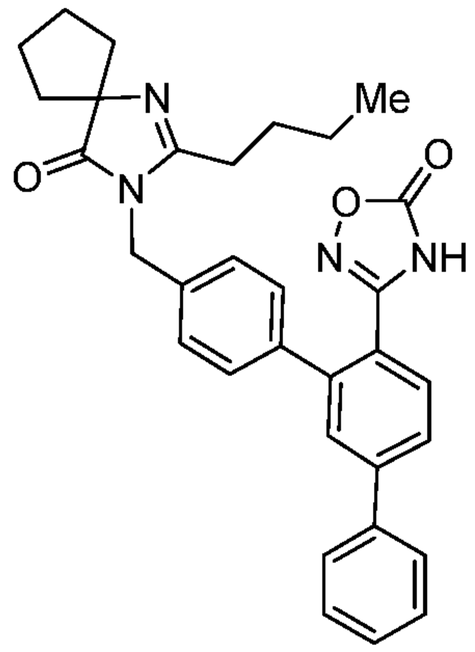
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
124		561.677	562.0; 1.44 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (br s, 1H), 7.98 - 7.87 (m, 5H), 7.82 - 7.73 (m, 2H), 7.18 (br d, *J*=7.7 Hz, 2H), 7.08 (br d, *J*=8.0 Hz, 2H), 4.68 (s, 2H), 2.81 (d, *J*=4.4 Hz, 3H), 2.29 (br t, *J*=7.4 Hz, 2H), 1.90 - 1.76 (m, 6H), 1.66 (br d, *J*=7.7 Hz, 2H), 1.50 - 1.41 (m, 2H), 1.29 - 1.18 (m, 2H), 0.78 (br t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
125		505.613	505.9; 1.48 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (d, *J*=1.6 Hz, 1H), 8.62 (d, *J*=3.8 Hz, 1H), 8.24 (br d, *J*=8.0 Hz, 1H), 7.90 (dd, *J*=8.0, 1.6 Hz, 1H), 7.84 - 7.74 (m, 2H), 7.53 (dd, *J*=7.9, 4.8 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 2H), 7.09 (d, *J*=8.1 Hz, 2H), 4.69 (s, 2H), 2.31 (t, *J*=7.5 Hz, 2H), 1.90 - 1.76 (m, 6H), 1.67 (br d, *J*=6.6 Hz, 2H), 1.49 (quin, *J*=7.5 Hz, 2H), 1.27 (dq, *J*=14.9, 7.4 Hz, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
126		534.651	535.2; 1.48 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (br d, *J*=8.2 Hz, 1H), 7.81 - 7.71 (m, 3H), 7.45 (br d, *J*=7.9 Hz, 2H), 7.29 - 7.04 (m, 5H), 4.73 (s, 2H), 4.56 (s, 2H), 2.38 (br t, *J*=7.4 Hz, 2H), 1.92 - 1.66 (m, 7H), 1.54 - 1.41 (m, 2H), 1.30 - 1.18 (m, 4H), 0.80 (br t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
127		522.616	523.0; 1.86 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 - 7.72 (m, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.64 - 7.57 (m, 3H), 7.55 - 7.49 (m, 1H), 7.24 - 7.14 (m, 3H), 7.02 (br d, *J*=8.0 Hz, 2H), 4.65 (s, 2H), 2.30 (br t, *J*=7.5 Hz, 2H), 1.92 - 1.75 (m, 8H), 1.66 (br d, *J*=7.9 Hz, 2H), 1.44 (quin, *J*=7.3 Hz, 2H), 1.27 - 1.17 (m, 3H) (1 exchangeable proton not observed)
128		534.651	535.0; 1.40 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (dd, *J*=18.5, 7.8 Hz, 2H), 7.45 - 7.31 (m, 5H), 7.14 (br d, *J*=7.9 Hz, 2H), 6.99 (br d, *J*=7.9 Hz, 2H), 4.64 (s, 2H), 4.49 (s, 2H), 2.73 (s, 1H), 2.30 (br t, *J*=7.5 Hz, 2H), 1.88 - 1.75 (m, 6H), 1.66 (br d, *J*=6.7 Hz, 2H), 1.46 (quin, *J*=7.5 Hz, 2H), 1.24 (sxt, *J*=7.4 Hz, 2H), 0.77 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
129		519.640	520.1; 1.37 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.91 (br d, *J*=7.9 Hz, 1H), 7.82 (s, 1H), 7.78 (d, *J*=7.9 Hz, 1H), 7.20 (br d, *J*=7.9 Hz, 2H), 7.10 (br d, *J*=7.9 Hz, 2H), 4.69 (s, 2H), 2.39 (s, 3H), 2.31 (br t, *J*=7.5 Hz, 2H), 1.89 - 1.79 (m, 6H), 1.67 (br d, *J*=5.8 Hz, 2H), 1.49 (quin, *J*=7.5 Hz, 2H), 1.33 - 1.23 (m, 2H), 0.82 (t, *J*=7.3 Hz, 3H) (1 exchangeble proton not observed)
130		510.653	511.4; 1.61 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (br s, 1H), 7.91 (br d, *J*=8.2 Hz, 1H), 7.84 (s, 1H), 7.75 - 7.67 (m, 3H), 7.21 - 7.14 (m, 2H), 7.10 (br d, *J*=7.9 Hz, 2H), 4.69 (s, 2H), 2.31 (br t, *J*=7.5 Hz, 2H), 1.90 - 1.78 (m, 6H), 1.68 (br d, *J*=5.2 Hz, 2H), 1.50 (quin, *J*=7.6 Hz, 2H), 1.28 (sxt, *J*=7.4 Hz, 2H), 0.82 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
131		510.653	511.2; 1.71 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.83 (br s, 1H), 7.72 (br s, 3H), 7.65 (br d, *J*=4.9 Hz, 1H), 7.24 - 7.05 (m, 4H), 4.69 (s, 2H), 2.31 (br t, *J*=7.2 Hz, 2H), 1.93 - 1.79 (m, 6H), 1.67 (br s, 2H), 1.49 (quin, *J*=7.4 Hz, 2H), 1.34 - 1.22 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
132		535.639	536.5; 1.36 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.33 (d, *J*=2.1 Hz, 1H), 7.90 (br d, *J*=8.1 Hz, 1H), 7.82 (s, 1H), 7.79 - 7.73 (m, 2H), 7.20 (br d, *J*=7.9 Hz, 2H), 7.08 (br d, *J*=8.0 Hz, 2H), 4.68 (s, 2H), 3.92 (s, 3H), 2.31 (br t, *J*=7.4 Hz, 2H), 1.89 - 1.77 (m, 6H), 1.67 (br d, *J*=6.6 Hz, 2H), 1.54 - 1.42 (m, 2H), 1.30 - 1.24 (m, 2H), 0.80 (br t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
133		575.703	576.2; 1.43 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (br d, *J*=7.9 Hz, 2H), 7.82 (br d, *J*=7.9 Hz, 1H), 7.74 (br d, *J*=7.9 Hz, 1H), 7.72 (s, 1H), 7.52 (br d, *J*=8.2 Hz, 2H), 7.20 (br d, *J*=7.9 Hz, 2H), 7.06 (br d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.99 (br d, *J*=17.4 Hz, 6H), 2.32 (br t, *J*=7.5 Hz, 2H), 1.90 - 1.79 (m, 6H), 1.67 (br d, *J*=5.8 Hz, 2H), 1.49 (quin, *J*=7.5 Hz, 2H), 1.31 - 1.24 (m, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)

Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
134		588.623	589.2; 1.99 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (br d, *J*=8.9 Hz, 2H), 7.84 - 7.77 (m, 1H), 7.74 (br d, *J*=8.2 Hz, 1H), 7.71 (s, 1H), 7.48 (br d, *J*=7.9 Hz, 2H), 7.20 (br d, *J*=7.9 Hz, 2H), 7.06 (br d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.32 (br t, *J*=7.5 Hz, 2H), 1.89 - 1.78 (m, 6H), 1.67 (br d, *J*=4.9 Hz, 2H), 1.49 (quin, *J*=7.5 Hz, 2H), 1.32 - 1.22 (m, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
135		540.606	541.1; 2.27 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (q, *J*=7.9 Hz, 2H), 7.67 (s, 1H), 7.56 - 7.47 (m, 2H), 7.39 - 7.31 (m, 1H), 7.17 (br d, *J*=7.9 Hz, 2H), 7.09 (br d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.29 (br t, *J*=7.5 Hz, 2H), 1.90 - 1.76 (m, 6H), 1.67 (br d, *J*=6.1 Hz, 2H), 1.46 (quin, *J*=7.3 Hz, 2H), 1.25 (sxt, *J*=7.3 Hz, 2H), 0.79 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
136		571.620	572.4; 1.60 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (br s, 1H), 7.98 - 7.90 (m, 1H), 7.84 (s, 1H), 7.82 - 7.76 (m, 1H), 7.70 (s, 1H), 7.52 - 7.44 (m, 1H), 7.15 - 7.07 (m, 2H), 6.98 (br s, 2H), 4.65 (s, 2H), 2.33 (d, *J*=5.3 Hz, 2H), 2.23 - 2.15 (m, 1H), 1.89 - 1.73 (m, 6H), 1.59 (d, *J*=5.9 Hz, 2H), 1.41 (br s, 2H), 1.12 (br s, 2H), 0.76 - 0.65 (m, 3H) (1 exchangeable proton not observed)
137		511.641	512.5; 1.33 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.42 (br s, 1H), 8.15 (br d, *J*=8.0 Hz, 1H), 8.11 (s, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.16 (br d, *J*=7.8 Hz, 2H), 7.10 (br d, *J*=8.0 Hz, 2H), 4.69 (s, 2H), 2.30 (br t, *J*=7.4 Hz, 2H), 1.92 - 1.77 (m, 6H), 1.67 (br d, *J*=6.8 Hz, 2H), 1.55 - 1.42 (m, 2H), 1.32 - 1.20 (m, 2H), 0.80 (br t, *J*=7.2 Hz, 3H) (1 exchangeable proton not observed)
138		519.640	520.1; 1.55 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (br d, *J*=7.6 Hz, 1H), 8.15 (s, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.81 (t, *J*=7.6 Hz, 1H), 7.77 (br d, *J*=6.4 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.17 (br d, *J*=7.0 Hz, 2H), 7.09 (br d, *J*=7.9 Hz, 2H), 4.69 (s, 2H), 2.55 (s, 3H), 2.31 (t, *J*=7.5 Hz, 2H), 1.93 - 1.76 (m, 6H), 1.68 (br d, *J*=7.6 Hz, 2H), 1.47 (quin, *J*=7.5 Hz, 2H), 1.26 (dq, *J*=14.8, 7.4 Hz, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)

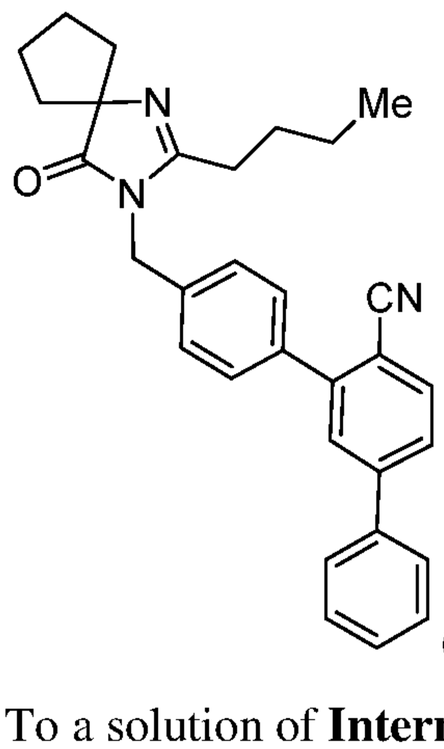
Ex #	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR
139		519.640	519.9; 1.52 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J*=4.9 Hz, 1H), 8.06 (br d, *J*=7.9 Hz, 1H), 8.01 (s, 1H), 7.89 (s, 1H), 7.70 (br s, 1H), 7.18 (br dd, *J*=10.7, 5.5 Hz, 3H), 7.02 (br d, *J*=7.9 Hz, 2H), 4.67 (s, 2H), 2.39 (s, 3H), 2.33 (br t, *J*=7.5 Hz, 2H), 1.94 - 1.77 (m, 6H), 1.68 (br d, *J*=7.0 Hz, 2H), 1.50 (quin, *J*=7.6 Hz, 2H), 1.33 - 1.22 (m, 2H), 0.81 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
140		505.613	506.2; 0.71 min (Method A2)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (br d, *J*=4.3 Hz, 1H), 8.12 - 8.00 (m, 3H), 7.89 (br t, *J*=7.2 Hz, 1H), 7.73 (br d, *J*=7.6 Hz, 1H), 7.41 - 7.32 (m, 1H), 7.19 (br d, *J*=7.6 Hz, 2H), 7.03 (br d, *J*=7.9 Hz, 2H), 4.67 (s, 2H), 2.34 (br t, *J*=7.5 Hz, 2H), 1.90 - 1.78 (m, 6H), 1.68 (br d, *J*=7.3 Hz, 2H), 1.51 (quin, *J*=7.5 Hz, 2H), 1.29 (dq, *J*=15.0, 7.5 Hz, 2H), 0.83 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)
141		535.652	536.1; 0.68 min (Method A2)	^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br d, *J*=5.8 Hz, 1H), 7.69 - 7.57 (m, 3H), 7.14 (d, *J*=2.2 Hz, 1H), 6.95 (dd, *J*=5.9, 2.3 Hz, 1H), 6.90 - 6.80 (m, 4H), 4.64 (s, 2H), 4.02 (s, 3H), 2.32 - 2.23 (m, 2H), 2.10 - 1.95 (m, 7H), 1.89 - 1.81 (m, 1H), 1.62 (dt, *J*=15.4, 7.7 Hz, 2H), 1.36 (dq, *J*=15.0, 7.4 Hz, 2H), 0.91 (t, *J*=7.4 Hz, 3H) (1 exchangeable proton not observed)
142		573.611	574.5; 1.66 min (Method A1)	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (d, *J*=8.2 Hz, 1H), 8.25 - 8.17 (m, 2H), 8.13 (s, 1H), 7.90 (d, *J*=7.6 Hz, 1H), 7.81 (d, *J*=8.2 Hz, 1H), 7.17 (d, *J*=7.9 Hz, 2H), 7.08 (d, *J*=7.9 Hz, 2H), 4.68 (s, 2H), 2.30 (t, *J*=7.6 Hz, 2H), 1.92 - 1.78 (m, 6H), 1.67 (br d, *J*=8.2 Hz, 2H), 1.44 (quin, *J*=7.5 Hz, 2H), 1.24 (dq, *J*=14.8, 7.3 Hz, 2H), 0.78 (t, *J*=7.3 Hz, 3H) (1 exchangeable proton not observed)

Example 143: 3-(4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4H)-one



(Ex. 143)

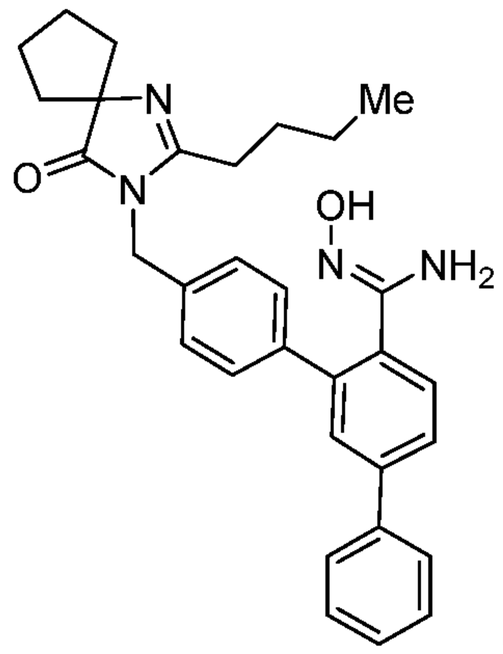
Intermediate 143a: 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(143a)

To a solution of **Intermediate 033a** (160 mg, 0.390 mmol) and **Intermediate 032a** (131 mg, 0.507 mmol) in dioxane (3 mL) was added K_3PO_4 (2 M, aq) (0.585 mL, 1.170 mmol) followed by $PdCl_2(dppf)_2$ (28.5 mg, 0.039 mmol). The resulting mixture was sparged with N_2 for 2 minutes before being sealed and heated at 120 °C for 45 min in the microwave. The reaction mixture was cooled to RT, diluted with EtOAc, washed with 1 M K_2HPO_4, dried over $MgSO_4$, filtered over Celite, and concentrated. The residue was purified by ISCO (40g, 0-100% EtOAc/Hex) to afford **Intermediate 143a** (149 mg, 0.323 mmol, 83 % yield) as a yellow oil. LC-MS (Method A2) RT = 0.95 min, MS (ESI) *m/z*: 462.0 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.83 (d, *J*=7.9 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.64 - 7.57 (m, 4H), 7.53 - 7.40 (m, 3H), 7.30 (d, *J*=8.1 Hz, 2H), 4.76 (s, 2H), 2.39 - 2.33 (m, 2H), 2.04 - 1.90 (m, 6H), 1.90 - 1.80 (m, 2H), 1.61 (dt, *J*=15.5, 7.6 Hz, 2H), 1.42 - 1.30 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H).

Intermediate 143b: (Z)-4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide



(143b)

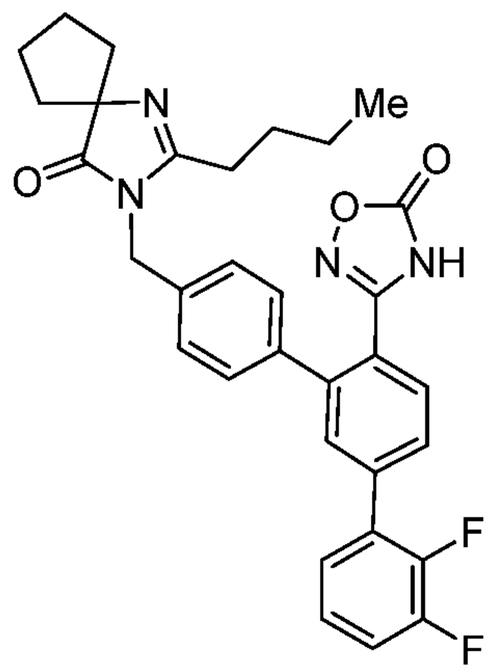
To a suspension of **Intermediate 143a** (145 mg, 0.314 mmol) and hydroxylamine hydrochloride (109 mg, 1.571 mmol) in DMSO (2 mL) was added $NaHCO_3$ (132 mg, 1.571 mmol). The reaction mixture was sealed and heated at 120 °C overnight. The reaction was cooled to RT and H_2O was added. The formed solid was filtered and washed with H_2O. The solid residue was solvated in DCM and washed with 10% LiCl (aq). The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in DMF and purified via preparative HPLC with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 10-100% B over 20 minutes, then a 2-minute hold at 100% B; Flow: 20 mL/min to yield **Intermediate 143b** (9.7 mg, 0.020 mmol. 31%). LC-MS (Method A2) RT = 0.69 min, MS (ESI) *m/z*: 495.1 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.03 - 7.83 (m, 2H), 7.81 - 7.72 (m, 3H), 7.68 (d, *J*=7.9 Hz, 1H), 7.56 - 7.40 (m, 6H), 7.26 (d, *J*=7.9 Hz, 2H), 4.77 (s, 2H), 2.39 (t, *J*=7.6 Hz, 2H), 1.87 (d, *J*=5.8 Hz, 6H), 1.72 (br. s., 2H), 1.52 (quin, *J*=7.4 Hz, 2H), 1.37 - 1.21 (m, 2H), 0.82 (t, *J*=7.3 Hz, 3H).

Example 143: 3-(4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4H)-one

To a solution of **Intermediate 143b** (35 mg, 0.071 mmol) in DMF (2 mL) was added DBU (0.053 mL, 0.354 mmol) followed by CDI (57.4 mg, 0.354 mmol). The reaction was allowed to stir at RT for 5 minutes. The reaction mixture was quenched with a few drops of methanol, filtered, and purified via preparative HPLC with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 30-85% B over 30 minutes, then a 3-minute hold at 100% B; Flow:

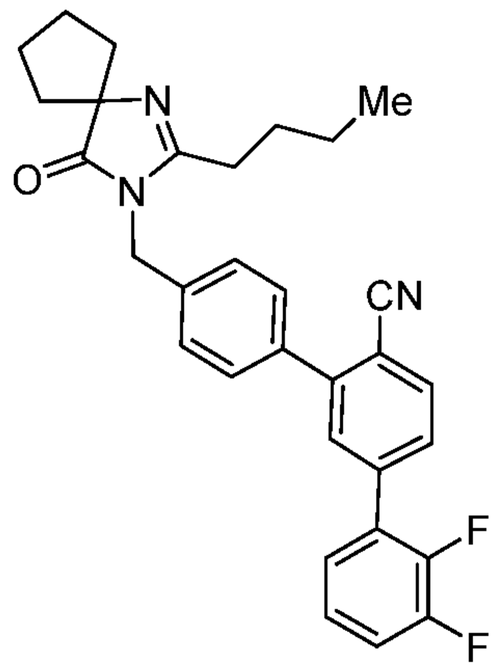
20 mL/min to yield **Example 143** (26.2 mg. 0.047 mmol, 67%). LC-MS (Method A2) RT = 0.87 min, MS (ESI) *m/z*: 521.1 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=8.1 Hz, 1H), 7.81 (d, *J*=7.5 Hz, 2H), 7.76 (d, *J*=5.6 Hz, 2H), 7.54 - 7.48 (m, 2H), 7.47 - 7.37 (m, 3H), 7.22 (d, *J*=7.8 Hz, 2H), 4.75 (s, 2H), 2.33 (t, *J*=7.4 Hz, 2H), 1.92 - 1.79 (m, 6H), 1.73 - 1.63 (m, 2H), 1.49 (quin, *J*=7.4 Hz, 2H), 1.27 (sxt, *J*=7.4 Hz, 2H), 0.81 (t, *J*=7.3 Hz, 3H) One exchangeable proton not observed.

Example 144: 3-(4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2,3-difluoro-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4H)-one



(Ex. 144)

Intermediate 144a: 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2,3-difluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile

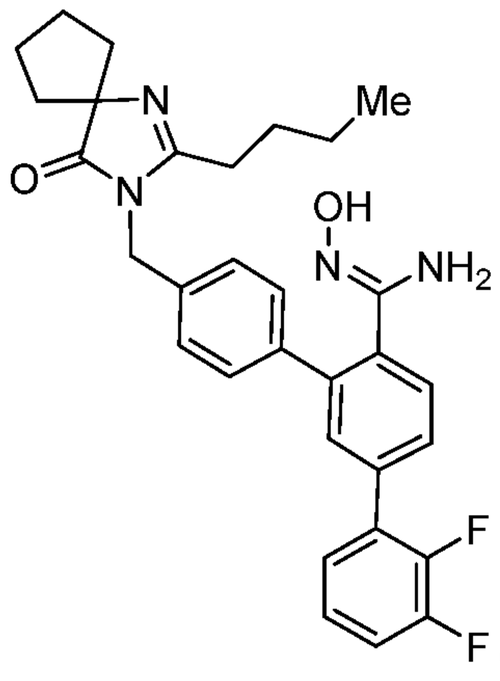


(144a)

Synthesized in an analogous manner to **Intermediate 143a** using **Intermediate 99a** (0.135 g, 0.231 mmol) and (2,3-difluorophenyl)boronic acid (0.102 g, 0.643 mmol) to yield **Intermediate 144a** (0.115 g, 0.231 mmol, 71.9% yield): LC-MS (Method A2) RT = 1.03 min, MS (ESI) *m/z*: 498.0 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.85 (d, *J*=8.1 Hz, 1H), 7.79 - 7.39 (m, 5H), 7.34 - 7.26 (m, 2H), 7.25 - 7.15 (m, 2H), 4.75 (d, *J*=3.3 Hz,

2H), 2.40 - 2.31 (m, 2H), 2.08 - 1.90 (m, 6H), 1.89 - 1.79 (m, 2H), 1.66 - 1.54 (m, 2H), 1.42 - 1.29 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H).

Intermediate 144b: (Z)-4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2,3-difluoro-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide



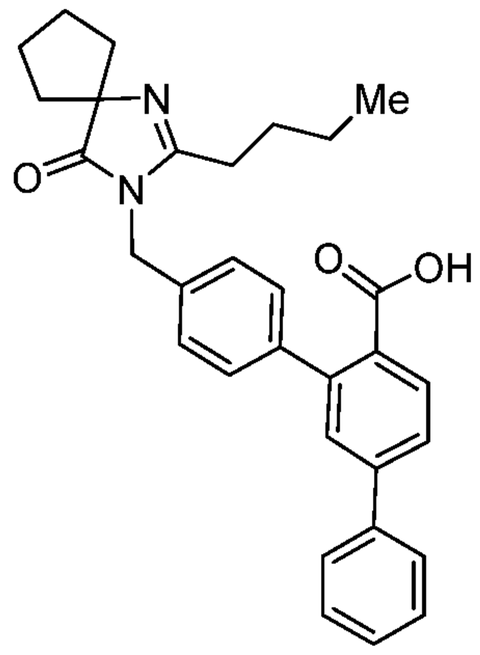
(144b)

Synthesized in an analogous manner to **Intermediate 143b** using **Intermediate 144a** (0.110 g, 0.221 mmol) and potassium *tert*-butoxide (0.184g 2.65 mmol) to yield **Intermediate 144b** (0.035g, 0.066 mmol, 30% yield): LC-MS (Method A2) RT = 0.82 min, MS (ESI) *m/z*: 531.1 $(M+H)^+$. Used without further purification in the next step.

Example 144: 3-(4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2,3-difluoro-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-oxadiazol-5(4H)-one

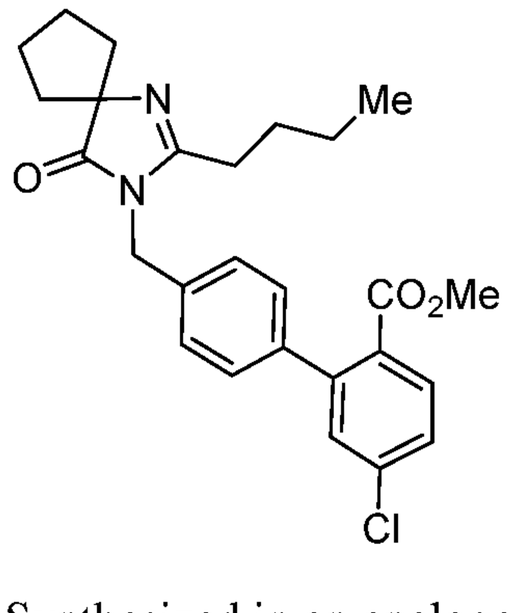
Synthesized in an analogous manner to **Intermediate 143** using **Intermediate 144b** (0.030 g, 0.057 mmol). Purified via preparative HPLC with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 25-65% B over 27 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min to yield **Example 144** (0.005 g, 0.009 mmol, 16% yield): LC-MS (Method A2) RT = 0.98 min, MS (ESI) *m/z*: 557.0 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.81 - 7.69 (m, 2H), 7.62 (s, 1H), 7.53 - 7.43 (m, 2H), 7.41 - 7.27 (m, 3H), 7.19 (d, *J*=7.9 Hz, 2H), 4.72 (s, 2H), 2.32 (t, *J*=7.5 Hz, 2H), 1.89 - 1.77 (m, 6H), 1.67 (d, *J*=7.6 Hz, 2H), 1.52 - 1.41 (m, 2H), 1.30 - 1.19 (m, 2H), 0.78 (t, *J*=7.3 Hz, 3H). One exchangeable proton not observed.

Example 145: 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylic acid



(ex. 145)

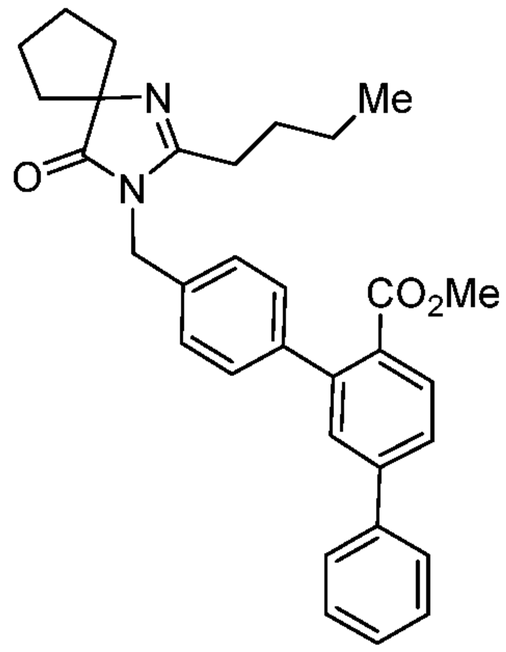
Intermediate 145a: methyl 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-chloro-[1,1'-biphenyl]-2-carboxylate



(145a)

Synthesized in an analogous manner to **Intermediate 143a** using **Intermediate 033a** (0.080 g, 0.195 mmol) and methyl 4-chloro-2-iodobenzoate (0.0694 g, 0.234 mmol) to yield **Intermediate 145a** (0.050 g, 0.110 mmol, 57% yield): LC-MS (Method A2) RT = 0.93 min, MS (ESI) *m/z*: 453.1 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.80 (d, *J*=8.4 Hz, 1H), 7.39 (dd, *J*=8.4, 2.2 Hz, 1H), 7.33 (d, *J*=2.0 Hz, 1H), 7.29 - 7.24 (m, 2H), 7.21 - 7.16 (m, 2H), 4.73 (s, 2H), 3.63 (s, 3H), 2.37 - 2.29 (m, 2H), 2.06 - 1.91 (m, 6H), 1.88 - 1.77 (m, 2H), 1.65 - 1.54 (m, 2H), 1.34 (dq, *J*=14.9, 7.4 Hz, 2H), 0.88 (t, *J*=7.4 Hz, 3H).

Intermediate 145b: methyl 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylate



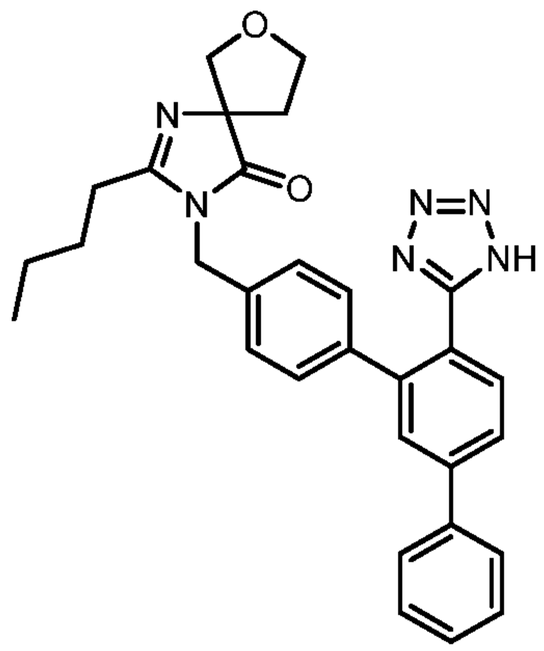
(145b)

Synthesized in an analogous manner to **Intermediate 143a** using **Intermediate 145a** (0.050 g, 0.110 mmol) and phenyl boronic acid (0.020 g, 0.166 mmol) to yield **Intermediate 145b** (0.050 g, 0.076 mmol, 69% yield): LC-MS (Method A2) RT = 0.99 min, MS (ESI) *m/z*: 495.1 $(M+H)^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.97 (d, *J*=8.3 Hz, 1H), 7.69 - 7.62 (m, 3H), 7.58 (d, *J*=1.7 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.44 - 7.39 (m, 1H), 7.38 - 7.35 (m, 1H), 7.31 - 7.27 (m, 1H), 7.23 (d, *J*=8.0 Hz, 2H), 4.77 (s, 2H), 3.68 (s, 3H), 2.41 - 2.35 (m, 2H), 2.09 - 1.94 (m, 6H), 1.90 - 1.80 (m, 2H), 1.67 - 1.58 (m, 2H), 1.43 - 1.32 (m, 2H), 0.93 - 0.88 (m, 3H).

Example 145: 4''-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylic acid

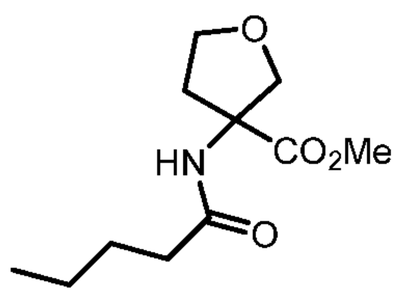
To a vial containing **Intermediate 145b** (0.040 g, 0.081 mmol) was added dioxane (647 µl) followed by MeOH (162 µl). NaOH (1 M aq) (323 µl, 0.323 mmol) was added, and the vial was sealed and heated at 80 °C overnight. The reaction mixture was cooled to RT and concentrated. The residue was dissolved in 2 mL of DMF and purified via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 20-60% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min to yield **Example 145** (0.015 g, 0.030 mmol, 38%): LC-MS (Method A2) RT = 0.91 min, MS (ESI) *m/z*: 481.1 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.81 - 7.76 (m, 1H), 7.76 - 7.69 (m, 3H), 7.56 (s, 1H), 7.51 - 7.45 (m, 2H), 7.41 (d, *J*=7.6 Hz, 3H), 7.18 (d, *J*=7.9 Hz, 2H), 4.73 (s, 2H), 2.34 (t, *J*=7.5 Hz, 2H), 1.91 - 1.77 (m, 6H), 1.68 (d, *J*=7.9 Hz, 2H), 1.48 (quin, *J*=7.4 Hz, 2H), 1.32 - 1.23 (m, 2H), 0.79 (t, *J*=7.3 Hz, 3H). One exchangeable proton not observed.

Example 146: 3-((6'-(1H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 146)

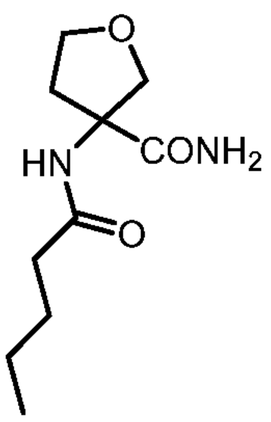
Intermediate 146a: methyl 3-pentanamidotetrahydrofuran-3-carboxylate



(146a)

To a solution of methyl 3-aminotetrahydrofuran-3-carb oxylate hydrochloride (1.0 g, 5.5 mmol) in CH_2Cl_2 (18 mL) was added 25% K_2CO_3 (18 mL, 36 mmol). The mixture was cooled with an ice bath. Pentanoyl chloride (0.91 mL, 7.7 mmol) in CH_2Cl_2 (4 mL) was added dropwise to the stirred solution. The reaction mixture was stirred at 0 °C for 2 h, and at rt for 3 h. The organic phase was collected. The aqueous phase was extracted (2X) with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (0% to 100% EtOAc in hexane over 15 min using a 40 g silica gel cartridge) to give **Intermediate 146a** (1.1 g, 4.8 mmol, 87 % yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (br s, 1H), 4.17 (d, *J*=9.6 Hz, 1H), 4.06 - 3.98 (m, 2H), 3.95 (d, *J*=9.4 Hz, 1H), 3.78 (s, 3H), 2.59 (dt, *J*=13.2, 7.8 Hz, 1H), 2.28 - 2.19 (m, 3H), 1.68 - 1.60 (m, 3H), 1.42 - 1.32 (m, 2H), 0.94 (t, *J*=7.3 Hz, 3H). LC-MS (Method A2): RT = 0.62 min, MS (ESI) m/z: 230.1 $(M+H)^+$.

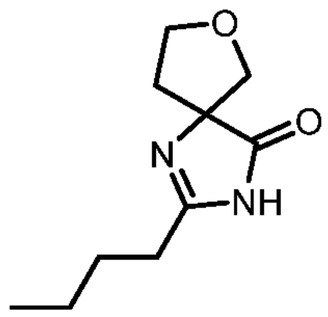
Intermediate 146b: 3-pentanamidotetrahydrofuran-3-carboxamide



(146b)

A mixture of **Intermediate 146a** (1.0 g, 4.4 mmol), NaCN (0.032 g, 0.65 mmol) in 7.0 N ammonia in MeOH (16 ml, 110 mmol) was sealed in a pressure flask and heated at 60 °C over the weekend. LC-MS indicated completion of reaction. Without removing the solvent, the crude product **Intermediate 146b** was taken to the next step. LC-MS (Method A2): RT = 0.50 min, MS (ESI) m/z: 215.1 $(M+H)^+$.

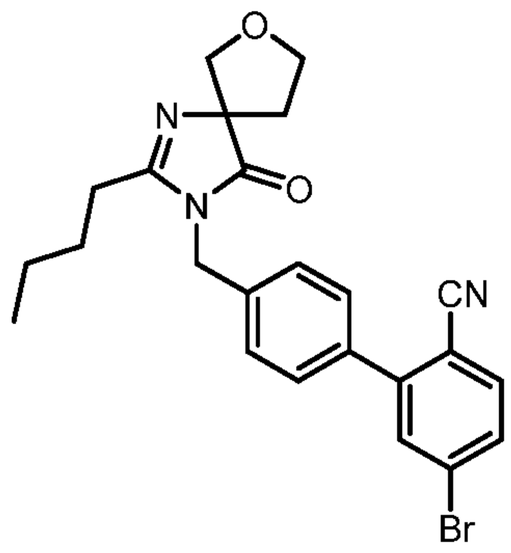
Intermediate 146c: 2-butyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one



(146c)

To a solution of **Intermediate 146b** (0.9 g, 4.20 mmol) in MeOH (15 mL) was added 2.0 N NaOH (11 mL, 21 mmol). The reaction mixture was heated at 50 °C overnight. LC-MS indicated completion of reaction. After cooling to rt, the reaction mixture was acidified with 3.0 N HCl to pH 6-7, extracted with THF/EtOAc (2 : 1, 3 x 80 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give **Intermediate 146c** (0.57 g, 2.9 mmol, 69 % yield) as oil. It was used for the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 - 4.09 (m, 2H), 3.98 - 3.88 (m, 2H), 2.51 (t, *J*=7.7 Hz, 2H), 2.35 (dtd, *J*=12.4, 7.9, 1.4 Hz, 1H), 2.16 (dt, *J*=12.2, 6.0 Hz, 1H), 1.69 (quin, *J*=7.6 Hz, 2H), 1.48 - 1.39 (m, 2H), 0.98 (td, *J*=7.3, 0.8 Hz, 3H). LC-MS (Method A2): RT = 0.45 min, MS (ESI) m/z: 197.1 $(M+H)^+$.

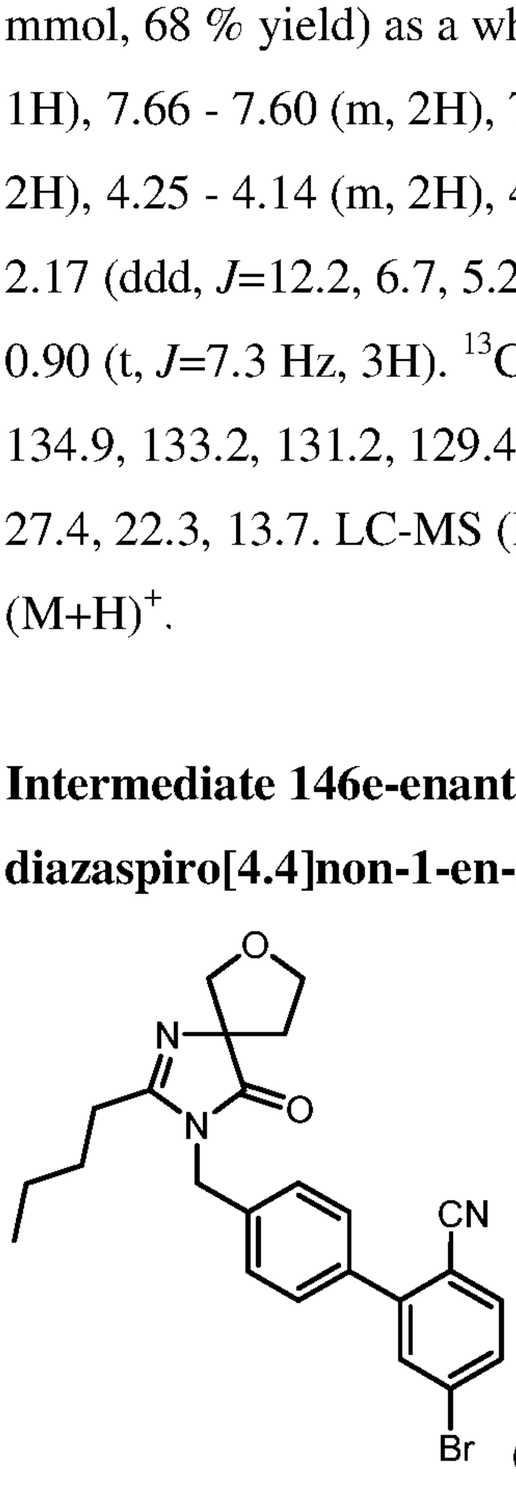
Intermediate 146d-racemate: 5-bromo-4'-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(146d-racemate)

Intermediate 146c (570 mg, 2.9 mmol) was dissolved in DMF (12 ml). NaH (128 mg, 3.2 mmol) was added. The mixture was stirred at rt for 15min, **I-002** (1.1 g, 3.1 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. LC-MS indicated completion of reaction. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (5% to 100% EtOAc in hexane over 18 min using a 40 g silica gel cartridge) to yield **Intermediate 146d**-racemate (920 mg, 2.0 mmol, 68 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=1.1 Hz, 1H), 7.66 - 7.60 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 4.84 - 4.71 (m, 2H), 4.25 - 4.14 (m, 2H), 4.03 - 3.97 (m, 1H), 3.95 - 3.90 (m, 1H), 2.44 - 2.35 (m, 3H), 2.17 (ddd, *J*=12.2, 6.7, 5.2 Hz, 1H), 1.66 (quin, *J*=7.6 Hz, 2H), 1.37 (sxt, *J*=7.4 Hz, 2H), 0.90 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7, 163.3, 146.2, 137.4, 136.6, 134.9, 133.2, 131.2, 129.4, 128.0, 127.4, 117.9, 110.1, 76.2, 75.8, 69.1, 43.5, 38.0, 28.8, 27.4, 22.3, 13.7. LC-MS (Method A2): RT = 0.91 min, MS (ESI) m/z: 466.4 and 468.4 $(M+H)^+$.

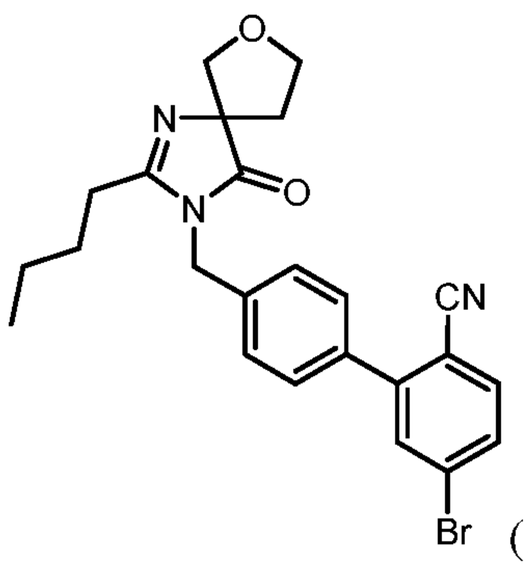
Intermediate 146e-enantiomer 1: 5-bromo-4'-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(146e-enantiomer 1)

Intermediate 146d-racemate (920 mg, 2.0 mmol) was resolved into two peaks by chiral HPLC using a Berger MG II instrument with the following preparative chromatographic conditions: Column: Chiralpak AD-H, 30 x 250 mm, 5 micron; Mobile Phase: 15% IPA/ 85% CO_2; Flow Conditions: 70 mL/min, 120 Bar, 40 °C; Detector Wavelength: 220 nm; injection details: 0.5 mL of ~26mg/mL in IPA:MeOH (1:1). Purity of each fraction was determined using the analytical chromatographic condition below: Instrument: Aurora Analytical SFC; Column: Chiralpak IC, 4.6 x 100 mm, 3 micron; Mobile Phase: 15% IPA / 85% CO_2; Flow Conditions: 1.0 mL/min, 150 Bar, 40 °C; Detector Wavelength: 220 nm; Injection Details: 5µL of ~1mg/mL in IPA. Peak 1 was collected and concentrated to give **Intermediate 146e**-enantiomer 1 (400 mg, 0.86 mmol, 44 % yield): enantiomeric excess > 99%. Chiral analytical RT = 9.4 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.66 (m, 1H), 7.65 - 7.59 (m, 2H), 7.57 - 7.51 (m, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 4.81 - 4.71 (m, 2H), 4.23 - 4.13 (m, 2H), 3.98 (d, *J*=8.6 Hz, 1H), 3.93 - 3.88 (m, 1H), 2.42 - 2.33 (m, 3H), 2.15 (ddd, *J*=12.3, 7.0, 5.2 Hz, 1H), 1.69 - 1.60 (m, 2H), 1.43 - 1.32 (m, 2H), 0.89 (t, *J*=7.4 Hz, 3H). LC-MS (Method A2): RT = 0.92 min, MS (ESI) m/z: 466.1 and 468.1 $(M+H)^+$.

Intermediate 146f-enantiomer 2: 5-bromo-4'-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile

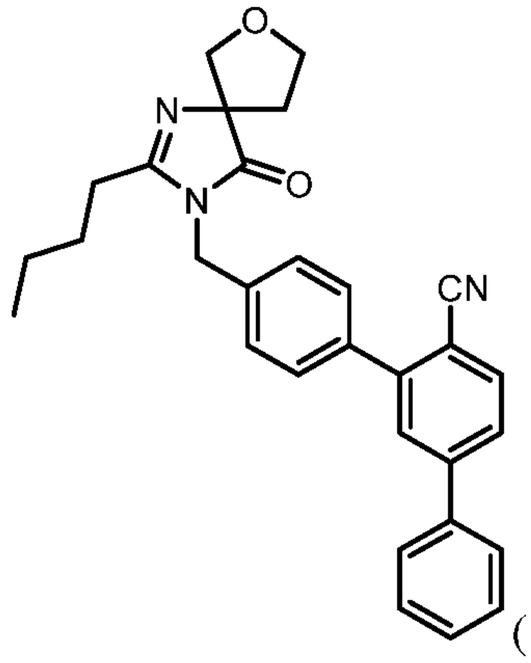


(146f-enantiomer 2)

Peak 2 was collected from the chiral separation of **Intermediate 146d**-racemate, and concentrated to give **Intermediate 146f**-enantiomer 2 (206 mg, 0.44 mmol, 22 % yield): enantiomeric excess 91%. Chiral analytical RT= 11.8 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=1.1 Hz, 1H), 7.67 - 7.61 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 4.84 - 4.74 (m, 2H), 4.26 - 4.15 (m, 2H), 4.03 - 3.98 (m, 1H), 3.96 - 3.91 (m, 1H),

2.44 - 2.36 (m, 3H), 2.18 (ddd, *J*=12.3, 6.9, 5.2 Hz, 1H), 1.67 (dt, *J*=15.4, 7.7 Hz, 2H), 1.43 - 1.34 (m, 2H), 0.91 (t, *J*=7.3 Hz, 3H). LC-MS (Method A2): RT = 0.93 min, MS (ESI) m/z: 466.1 and 468.1 $(M+H)^+$.

Intermediate 146g: 4''-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(146g)

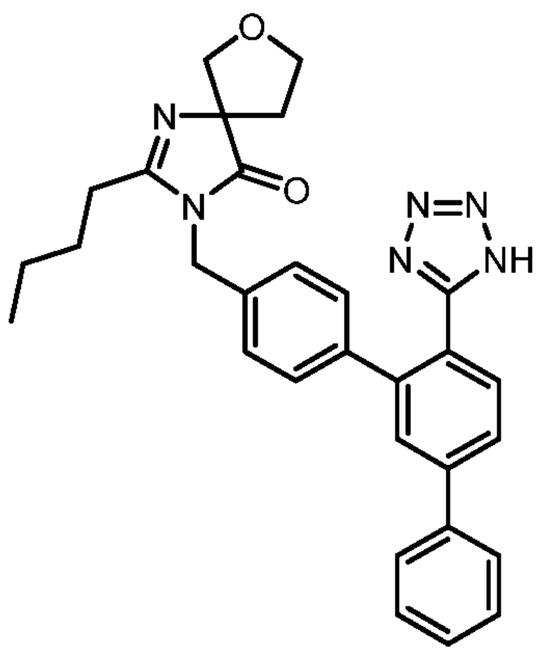
A solution of **Intermediate 146e**-enantiomer 1 (30 mg, 0.064 mmol), phenylboronic acid (17 mg, 0.14 mmol) and Pd-XPhos G3 (2.2 mg, 2.6 µmol) in THF (1.5 mL) and K_3PO_4 (1.0 M, 0.13 mL, 0.13 mmol) was degassed with Ar for 1 min. The reaction mixture was sealed in a pressure vial and heated at 120 °C in a microwave reactor for 45 min. LC-MS indicated completion of reaction. The reaction mixture was concentrated and purified by flash chromatography (10% to 100% EtOAc in hexane over 10 min using a 4 g silica gel cartridge) to yield **Intermediate 146g** (30 mg, 0.065 mmol, 100 % yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J*=8.0 Hz, 1H), 7.74 - 7.67 (m, 2H), 7.64 (br dd, *J*=7.4, 4.4 Hz, 4H), 7.54 - 7.48 (m, 2H), 7.48 - 7.43 (m, 1H), 7.33 (d, *J*=8.0 Hz, 2H), 4.85 - 4.73 (m, 2H), 4.26 - 4.16 (m, 2H), 4.04 - 3.98 (m, 1H), 3.96 - 3.91 (m, 1H), 2.45 - 2.37 (m, 3H), 2.22 - 2.14 (m, 1H), 1.67 (quin, *J*=7.6 Hz, 2H), 1.39 (dq, *J*=15.0, 7.4 Hz, 2H), 0.91 (t, *J*=7.4 Hz, 3H). LC-MS (Method A2): RT = 0.96 min, MS (ESI) m/z: 464.2 $(M+H)^+$.

Example 146

Intermediate 146g (30 mg, 0.065 mmol) was dissolved in toluene (1294 µl). Bu_2SnO (35 mg, 0.14 mmol) and TMS-N_3 (103 µl, 0.78 mmol) were added and the reaction sealed in a pressure vial and heated at 100 °C overnight. LC-MS indicated completion of reaction.

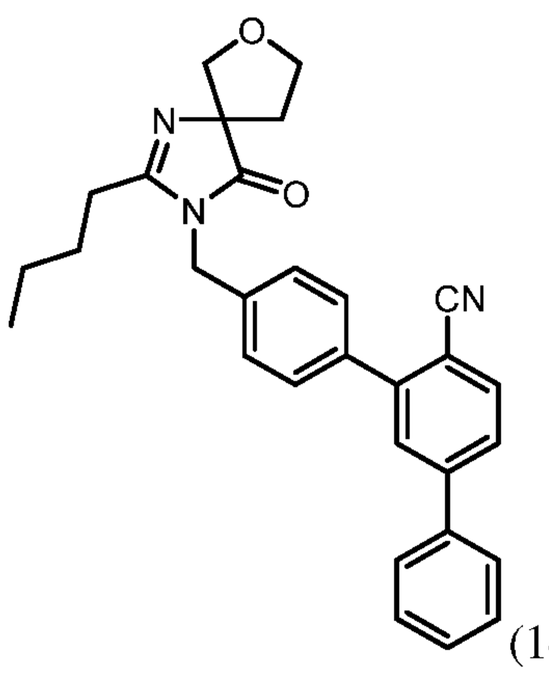
Toluene was removed by blowing a slow stream of N_2. The mixture was purified using a preparative HPLC (method E) to yield **Example 146** (22 mg, 0.042 mmol, 65 % yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J*=8.0 Hz, 1H), 7.75 (dd, *J*=8.1, 1.8 Hz, 1H), 7.68 - 7.63 (m, 3H), 7.53 - 7.47 (m, 2H), 7.47 - 7.42 (m, 1H), 7.28 - 7.24 (m, 2H), 7.23 - 7.19 (m, 2H), 4.86 (s, 2H), 4.25 - 4.15 (m, 2H), 4.08 - 4.01 (m, 2H), 2.68 - 2.62 (m, 2H), 2.52 - 2.44 (m, 1H), 2.41 - 2.34 (m, 1H), 1.72 (quin, *J*=7.7 Hz, 2H), 1.43 (sxt, *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). LC-MS (Method A2): RT = 0.84 min, MS (ESI) *m/z*: 507.0 $(M+H)^+$. Analytical HPLC purity (Method A2): 98%

Example 147: 3-((6'-(1H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 147)

Intermediate 147a: 4''-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(147a)

In a procedure similar to that of 146g, using **Intermediate 146f**-enantiomer 2 (30 mg, 0.064 mmol), phenylboronic acid (17 mg, 0.14 mmol), Pd-XPhos G3 (2.2 mg, 2.6 μmol)

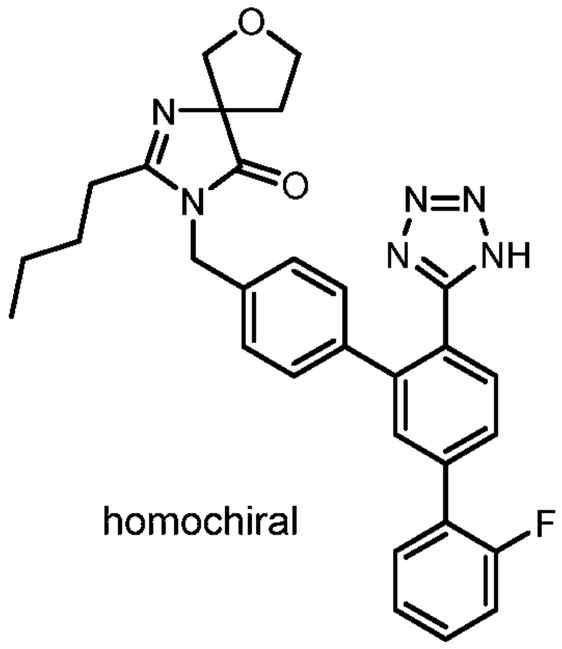
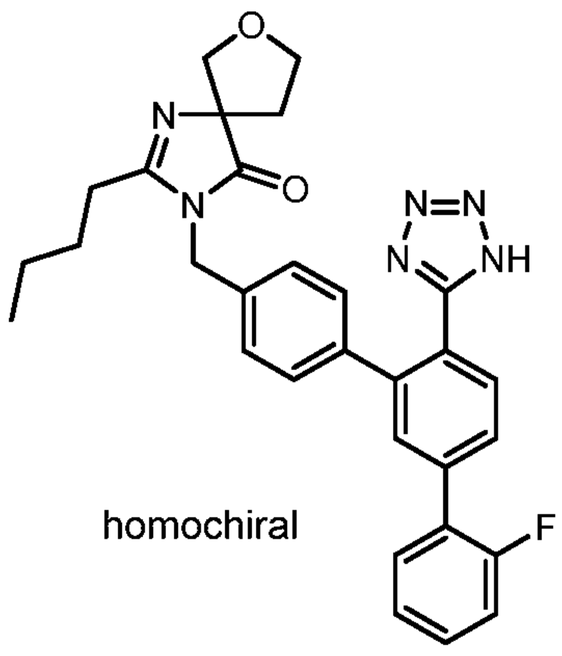
and K_3PO_4 salt (1.0 M, 0.13 mL, 0.123 mmol), **Intermediate 147a** (30 mg, 0.065 mmol, 100 % yield) was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J*=8.0 Hz, 1H), 7.74 - 7.67 (m, 2H), 7.64 (br dd, *J*=7.4, 4.4 Hz, 4H), 7.54 - 7.48 (m, 2H), 7.48 - 7.43 (m, 1H), 7.33 (d, *J*=8.0 Hz, 2H), 4.85 - 4.73 (m, 2H), 4.26 - 4.16 (m, 2H), 4.04 - 3.98 (m, 1H), 3.96 - 3.91 (m, 1H), 2.45 - 2.37 (m, 3H), 2.22 - 2.14 (m, 1H), 1.67 (quin, *J*=7.6 Hz, 2H), 1.39 (dq, *J*=15.0, 7.4 Hz, 2H), 0.91 (t, *J*=7.4 Hz, 3H). LC-MS (Method A2): RT = 0.96 min, MS (ESI) m/z: 464.2 $(M+H)^+$.

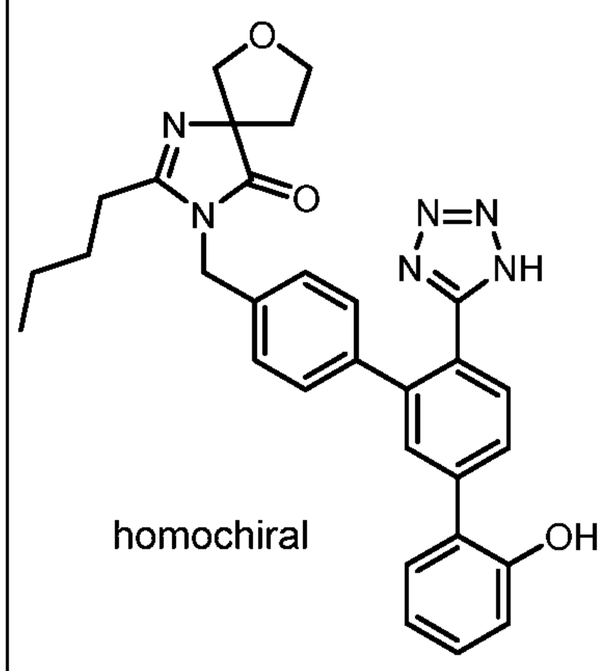
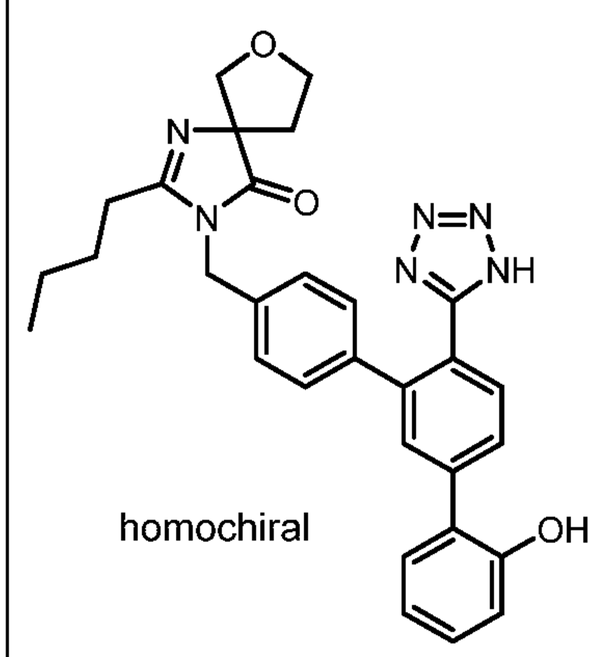
Example 147:

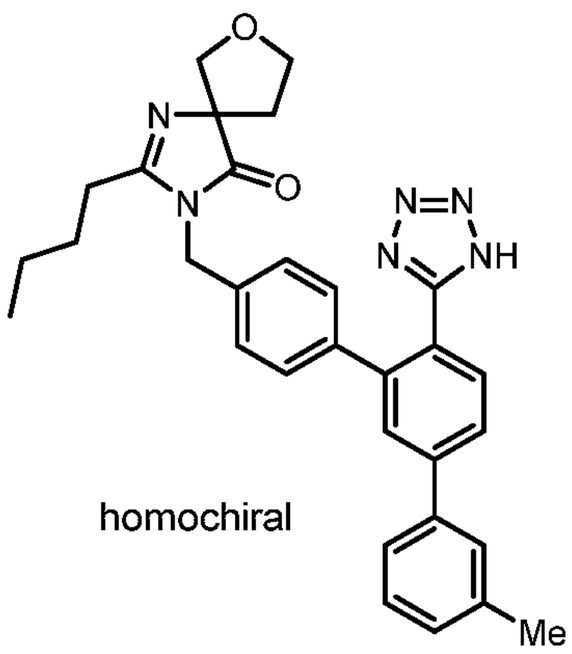
In a procedure similar to that of **Example 146**, using **Intermediate 147a** (30 mg, 0.065 mmol), Bu_2SnO (35 mg, 0.14 mmol) and TMS-N_3 (103 µl, 0.78 mmol), **Example 147** (19 mg, 0.037 mmol, 56.8 % yield) was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J*=8.0 Hz, 1H), 7.75 (dd, *J*=8.1, 1.8 Hz, 1H), 7.68 - 7.63 (m, 3H), 7.53 - 7.47 (m, 2H), 7.47 - 7.42 (m, 1H), 7.28 - 7.24 (m, 2H), 7.23 - 7.19 (m, 2H), 4.86 (s, 2H), 4.25 - 4.15 (m, 2H), 4.08 - 4.01 (m, 2H), 2.68 - 2.62 (m, 2H), 2.52 - 2.44 (m, 1H), 2.41 - 2.34 (m, 1H), 1.72 (quin, *J*=7.7 Hz, 2H), 1.43 (sxt, *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). LC-MS (Method A2): RT = 0.84 min, MS (ESI) *m/z*: 507.0 $(M+H)^+$. Analytical HPLC purity (Method A2): 100%.

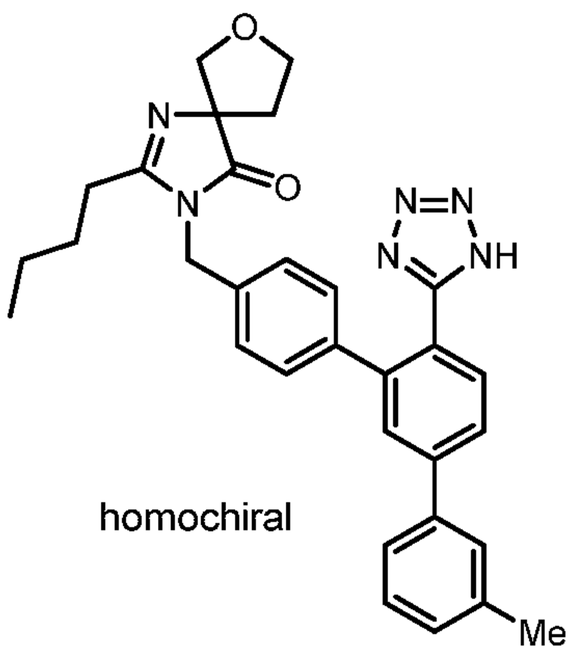
The following examples have been similarly prepared from **Intermediate 146e**-enantiomer 1 and **Intermediate 146f**-enantiomer 2 with selected boronic acids as described above for **Example 146**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A1 or Method A2.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; Purity (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm

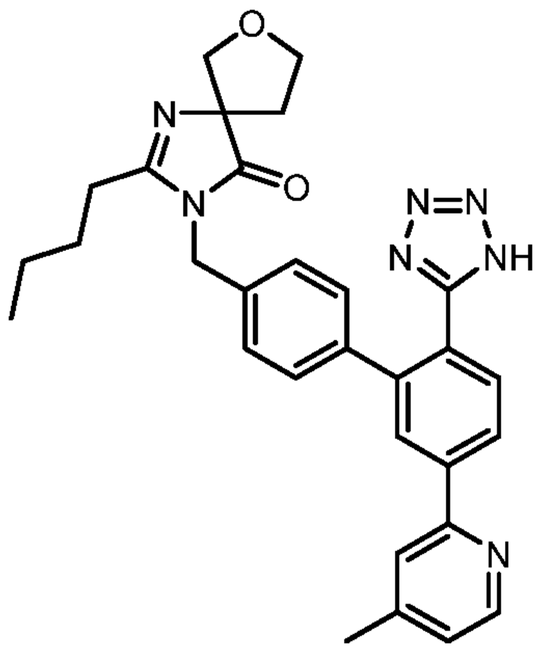
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; Purity (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
148		524.6	525.1; 1.70 min; 97% (Method A2)	7.80 - 7.72 (m, 2H), 7.72 - 7.61 (m, 2H), 7.53 - 7.44 (m, 1H), 7.40 - 7.31 (m, 2H), 7.16 (s, 2H), 7.14 - 7.06 (m, 2H), 4.70 (s, 2H), 3.98 (br t, *J*=7.0 Hz, 2H), 3.78 - 3.68 (m, 1H), 2.33 (br t, *J*=7.3 Hz, 2H), 2.17 (dt, *J*=12.4, 7.7 Hz, 1H), 2.00 (dt, *J*=12.0, 5.8 Hz, 1H), 1.48 (quin, *J*=7.4 Hz, 2H), 1.32 - 1.18 (m, 2H), 0.79 (t, *J*=7.3 Hz, 3H).
149		524.6	525.1; 1.67 min; 95% (Method A2)	7.80 - 7.72 (m, 2H), 7.72 - 7.61 (m, 2H), 7.54 - 7.44 (m, 1H), 7.41 - 7.30 (m, 2H), 7.20 - 7.14 (m, 2H), 7.14 - 7.06 (m, 2H), 4.70 (s, 2H), 3.98 (br t, *J*=6.9 Hz, 2H), 3.77 - 3.68 (m, 1H), 2.33 (br t, *J*=7.5 Hz, 2H), 2.17 (dt, *J*=12.5, 7.9 Hz, 1H), 2.00 (dt, *J*=12.1, 5.9 Hz, 1H), 1.48 (quin, *J*=7.5 Hz, 2H), 1.30 - 1.20 (m, 2H), 0.79 (t, *J*=7.3 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; Purity (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
150		522.6	523.4; 1.49 min; 96% (Method A2)	7.65 - 7.57 (m, 2H), 7.53 (s, 1H), 7.37 (br d, *J*=7.6 Hz, 1H), 7.22 - 7.12 (m, 3H), 7.05 (br d, *J*=7.9 Hz, 2H), 6.97 (d, *J*=8.2 Hz, 1H), 6.91 (br t, *J*=7.3 Hz, 1H), 4.69 (s, 2H), 3.99 (br t, *J*=6.9 Hz, 2H), 3.79 - 3.74 (m, 1H), 3.74 - 3.69 (m, 1H), 2.37 (br t, *J*=7.3 Hz, 2H), 2.22 - 2.14 (m, 1H), 2.01 (dt, *J*=12.0, 5.8 Hz, 1H), 1.52 (quin, *J*=7.5 Hz, 2H), 1.29 (dq, *J*=14.7, 7.3 Hz, 2H), 0.82 (t, *J*=7.3 Hz, 3H).
151		522.6	523.2; 1.45 min; 97% (Method A2)	7.62 (s, 2H), 7.53 (s, 1H), 7.37 (br d, *J*=7.3 Hz, 1H), 7.23 - 7.13 (m, 3H), 7.05 (br d, *J*=7.9 Hz, 2H), 6.98 (d, *J*=7.9 Hz, 1H), 6.91 (t, *J*=7.3 Hz, 1H), 4.69 (s, 2H), 3.99 (br t, *J*=6.9 Hz, 2H), 3.80 - 3.75 (m, 1H), 3.74 - 3.69 (m, 1H), 2.37 (t, *J*=7.3 Hz, 2H), 2.18 (dt, *J*=12.4, 7.9 Hz, 1H), 2.04 - 1.98 (m, 1H), 1.56 - 1.48 (m, 2H), 1.29 (dq, *J*=14.9, 7.3 Hz, 2H), 0.82 (t, *J*=7.3 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; Purity (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
152		520.6	521.2; 1.84 min; 99% (Method A2)	7.82 (br d, *J*=7.0 Hz, 1H), 7.76 - 7.69 (m, 2H), 7.63 (s, 1H), 7.59 (br d, *J*=7.9 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.25 (br d, *J*=7.3 Hz, 1H), 7.21 (br d, *J*=8.2 Hz, 2H), 7.12 (br d, *J*=7.9 Hz, 2H), 4.72 (s, 2H), 4.00 (br t, *J*=6.7 Hz, 2H), 3.80 - 3.75 (m, 1H), 3.75 - 3.69 (m, 1H), 2.41 (s, 3H), 2.36 (br t, *J*=7.3 Hz, 2H), 2.19 (dt, *J*=12.4, 7.9 Hz, 1H), 2.01 (dt, *J*=12.1, 6.0 Hz, 1H), 1.52 (quin, *J*=7.5 Hz, 2H), 1.30 (sxt, *J*=7.4 Hz, 2H), 0.83 (t, *J*=7.3 Hz, 3H)

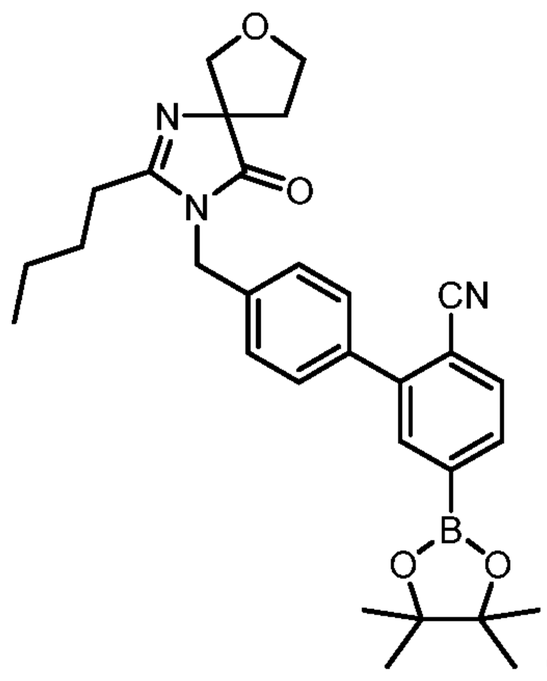
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; Purity (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
153	 homochiral	520.6	521.3; 1.80 min; 100% (Method A2)	7.84 (br d, *J*=7.6 Hz, 1H), 7.78 - 7.70 (m, 2H), 7.65 (s, 1H), 7.61 (br d, *J*=7.6 Hz, 1H), 7.41 (t, *J*=7.5 Hz, 1H), 7.26 (br d, *J*=7.3 Hz, 1H), 7.22 (br d, *J*=7.6 Hz, 2H), 7.13 (br d, *J*=7.9 Hz, 2H), 4.73 (s, 2H), 4.01 (br t, *J*=6.7 Hz, 2H), 3.82 - 3.76 (m, 1H), 3.75 - 3.70 (m, 1H), 2.42 (s, 3H), 2.37 (br t, *J*=7.5 Hz, 2H), 2.19 (dt, *J*=12.4, 7.9 Hz, 1H), 2.02 (dt, *J*=12.0, 5.8 Hz, 1H), 1.53 (quin, *J*=7.5 Hz, 2H), 1.35 - 1.26 (m, 2H), 0.84 (t, *J*=7.3 Hz, 3H)

Example 154: 2-butyl-3-((5'-(4-methylpyridin-2-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 154)

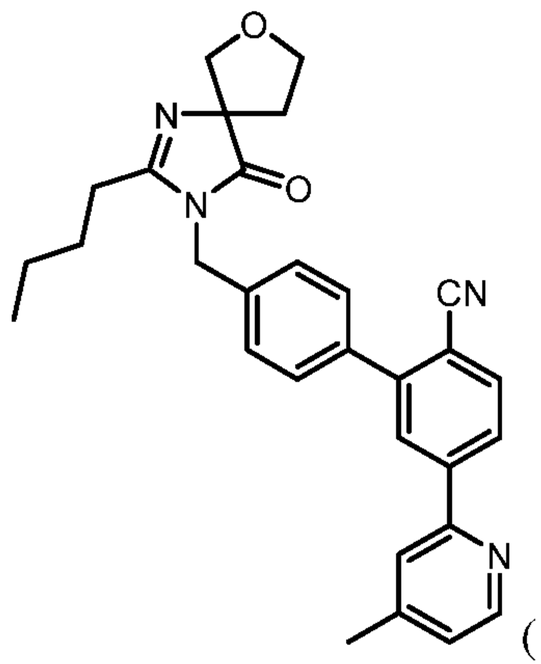
Intermediate 154a: 4'-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(154a)

Intermediate 146e-enantiomer 1 (140 mg, 0.30 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (99 mg, 0.39 mmol), KOAc (74 mg, 0.75 mmol) in dioxane (2 mL) was degassed by bubbling Ar for 1 min, then Pd(dppf)Cl_2 complex with CH_2Cl_2 (1 : 1) (12 mg, 0.015 mmol) was added. The mixture was sealed in a pressure vial and heated in an oil bath at 125 °C for 1 h. The reaction mixture was directly loaded onto a silica gel cartridge, purified by flash chromatography (0% to 15% MeOH in CH_2Cl_2 over 12 min using a 12 g silica gel cartridge). The desired fractions were combined, concentrated and lyophilized to yield **Intermediate 154a** (123 mg, 0.24 mmol, 80 % yield) as solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.88 (d, *J*=7.7 Hz, 1H), 7.82 - 7.75 (m, 1H), 7.60 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 4.83 - 4.74 (m, 2H), 4.27 - 4.16 (m, 2H), 4.03 - 3.99 (m, 1H), 3.96 - 3.92 (m, 1H), 2.45 - 2.38 (m, 3H), 2.23 - 2.16 (m, 1H), 1.67 (br t, *J*=7.6 Hz, 2H), 1.38 (s, 12H), 0.92 (t, *J*=7.3 Hz, 3H). LC-MS (Method A2): RT = 0.70 min, MS (ESI) *m/z*: 432.1 $(M+H)^+$.

Intermediate 154b: 4'-((2-butyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



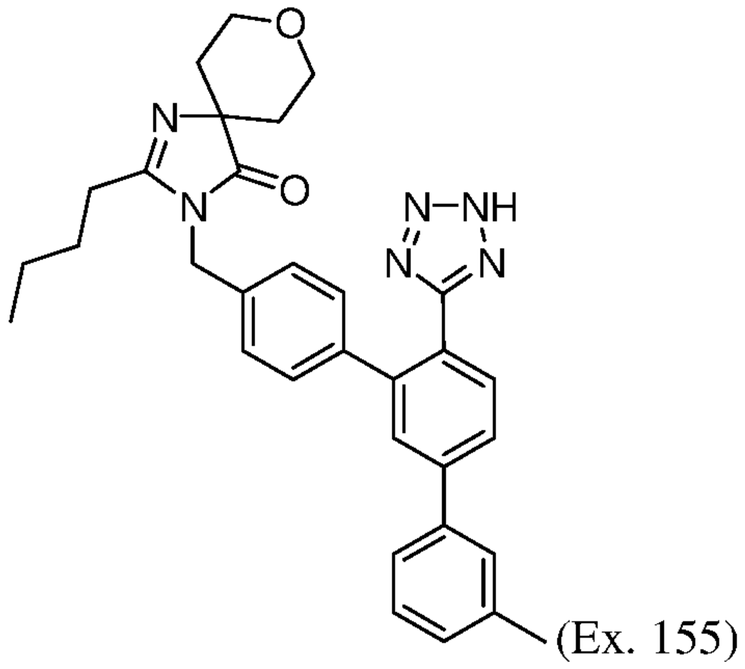
(154b)

A solution of **Intermediate 154a** (37 mg, 0.073 mmol), 2-bromo-4-methylpyridine (25 mg, 0.15 mmol) and Pd-XPhos G3 (2.5 mg, 2.9 µmol) in THF (1.5 mL) and K_3PO_4 (1.0 M, 0.15 mL, 0.15 mmol) was degassed with Ar for 1 min. The reaction mixture was sealed in a pressure vial and heated at 120 °C in a microwave reactor for 45 min. LC-MS indicated completion of reaction. The reaction mixture was concentrated and purified by column chromatography (0% to 15% MeOH in CH_2Cl_2 over 10 min using a 4 g silica gel cartridge). The desired fractions were combined and further purified by preparative HPLC (method E) to yield **Intermediate 154b** (20 mg, 0.042 mmol, 58 % yield) as a white lyophilate. LC-MS (Method A2): RT = 0.75 min, MS (ESI) m/z: 479.0 $(M+H)^+$.

Example 154

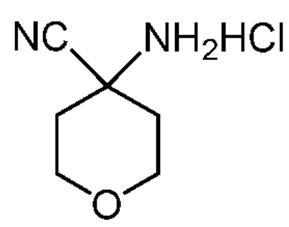
Intermediate 154b (20 mg, 0.042 mmol) was dissolved in toluene (836 µl). Bu_2SnO (26 mg, 0.10 mmol) and TMS-N_3 (83 µl, 0.63 mmol) were added, and the reaction sealed in a pressure vial and heated at 105 °C overnight. LC-MS indicated completion of reaction. Toluene was removed by blowing a slow stream of N_2. The mixture was purified by preparative HPLC (method G) to yield **Example 154** (7.3 mg, 0.011 mmol, 26.7 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (d, *J*=5.2 Hz, 1H), 8.28 (br d, *J*=7.9 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.33 (br d, *J*=4.9 Hz, 1H), 7.25 (s, 1H), 7.23 - 7.16 (m, 4H), 7.15 (s, 1H), 7.05 (s, 1H), 4.76 (s, 2H), 4.01 (t, *J*=6.7 Hz, 2H), 3.81 - 3.75 (m, 1H), 2.45 (s, 3H), 2.41 (br t, *J*=7.6 Hz, 2H), 2.21 (dt, *J*=12.6, 7.7 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.53 (quin, *J*=7.5 Hz, 2H), 1.30 (dq, *J*=14.9, 7.3 Hz, 2H), 0.84 (t, *J*=7.3 Hz, 3H). LC-MS (Method A2): RT = 1.0 min, MS (ESI) *m/z*: 522.0 $(M+H)^+$. Analytical HPLC purity (Method A2): 97%.

Example 155: 2-butyl-3-((3''-methyl-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one



(Ex. 155)

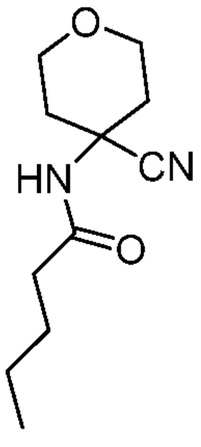
Intermediate 155a: 4-aminotetrahydro-2H-pyran-4-carbonitrile hydrochloride



(155a)

To a solution of tetrahydro-4H-pyran-4-one (1.3g, 13 mmol) in MeOH (4 mL) was added 7N ammonia/MeOH (3.71 mL, 26.0 mmol) at rt. The mixture was cooled with an ice bath and AcOH (0.82 mL, 14.28 mmol) was added dropwise. The mixture was stirred at rt for 10 min then NaCN (0.636 g, 12.98 mmol) was added in one portion. The mixture was heated up to 50°C in oil bath for 2h and rt overnight. The mixture was concentrated, EtOAc was added to the concentrated mixture and stir for 15 min. The slurry was removed by filtration and the wet cake was washed with EtOAc twice. The combined filtrates were concentrated and the crude sample was resolved in DCM (20 mL) and treated with 4N HCl in dioxane (4.87 mL, 19.48 mmol) at rt for 15 min. Precipitation was formed and the mixture was concentrated. The residual was triturated in ether. The title compound (**Intermediate 155a**, 2.1 g, 12.91 mmol, 99 % yield) was obtained by filtration as an off-white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.13 (dd, J=12.7, 4.7 Hz, 2H), 3.71 - 3.63 (m, 2H), 2.24 (dd, J=12.9, 1.4 Hz, 2H), 2.08 - 1.91 (m, 2H).

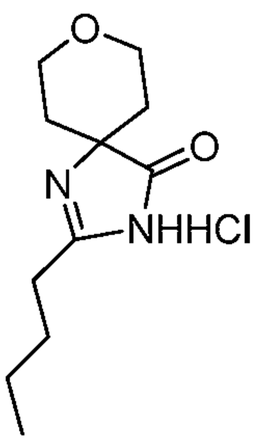
Intermediate 155b: N-(4-cyanotetrahydro-2H-pyran-4-yl)pentanamide



(155b)

To a solution of 4-aminotetrahydro-2H-pyran-4-carbonitrile hydrochloride (**155a,** 230mg, 1.414 mmol) in DCM (4 mL) was added potassium carbonate (1016 mg, 7.35 mmol) in H_2O (4 mL). The mixture was cooled with an ice bath. Pentanoyl chloride (0.235 mL, 1.980 mmol) in DCM (4 mL) was added dropwise to the stirred solution. The reaction mixture was stirred at 0 °C for 2 h, and at rt for 3 h. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 155b**, 240 mg, 1.141 mmol, 81 % yield) as oil. LC-MS (Method A5): 1.63 min, $[M + H]^+$= 221.1; ^1H NMR (500 MHz, MeOH-d_4) δ 8.43 (br s, 1H), 3.91 (dt, *J*=12.6, 4.0 Hz, 2H), 3.72 (ddd, *J*=12.4, 10.1, 2.5 Hz, 2H), 2.33 (dt, *J*=13.5, 1.9 Hz, 2H), 2.26 (t, *J*=7.4 Hz, 2H), 1.93 (ddd, *J*=13.8, 10.0, 4.0 Hz, 2H), 1.74 - 1.56 (m, 2H), 1.46 - 1.29 (m, 2H), 0.96 (t, *J*=7.4 Hz, 3H).

Intermediate 155c: 2-butyl-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one hydrochloride

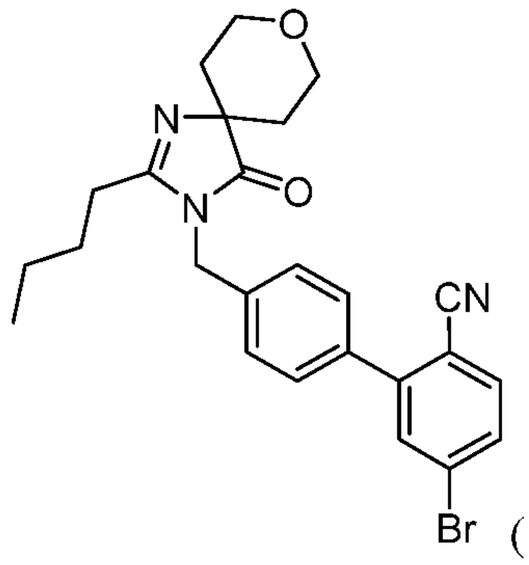


(155c)

To a solution of N-(4-cyanotetrahydro-2H-pyran-4-yl)pentanamide (**Intermediate 155b**, 160 mg, 0.761 mmol) in n-propanol (2 mL) was added 4N HCl in dioxane (1.902 mL, 7.61 mmol) dropwise. The mixture was heated up to 50°C in oil bath for overnight. The mixture was concentrated and dried under vacuum to give the title compound (**Intermediate 155c**, 188 mg, 0.761 mmol, 100 % yield) as a whit solid. LC-MS (Method A5): 0.91 min, $[M + H]^+$= 221.1; ^1H NMR (500 MHz, MeOH-d_4) δ 4.16 - 3.93 (m, 2H),

3.86 - 3.73 (m, 2H), 2.99 - 2.70 (m, 2H), 2.18 - 2.03 (m, 2H), 1.90 (br dd, *J*=7.6, 4.0 Hz, 2H), 1.86 - 1.75 (m, 2H), 1.55 - 1.45 (m, 2H), 1.04 (t, *J*=7.4 Hz, 3H).

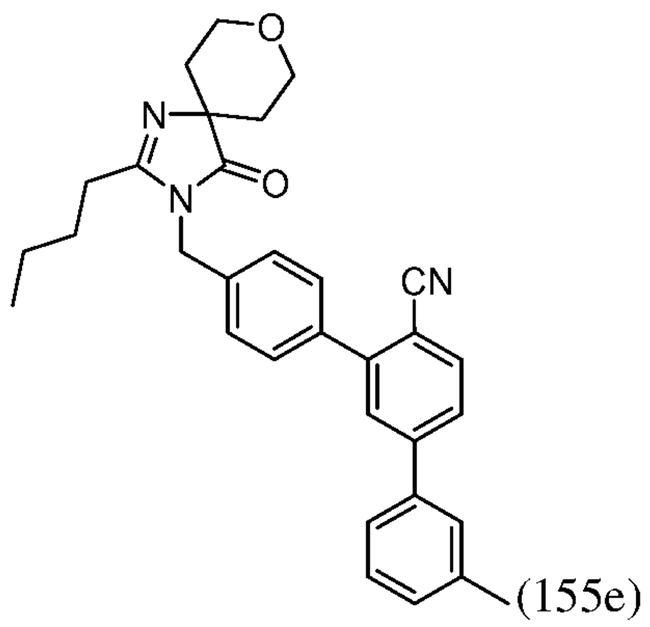
Intermediate 155d: 5-bromo-4'-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)biphenyl-2-carbonitrile



(155d)

2-butyl-8-oxa-1, 3-diazaspiro[4.5]dec-1-en-4-one, HCl (**Intermediate 155c**, 260 mg, 1.054 mmol) was dissolved in DMF (5 mL). NaH (105 mg, 2.63 mmol) was added. The mixture was stirred at rt for 15min, 5-bromo-4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile (**I-002**, 388 mg, 1.106 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 155d**, 383 mg, 0.797 mmol, 76 % yield) as off white solid. LC-MS (Method A5): 2.44 min, $[M + H]^+$= 480.1 and 482.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=1.1 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.55 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 4.77 (s, 2H), 4.09 - 4.02 (m, 2H), 4.01 - 3.94 (m, 2H), 2.45 - 2.35 (m, 2H), 2.11 - 1.99 (m, 2H), 1.64 (dt, *J*=15.1, 7.6 Hz, 2H), 1.50 (br d, *J*=13.5 Hz, 2H), 1.42 - 1.35 (m, 2H), 0.91 (t, *J*=7.3 Hz, 3H).

Intermediate 155e: 4''-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)-3-methyl-[1,1':3',1''-terphenyl]-4'-carbonitrile



(155e)

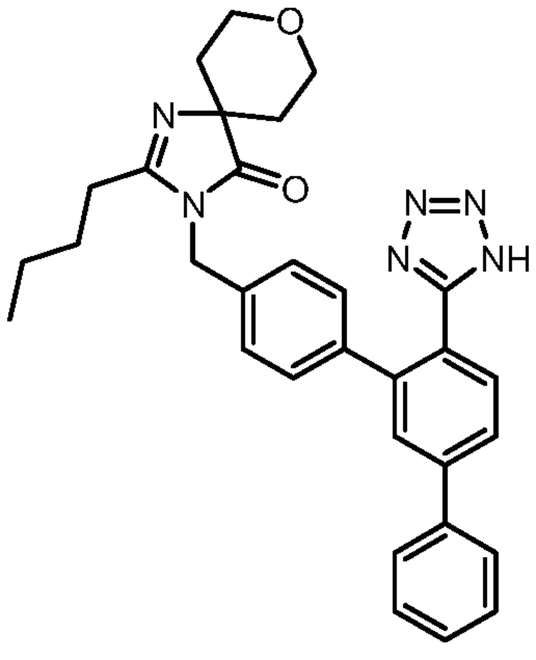
A mixture of 5-bromo-4'-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 155d**, 25 mg, 0.052 mmol) and m-tolylboronic acid (21.23 mg, 0.156 mmol) in THF (1 mL) was treated with 1.5 M Na_2CO_3 (0.104 mL, 0.156 mmol) followed by $PdCl_2(dppf)$ (4.25 mg, 5.20 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 120 °C for 30 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 155e,** 25 mg, 0.051 mmol, 98 % yield) as an amber oil. LC-MS (Method A5): 2.57min, $[M + H]^+$= 492.2; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J*=8.0 Hz, 1H), 7.70 (d, *J*=1.4 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.62 (d, *J*=8.0 Hz, 2H), 7.44 (d, *J*=7.2 Hz, 2H), 7.42 - 7.37 (m, 1H), 7.33 (d, *J*=8.0 Hz, 2H), 7.29 - 7.26 (m, 1H), 4.78 (s, 2H), 4.09 - 4.03 (m, 2H), 4.02 - 3.95 (m, 2H), 2.46 (s, 3H), 2.44 - 2.39 (m, 2H), 2.11 - 2.02 (m, 2H), 1.71 - 1.59 (m, 2H), 1.52 (br d, *J*=13.2 Hz, 2H), 1.40 (sxt, *J*=7.4 Hz, 2H), 0.92 (t, *J*=7.3 Hz, 3H).

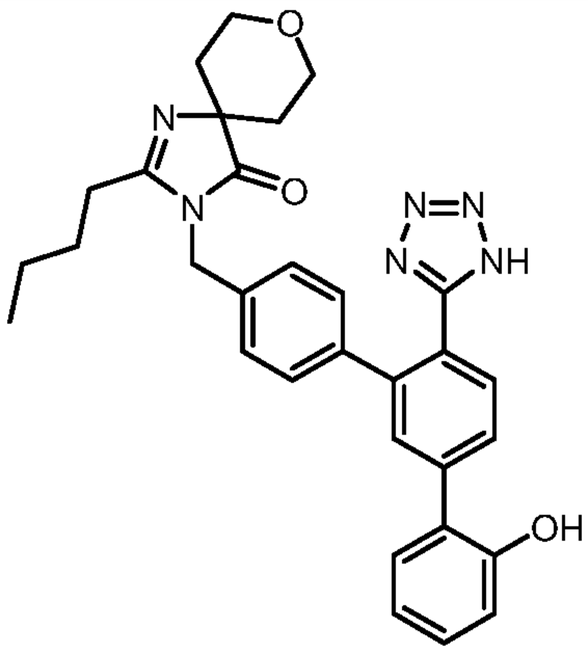
Example 155: 2-butyl-3-((3''-methyl-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one

To a solution of 4"-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1"-terphenyl]-4'-carbonitrile (**Intermediate 155e** ,24 mg, 0.051 mmol) in toluene (1.5 mL) was added dibutyltin oxide (25.3 mg, 0.102 mmol) and TMS-N_3 (0.067 mL, 0.509 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B:

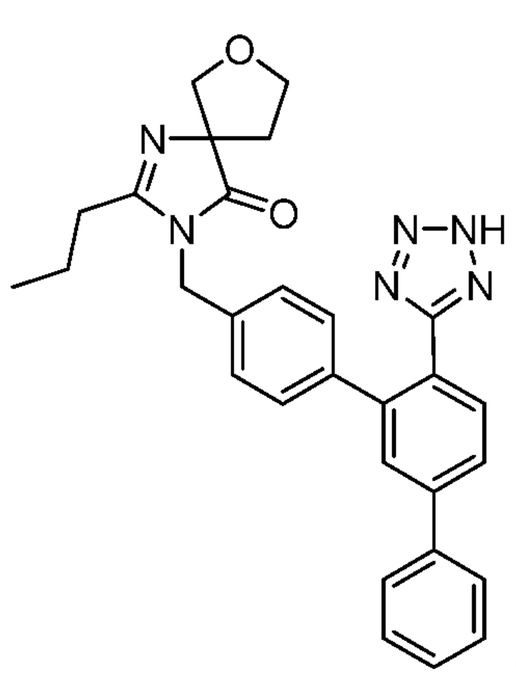
95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 24-64% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min) to afford 14.1 mg (0.026 mmol, 51.9 % yield) of the title compound **Example 155**. LC-MS (Method A3): 1.41min, $[M + H]^+$= 535.25; ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 - 7.76 (m, 1H), 7.75 - 7.70 (m, 1H), 7.66 (d, *J*=1.4 Hz, 1H), 7.59 (s, 1H), 7.56 (br d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.23 (br d, *J*=7.6 Hz, 1H), 7.20 (br d, *J*=8.0 Hz, 2H), 7.08 (br d, *J*=8.1 Hz, 2H), 4.69 (s, 2H), 3.99 - 3.84 (m, 2H), 3.82 - 3.73 (m, 2H), 2.40 (s, 3H), 2.35 (t, *J*=7.5 Hz, 2H), 1.89 - 1.76 (m, 2H), 1.52 (quin, *J*=7.3 Hz, 2H), 1.39 - 1.24 (m, 4H), 0.82 (t, *J*=7.3 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 155d** as described above for **Example 155**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^1H NMR (500MHz, DMSO-d_6) δ ppm
156		520.64	521.06; 1.53min (Method A3)	7.85 - 7.76 (m, 3H), 7.74 (d, *J*=7.9 Hz, 1H), 7.70 (s, 1H), 7.55 - 7.48 (m, 2H), 7.46 - 7.40 (m, 1H), 7.20 (d, *J*=7.9 Hz, 2H), 7.09 (br d, *J*=7.9 Hz, 2H), 4.71 (s, 2H), 3.88 (br d, *J*=11.3 Hz, 2H), 3.83 - 3.68 (m, 2H), 2.52 (br s, 6H), 2.36 (t, *J*=7.5 Hz, 2H), 1.87 - 1.77 (m, 2H), 1.57 - 1.43 (m, 2H), 1.40 - 1.20 (m, 4H), 0.82 (t, *J*=7.3 Hz, 3H).

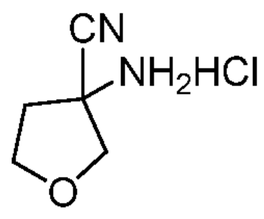
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
157		536.64	537.13; 1.34 (Method A3)	7.64 (s, 2H), 7.57 (s, 1H), 7.37 (br d, *J*=7.6 Hz, 1H), 7.23 - 7.18 (m, 1H), 7.16 (br d, *J*=8.0 Hz, 2H), 7.05 (br d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=8.1 Hz, 1H), 6.91 (t, *J*=7.5 Hz, 1H), 4.68 (s, 2H), 3.92 - 3.84 (m, 2H), 3.82 - 3.72 (m, 2H), 2.35 (br t, *J*=7.5 Hz, 2H), 1.87 - 1.72 (m, 2H), 1.51 (dt, *J*=14.7, 7.4 Hz, 2H), 1.38 - 1.21 (m, 4H), 0.81 (t, *J*=7.3 Hz, 3H)

Example 158-enantiomer 1: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one:



(Ex. 158)

Intermediate 158a: 3-aminotetrahydrofuran-3-carbonitrile hydrochloride

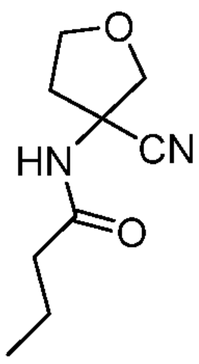


(158a)

To a solution of dihydrofuran-3(2H)-one (0.8 g, 9.29 mmol) in MeOH (4 mL) was added 7N ammonia/MeOH (2.66 mL, 18.59 mmol) at rt. The mixture was cooled with an ice bath and AcOH (0.585 mL, 10.22 mmol) was added dropwise. The mixture was stirred at rt for 10 min then NaCN (0.455 g, 9.29 mmol) was added in one portion. The mixture was heated up to 50°C in oil bath for 2h and rt for overnight. The mixture was

concentrated, EtOAc was added to the concentrated mixture and stir for 15 min. The slurry was removed by filtration and the wet cake was washed with EtOAc for 2 times. The combined filtrates were concentrated and the crude sample was resolved in DCM (20 mL) and treated with 4N HCl in dioxane (3.48 mL, 13.94 mmol) at rt for 15 min. Precipitation was formed and the mixture was concentrated. The residual was triturated in ether. The title compound (**Intermediate 158a**, 1.30 g, 8.92 mmol, 96 % yield) was obtained by filtration as an off-white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.22 - 4.14 (m, 2H), 4.13 - 4.09 (m, 1H), 4.02 (td, *J*=8.9, 6.6 Hz, 1H), 2.80 (ddd, *J*=14.2, 8.7, 5.5 Hz, 1H), 2.46 (dt, *J*=14.4, 7.3 Hz, 1H).

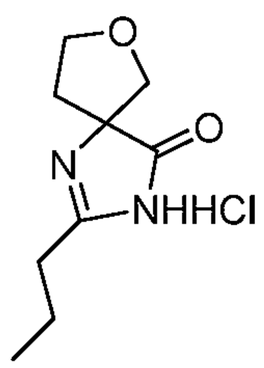
Intermediate 158b: N-(3-cyanotetrahydrofuran-3-yl)butyramide



(158b)

To a solution of 3-aminotetrahydrofuran-3-carbonitrile, HCl (**Intermediate 158a**, 400 mg, 2.69 mmol) in DCM (8 mL) was added potassium carbonate (1935 mg, 14.00 mmol) in H_2O (8 mL). The mixture was cooled with an ice bath, butyryl chloride (0.394 mL, 3.77 mmol) in DCM (4 mL) was added dropwise to the stirred solution. The reaction mixture was stirred at 0 °C for 2 h, and at rt for 3 h. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 158b**, 410 mg, 2.250 mmol, 84 % yield) as oil. LC-MS (Method A5): 0.92 min, $[M + H]^+$= 183.1; ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.24 (d, *J*=9.4 Hz, 1H), 4.05 - 3.98 (m, 1H), 3.98 - 3.92 (m, 2H), 2.69 - 2.55 (m, 1H), 2.50 - 2.36 (m, 1H), 2.28 - 2.12 (m, 2H), 1.76 - 1.58 (m, 2H), 1.04 - 0.85 (m, 3H).

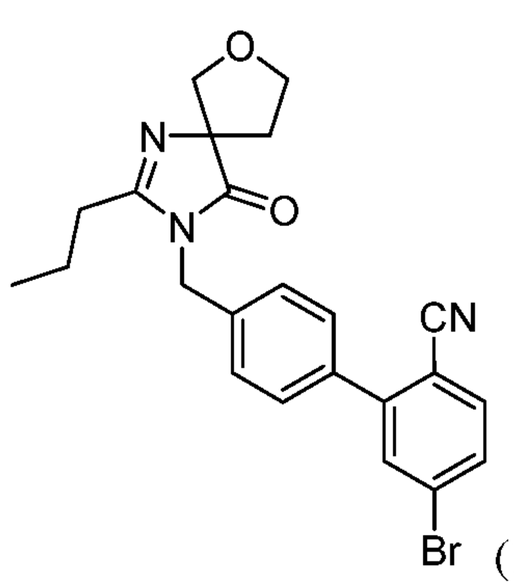
Intermediate 158c: 2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride



(158c)

To a solution of N-(3-cyanotetrahydrofuran-3-yl)butyramide (**Intermediate 158b**, 410 mg, 2.250 mmol) in n-propanol (6 mL) was added 4N HCl in dioxane (5.62 mL, 22.50 mmol) dropwise. The mixture was heated up to 50°C in oil bath for overnight. The mixture was concentrated and dried under vacuum to give the title compound (**Intermediate 158c**, 492 mg, 2.250 mmol, 100 % yield) as a white solid. LC-MS (Method A5): 0.40 min, $[M + H]^+$= 221.1; ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.23 - 4.12 (m, 2H), 4.11 - 4.00 (m, 1H), 3.93 (d, *J*=10.2 Hz, 1H), 2.85 (t, *J*=7.7 Hz, 2H), 2.62 - 2.49 (m, 1H), 2.41 (dt, *J*=13.7, 6.8 Hz, 1H), 1.98 - 1.74 (m, 2H), 1.11 (t, *J*=7.4 Hz, 3H).

Intermediate 158d: 5-bromo-4'-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile

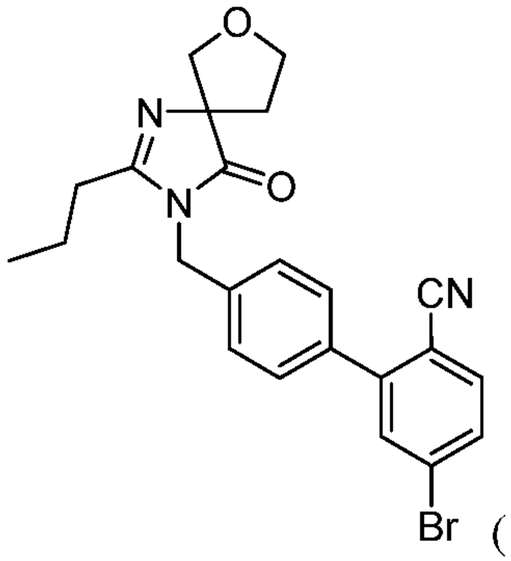


(158d)

2-Propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one, HCl (**Intermediate 158c**, 492 mg, 2.25 mmol) was dissolved in DMF (10 mL). NaH (225 mg, 5.63 mmol) was added. The mixture was stirred at rt for 15min, 5-bromo-4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile (**I-002**, 829 mg, 2.363 mmol) was added at 0°C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 158d**, 620 mg, 1.371 mmol, 60.9 % yield) as as a white solid. LC-MS (Method A5): 2.30 min, $[M + H]^+$= 452.1 and 454.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=1.1 Hz, 1H), 7.67 - 7.62 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H), 4.78 (d, *J*=6.6 Hz,

2H), 4.27 - 4.17 (m, 2H), 4.05 - 3.97 (m, 1H), 3.96 - 3.89 (m, 1H), 2.50 - 2.32 (m, 3H), 2.18 (ddd, *J*=12.3, 6.8, 5.4 Hz, 1H), 1.79 - 1.63 (m, 2H), 0.99 (t, *J*=7.4 Hz, 3H).

Intermediate 158e-enantiomer 1: 5-bromo-4'-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile

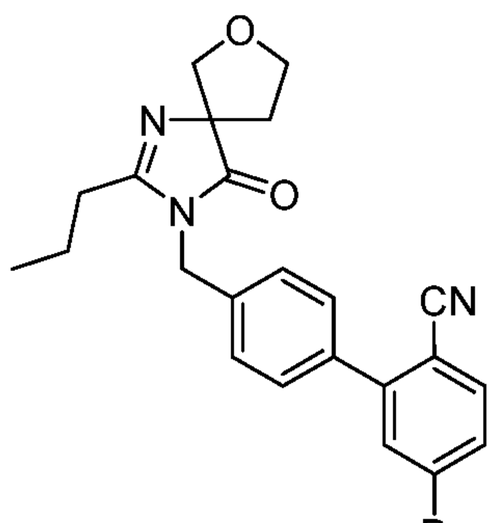


(158e, enantiomer 1)

Intermediate 158d-racemate (620 mg, 1.371 mmol) were resolved into two peaks on Instrument PIC Solution SFC Prep-200 with the following preparative chromatographic conditions: Column: Chiralpak AD-H, 30 x 250 mm, 5 micron; Mobile Phase: 20% IPA/ 80% CO_2; Flow Conditions: 85 mL/min, 120 Bar, 40 °C; Detector Wavelength: 220 nm; injection details: 0.5 mL of ~155mg/mL in IPA/ACN. Purity of each fraction was determined using the analytical chromatographic condition below: Instrument: Aurora Analytical SFC; Column: Chiralpak AD-H, 4.6 x 250 mm, 5 micron; Mobile Phase: 20% IPA / 80% CO2; Flow Conditions: 2.0 mL/min, 150 Bar, 40 °C; Detector Wavelength: 220 nm; Injection Details: 10µL of ~0.2mg/mL in MeOH.

Peak 1 was collected and concentrated to give **Intermediate 158e-enantiomer 1** (200 mg, 0.44 mmol, 32 % yield): enantiomeric excess > 99%. Chiral analytical RT = 7.75 min. LC-MS (Method A5): 2.30 min, $[M + H]^+$= 452.1 and 454.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=1.4 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.3 Hz, 2H), 4.78 (d, *J*=6.6 Hz, 2H), 4.28 - 4.09 (m, 2H), 4.03 - 3.98 (m, 1H), 3.96 - 3.91 (m, 1H), 2.52 - 2.28 (m, 3H), 2.18 (ddd, *J*=12.3, 6.9, 5.2 Hz, 1H), 1.76 - 1.65 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H).

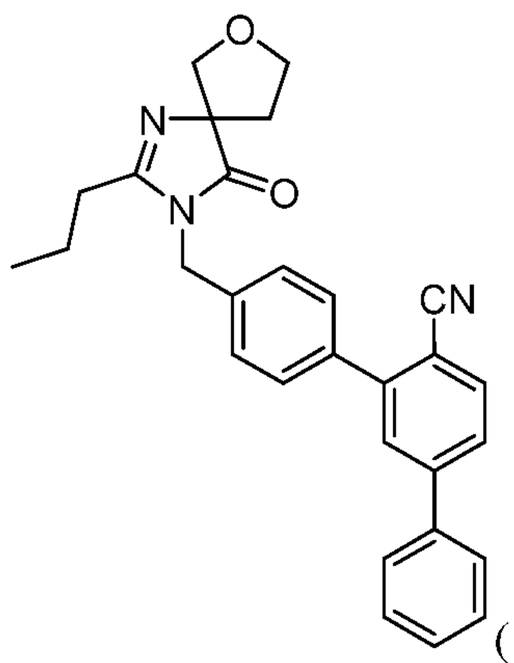
Intermediate 158f-enantiomer 2: 5-bromo-4'-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile



(158f, enantiomer 2)

Peak 2 was collected and concentrated to give **Intermediate 158f-enantiomer 2** (200 mg, 0.44 mmol, 32 % yield): enantiomeric excess: 94%. Chiral analytical RT = 10.01 min. LC-MS (Method A5): 2.30 min, $[M + H]^+$= 452.1 and 454.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=1.4 Hz, 1H), 7.64 - 7.60 (m, 2H), 7.54 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 4.77 (d, *J*=6.3 Hz, 2H), 4.26 - 4.11 (m, 2H), 3.99 (d, *J*=8.8 Hz, 1H), 3.94 - 3.86 (m, 1H), 2.49 - 2.31 (m, 3H), 2.16 (ddd, *J*=12.3, 6.7, 5.5 Hz, 1H), 1.83 - 1.64 (m, 2H), 0.97 (t, *J*=7.4 Hz, 3H).

Intermediate 158g: 4''-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(158g)

A mixture of 5-bromo-4'-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile (**Intermediate 158e**, 25 mg, 0.055 mmol) and phenylboronic acid (10.11 mg, 0.083 mmol) in THF (1 mL) was treated with 1.5 M Na_2CO_3 (0.111 mL, 0.166 mmol) followed by $PdCl_2$(dppf) (4.51 mg, 5.53 μmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 120 °C for 30 min. The cooled reaction mixture

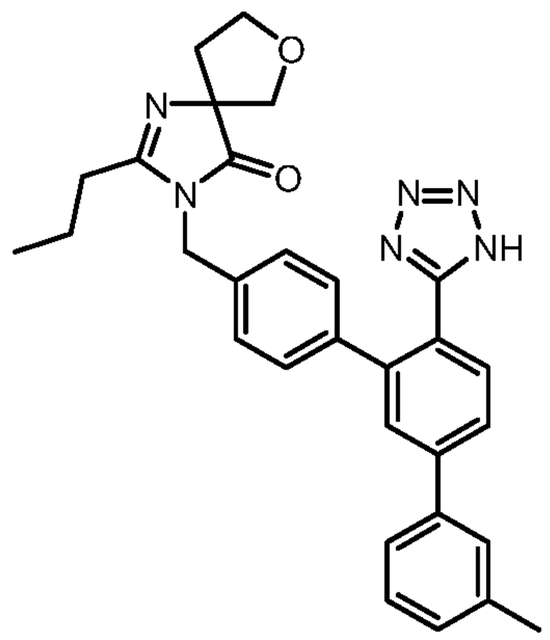
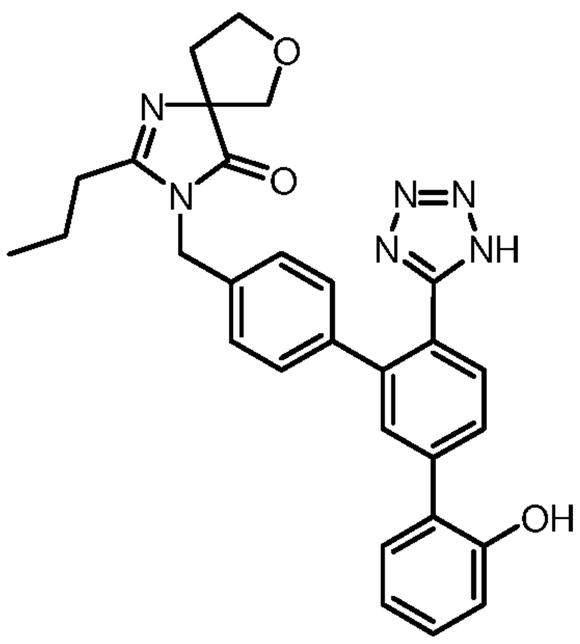
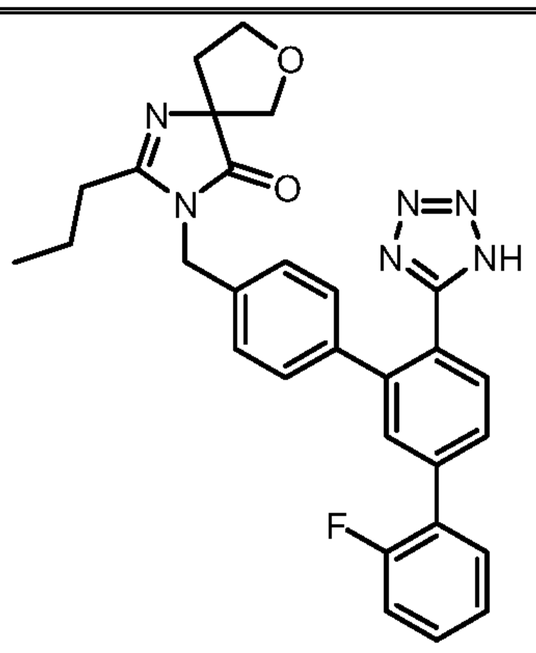
was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 158g,** 24 mg, 0.055 mmol, 100% yield) as an amber oil. LC-MS (Method A5): 2.46 min, $[M + H]^+$=450.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J*=8.0 Hz, 1H), 7.70 (d, *J*=1.4 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.62 (d, *J*=8.0 Hz, 2H), 7.44 (d, *J*=7.2 Hz, 2H), 7.42 - 7.37 (m, 1H), 7.33 (d, *J*=8.0 Hz, 2H), 7.29 - 7.26 (m, 1H), 4.78 (s, 2H), 4.09 - 4.03 (m, 2H), 4.02 - 3.95 (m, 2H), 2.46 (s, 3H), 2.44 - 2.39 (m, 2H), 2.11 - 2.02 (m, 2H), 1.71 - 1.59 (m, 2H), 1.52 (br d, *J*=13.2 Hz, 2H), 1.40 (sxt, *J*=7.4 Hz, 2H), 0.92 (t, *J*=7.3 Hz, 3H).

Example 158-enantiomer 1: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one

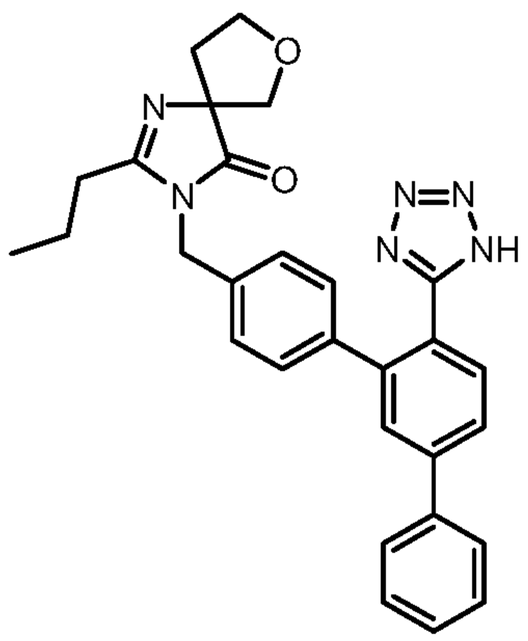
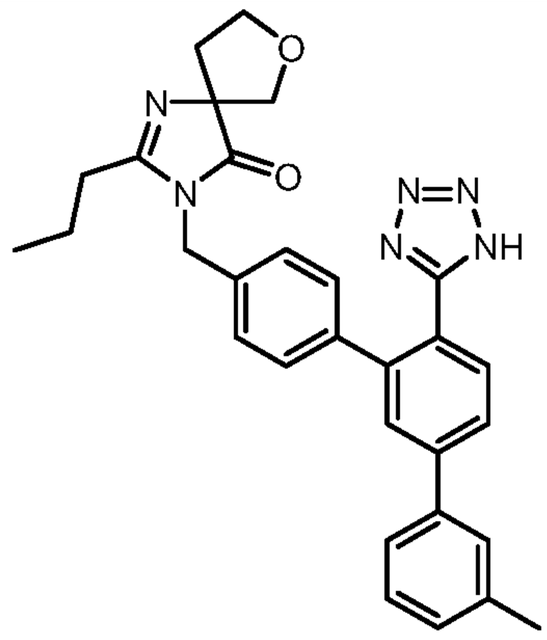
To a solution of 4''-((4-oxo-2-propyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (**Intermediate 158g** ,24 mg, 0.055 mmol) in toluene (1.5 mL) was added dibutyltin oxide (27.7 mg, 0.111 mmol) and TMS-N_3 (0.074 mL, 0.556 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC for two times (First: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 6-52% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min; Second: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 11-51% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min.) to afford 8.0 mg (0.016 mmol, 29.2 % yield) of the title compound **Example 158-enantiomer 1**. LC-MS (Method A3): 1.38 min, $[M + H]^+$= 493.18; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (br d, *J*=7.4 Hz, 2H), 7.74 (s, 2H), 7.64 (s, 1H), 7.50 (br t, *J*=7.7 Hz, 2H), 7.45 - 7.34 (m, 1H), 7.23 (br d, *J*=8.0 Hz, 2H), 7.08 (br d, *J*=7.9 Hz, 2H), 4.70 (s, 2H), 4.01 (t, *J*=6.8 Hz, 2H), 3.82 - 3.70 (m, 2H), 2.36 (t, *J*=7.2 Hz, 2H), 2.19 (dt, *J*=12.3, 7.7 Hz, 1H), 2.09 - 1.98 (m, 1H), 1.67 - 1.55 (m, 2H), 0.91 (t, *J*=7.4 Hz, 3H).

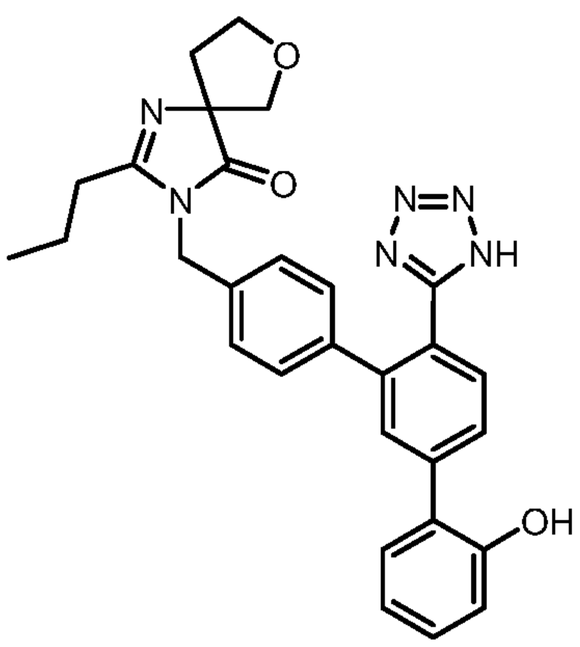
The following examples have been similarly prepared from **Intermediate 158e-enantiomer 1** as described above for **Example 158-enantiomer 1**. Two analytical LC-

MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

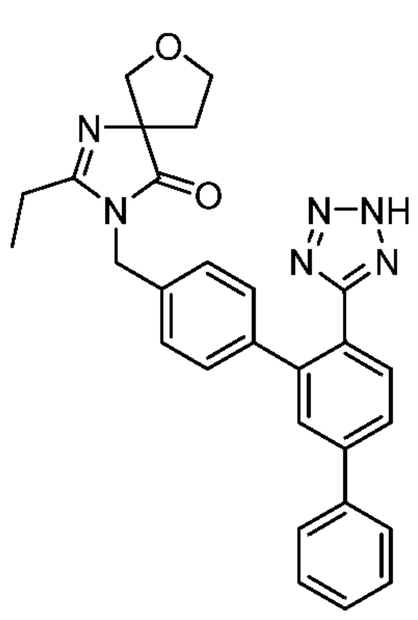
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
159		506.61	507.03; 1.5 min (Method A3)	7.79 - 7.69 (m, 2H), 7.64 (d, *J*=1.4 Hz, 1H), 7.59 (s, 1H), 7.55 (br d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.26 - 7.17 (m, 3H), 7.08 (br d, *J*=8.0 Hz, 2H), 4.69 (s, 2H), 4.00 (dd, *J*=7.6, 6.0 Hz, 2H), 3.82 - 3.66 (m, 2H), 2.39 (s, 3H), 2.38 - 2.29 (m, 2H), 2.18 (dt, *J*=12.4, 7.8 Hz, 1H), 2.02 (td, *J*=11.8, 5.4 Hz, 1H), 1.73 - 1.50 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H)
160		508.58	509.01; 1.19 min (Method A3)	7.65 (s, 2H), 7.58 (s, 1H), 7.38 (br d, *J*=6.9 Hz, 1H), 7.26 - 7.13 (m, 3H), 7.07 (br d, *J*=7.7 Hz, 2H), 6.98 (d, *J*=8.0 Hz, 1H), 6.91 (br t, *J*=7.4 Hz, 1H), 4.69 (s, 2H), 4.05 - 3.96 (m, 2H), 3.80 - 3.68 (m, 2H), 2.34 (br t, *J*=7.2 Hz, 2H), 2.23 - 2.15 (m, 1H), 2.07 - 1.97 (m, 1H), 1.58 (br dd, *J*=14.6, 7.4 Hz, 2H), 0.88 (q, *J*=7.2 Hz, 3H)
161		510.57	511.01; 1.38min (Method A3)	7.72 (d, *J*=7.9 Hz, 1H), 7.69 - 7.61 (m, 2H), 7.55 (s, 1H), 7.52 - 7.41 (m, 1H), 7.40 - 7.30 (m, 2H), 7.17 (br d, *J*=7.9 Hz, 2H), 7.07 (br d, *J*=7.9 Hz, 2H), 4.69 (s, 2H), 3.99 (br t, *J*=6.7 Hz, 2H), 3.86 - 3.66 (m, 2H), 2.33 (br t, *J*=7.2 Hz, 2H), 2.17 (dt, *J*=12.4, 7.8 Hz, 1H), 2.01 (dt, *J*=12.1, 5.9 Hz, 1H), 1.64 - 1.46 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H)

The following examples have been similarly prepared from **Intermediate 158f-enantiomer 2** as described above for **Example 158**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
162		492.58	493.32; 1.34 min (Method A3)	7.77 (br d, *J*=7.6 Hz, 2H), 7.72 (s, 2H), 7.62 (s, 1H), 7.49 (br t, *J*=7.4 Hz, 2H), 7.44 - 7.34 (m, 1H), 7.22 (br d, *J*=7.9 Hz, 2H), 7.07 (br d, *J*=7.7 Hz, 2H), 4.69 (s, 2H), 4.00 (br t, *J*=6.7 Hz, 2H), 3.84 - 3.63 (m, 2H), 2.36 (br t, *J*=7.2 Hz, 2H), 2.19 (dt, *J*=12.2, 7.8 Hz, 1H), 2.07 - 1.95 (m, 1H), 1.67 - 1.46 (m, 2H), 0.90 (br t, *J*=7.3 Hz, 3H)
163		506.61	507.4; 1.73 min (Method A3)	7.79 - 7.66 (m, 2H), 7.62 (br d, *J*=10.1 Hz, 2H), 7.57 (br d, *J*=7.3 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.38 (t, *J*=7.8 Hz, 1H), 7.25 - 7.18 (m, 3H), 7.07 (br d, *J*=8.2 Hz, 2H), 4.70 (s, 2H), 4.00 (br t, *J*=6.7 Hz, 2H), 3.79 - 3.70 (m, 2H), 2.40 (s, 3H), 2.36 (br t, *J*=7.3 Hz, 2H), 2.25 - 2.14 (m, 1H), 2.06 - 1.96 (m, 1H), 1.65 - 1.54 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H)

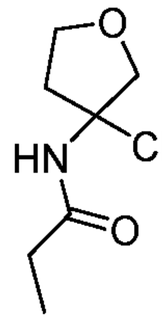
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
164		508.58	509.01; 1.18 min (Method A3)	7.76 (br s, 1H), 7.68 (br s, 2H), 7.41 (br d, *J*=7.6 Hz, 1H), 7.23 (br t, *J*=7.6 Hz, 1H), 7.13 (br s, 4H), 6.99 (d, *J*=8.2 Hz, 1H), 6.93 (br t, *J*=7.5 Hz, 1H), 4.70 (s, 2H), 3.99 (br t, *J*=6.6 Hz, 2H), 3.81 - 3.68 (m, 2H), 2.32 (br t, *J*=7.2 Hz, 2H), 2.18 (dt, *J*=12.2, 7.6 Hz, 1H), 2.01 (dt, *J*=11.8, 5.8 Hz, 1H), 1.61 - 1.49 (m, 2H), 0.88 - 0.84 (m, 3H)

Example 165: 4''-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(Ex. 165, enantiomer 1)

Intermediate 165a: N-(3-cyanotetrahydrofuran-3-yl)propionamide

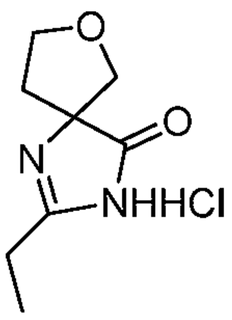


(165a)

To a solution of **Intermediate 158a** (600 mg, 4.04 mmol) in DCM (10 mL) was added potassium carbonate (2902 mg, 21.00 mmol) in H_2O (10 mL). The mixture was cooled with an ice bath, ropionyl chloride (523 mg, 5.65 mmol) in DCM (4 mL) was added

dropwise to the stirred solution. The reaction mixture was stirred at 0°C for 2 h, and at rt for 3 h. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 165a**, 500 mg, 2.97 mmol, 73.6 % yield) as oil. LC-MS (Method A5): 0.39 min, $[M + H]^+$=169.1; ^{1}H NMR (500 MHz, MeOH-d_4) δ 9.37 (br s, 1H), 4.80 (d, *J*=9.4 Hz, 1H), 4.61 - 4.43 (m, 3H), 3.18 (ddd, *J*=13.3, 7.6, 6.9 Hz, 1H), 3.05 (ddd, *J*=13.3, 7.5, 5.9 Hz, 1H), 2.82 (q, *J*=7.7 Hz, 2H), 1.63 (t, *J*=7.6 Hz, 3H)

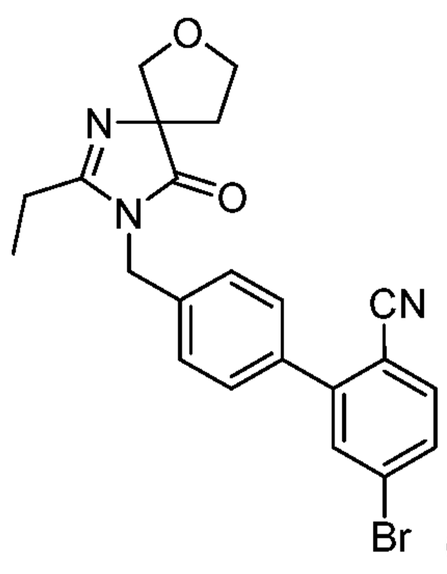
Intermediate 165b: 2-ethyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride



(165b)

To a solution of **Intermediate 165a** (500 mg, 2.97 mmol) in n-propanol (7.5 mL) was added 4N HCl in dioxane (7.43 mL, 29.7 mmol) dropwise. The mixture was heated up to 50°C in oil bath for overnight. The mixture was concentrated and dried under vacuum to give the title compound (**Intermediate 165b**, 600 mg, 2.93 mmol, 99 % yield) as a whit solid. LC-MS (Method A5): 0.28 min, $[M + H]^+$=169.1; ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.77 - 4.72 (m, 2H), 4.65 - 4.61 (m, 1H), 4.53 (d, *J*=9.9 Hz, 1H), 3.57 (q, *J*=7.4 Hz, 2H), 3.11 - 2.99 (m, 1H), 2.94 (dt, *J*=13.4, 8.0 Hz, 1H), 1.98 (t, *J*=7.6 Hz, 3H).

Intermediate 165c: 5-bromo-4'-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile

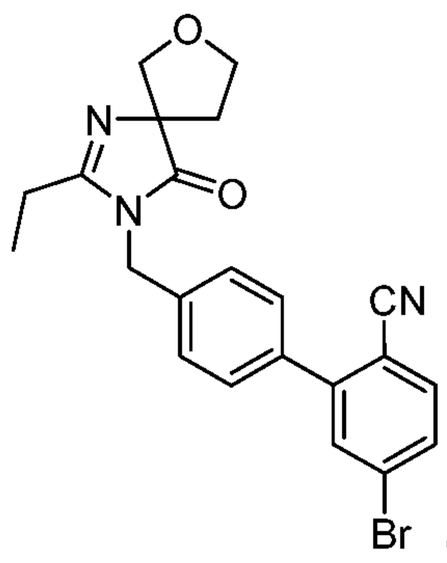


(165 c, racemate)

Intermediate 165b (400 mg, 1.954 mmol) was dissolved in DMF (10 mL). NaH (176 mg, 4.40 mmol) was added. The mixture was stirred at rt for 15min, 5-bromo-4'-

(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile (**I-002**, 720 mg, 2.052 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (DCM/AcOEt, 0-100%) to give the title compound (**Intermediate 165c**, 450 mg, 1.027 mmol, 52.5 % yield) as a white solid. LC-MS (Method A5): 2.29 min, $[M + H]^+$= 438.1 and 440.1; ^1H NMR (500 MHz, MeOH-d_4) δ 7.76 (d, *J*=1.4 Hz, 1H), 7.73 - 7.69 (m, 2H), 7.58 (d, *J*=8.3 Hz, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 4.85 (d, *J*=5.0 Hz, 2H), 4.23 - 4.12 (m, 2H), 4.00 - 3.93 (m, 1H), 3.92 - 3.80 (m, 1H), 2.51 (q, *J*=7.2 Hz, 2H), 2.37 (dt, *J*=12.7, 7.7 Hz, 1H), 2.17 (ddd, *J*=12.4, 6.9, 5.4 Hz, 1H), 1.20 (t, *J*=7.4 Hz, 3H).

Intermediate 165d-enantiomer 1: 5-bromo-4'-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile



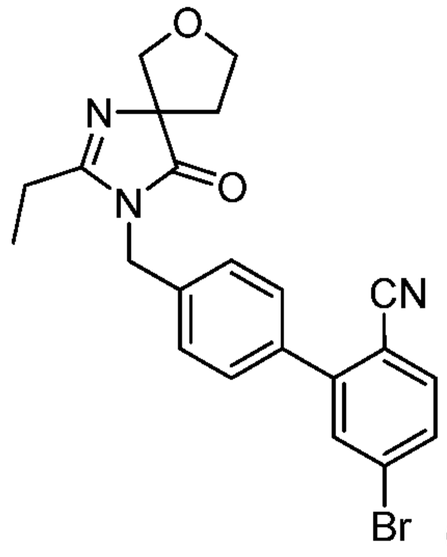
(165d)

Intermediate 165c-racemate (450 mg, 1.027 mmol) were resolved into two peaks on Instrument PIC Solution SFC Prep-200 with the following preparative chromatographic conditions: Column: Chiralpak AD-H, 30 x 250 mm, 5 micron; Mobile Phase: 20% IPA/ 80% CO_2; Flow Conditions: 85 mL/min, 120 Bar, 40 °C; Detector Wavelength: 220 nm; injection details: 0.5 mL of ~155mg/mL in IPA/MeOH. Purity of each fraction was determined using the analytical chromatographic condition below: Instrument: Aurora Analytical SFC; Column: Chiralpak AD-H, 4.6 x 250 mm, 5 micron; Mobile Phase: 20% IPA / 80% CO2; Flow Conditions: 2.0 mL/min, 150 Bar, 40 °C; Detector Wavelength: 220 nm; Injection Details: 10μL of ~0.2mg/mL in MeOH.

Peak 1 was collected and concentrated to give **Intermediate 165d-enantiomer 1** (100 mg, 0.23mmol, 22 % yield): enantiomeric excess > 99%. Chiral analytical RT = 8.72 min. LC-MS (Method A5): 2.29 min, $[M + H]^+$= 438.1 and 440.1; ^1H NMR (500 MHz,

$CDCl_3$) δ 7.69 (d, *J*=1.1 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H), 4.78 (d, *J*=6.6 Hz, 2H), 4.30 - 4.12 (m, 2H), 4.02 - 3.97 (m, 1H), 3.96 - 3.85 (m, 1H), 2.55 - 2.28 (m, 3H), 2.19 (ddd, *J*=12.4, 6.9, 5.5 Hz, 1H), 1.27 - 1.23 (m, 3H).

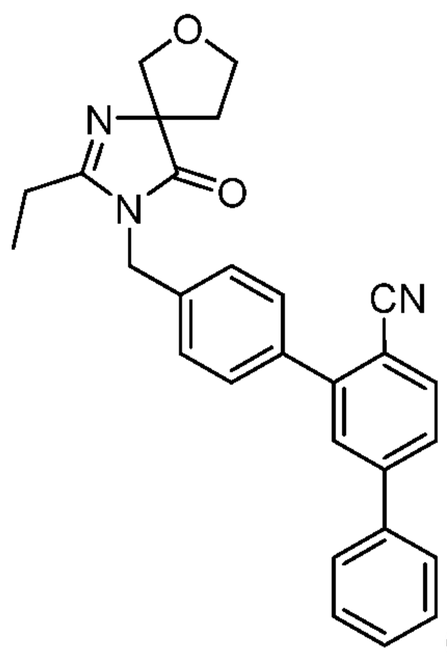
Intermediate 165e-enantiomer 2: 5-bromo-4'-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile



(165e)

Peak 2 was collected and concentrated to give **Intermediate 165e-enantiomer 2** (100 mg, 0.23mmol, 22 % yield): enantiomeric excess 95.4%. Chiral analytical RT = 11.52 min. LC-MS (Method A5): 2.29 min, $[M + H]^+$= 438.1 and 440.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.64 (d, *J*=2.8 Hz, 2H), 7.56 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 4.78 (d, *J*=6.6 Hz, 2H), 4.28 - 4.11 (m, 2H), 4.02 - 3.98 (m, 1H), 3.97 - 3.87 (m, 1H), 2.49 - 2.31 (m, 3H), 2.25 - 2.10 (m, 1H), 1.25 - 1.22 (m, 3H).

Intermediate 165f: 4''-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(165f)

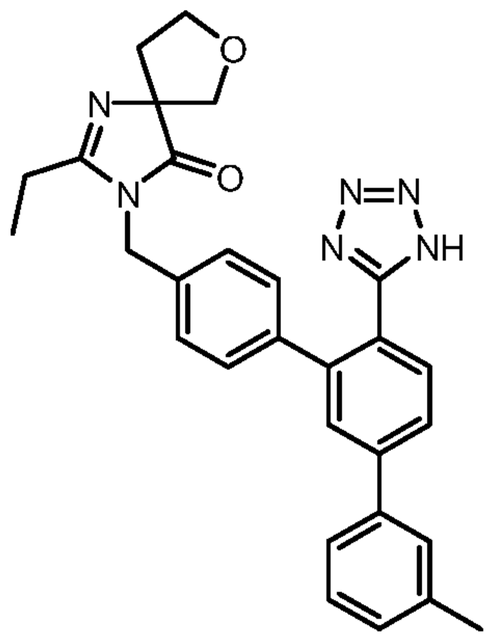
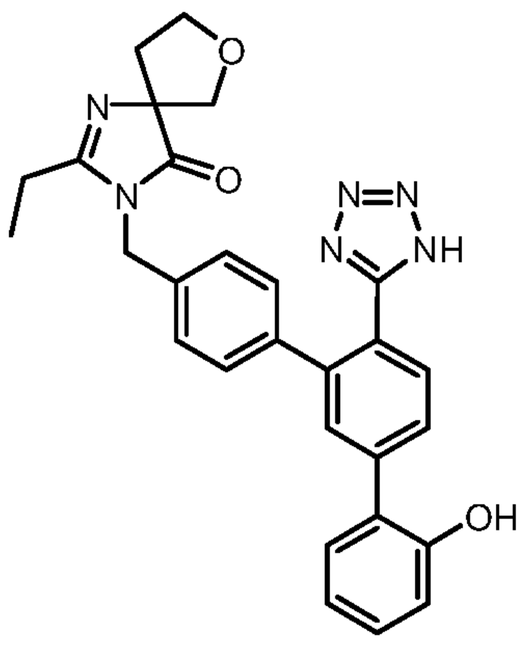
A mixture of **Intermediate 165d-enantiomer 1**, 25 mg, 0.057 mmol) and phenylboronic acid (10.43 mg, 0.086 mmol) in THF (1 mL) was treated with 1.5 M Na_2CO_3 (0.114 mL, 0.171 mmol) followed by $PdCl_2$(dppf) (4.66 mg, 5.70 μmol). The resulting mixture was

degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 120 °C for 30 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 165f,** 24 mg, 0.057 mmol, 100% yield) as an amber oil. LC-MS (Method A5): 2.48 min, $[M + H]^+$=436.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.0 Hz, 1H), 7.72 (s, 1H), 7.70 (br d, *J*=8.0 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 4H), 7.55 - 7.49 (m, 2H), 7.49 - 7.43 (m, 1H), 7.34 (d, *J*=8.0 Hz, 2H), 4.79 (d, *J*=6.3 Hz, 2H), 4.29 - 4.16 (m, 2H), 4.11 - 3.98 (m, 1H), 3.97 - 3.86 (m, 1H), 2.68 - 2.35 (m, 3H), 2.20 (dt, *J*=12.4, 6.2 Hz, 1H), 1.27 - 1.23 (m, 3H).

Example 165-enantiomer 1: 4''-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile

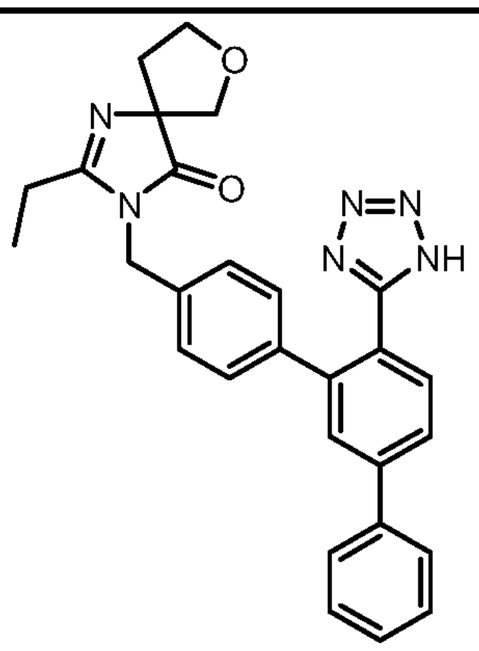
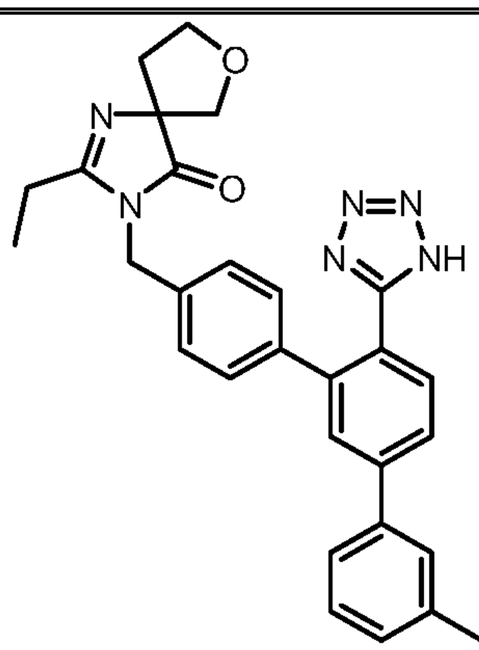
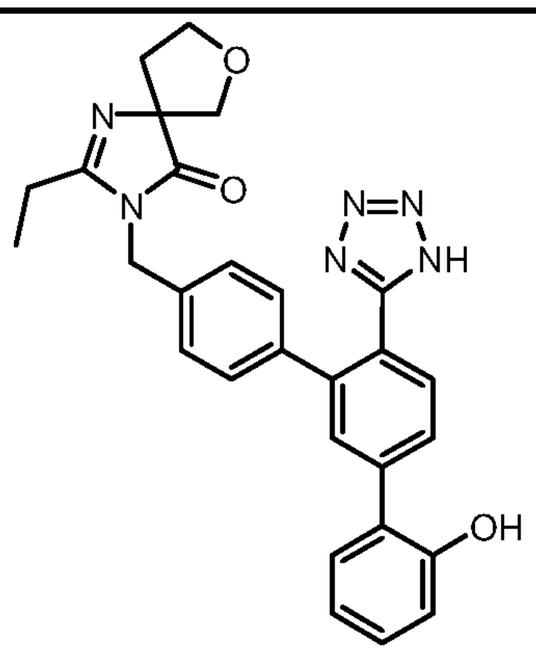
To a solution of **Intermediate 165f**, 25 mg, 0.057 mmol) in toluene (1.5 mL) was added dibutyltin oxide (28.4 mg, 0.114 mmol) and TMS-N_3 (0.076 mL, 0.570 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 11-51% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.) to afford 22.7 mg (0.047mmol, 83 % yield) of the title compound **Example 165-enantiomer 1**. LC-MS (Method A3): 1.29 min, $[M + H]^+$= 479.04; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 - 7.79 (m, 3H), 7.75 (br d, *J*=10.1 Hz, 2H), 7.57 - 7.49 (m, 2H), 7.47 - 7.40 (m, 1H), 7.39 - 7.38 (m, 1H), 7.20 (br d, *J*=7.9 Hz, 2H), 7.12 (br d, *J*=7.9 Hz, 2H), 4.71 (s, 2H), 4.00 (br t, *J*=6.7 Hz, 2H), 3.81 - 3.69 (m, 2H), 2.39 (q, *J*=7.3 Hz, 2H), 2.18 (dt, *J*=12.4, 7.7 Hz, 1H), 2.02 (dt, *J*=12.2, 5.8 Hz, 1H), 1.08 (t, *J*=7.3 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 165d-enantiomer 1** as described above for **Example 165-enantiomer 1**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

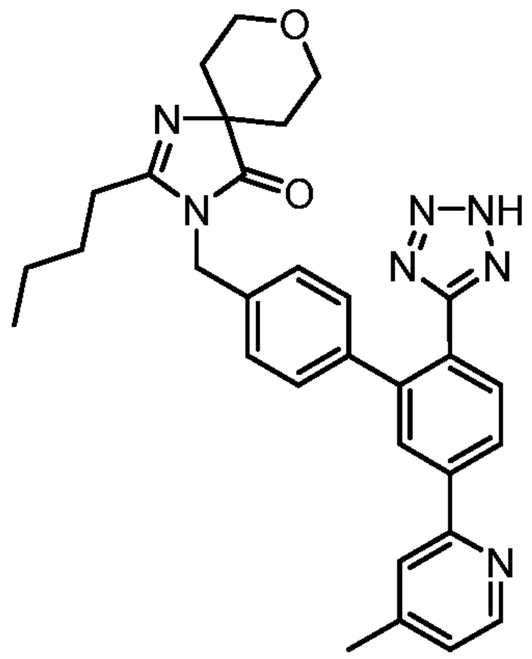
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
166		492.58	493.3; 1.46min (Method A3)	7.81 - 7.76 (m, 1H), 7.75 - 7.71 (m, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 7.57 (br d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.25 - 7.18 (m, 3H), 7.11 (d, *J*=8.0 Hz, 2H), 4.70 (s, 2H), 4.01 (dd, *J*=7.4, 6.1 Hz, 2H), 3.80 - 3.64 (m, 2H), 2.45 - 2.33 (m, 5H), 2.19 (dt, *J*=12.4, 7.7 Hz, 1H), 2.03 (dt, *J*=12.2, 5.9 Hz, 1H), 1.09 (t, *J*=7.3 Hz, 3H)
167		494.56	495.38; 1.15min (Method A3)	7.72 - 7.64 (m, 2H), 7.62 (s, 1H), 7.40 (br d, *J*=7.6 Hz, 1H), 7.21 (br t, *J*=7.3 Hz, 1H), 7.18 - 7.13 (m, 2H), 7.12 - 7.06 (m, 2H), 6.98 (br d, *J*=7.6 Hz, 1H), 6.92 (br t, *J*=7.2 Hz, 1H), 4.69 (br s, 2H), 4.00 (br t, *J*=6.6 Hz, 2H), 3.81 - 3.69 (m, 2H), 2.43 - 2.31 (m, 2H), 2.24 - 2.11 (m, 1H), 2.06 - 1.99 (m, 1H), 1.07 (br t, *J*=7.3 Hz, 3H)

The following examples have been similarly prepared from **5-bromo-4'-((2-ethyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile (165e-enantiomer 2** as described above for **Example 165-enantiomer 1**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm

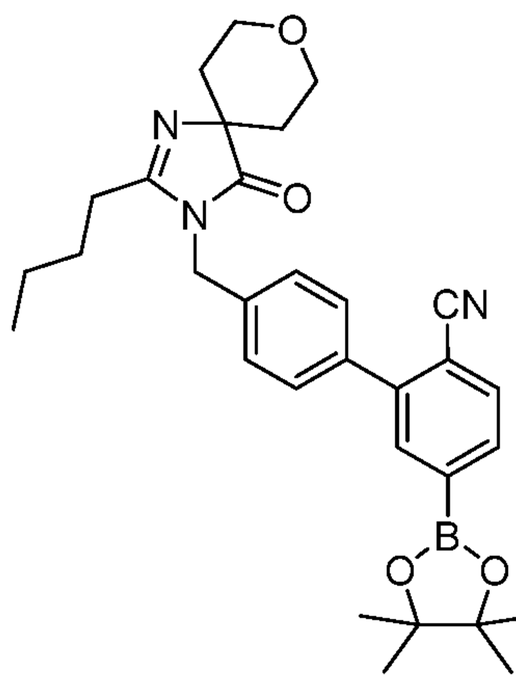
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
168		478.56	479.23; 1.33 min (Method A3)	7.84 - 7.76 (m, 3H), 7.75 - 7.72 (m, 1H), 7.68 (s, 1H), 7.50 (t, *J*=7.6 Hz, 2H), 7.45 - 7.36 (m, 1H), 7.21 (d, *J*=8.1 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 4.70 (s, 2H), 4.01 (dd, *J*=7.5, 6.1 Hz, 2H), 3.80 - 3.68 (m, 2H), 2.39 (q, *J*=7.3 Hz, 2H), 2.18 (dt, *J*=12.3, 7.8 Hz, 1H), 2.09 - 1.96 (m, 1H), 1.09 (t, *J*=7.3 Hz, 3H)
169		492.58	493.02; 1.4 min (Method A3)	7.84 - 7.77 (m, 1H), 7.75 - 7.69 (m, 2H), 7.63 (s, 1H), 7.59 (br d, *J*=7.9 Hz, 1H), 7.39 (t, *J*=7.6 Hz, 1H), 7.24 (br d, *J*=7.3 Hz, 1H), 7.19 (d, *J*=7.9 Hz, 2H), 7.11 (br d, *J*=7.9 Hz, 2H), 4.70 (s, 2H), 4.00 (t, *J*=6.7 Hz, 2H), 3.82 - 3.66 (m, 2H), 2.46 - 2.32 (m, 5H), 2.18 (dt, *J*=12.5, 7.8 Hz, 1H), 2.02 (dt, *J*=12.1, 5.9 Hz, 1H), 1.08 (t, *J*=7.3 Hz, 3H)
170		494.56	495.25; 1.09min (Method A3)	7.70 - 7.58 (m, 2H), 7.56 (s, 1H), 7.42 - 7.31 (m, 1H), 7.23 - 7.12 (m, 3H), 7.07 (br d, *J*=8.1 Hz, 2H), 6.97 (d, *J*=7.9 Hz, 1H), 6.91 (t, *J*=7.3 Hz, 1H), 4.68 (s, 2H), 4.00 (dd, *J*=7.6, 6.0 Hz, 2H), 3.87 - 3.61 (m, 2H), 2.39 (q, *J*=7.3 Hz, 2H), 2.18 (dt, *J*=12.4, 7.8 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.08 (t, *J*=7.3 Hz, 3H)

Example 171: 2-butyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-8-oxa-1, 3-diazaspiro[4.5]dec-1-en-4-one



(Ex. 171)

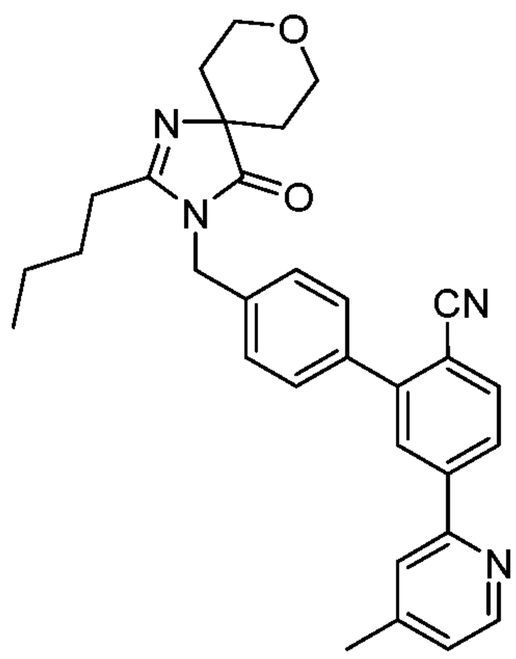
Intermediate 171a: 4'-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(171a)

Intermediate 155d (240 mg, 0.500 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (190 mg, 0.749 mmol), KOAc (123 mg, 1.249 mmol) in dioxane (4 mL) was degassed by bubbling Ar for 1 min, then $Pd(dppf)Cl_2$ (20.40 mg, 0.025 mmol) was added. The mixture was sealed in a pressure vial and heated in an oil bath at 125 °C for 1 h. The reaction mixture was directly loaded onto a silica gel cartridge, purified by ISCO (DCM/MeOH, 0-20%) to afford the title compound (**Intermediate 171a,** 240 mg, 0.455 mmol, 91 % yield). LC-MS (Method A5): 2.22 min, $[M + H]^+$=446.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.87 (dd, *J*=7.7, 0.8 Hz, 1H), 7.77 (d, *J*=7.7 Hz, 1H), 7.58 (d, *J*=8.0 Hz, 2H), 7.32 - 7.26 (m, 2H), 4.77 (s, 2H), 4.09 - 4.03 (m, 2H), 4.02 - 3.94 (m, 2H), 2.46 - 2.32 (m, 2H), 2.06 (ddd, *J*=13.5, 9.6, 4.4 Hz, 2H), 1.65 (br t, *J*=7.7 Hz, 2H), 1.52 (br d, *J*=13.5 Hz, 2H), 1.42 - 1.38 (m, 2H), 1.27 (s, 12H), 0.92 (t, *J*=7.3 Hz, 3H).

Intermediate 171b: 4'-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(171b)

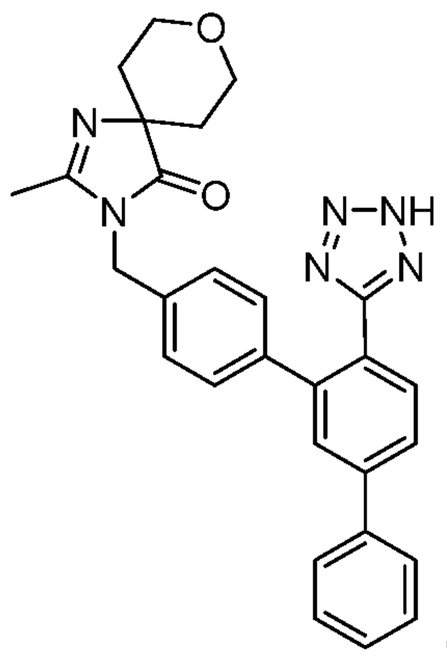
A solution of **Intermediate 171a** (30mg, 0.057 mmol), 2-bromo-4-methylpyridine (24.46 mg, 0.142 mmol) and Pd-XPhos G3 (1.926 mg, 2.275 µmol) in THF (1.5 mL) was added K_3PO_4 (1.0 M, 0.114 mL, 0.114 mmol). The mixture was degassed with Ar for 1 min. then sealed in a pressure vial and heated at 120 °C in a microwave reactor for 45 min. The reaction mixture was concentrated and purified by ISCO (DCM/MeOH, 0-20%) to afford the title compound (**Intermediate 171b,** 28 mg, 0.057 mmol, 100 % yield). LC-MS (Method A5): 2.18 min, $[M + H]^+$= 393.3; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 - 8.51 (m, 1H), 8.26 - 8.13 (m, 1H), 8.09 - 7.80 (m, 1H), 7.67 - 7.60 (m, 2H), 7.52 (d, *J*=8.3 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.26 (d, *J*=8.0 Hz, 1H), 7.17 (dd, *J*=8.3, 5.2 Hz, 1H), 6.95 - 6.84 (m, 1H), 4.77 (d, *J*=12.7 Hz, 2H), 4.11 - 4.03 (m, 2H), 4.02 - 3.93 (m, 2H), 2.47 (d, *J*=8.0 Hz, 3H), 2.44 - 2.38 (m, 2H), 2.10 - 2.01 (m, 2H), 1.72 - 1.57 (m, 2H), 1.53 (br d, *J*=13.2 Hz, 2H), 1.38 (br dd, *J*=14.6, 7.4 Hz, 2H), 0.93 - 0.83 (m, 3H).

Example 171: 2-butyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one

To a solution of 4'-((2-butyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)-5-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 171b**, 28.1 mg, 0.057 mmol) in toluene (1.5 mL) was added dibutyltin oxide (28.4 mg, 0.114 mmol) and TMS-N_3 (0.076 mL, 0.570 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19

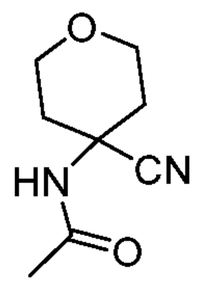
x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 12-52% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min) to afford 5.4 mg (9.68 μmol, 16.98 % yield) of the title compound **Example 171**. LC-MS (Method A3): 1.36 min, [M + H]$^+$= 536.09; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (br s, 2H), 8.35 - 7.71 (m, 4H), 7.33 - 6.91 (m, 4H), 4.68 (br s, 2H), 3.99 - 3.81 (m, 2H), 3.80 - 3.61 (m, 2H), 2.40 (br s, 3H), 2.34 (br d, *J*=7.9 Hz, 2H), 1.94 - 1.64 (m, 2H), 1.60 - 1.40 (m, 2H), 1.37 - 1.23 (m, 4H), 0.91 - 0.77 (m, 3H).

Example 172: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-methyl-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one



(Ex. 172)

Intermediate 172a: N-(4-cyanotetrahydro-2H-pyran-4-yl)acetamide

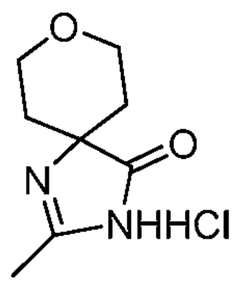


(172a)

To a solution of **Intermediate 155a** (500mg, 3.07 mmol) in DCM (6 mL) was added potassium carbonate (2.2 g, 16 mmol) in H_2O (8 mL). The mixture was cooled with an ice bath. Acetyl chloride (0.306 mL, 4.30 mmol) in DCM (4 mL) was added dropwise to the stirred solution. The reaction mixture was stirred at 0 °C for 2 h, and at rt for 3 h. The organic phase was collected. The aqueous phase was extracted (2X) with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by ISCO (DCM/AcOEt, 0-100%) to give the title compound (**Intermediate 172a**, 100 mg, 0.595 mmol, 19.34 % yield) as oil. ^{1}H NMR (500 MHz,

MeOH-d_4) δ 3.92 (dt, *J*=12.4, 4.1 Hz, 2H), 3.78 - 3.62 (m, 2H), 2.33 (br d, *J*=13.5 Hz, 2H), 2.01 (s, 3H), 1.93 (ddd, *J*=13.8, 10.0, 4.0 Hz, 2H).

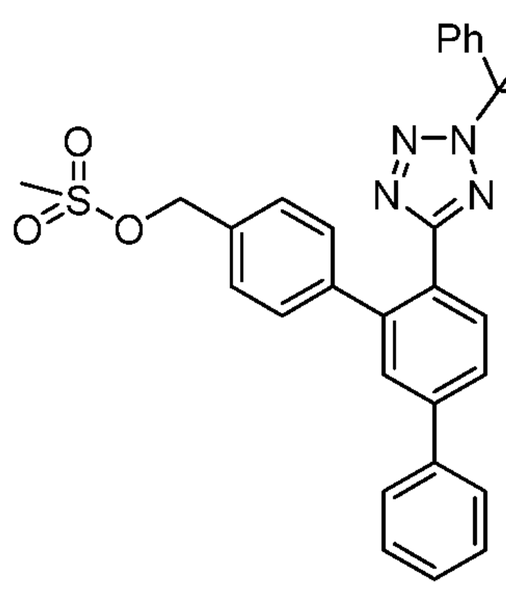
Intermediate 172b: 2-methyl-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one hydrochloride



(172b)

To a solution of **Intermediate 172a** (100 mg, 0.595 mmol) in n-propanol (1.5 mL) was added 4N HCl in dioxane (1.486 mL, 5.95 mmol) dropwise. The mixture was heated up to 50°C in oil bath for overnight. The mixture was concentrated and dried under vacuum to give the title compound (**Intermediate 172b**, 120 mg, 0.586 mmol, 99 % yield) as a whit solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.11 - 4.01 (m, 2H), 3.76 (ddd, *J*=12.3, 9.4, 3.0 Hz, 2H), 2.61 (s, 3H), 2.11 (ddd, *J*=14.0, 9.6, 4.4 Hz, 2H), 1.93 - 1.80 (m, 2H).

Intermediate 172c: (6'-(2-trityl-2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl methanesulfonate



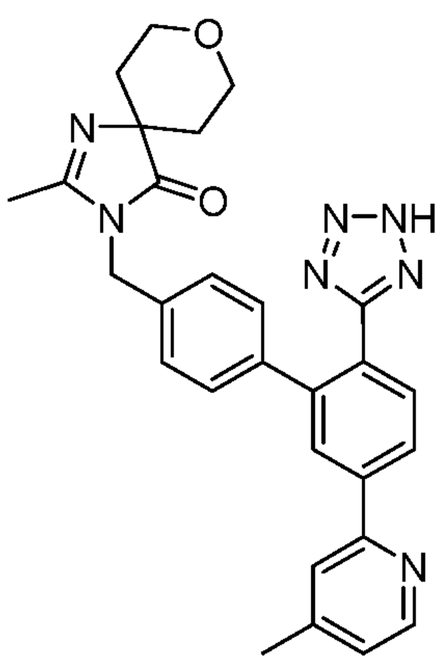
(172c)

A solution of **I-003** (3 g, 5.26 mmol) and TEA (1.832 ml, 13.14 mmol) in THF (10 mL) was cooled to 0°C and treated with methanesulfonyl chloride (0.498 ml, 6.31 mmol) dropwise. The mixture was slowly warmed to rt and stirred at rt for 1h. The reaction was diluted with DCM, quenched with sat. NH_4Cl and extracted with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to the title compound (**Intermediate 172c**, 3.4 g, 5.24 mmol, 100 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J*=8.0 Hz, 1H), 7.75 (dd, *J*=8.1, 1.8 Hz, 1H), 7.68 (d, *J*=7.4 Hz, 2H), 7.64 (d, *J*=1.7 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.44 - 7.35 (m, 4H), 7.33 - 7.30 (m, 4H), 7.29 (s, 3H), 7.28 - 7.24 (m, 2H), 7.23 - 7.20 (m, 2H), 6.95 (d, *J*=7.7 Hz, 5H), 5.17 (s, 2H), 2.87 (s, 3H).

Example 172: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-methyl-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one

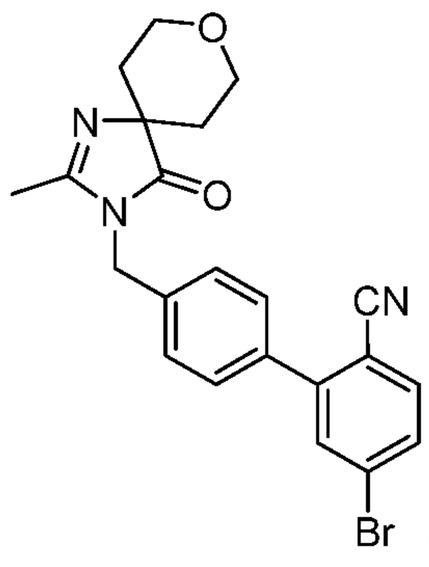
Intermediate 172b (23 mg, 0.112 mmol) was dissolved in DMF (1 mL). NaH (10.11 mg, 0.253 mmol) was added. The mixture was stirred at rt for 15min, **Intermediate 172c** (72.9 mg, 0.112 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) and concentrated. The sample was re-dissolved in DCM (1 mL) and treated with 0.1 ml of 4N HCl in dioxane for 1h. The reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 8-48% B over 23 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 22.4 mg (0.047 mmol, 41.6 % yield) of the title compound **Example 172**. LC-MS (Method A3): Retention Time: 1.26 min, $[M + H]^+$= 479.1; ^1H NMR (500 MHz, DMSO-d_6) δ 7.79 (br d, *J*=7.8 Hz, 3H), 7.76 - 7.71 (m, 1H), 7.69 (s, 1H), 7.50 (t, *J*=7.6 Hz, 2H), 7.45 - 7.36 (m, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 4.70 (s, 2H), 3.87 (dt, *J*=11.3, 3.8 Hz, 2H), 3.80 - 3.67 (m, 2H), 2.09 (s, 3H), 1.86 - 1.74 (m, 2H), 1.34 (br d, *J*=13.5 Hz, 2H).

Example 173: 2-methyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one



(Ex. 173)

Intermediate 173a: 5-bromo-4'-((2-methyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)biphenyl-2-carbonitrile

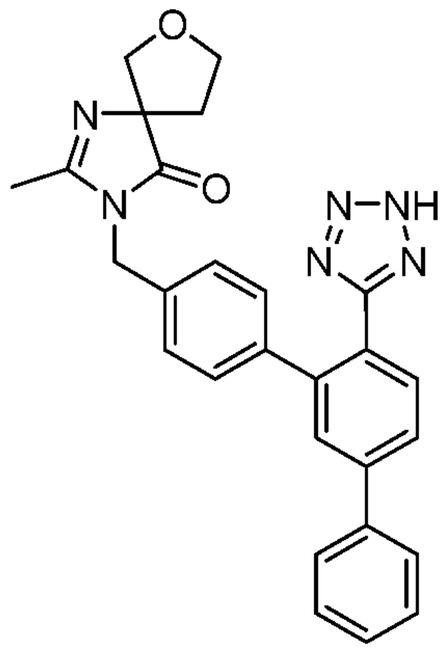


(173a)

Intermediate 172b (100mg, 0.489 mmol) was dissolved in DMF (3 mL). NaH (44.0 mg, 1.099 mmol) was added. The mixture was stirred at rt for 15min, **I-002** (172 mg, 0.489 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (Hexanes/AcOEt, 0-100%) to give the title compound (**Intermediate 173a**, 120mg, 0.274 mmol, 56.0 % yield) as a white solid. LC-MS (Method A5): 2.30 min, $[M + H]^+$= 438.1 and 440.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J*=1.4 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.54 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=8.3 Hz, 2H), 4.76 (s, 2H), 4.07 - 3.99 (m, 2H), 3.99 - 3.88 (m, 2H), 2.18 (s, 3H), 2.07 (ddd, *J*=13.8, 9.9, 4.4 Hz, 2H), 1.48 (br d, *J*=13.5 Hz, 2H).

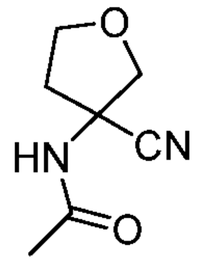
Example 173: 2-methyl-3-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]dec-1-en-4-one has been similarly prepared from **5-bromo-4'-((2-methyl-4-oxo-8-oxa-1,3-diazaspiro[4.5]dec-1-en-3-yl)methyl)biphenyl-2-carbonitrile (Intermediate 173a)** as described above for **Example 171**. LC-MS (Method A5): 1.06 min, $[M + H]^+$= 494.23; ^1H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, *J*=4.9 Hz, 1H), 8.22 (br d, *J*=8.5 Hz, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.25 (br d, *J*=4.6 Hz, 1H), 7.22 - 7.16 (m, 2H), 7.12 (br d, *J*=7.9 Hz, 2H), 4.71 (s, 2H), 3.95 - 3.83 (m, 2H), 3.80 - 3.69 (m, 2H), 2.42 (s, 3H), 2.09 (s, 3H), 1.87 - 1.76 (m, 2H), 1.33 (br d, *J*=13.1 Hz, 2H).

Example 174-enantiomer 1: 3-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-methyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one



(Ex. 174)

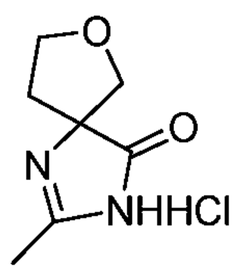
Intermediate 174a: N-(3-cyanotetrahydrofuran-3-yl)acetamide



(174a)

To a solution of **Intermediate 158a** (500 mg, 2.7 mmol) in DCM (10 mL) was added triethylamine (1.876 mL, 13.46 mmol). The mixture was cooled with an ice bath, acetyl chloride (0.335 mL, 4.71 mmol) in DCM (2 mL) was added dropwise to the stirred solution. The reaction mixture was concentrated and the residue was directly purified by ISCO (DCM/MeOH, 0-20%) to give the title compound (**Intermediate 174a**, 300 mg, 1.946 mmol, 72.0 % yield) as oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.22 (d, *J*=9.6 Hz, 1H), 4.05 - 3.91 (m, 3H), 2.61 (ddd, *J*=13.3, 7.8, 6.9 Hz, 1H), 2.43 (ddd, *J*=13.4, 7.4, 5.9 Hz, 1H), 2.01 (s, 3H).

Intermediate 174b: 2-methyl-7-oxa-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride

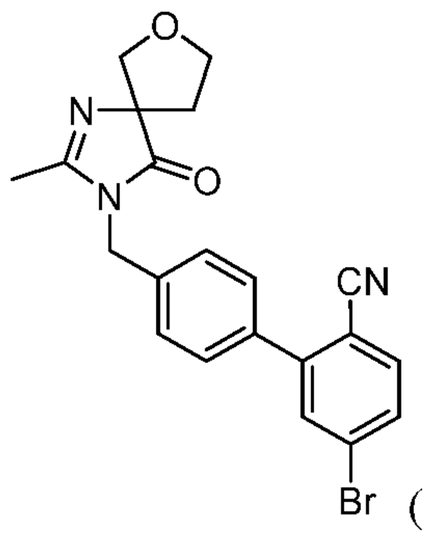


(174b)

To a solution of **Intermediate 174a** (300 mg, 1.946 mmol) in n-propanol (3 mL) was added 4N HCl in dioxane (4.86 mL, 19.46 mmol) dropwise. The mixture was heated up to 50°C in oil bath for overnight. The mixture was concentrated and dried under vacuum to give the title compound (**Intermediate** 1**74b**, 492 mg, 2.250 mmol, 100 % yield) as a white solid. LC-MS (Method A5): 0.34 min, $[M + H]^+$=155.1; ^{1}H NMR (500 MHz,

MeOH-d_4) δ 4.20 - 4.11 (m, 2H), 4.07 - 4.02 (m, 1H), 3.91 (d, *J*=9.9 Hz, 1H), 2.58 (s, 2H), 2.57 - 2.49 (m, 1H), 2.40 (dt, *J*=13.7, 6.8 Hz, 1H).

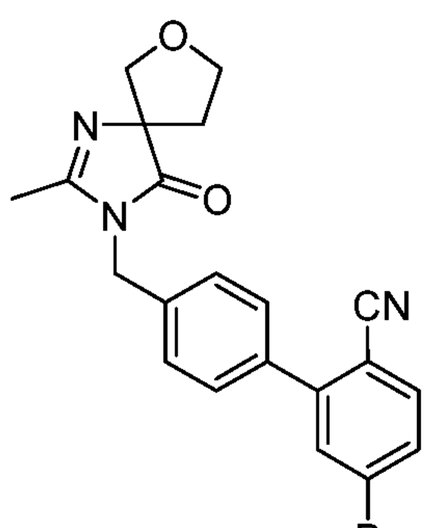
Intermediate 174c: 5-bromo-4'-((2-methyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile



(174c)

Intermediate 174b (371 mg, 1.946 mmol) was dissolved in DMF (8mL). NaH (175 mg, 4.38 mmol) was added. The mixture was stirred at rt for 15min, **I-002** (683 mg, 1.946 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO (DCM/AcOEt, 0-100%) to give the title compound (**Intermediate 174c**, 560 mg, 1.320 mmol, 67.8 % yield) as a white solid. LC-MS (Method A5): 2.24 min, $[M + H]^+$= 424.1 and 426.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=1.1 Hz, 1H), 7.66 - 7.61 (m, 2H), 7.56 (d, *J*=8.3 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 4.78 (d, *J*=6.3 Hz, 2H), 4.31 - 4.12 (m, 2H), 4.01 (d, *J*=8.8 Hz, 1H), 3.95 - 3.82 (m, 1H), 2.41 (dt, *J*=12.4, 8.0 Hz, 1H), 2.27 - 2.10 (m, 4H).

Intermediate 174d-enantiomer 1: 5-bromo-4'-((2-methyl-4-oxo-7-oxa-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)biphenyl-2-carbonitrile



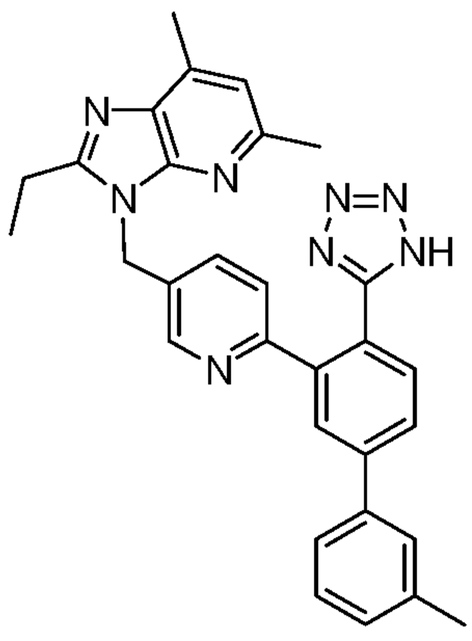
(174d)

Intermediate 174c-racemate (1.2 g, 2.83 mmol) were resolved into two peaks on Instrument PIC Solution SFC Prep-200 with the following preparative chromatographic conditions: Column: Chiralpak AD-H, 30 x 250 mm, 5 micron; Mobile Phase: 25% IPA/

75% CO_2; Flow Conditions: 85 mL/min, 120 Bar, 40 °C; Detector Wavelength: 238 nm; injection details: 1 mL of ~30mg/mL in MeOH/ACN. Purity of each fraction was determined using the analytical chromatographic condition below: Instrument: Aurora Analytical SFC; Column: Chiralpak AD-H 4.6 x 250 mm, 5 micron; Mobile Phase: 25% IPA / 75% CO2; Flow Conditions: 2.0 mL/min, 150 Bar, 40 °C; Detector Wavelength: 220nm; Injection Details: 10µL of 0.2mg/mL in MeOH. Peak 1 was collected and concentrated to give **Intermediate 174d-enantiomer 1** (300 mg, 0.707mmol, 25 % yield): enantiomeric excess > 99.0%. Chiral analytical RT = 8.14 min. LC-MS (Method A5): 2.24 min, $[M + H]^+$= 424.1 and 426.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=1.1 Hz, 1H), 7.67 - 7.61 (m, 2H), 7.57 (d, *J*=8.3 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 4.79 (d, *J*=6.3 Hz, 2H), 4.26 - 4.16 (m, 2H), 4.05 - 3.98 (m, 1H), 3.93 (d, *J*=8.5 Hz, 1H), 2.57 - 2.29 (m, 1H), 2.25 - 2.11 (m, 4H)

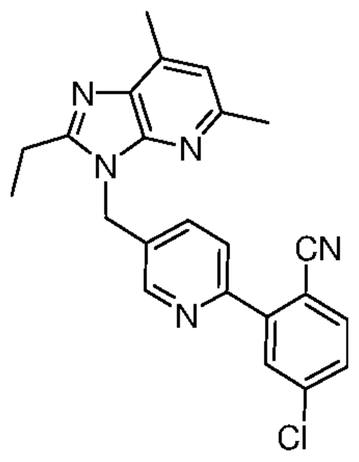
Example 174-enantiomer 1 was prepared from **Intermediate 174d-enantiomer 1** as described above for **Example 165.** LC-MS (Method A3): 1.3 min, $[M + H]^+$= 465.25; ^1H NMR (500 MHz, DMSO-d_6) δ 7.80 (br d, *J*=7.9 Hz, 3H), 7.76 - 7.72 (m, 1H), 7.70 (s, 1H), 7.55 - 7.47 (m, 2H), 7.45 - 7.36 (m, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 7.12 (br d, *J*=7.9 Hz, 2H), 4.71 (s, 2H), 4.06 - 3.94 (m, 2H), 3.75 (q, *J*=8.9 Hz, 2H), 2.17 (dt, *J*=12.3, 7.9 Hz, 1H), 2.08 (s, 3H), 2.02 (dt, *J*=11.7, 6.0 Hz, 1H).

Example 175: 2-ethyl-5, 7-dimethyl-3-((6-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyridin-3-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex. 175)

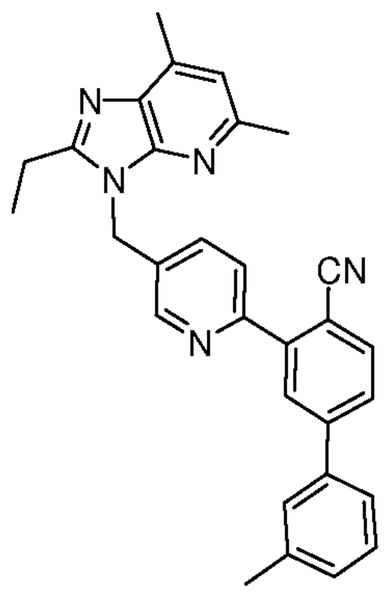
Intermediate 175a: 4-chloro-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)benzonitrile



175a

A mixture of **Intermediate 039a** (100 mg, 0.290 mmol) and (5-chloro-2-cyanophenyl)boronic acid (68.3 mg, 0.377 mmol) in THF (3 mL) was treated with 1.5 M Na_2CO_3 (0.579 mL, 0.869 mmol) followed by $PdCl_2(dppf)$ (11.83 mg, 0.014 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125 °C for 70 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude sample in 2 ml of DCM was treated with TEA (0.202 mL, 1.448 mmol) followed by TFAA (0.061 mL, 0.434 mmol). The mixture was stirred at RT for 1 hour, then concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 175a,** 65 mg, 0.162 mmol, 55.8 % yield) as an amber oil. LC-MS (Method A5): 2.18 min, $[M + H]^+$ = 402.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J*=1.7 Hz, 1H), 7.86 (d, *J*=1.9 Hz, 1H), 7.74 (dd, *J*=9.9, 8.5 Hz, 2H), 7.63 (dd, *J*=8.3, 2.2 Hz, 1H), 7.50 (dd, *J*=8.4, 2.1 Hz, 1H), 6.94 (s, 1H), 5.56 (s, 2H), 2.88 (q, *J*=7.7 Hz, 2H), 2.66 (s, 3H), 2.62 (s, 3H), 1.40 (t, *J*=7.6 Hz, 3H).

Intermediate 175b: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)-3'-methylbiphenyl-4-carbonitrile



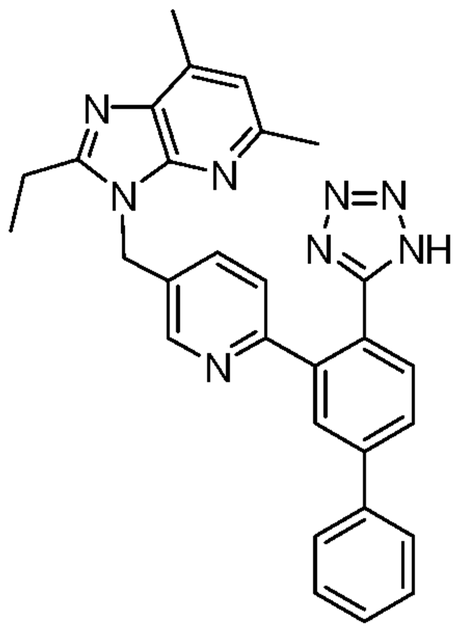
(175b)

A mixture of **Intermediate 175a** (32 mg, 0.080 mmol) and m-tolylboronic acid (32.5 mg, 0.239 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.143 mL, 0.143 mmol) followed by Pd-XPhos G3 (6.74 mg, 7.96 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 175b,** 36 mg, 0.079 mmol, 99 % yield) as an amber oil. LC-MS (Method A5): 2.44 min, $[M + H]^+$=458.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J*=1.4 Hz, 1H), 8.04 (d, *J*=1.7 Hz, 1H), 7.86 (d, *J*=8.3 Hz, 1H), 7.79 (d, *J*=8.3 Hz, 1H), 7.73 (dd, *J*=8.3, 1.7 Hz, 1H), 7.65 (dd, *J*=8.0, 2.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.38 (t, *J*=7.6 Hz, 1H), 7.26 (d, *J*=7.4 Hz, 1H), 6.94 (s, 1H), 5.57 (s, 2H), 2.90 (q, *J*=7.6 Hz, 2H), 2.66 (s, 3H), 2.63 (s, 3H), 2.45 (s, 3H), 1.41 (t, *J*=7.6 Hz, 3H).

Example 175: 3-((6'-(2*H*-tetrazol-5-yl)-2''-(trifluoromethoxy)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine

To a solution of 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)-3'-methyl-[1,1'-biphenyl]-4-carbonitrile (**Intermediate 175b**, 36 mg, 0.079 mmol) in toluene (1.5 mL) was added dibutyltin oxide (39.2 mg, 0.157 mmol) and TMS-N_3 (0.104 mL, 0.787 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. to afford 29.6 mg (0.057 mmol, 72 % yield) of the title compound **Example 175**. LC-MS (Method A3): 1.47 min, $[M + H]^+$=501.23; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.95 (s, 1H), 7.91 (br d, J=8.2 Hz, 1H), 7.78 (d, J=7.9 Hz, 1H), 7.64 (s, 1H), 7.61 (br d, J=7.9 Hz, 1H), 7.56 - 7.54 (m, 1H), 7.53 - 7.48 (m, 1H), 7.40 (t, J=7.5 Hz, 1H), 7.26 (br d, J=7.3 Hz, 1H), 6.98 (s, 1H), 5.52 (s, 2H), 2.85 (q, J=7.6 Hz, 2H), 2.56 (s, 6H), 2.40 (s, 3H), 1.27 (t, J=7.5 Hz, 3H).

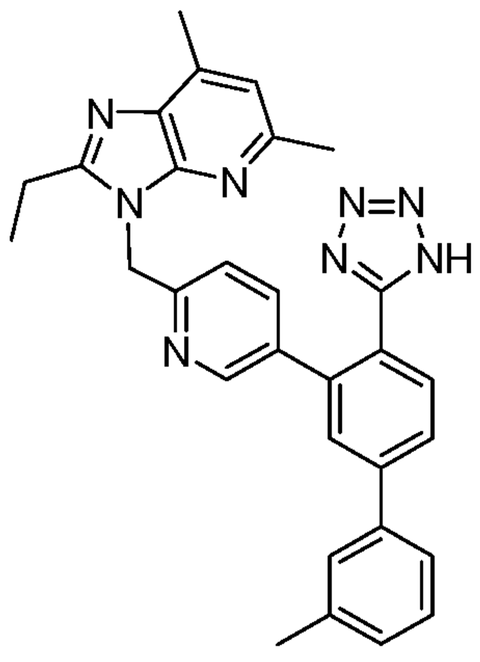
Example 176: 3-((6-(4-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)pyridin-3-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex. 176)

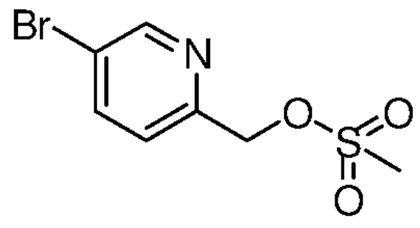
Example 176 has been similarly prepared from **Intermediate 175a** as described above for **Example 001**. LC-MS (Method A3): 1.37 min, $[M + H]^+$=487.22; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.94 (s, 1H), 7.90 (br d, J=8.0 Hz, 1H), 7.83 - 7.73 (m, 3H), 7.51 (br t, J=7.4 Hz, 3H), 7.44 (br d, J=4.7 Hz, 2H), 6.97 (s, 1H), 5.51 (s, 2H), 2.84 (q, J=7.3 Hz, 2H), 2.55 (s, 6H), 1.26 (t, J=7.4 Hz, 3H).

Example 177: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyridin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex. 177)

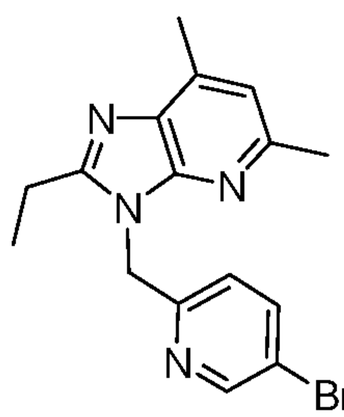
Intermediate 177a: (5-bromopyridin-2-yl)methyl methanesulfonate



(177a)

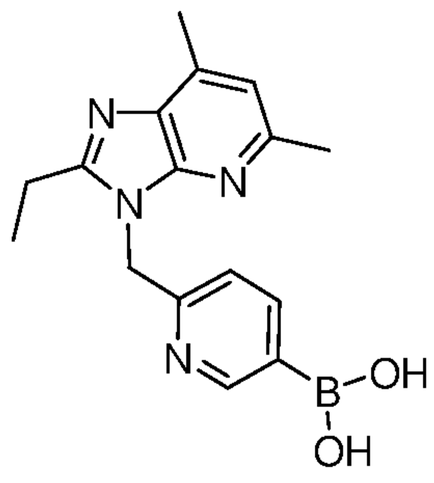
A solution of (5-bromopyridin-2-yl)methanol (500 mg, 2.66 mmol) in THF (10 mL) was cooled to 0 °C and treated with TEA (0.482 mL, 3.46 mmol) and methanesulfonyl chloride (0.252 mL, 3.19 mmol). The mixture was slowly warmed to RT and stirred for 1hour. The reaction was diluted with DCM, quenched with a saturated aqueous solution of NH_4Cl and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to (5-bromopyridin-2-yl)methyl methanesulfonate (**Intermediate 177a**, 700 mg, 2.63 mmol, 99 % yield) which was used for next step without purification. LC-MS (Method A5): 1.72 min, $[M + H]^+$=265.9 and 267.9; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J*=2.2 Hz, 1H), 7.90 (dd, *J*=8.3, 2.2 Hz, 1H), 7.39 (d, *J*=8.3 Hz, 1H), 5.29 (s, 2H), 3.10 (s, 3H).

Intermediate 177b: 3-((5-bromopyridin-2-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine


(177b)

To a solution of **Intermediate 001c** (200mg, 1.141 mmol) in DMF (4.1 mL) was added sodium hydride (59.3 mg, 1.484 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of **Intermediate 177a** (349 mg, 1.313 mmol) in DMF (1.6 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 177b,** 320 mg, 0.927 mmol, 81 % yield) as a white solid. LC-MS (Method A5): 2.02 min, $[M + H]^+$=345.1 and 347.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J*=2.2 Hz, 1H), 7.69 (dd, *J*=8.3, 2.2 Hz, 1H), 7.07 - 6.69 (m, 2H), 5.52 (s, 2H), 2.87 (q, *J*=7.4 Hz, 2H), 2.64 (s, 3H), 2.58 (s, 3H), 1.34 (t, *J*=7.6 Hz, 3H).

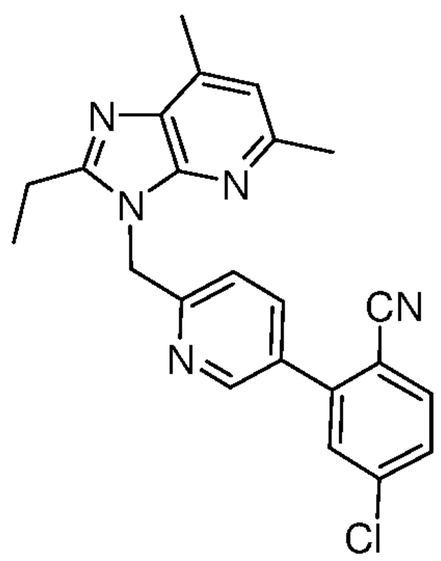
Intermediate 177c: 6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-ylboronic acid



(177c)

A solution of **Intermediate 177b (** 320 mg, 0.927 mmol), KOAc (182 mg, 1.854 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (259 mg, 1.020 mmol) and $PdCl_2$(dppf) (37.8 mg, 0.046 mmol) in dioxane (5mL) was degassed with N_2 for 2 min before the reaction vessel was sealed and heated at 100°C for overnight. The mixture was cooled and filtered through celite and purified via preparative HPLC (Column: Phenomenex AXIA Luna 100 x 30mm 5u s; Mobile Phase A: 10:90 ACN: H_2O with 10 mM TFA; Mobile Phase B: 90:10 ACN: H_2O with 10 mM TFA; Gradient: 0-100% B over 10 minutes, then a 2-minute hold at 100% B; Flow: 40 mL/min.) to afford 400 mg (0.92 mmol, 98 % yield) of the title compound (**Intermediate 177c)** as TFA salt. LC-MS (Method A5): 1.58 min, $[M + H]^+$=311.2; ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.64 (br d, *J*=10.7 Hz, 1H), 8.24 - 8.03 (m, 1H), 7.58 (br t, *J*=7.0 Hz, 1H), 7.34 (s, 1H), 5.89 (br d, *J*=5.5 Hz, 2H), 4.92 (br s, 2H), 2.67 (s, 3H), 2.60 (s, 3H), 1.46 (t, *J*=7.6 Hz, 3H).

Intermediate 177d: 4-chloro-2-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)benzonitrile

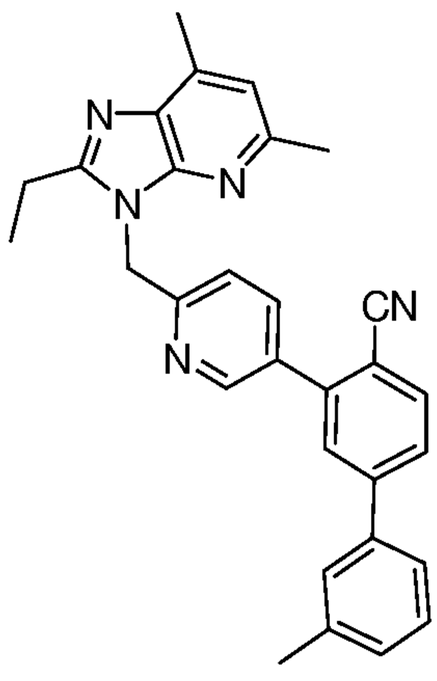


(177d)

A mixture of **Intermediate 177c** (177 mg, 0.418 mmol) and 4-chloro-2-iodobenzonitrile (100 mg, 0.380 mmol) in THF (5 mL) was treated with 1.5 M Na_2CO_3 (1.012 mL, 1.518 mmol) followed by $PdCl_2$(dppf) (15.50 mg, 0.019 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and

irradiated in a microwave reactor at 100 °C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 177d,** 120 mg, 0.299 mmol, 79 % yield) as a yellow oil. LC-MS (Method A5): 2.17 min, $[M + H]^+$ = 402.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J*=2.2 Hz, 1H), 7.80 (dd, *J*=8.1, 2.3 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 1H), 7.54 - 7.43 (m, 2H), 7.13 (d, *J*=8.3 Hz, 1H), 6.92 (s, 1H), 5.66 (s, 2H), 2.92 (q, *J*=7.4 Hz, 2H), 2.66 (s, 3H), 2.61 (s, 3H), 1.37 (t, *J*=7.6 Hz, 3H).

Intermediate 177e: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)-3'-methylbiphenyl-4-carbonitrile



(177e)

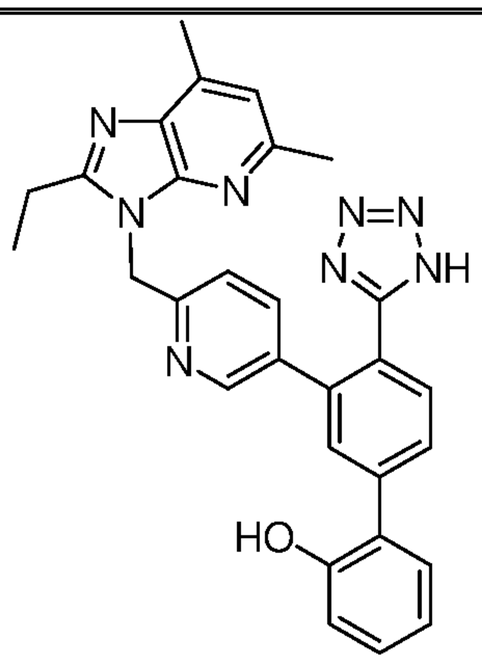
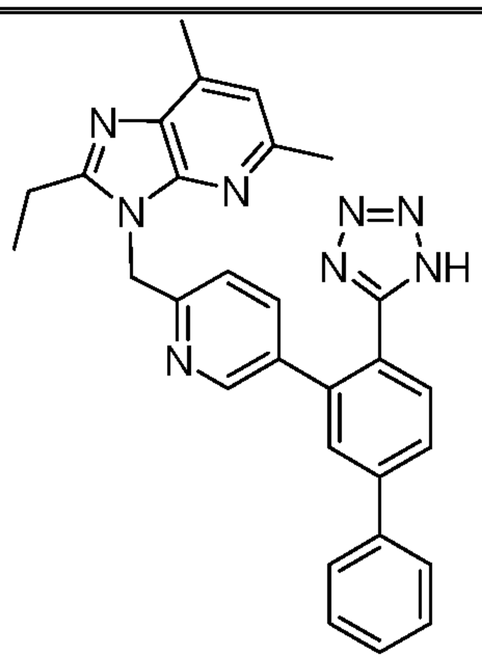
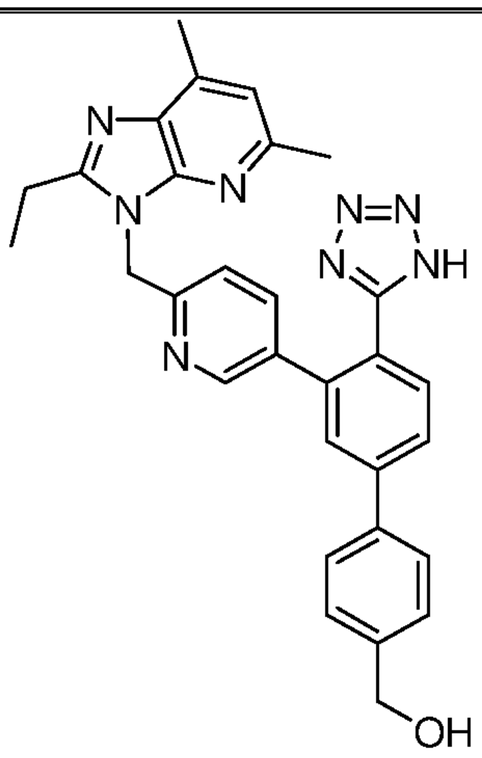
A mixture of **Intermediate 177d** (33 mg, 0.082 mmol) and m-tolylboronic acid (33.5 mg, 0.246 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.148 mL, 0.148 mmol) followed by Pd-XPhos G3 (6.95 mg, 8.21 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 177e,** 26 mg, 0.057 mmol, 69.2 % yield) as an amber oil. LC-MS (Method A5): 2.44 min, $[M + H]^+$=458.2; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J*=1.7 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.72 (dd, *J*=8.3, 1.7 Hz, 1H), 7.69 (d, *J*=1.4 Hz, 1H), 7.47 - 7.37 (m, 4H), 7.15 (d, *J*=8.3 Hz, 1H), 6.93 (s, 1H), 5.68 (s, 2H), 2.95 (q, *J*=7.4 Hz, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 2.46 (s, 3H), 1.39 (t, *J*=7.6 Hz, 3H).

Example 177: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyridin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine

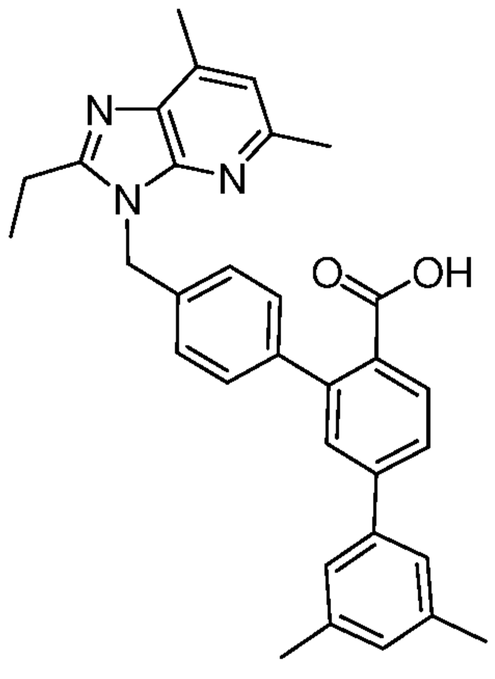
To a solution of **Intermediate 177e** (26 mg, 0.057 mmol) in toluene (1.5 mL) was added dibutyltin oxide (28.3 mg, 0.114 mmol) and TMS-N_3 (0.075 mL, 0.568 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 19-59% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 12.5 mg (0.025 mmol, 43.6 % yield) of the title compound **Example 177**. LC-MS (Method A3): 1.54 min, $[M + H]^+$=501.07; ^1H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, *J*=1.5 Hz, 1H), 7.84 - 7.73 (m, 2H), 7.63 (br d, *J*=15.9 Hz, 2H), 7.60 - 7.53 (m, 2H), 7.36 (t, *J*=7.6 Hz, 1H), 7.21 (br d, *J*=7.3 Hz, 1H), 7.06 (d, *J*=7.9 Hz, 1H), 6.94 (s, 1H), 5.55 (s, 2H), 2.85 (q, *J*=7.3 Hz, 2H), 2.55 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H), 1.29 (t, *J*=7.5 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 177d** as described above for **Example 177**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^1H NMR (500MHz, DMSO-d_6) δ ppm

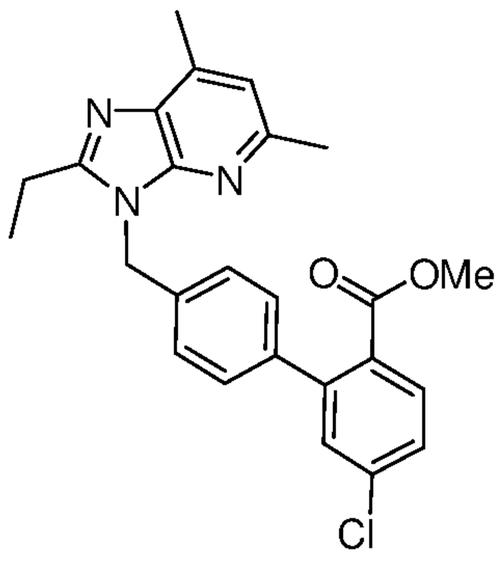
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
178		502.58	503.28; 1.27min (Method A3)	8.28 (s, 1H), 7.76 (s, 2H), 7.62 (s, 1H), 7.57 (br d, J=7.9 Hz, 1H), 7.41 (br d, J=7.3 Hz, 1H), 7.22 (br t, J=7.6 Hz, 1H), 7.09 (d, J=8.2 Hz, 1H), 6.99 (d, J=7.9 Hz, 1H), 6.96 - 6.89 (m, 2H), 5.56 (s, 2H), 2.83 (q, J=7.5 Hz, 2H), 2.57 (s, 3H), 2.50 (s, 3H), 1.27 (t, J=7.5 Hz, 3H)
179		486.58	487.31; 1.58 min (Method A3)	8.33 (d, *J*=1.5 Hz, 1H), 7.93 (br d, *J*=8.2 Hz, 1H), 7.86 - 7.74 (m, 4H), 7.61 (dd, *J*=7.9, 2.1 Hz, 1H), 7.55 - 7.47 (m, 2H), 7.47 - 7.36 (m, 1H), 7.17 (d, *J*=8.2 Hz, 1H), 6.96 (s, 1H), 5.58 (s, 2H), 2.83 (q, *J*=7.6 Hz, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 1.26 (t, *J*=7.5 Hz, 3H)
180		516.61	517.2; 1.11 min (Method A3)	8.34 (s, 1H), 7.95 (br d, J=8.2 Hz, 1H), 7.89 - 7.77 (m, 4H), 7.64 (dd, J=8.2, 1.8 Hz, 1H), 7.46 (br d, J=7.9 Hz, 2H), 7.27 (s, 1H), 7.07 (s, 1H), 5.67 (s, 2H), 4.58 (s, 2H), 2.93 (q, J=7.5 Hz, 2H), 2.57 (s, 2H), 2.56 (br s, 3H), 1.30 (t, J=7.5 Hz, 3H)

Example 181: 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3,5-dimethyl-[1,1':3',1''-terphenyl]-4'-carboxylic acid



(Ex. 181)

Intermediate 181a: methyl 5-chloro-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)biphenyl-2-carboxylate



(181a)

A mixture of **Intermediate 001d** (100 mg, 0.256 mmol), and methyl 4-chloro-2-iodobenzoate (68.9 mg, 0.232 mmol) in THF (5 mL) was treated with 1.5 M Na_2CO_3 (0.465 mL, 0.697 mmol) followed by $PdCl_2$(dppf) (9.49 mg, 0.012 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 100 °C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 181a,** 100 mg, 0.230 mmol, 99 % yield) as a yellow oil. LC-MS (Method A5): 2.30 min, $[M + H]^+$ = 434.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.3 Hz, 1H), 7.40 (dd, *J*=8.4, 2.1 Hz, 1H), 7.33 (d, *J*=1.9 Hz, 1H), 7.25 - 7.20 (m, 2H), 7.19 - 7.14 (m, 2H), 6.93 (s, 1H), 5.53

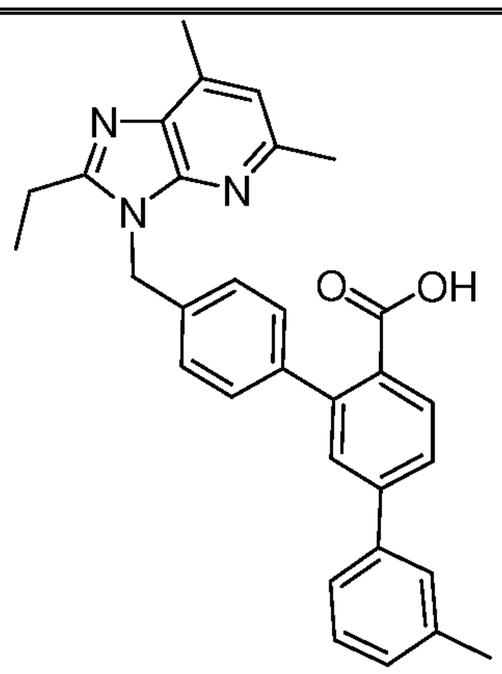
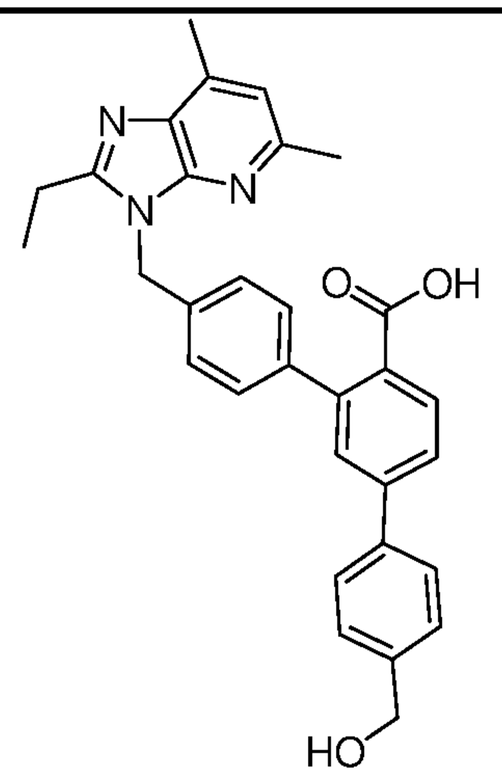
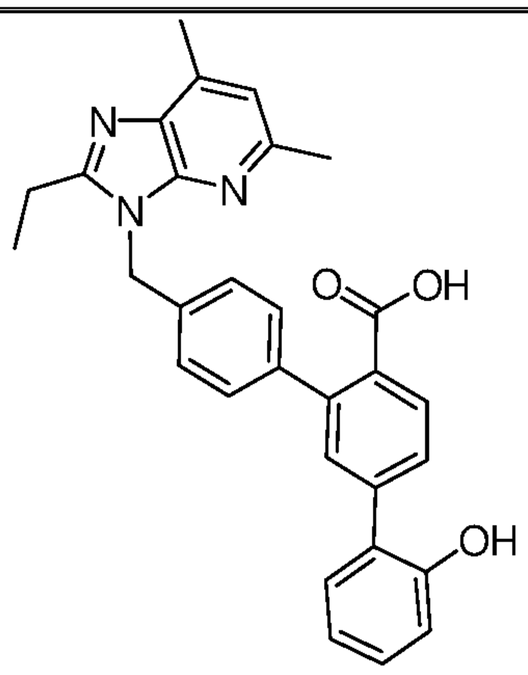
(s, 2H), 3.63 (s, 3H), 2.84 (q, *J*=7.5 Hz, 2H), 2.67 (s, 3H), 2.63 (s, 3H), 1.35 (t, *J*=7.6 Hz, 3H).

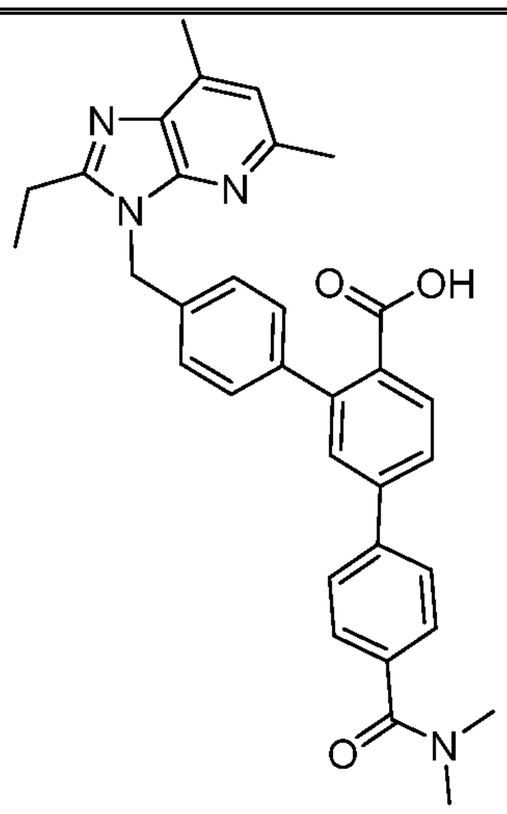
Example 181: 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3,5-dimethyl-[1,1':3',1''-terphenyl]-4'-carboxylic acid

A mixture of **Intermediate 181[a]** (20 mg, 0.046 mmol) and (3,5-dimethylphenyl)boronic acid (20.74 mg, 0.138 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.083 mL, 0.083 mmol) followed by Pd-XPhos G3 (1.951 mg, 2.304 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.138 mL, 0.277 mmol). The mixture was reheated in a microwave reactor at 100 °C for 15 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 28-68% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min.) to afford 8.5 mg (0.017 mmol, 37.7 % yield) of the title compound **Example 181**. LC-MS (Method A3): 1.81 min, $[M + H]^+$= 490.34;. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (br d, *J*=8.0 Hz, 1H), 7.69 (br d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.36 (br d, *J*=8.0 Hz, 2H), 7.33 (s, 1H), 7.34 - 7.31 (m, 1H), 7.19 (br d, *J*=7.9 Hz, 2H), 7.03 (s, 1H), 6.96 (s, 1H), 5.51 (s, 2H), 2.83 (q, *J*=7.5 Hz, 2H), 2.54 (s, 6H), 2.33 (s, 6H), 1.29 (t, *J*=7.4 Hz, 3H).

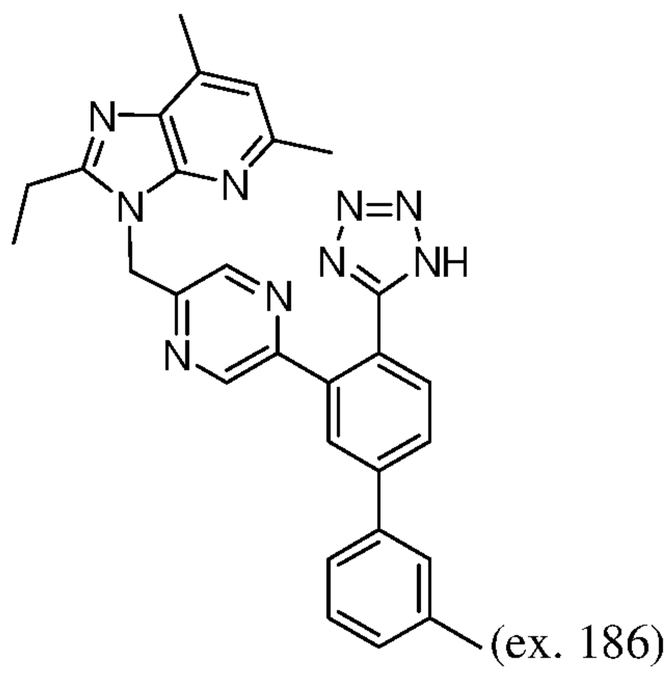
The following examples have been similarly prepared from **Intermediate 181a** as described above for **Example 181**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm

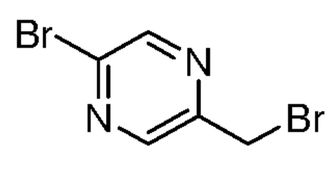
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
182		475.59	476.13; 1.67 min (Method A3)	7.76 (br d, J=7.9 Hz, 1H), 7.69 (br d, J=7.6 Hz, 1H), 7.65 - 7.47 (m, 5H), 7.39 - 7.31 (m, 2H), 7.20 (br d, J=7.0 Hz, 1H), 7.15 (br d, J=7.6 Hz, 1H), 6.97 (s, 1H), 5.50 (s, 2H), 2.81 (q, J=7.5 Hz, 2H), 2.55 (s, 3H), 2.51 (s, 3H), 2.35(s, 3H), 1.28 - 1.23 (m, 3H).
183		491.59	492.29; 1.16 min (Method A3)	7.83 (d, J=7.9 Hz, 1H), 7.74 (br d, J=8.2 Hz, 1H), 7.72 (d, J=7.9 Hz, 2H), 7.57 (s, 1H), 7.42 (br d, J=7.9 Hz, 2H), 7.39 (br d, J=7.9 Hz, 2H), 7.25 (br d, J=7.6 Hz, 2H), 7.16 - 7.10 (m, 1H), 5.61 (s, 2H), 4.55 (s, 2H), 2.97 (q, J=7.6 Hz, 2H), 2.57 (s, 3H), 2.56 (s, 3H), 1.29 (t, J=7.5 Hz, 3H)
184		477.56	478.32; 1.27 min (Method A3)	7.74 (br d, J=7.9 Hz, 1H), 7.60 (br d, J=7.6 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.26 (m, 3H), 7.18 (br t, J=7.5 Hz, 1H), 7.14 (br d, J=7.6 Hz, 2H), 6.98 - 6.90 (m, 2H), 6.88 (br t, J=7.2 Hz, 1H), 5.49 (s, 2H), 2.80 (q, J=7.3 Hz, 2H), 2.54 (s, 6H), 1.23 (br d, J=7.6 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
185		532.64	533.24; 1.34min (Method A3)	7.86 - 7.80 (m, 2H), 7.78 (br d, J=7.9 Hz, 2H), 7.63 (s, 1H), 7.58 - 7.46 (m, 2H), 7.39 (br d, J=7.9 Hz, 2H), 7.18 (br d, J=8.2 Hz, 2H), 6.98 (s, 1H), 5.53 (s, 2H), 3.03 - 2.93 (m, 6H), 2.84 (q, J=7.4 Hz, 2H), 2.56 (s, 3H), 2.54 (s, 3H), 1.28 (t, J=7.5 Hz, 3H)

Example 186: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrazin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine

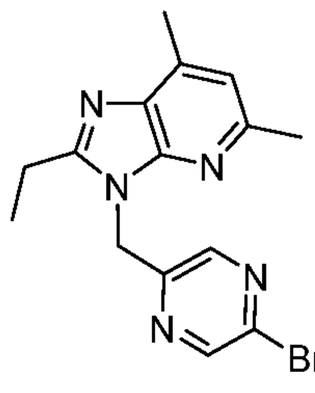

(ex. 186)

Intermediate 186a: 2-bromo-5-(bromomethyl)pyrazine


(186a)

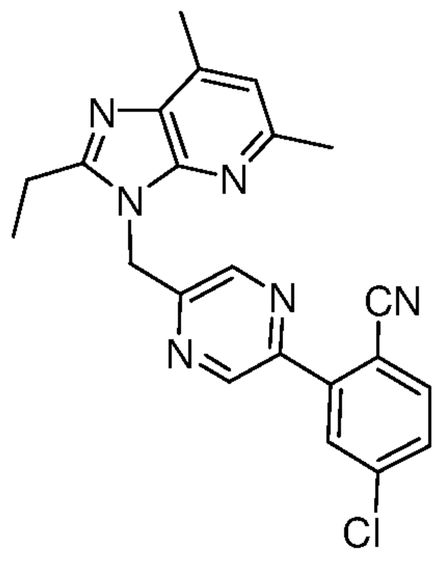
2-bromo-5-methylpyrazine (300 mg, 1.734 mmol) was dissolved in carbon tetrachloride (8 mL), NBS (370 mg, 2.081 mmol) and benzoyl peroxide (21.00 mg, 0.087 mmol) were added , and the resulting mixture was heated and refluxed for overnight. The reaction solution was returned to RT, concentrated under reduced pressure and purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 186a,** 140 mg, 0.556 mmol, 32.1 % yield) as a white solid. LC-MS (Method A5): 1.77 min, $[M + H]^+$= 250.9 and 251.9; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 2H), 4.58 (s, 2H).

Intermediate 186b: 3-((5-bromopyrazin-2-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine


(186b)

To a solution of **Intermediate 001c** (108 mg, 0.618 mmol) in DMF (2.0 mL) was added sodium hydride (29.6 mg, 0.741 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of **Intermediate 186[a]** (140 mg, 0.648 mmol) in DMF (0.8 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 186b,** 140 mg, 0.404 mmol, 65.5 % yield) as a white solid. LC-MS (Method A5): 1.90 min, $[M + H]^+$=346.0 and 348.0; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J*=1.1 Hz, 1H), 8.36 (s, 1H), 6.89 (s, 1H), 5.53 (s, 2H), 2.96 (q, *J*=7.7 Hz, 3H), 2.62 (s, 3H), 2.57 (s, 3H), 1.40 (t, *J*=7.6 Hz, 3H).

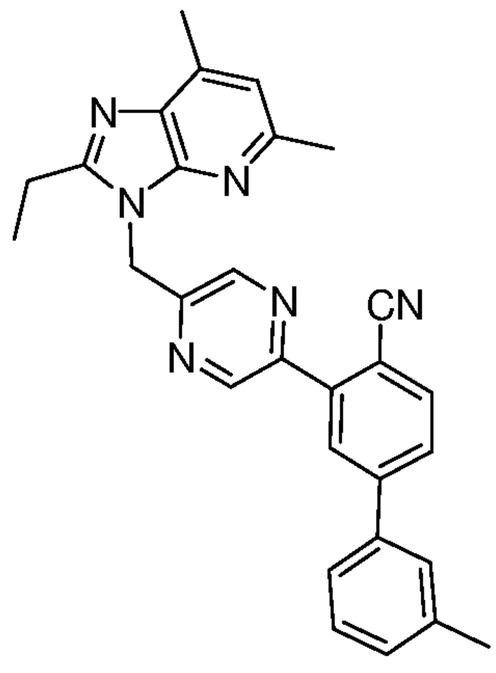
Intermediate 186c: 4-chloro-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)benzonitrile



(186c)

A mixture of **Intermediate 186b** (100 mg, 0.289 mmol) and (5-chloro-2-cyanophenyl)boronic acid (68.1 mg, 0.375 mmol) in THF (3 mL) was treated with 1.5 M Na_2CO_3 (0.578 mL, 0.866 mmol) followed by $PdCl_2$(dppf) (11.79 mg, 0.014 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125°C for 1 hour. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude sample in 2 ml of DCM was treated with TEA (0.201 mL, 1.444 mmol) followed by TFAA (0.061 mL, 0.433 mmol). The mixture was stirred at RT for 1 hour, then concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 186c,** 80 mg, 0.199 mmol, 68.8 % yield) as an amber oil. LC-MS (Method A5): 2.16 min, $[M + H]^+$ = 403.1; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (d, *J*=1.4 Hz, 1H), 8.70 (d, *J*=0.8 Hz, 1H), 7.84 (d, *J*=1.9 Hz, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.56 (dd, *J*=8.3, 1.9 Hz, 1H), 6.92 (s, 1H), 5.68 (s, 2H), 3.00 (q, *J*=7.4 Hz, 2H), 2.65 (s, 3H), 2.60 (s, 3H), 1.43 (t, *J*=7.6 Hz, 3H).

Intermediate 186d: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)-3'-methylbiphenyl-4-carbonitrile



(186d)

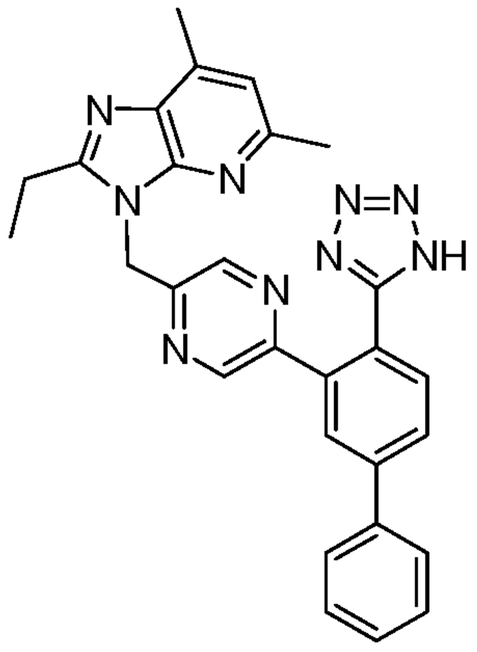
A mixture of **Intermediate 186c** (40 mg, 0.099 mmol) and tolylboronic acid (40.5 mg, 0.298 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.179 mL, 0.179 mmol) followed by Pd-XPhos G3 (8.40 mg, 9.93 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 60 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 186d,** 45 mg, 0.098 mmol, 99 % yield) as a colorless oil. LC-MS (Method A5): 2.37 min, $[M + H]^+$=459.2; ^1H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, *J*=1.1 Hz, 1H), 8.71 (s, 1H), 7.99 (d, *J*=1.4 Hz, 1H), 7.89 (d, *J*=8.0 Hz, 1H), 7.77 (dd, *J*=8.0, 1.7 Hz, 1H), 7.46 - 7.41 (m, 2H), 7.40 - 7.33 (m, 1H), 7.30 - 7.23 (m, 1H), 6.91 (s, 1H), 5.68 (s, 2H), 3.01 (q, *J*=7.4 Hz, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 2.44 (s, 3H), 1.42 (t, *J*=7.6 Hz, 3H)

Example 186: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrazin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine

To a solution of **Intermediate 186d** (35 mg, 0.076 mmol) in toluene (1.5 mL) was added dibutyltin oxide (38.0 mg, 0.153 mmol) and TMS-N_3 (0.101 mL, 0.763 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 20-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 23.1 mg (0.046 mmol, 60.3 % yield) of the title compound **Example 186**. LC-MS (Method A3): 1.49 min, $[M + H]^+$=502.25; ^1H

NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.28 (br s, 1H), 7.92 (br d, *J*=7.9 Hz, 1H), 7.87 - 7.78 (m, 2H), 7.59 (br s, 1H), 7.56 (br d, *J*=7.6 Hz, 1H), 7.37 (br t, *J*=7.5 Hz, 1H), 7.21 (br d, *J*=7.3 Hz, 1H), 6.94 (s, 1H), 5.64 (s, 2H), 2.95 - 2.90 (m, 2H), 2.75 (s, 2H), 2.56 (s, 3H), 2.52 (br s, 3H), 2.39 (s, 3H), 1.31 (br t, *J*=7.3 Hz, 3H).

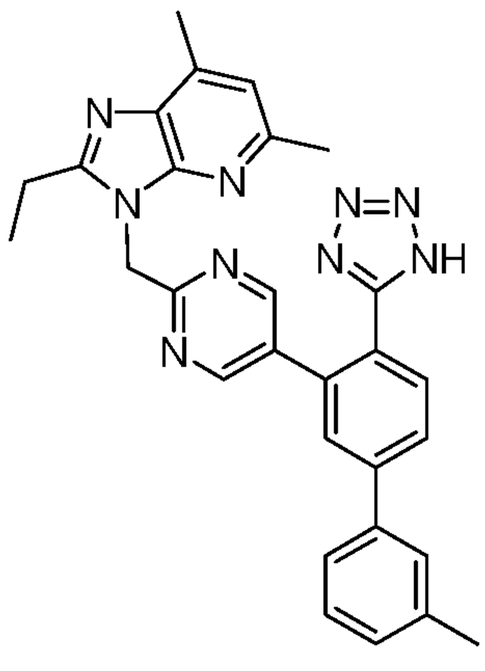
Example 187: 3-((5-(4-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)pyrazin-2-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex. 187)

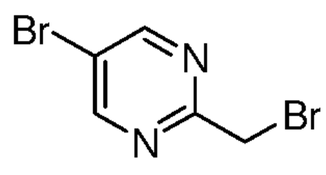
Example 187 has been similarly prepared from **Intermediate 186c** as described above for **Example 186**. LC-MS (Method A3): 1.32 min, $[M + H]^+$=488.22; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.65 (s, 1H), 8.06 (s, 1H), 8.02 (br d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.86 (br d, *J*=7.6 Hz, 2H), 7.56 - 7.50 (m, 2H), 7.48 - 7.43 (m, 1H), 7.12 (s, 1H), 5.80 (s, 2H), 3.12 - 2.96 (m, 2H), 2.56 (s, 6H), 1.40 - 1.32 (m, 3H).

Example 188: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrimidin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine



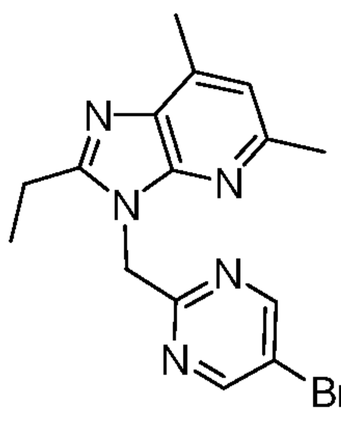
(Ex. 188)

Intermediate 188a: 5-bromo-2-(bromomethyl)pyrimidine


(188a)

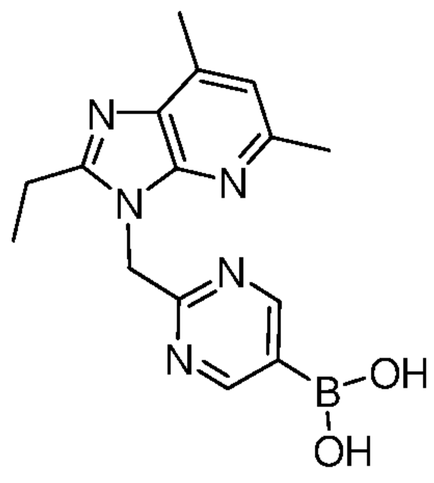
5-bromo-2-methylpyrimidine (1.0 g, 5.78 mmol) was dissolved in carbon tetrachloride (15 mL), NBS (1.234 g, 6.94 mmol) and benzoyl peroxide (0.070 g, 0.289 mmol) were added , and the resulting mixture was heated and refluxed for overnight. The reaction solution was returned to RT, concentrated under reduced pressure and purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 188a,** 370mg, 1.469 mmol, 25.4 % yield) as a white solid. LC-MS (Method A5): 1.77 min, $[M + H]^+$= 252.8; ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 2H), 4.60 (s, 2H).

Intermediate 188b: 3-((5-bromopyrimidin-2-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine


(188b)

To a solution of **Intermediate 001c** (370 mg, 2.111 mmol) in DMF (7.5 mL) was added sodium hydride (110 mg, 2.74 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of **Intermediate 188a** (558 mg, 2.217 mmol) in DMF (3.0 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 188b,** 320 mg, 0.924 mmol, 43.8 % yield) as a white solid. LC-MS (Method A5): 1.80 min, $[M + H]^+$=346.1 and 348.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 2H), 6.89 (s, 1H), 5.66 (s, 2H), 2.83 (q, *J*=7.7 Hz, 2H), 2.66 (s, 3H), 2.56 (s, 3H), 1.37 (t, *J*=7.6 Hz, 3H).

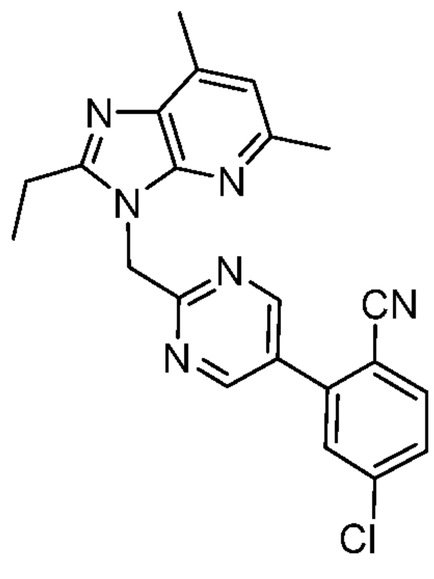
Intermediate 188c: 2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-ylboronic acid



(188c)

Intermediate 188b (320 mg, 0.924 mmol), KOAc (181 mg, 1.848 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (258 mg, 1.017 mmol) and $PdCl_2$(dppf) (37.7 mg, 0.046 mmol) in dioxane (5.0 mL) was degassed with N_2 for 2 min before the reaction vessel was sealed and heated at 100°C for overnight. The mixture was cooled and filtered through CELITE and purified via preparative HPLC (Column: Phenomenex AXIA Luna 100 x 30mm 5u s; Mobile Phase A: 10:90 ACN: H_2O with 10 mM TFA; Mobile Phase B: 90:10 ACN: H_2O with 10 mM TFA; Gradient: 0-100% B over 10 minutes, then a 2-minute hold at 100% B; Flow: 40 mL/min.) to afford 390 mg (0.917 mmol, 99 % yield) of the title compound (**Intermediate 188c**) as TFA salt. LC-MS (Method A5): 1.60 min, $[M + H]^+$=312.2; ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 2H), 7.16 (s, 1H), 5.95 (s, 2H), 3.17 (q, *J*=7.6 Hz, 2H), 2.66 (s, 3H), 2.58 (s, 3H), 1.52 - 1.40 (m, 3H).

Intermediate 188d: 4-chloro-2-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)benzonitrile

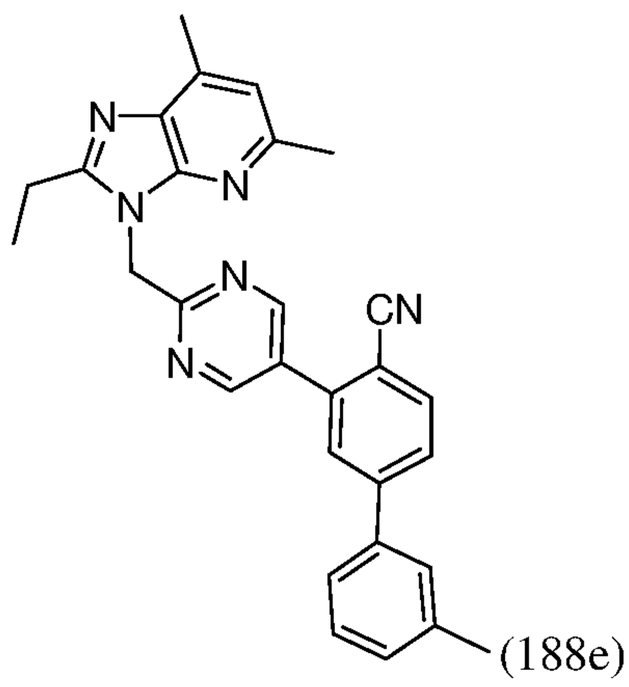


(188d)

A mixture of **Intermediate 188c** (200 mg, 0.470 mmol) and 4-chloro-2-iodobenzonitrile 124 mg, 0.470 mmol) in THF (8 mL) was treated with 1.5 M Na_2CO_3 (1.254 mL, 1.882 mmol)) followed by $PdCl_2$(dppf) (19.21 mg, 0.024 mmol). The resulting mixture was

degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 100 °C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 188d,** 100 mg, 0.248 mmol, 52.8 % yield) as an off-white solid. LC-MS (Method A5): 2.09 min, $[M + H]^+ = 403.1$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 2H), 7.78 (d, *J*=8.3 Hz, 1H), 7.57 (d, *J*=8.3 Hz, 1H), 6.90 (s, 1H), 5.80 (s, 2H), 2.88 (q, *J*=7.4 Hz, 2H), 2.67 (s, 3H), 2.57 (s, 3H), 1.40 (t, *J*=7.6 Hz, 3H).

Intermediate 188e: 3-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)-3'-methylbiphenyl-4-carbonitrile



(188e)

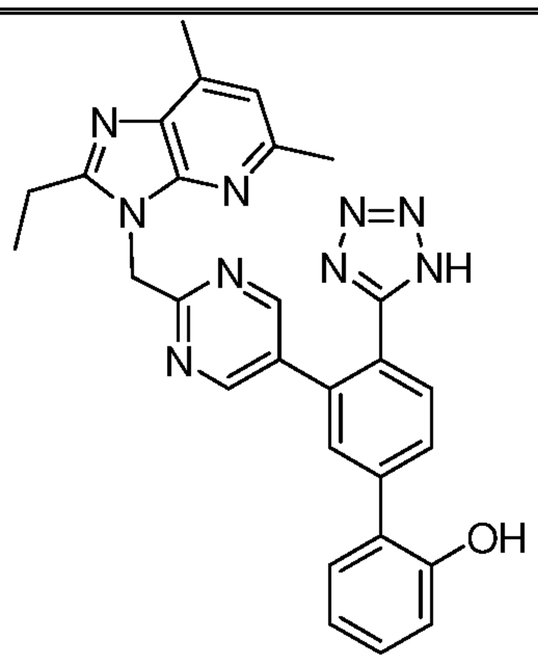
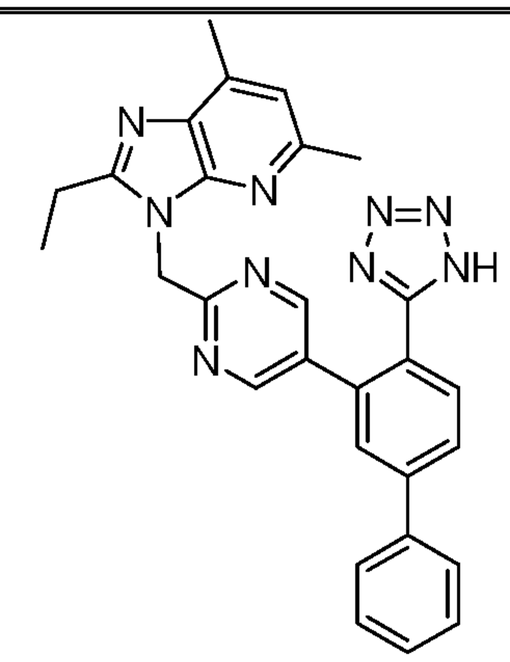
A mixture of **Intermediate 188d** (25 mg, 0.062 mmol) and), m-tolylboronic acid (25.3 mg, 0.186 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.112 mL, 0.112 mmol) followed by Pd-XPhos G3 (5.25 mg, 6.21 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 188e,** 28 mg, 0.061 mmol, 98 % yield) as a colorless oil. LC-MS (Method A5): 2.41 min, $[M + H]^+$=459.2; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 2H), 7.90 (d, *J*=8.0 Hz, 1H), 7.78 (dd, *J*=8.0, 1.7 Hz, 1H), 7.66 (d, *J*=1.7 Hz, 1H), 7.48 - 7.37 (m, 3H), 7.34 - 7.23 (m, 1H), 6.91 (s, 1H), 5.82 (s, 2H), 2.91 (q, *J*=7.7 Hz, 2H), 2.68 (s, 3H), 2.59 (s, 3H), 2.46 (s, 3H), 1.42 (t, *J*=7.6 Hz, 3H)

Example 188: 2-ethyl-5,7-dimethyl-3-((5-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrimidin-2-yl)methyl)-3H-imidazo[4,5-b]pyridine

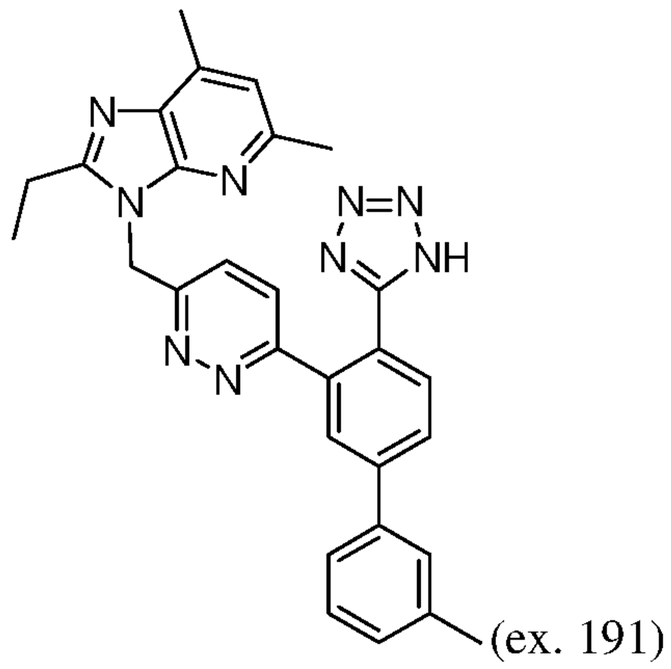
To a solution of **Intermediate 188e** (28.4 mg, 0.062 mmol) in toluene (1.5 mL) was added dibutyltin oxide (30.9 mg, 0.124 mmol) and TMS-N_3 (0.082 mL, 0.620 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 20-60% B over 23 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min) to afford 19.5 mg (0.038 mmol, 61.4 % yield) of the title compound **Example 188**. LC-MS (Method A3): 1.5 min, $[M + H]^+$= 502.21; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 2H), 7.95 (s, 2H), 7.85 (s, 1H), 7.66 (s, 1H), 7.62 (br d, *J*=7.7 Hz, 1H), 7.39 (t, *J*=7.6 Hz, 1H), 7.25 (br d, *J*=7.5 Hz, 1H), 6.92 (s, 1H), 5.70 (s, 2H), 3.05 - 2.67 (m, 2H), 2.53 (br s, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 0.88 (br t, *J*=7.2 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 188d** as described above for **Example 188**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm

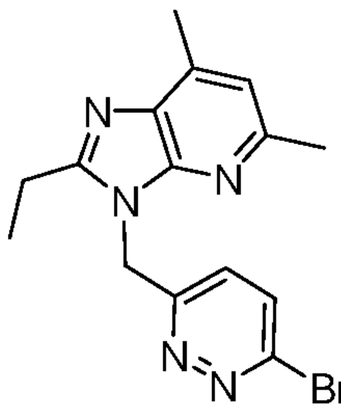
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
189		503.57	504.18; 1.2 min (Method A3)	8.61 (s, 2H), 7.88 (s, 2H), 7.71 (s, 1H), 7.43 (br d, J=7.6 Hz, 1H), 7.29 - 7.19 (m, 1H), 6.99 (d, J=7.9 Hz, 1H), 6.95 - 6.80 (m, 2H), 5.70 (s, 2H), 2.79 (q, J=7.3 Hz, 2H), 2.52 (br s, 3H), 2.47 (s, 3H), 1.28 (t, J=7.5 Hz, 3H)
190		487.57	488.04; 1.37 min (Method A3)	8.66 (s, 2H), 8.03 - 7.93 (m, 2H), 7.90 (s, 1H), 7.85 (br d, J=7.3 Hz, 2H), 7.60 - 7.47 (m, 2H), 7.48 - 7.39 (m, 1H), 6.93 (s, 1H), 5.71 (s, 2H), 2.81 (q, J=7.6 Hz, 2H), 2.55 (s, 3H), 2.47 (s, 3H), 1.29 (t, J=7.3 Hz, 3H)

Example 191: 2-ethyl-5,7-dimethyl-3-((6-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyridazin-3-yl)methyl)-3H-imidazo[4,5-b]pyridine



(ex. 191)

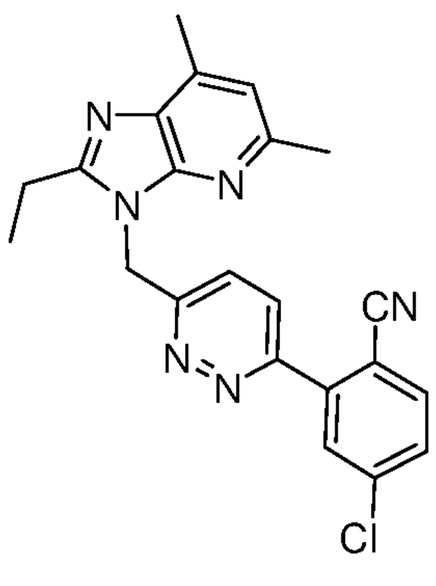
Intermediate 191a: 3-((6-bromopyridazin-3-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(191a)

To a solution of **Intermediate 001c** (200 mg, 1.141 mmol) in DMF (4.0 mL) was added sodium hydride (100 mg, 2.51 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of 3-bromo-6-(bromomethyl)pyridazine, hydrobromide (399 mg, 1.198 mmol) in DMF (1.6 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 191a,** 270 mg, 0.780 mmol, 68.3 % yield) as a white solid. LC-MS (Method A5): 1.70 min, $[M + H]^+$=346.0 and 348.0; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.8 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 6.93 (s, 1H), 5.75 (s, 2H), 2.95 (q, *J*=7.5 Hz, 2H), 2.64 (s, 3H), 2.61 (s, 3H), 1.37 (t, *J*=7.6 Hz, 3H).

Intermediate 191b: 4-chloro-2-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridazin-3-yl)benzonitrile

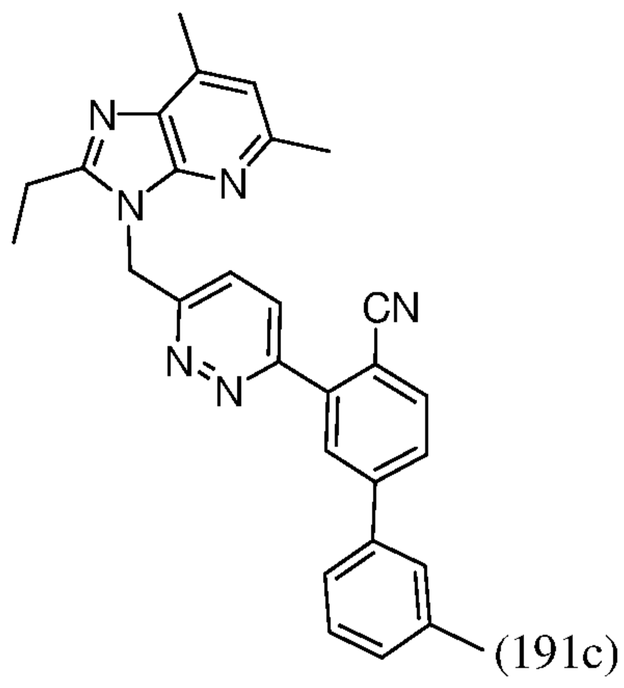


(191b)

A mixture of **Intermediate 191a** (100 mg, 0.289 mmol) and 4-chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile (94 mg, 0.375 mmol) in THF (3 mL) was treated with 1.5 M Na_2CO_3 (0.578 mL, 0.866 mmol) followed by $PdCl_2$(dppf) (11.79 mg,

0.014 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125°C for 75 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude sample in 2 ml of DCM was treated with TEA (0.201 mL, 1.444 mmol) followed by TFAA (0.061 mL, 0.433 mmol). The mixture was stirred at RT for 1 hour, then concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 191b,** 40mg, 0.099 mmol, 34.4 % yield) as an amber oil. LC-MS (Method A5): 2.04 min, $[M + H]^+ = 403.0$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J*=1.9 Hz, 1H), 7.95 (d, *J*=8.8 Hz, 1H), 7.79 (d, *J*=8.3 Hz, 1H), 7.65 - 7.55 (m, 2H), 6.95 (s, 1H), 5.89 (s, 2H), 3.01 (q, *J*=7.4 Hz, 2H), 2.65 (s, 3H), 2.63 (s, 3H), 1.40 (t, *J*=7.6 Hz, 3H)

Intermediate 191c: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridazin-3-yl)-3'-methylbiphenyl-4-carbonitrile



(191c)

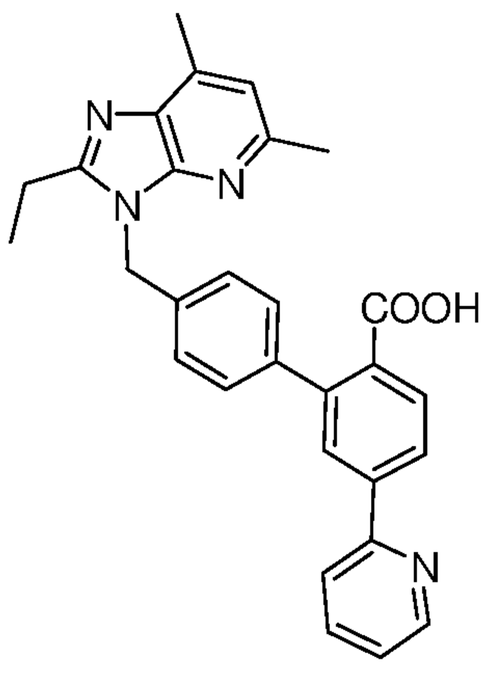
A mixture of **Intermediate 191b** (40 mg, 0.099 mmol) and m-tolylboronic acid (40.5 mg, 0.298 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.179 mL, 0.179 mmol) followed by Pd-XPhos G3 (8.40 mg, 9.93 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 60 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 191c,** 35 mg, 0.076 mmol, 77 % yield) as a colorless oil. LC-MS (Method A5): 2.35 min, $[M + H]^+$=459.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J*=1.1 Hz, 1H), 8.01 (d, *J*=8.8 Hz, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 7.83 (dd, *J*=8.0, 1.4 Hz, 1H), 7.63 (d, *J*=8.8 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.40 (t, *J*=7.6 Hz,

1H), 7.33 - 7.20 (m, 1H), 6.95 (s, 1H), 5.90 (s, 2H), 3.04 (q, *J*=7.5 Hz, 2H), 2.66 (s, 3H), 2.64 (s, 3H), 2.46 (s, 3H), 1.41 (t, *J*=7.6 Hz, 3H).

Example 191: 2-ethyl-5,7-dimethyl-3-((6-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyridazin-3-yl)methyl)-3H-imidazo[4,5-b]pyridine

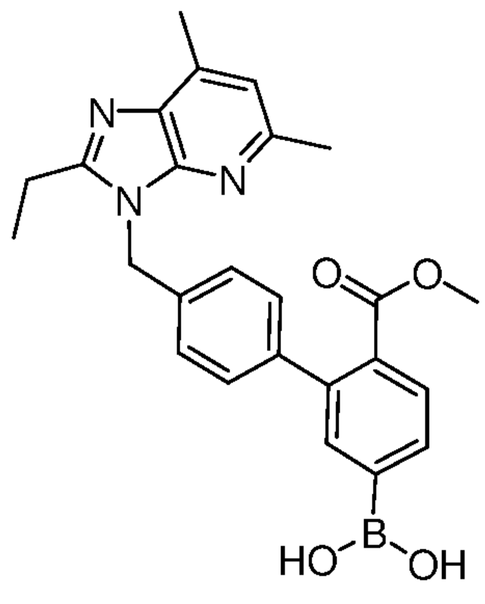
To a solution of **Intermediate 191c** (35 mg, 0.076 mmol) in toluene (1.5 mL) was added dibutyltin oxide (38.0 mg, 0.153 mmol) and TMS-N_3 (0.101 mL, 0.763 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 22 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min) to afford 18.2 mg (0.036 mmol, 46.7 % yield) of the title compound **Example 191**. LC-MS (Method A3): 1.38 min, $[M + H]^+$= 502.26; ^1H NMR (500 MHz, DMSO-d_6) δ 8.08 - 7.94 (m, 2H), 7.91 (d, *J*=7.9 Hz, 1H), 7.75 (d, *J*=8.9 Hz, 1H), 7.65 (s, 1H), 7.61 (br d, *J*=7.6 Hz, 1H), 7.57 (d, *J*=8.5 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.25 (br d, *J*=7.6 Hz, 1H), 6.96 (s, 1H), 5.78 (s, 2H), 2.98 - 2.78 (m, 2H), 2.56 (s, 3H), 2.51 (br s, 3H), 2.39 (s, 3H), 1.28 (t, *J*=7.5 Hz, 3H).

Example 192: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(pyridin-2-yl)biphenyl-2-carboxylic acid



(Ex 192)

Intermediate 192a: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(methoxycarbonyl)biphenyl-3-ylboronic acid



(192a)

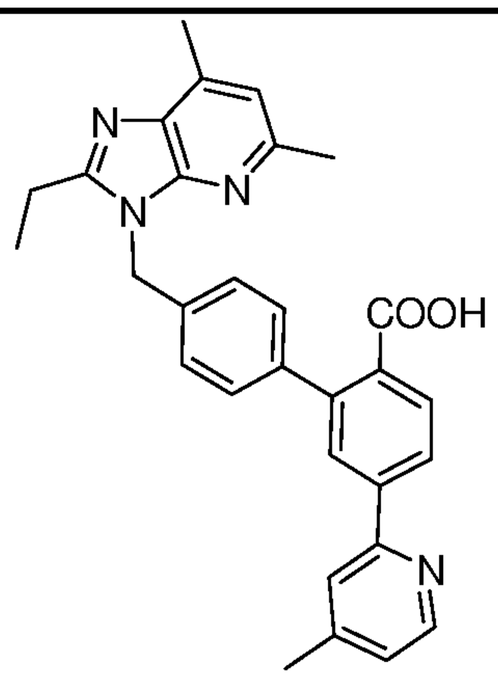
To a pressure-rated vial containing **Intermediate 181a** (100 mg, 0.230 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (10.99 mg, 0.023 mmol), $Pd_2(dba)_3$ (21.10 mg, 0.023 mmol) and bis(pinacolato)diboron (117 mg, 0.461 mmol) was added dioxane (2 ml) followed by KOAc (113 mg, 1.152 mmol). The reaction mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and heated at 105°C for 60 min. The mixture was cooled and filtered through celite and purified via preparative HPLC (Column: Phenomenex AXIA Luna 100 x 30mm 5u s; Mobile Phase A: 10:90 ACN: H_2O with 10 mM TFA; Mobile Phase B: 90:10 ACN: H_2O with 10 mM TFA; Gradient: 0-100% B over 10 minutes, then a 2-minute hold at 100% B; Flow: 40 mL/min.) to afford the title compound (**Intermediate 192a,** 88 mg, 0.199 mmol, 86 % yield)**.** LC-MS (Method A5): 2.16 min, $[M + H]^+$=444.1; ^1H NMR (500 MHz, MeOH-d_4) δ 7.91-7.52 (m, 3H), 7.42 - 7.28 (m, 5H), 5.79 (s, 2H), 3.74 - 3.59 (m, 3H), 3.23 (q, *J*=7.6 Hz, 2H), 2.72 (s, 3H), 2.68 (s, 3H), 1.39 (t, *J*=7.6 Hz, 3H).

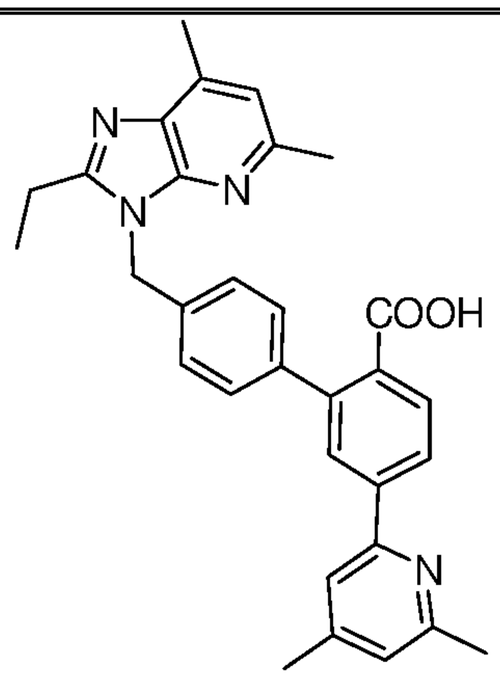
Example 192: 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(pyridin-2-yl)biphenyl-2-carboxylic acid

A mixture of **Intermediate 192a** (22 mg, 0.050 mmol) and 2-bromopyridine (23.52 mg, 0.149 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.089 mL, 0.089 mmol) followed by Pd-XPhos G3 (4.20 mg, 4.96 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 130 °C for 30 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH ((0.248 mL, 0.496 mmol). The mixture was reheated in a microwave reactor at 100 °C for 1 hour. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95

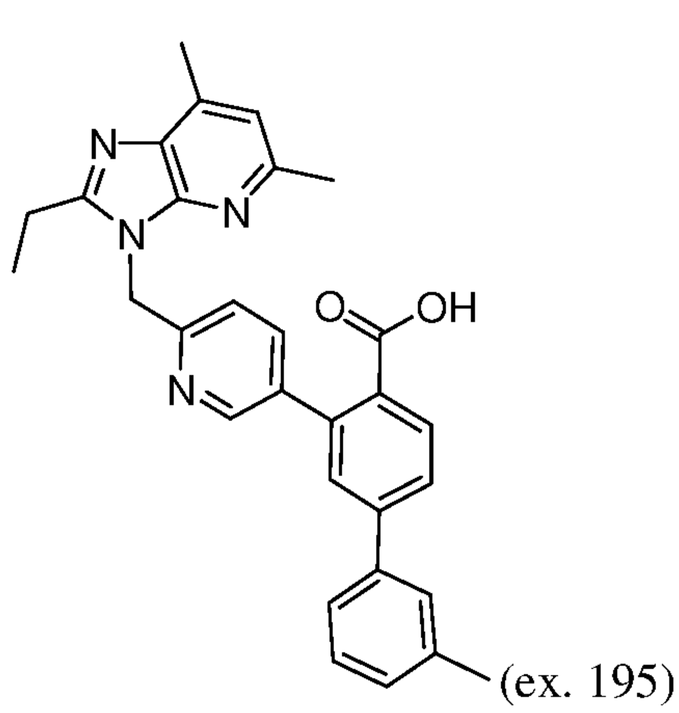
ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 40-80% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min) to afford 2.3 mg (0.005 mmol, 9.6 % yield) of the title compound **Example 192**. LC-MS (Method A3): 1.14 min, $[M + H]^+$= 463.16;. ^1H NMR (500 MHz, DMSO-d_6) δ 8.67 (br d, *J*=4.3 Hz, 1H), 8.07 (br dd, *J*=17.5, 8.1 Hz, 2H), 7.99 (s, 1H), 7.89 (br t, *J*=7.6 Hz, 1H), 7.73 (br d, *J*=7.9 Hz, 1H), 7.40 (br d, *J*=7.6 Hz, 3H), 7.16 (br d, *J*=7.9 Hz, 2H), 6.97 (s, 1H), 5.52 (s, 2H), 2.83 (q, *J*=7.3 Hz, 2H), 2.54 (s, 6H), 1.28 (t, *J*=7.3 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 192a** as described above for **Example 192**. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method A3, Method A4 or Method A5.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^1H NMR (500MHz, DMSO-d_6) δ ppm
193		476.58	477.21; 1.23 min (Method A1)	8.52 (d, J=4.9 Hz, 1H), 8.13 (br d, J=8.5 Hz, 1H), 8.00 (s, 1H), 7.93 (s, 1H), 7.84 (d, J=7.9 Hz, 1H), 7.36 (br d, J=7.9 Hz, 2H), 7.25 (br d, J=4.6 Hz, 1H), 7.21 (br d, J=7.9 Hz, 2H), 7.04 (s, 1H), 5.56 (s, 2H), 2.92 - 2.83 (m, 2H), 2.55 (br s, 3H), 2.54 (s, 3H), 2.39 (s, 3H), 1.27 (t, J=7.5 Hz, 3H)

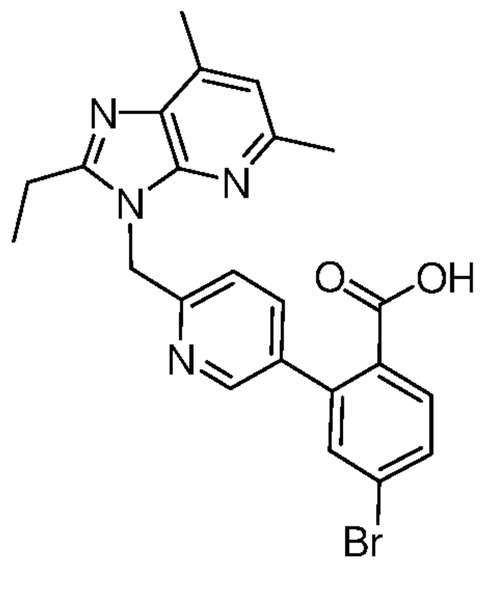
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT; (Method)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
194		490.61	491.26;1.41 min (Method A3)	8.13 (br d, J=8.2 Hz, 1H), 8.00 (s, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.73 (s, 1H), 7.36 (br d, J=7.9 Hz, 2H), 7.19 (br d, J=7.6 Hz, 2H), 7.10 (s, 1H), 6.98 (s, 1H), 5.53 (s, 2H), 2.84 (q, J=7.4 Hz, 2H), 2.56 (s, 3H), 2.54 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H), 1.29 (t, J=7.5 Hz, 3H).

Example 195: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)-3'-methylbiphenyl-4-carboxylic acid



(ex. 195)

Intermediate 195a: 4-bromo-2-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)benzoic acid



(195a)

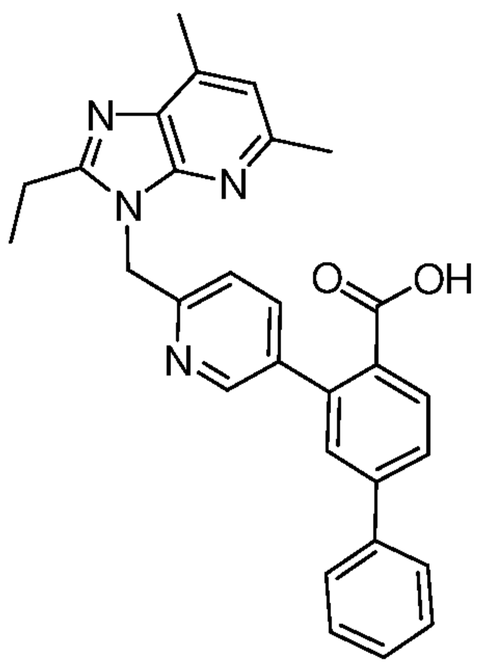
A mixture of **Intermediate 177c** (crude boronic ester, 60 mg, 0.107 mmol) and 4-bromo-2-iodobenzoic acid (35.0 mg, 0.107 mmol) in NMP/H_2O (1:1, 1 mL) was treated with K2CO3 (32.6 mg, 0.236 mmol) followed by $Pd_2(dba)_3$ (9.80 mg, 10.71 μmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 120 °C for 15 min. The mixture was cooled and filtered through celite and purified via preparative HPLC (Column: Phenomenex AXIA Luna 100 x 30mm 5u s; Mobile Phase A: 10:90 ACN: H_2O with 10 mM TFA; Mobile Phase B: 90:10 ACN: H_2O with 10 mM TFA; Gradient: 0-100% B over 10 minutes, then a 2-minute hold at 100% B; Flow: 40 mL/min.) to afford the title compound (**Intermediate 195a,** 17 mg, 0.037 mmol, 34.5 % yield). LC-MS (Method A5): 2.27 min, $[M + H]^+$=465.1 and 467.1. ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (br d, *J*=8.0 Hz, 1H), 7.76 (br s, 1H), 7.65 (br d, *J*=7.7 Hz, 1H), 7.44 (br s, 2H), 5.84 (br s, 2H), 3.26 (br s, 2H), 2.72 - 2.54 (m, 6H), 1.38 (br s, 3H).

Example 195: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)-3'-methylbiphenyl-4-carboxylic acid

A mixture of **Intermediate 195a** (17 mg, 0.037 mmol) and m-tolylboronic acid (14.90 mg, 0.110 mmol) in THF (1 mL) was treated with 1.5 M Na_2CO_3 (0.073 mL, 0.110 mmol) followed by $PdCl_2$(dppf) (2.98 mg, 3.65 μmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 135 °C for 30 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 17-57% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min.) to afford 7.8

mg (0.016 mmol, 44.8 % yield) of the title compound **Example 195**. LC-MS (Method A3): 1.44 min, $[M + H]^+$= 477.11; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.87 (br d, *J*=8.2 Hz, 1H), 7.81 (br d, *J*=7.9 Hz, 1H), 7.75 (br d, *J*=7.6 Hz, 1H), 7.59 (s, 2H), 7.54 (br d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.8 Hz, 1H), 7.21 (br d, *J*=7.3 Hz, 1H), 7.18 (d, *J*=8.2 Hz, 1H), 6.94 (s, 1H), 5.59 (s, 2H), 2.87 (q, *J*=7.3 Hz, 2H), 2.52 (br s, 3H), 2.50 (br s, 3H), 2.37 (s, 3H), 1.29 (t, *J*=7.5 Hz, 3H).

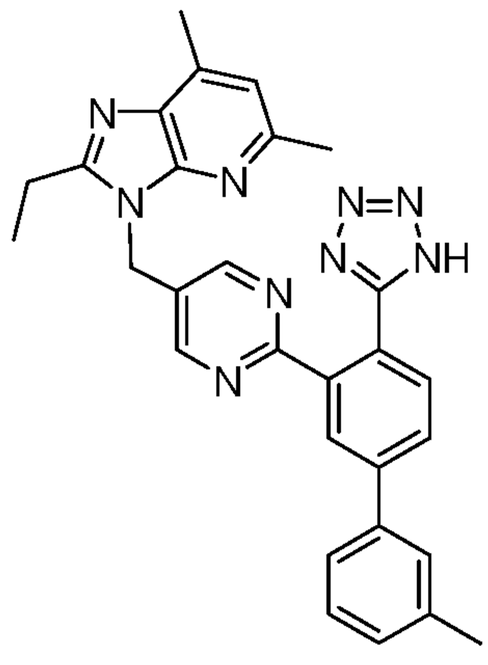
Example 196: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-3-yl)-[1,1'-biphenyl]-4-carboxylic acid



(Ex. 196)

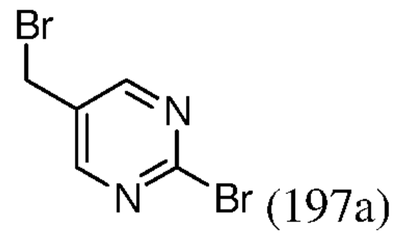
Example 196 has been similarly prepared from **Intermediate 195a** as described above for **Example 195**. LC-MS (Method A3): 1.42 min, $[M + H]^+$=463.32; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.95 (d, *J*=7.9 Hz, 1H), 7.81 (br d, *J*=7.9 Hz, 2H), 7.77 (br d, *J*=7.6 Hz, 2H), 7.63 (s, 1H), 7.52 - 7.46 (m, 2H), 7.44 - 7.38 (m, 1H), 7.20 (br d, *J*=8.2 Hz, 1H), 6.94 (s, 1H), 5.60 (s, 2H), 2.87 (q, *J*=7.4 Hz, 2H), 2.52 (br s, 3H), 2.50 (br s, 3H), 1.29 (t, *J*=7.3 Hz, 3H).

Example 197: 2-ethyl-5,7-dimethyl-3-((2-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrimidin-5-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex. 197)

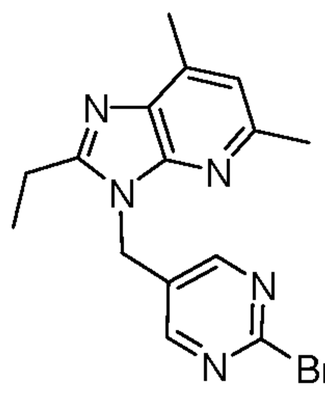
Intermediate 197a: 2-bromo-5-(bromomethyl)pyrimidine



(197a)

To a suspension of (2-chloropyrimidin-5-yl)methanol (330 mg, 2.283 mmol) in DCM (6.0 mL) was added a solution of PBr_3 (0.323 ml, 3.42 mmol) in DCM (0.3 mL) dropwise. The resulting mixture was stirred at RT for overnight. The mixture was concentrated under reduced pressure and purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 197a,** 110 mg, 0.437 mmol, 19.13 % yield) as a white solid. LC-MS (Method A5): 1.72 min, $[M + H]^+$= 252.8; ^1H NMR (500 MHz, MeOH-d_4) δ 8.67 (s, 2H), 4.68 (s, 2H).

Intermediate 197b: 3-((2-bromopyrimidin-5-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

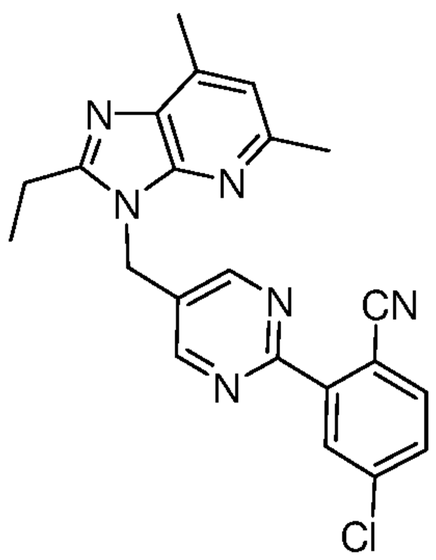


(197b)

To a solution of **Intermediate 001c** (69.6 mg, 0.397 mmol) in DMF (2.0 mL) was added sodium hydride (20.64 mg, 0.516 mmol)) at RT and the reaction was stirred vigorously for 30 min. Then a solution of **Intermediate 197a** (100 mg, 0.397 mmol) in DMF (0.8 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before

being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 197b,** 71 mg, 0.205 mmol, 51.7 % yield) as a white solid. LC-MS (Method A5): 1.80 min, $[M + H]^+$=346.0 and 348.0; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.56 (s, 1H), 6.93 (s, 1H), 5.42 (d, *J*=12.9 Hz, 2H), 2.89 (q, *J*=7.4 Hz, 2H), 2.64 (s, 3H), 2.59 (d, *J*=1.1 Hz, 3H), 1.43 (t, *J*=7.6 Hz, 3H).

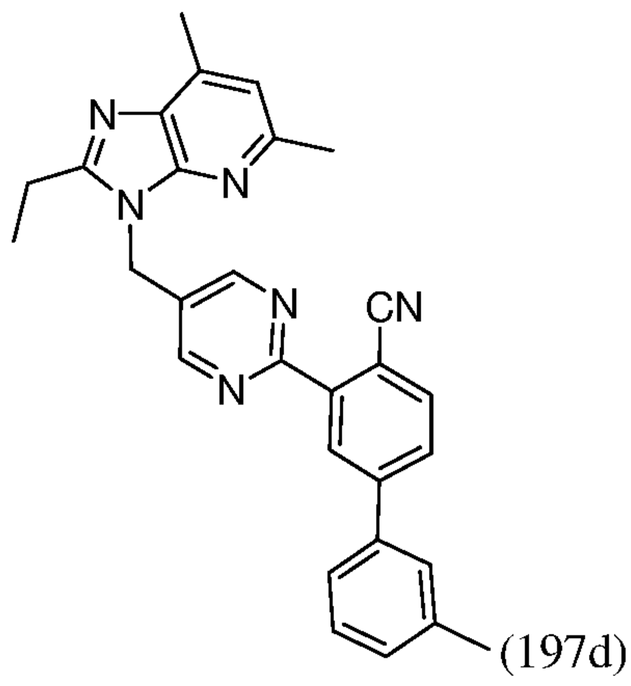
Intermediate 197c: 4-chloro-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-2-yl)benzonitrile



(197c)

A mixture of **Intermediate 197b** (70 mg, 0.202 mmol) and (5-chloro-2-cyanophenyl)boronic acid (47.7 mg, 0.263 mmol) in THF (3 mL) was treated with 1.5 M Na_2CO_3 (0.404 mL, 0.607 mmol) followed by $PdCl_2$(dppf) (16.51 mg, 0.020 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 130°C for 75 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude sample in 2 ml of DCM was treated with TEA (0.141 mL, 1.011 mmol) followed by TFAA (0.043 mL, 0.303 mmol). The mixture was stirred at RT for 1 hour, then concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 197c,** 40 mg, 0.099 mmol, 49.1 % yield) as an amber oil. LC-MS (Method A5): 2.27 min, $[M + H]^+$ = 403.1.

Intermediate 197d: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-2-yl)-3'-methylbiphenyl-4-carbonitrile



(197d)

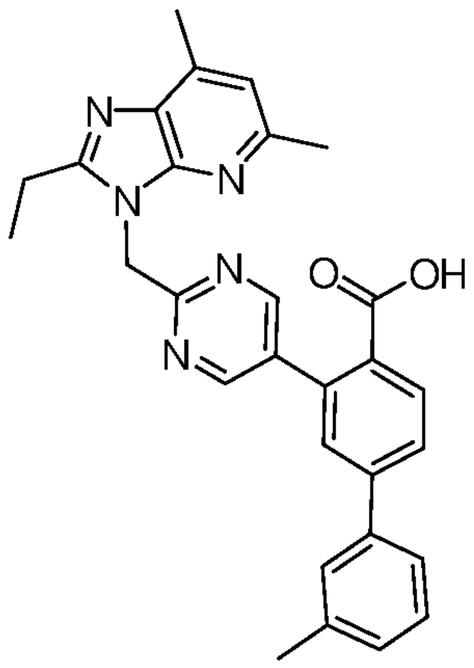
A mixture of **Intermediate 197c** (20 mg, 0.050 mmol) m-tolylboronic acid (6.75 mg, 0.050 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.089 mL, 0.089 mmol) followed by Pd-XPhos G3 (4.20 mg, 4.96 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 60 min. The cooled reaction mixture was concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 197d,** 20 mg, 0.044 mmol, 88%) as a colorless oil. LC-MS (Method A5): 2.49 min, $[M + H]^+$=459.0; ^1H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 2H), 8.61 (d, *J*=1.9 Hz, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 7.79 (dd, *J*=8.1, 1.8 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.39 (t, *J*=7.6 Hz, 1H), 7.27 (d, *J*=7.7 Hz, 1H), 6.95 (s, 1H), 5.54 (s, 2H), 2.93 (q, *J*=7.6 Hz, 2H), 2.66 (s, 3H), 2.63 (s, 3H), 2.46 (s, 3H), 1.44 (t, *J*=7.6 Hz, 3H)

Example 197: 2-ethyl-5,7-dimethyl-3-((2-(3'-methyl-4-(1H-tetrazol-5-yl)biphenyl-3-yl)pyrimidin-5-yl)methyl)-3H-imidazo[4,5-b]pyridine

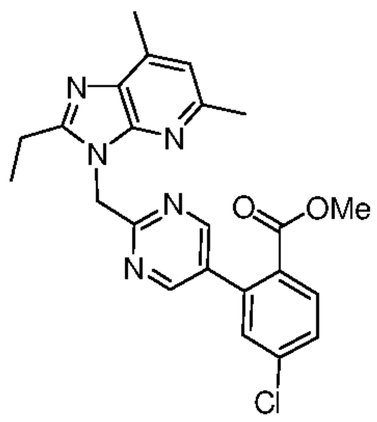
To a solution of **Intermediate 197d** (20 mg, 0.044 mmol) in toluene (1.5 mL) was added dibutyltin oxide (21.71 mg, 0.087 mmol) and TMS-N_3 (0.058 mL, 0.436 mmol). Then the reaction vessel was sealed and the mixture was heated at 100 °C overnight behind a blast shield (according to the procedure described in *J. Org. Chem*, 1993, *58*, 4139). After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min) to afford 17.8 mg (0.035 mmol, 81 % yield) of the title compound **Example 197**. LC-MS (Method A3): 1.44 min, $[M + H]^+$=502.04; ^1H NMR (500 MHz,

DMSO-d_6) δ 8.67 (s, 2H), 8.15 (s, 1H), 7.93 (br d, *J*=7.9 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.67 - 7.51 (m, 2H), 7.40 (t, *J*=7.6 Hz, 1H), 7.25 (br d, *J*=7.3 Hz, 1H), 6.98 (s, 1H), 5.53 (s, 2H), 2.92 (q, *J*=7.4 Hz, 2H), 2.56 (s, 3H), 2.54 (s, 3H), 2.40 (s, 3H), 1.31 (t, *J*=7.5 Hz, 3H).

Example 198: 3-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)-3'-methylbiphenyl-4-carboxylic acid



Intermediate 198a: methyl 4-chloro-2-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)benzoate



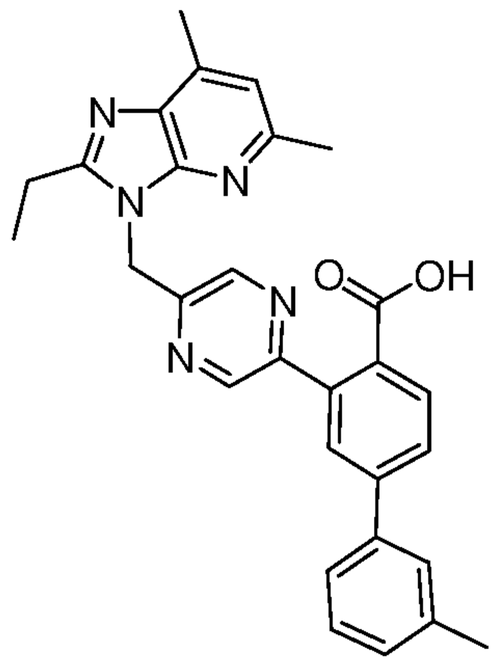
A mixture of (2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)boronic acid (**Intermediate 188c**, 45 mg, 0.145 mmol) and methyl 4-chloro-2-iodobenzoate (40 mg, 0.135 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.270 mL, 0.405 mmol) followed by $PdCl_2$(dppf) (5.51 mg, 6.75 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 100 °C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 198a,** 36

mg, 0.083 mmol, 61.2 % yield) as a yellow oil. LC-MS (Method A5): 2.20 min, $[M + H]^+$ = 436.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.67 - 8.44 (m, 1H), 8.03 (d, *J*=8.5 Hz, 1H), 7.52 (dd, *J*=8.5, 2.2 Hz, 1H), 6.90 (s, 1H), 5.78 (s, 2H), 3.72 (s, 3H), 2.87 (q, *J*=7.7 Hz, 2H), 2.67 (s, 3H), 2.59 (s, 3H), 1.39 (t, *J*=7.6 Hz, 3H)

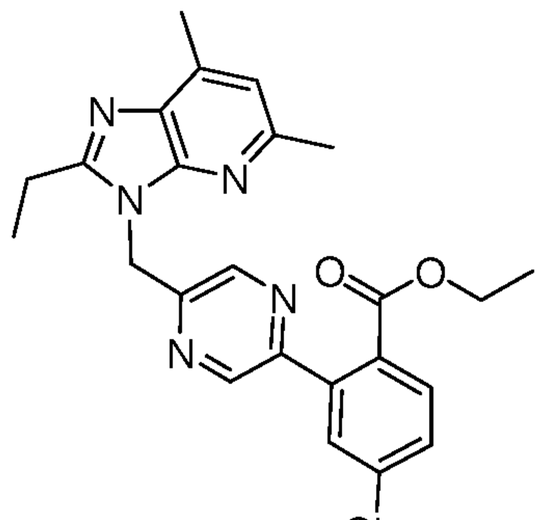
Example 198: 3-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)-3'-methylbiphenyl-4-carboxylic acid

A mixture of methyl 4-chloro-2-(2-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-5-yl)benzoate (**Intermediate 198a**,18mg, 0.041 mmol) and m-tolylboronic acid (16.84 mg, 0.124 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.074 mL, 0.074 mmol) followed by Pd-XPhos G3 (1.748 mg, 2.065 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.124 mL, 0.248 mmol). The mixture was reheated in a microwave reactor at 100 °C for 30 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 30-70% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.) to afford 10.6 mg (0.022 mmol, 53.8 % yield) of the title compound **Example 198**. LC-MS (Method A3): 1.42 min, $[M + H]^+$= 478.35; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 2H), 8.05 (d, *J*=8.2 Hz, 1H), 7.85 (br d, *J*=7.6 Hz, 1H), 7.70 (s, 1H), 7.62 (s, 1H), 7.58 (br d, *J*=7.4 Hz, 1H), 7.37 (t, *J*=7.6 Hz, 1H), 7.24 (br d, *J*=7.4 Hz, 1H), 6.92 (s, 1H), 5.72 (s, 2H), 2.84 (q, *J*=7.5 Hz, 2H), 2.55 (s, 3H), 2.48 (s, 3H), 2.39 (s, 3H), 1.31 (t, *J*=7.4 Hz, 3H).

Example 199: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)-3'-methylbiphenyl-4-carboxylic acid



Intermediate 199a: ethyl 4-chloro-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)benzoate

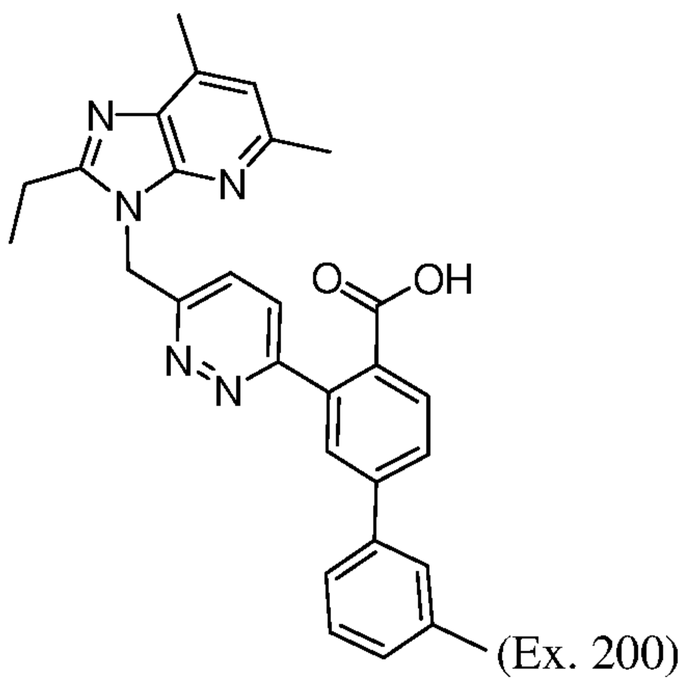


A mixture **Intermediate 186b** (40mg, 0.116 mmol) and (5-chloro-2-(ethoxycarbonyl)phenyl)boronic acid (31.7 mg, 0.139 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.231 mL, 0.347 mmol) followed by $PdCl_2$(dppf) (9.43 mg, 0.012 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125°C for 45 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 199a,** 44 mg, 0.098 mmol, 85 % yield) as an amber oil. LC-MS (Method A5): 2.23 min, $[M + H]^+$ = 450.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J*=8.5 Hz, 2H), 7.90 (d, *J*=8.8 Hz, 1H), 7.54 - 7.47 (m, 2H), 6.91 (s, 1H), 5.65 (s, 2H), 4.21 - 4.06 (m, 2H), 3.02 (q, *J*=7.4 Hz, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 1.44 (t, *J*=7.6 Hz, 3H)

Example 199: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)-3'-methylbiphenyl-4-carboxylic acid

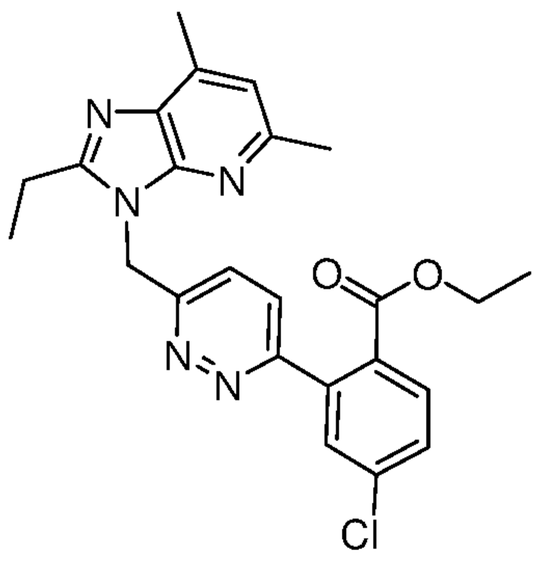
A mixture of ethyl 4-chloro-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrazin-2-yl)benzoate (**Intermediate 199a**, 44 mg, 0.098 mmol) and m-tolylboronic acid (39.9 mg, 0.293 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.176 mL, 0.176 mmol) followed by Pd-XPhos G3 (8.28 mg, 9.78 μmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.293 mL, 0.587 mmol). The mixture was reheated in a microwave reactor at 100 °C for 30 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.) to afford 13.3 mg (0.027 mmol, 27.3 % yield) of the title compound **Example 199**. LC-MS (Method A3): 1.4 min, $[M + H]^+$= 478.22; ^1H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.94 - 7.87 (m, 1H), 7.86 - 7.76 (m, 2H), 7.60 (s, 1H), 7.56 (br d, *J*=7.6 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.24 (br d, *J*=7.3 Hz, 1H), 6.95 (s, 1H), 5.69 (s, 2H), 2.93 (q, *J*=7.6 Hz, 2H), 2.56 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H), 1.32 (t, *J*=7.5 Hz, 3H).

Example 200: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridazin-3-yl)-3'-methylbiphenyl-4-carboxylic acid



(Ex. 200)

Intermediate 200a: ethyl 4-chloro-2-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridazin-3-yl)benzoate



(200a)

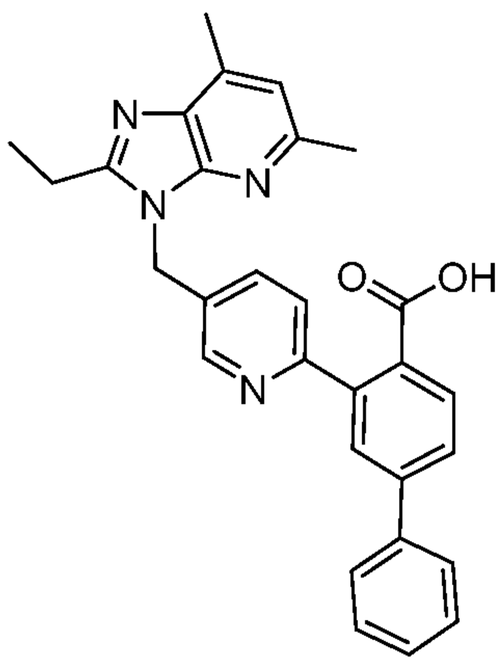
A mixture of **Intermediate 191a** (50 mg, 0.144 mmol) and (5-chloro-2-(ethoxycarbonyl)phenyl)boronic acid (39.6 mg, 0.173 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.289 mL, 0.433 mmol)) followed by $PdCl_2$(dppf) (11.79 mg, 0.014 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125°C for 45 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 200a,** 40 mg, 0.089 mmol, 61.6 % yield) as an amber oil. LC-MS (Method A5): 2.19 min, $[M + H]^+$ = 450.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.5 Hz, 1H), 7.53 (s, 1H), 7.54 (br d, *J*=2.2 Hz, 1H), 7.48 (d, *J*=0.8 Hz, 2H), 6.93 (s, 1H), 5.85 (s, 2H), 4.14 (q, *J*=7.2 Hz, 2H), 3.01 (q, *J*=7.4 Hz, 2H), 2.65 (s, 3H), 2.62 (s, 3H), 1.39 (t, *J*=7.4 Hz, 3H), 1.06 (t, *J*=7.2 Hz, 3H)

Example 200: 3-(6-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridazin-3-yl)-3'-methylbiphenyl-4-carboxylic acid

A mixture of **Intermediate 200a** (20mg, 0.044 mmol) and m-tolylboronic acid (18.13 mg, 0.133 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.080 mL, 0.080 mmol) followed by Pd-XPhos G3 (3.76 mg, 4.45 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.133 mL, 0.267 mmol). The mixture

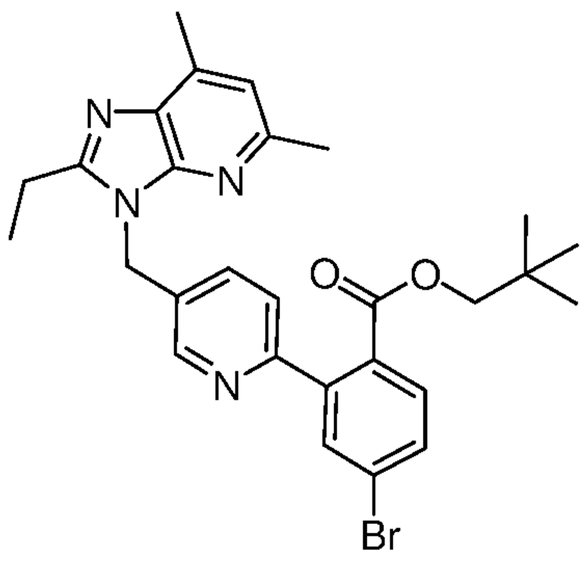
was reheated in a microwave reactor at 100 °C for 1 hour. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 19-59% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min.) to afford 14.5 mg (0.032 mmol, 71.8 % yield) of the title compound **Example 200**. LC-MS (Method A3): 1.35 min, $[M + H]^+$= 478.1; ^1H NMR (500 MHz, DMSO-d_6) δ 8.01 - 7.92 (m, 2H), 7.92 - 7.87 (m, 1H), 7.82 (s, 1H), 7.65 (d, *J*=8.7 Hz, 1H), 7.62 (s, 1H), 7.58 (br d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.25 (br d, *J*=7.4 Hz, 1H), 6.99 (s, 1H), 5.83 (s, 2H), 2.92 (q, *J*=7.4 Hz, 2H), 2.53 (s, 3H), 2.51 (s, 3H), 2.38 (s, 3H), 1.30 (t, *J*=7.4 Hz, 3H)

Example 201: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)biphenyl-4-carboxylic acid



(Ex. 201)

Intermediate 201a: neopentyl 4-bromo-2-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)benzoate



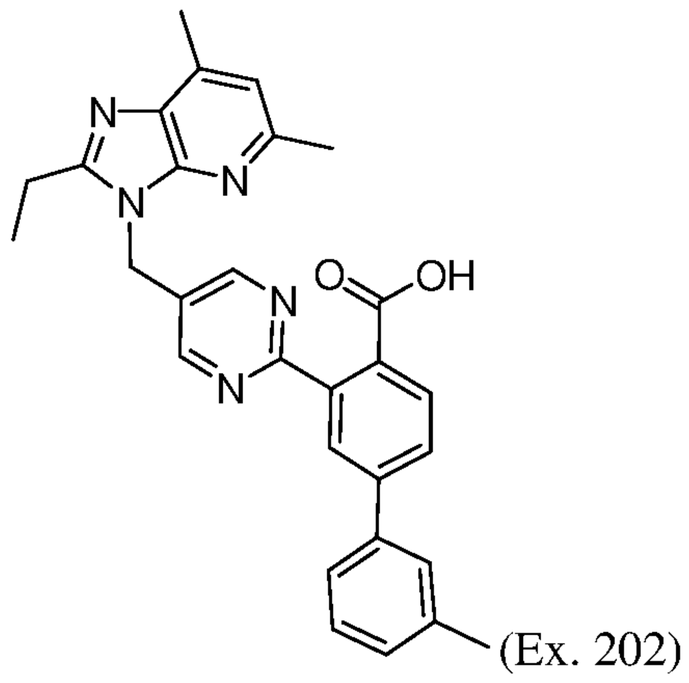
(Ex. 201a)

A mixture of **Intermediate 039a** (50 mg, 0.145 mmol) and (5-bromo-2-((neopentyloxy)carbonyl)phenyl)boronic acid (59.3 mg, 0.188 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.290 mL, 0.434 mmol) followed by $PdCl_2$(dppf) (11.83 mg, 0.014 mmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 130°C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 201a,** 20 mg, 0.037 mmol, 25.8 % yield) as an amber oil. LC-MS (Method A5): 2.51min, $[M + H]^+$ = 535.2 and 537.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J*=1.4 Hz, 1H), 7.72 (d, *J*=8.3 Hz, 1H), 7.68 (d, *J*=1.7 Hz, 1H), 7.62 (dd, *J*=8.3, 1.9 Hz, 1H), 7.56 (dd, *J*=8.1, 2.1 Hz, 1H), 7.39 (d, *J*=8.3 Hz, 1H), 6.93 (s, 1H), 5.51 (s, 2H), 3.74 (s, 2H), 2.89 (q, *J*=7.7 Hz, 2H), 2.65 (s, 3H), 2.62 (s, 3H), 1.42 (t, *J*=7.6 Hz, 3H), 0.71 (s, 9H).

Example 201: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)biphenyl-4-carboxylic acid

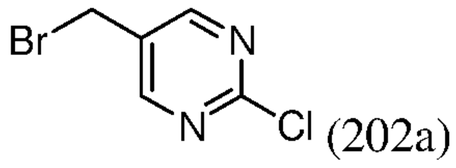
A mixture of **Intermediate 201a** (20 mg, 0.037 mmol) and phenylboronic acid (13.66 mg, 0.112 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.075 mL, 0.112 mmol) followed by $PdCl_2$(dppf) (3.05 mg, 3.73 µmol).The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 130 °C for 30 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.131 mL, 0.261 mmol). The mixture was reheated in a microwave reactor at 100 °C for 15 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 15-55% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.) to afford 7.6 mg (0.016 mmol, 41.3 % yield) of the title compound **Example 201**. LC-MS (Method A3): 1.37 min, $[M + H]^+$= 463.31; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.83 - 7.79 (m, 2H), 7.78 (s, 1H), 7.75 (br d, *J*=7.5 Hz, 2H), 7.64 (s, 2H), 7.51 - 7.47 (m, 2H), 7.44 - 7.39 (m, 1H), 6.99 (s, 1H), 5.57 (s, 2H), 2.89 (q, *J*=7.4 Hz, 2H), 2.55 (s, 3H), 2.53 (s, 3H), 1.29 (t, *J*=7.4 Hz, 3H).

Example 202: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-2-yl)-3'-methylbiphenyl-4-carboxylic acid



(Ex. 202)

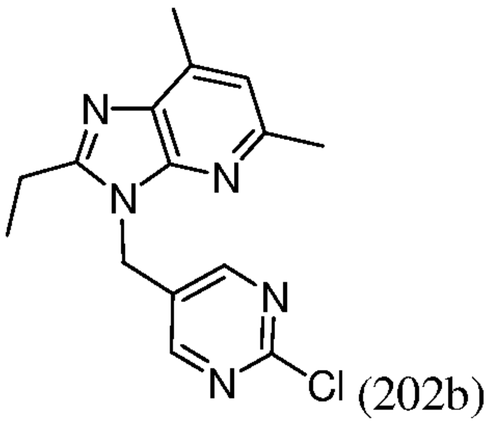
Intermediate 202a: 5-(bromomethyl)-2-chloropyrimidine



(202a)

2-chloro-5-methylpyrimidine (200mg, 1.556 mmol) was dissolved in carbon tetrachloride (5 mL), NBS (332 mg, 1.867 mmol) and benzoyl peroxide (18.84 mg, 0.078 mmol) were added , and the resulting mixture was heated and refluxed for overnight. The reaction solution was returned to RT, concentrated under reduced pressure and purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 202a,** 116 mg, 0.559 mmol, 35.9 % yield) as a white solid. LC-MS (Method A5): 1.62 min, $[M + H]^+$= 206.9 and 208.9; ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 2H), 4.44 (s, 2H).

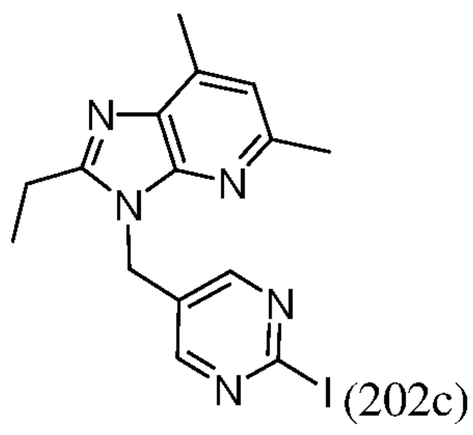
Intermediate 202b: 3-((2-chloropyrimidin-5-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(202b)

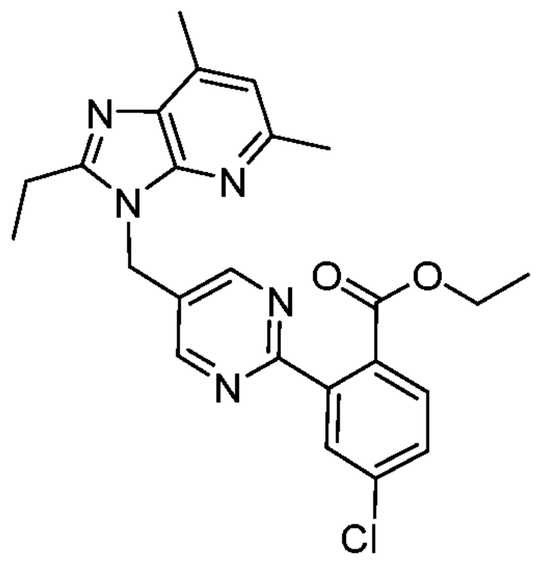
To a solution of **Intermediate 001c** (90 mg, 0.514 mmol) in DMF (2.0 mL) was added sodium hydride (26.7 mg, 0.668 mmol) at RT and the reaction was stirred vigorously for 30 min. Then a solution of **Intermediate 202a** (112 mg, 0.539 mmol) in DMF (0.8 mL) was added and the resulting reaction mixture was allowed to stir for 2 h before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with EtOAc and extracted. The organic phase was dried over $MgSO_4$, filtered and concentrated before being purified by ISCO (Hex/EtOAc, 0-100%) to afford the title compound (**Intermediate 202b,** 87 mg, 0.288 mmol, 56.1 % yield) as a white solid. LC-MS (Method A5): 1.79 min, $[M + H]^+$=302.2; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 2H), 6.92 (s, 1H), 5.42 (s, 2H), 2.88 (q, *J*=7.6 Hz, 2H), 2.62 (s, 3H), 2.58 (s, 3H), 1.41 (t, *J*=7.6 Hz, 3H).

Intermediate 202c: 2-ethyl-3-((2-iodopyrimidin-5-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine


(202c)

HI (306 µl, 2.320 mmol) precooled to 0 °C was added to 3-((2-chloropyrimidin-5-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (70 mg, 0.232 mmol) in a small vial. The mixture was kept and vigorously stirred at 0 °C for 50 min. The light brownish green suspension was quickly neutralized at 0 °C with a saturated aqueous solution of potassium carbonate and decolorized with potassium disulfite at 0 °C. The aqueous solution was extracted with diethyl ether, dried over desiccated $MgSO_4$, filtered, and evaporated under reduced pressure. The crude sample was purified by ISCO (Hexanes/AcOEt, 0-100%) to afford the title compound (**Intermediate 202c,** 30mg, 0.076 mmol, 32.9 % yield). LC-MS (Method A5): 1.89 min, $[M + H]^+$=394.0; ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 2H), 6.92 (s, 1H), 5.38 (s, 2H), 2.88 (q, *J*=7.5 Hz, 2H), 2.63 (s, 3H), 2.58 (s, 3H), 1.42 (t, *J*=7.6 Hz, 3H)

Intermediate 202d:



(202d)

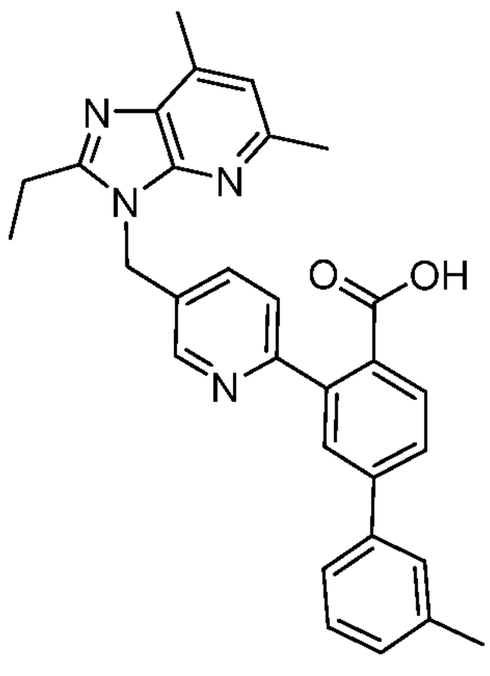
A mixture of **Intermediate 202c** (30mg, 0.076 mmol) and (5-chloro-2-(ethoxycarbonyl)phenyl)boronic acid (20.91 mg, 0.092 mmol) in THF (1.5 mL) was treated with 1.5 M Na_2CO_3 (0.153 mL, 0.229 mmol) followed by $PdCl_2$(dppf) (6.23 mg, 7.63 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 125°C for 30 min. The cooled reaction mixture was diluted with DCM and extracted. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness and the residue purified by ISCO (DCM/MeOH, 0-20%) to afford the title compound (**Intermediate 202d,** 22 mg, 0.049 mmol, 64.1 % yield) as an amber oil. LC-MS (Method A5): 2.29 min, $[M + H]^+$ = 450.1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 2H), 7.98 (d, *J*=1.9 Hz, 1H), 7.68 (d, *J*=8.3 Hz, 1H), 7.49 (dd, *J*=8.3, 1.9 Hz, 1H), 6.94 (s, 1H), 5.50 (s, 2H), 4.19 (q, *J*=7.2 Hz, 2H), 2.93 (q, *J*=7.7 Hz, 2H), 2.65 (s, 3H), 2.61 (s, 3H), 1.44 (t, *J*=7.4 Hz, 3H), 1.09 (t, *J*=7.2 Hz, 3H)

Example 202: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyrimidin-2-yl)-3'-methylbiphenyl-4-carboxylic acid

A mixture of **Intermediate 202d** (20mg, 0.044 mmol) and m-tolylboronic acid (18.13 mg, 0.133 mmol) in THF (1 mL) was treated with 1.0 M phosphoric acid, potassium salt (0.080 mL, 0.080 mmol) followed by Pd-XPhos G3 (3.76 mg, 4.45 µmol). The resulting mixture was degassed with N_2 for 2 min before the reaction vessel was sealed and irradiated in a microwave reactor at 140 °C for 45 min. The cooled reaction mixture was treated with MeOH (0.5 mL) and 2.0 M NaOH (0.133 mL, 0.267 mmol). The mixture was reheated in a microwave reactor at 100 °C for 30 min. After cooling, the reaction mixture was concentrated, re-solvated in DMF, filtered then purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase

A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 15-55% B over 25 minutes, then a 6-minute hold at 100% B; Flow: 20 mL/min.) to afford 8.5 mg (0.018 mmol, 39.5 % yield) of the title compound **Example 202**. LC-MS (Method A3): 1.4 min, $[M + H]^+$= 478.06; ^1H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 2H), 8.06 (d, *J*=1.6 Hz, 1H), 7.84 (dd, *J*=8.0, 1.7 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.55 (s, 1H), 7.52 (br d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.24 (br d, *J*=7.4 Hz, 1H), 7.02 (s, 1H), 5.60 (s, 2H), 2.98 (q, *J*=7.3 Hz, 2H), 2.56 (br s, 3H), 2.54 (s, 3H), 2.39 (s, 3H), 1.33 (t, *J*=7.4 Hz, 3H).

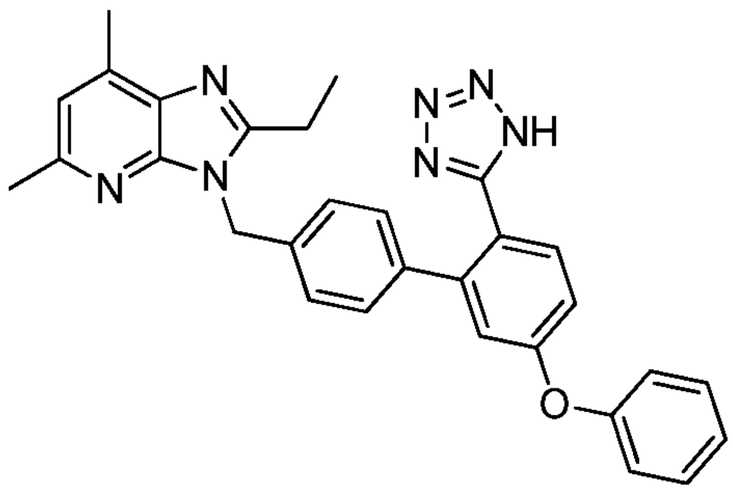
Example 203: 3-(5-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)pyridin-2-yl)-3'-methyl-[1,1'-biphenyl]-4-carboxylic acid



(Ex. 203)

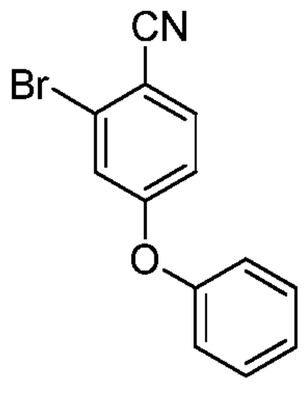
Example 203 has been similarly prepared from **Intermediate 201[a]** as described above for **Example 201**. LC-MS (Method A3): 1.63 min, $[M + H]^+$= 477.16; ^1H NMR (500 MHz, DMSO-d_6) δ 7.89 - 7.64 (m, 4H), 7.60 (br s, 1H), 7.56 (br d, *J*=7.3 Hz, 1H), 7.38 (br t, *J*=7.5 Hz, 1H), 7.30 - 7.18 (m, 2H), 7.12 - 6.94 (m, 2H), 5.66 (br s, 2H), 2.96 (br d, *J*=4.6 Hz, 2H), 2.52 (br s, 6H), 2.38 (s, 3H), 1.30 (br s, 3H).

Example 204: 2-Ethyl-5, 7-dimethyl-3-((5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex: 204)

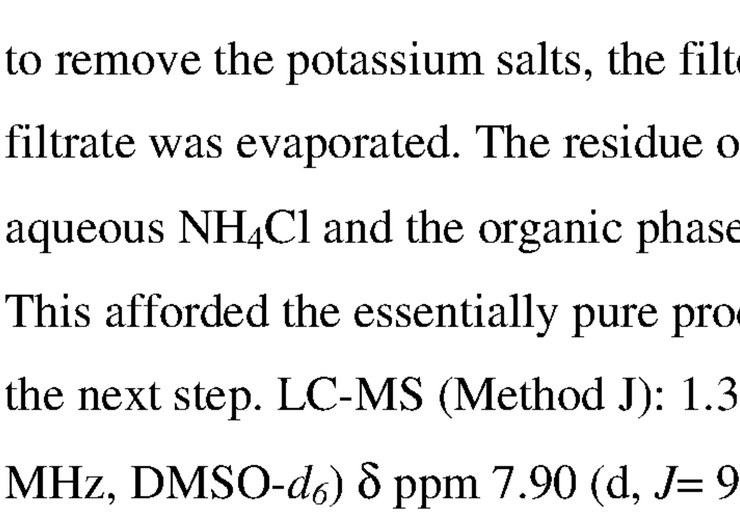
Intermediate 204a: 2-Bromo-4-phenoxybenzonitrile



(204a)

To a solution of 2-bromo-4-fluorobenzonitrile (0.400 g, 2.000 mmol) and phenol (0.207 g, 2.200 mmol) in DMF (10 mL) was added potassium carbonate (0.332 g, 2.400 mmol) and the resulting mixture was stirred at 50°C in a sealed vial overnight. After 16 h, LC-MS showed that the reaction was essentially complete (co-injection with starting material), with a single major peak (target mass not observed). The mixture was filtered to remove the potassium salts, the filter-cake was washed with a DMF (2 mL) and the filtrate was evaporated. The residue obtained was partitioned with EtOAc-saturated aqueous NH_4Cl and the organic phase was separated, dried (Na_2SO_4) and evaporated. This afforded the essentially pure product (0.466 g, 85% yield) which was used as such in the next step. LC-MS (Method J): 1.330 min, $[M + H]^+$ = *no ion observed*; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 (d, *J*= 9.0 Hz, 1H), 7.48 (t, *J*= 8.2 Hz, 1H), 7.39 (d, *J*= 2.3 Hz, 1H), 7.29 (t, *J*= 7.4 Hz, 1H), 7.17 (d, *J*= 7.4 Hz, 1H), 7.05 (dd, *J*= 2.3, 8.6 Hz, 1H).

Intermediate 204b: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile



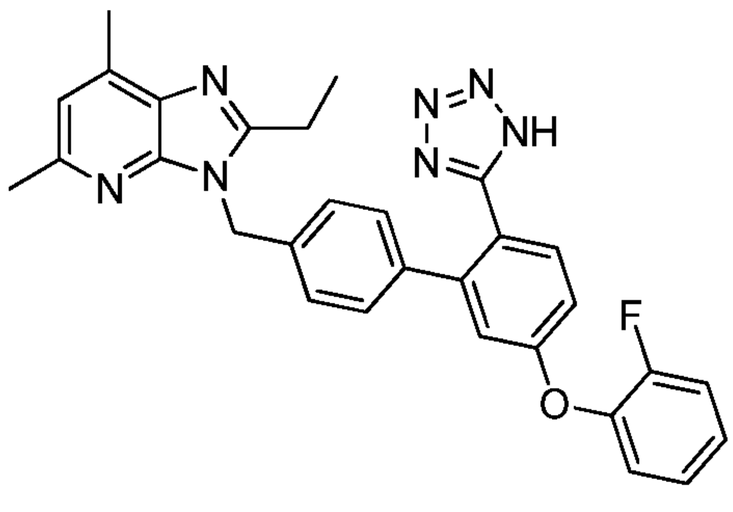
(204b)

A mixture of **Intermediate 001d** (0.060 g, 0.153 mmol), **Intermediate 204a** (0.053 g, 0.192 mmol) and 2 M Na_2CO_3 (0.192 mL, 0.383 mmol) in toluene-ethanol (9:1, 5 mL) was purged with a stream of N_2 for 5 min in a sealable vial. To this mixture was added $Pd(Ph_3P)_4$ (0.018 g, 0.015 mmol), the vial was sealed and the mixture was stirred at 95°C (block temperature) for 3 h. The cooled mixture was diluted with EtOAc and the organic phase was separated, dried (Na_2SO_4) and evaporated to give a golden yellow gum. This material was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile (0.041 g, 58.3% yield) as a colourless gum. This gum was lyophilized from ACN-H_2O to give a white solid which was used as such in the next step.
LC-MS (Method J): 1.479 min, $[M + H]^+$ = 459.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 (d, *J*= 8.6 Hz, 1H), 7.50 (d, *J*= 8.2 Hz, 2H), 7.45 (m, 2H), 7.27-7.21 (m, 3H), 7.17 (m, 2H), 7.08 (d, *J*= 2.7 Hz, 1H), 7.02 (dd, *J*= 2.7, 8.6 Hz, 1H), 6.94 (s, 1H), 5.51 (s, 2H), 2.78 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 2.48 (*hidden*, 3H), 1.23 (t, *J*= 7.4 Hz, 3H).

Example 204: 2-Ethyl-5, 7-dimethyl-3-((5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

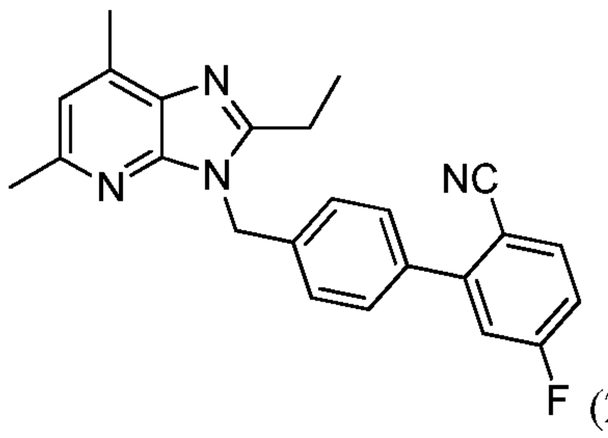
To a mixture of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile (0.012 g, 0.026 mmol), TMS-N_3 (0.037 mL, 0.262 mmol) and dibutyltin oxide (0.013 g, 0.052 mmol) was added toluene (2 mL). The vial was briefly purged with N_2 and then it was sealed and the mixture was stirred at 120°C (block temperature) for 16 h. The cooled mixture was evaporated and the residual gum was taken up in DMF (acidified with a 10 drops of AcOH) and filtered using a 0.45 µm syringe filter. The filtrate was submitted to preparative LC (Method D) and the product-containing fractions were combined and evaporated to give a white solid. This material was lyophilized from ACN-H_2O to give 2-ethyl-5,7-dimethyl-3-((5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine (0.005 g, 38.1% yield) as a white solid.
LC-MS (Method J): 1.547 min, $[M + H]^+$ = 502.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.63 (d, *J*= 8.6 Hz, 1H), 7.43 (t, *J*= 8.6 Hz, 2H), 7.20 (t, *J*= 7.4 Hz, 1H), 7.14 (d, *J*= 7.4 Hz, 2H), 7.09 (dd, *J*= 2.3, 8.6 Hz, 1H), 7.03 (d, *J*= 2.7 Hz, 1H), 7.01 (s, 4H), 6.92 (s, 1H), 5.41 (s, 2H), 2.72 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.19 (t, *J*= 7.4 Hz, 3H).

Example 205: 2-Ethyl-3-((5'-(2-fluorophenoxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex: 205)

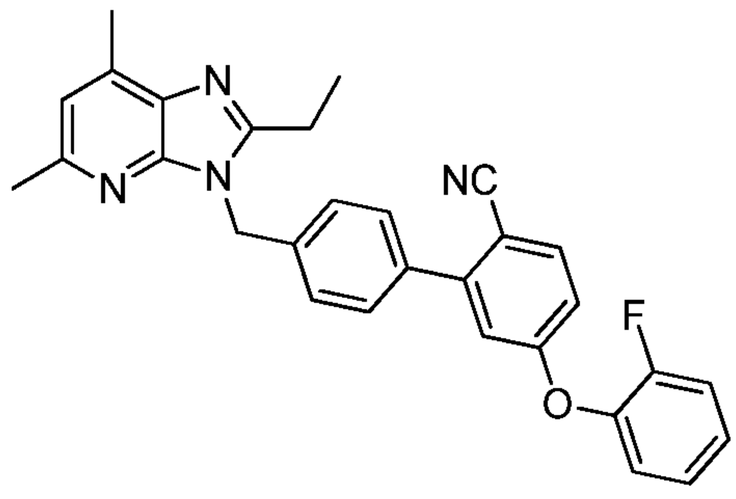
Intermediate 205a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile



(205a)

A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.262 g, 0.670 mmol), 2-bromo-4-fluorobenzonitrile (0.147 g, 0.736 mmol) and 2 M Na_2CO_3 (0.837 mL, 1.674 mmol) in toluene-ethanol (9:1, 10 mL) was purged with a stream of N_2 for 5 min in a sealable vial. To this mixture was added $Pd(Ph_3P)_4$ (0.077 g, 0.067 mmol), the vial was sealed and the mixture was stirred at 95°C (block temperature) for 2 h. The cooled mixture was diluted with EtOAc and the organic phase was separated, dried (Na_2SO_4) and evaporated to give a pale yellow gum. This material was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (0.174 g, 67.6% yield) as a colourless gum which solidified on standing in vacuo to give a waxy solid. This material was used as such in the next step. LC-MS (Method J): 1.331 min, $[M + H]^+ = 385.1$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (dd, *J*= 5.5, 8.6 Hz, 1H), 7.55 (d, *J*= 8.2 Hz, 2H), 7.50 (dd, *J*= 2.7, 9.8 Hz, 1H), 7.43 (dt, *J*= 2.7, 8.6 Hz, 1H), 7.25 (d, *J*= 8.2 Hz, 2H), 6.94 (s, 1H), 5.53 (s, 2H), 2.80 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 1.23 (t, *J*= 7.4 Hz, 3H).

Intermediate 205b: 4'-((2-Ethyl-5, 7-dimethyl-3H-imidazo[4, 5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1, 1'-biphenyl]-2-carbonitrile



(205b)

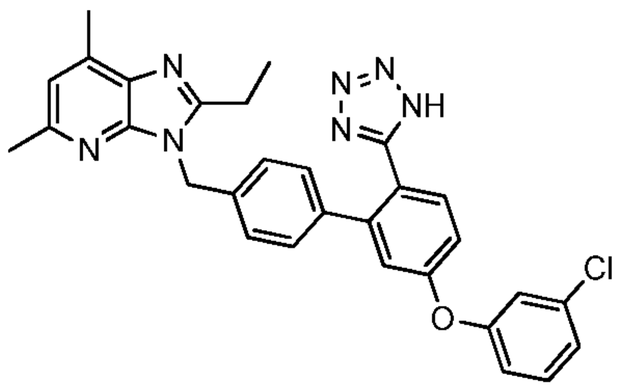
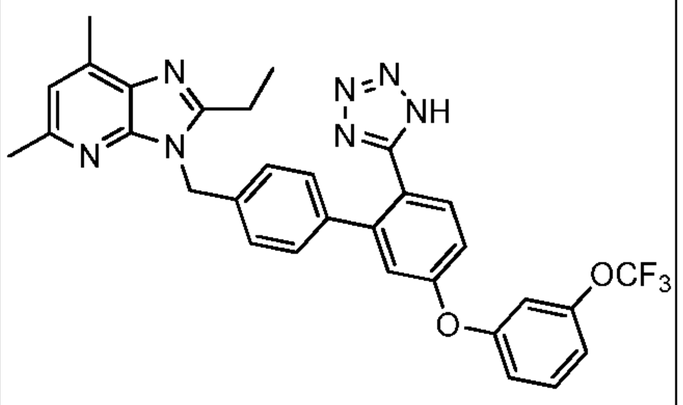
To a solution of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.065 mmol) and 2-fluorophenol (8.02 mg, 0.072 mmol) in DMF (1 mL) was added potassium carbonate (10.78 mg, 0.078 mmol) and the resulting mixture was stirred at 90°C (block temperature) in a sealed vial for 16 h. The cooled mixture was filtered through a small plug of cotton wool to remove the potassium salts and the residue was washed with a little DMF. The filtrate was evaporated to give a pale purple gum which was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give a colourless gum. This material was lyophilized from ACN-H_2O to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-carbonitrile (0.026 g, 84% yield) as a white solid which was used as such in the next step. LC-MS (Method J): 1.439 min, $[M + H]^+ = 477.1$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.91 (d, *J*= 8.6 Hz, 1H), 7.50 (d, *J*= 8.2 Hz, 2H), 7.45-7.26 (m, 4H), 7.22 (d, *J*= 8.2 Hz, 2H), 7.11 (d, *J*= 2.7 Hz, 1H), 7.01 (dd, *J*= 2.3, 8.6 Hz, 1H), 6.94 (s, 1H), 5.51 (s, 2H), 2.79 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 2.48 (*hidden*, 3H), 1.23 (t, *J*= 7.4 Hz, 3H).

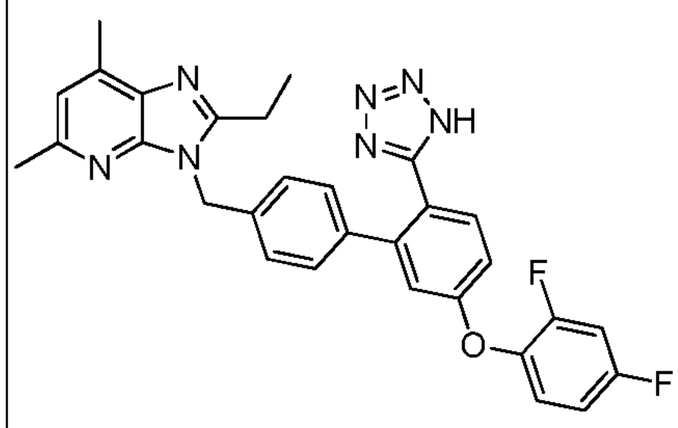
Example 205: 2-Ethyl-3-((5'-(2-fluorophenoxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

To a sealable vial containing 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-carbonitrile (0.012 g, 0.025 mmol) and dibutyltin oxide (0.013 g, 0.050 mmol) in toluene (2 mL) was added TMS-N_3 (0.033 mL, 0.252 mmol). The vial was then sealed and the mixture were stirred at 100°C (block temperature) for 18 h. Another portion of dibutyltin oxide (0.013 g, 0.050 mmol) and TMS-N_3 (0.033 mL, 0.252 mmol) was added and the mixture was heated at 120°C for an additional 18 h. The cooled mixture was evaporated and the residue was taken up in DMF (1.8 mL, acidified with 10 drops of AcOH) and submitted to purification by preparative LC (Method D). The product-containing fractions were combined and evaporated to give

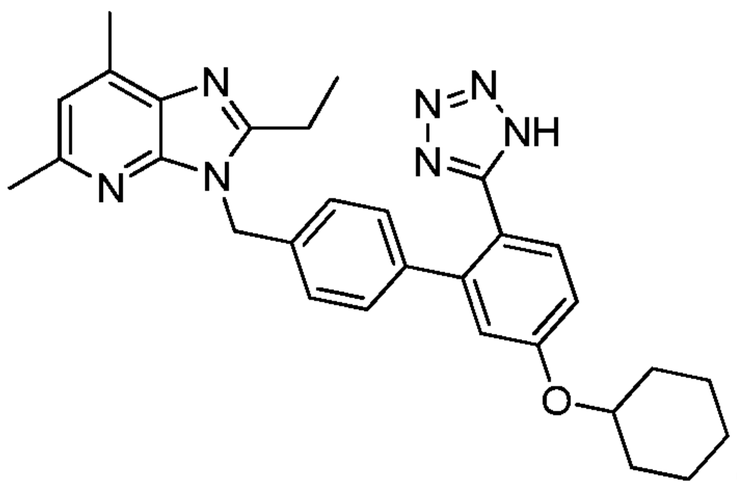
a pale yellow-brown glass. This material was lyophilized from ACN-H_2O to give 2-ethyl-3-((5'-(2-fluorophenoxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.013 g, 99% yield) as a beige solid. LC-MS (Method J): 1.341 min, $[M + H]^+ = 520.1$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.62 (d, *J*= 8.6 Hz, 1H), 7.44-7.31 (m, 2H), 7.27 (m, 2H), 7.07-7.02 (m, 2H), 7.01 (s, 4H), 6.92 (s, 1H), 5.41 (s, 2H), 2.72 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H) 1.19 (t, *J*= 7.4 Hz, 3H).

The following examples have been similarly prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 205a**) as described above for **Example 205**. Two analytical LC injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method J.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^1H NMR (400MHz, DMSO-d_6) δ ppm
206		536.03	536.1; 1.426 min (Method J)	7.64 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 8.2 Hz, 1H), 7.26-7.21 (m, 2H), 7.14 (dd, *J*= 2.3, 8.2 Hz, 1H), 7.11-7.08 (m, 2H), 7.01 (m, 4H), 6.92 (s, 1H), 5.41 (s, 2H), 2.73 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.19 (t, *J*= 7.4 Hz, 3H).
207		585.58	586.1; 1.438 min (Method J)	7.66 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.19-7.12 (m, 5H), 7.01 (m, 4H), 6.92 (s, 1H), 5.41 (s, 2H), 2.72 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.19 (t, *J*= 7.4 Hz, 3H).

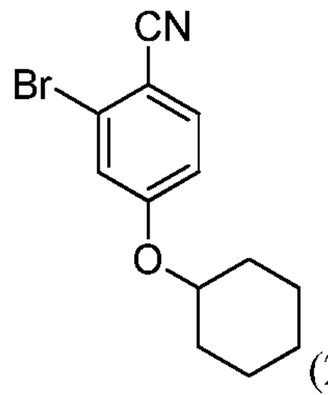
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
208		537.56	538.2; 1.387 min (Method J)	7.58 (d, *J* = 8.6 Hz, 1H), 7.49 (ddd, *J* = 3.1, 9.0, 11.7 Hz, 1H), 7.41 (dt, *J*= 5.5, 9.0 Hz, 1H), 7.14 (m, 1H), 7.02 (m, 1H), 7.00 (m, 5H), 6.92 (s, 1H), 5.40 (s, 2H), 2.73 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.20 (t, *J*= 7.4 Hz, 1H).

Example 209: 3-((5'-(Cyclohexyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex: 209)

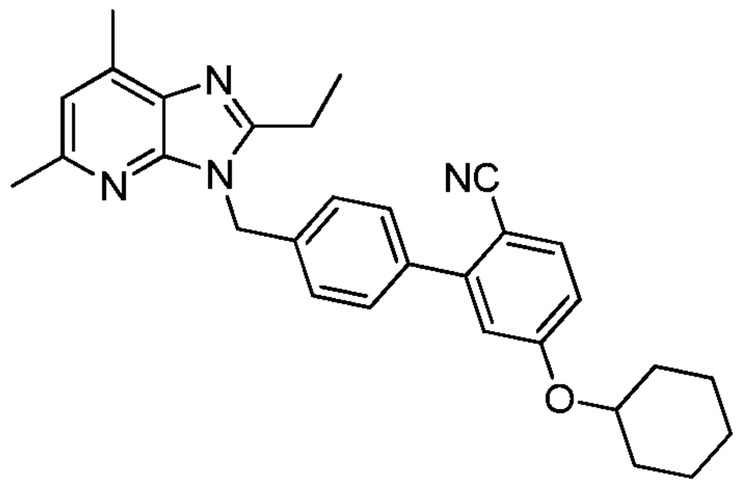
Intermediate 209a: 2-Bromo-4-(cyclohexyloxy)benzonitrile



(209a)

A mixture of 2-bromo-4-fluorobenzonitrile (0.400 g, 2.000 mmol), cyclohexanol (0.458 mL, 4.400 mmol) and potassium carbonate (0.664 g, 4.800 mmol) in DMF (10 mL) was reacted according to the method described for the preparation of **Intermediate 204a**. This afforded 2-bromo-4-(cyclohexyloxy)benzonitrile (0.042 g, 8.0% yield)) as a white solid which was used as such in the next step. LC-MS (Method J): 1.396 min, $[M + H]^+$ = *no ion observed*; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.11 (dd, *J* = 2.3, 8.6 Hz, 1H), 4.54 (m, 1H), 1.88 (m, 2H), 1.69 (m, 2H), 1.50 (m, 1H), 1.46-1.33 (m, 4H), 1.25 (m, 1H).

Intermediate 209b: 5-(Cyclohexyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



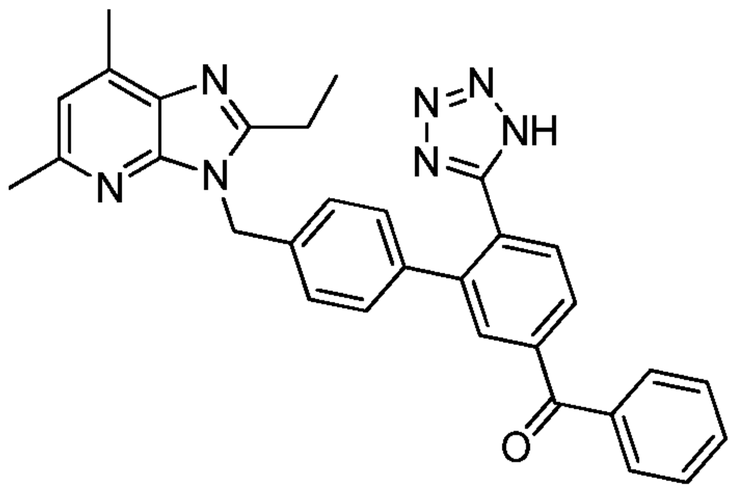
(209b)

A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.056 g, 0.143 mmol), 2-bromo-4-(cyclohexyloxy)-benzonitrile (0.040 g, 0.143 mmol) was reacted according to the method described for the preparation of **Intermediate 204b**. This afforded 5-(cyclohexyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.044 g, 66.2% yield) as a colourless gum. This gum was lyophilized from ACN-H_2O to give a white solid which was used as such in the next step. LC-MS (Method J): 1.577 min, $[M + H]^+$ = 465.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.08 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.94 (s, 1H), 5.52 (s, 2H), 4.54 (m, 1H), 2.81 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 2.48 (*hidden*, 3H), 1.92 (m, 2H), 1.66 (m, 2H), 1.49 (m, 2H), 1.44-1.32 (m, 4H), 1.24 (t, *J*= 7.4 Hz, 1H).

Example 209: 3-((5'-(Cyclohexyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

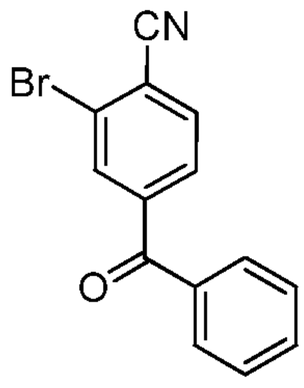
The title compound was prepared from 5-(cyclohexyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.014 g, 0.030 mmol), according to the procedure described for the preparation of **Example 204**, to give 3-((5'-(cyclohexyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.009 g, 58.8% yield) as an off-white solid. LC-MS (Method J): 1.426 min, $[M + H]^+$ = 508.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.50 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.02 (m, 4H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.93 (s, 1H), 5.42 (s, 2H), 4.49 (m, 1H), 2.74 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.92 (m, 2H), 1.68 (m, 2H), 1.53-1.32 (m, 6H), 1.21 (t, *J*= 7.4 Hz, 1H).

Example 210: (4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)(phenyl)methanone



(Ex: 210)

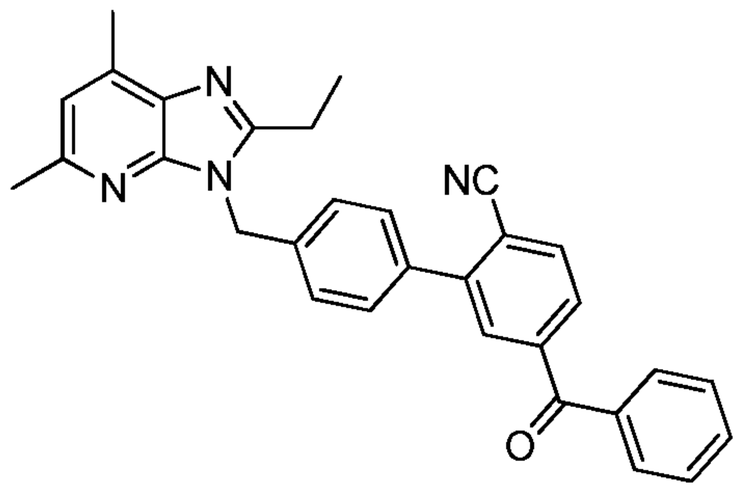
Intermediate 210a: 4-Benzoyl-2-bromobenzonitrile



(210a)

To a vial containing 4-benzoylbenzonitrile (0.181 g, 0.873 mmol; prepared according to the procedure described by L.J. Gooβen and K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 3458), NBS (0.171 g, 0.961 mmol), p-toluenesulfonic acid monohydrate (0.083 g, 0.437 mmol) and palladium (II) acetate (0.020 g, 0.087 mmol), was added DCE (10 mL). The vial was briefly purged with N_2 and then it was sealed and the mixture was stirred at 80°C (block temperature) overnight. The cooled mixture was evaporated and the residue was taken up in a minimum volume of DCM and then adsorbed on a silica gel pre-column. Flash chromatography (ISCO/ 0-50% EtOAc-hexane) gave 4-benzoyl-2-bromobenzonitrile (0.138 g, 55.2% yield) as a white crystalline solid. LC-MS (Method J): 1.272 min, $[M + H]^+$ = *no ion observed*; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.11 (d, *J*= 7.8 Hz, 1H), 8.09 (d, *J*= 1.2 Hz, 1H), 7.81 (dd, *J*= 1.6, 7.8 Hz, 1H), 7.76 (d, *J*= 7.4 Hz, 2H), 7.72 (t, *J*= 7.4 Hz, 1H), 7.58 (t, *J*= 7.6 Hz, 2H).

Intermediate 210b: 5-Benzoyl-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



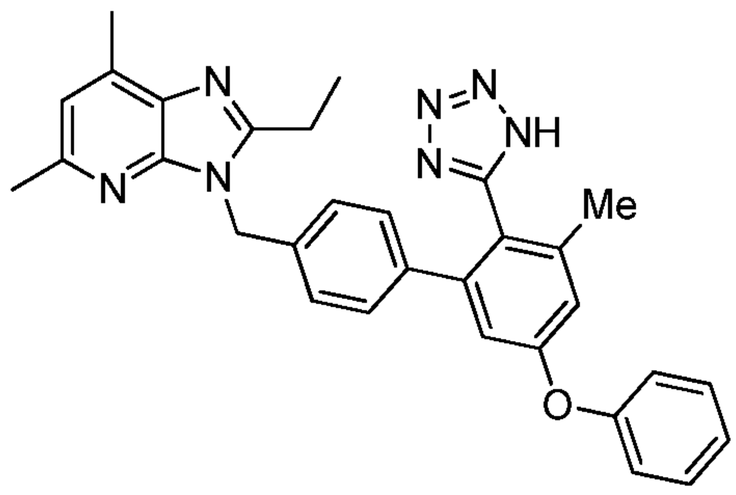
(210b)

A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (0.079 g, 0.202 mmol) and 4-benzoyl-2-bromobenzonitrile (0.072 g, 0.253 mmol) was reacted according to the method described for the preparation of **Intermediate 204b**. This afforded 5-benzoyl-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.077 g, 81% yield) as a foam which was used as such in the next step. LC-MS (Method J): 1.409 min, $[M + H]^+ = 471.1$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.85-7.90 (m, 2H), 7.78-7.83 (m, 3H), 7.62-7.72 (m, 2H), 7.45-7.57 (m, 6H), 6.91 (s, 1H), 5.54 (s, 2H), 2.78-2.88 (m, 2H), 2.65 (s, 3H),) 2.59-2.62 (m, 3H), 1.35 (t, *J*= 7.6 Hz, 3H).

Example 210: (4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)(phenyl)methanone

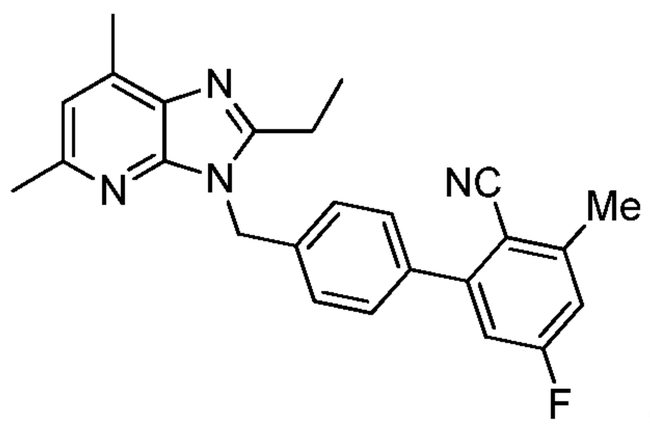
The title compound was prepared from 5-benzoyl-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.031 g, 0.065 mmol), according to the procedure described for the preparation of **Example 204**, to give (4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)(phenyl)-methanone (0.022 g, 62% yield) as a white solid. LC-MS (Method J): 1.366 min, $[M + H]^+ = 514.2$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (d, *J*= 7.8 Hz, 1H), 7.90 (dd, *J*= 8.2, 1.6 Hz, 1H), 7.81-7.87 (m, 3H), 7.60-7.67 (m, 1H), 7.49-7.55 (m, 2H), 7.18 (m, *J*= 8.2 Hz, 2H), 7.08 (m, *J*= 8.2 Hz, 2H), 6.91 (s, 1H), 5.46 (s, 2H), 2.70 (q, *J*= 7.4 Hz, 2H), 2.57 (s, 3H), 2.51 (s, 3H), 1.20 (t, *J*= 7.6 Hz, 3H).

Example 211: 2-Ethyl-5,7-dimethyl-3-((3'-methyl-5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex: 211)

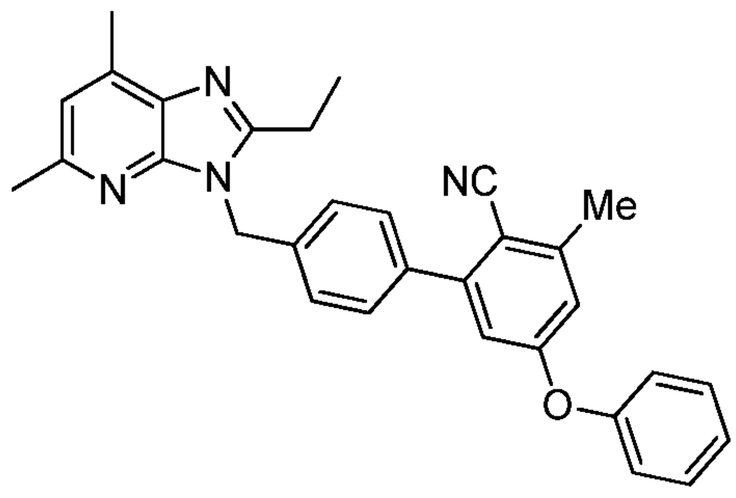
Intermediate 211a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-3-methyl-[1,1'-biphenyl]-2-carbonitrile



(211a)

The title compound was prepared from 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (0.300 g, 0.767 mmol) and 2-bromo-4-fluoro-6-methylbenzonitrile (0.180 g, 0.843 mmol), according to the method described for the synthesis of **Intermediate 205a**, to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-3-methyl-[1,1'-biphenyl]-2-carbonitrile (0.220 g, 72.0% yield) as a colourless gum. This material was lyophilized from ACN-H_2O to give a white solid which was used as such in the next step. LC-MS (Method J): 1.435 min, $[M + H]^+ = 399.2$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.52 (d, *J*= 8.2 Hz, 2H), 7.39 (dd, *J*= 2.3, 9.4 Hz, 1H), 7.28 (dd, *J*= 2.3, 9.4 Hz, 1H), 7.23 (d, *J*= 8.2 Hz, 2H), 6.94 (s, 1H), 5.53 (s, 2H), 2.79 (q, *J*= 7.4 Hz, 2H), 2.53 (s, 3H), 2.50 (s, 3H), 2.49 (s, 3H), 1.23 (t, *J*= 7.4 Hz, 3H).

Intermediate 211b: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3-methyl-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile



(211b)

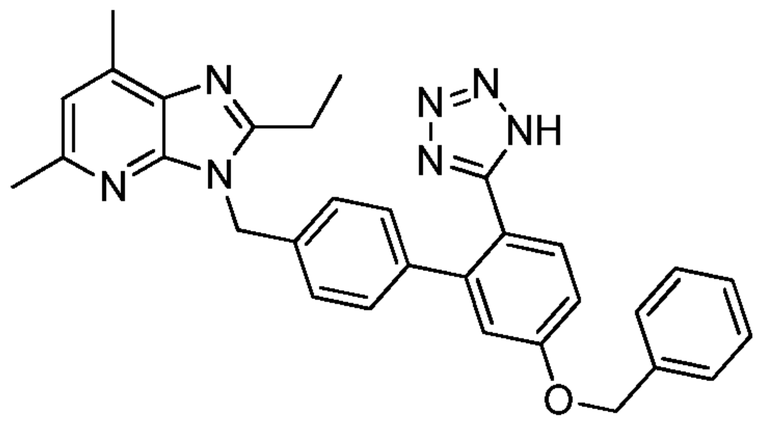
The title compound was prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-3-methyl-[1,1'-biphenyl]-2-carbonitrile (0.030 g, 0.075 mmol) and phenol (7.79 mg, 0.083 mmol), according to the method described for the synthesis of **Intermediate 205b**, to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3-methyl-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile (0.031 g, 87% yield) as a colourless gum. This material was lyophilized from ACN-H_2O to give a white solid which was used as such in the next step.

LC-MS (Method J): 1.571 min, $[M + H]^+ = 473.2$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.46 (d, *J*= 8.2 Hz, 2H), 7.44 (m, 2H), 7.25 (d, *J*= 7.4 Hz, 1H), 7.20 (d, *J*= 8.2 Hz, 2H), 7.14 (dd, *J*= 1.2, 8.6 Hz, 2H), 6.99 (d, *J*= 2.0 Hz, 1H), 6.94 (s, 1H), 6.85 (d, *J*= 2.3 Hz, 1H), 5.50 (s, 2H), 2.78 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 9H), 1.22 (t, *J*= 7.4 Hz, 3H).

Example 211: 2-Ethyl-5,7-dimethyl-3-((3'-methyl-5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

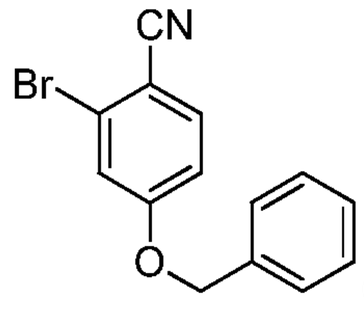
The title compound was prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3-methyl-5-phenoxy-[1,1'-biphenyl]-2-carbonitrile (0.016 g, 0.034 mmol), according to the procedure described for the preparation of **Example 204**, to give 2-ethyl-5,7-dimethyl-3-((3'-methyl-5'-phenoxy-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine (0.012 g, 68.7% yield) as a white solid. LC-MS (Method J): 1.398 min, $[M + H]^+ = 516.2$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.42 (dd, *J*= 7.8, 8.6 Hz, 2H), 7.18 (t, *J*= 7.2 Hz, 1H), 7.12 (d, *J*= 7.4 Hz, 2H), 7.01 (d, *J*= 2.3 Hz, 1H), 6.93 (s, 3H), 6.91 (s, 1H), 6.84 (d, *J*= 2.3 Hz, 1H), 5.36 (s, 2H), 2.67 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 3H), 2.47 (s, 3H), 2.00 (s, 3H), 1.14 (t, *J*= 7.4 Hz, 3H).

Example 212: 3-((5'-(Benzyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex: 212)

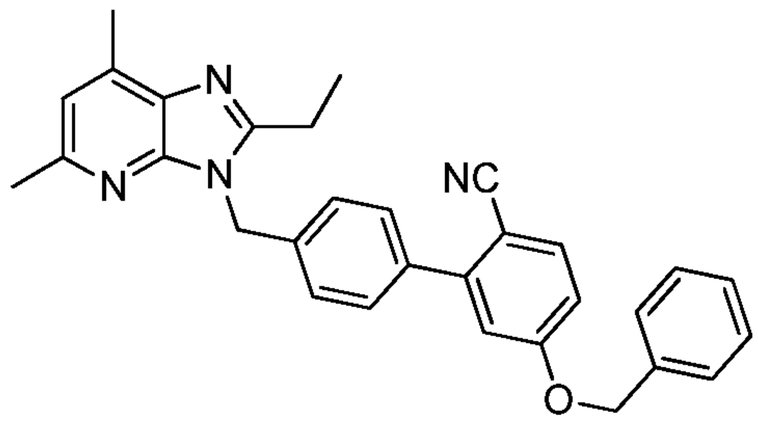
Intermediate 212a: 4-(Benzyloxy)-2-bromobenzonitrile



(212a)

To a solution of benzyl alcohol (0.228 mL, 2.200 mmol) in dry DMF (10 mL) was added 60% sodium hydride (0.096 g, 2.400 mmol) and the resulting mixture was stirred at RT under N_2 for 30 min. To the resulting clear solution was added 2-bromo-4-fluorobenzonitrile (0.400 g, 2.000 mmol) all at once and stirring was continued at RT for 3 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (2 mL) and then it was poured into ice-saturated aqueous NH_4Cl and extracted with EtOAc (x2). The combined organic phase was washed (H_2O, brine), dried (Na_2SO_4) and evaporated to give the crude product as an oil which solidified on standing in vacuo. This material was purified by flash chromatography (ISCO/ 0-50% EtOAc-hexane) to give 4-(benzyloxy)-2-bromobenzonitrile (0.394 g, 68.4% yield) as an off-white crystalline solid which was used as such in the next step. LC-MS (Method J): 1.349 min, $[M + H]^+$ = *no ion observed*; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.85 (d, *J*= 8.6 Hz, 1H), 7.54 (d, *J*= 2.3 Hz, 1H), 7.45-7.32 (m, 5H), 7.19 (dd, *J*= 2.3, 8.6 Hz, 1H), 5.22 (s, 2H).

Intermediate 212b: 5-(Benzyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(212b)

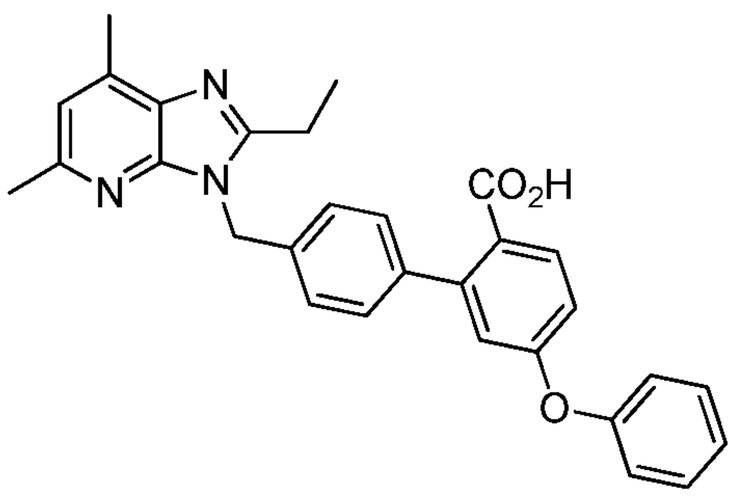
A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (0.056 g, 0.143 mmol) and 4-(benzyloxy)-2-

bromobenzonitrile (0.049 g, 0.172 mmol) was reacted according to the method described for the preparation of **Intermediate 204b**. This afforded 5-(benzyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.031 g, 45.8% yield) as a colourless gum which was used as such in the next step. LC-MS (Method J): 1.502 min, $[M + H]^+ = 473.2$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.83 (d, *J*= 9.0 Hz, 1H), 7.52 (d, *J*= 8.2 Hz, 2H), 7.43 (d, *J*= 7.0 Hz, 2H), 7.38 (t, *J*= 7.2 Hz, 2H), 7.35-7.30 (m, 1H), 7.23 (d, *J*= 8.6 Hz, 2H), 7.17 (s, 1H), 7.15 (m, 1H), 6.94 (s, 1H), 5.52 (s, 2H), 5.22 (s, 2H), 2.80 (q, *J*= 7.4 Hz, 2H), 2.50 (s, 3H), 2.48 (*hidden*, 3H), 1.24 (t, *J*= 7.4 Hz, 3H).

Example 212: 3-((5'-(Benzyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

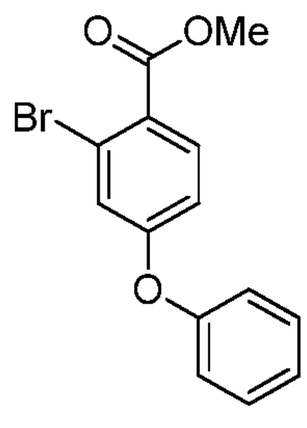
The title compound was prepared from 5-(benzyloxy)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.013 g, 0.028 mmol), according to the procedure described for the preparation of **Example 204**, to give 3-((5'-(benzyloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.014 g, 99% yield) as a white solid. LC-MS (Method J): 1.365 min, $[M + H]^+ = 516.2$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.54 (d, *J*= 8.6 Hz, 1H), 7.45 (d, *J*= 7.0 Hz, 2H), 7.38 (t, *J*= 7.0 Hz, 2H), 7.32 (m, 1H), 7.16 (dd, *J*= 2.3, 8.2 Hz, 1H), 7.09 (d, *J*= 2.3 Hz, 1H), 7.02 (s, 4H), 6.93 (s, 1H), 5.42 (s, 2H), 5.21 (s, 2H), 2.74 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.20 (t, *J*= 7.4 Hz, 3H).

Example 213: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylic acid



(Ex: 213)

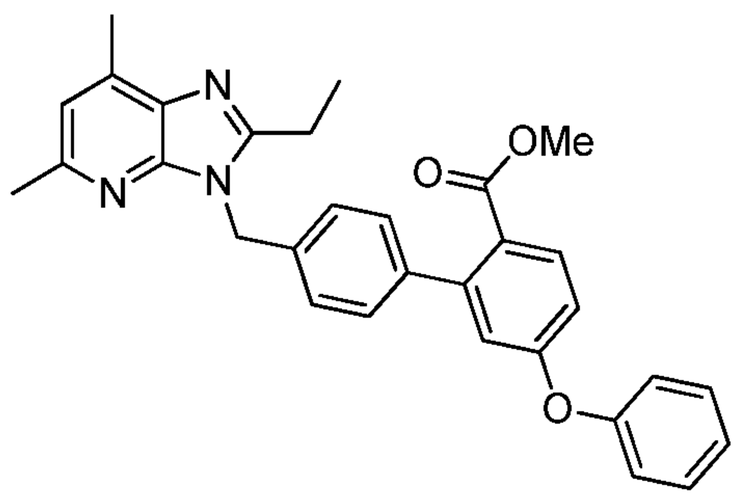
Intermediate 213a: Methyl 2-bromo-4-phenoxybenzoate



(213a)

To a solution of phenol (0.207 g, 2.200 mmol) in dry DMF (10 mL) was added 60% sodium hydride (0.096 g, 2.400 mmol) and the resulting mixture was stirred at RT under N_2 for 30 min. To the resulting clear solution was added methyl 2-bromo-4-fluorobenzoate (0.476 g, 2.000 mmol) all at once and stirring was continued at RT for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and then it was poured into ice H_2O and extracted with EtOAc (x2). The combined organic phase was dried (Na_2SO_4) and evaporated to give a colourless oil. This oil was purified by flash chromatography (ISCO/ 0-30% EtOAc-hexane) to give methyl 2-bromo-4-phenoxybenzoate (0.358 g, 58.3% yield) as a colourless oil which was used as such in the next step. LC-MS (Method J): 1.391 min, $[M + H]^+ = 307.0$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.83 (d, *J*= 8.6 Hz, 1H), 7.46 (dd, *J*= 7.4, 8.6 Hz, 2H), 7.26 (m, 2H), 7.15 (dd, *J*= 1.2, 9.0 Hz, 2H), 7.02 (dd, *J*= 2.3, 8.6 Hz, 1H), 3.81 (s, 3H).

Intermediate 213b: Methyl 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylate



(213b)

A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.060 g, 0.153 mmol), methyl 2-bromo-4-phenoxybenzoate (0.059 g, 0.192 mmol) and 2 M Na_2CO_3 (0.230 mL, 0.460 mmol) in toluene-methanol (9:1, 5 mL) was purged with a stream of N_2 for 5 min in a sealable vial. To this mixture was added $Pd(Ph_3P)_4$ (0.018 g, 0.015 mmol), the vial was sealed and the mixture was stirred at 95°C (block temperature) for 16 h. The cooled mixture was diluted with EtOAc and the organic phase was separated, dried (Na_2SO_4) and evaporated to give

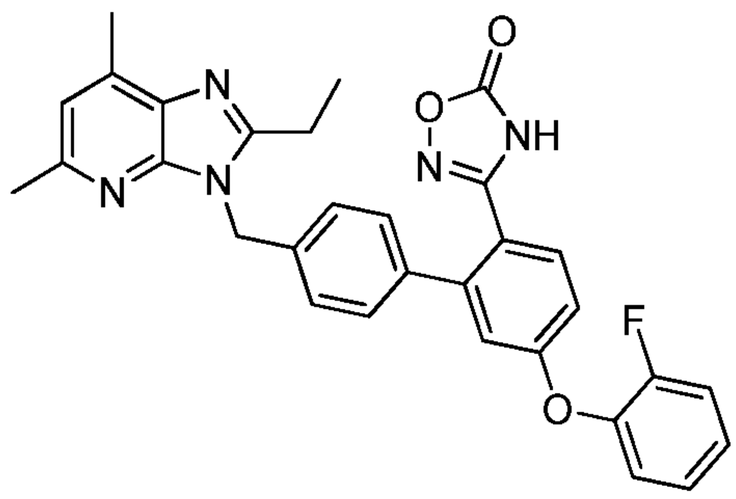
a gum. This material was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give the impure product as a colourless gum.

This gum was repurified by preparative LC (Method D) to give methyl 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylate (0.020 g, 26.5% yield) as a gum. This gum was lyophilized from ACN-H_2O to give a white solid which was used as such in the next step. LC-MS (Method J): 1.563 min, $[M + H]^+$ = 492.2; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 (d, *J*= 8.6 Hz, 1H), 7.42 (dd, *J*= 7.4, 8.2 Hz, 2H), 7.21 (d, *J*= 8.6 Hz, 1H), 7.19 (d, *J*= 8.2 Hz, 2H), 7.11 (t, *J*= 8.2 Hz, 4H), 6.98 (dd, *J*= 2.7, 8.6 Hz, 1H), 6.94 (s, 1H), 6.87 (d, *J*= 2.3 Hz, 1H), 5.47 (s, 2H), 3.52 (s, 3H), 2.76 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.21 (t, *J*= 7.4 Hz, 3H).

Example 213: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylic acid

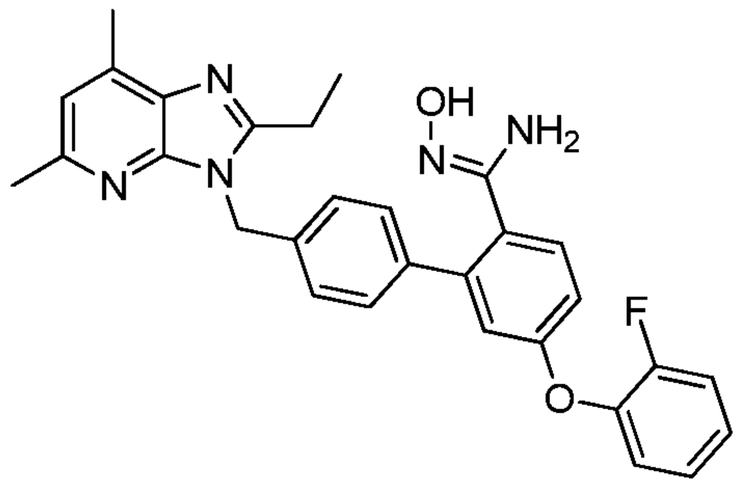
To a solution of methyl 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylate (0.010 g, 0.020 mmol) in THF (2 mL) was added a solution of LiOH monohydrate (1.742 mg, 0.041 mmol) in H_2O (1 mL) and the resulting solution was stirred at RT for 18 h and then it was heated at 80°C in a sealed vial for 2 days. The volatiles were then removed in vacuo, the residue was taken up in DMF (1.8 mL, acidified with 10 drops of AcOH) and the mixture was submitted to preparative LC purification (Method D). The product-containing fractions were combined and evaporated to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-phenoxy-[1,1'-biphenyl]-2-carboxylic acid (0.005 g, 51.5% yield) as a white solid. LC-MS (Method J): 1.408 min, $[M + H]^+$ = 478.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (br s, 1H), 7.76 (d, *J*= 8.6 Hz, 1H), 7.41 (dd, *J*= 7.4, 8.6 Hz, 2H), 7.22 (d, *J*= 8.6 Hz, 2H), 7.18 (d, *J*= 7.4 Hz, 2H), 7.10 (t, *J*= 8.2 Hz, 4H), 6.95 (dd, *J*= 2.3, 8.6 Hz, 1H), 6.93 (s, 1H), 6.82 (d, *J*= 2.3 Hz, 1H), 5.46 (s, 2H), 2.76 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.22 (t, *J*= 7.4 Hz, 3H).

Example 214: 3-(4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-yl)-1,2,4-oxadiazol-5(4H)-one



(Ex: 214)

Intermediate 214a: (Z)-4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-N'-hydroxy-[1,1'-biphenyl]-2-carboximidamide



(214a)

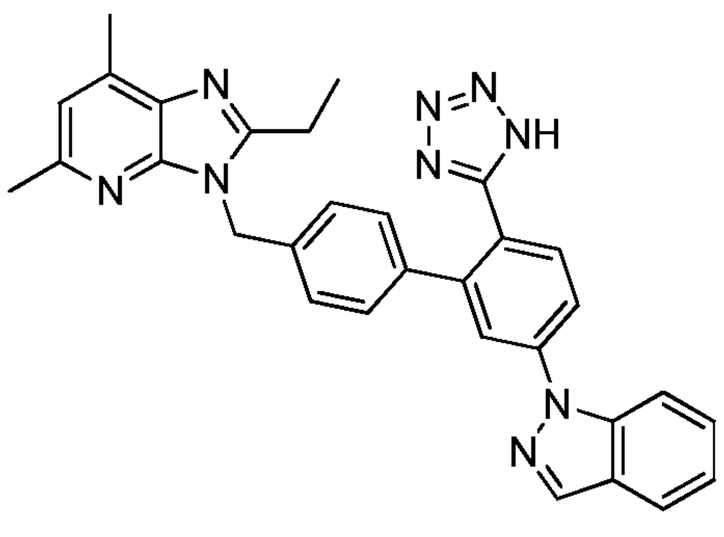
To a sealable vial was added 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-carbonitrile (**205b**, 0.042 g, 0.088 mmol), 1-butyl-3-methylimidazolium acetate (1.00 g, 5.04 mmol) and hydroxylamine hydrochloride (0.153 g, 2.203 mmol). The vial was sealed and the mixture were stirred at 50°C (block temperature) for 16 h. The cooled mixture was diluted with DMF (1 mL) and then H_2O (0.5 mL) was added. The solution was acidified by the dropwise addition of TFA (0.5 mL) and the volume was adjusted with DMF to give 2 x 1.8 mL samples that were submitted to preparative LC purification (Method D). The product-containing fractions were combined and evaporated to give (Z)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-N'-hydroxy-[1,1'-biphenyl]-2-carboximidamide (0.032 g, 71.3% yield) as a gum. This material was used as such in the next step. LC-MS (Method J): 1.227 min, $[M + H]^+ = 510.2$.

Example 214: 3-(4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-yl)-1,2,4-oxadiazol-5(4H)-one

To a sealable vial was added (Z)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-N'-hydroxy-[1,1'-biphenyl]-2-carboximidamide (0.032 g, 0.063 mmol), N,N'-carbonyldiimidazole (0.072 g, 0.445 mmol), DBU (0.067 mL, 0.445

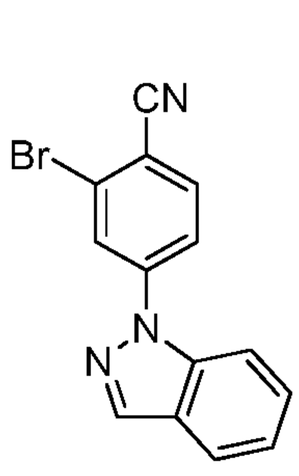
mmol) and dry THF (3 mL). The vial was then sealed and the mixture was stirred at 50°C (block temperature) for 2 h. The cooled mixture was evaporated and the residue was taken up in DMF (2 x 1.8 mL, acidified with 20 drops of AcOH) and submitted to preparative LC purification (Method D). The product-containing fractions were combined and evaporated to give 3-(4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2-fluorophenoxy)-[1,1'-biphenyl]-2-yl)-1,2,4-oxadiazol-5(4H)-one (0.023 g, 48.3 % yield) as a white solid. LC-MS (Method J): 1.391 min, $[M + H]^+ = 536.3$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.29 (br s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.42 (m, 1H), 7.36-7.29 (m, 2H), 7.27 (dd, J = 2.0, 7.4 Hz, 1H), 7.23 (d, J= 8.2 Hz, 2H), 7.13 (d, J= 8.2 Hz, 2H), 7.03 (dd, J= 2.7, 8.2 Hz, 1H), 7.01 (m, 1H), 6.93 (s, 1H), 5.47 (s, 2H), 2.75 (q, J= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.19 (t, J= 7.4 Hz, 3H).

Example 215: 3-((5'-(1H-Indazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

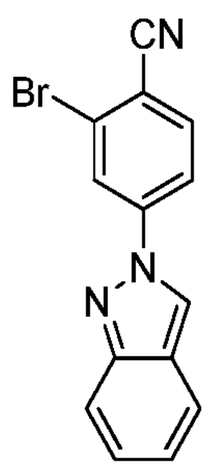


(Ex: 215)

Intermediate 215a and 215b: 2-Bromo-4-(1H-indazol-1-yl)benzonitrile and 2-Bromo-4-(2H-indazol-2-yl)benzonitrile



(215a)

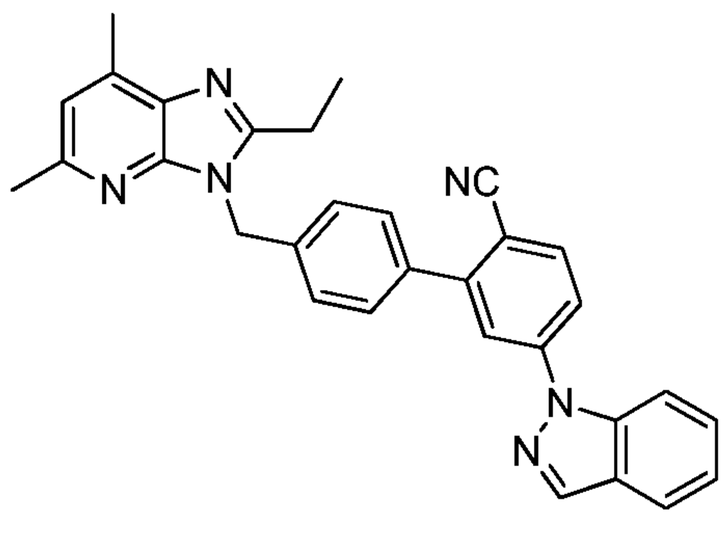


(215b)

A mixture of 2-bromo-4-fluorobenzonitrile (0.200 g, 1.000 mmol), 1H-indazole (0.130 g, 1.100 mmol) and potassium carbonate (0.276 g, 2.000 mmol) in dry DMF (5 mL) was stirred at 120°C (block temperature) in a sealed vial for 16 h. The cooled mixture was filtered through a small plug of cotton wool to remove the potassium salts and the residue was washed with a little DMF. The filtrate was evaporated to give a turbid orange gum

which was purified by flash chromatography (ISCO/ 50-100% DCM-hexane) to give 2-bromo-4-(1H-indazol-1-yl)benzonitrile (**Intermediate 215a**, 0.179 g, 60.0% yield) as a white solid. LC-MS (Method J): 1.402 min, $[M + H]^+$ = 297.9, 299.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.53 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.07 (dd, *J*= 2.0, 8.6 Hz, 1H), 8.03 (d, *J*= 8.6 Hz, 1H), 7.94 (d, *J*= 7.8 Hz, 1H), 7.59 (dd, *J*= 7.4, 8.2 Hz, 1H), 7.35 (t, *J*= 7.4 Hz, 1H). Further elution afforded 2-bromo-4-(2H-indazol-2-yl)benzonitrile (**Intermediate 215b**, 0.078 g, 26.2% yield) as a white solid. LC-MS (Method J): 1.385 min, $[M + H]^+$ = 298.0, 300.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.32 (s, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.33 (dd, *J* = 2.0, 8.6 Hz, 1H), 8.16 (d, *J*= 8.6 Hz, 1H), 7.76 (d, *J*= 8.6 Hz, 1H), 7.70 (d, *J*= 9.0 Hz, 1H), 7.35 (dd, *J*= 6.7, 7.8 Hz, 1H), 7.12 (dd, *J*= 6.7, 8.2 Hz, 2H).

Intermediate 215c: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1H-indazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile



(215c)

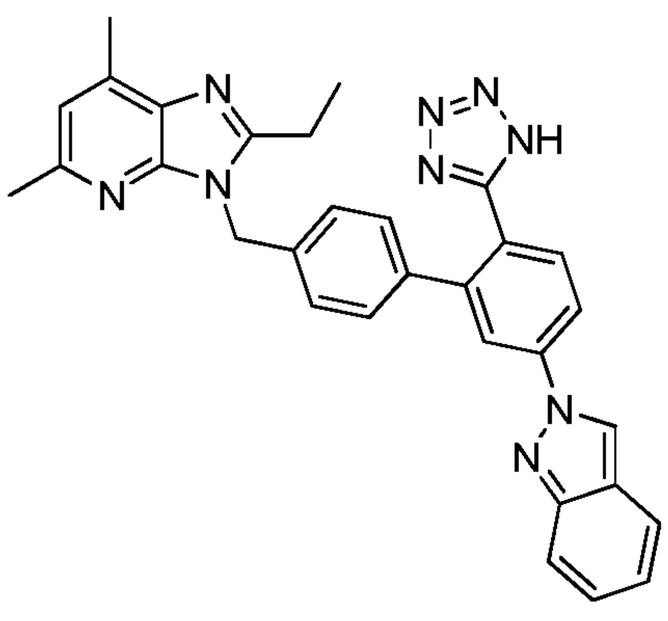
A mixture of 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.100 g, 0.256 mmol), 2-bromo-4-(1H-indazol-1-yl)benzonitrile (**215a**, 0.084 g, 0.281 mmol) and 2 M Na_2CO_3 (0.319 mL, 0.639 mmol) in toluene-ethanol (9:1, 5 mL) was purged with a stream of N_2 for 5 min in a sealable vial. To this mixture was added $Pd(Ph_3P)_4$ (0.030 g, 0.026 mmol), the vial was sealed and the mixture was stirred at 95°C (block temperature) for 16 h. The cooled mixture was diluted with EtOAc and the organic phase was separated, dried (Na_2SO_4) and evaporated to give a pale yellow gum. This material was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1H-indazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile (0.106 g, 86% yield) as a colourless gum which solidified on standing in vacuo to give a waxy solid. This material was used as such in the next step. LC-MS (Method J): 1.396 min, $[M + H]^+$ = 483.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (s, 1H), 8.12 (d, *J*=

8.2 Hz, 1H), 8.20 (d, *J*= 8.2 Hz, 2H), 7.95 (d, *J*= 2.3 Hz, 1H), 7.92 (d, *J*= 8.2 Hz, 1H), 7.66 (d, *J*= 7.8 Hz, 2H), 7.60 (dd, *J*= 6.7, 11.7 Hz, 2H), 7.54 (m, 2H), 7.32 (t, *J*= 7.8 Hz, 1H), 7.28 (d, *J*= 7.8 Hz, 2H), 6.95 (s, 1H), 5.55 (s, 2H), 2.82 (q, *J*= 7.4 Hz, 2H), 2.51 (s, 3H), 2.50 (s, 3H), 1.25 (t, *J*= 7.4 Hz, 3H).

Example 215: 3-((5'-(1H-Indazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

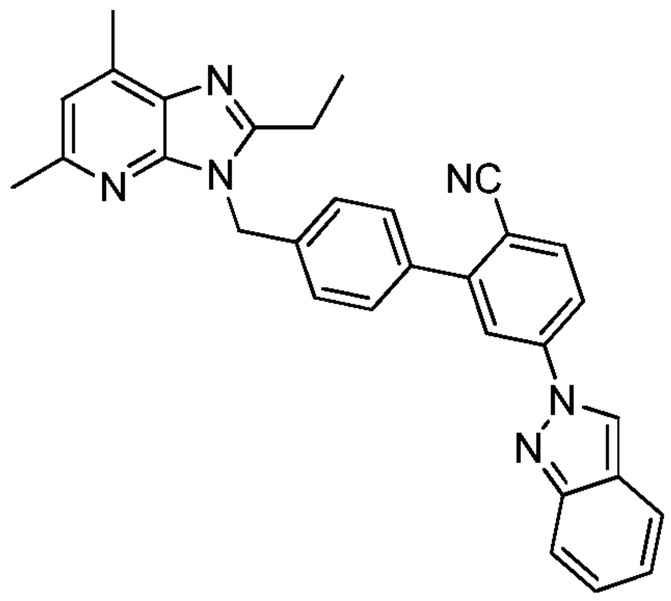
To a sealable vial containing 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1H-indazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.052 mmol) and dibutyltin oxide (0.026 g, 0.104 mmol) in toluene (2 mL) was added TMS-N_3 (0.138 mL, 1.036 mmol). The vial was sealed and the mixture were stirred at 120°C (block temperature) for 16 h. The cooled mixture was evaporated and the residue was taken up in DMF (1.8 mL, acidified with 15 drops of AcOH) and submitted to preparative LC purification (Method D). The product-containing fractions were combined and evaporated to give 3-((5'-(1H-indazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.020 g, 73.5% yield) as a white solid. LC-MS (Method J): 1.342 min, $[M + H]^+$ = 526.2; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (s, 1H), 7.98 (d, *J*= 8.6 Hz, 2H), 7.91 (d, *J*= 7.8 Hz, 1H), 7.85 (d, *J*= 8.2 Hz, 1H), 7.83 (br s, 1H), 7.53 (dd, *J*= 7.4, 8.2 Hz, 1H), 7.30 (dd, *J*= 7.0, 7.8 Hz, 1H), 7.17 (d, *J*= 8.2 Hz, 2H), 7.06 (d, *J*= 8.2 Hz, 2H), 6.93 (s, 1H), 5.45 (s, 2H), 2.75 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.21 (t, *J*= 7.4 Hz, 3H).

Example 216: 3-((5'-(2H-Indazol-2-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex: 216)

Intermediate 216a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2H-indazol-2-yl)-[1,1'-biphenyl]-2-carbonitrile



(216a)

The title compound was prepared from 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.080 g, 0.204 mmol) and 2-bromo-4-(2H-indazol-2-yl)benzonitrile (**215b**, 0.067 g, 0.225 mmol), according to the method described for the preparation of **Intermediate 215c** to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2H-indazol-2-yl)-[1,1'-biphenyl]-2-carbonitrile (0.066 g, 66.9% yield) as a colourless gum which solidified on standing in vacuo to give a waxy solid. This material was used as such in the next step. LC-MS (Method J): 1.375 min, $[M + H]^+ = 483.1$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.34 (s, 1H), 8.31 (s, 1H), 8.29 (dd, J = 2.0, 6.7 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.75 (d, J= 8.2 Hz, 1H), 7.68 (t, J= 8.8 Hz, 2H), 7.63-7.51 (m, 2H), 7.33 (dd, J= 6.3 Hz, 1H), 7.30 (d, J= 8.2 Hz, 2H), 7.11 (dd, J= 7.0, 8.6 Hz, 1H), 6.96 (s, 1H), 5.56 (s, 2H), 2.83 (q, J= 7.4 Hz, 2H), 2.51 (s, 3H), 2.50 (s, 3H), 1.26 (t, J= 7.4 Hz, 3H).

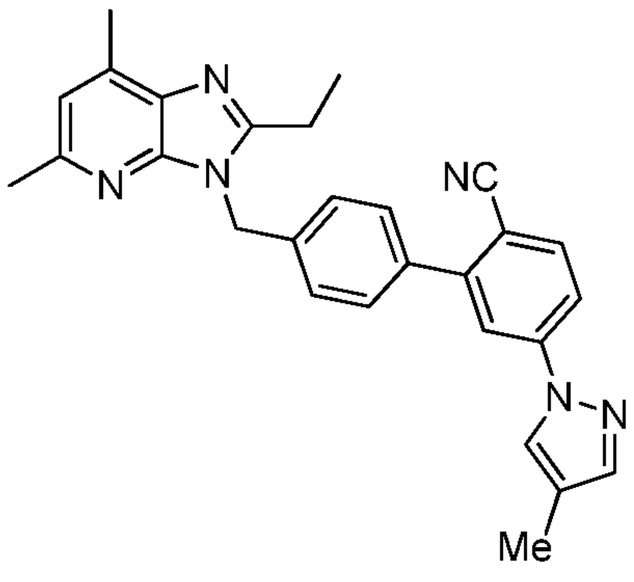
Example 216: 3-((5'-(2H-Indazol-2-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

The title compound was prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(2H-indazol-2-yl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.052 mmol), according to the method described for the preparation of **Example 215** to give 3-((5'-(2H-indazol-2-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.019 g, 69.8% yield) as a pale yellow solid. LC-MS (Method J): 1.318 min, $[M + H]^+ = 526.2$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (s, 1H), 8.24 (dd, J = 2.0, 8.2 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.85 (d, J= 8.6 Hz, 1H), 7.75 (d, J= 8.6 Hz, 1H), 7.69 (d, J= 9.0 Hz, 1H), 7.52 (dd, J= 6.7, 9.0 Hz, 1H), 7.17 (d, J= 8.2 Hz, 2H), 7.11 (d, J= 8.6 Hz, 1H), 7.07 (d, J= 8.2 Hz, 2H), 6.94 (s, 1H), 5.46 (s, 2H), 2.77 (q, J= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.23 (t, J= 7.4 Hz, 3H).

Example 217: 2-Ethyl-5,7-dimethyl-3-((5'-(4-methyl-1H-pyrazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

(Ex: 217)

Intermediate 217a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(4-methyl-1H-pyrazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile



(217a)

To a solution of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (**205a**, 0.088 g, 0.229 mmol) and 4-methyl-1H-pyrazole (0.028 g, 0.343 mmol) in DMF (3 mL) was added potassium carbonate (0.095 g, 0.687 mmol) and the resulting mixture was stirred at 120°C (block temperature) in a sealed vial for 18 h. The cooled mixture was filtered (0.45 µm syringe filter) to remove the potassium salts and the residue was washed with a little DMF. The combined filtrate was evaporated to give a gum which was purified by flash chromatography (ISCO/ 0-100% EtOAc-DCM) to give 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(4-methyl-1H-pyrazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile (0.102 g, 100% yield) as a colourless gum which solidified on standing in vacuo to give a white solid. This material was used as such in the next step. LC-MS (Method J): 1.340 min, $[M + H]^+$ = 447.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.50 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.96 (d, J= 7.8 Hz, 1H), 7.95 (s, 1H), 7.65 (s, 1H), 7.59 (d, J= 8.2 Hz, 2H), 7.27 (d, J= 8.2

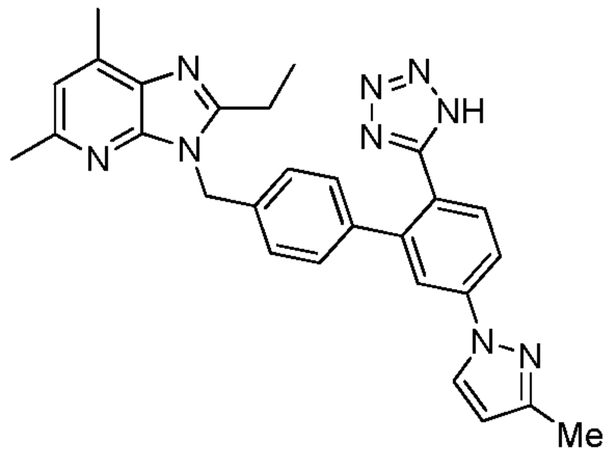
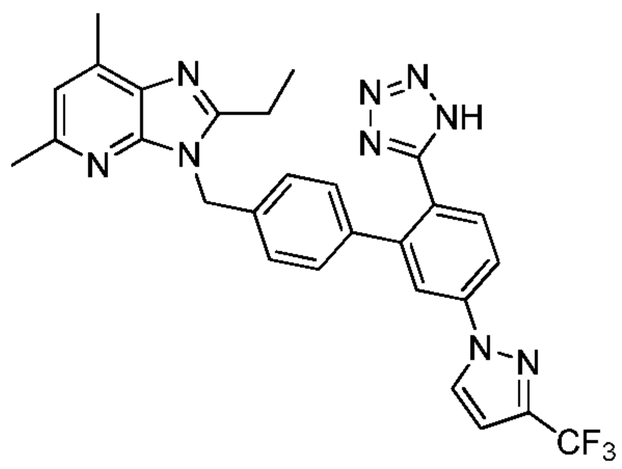
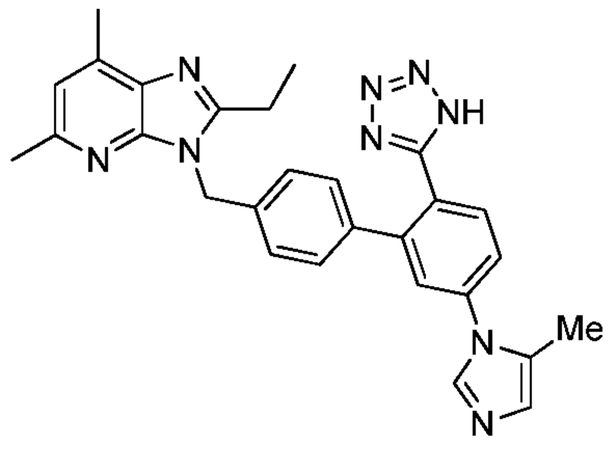
Hz, 2H), 6.95 (s, 1H), 5.55 (s, 2H), 2.81 (q, *J*= 7.4 Hz, 2H), 2.51 (s, 3H), 2.50 (s, 3H), 2.07 (s, 3H), 1.25 (t, *J*= 7.4 Hz, 3H).

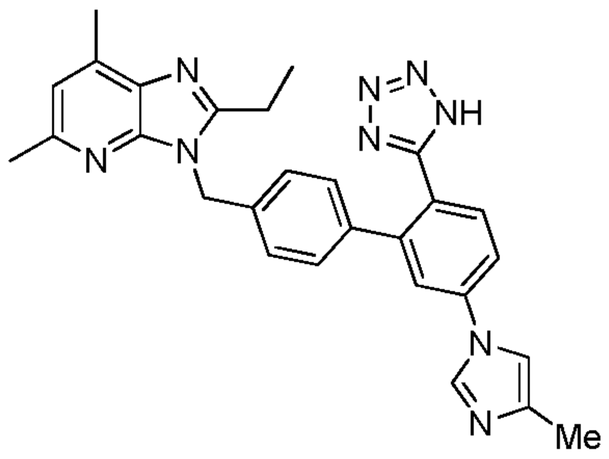
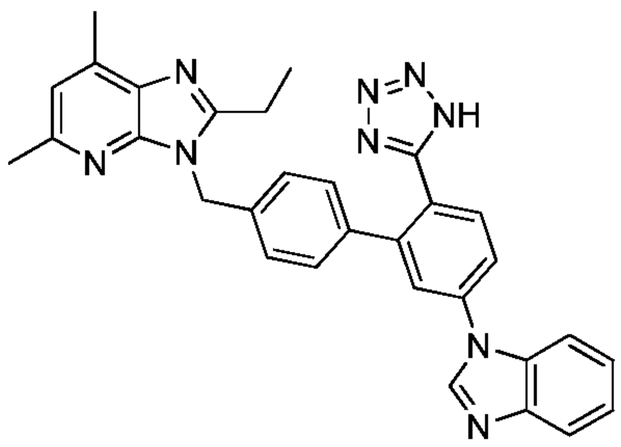
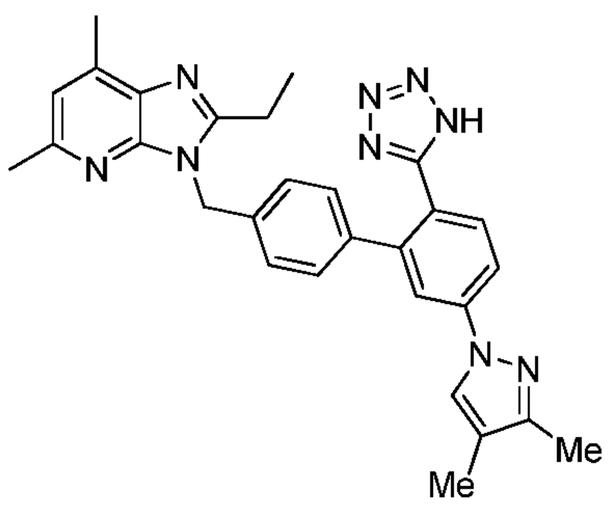
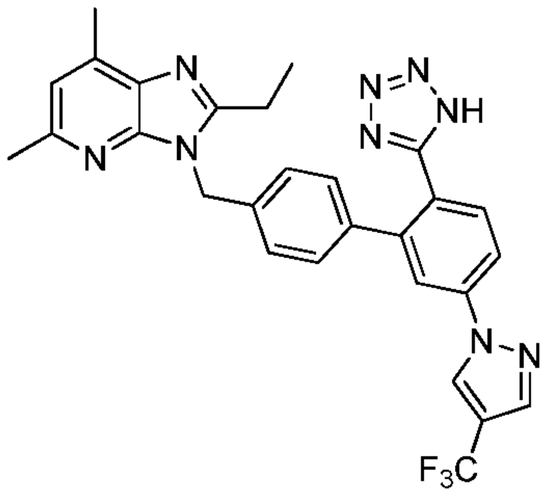
Example 217: 2-Ethyl-5,7-dimethyl-3-((5'-(4-methyl-1H-pyrazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

To a sealable vial containing 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(4-methyl-1H-pyrazol-1-yl)-[1,1'-biphenyl]-2-carbonitrile (0.100 g, 0.224 mmol) and dibutyltin oxide (0.084 g, 0.336 mmol) in toluene (4 mL) was added TMS-N_3 (0.297 mL, 2.239 mmol). The vial was sealed and the mixture were stirred at 120°C (block temperature) for 16 h. The cooled mixture was evaporated and the residue was taken up in DMF (4 x 1.8 mL, acidified with 20 drops of AcOH) and submitted to preparative LC purification (Method D). The product-containing fractions were combined and evaporated to give a gum which was lyophilized from ACN-H_2O to give 2-ethyl-5,7-dimethyl-3-((5'-(4-methyl-1H-pyrazol-1-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine (0.062 g, 56.6% yield) as a white solid. LC-MS (Method J): 1.515 min, $[M + H]^+$ = 490.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.10 (d, *J*= 8.2 Hz, 2H), 7.01 (d, *J*= 8.2 Hz, 2H), 6.93 (s, 1H), 5.43 (s, 2H), 2.76 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 2.08 (s, 3H), 1.22 (t, *J*= 7.4 Hz, 3H).

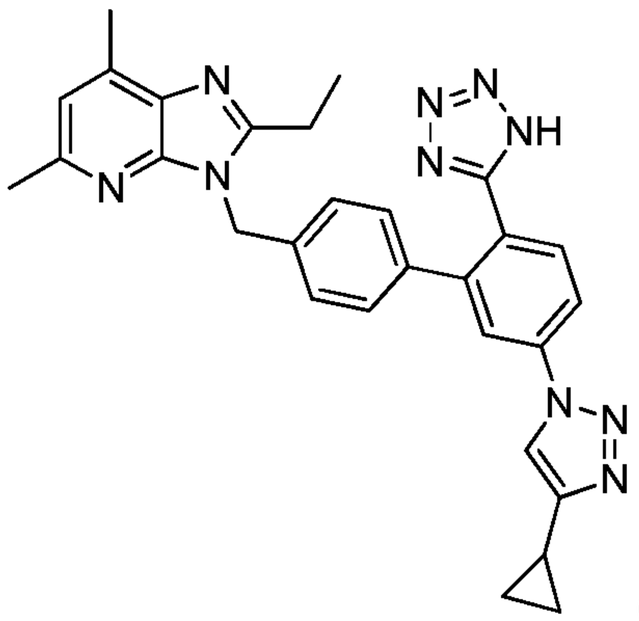
The following examples have been similarly prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 205a**) as described above for **Example 217**. Two analytical LC injections were used to determine the final purity; the retention time of one of them is reported for each compound and is referred as Method J.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
218		489.75	490.1; 1.479 min (Method J)	8.54 (d, *J* = 2.3 Hz, 1H), 7.94 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.85 (d, *J*= 2.0 Hz, 1H), 7.72 (d, *J*= 8.2 Hz, 1H), 7.11 (d, *J*= 8.2 Hz, 2H), 7.05 (d, *J*= 8.6 Hz, 2H), 6.93 (s, 1H), 6.36 (d, *J*= 2.3 Hz, 1H), 5.45 (s, 2H), 2.75 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 2.26 (s, 3H), 1.22 (t, *J*= 7.4 Hz, 3H).
219		543.55	544.2; 1.520 min (Method J)	8.89 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.93 (s, 1H), 7.81 (d, *J*= 8.6 Hz, 1H), 7.14 (d, *J*= 8.2 Hz, 2H), 7.08 (d, *J*= 2.7 Hz, 1H), 7.05 (d, *J*= 8.2 Hz, 2H), 6.93 (s, 1H), 5.45 (s, 2H), 2.76 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.23 (t, *J*= 7.4 Hz, 3H).
220		489.57	490.1; 1.110 min (Method J)	(MeOH-d_4): 8.57 (br s, 1H), 8.15 (br s, 1H), 7.97 (s, 1H), 7.83 (br s, 1H), 7.61 (s, 2H), 7.13 (d, *J*= 7.0 Hz, 2H), 7.06 (d, *J*= 7.4 Hz, 2H), 7.01 (s, 1H), 5.53 (s, 2H), 2.84 (q, *J*= 7.8 Hz, 2H), 2.59 (s, 3H), 2.56 (s, 3H), 2.31 (br s, 3H), 1.25 (t, *J*= 7.4 Hz, 3H).

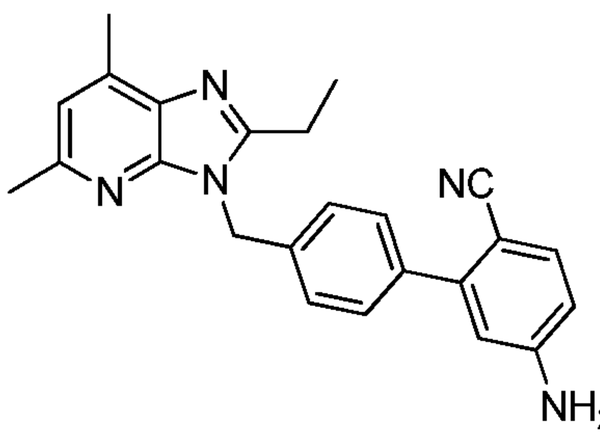
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
221		489.57	490.1; 1.153 min (Method J)	(MeOH-d_4): 8.64 (s, 1H), 8.10 (s, 1H), 7.78 (d, *J*= 9.0 Hz, 1H), 7.72-7.71 (m, 2H), 7.59 (s, 1H), 7.14 (d, *J*= 8.2 Hz, 2H), 7.07 (d, *J*= 8.2 Hz, 2H), 7.02 (s, 1H), 5.54 (s, 2H), 2.85 (q, *J*= 7.8 Hz, 2H), 2.59 (s, 3H), 2.56 (s, 3H), 2.31 (s, 3H), 1.25 (t, *J*= 7.4 Hz, 3H).
222		525.61	526.2; 1.473 min (Method J)	8.69 (s, 1H), 7.84 (m, 2H), 7.85 (d, *J*= 2.0 Hz, 1H), 7.76 (dd, *J*= 7.0, 8.6 Hz, 1H), 7.72 (m, 1H), 7.33 (m, 1H), 7.17 (d, *J*= 8.2 Hz, 2H), 7.04 (d, *J*= 7.8 Hz, 2H), 6.92 (s, 1H), 5.44 (s, 2H), 2.75 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.22 (t, *J*= 7.4 Hz, 3H).
223		503.60	504.1; 1.329 min (Method J)	8.35 (s, 1H), 7.88 (dd, *J*= 2.0, 8.2 Hz, 1H), 7.80 (d, *J*= 2.0 Hz, 1H), 7.69 (d, *J*= 8.2 Hz, 1H), 7.10 (d, *J*= 7.8 Hz, 2H), 7.05 (d, *J*= 8.2 Hz, 2H), 6.93 (s, 1H), 5.45 (s, 2H), 2.75 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 2.17 (s, 3H), 2.00 (s, 3H), 1.22 (t, *J*= 7.4 Hz, 3H).
224		543.55	544.1; 1.317 min (Method J)	9.37 (s, 1H), 8.26 (s, 1H), 8.05 (d, *J*= 8.2 Hz, 1H), 8.00 (s, 1H), 7.81 (d, *J*= 8.2 Hz, 1H), 7.13 (d, *J*= 8.2 Hz, 2H), 7.06 (d, *J*= 8.2 Hz, 2H), 6.93 (s, 1H), 5.45 (s, 2H), 2.76 (q, *J*= 7.4 Hz, 2H), 2.48 (*hidden*, 6H), 1.22 (t, *J*= 7.4 Hz, 3H).

Example 225: 3-((5'-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-2'-(5H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex: 225)

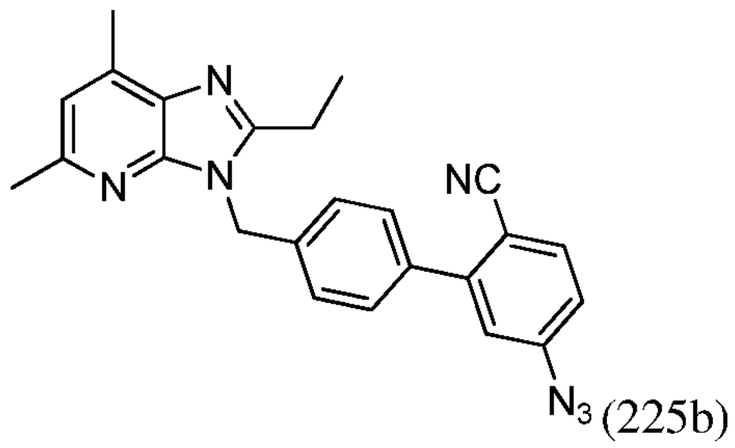
Intermediate 225a: 5-Amino-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(225a)

To a mixture of 4-amino-2-bromobenzonitrile (1.00 g, 5.08 mmol), 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 1.773 g, 4.53 mmol) and K_2CO_3 (2.505 g, 18.13 mmol) was added 1,4-dioxane and H_2O (2:1, 30 mL). The reaction mixture was then purged with a stream of N_2 for 5 min in a sealable vial before $Pd(Ph_3P)_4$ (0.262 g, 0.227 mmol) was added. The reaction vial was sealed and the mixture heated at 100°C for 18h. The cooled reaction mixture was then diluted with EtOAc (50 mL), washed with H_2O and brine, dried (Na_2SO_4) and evaporated. The crude residue was purified by flash chromatography (ISCO, 0-100% EtOAc-DCM) to afford the title compound (1.46 g, 4.53 mmol, 85%) as a white solid. LC-MS (Method H): 1.220 min, $[M + H]^+$= 382.5; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 - 7.55 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.90 (s, 1H), 6.51 - 6.68 (m, 2H), 5.51 (s, 2H), 4.17 (br s, 2H), 2.81 (d, *J* = 7.4 Hz, 2H), 2.59 (s, 3H), 2.64 (s, 3H), 1.33 (t, *J* = 7.4 Hz, 3H).

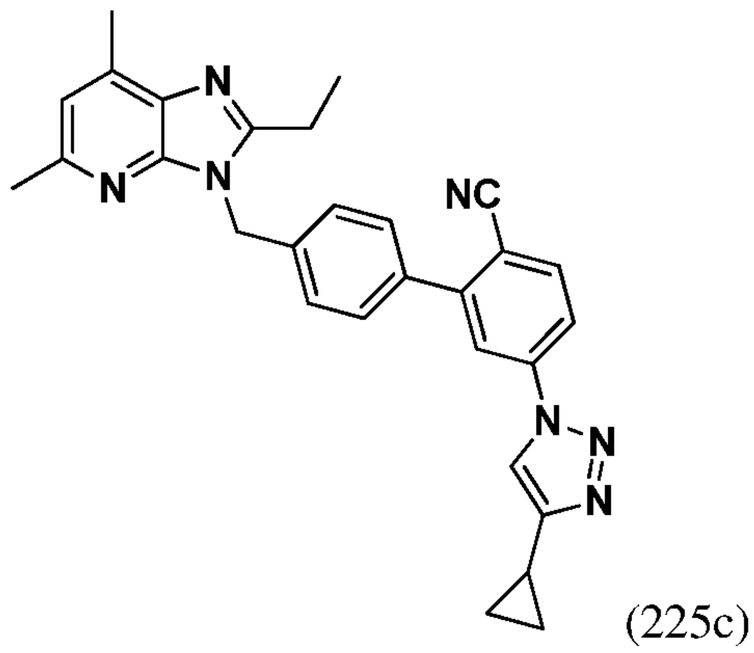
Intermediate 225b: 5-Azido-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(225b)

To a solution of 5-amino-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.500 g, 1.311 mmol) in ACN (40 mL) was added TFA (0.202 mL, 2.622 mmol) and the mixture was cooled at -5°C. To this cold mixture was added tert-butyl nitrite (0.624 mL, 5.240 mmol), followed after 10 min with TMS-N_3 (0.522 mL, 3.930 mmol). The mixture was then stirred at RT for 4 h, after which it was evaporated to dryness. The crude residue obtained was purified by flash chromatography (ISCO, 0-100% EtOAc-DCM) to provide 5-azido-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.467 g, 1.088 mmol, 83% yield). LC-MS (Method H): 1.335 min, $[M + H]^+$= 408.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.16 - 7.26 (m, 2H), 7.08 (s, 1H), 5.59 (s, 2H), 2.93 (q, J = 7.2 Hz, 2H), 2.49 (s, 6H), 1.21 (t, J = 7.4 Hz, 3H).

Intermediate 225c: 5-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



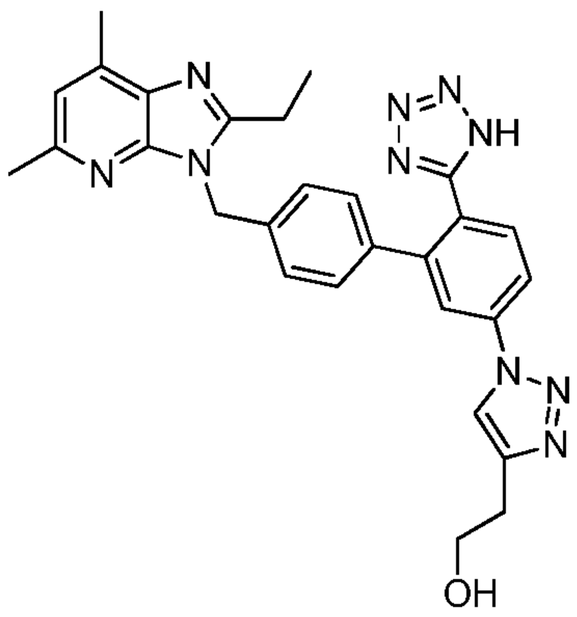
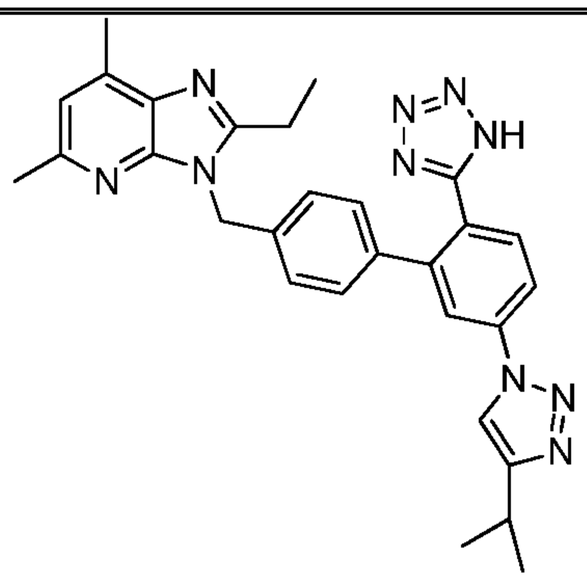
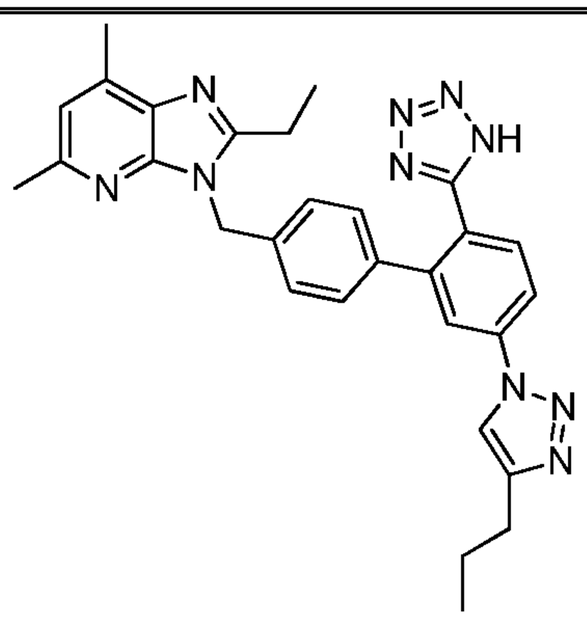
(225c)

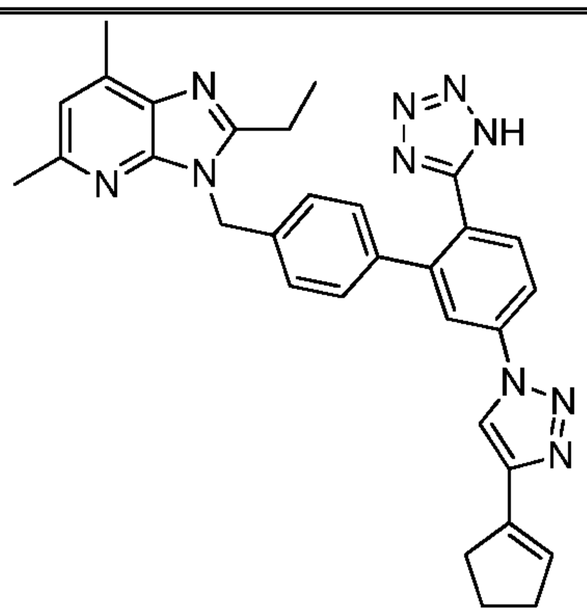
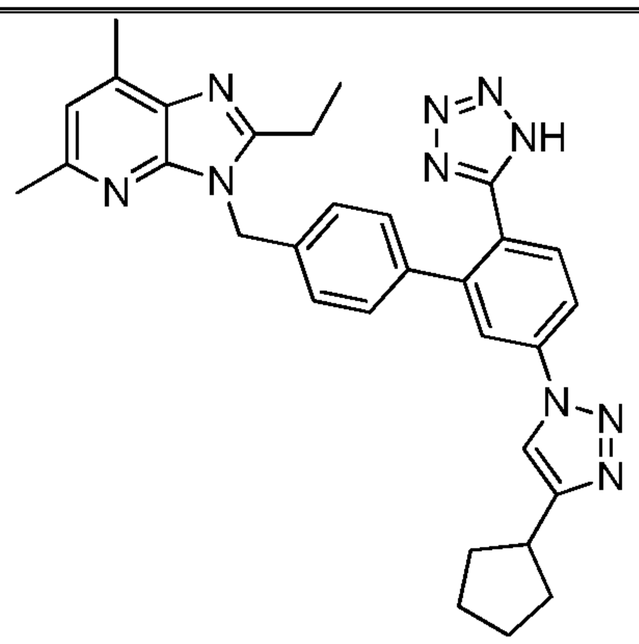
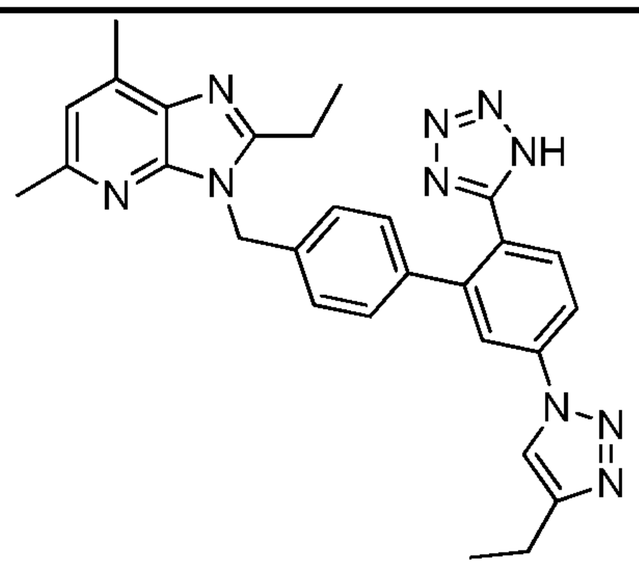
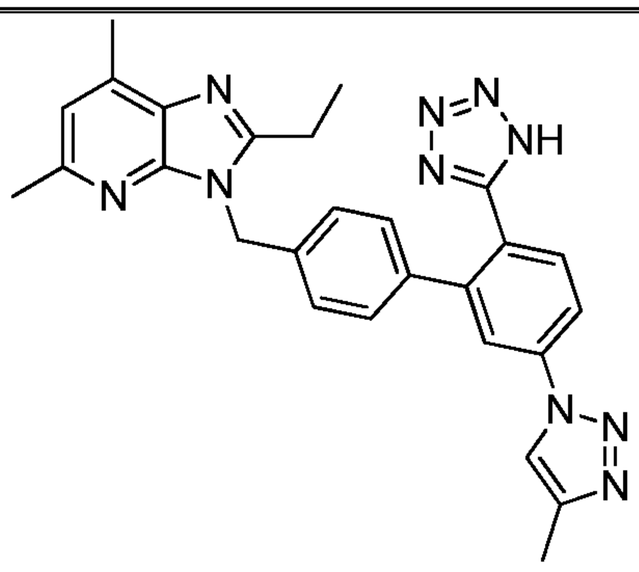
To a mixture of 5-azido-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.030 g, 0.074 mmol) and ethynylcyclopropane (0.049 g, 0.736 mmol) in a mixture of t-BuOH:H_2O (3:1, 4 mL) were added $CuSO_4.5H_2O$ (0.002 g, 0.008 mmol) and sodium ascorbate (0.007 g, 0.040 mmol). The reaction mixture was stirred for at RT for 16 h and then it was diluted with EtOAc (25 mL) and washed with saturated aqueous NH_4Cl and H_2O. The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. The crude product thus obtained was washed with hexane (5 mL) to remove excess alkyne and dried in vacuo to afford the title compound (0.025 g, 0.074 mmol, 64.8%) which was used as such for the next step without further purification. LC-MS (Method H): 1.313 min, $[M + H]^+$= 474.2.

Example 225: 3-((5'-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-2'-(5H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

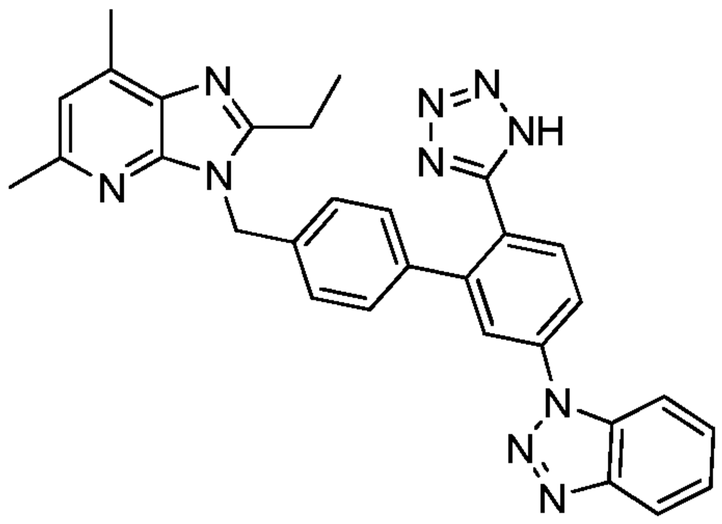
To a mixture of 5-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.053 mmol), TMS-N_3 (0.148 mL, 1.056 mmol) and dibutyltin oxide (0.027 g, 0.106 mmol) was added toluene (2 mL), the vial was briefly purged with N_2 and then it was sealed. The mixture was stirred at 120°C for 16 h and then the cooled mixture was filtered through a small plug of cotton wool and the filtrate was evaporated to give a gum. This gum was purified by preparative LC (Method F) to afford 3-((5'-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2'-(5H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (0.015 g, 0.053 mmol, 52.3% yield) as a white solid. LC-MS (Method H) at 1.259 min, $[M + H]^+$= 517.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.11 - 7.19 (m, J = 7.8 Hz, 2H), 7.01 - 7.11 (m, J = 8.2 Hz, 2H), 6.95 (s, 1H), 5.47 (s, 2H), 2.78 (q, J = 7.4 Hz, 3H), 2.48 (*hidden*, 6H), 1.96 - 2.08 (m, 1H), 1.18 - 1.31 (m, 3H), 0.91 - 1.02 (m, 2H), 0.71 - 0.82 (m, 2H).

The following examples have been similarly prepared from 5-azido-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile **(Intermediate 225b)** as described for the synthesis of **Example 225** above. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method H.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
226		520.5	521.2; 1.18 min	8.74 (s, 1H), 8.03 (dd, *J* = 1.96, 8.22 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.10 - 7.19 (d, *J* = 8.2 Hz, 2H), 7.02 - 7.08 (d, *J* = 8.2 Hz, 2H), 6.95 (s, 1H), 6.53 (s, 1H), 5.46 (s, 2H), 4.76 (m, 1H), 3.64 - 3.73 (m, 2H), 2.86 (t, *J* = 6.85 Hz, 2H), 2.78 (q, *J* = 7.70 Hz, 2H), 2.48 (*hidden*, 6H), 1.25 (t, *J* = 7.43 Hz, 3H).
227		518.6	519.2; 1.283 min	8.73 (s, 1H), 7.99 (d, *J* = 7.04 Hz, 1H), 7.87 (br s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.11 - 7.22 (d, *J* = 7.8 Hz, 2H), 6.99 - 7.08 (d, *J* = 8.2 Hz, 2H), 6.94 (s, 1H), 6.53(s, 1H), 5.45 (s, 2H), 3.06 (td, *J* = 6.8, 13.7 Hz, 1H), 2.78 (q, *J* = 7.30 Hz, 2H), 2.50 (*hidden*, 6H), 1.30 (d, *J* = 7.04 Hz, 6H), 1.25 (t, *J* = 7.4 Hz, 3H).
228		518.6	519.2; 1.294 min	8.73 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.09 - 7.18 (d, *J* = 8.2 Hz, 2H), 7.00 - 7.08 (d, *J* = 7.8 Hz, 2H), 6.93 (s, 1H), 6.50 (s, 1H), 5.44 (s, 2H), 2.76 (q, *J* = 7.4 Hz, 2H), 2.63 - 2.70 (m, 2H), 2.50 (*hidden*, 6H), 1.61 - 1.71 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 4H), 0.94 (t, *J* = 7.4 Hz, 3H).

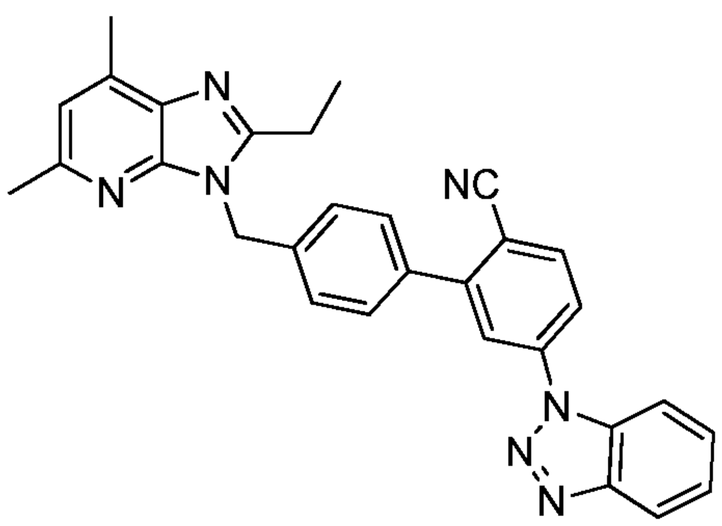
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
229		542.6	543.2; 1.356 min	8.95 (s, 1H), 8.24 (br s, 1H), 7.92 (dd, *J* = 2.4, 7.8 Hz, 2H), 7.76 - 7.83 (m, 2H), 7.12 - 7.20 (d, *J* = 7.8 Hz, 2H), 6.99 - 7.04 (d, *J* = 8.22 Hz, 2H), 6.94 (s, 1H), 6.53 (br s, 1H), 6.32 (t, *J* = 2.15 Hz, 1H), 5.45 (s, 2H), 2.80 (q, *J* = 7.4 Hz, 3H), 2.50 (*hidden*, 6H), 2.65 - 2.72 (m, 2H), 1.93 - 2.02 (m, 2H), 1.24 - 1.31 (m, 5H).
230		544.2	545.2; 1.344 min	(MeOH-d_4) 8.49 (s, 1H), 7.95 - 8.08 (m, 2H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.16 - 7.24 (d, *J* = 8.2 Hz, 2H), 7.10 - 7.16 d, *J* = 8.2 Hz, 2H), 7.05 (s, 1H), 5.58 (s, 2H), 2.88 (q, *J* = 7.7 Hz, 2H), 2.59 (s, 3H), 2.62 (s, 3H), 2.09 - 2.23 (m, 2H), 1.67 - 1.89 (m, 6H), 1.33 (s, 1H), 1.28 (t, *J* = 7.4 Hz, 3H).
231		504.5	505.5, 1.24 min	(MeOH-d_4) 8.45 (s, 1H), 7.97 (s, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.03 (s, 1H), 5.55 (s, 2H), 2.85 (qd, *J* = 7.5, 14.9 Hz, 4H), 2.59 (s, 3H), 2.62 (s, 3H), 1.36 (t, *J* = 7.6 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H)
232		490.5	491.2; 1.396 min	(MeOH-d_4) 8.42 (s, 1H), 7.95 - 8.03 (m, 2H), 7.83 (d, J = 8.61 Hz, 1H), 7.15 - 7.21 (d, J = 8.22 Hz, 2H), 7.07 - 7.11 (d, J = 8.22 Hz, 2H), 7.04 (s, 1H), 5.57 (s, 2H), 2.87 (q, J = 7.43 Hz, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.43 (s, 3H), 1.28 (t, J = 7.63 Hz, 3H).

Example 233: 1-(4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)-1H-benzo[d][1,2,3]triazole



(Ex. 233)

Intermediate 233a: 5-(1H-Benzo[d][1,2,3]triazol-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(233a)

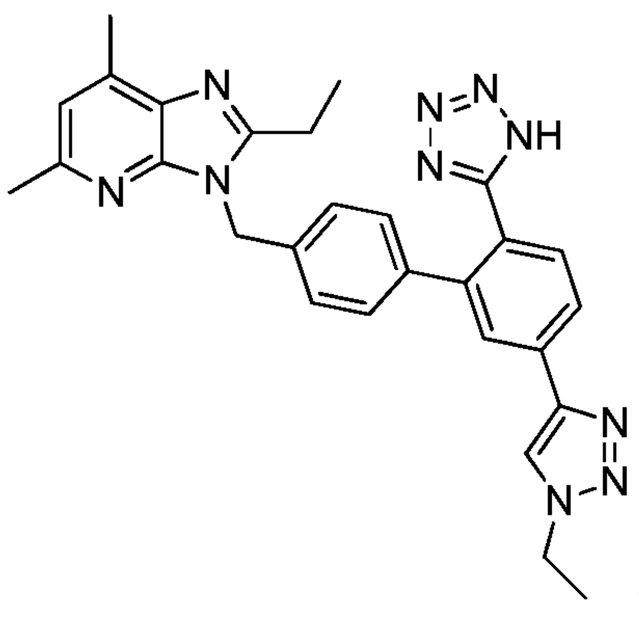
To a mixture of 5-azido-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 225b**, 0.030 g, 0.074 mmol) and trimethylsilyl)phenyl trifluoromethanesulfonate (0.088 g, 0.294 mmol) in ACN (4 mL) was added CsF (0.0122 g, 0.074 mmol) and the mixture was stirred at RT for 7 h. The mixture was then diluted with EtOAc (25 mL) and the organic layer was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4) and evaporated to dryness. This gave crude 5-(1H-benzo[d][1,2,3]triazol-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.052 mmol, 70.2% yield) which was used as such for the next step. LC-MS (Method H): 1.366 min, $[M + H]^+$= 484.2.

Example 233: 1-(4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)-1H-benzo[d][1,2,3]triazole

To a mixture of 5-(1H-benzo[d][1,2,3]triazol-1-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.052 mmol), TMS-N_3 (0.144 mL, 1.034 mmol) and dibutyltin oxide (0.0263 g, 0.103 mmol) was added

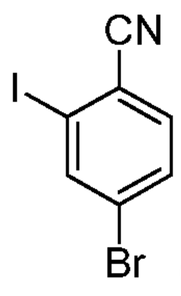
toluene (3 mL). The vial was briefly purged with N_2 and then it was sealed and the mixture was stirred at 120°C for 16 h. The cooled mixture was evaporated to give a gum which was purified by preparative LC (Method F) to provide 1-(4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-6-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)-1H-benzo[d][1,2,3]triazole (0.010 g, 36.7% yield) as a white solid. HRMS (ESI): Calcd. for $C_{30}H_{28}N_7O$ [M+H] *m/z* 527.2415; found 527.2418; ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 8.14 (d, *J* = 8.6 Hz, 1H), 7.83 - 8.03 (m, 4H), 7.70 (t, *J* = 7.43 Hz, 1H), 7.51 - 7.60 (m, 1H), 7.18 - 7.26 (d, *J* = 7.8 Hz, 2H), 7.05 - 7.14 (d, *J* = 7.8 Hz, 2H), 7.03 (s, 1H), 5.56 (s, 2H), 2.87 (q, *J* = 7.7 Hz, 2H), 2.61 (s, 3H), 2.58 (s, 3H), 1.28 (t, *J* = 7.43 Hz, 3H).

Example 234: 2-Ethyl-3-((5'-(1-ethyl-1H-1,2,3-triazol-4-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



(Ex. 234)

Intermediate 234a: 4-Bromo-2-iodobenzonitrile

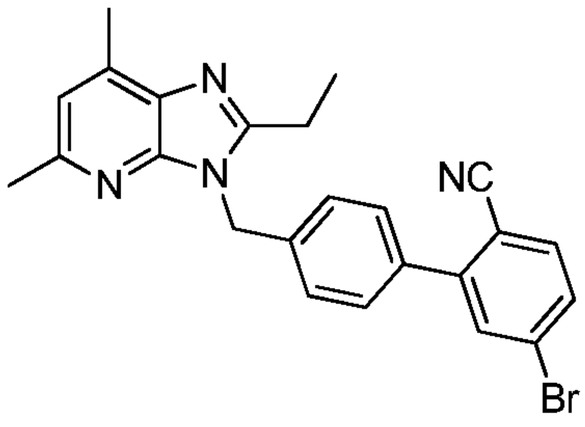


(234a)

To a mixture of 2-amino-4-bromobenzonitrile (1.00 g, 5.08 mmol) in 4 M aqueous HCl (7.5 mL) cooled at 0°C was added a solution of sodium nitrite (0.490 g, 7.11 mmol) in H_2O (3 mL), followed after 10 min by the dropwise addition of a solution of potassium iodide (2.106 g, 12.69 mmol) in H_2O (3 mL). The reaction mixture was subsequently allowed to warm to RT and then it was extracted with EtOAc (50 mL). The organic layer was separated, washed (10% aqueous $Na_2S_2O_5$, brine), dried (Na_2SO_4) and evaporated under reduced pressure. The residue obtained was purified by flash chromatography

(ISCO, 0 to 100 % EtOAc-hexane) to provide 4-bromo-2-iodobenzonitrile (1.17 g, 3.81 mmol, 75% yield). LC-MS (Method H): 1.239 min, $[M + H]^+$= *no ion observed*. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46 (d, *J*= 8.22 Hz, 1H), 7.61 (dd, *J*= 8.22 Hz, 1.76 Hz, 1H), 8.10 (d, *J*= 1.96 Hz, 1H).

Intermediate 234b: 5-Bromo-4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile



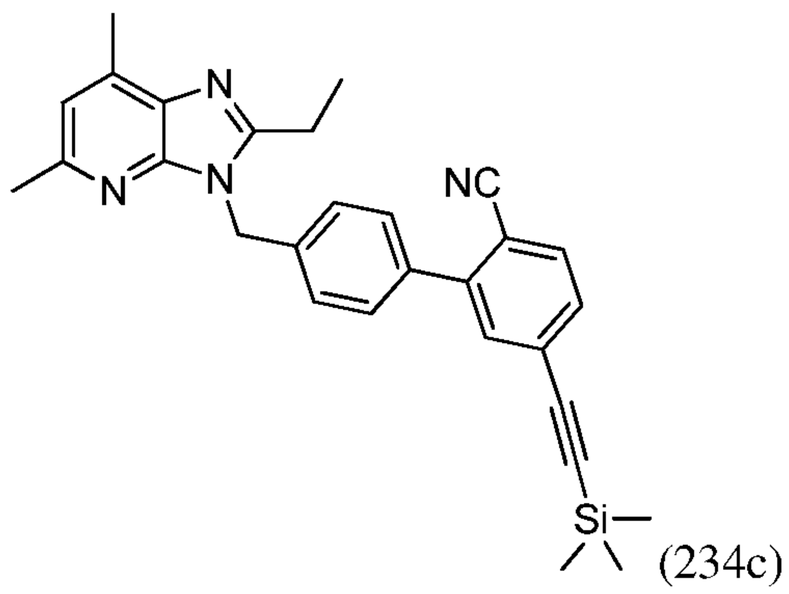
(234b)

Method A: A mixture of 4-bromo-2-iodobenzonitrile (0.300 g, 0.974 mmol), 2-ethyl-5,7-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3H-imidazo[4,5-b]pyridine (**001d**, 0.419 g, 1.072 mmol) and K_2CO_3 (0.539 g, 3.900 mmol) in 1,4-dioxane and H_2O (2:1, 15 mL) was purged with a stream of N_2 for 10 min and then $Pd(Ph_3P)_4$ (0.113 g, 0.097 mmol) was added. The reaction vial was then sealed and the mixture was stirred at 95°C for 3 h. The cooled reaction mixture was then diluted with EtOAc (50 mL) and the organic layer was washed (H_2O, brine), dried (Na_2SO_4) and evaporated to dryness. The crude residue obtained was purified by flash chromatography (ISCO/ 0 to 100% EtOAc-hexane) to give the title compound (0.270 g, 0.650 mmol, 89% yield) as a white foam. LC-MS (Method H): 1.354 min, (M+H)= 445.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 - 7.94 (m, 3 H), 7.54 (d, *J*=8.22 Hz, 2 H), 7.24 (d, *J*=8.2 Hz, 2 H), 6.94 (s, 1 H), 5.53 (s, 2 H) 2.80 (q, *J*=7.43 Hz, 2 H), 2.50 (*hidden*, 6 H), 1.23 (t, *J*=7.43 Hz, 3 H).

Method B: To an ice-cold solution of 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (**001c**, 2.00 g, 11.41 mmol) in dry DMF (40 mL) was added NaH (60% in oil, 0.593 g, 14.84 mmol). The resulting brown mixture was stirred for 5 min and then the cooling bath was removed and stirring was continued at RT for 1 h. The resulting brown solution was re-cooled at 0°C and a solution of 5-bromo-4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile (**I-001,** 4.41 g, 12.55 mmol) in dry DMF (30 mL) was added dropwise. The reaction mixture was then stirred at RT for 3 h, before being poured into ice-H_2O (100 mL) containing saturated aqueous NH_4Cl (50 mL) and vigorously stirring. This suspension was then extracted with DCM (100 mL) and the organic phase was washed

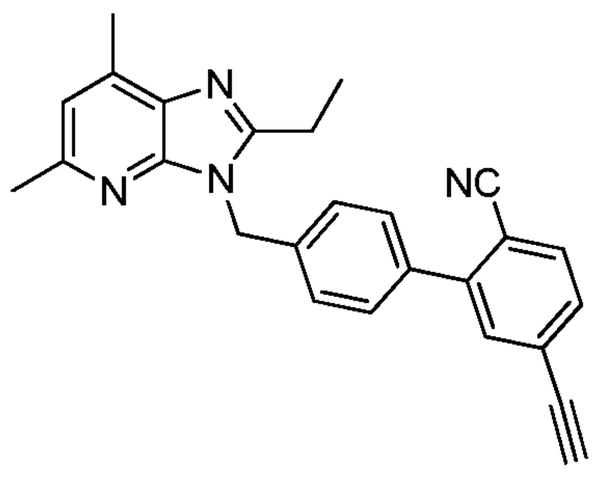
(50% brine), dried (Na_2SO_4) and evaporated to give a pale amber gum. This gum was purified by flash chromatography (ISCO/ 0-100% EtOAc-hexane) to afford 5-bromo-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (3.01 g, 59 % yield) as a white solid. This material was identical (LC-MS, ^{1}H NMR) with the material prepared by **Method A** above.

Intermediate 234c: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-2-carbonitrile


(234c)

In a 50 mL vial was added 5-bromo-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (1.00 g, 2.245 mmol) in THF (10 mL) and TEA (20 mL) to give a colorless solution. This mixture was degassed with a stream of N_2 for 5 min and then [$Pd(PPh_3)_2 Cl_2$] (0.079 g, 0.112 mmol) and copper (I) iodide (0.043 g, 0.225 mmol) were added. To this mixture was added ethynyltrimethylsilane (1.598 mL, 11.230 mmol) dropwise and then it was stirred at 70°C for 2 h. The reaction mixture was then cooled to RT and the volatiles were removed under reduced pressure. The residue was taken up in EtOAc (50 mL) and the mixture was filtered through a pad of Celite®, which was then washed with additional EtOAc (50 mL). The filtrate was evaporated to dryness and the residue was purified by flash chromatography (ISCO, 0 to 100 % EtOAc-hexane) to afford 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-2-carbonitrile (0.600 g, 1.297 mmol, 57.8% yield) as a light brown oil. LC-MS (Method H): 1.553 min, (M+H)= 463.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.91 (d, J = 8.2 Hz, 1H), 7.49 - 7.62 (m, 4H), 7.23 (d, J = 8.2 Hz, 2H), 6.95 (s, 1H), 5.53 (s, 2H), 2.80 (q J = 7.4 Hz, 2H), 2.51 (*hidden*, 6H), 1.23 (t, J = 7.4 Hz, 3H), 0.22 (s, 9H).

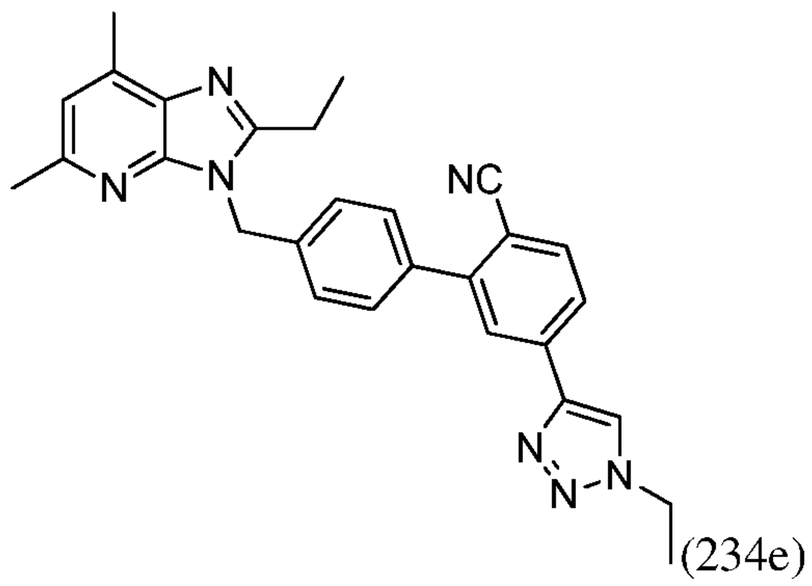
Intermediate 234d: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-ethynyl-[1,1'-biphenyl]-2-carbonitrile



(234d)

To a solution of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-2-carbonitrile (0.600 g, 1.297 mmol) in THF (15 mL) and MeOH (15 mL) was added K_2CO_3 (0.538 g, 3.890 mmol) and the mixture was stirred at RT for 3 h. The resulting mixture was filtered through a pad of Celite®, which was subsequently washed with EtOAc (100 mL). The filtrate was evaporated to dryness to provide 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-ethynyl-[1,1'-biphenyl]-2-carbonitrile (0.535 g, 1.232 mmol, 95% yield) as a brown foam which was used as such in the next step. LC-MS (Method H): 1.310 min, $[M + H]^+$= 391.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 1.2 Hz, 1H), 7.50 - 7.54 (m, 1H), 7.45 - 7.50 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.92 (s, 1H), 5.53 (s, 2H), 3.48 (s, 1H), 2.83 (q, *J* = 7.4 Hz, 2H), 2.66 (s, 3H), 2.61 (s, 3H), 1.34 (t, *J* = 7.4 Hz, 3H).

Intermediate 234e: 5-(1-Ethyl-1H-1,2,3-triazol-4-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile



(234e)

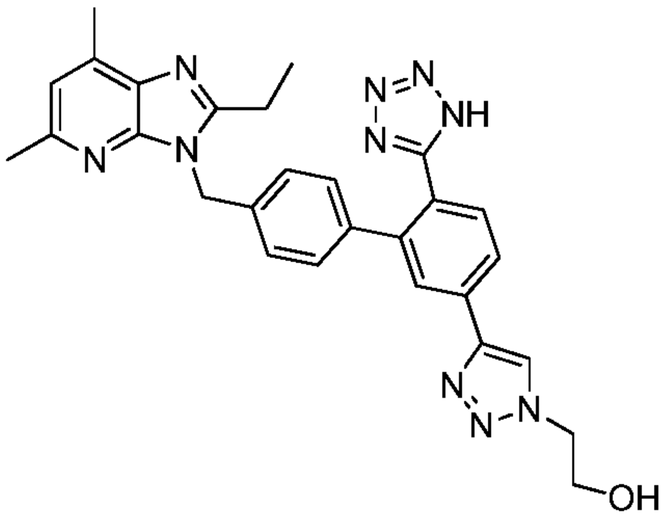
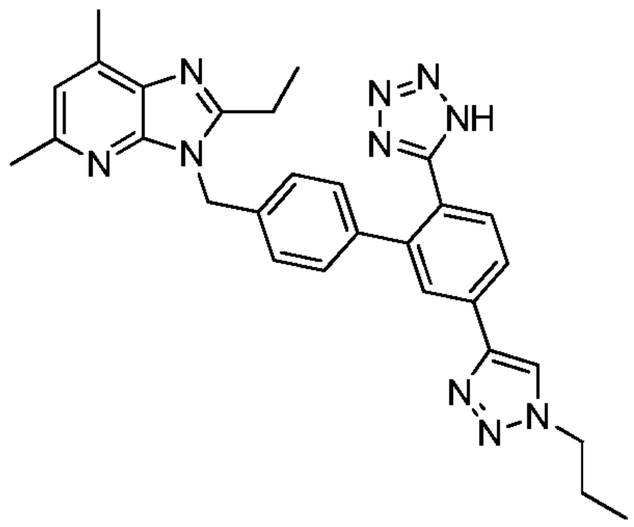
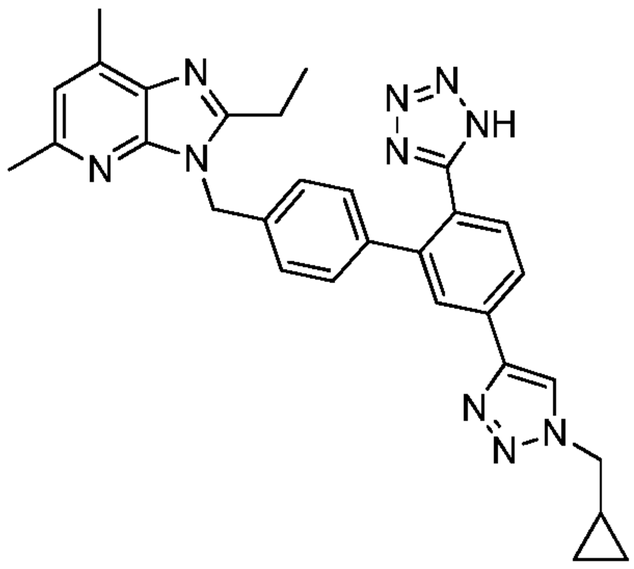
To a mixture of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-ethynyl-[1,1'-biphenyl]-2-carbonitrile (0.030 g, 0.077 mmol) and excess azidoethane [prepared by reacting a solution of bromoethane (0.250 g, 2.294 mmol) and sodium azide (0.373 g, 5.740 mmol) in 5 mL of DMSO for 4 h at RT; the mixture was filtered and the

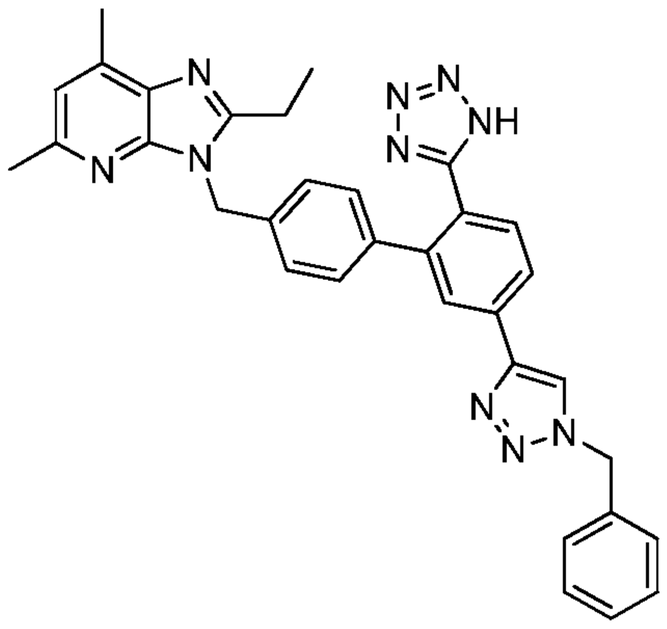
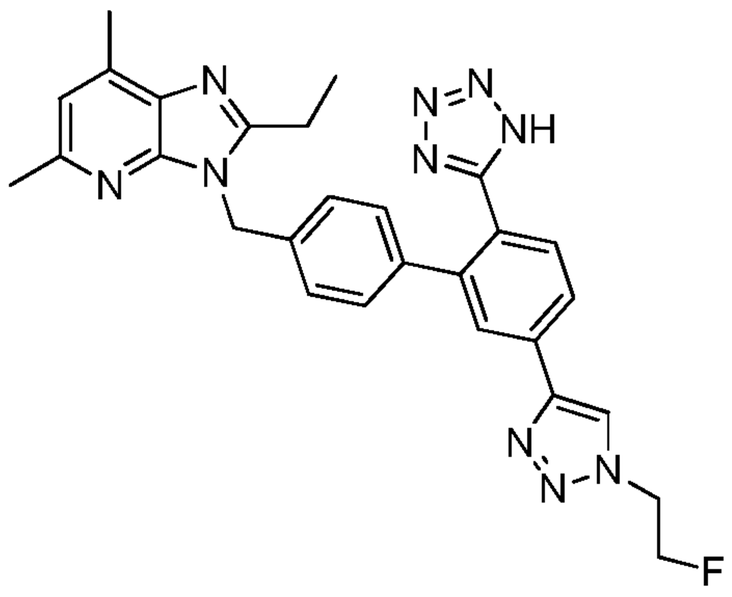
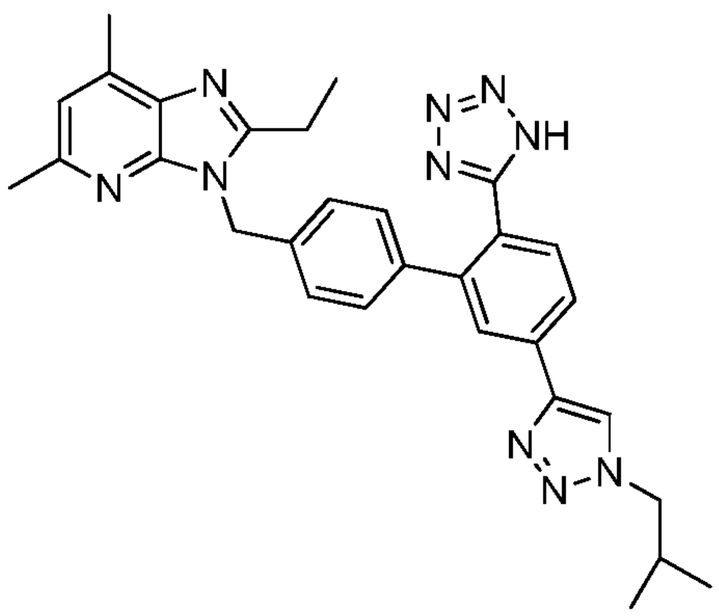
DMSO solution of the alkyne was used as such] in DMSO (4 mL) and H_2O (2 mL) was added sodium ascorbate (0.0034 g, 0.015 mmol) and $CuSO_4.5H_2O$ (0.0013 g, 0.004 mmol). The reaction was stirred at RT for 16 h and then it was poured into a mixture of saturated aqueous NH_4Cl (10 mL) and EtOAc (25 mL). The aqueous layer was separated and re-extracted with EtOAc (30 mL) and then the combined organic extract was washed (H_2O and brine), dried (Na_2SO_4) and evaporated to provide 5-(1-ethyl-1H-1,2,3-triazol-4-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.054 mmol, 70.5% yield) as an oil which was used as such for the next reaction. LC-MS (Method H): 1.272 min, (M+H)= 462.2.

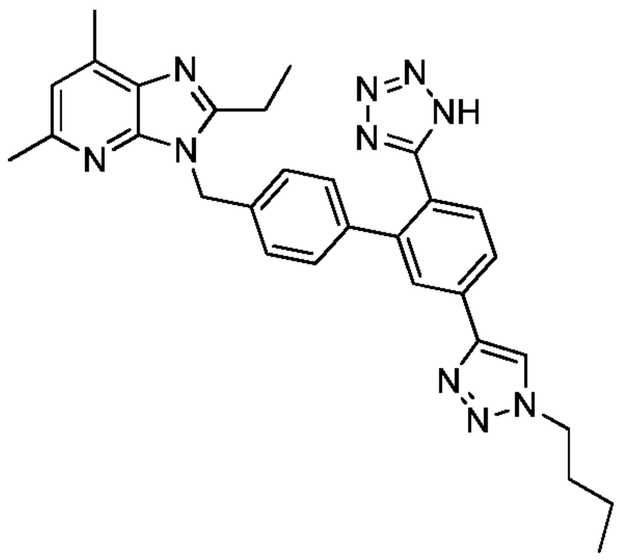
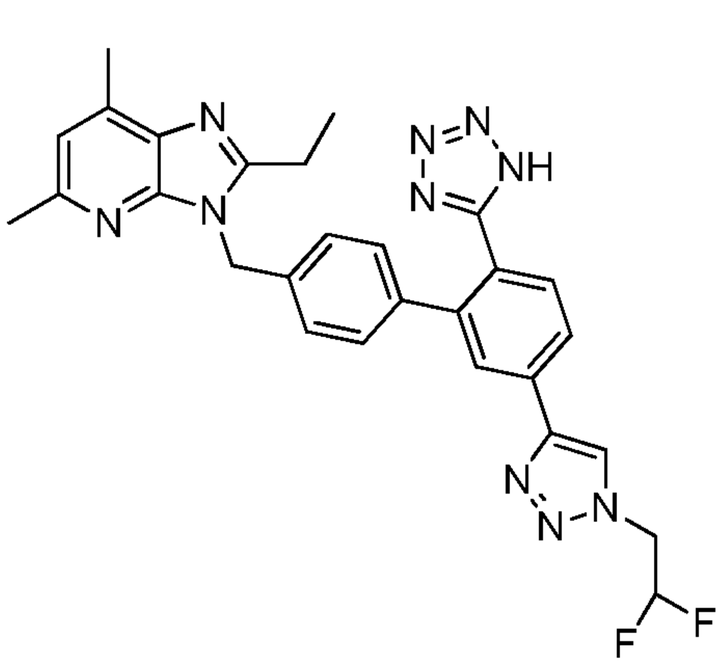
Example 234: 2-Ethyl-3-((5'-(1-ethyl-1H-1,2,3-triazol-4-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

To a mixture of 5-(1-ethyl-1H-1,2,3-triazol-4-yl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile (0.025 g, 0.054 mmol), TMS-N_3 (0.151 mL, 1.083 mmol) and dibutyltin oxide (0.0275 g, 0.108 mmol) was added toluene (2 mL), the vial was briefly purged with N_2 and then it was sealed and heated at 120°C for 16 h. The cooled mixture was evaporated to give a gum which was purified by preparative LC (Method F) to give the title compound (0.007 g, 25.6% yield) as a white solid. HRMS (ESI): Calcd. for $C_{30}H_{28}N_7O$ $[M + H]^+$ *m/z* 505.2571; found 505.2584. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.74 (s, 1H), 7.95 (br s, 1H), 7.86 (br s, 1H), 7.72 (br s, 1H), 7.08 - 7.15 (m, 1H), 7.04 (br s, 2H), 6.95 (s, 1H), 6.53 (s, 1H), 5.46 (s, 2H), 4.43 (q, *J* = 7.4 Hz, 2H), 2.78 (q, *J* = 7.7 Hz, 3H), 2.54 (*hidden*, 6H), 1.55 (t, *J* = 7.4 Hz, 4H), 1.25 (t, *J* = 7.7 Hz, 3H).

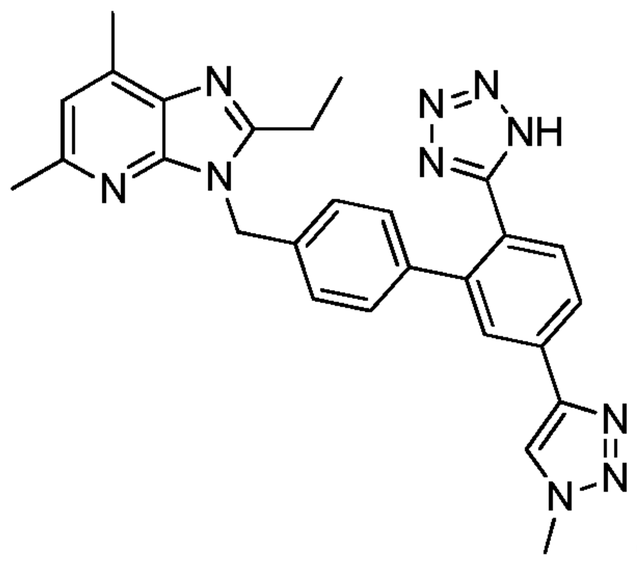
The following examples have been similarly prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-ethynyl-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 234d**) as described for the synthesis of **Example 234** above. Two analytical LC-MS injections were used to determine the final purity. The retention time of one of them is reported for each compound and is referred as Method H.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
235		520.5	521.2; 1.161 min	8.75 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.97 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.03 - 7.14 (m, 4H), 6.96 (s, 1H), 5.47 (s, 2H), 5.08 (t, *J* = 5.3 Hz, 1H), 4.46 (t, *J* = 5.3 Hz, 2H), 3.79 - 3.87 (m, 2H), 2.77 (q, *J* = 7.4 Hz, 2H), 2.55 (s, 6H), 1.23 (t, *J* = 7.4 Hz, 3H).
236		518.6	519.30; 1.241 min	8.75 (s, 1H), 7.98 (d, *J*=7.8 Hz, 1H), 7.90 (s, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 7.01 - 7.18 (m, 4 H), 6.95 (s, 1H), 6.53 (s, 1H), 5.46 (s, 2H), 4.37 (t, *J*=6.8 Hz, 2H), 2.78 (q, *J*=7.4 Hz, 2H), 2.50 (s, 6 H), 1.78 - 1.93 (m, 2H), 1.24 (t, *J*=7.4 Hz, 6H).
237		530.58	531.30; 1.25 min	(MeOH-d_4) 8.55 (s, 1H), 7.92 - 8.04 (m, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.04 (s, 1H), 5.57 (s, 2H), 4.33 (d, *J* = 7.0 Hz, 2H), 2.87 (q, *J* = 7.4 Hz, 2H), 2.54 (s, 3H), 2.69 (s, 3H), 1.40 (m, 1H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.64 - 0.75 (m, 2H), 0.47 - 0.56 (m, 2H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
238		566.5	567.2; 1.292 min	(MeOH-d_4) 8.52 (s, 1 H), 7.97 - 8.06 (m, 2H), 7.75 (d, *J*=8.2 Hz, 1H), 7.36 - 7.44 (m, 3 H), 7.32 (s, 1H), 7.28 (d, *J*=8.2 Hz, 2H), 7.20 (d, *J*=8.2 Hz, 2H), 5.74 (s, 2H), 5.68 (s, 2H), 3.12 (d, *J*=7.4 Hz, 2H), 2.67 (s, 6H), 1.33 (t, J=7.4 Hz, 3H).
239		522.5	523.20; 1.186 min	(MeOH-d_4) 8.52 (s, 1 H), 8.29 (br. s., 1H), 7.88 - 8.00 (m, 2H), 7.70 (d, *J*=7.8 Hz, 1H), 7.16 (d, *J*=7.8 Hz, 2H), 7.06 (m, 2H), 5.56 (s, 2H), 4.91 - 4.99 (m, 1H) 4.72 - 4.86 (m, 3H), 2.87 (q, *J*=7.4 Hz, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.27 (t, *J*=7.4 Hz, 3H).
240		532.6	533.2 1.313 min	(MeOH-d_4) 8.47 (s, 1H), 7.91 - 8.01 (m, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.11 - 7.20 (m, 2H), 7.00 - 7.11 (m, 3H), 5.56 (s, 2H), 4.29 (d, *J* = 7.4 Hz, 2H), 2.87 (q, *J* = 7.7 Hz, 3H), 2.62 (s, 3H), 2.59 (s, 3H), 2.22 - 2.34 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H), 0.93 - 1.01 (m, 6H).

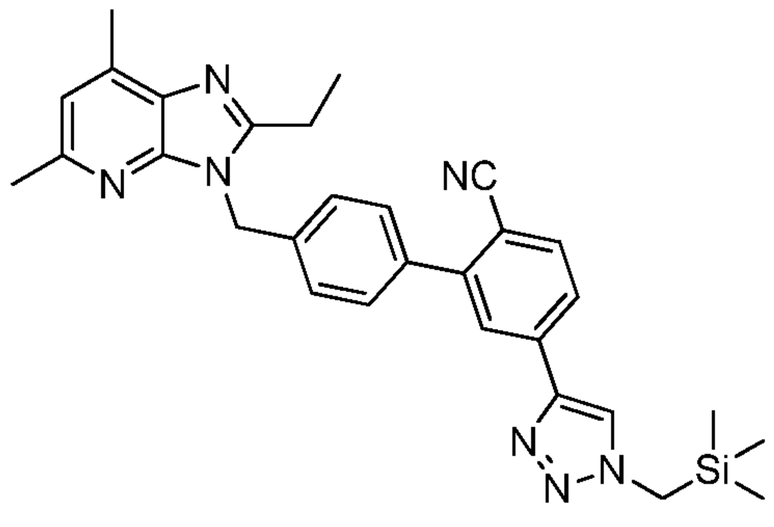
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
241		532.2	533.2; 1.313 min	(MeOH-d_4) 8.48 (s, 1H), 7.94 - 7.99 (m, 2H), 7.70 (d, J = 7.8 Hz, 1H), 7.13 - 7.19 (d, J = 8.2 Hz, 1H), 7.05 - 7.11 (m, J = 8.2 Hz, 2H), 7.04 (s, 1H), 5.56 (s, 2H), 4.48 (m, 2H), 2.87 (q, J = 7.4 Hz, 2H), 2.59 (s, 3H), 2.62 (s, 3H), 1.92 - 2.00 (m, 2H), 1.40 (dd, J = 7.04, 14.87 Hz, 2H), 1.27 (t, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H).
242		540.2	541.2; 1.200 min	8.81 (s, 1H), 7.97 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.95 (s, 1H), 6.53 (t, J = 64.0 Hz 1H), 5.47 (s, 1H), 5.02 (dt, J = 3.1, 15.8 Hz, 2H), 2.78 (q, J = 7.4 Hz, 1H), 2.50 (*hidden*, 6H), 1.24 (t, J = 7.4 Hz, 2H)

Example 243: 2-Ethyl-5,7-dimethyl-3-((5'-(1-methyl-1H-1,2,3-triazol-4-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex. 243)

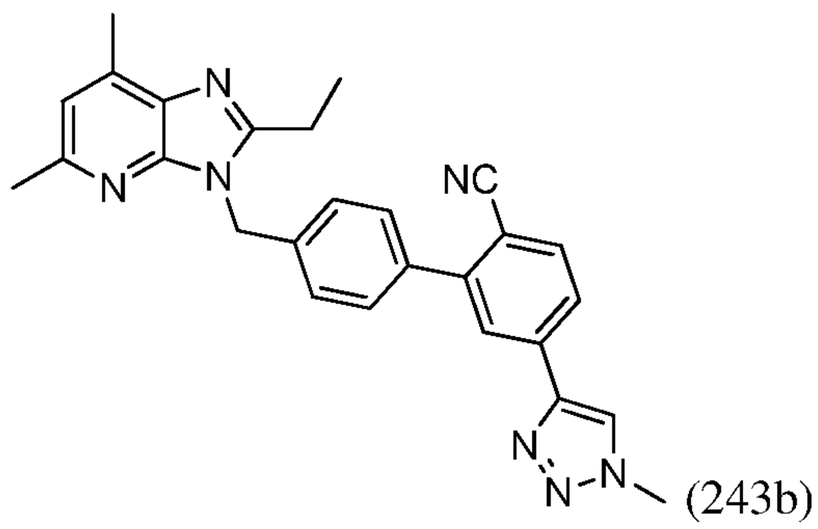
Intermediate 243a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile



(242a)

To a mixture of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-ethynyl-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 234d**, 0.030 g, 0.077 mmol) and (azidomethyl)trimethylsilane (0.0198 g, 0.154 mmol) in t-BuOH-H_2O (3:1) was added sodium ascorbate (0.006 g, 0.031 mmol) and $CuSO_4.5H_2O$ (0.0014 g, 0.008 mmol). The reaction mixture was stirred at RT for 16 h and then it was poured into saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (25 mL) and the organic phase was washed (H_2O, brine), dried (Na_2SO_4) and evaporated to dryness to afford 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile (0.030 g, 0.077 mmol, 75% yield). LC-MS (Method H): 1.339 min, $[M + H]^+$= 520.2. This material was used as such for next reaction.

Intermediate 243b: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-methyl-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile



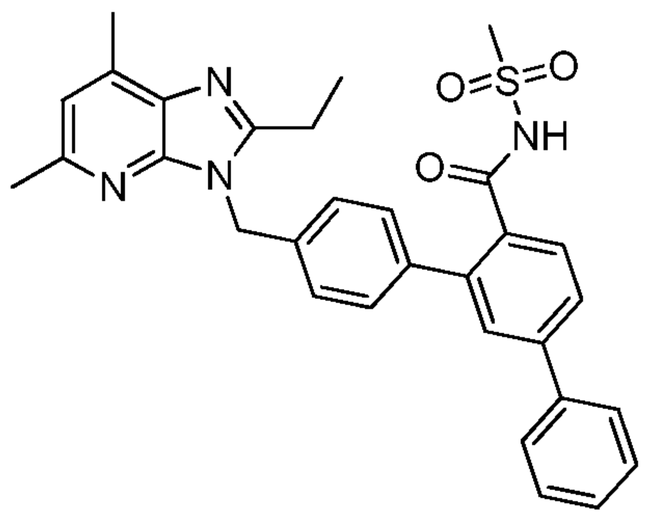
(243b)

To an ice-cold solution of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-((trimethylsilyl)methyl)-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile (0.030 g, 0.058 mmol) in THF (4 mL) was added TBAF (1M in THF, 0.231 mL, 0.231mmol). The reaction mixture was stirred at RT for 1 h before being quenched with saturated aqueous NH_4Cl (5 mL). This mixture was extracted with EtOAc (25 mL) and the organic extract was separated, dried (Na_2SO_4) and evaporated to dryness. The crude the residual gum obtained was purified by preparative LC (Method F) to provide 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-methyl-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile (0.015 g, 0.034 mmol, 58% yield). LC-MS (Method H): 1.262 min, $[M + H]^+$= 448.2.

Example 243: 2-Ethyl-5,7-dimethyl-3-((5'-(1-methyl-1H-1,2,3-triazol-4-yl)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

To a mixture of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(1-methyl-1H-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-2-carbonitrile (0.015 g, 0.034 mmol), TMS-N_3 (0.094 mL, 0.670 mmol) and dibutyltin oxide (0.017 g, 0.067 mmol) was added toluene (2 mL), the vial was briefly purged with N_2 and then it was sealed and the mixture was stirred at 120°C for 16 h. The cooled mixture was evaporated to give a gum which was purified by preparative LC (Method F) to afford the title compound (0.006 g, 36.5% yield) as a white solid. HRMS (ESI): Calcd. for $C_{27}H_{27}N_{10}$ $[M + H]^+$ *m/z* 491.2420; found 491.2498. ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 8.45 (s, 1H), 7.94 - 8.05 (m, 2H), 7.76 (d, *J*=7.8 Hz, 1H), 7.48 (s, 1 H), 7.15 - 7.34 (m, 4H), 5.72 (s, 2H), 4.19 (s, 3H), 3.11 (q, *J*=7.4 Hz, 2H), 2.60 (s, 3H), 2.71 (s, 3H), 1.32 (t, J= 7.4, 3H).

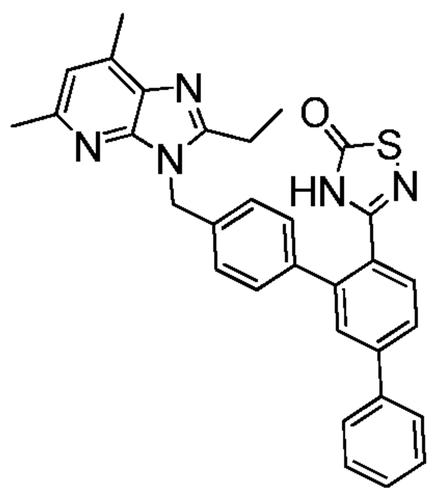
Example 244: 4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N-(methylsulfonyl)-[1,1':3',1''-terphenyl]-4'-carboxamide



(Ex. 244)

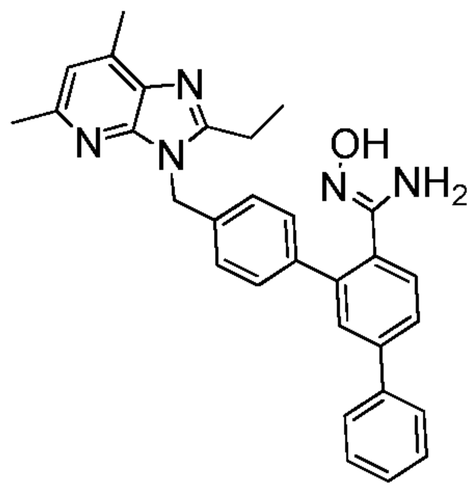
A solution of 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylic acid (**Ex. 031**, 0.030 g, 0.065 mmol) in DMF (1 mL) was treated with HATU (0.023 g, 0.078 mmol), followed by methanesulfonamide (0.007 g, 0.078 mmol) and Hünig's Base (0.023 mL, 0.130 mmol). After stirring at RT for 18 h the solution was poured into H_2O (3 mL) and extracted with EtOAc (20 mL). The EtOAc layer was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The crude residual gum was purified by preparative LC (Method F) to afford the title compound (0.008 g, 0.015 mmol, 22.3% yield). LC-MS (Method H): 1.324 min, (M+H)= 539.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (d, J=7.8 Hz, 1H), 7.69 (dd, J=8.2, 1.6 Hz, 1H), 7.61 (d, J=7.4 Hz, 2H), 7.57 (s, 1H), 7.44 - 7.50 (m, 2H), 7.37 - 7.44 (m, 3H), 7.23 - 7.29 (m, 2H), 6.91 (s, 1H), 5.55 (s, 2H), 3.13 (s, 3H), 2.84 (q, J=7.4 Hz, 2H), 2.65 (s, 3H), 2.60 (s, 3H), 1.37 (t, J=7.4 Hz, 3H).

Example 245: 3-(4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-thiadiazol-5(4H)-one



(Ex. 245)

Intermediate: 245a: (Z)-4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide



(245a)

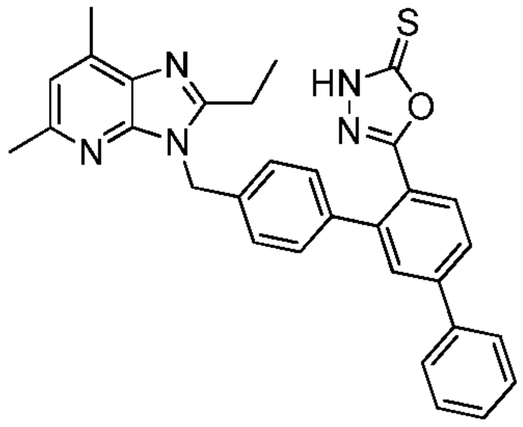
Hydroxylamine hydrochloride (0.785 g, 11.30 mmol) was added to a vial containing 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (**032b**, 0.200 g, 0.452 mmol) and 1-butyl-3-methylimidazolium acetate (3.00 g, 15.13 mmol). This mixture was heated at 50°C for 18 h and then it was allowed to cool to RT. DMSO (1 mL) was added, followed by H_2O (0.5 mL) and formic acid (0.06 mL, 15.13 mmol) to acidify to a pH of about 4. The solution was submitted to purification by preparative LC (Method F) to provide (Z)-4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide (0.120 g, 0.252 mmol, 55.8% yield). LC-MS (Method H): 1.229 min, (M+H)= 476.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 - 7.68 (m, 5H), 7.41 - 7.49 (m, 4H), 7.34 - 7.40 (m, 1H), 7.20 (d, *J*=7.8 Hz, 2H), 6.92 (s, 1 H), 5.51 (s, 2H), 4.48 (br s, 2H), 4.48 (br s, 2H), 2.83 (q, *J*=7.4 Hz, 2H), 2.65 (s, 3 H), 2.61 (s, 3H),1.32 (t, *J*=7.4 Hz, 3H).

Example 245: 3-(4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,2,4-thiadiazol-5(4H)-one

To a solution of (Z)-4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-N'-hydroxy-[1,1':3',1''-terphenyl]-4'-carboximidamide (0.100 g, 0.210 mmol) in anhydrous THF (2 mL), at RT under N_2, was added di(1H-imidazol-1-yl)methanethione (0.056 g, 0.315 mmol) and the solution was stirred at 35°C for 1 h. The reaction was then quenched with H_2O and extracted with EtOAc (25 mL). The organic extract was dried (Na_2SO_4) filtered, and evaporated to dryness. The crude residue obtained was dissolved in anhydrous THF (2 mL), then $BF_3.OEt_2$ (0.167 mL, 0.631 mmol) was added dropwise and the resulting mixture was stirred at RT for 16 h. The resulting mixture was diluted with H_2O and extracted with CH_2Cl_2 (25 mL). The organic extract was washed (1M HCl), dried (Na_2SO_4) and evaporated under reduced pressure. The residual gum obtained was taken up in DMF (1.8 mL) and purified by preparative LC (Method F) to give the title compoud (0.013g, 0.027 mmol, 13% yield) as a white solid. LC-MS (Method H): 1.374

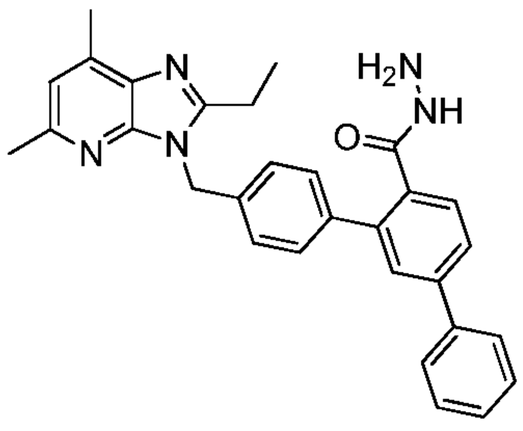
min, (M+H)= 518.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (d, J=7.8 Hz, 1 H), 7.83 - 7.87 (m, 1H), 7.76 - 7.83 (m, 3H), 7.63 (d, J=8.2 Hz, 2H), 7.37 - 7.51 (m, 3H), 7.29 (d, J=8.2 Hz, 2H) 6.99 (s, 1H), 5.57 (s, 2H), 2.86 (q, J=7.4 Hz, 2H), 2.51 (s, 6H), 1.25 (t, J=7.4 Hz, 3H).

Example 246: 5-(4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,3,4-oxadiazole-2(3H)-thione



(Ex. 246)

Intermediate 246a: 4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbohydrazide



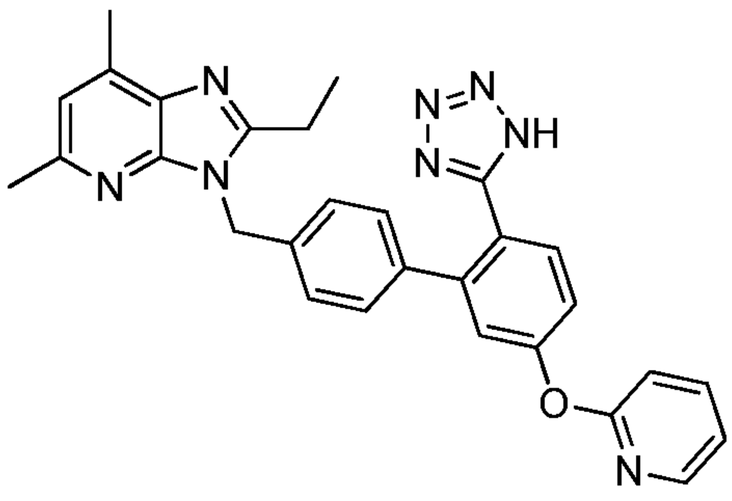
(246a)

To a mixture of 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carboxylic acid (**Ex. 031**, 0.100 g, 0.217 mmol), HATU (0.099 g, 0.260 mmol), and hydrazine (1.0M in THF, 0.260 mL, 0.260 mmol) in DMF (1.30 mL) was added Hünig's base (0.076 mL, 0.433 mmol) and the mixture was stirred at RT for 18 h. The resulting mixture was poured into H_2O (3 mL) and was extracted with EtOAc (25 mL). The organic extract was washed (H_2O, brine), dried (Na_2SO_4) and evaporated to dryness. The residue obtained was purified by prep LC (Method F) to give 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbohydrazide (0.081 g, 0.170 mmol, 79% yield). LC-MS (Method H): 1.344 min, (M+H)= 476.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (s, 1H), 7.70 - 7.77 (m, 1 H), 7.65 (dd, J=8.0, 1.8 Hz, 1H), 7.59 - 7.63 (m, 2H), 7.55 (d, J=1.6 Hz, 1H), 7.43 - 7.50 (m, 2H), 7.36 - 7.43 (m, 3H), 7.21 (d, J=7.8 Hz, 2H), 6.93 (s, 1H) , 5.53 (s, 2H), 2.97 (s, 1H), 2.90 (s, 1 H), 2.78 - 2.89 (m, 2H), 2.65 (s, 3H), 2.62 (s, 3H), 1.34 (t, J=7.4 Hz, 3H).

Example 246: 5-(4''-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-yl)-1,3,4-oxadiazole-2(3H)-thione

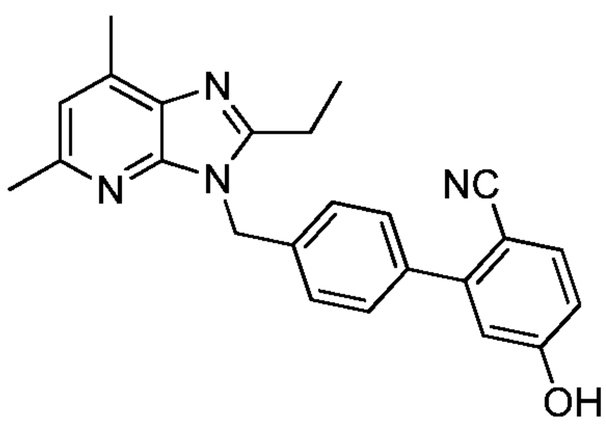
To a solution of 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbohydrazide (0.015 g, 0.032 mmol) in ethanol (0.2 mL) was added CS_2 (0.002 mL, 0.033 mmol) and KOH (0.002 g, 0.032 mmol) at 0°C. The resulting solution was heated at reflux for 12 h and then the volatiles were removed under reduced pressure and the residue was dissolved in H_2O and the solution was acidified with dilute aqueous HCl. This mixture was evaporated and the residual gum was submitted to prep LC (Method F) to give the title compound (0.0073 g, 0.014 mmol, 44.7% yield). LC-MS (Method H): 1.495 min, (M+H)= 518.1, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 (d, J=8.2 Hz, 1H), 7.72 (d, J=7.8 Hz, 1H), 7.59 - 7.68 (m, 3H), 7.38 - 7.52 (m, 3H), 7.30 (d, J=7.8 Hz, 2H), 7.17 (d, J=7.4 Hz, 2H), 6.93 (s, 1H), 5.52 (br s, 2H), 2.77 (q, J=7.4 Hz, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 1.04 (t, J=7.4 Hz, 3H).

Example 247: 2-Ethyl-5,7-dimethyl-3-((5'-(pyridin-2-yloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine



(Ex: 247)

Intermediate 247a: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-hydroxy-[1,1'-biphenyl]-2-carbonitrile

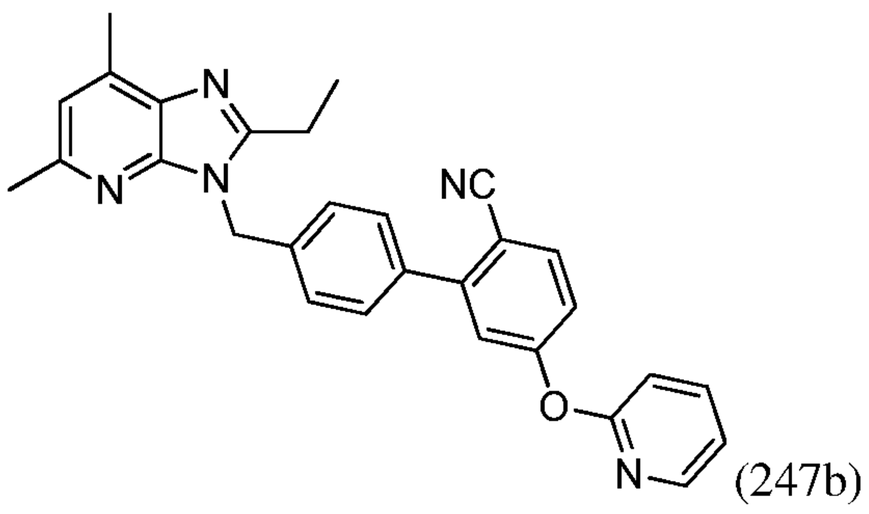


(247a)

In a 75-mL vial, a stream of Ar was passed through a mixture of **Intermediate 001d** (0.35 g, 0.89 mmol), 2-bromo-4-hydroxybenzonitrile (0.21 g, 1.07 mmol) and 2M Na_2CO_3 (1.3 mL, 2.7 mmol) in toluene (6 mL) and ethanol (0.6 mL). After 5 minutes, $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol) was added, Ar was bubbled through the mixture for an

additional 5 min and the sealed vial was heated at 95°C for 16 h. The mixture was then allowed to cool to RT and saturated aqueous ammonium chloride (20 mL) and EtOAc (20 mL) were added. The aqueous layer was separated and extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with brine, dried (anhydrous $MgSO_4$), filtered and evaporated. The residue was triturated in DCM and the precipitate was filtered to afford the title compound (0.091 g). The mother liquor was evaporated and the residue was purified using a 24g- RediSep column (ISCO/ 0-100% EtOAc-DCM) to afford another 0.069 g of the title compound which was combined with the material obtained from trituration to give 0.160 g (47% yield) of the desired product. LC-MS (Method H): 1.29 min, $[M + H]^+$=383.1. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 10.75 (br s, 1H), 7.71 (d, *J*=8.6 Hz, 1H), 7.47 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 6.94 (s, 1H), 6.89 (dd, *J*=8.6, 2.4 Hz, 1H), 6.85 (d, *J*=2.4 Hz, 1H), 5.52 (s, 2H), 2.80 (q, *J*=7.4 Hz, 2H), 2.51 (s, 6H), 1.24 (t, *J*=7.4 Hz, 3H).

Intermediate 247b: 4'-((2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(pyridin-2-yloxy)-[1,1'-biphenyl]-2-carbonitrile



(247b)

In a conical 2-mL vial, a stream of Ar was passed through a suspension of 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-hydroxy-[1,1'-biphenyl]-2-carbonitrile (0.044 g, 0.11 mmol), 2-chloropyridine (0.032 mL, 0.34 mmol) and cesium carbonate (0.110 g, 0.34 mmol) in toluene (0.4 mL). After 5 min, palladacycle precatalyst J009 PreCat (2.0 mg, 2.2 µmol) was added and Ar was bubbled through the mixture for an additional 5 min. The sealed vial was then heated at 100°C for 24 h and allowed to cool to RT. Saturated aqueous ammonium chloride (5 mL) and EtOAc (10 mL) were added and the separated aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried (anhydrous $MgSO_4$), filtered and evaporated. The residue was purified using a 24g- RediSep column (ISCO/ 0-100% EtOAc-DCM) to afford 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-

yl)methyl)-5-(pyridin-2-yloxy)-[1,1'-biphenyl]-2-carbonitrile (0.026 g, 50% yield). LC-MS (Method H): 1.37 min, $[M + H]^+$=460.2. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.18 (dd, *J*=5.1, 2.0 Hz, 1H), 7.88 (dd, *J*=7.4, 1.6 Hz, 1H), 7.83 (d, *J*=8.6 Hz, 1H), 7.50 - 7.56 (m, 2H), 7.26 (m, 4H), 7.11 (d, *J*=8.3 Hz, 1H), 7.03 (s, 1H), 5.62 (s, 2H), 2.89 (q, *J*=7.5 Hz, 2H), 2.61 (s, 3H), 2.58 (s, 3H), 1.28 (t, *J*=7.5 Hz, 3H).

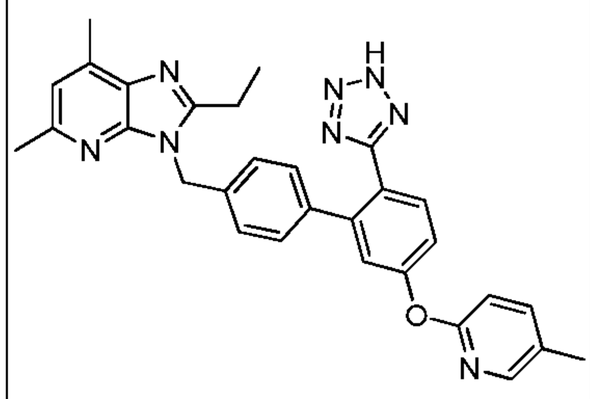
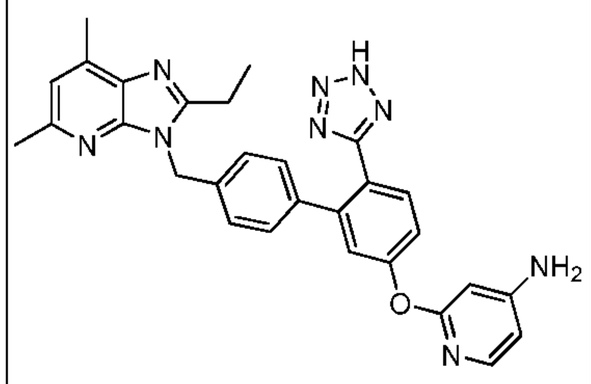
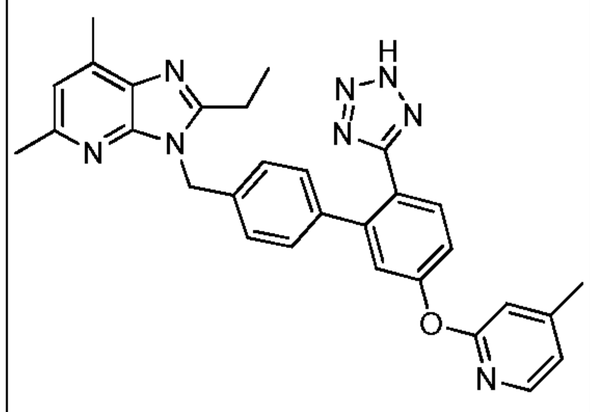
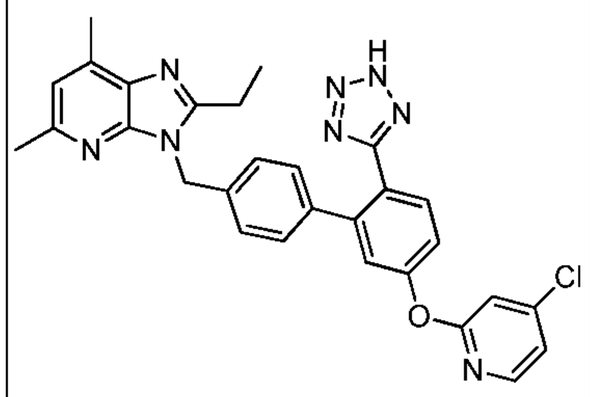
Example 247: 2-Ethyl-5,7-dimethyl-3-((5'-(pyridin-2-yloxy)-2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3H-imidazo[4,5-b]pyridine

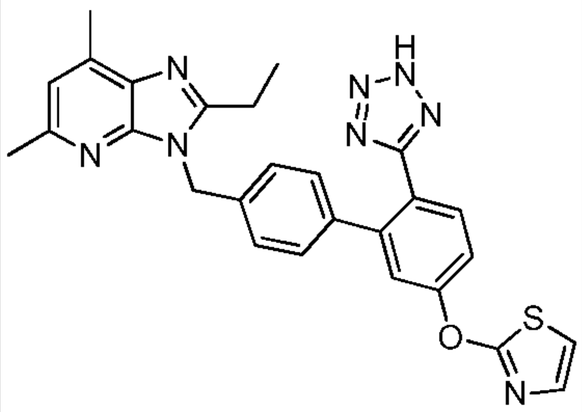
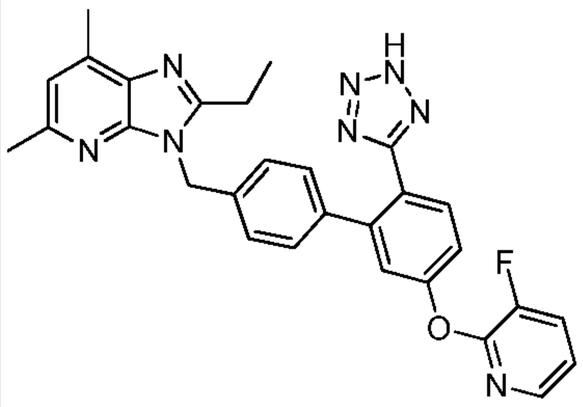
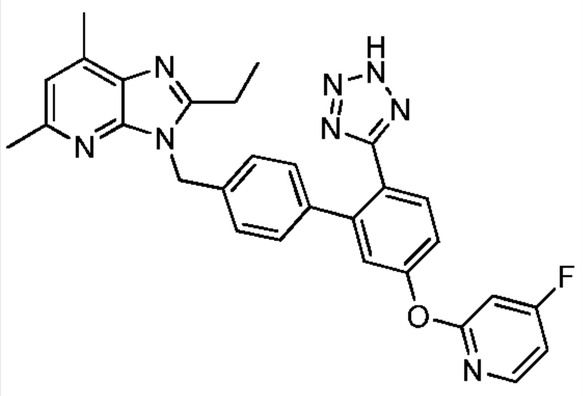
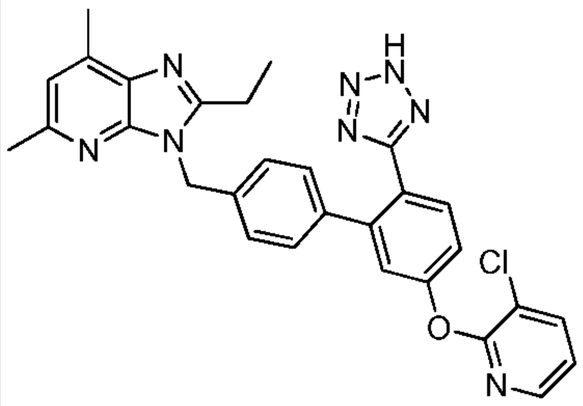
In a conical 2-mL vial was added 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-(pyridin-2-yloxy)-[1,1'-biphenyl]-2-carbonitrile (0.020 g, 0.044 mmol), dibutyltin oxide (0.012 g, 0.048 mmol) and TMS-N_3 (0.046 mL, 0.35 mmol) in toluene (0.250 mL) and the sealed vial was heated at 100°C for 12 h. The mixture was allowed to cool to RT and the volatiles were then removed under reduced pressure. The residue was dissolved in DMSO and filtered through a 0.46 µm syringe filter and purified by preparative HPLC (Method D) to afford the title compound. (0.0133 g, 61% yield). LC-MS (Method H): 1.30 min, $[M + H]^+$=503.2 ; ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.22 (m, 1 H), 7.90 (m, 1H), 7.68 (d, *J*=8.6 Hz, 1H), 7.28 - 7.34 (m, 1H), 7.25 (d, *J*=2.4 Hz, 1H), 7.19 (m, 1H), 7.15 (m, 1H), 7.04 (m, 4H), 6.94 (s, 1H), 5.44 (s, 2 H), 2.74 (q, *J*=7.6 Hz, 2 H), 2.51 (s, 6H), 1.20 (t, *J*=7.6 Hz, 3H).

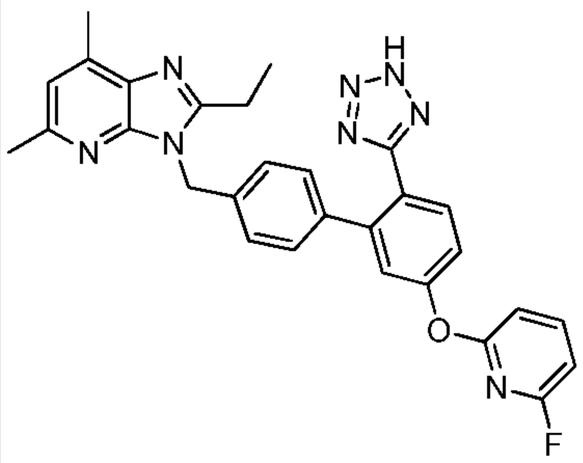
The following examples have been similarly prepared from **Intermediate 247a** as described above for **Example 247**.

In **Example 249**, 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-hydroxy-[1,1'-biphenyl]-2-carbonitrile is reacted, as described above, with tert-butyl (2-chloropyridin-4-yl)carbamate instead of 2-chloropyridine. The resulting **Intermediate 007b** was obtained. In the subsequent step, Boc-deprotection was concomitant to tetrazole formation to afford **Ex. 249**.

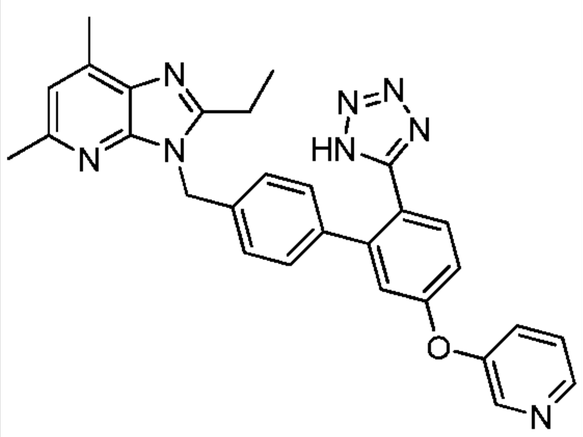
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm

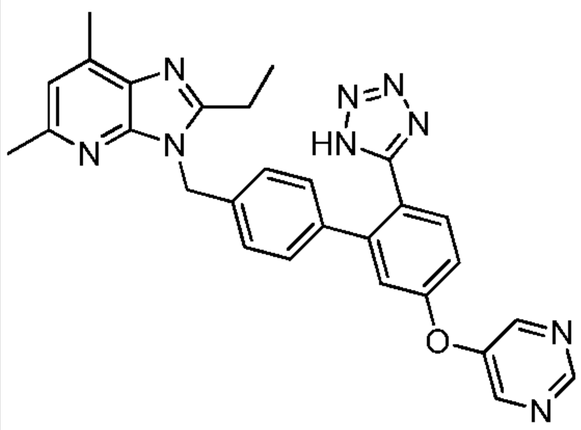
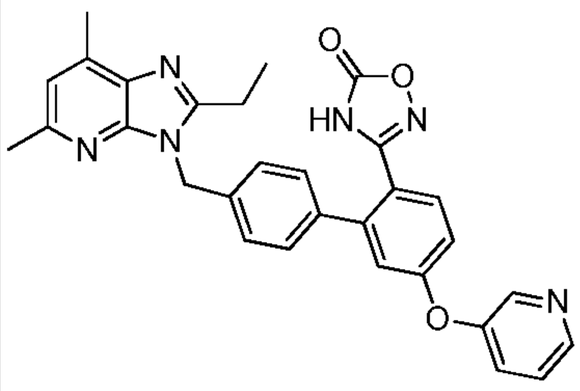
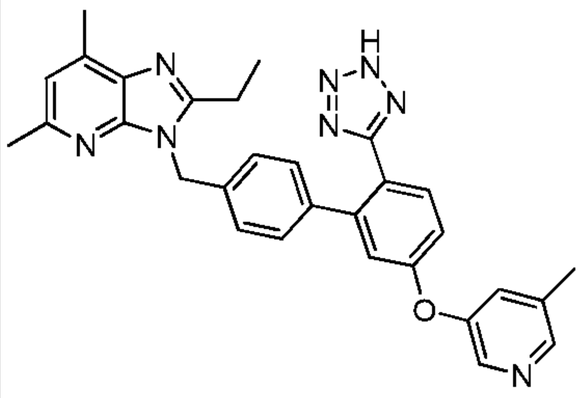
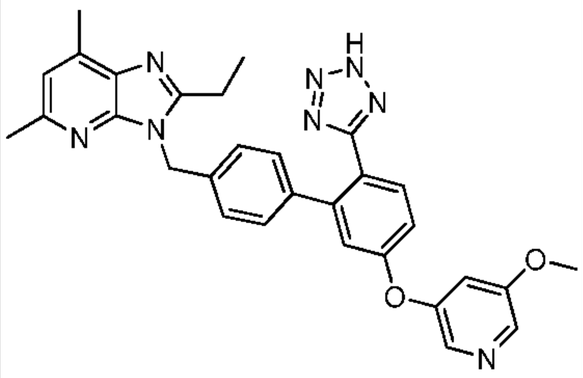
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
248		516.60	517.20; 1.30 min	8.01 (m, 1H), 7.72 (dd, *J*=8.2, 2.7 Hz, 1H), 7.66 (d, *J*=8.2 Hz, 1H), 7.26 (m, 1H), 7.19 (d, *J*=2.3 Hz, 1H), 7.04 (m, 5H), 6.94 (s, 1H), 5.43 (s, 2H), 2.74 (q, *J*=7.6 Hz, 2 H), 2.49 (s, 6H), 2.25 (s, 3H), 1.20 (t, *J*=7.6 Hz, 3H)
249		517.58	518.20; 1.11 min	7.63 (m, 2H), 7.20 (dd, *J*=8.6, 2.8 Hz, 1H), 7.13 (d, *J*=2.4 Hz, 1H), 7.03 (m, 4H), 6.94 (s, 1H), 6.31 (dd, *J*=5.9, 2.0 Hz, 1H), 6.23 (s, 2H), 6.09 (d, *J*=2.0 Hz, 1H), 5.43 (s, 2H), 2.74 (q, *J*=7.6 Hz, 2 H), 2.52 (s, 6H), 1.21 (t, *J*=7.6 Hz, 3H)
250		516.60	517.20; 1.29 min	8.04 (d, *J*=5.5 Hz, 1H), 7.67 (d, *J*=8.6 Hz, 1H), 7.28 (m, 1H), 7.21 (d, *J*=2.3 Hz, 1H), 7.04 (m, 5H), 7.01 (m, 1H), 6.94 (s, 1H), 5.44 (s, 2H), 2.74 (q, *J*=7.6 Hz, 2 H), 2.50 (s, 6H), 2.35 (s, 3H), 1.20 (t, *J*=7.6 Hz, 3H)
251		537.02	537.10; 1.36 min	8.16 (d, *J*=5.5 Hz, 1H), 7.70 (d, *J*=8.6 Hz, 1H), 7.33 (m, 4H), 7.04 (m, 4H), 6.94 (s, 1H), 5.44 (s, 2H), 2.74 (q, *J*=7.4 Hz, 2 H), 2.50 (s, 6H), 1.20 (t, *J*=7.4 Hz, 3H)

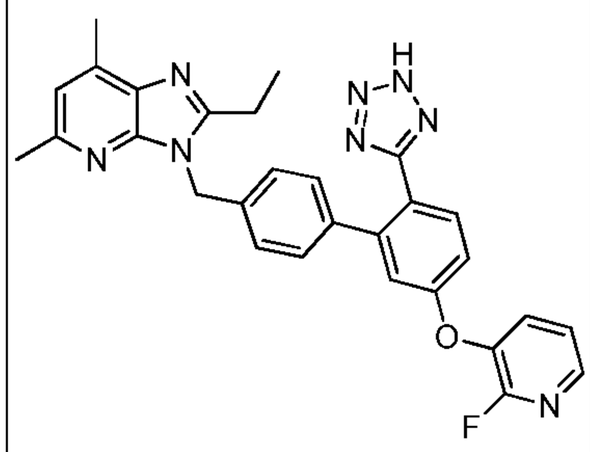
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
252		508.60	509.10; 1.26 min	7.73 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.30 (m, 2H), 7.04 (m, 4H), 6.93 (s, 1H), 5.43 (s, 2H), 2.74 (q, *J* = 7.4 Hz, 2H), 2.51 (s., 6H), 1.19 (t, *J* = 7.4 Hz, 3H)
253		520.56	521.20; 1.27 min	7.99 (d, *J* = 4.7 Hz, 1H), 7.90 (t, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.37 (dd, *J*=8.6, 2.4 Hz, 1 H), 7.33 (d, *J*=2.4 Hz, 1 H), 7.25 (m, 1H), 7.04 (m, 4H), 6.94 (s, 1H), 5.44 (s, 2H), 2.74 (q, *J* = 7.4 Hz, 2H), 2.51 (s., 6H), 1.19 (t, *J* = 7.4 Hz, 3H)
254		520.56	521.20; 1.28 min	8.20 (dd, *J*=9.0, 5.9 Hz, 1 H), 7.68 (d, *J*=8.6 Hz, 1 H), 7.33 (dd, *J*=8.6, 2.4 Hz, 1 H), 7.28 (d, *J*=2.4 Hz, 1 H), 7.14 (m, 2H), 7.04 (m, 4H), 6.94 (s, 1H), 5.43 (s, 2H), 2.74 (q, *J* = 7.4 Hz, 2H), 2.51 (s., 6H), 1.21 (t, *J* = 7.4 Hz, 3H)
255		537.02	537.20; 1.30 min	8.23-8.02 (m, 2 H), 7.70 (d, *J*=8.6 Hz, 1 H), 7.35 (m, 1 H), 7.30 (d, *J*=2.4 Hz, 1 H), 7.22 (dd, *J*=7.8, 4.7 Hz, 1 H), 7.04 (m, 4H), 6.94 (s, 1H), 5.44 (s, 2H), 2.74 (q, *J* = 7.4 Hz, 2H), 2.50 (s., 6H), 1.20 (t, *J* = 7.4 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
256		520.56	521.10; 1.27 min	(MeOH-d_4) : 7.95 (m, 1 H), 7.70 (d, *J*=8.2 Hz, 1 H), 7.29 (m, 2 H), 7.09 (m, 4H), 7.03 (s, 1 H), 6.96 (m, 1H), 6.78 (m, 1H), 5.55 (s, 2H), 2.85 (q, *J* = 7.8 Hz, 2H), 2.60 (s., 3H), 2.57 (s, 3H), 1.25 (t, *J* = 7.8 Hz, 3H)

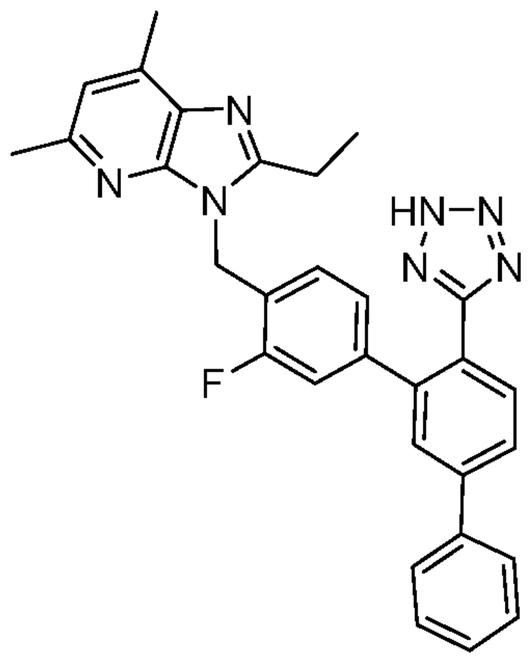
The following examples were prepared from 4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-5-fluoro-[1,1'-biphenyl]-2-carbonitrile (**Intermediate 205a**) and the appropriate 3-hydroxypyridine or 3-hydroxypyrimidine, using a method similar to that described for the synthesis of **Intermediate 205b** and **Example 205**. **Example 259** was prepared according to the method described for the synthesis of **Example 214**.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
257		502.57	503.10; 1.28 min	(MeOH-d_4): 8.81 (m, 2H), 7.69 (d, *J*=9.0 Hz, 1H), 7.61 (d, *J*=1.6 Hz, 1H), 7.50 (m, 1H), 7.19 (m, 2H) 7.08 (m, 4H), 7.05 (s, 1H), 5.56 (s, 2H), 2.86 (q, *J*=7.6 Hz, 2H), 2.61 (s, 3H), 2.58 (s, 3H), 1.25 (t, *J*=7.6 Hz, 3H)

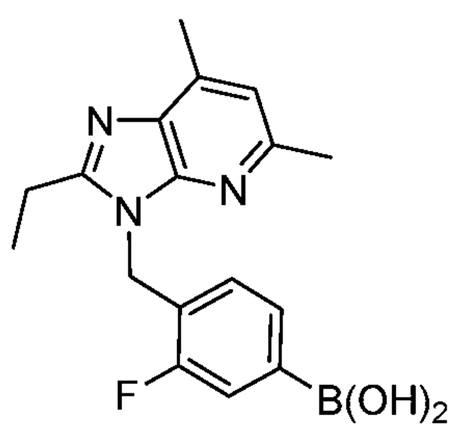
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
258		503.56	504.20; 1.25 min	9.06 (s, 1H) 8.78 (s, 2H) 7.70 (d, *J*=8.22 Hz, 1H), 7.31 (dd, *J*=8.6, 2.3 Hz,1H), 7.26 (m, 1H), 7.05 (m, 4H), 6.94 (s, 1H), 5.44 (s, 2H), 2.74 (q, *J*=7.6 Hz, 2 H), 2.50 (s, 6H), 1.21 (t, *J*=7.6 Hz, 3H)
259		518.56	519.10; 1.81 min	8.45 (d, *J*=2.74 Hz, 2 H), 7.83 (d, *J*=8.61 Hz, 1 H), 7.38 - 7.43 (m, 1 H), 7.32 - 7.37 (m, 1 H) , 7.25 (d, *J*=8.22 Hz, 2 H), 7.17 (d, *J*=8.22 Hz, 2 H), 7.07 (dd, *J*=8.61, 2.35 Hz, 1 H), 6.96 (d, *J*=2.35 Hz, 1 H), 6.90 (s, 1 H), 5.49 (s, 2 H), 2.81 (q, *J*=7.70 Hz, 2 H), 2.62 (s, 3 H), 2.57 (s, 3 H), 1.34 (t, *J*=7.63 Hz, 3 H)
260		516.60	517.20; 1.28 min	8.28 (m, 2H), 7.66 (d, *J*=8.6 Hz, 1H), 7.44 (br. S, 1H), 7.15 (dd, *J*=8.2, 2.4 Hz, 1H), 7.11 (m, 1H), 7.02 (m, 4H), 6.92 (s, 1H), 5.42 (s, 2H), 2.72 (q, *J*=7.6 Hz, 2 H), 2.49 (s, 6H), 2.29 (s, 3H), 1.19 (t, *J*=7.6 Hz, 3H)
261		532.60	533.20; 1.30 min	8.20 (d, *J*=2.4 Hz, 1H), 8.08 (d, *J*=2.3 Hz, 1H), 7.68 (d, *J*=8.6 Hz, 1H), 7.29 (m, 1H), 7.23 (m, 1H), 7.15 (m, 1H), 7.04 (m, 4H), 6.95 (s, 1H), 5.44 (s, 2H), 3.83 (s, 3H), 2.74 (q, *J*=7.4 Hz, 2 H), 2.51 (s, 6H), 1.21 (t, *J*=7.4 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method H)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
262		520.56	521.20; 1.36 min	(MeOH-d_4) : 8.06 (m, 1 H), 7.79 (m, 1H), 7.68 (d, *J*=8.6 Hz, 1 H), 7.40 (m, 1 H), 7.21 (m, 3H), 7.13 (m, 4H), 5.67 (s, 2H), 3.04 (q, *J* = 7.4 Hz, 2H), 2.65 (s., 3H), 2.64 (s, 3H), 1.30 (t, *J* = 7.4 Hz, 3H)

Example 264: 2-ethyl-3-((3-fluoro-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine



Intermediate 264a: (4-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3-fluorophenyl)boronic acid, TFA salt

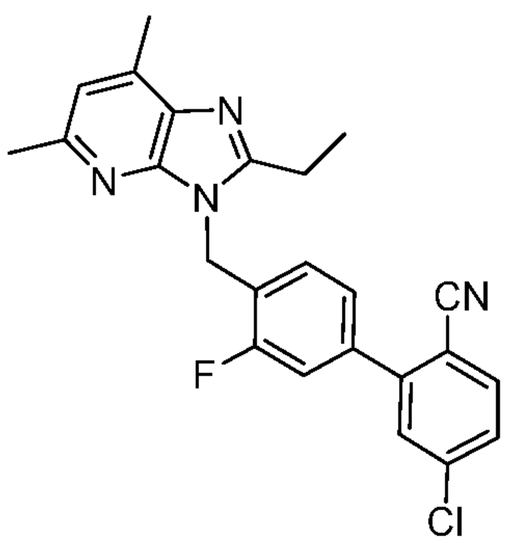


Intermediate 264a was prepared in a similar manner as for **Intermediate 001d**, by replacing 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with 2-

(4-(bromomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

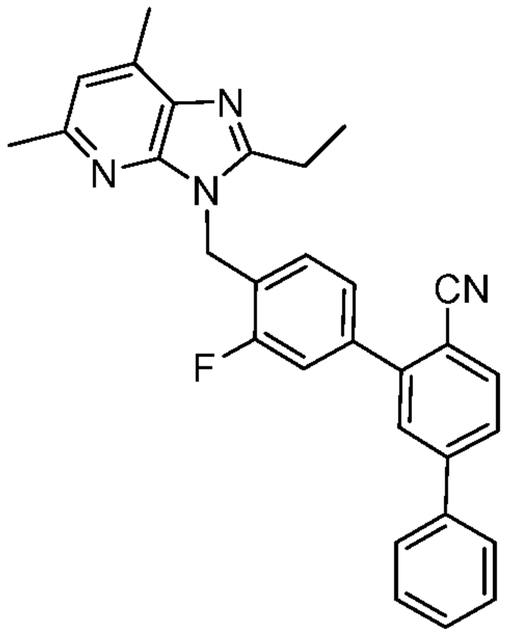
Intermediate 264a was purified by preparative HPLC (method E). LC-MS (Method A5): 0.62 min, $[M + H]^+ = 328.0$; ^1H NMR (400 MHz, MeOH-d_4) δ 7.54 - 7.42 (m, 2H), 7.39 (s, 1H), 7.30 (t, *J*=7.6 Hz, 1H), 5.83 (s, 2H), 3.26 (q, *J*=7.7 Hz, 2H), 2.72 - 2.66 (m, 6H), 1.41 (t, *J*=7.6 Hz, 3H).

Intermediate 264b: 5-chloro-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3'-fluoro-[1,1'-biphenyl]-2-carbonitrile



Intermediate 264a was reacted with 4-chloro-2-iodobenzonitrile in a manner analogous to **Intermediate 177d** to give **Intermediate 264b**. LC-MS (Method A5): 0.85 min, $[M + H]^+ = 419.0$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J=8.1 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.35 - 7.30 (m, 1H), 7.23 - 7.15 (m, 1H), 7.00 (t, J=7.8 Hz, 1H), 6.92 (s, 1H), 5.58 (s, 2H), 2.87 (q, J=7.6 Hz, 2H), 2.65 (s, 3H), 2.61 (s, 3H), 1.38 (t, J=7.5 Hz, 3H).

Intermediate 264c: 4''-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-3''-fluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile

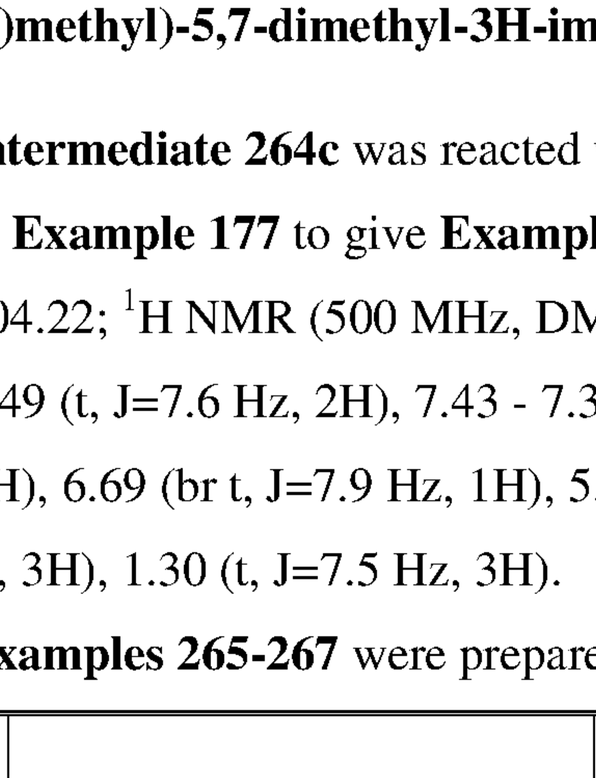


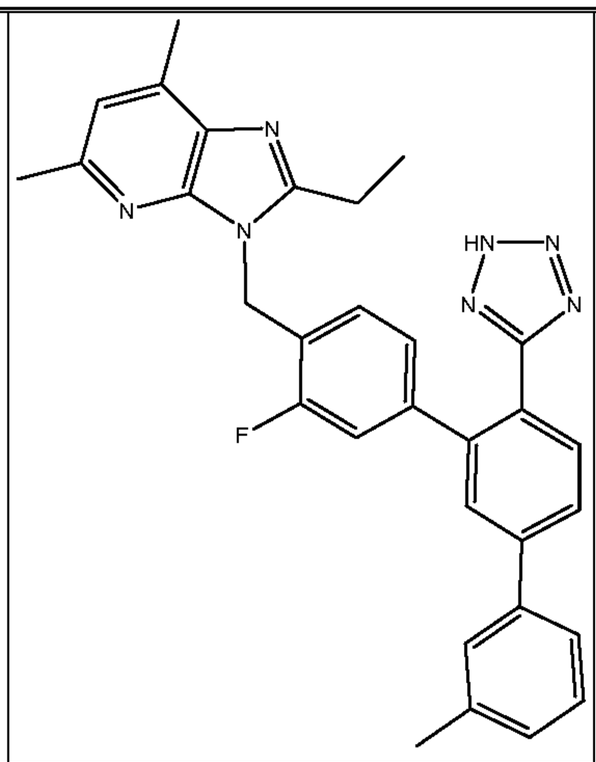
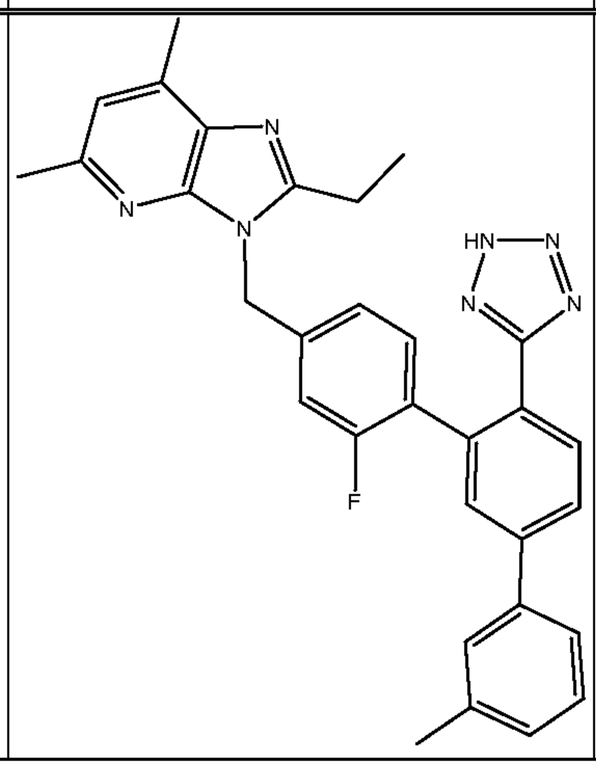
Intermediate 264b was reacted with phenyllboronic acid in a manner analogous to **Intermediate 177e** to give **Intermediate 264c**. LC-MS (Method A5): 0.93 min, $[M + H]^+$ = 461.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 1H), 7.70 - 7.66 (m, 2H), 7.61 (d, J=7.4 Hz, 2H), 7.53 - 7.42 (m, 3H), 7.39 (dd, J=10.6, 1.5 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.02 (t, J=7.7 Hz, 1H), 6.93 (s, 1H), 5.60 (s, 2H), 2.89 (q, J=7.7 Hz, 2H), 2.66 (s, 3H), 2.62 (s, 3H), 1.39 (t, J=7.4 Hz, 3H).

Example 264: 2-ethyl-3-((3-fluoro-6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridine

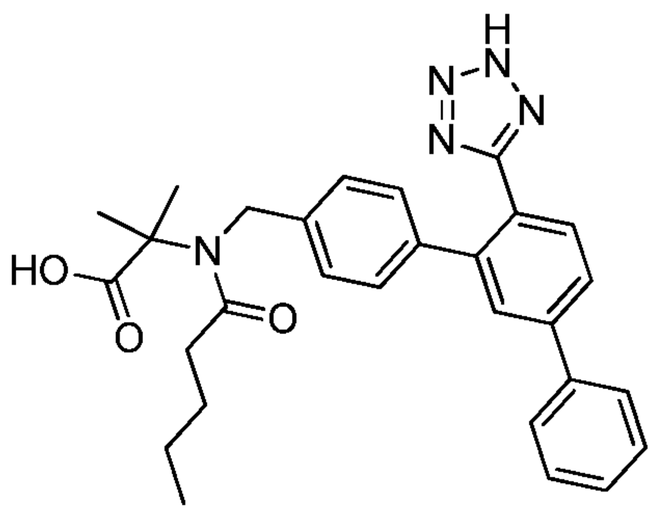
Intermediate 264c was reacted with dibutyltin oxide and TMS-N_3 in a manner analogous to **Example 177** to give **Example 264**. LC-MS (Method A4): 1.70 min, $[M + H]^+$ = 504.22; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 - 7.77 (m, 2H), 7.75 (s, 2H), 7.63 (s, 1H), 7.49 (t, J=7.6 Hz, 2H), 7.43 - 7.38 (m, 1H), 7.10 (br d, J=11.3 Hz, 1H), 6.99 - 6.94 (m, 2H), 6.69 (br t, J=7.9 Hz, 1H), 5.50 (s, 2H), 3.40 (br s, 3H), 2.83 (q, J=7.3 Hz, 2H), 1.93 (s, 3H), 1.30 (t, J=7.5 Hz, 3H).

Examples 265-267 were prepared using the methods descibed for **Example 264**:

Ex	Structure	MW	LCMS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-*d6*) δ ppm
265		503.58	504.23; 1.66 min (Method A4)	7.92 (s, 2H), 7.80 (d, J=7.7 Hz, 2H), 7.72 (s, 1H), 7.53 - 7.47 (m, 2H), 7.46 - 7.40 (m, 1H), 7.36 (t, J=7.8 Hz, 1H), 6.98 (s, 1H), 6.94 (d, J=9.0 Hz, 2H), 5.51 (s, 2H), 2.83 (q, J=7.5 Hz, 2H), 2.54 (s, 3H), 2.53 (s, 3H), 1.29 (t, J=7.5 Hz, 3H).

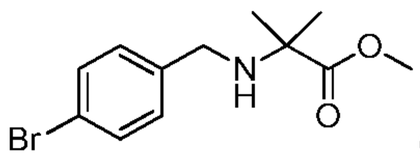
266		517.24	518.05; 1.81 min (Method A4)	7.96 (s, 1H), 7.83 (br d, J=7.9 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.59 (br d, J=7.9 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.24 (br d, J=7.6 Hz, 1H), 7.14 (br d, J=11.3 Hz, 1H), 6.96 (s, 1H), 6.90 (br d, J=7.9 Hz, 1H), 6.74 (br t, J=7.8 Hz, 1H), 5.50 (s, 2H), 2.80 (q, J=7.3 Hz, 2H), 2.56 (s, 6H), 2.39 (s, 3H), 1.27 (t, J=7.5 Hz, 3H).
267		517.24	518.22; 1.78 min (Method A4)	7.97 - 7.91 (m, 2H), 7.77 (br d, J=7.9 Hz, 1H), 7.58 - 7.50 (m, 3H), 7.35 (t, J=7.6 Hz, 1H), 7.25 (t, J=7.8 Hz, 1H), 7.20 (br d, J=7.6 Hz, 1H), 6.97 (s, 1H), 6.93 - 6.85 (m, 2H), 5.50 (s, 2H), 2.83 (q, J=7.5 Hz, 2H), 2.54 (s, 3H), 2.53 (br s, 3H), 1.92 (s, 3H), 1.29 (t, J=7.3 Hz, 3H).

Example 268: 2-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-2-methylpropanoic acid



(Ex. 268)

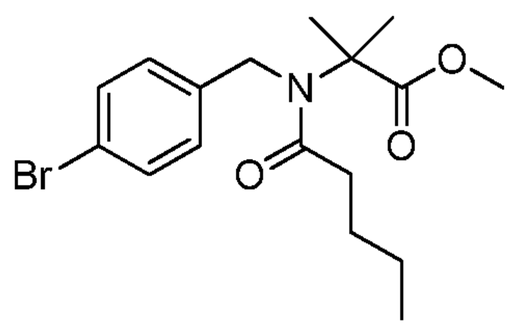
Intermediate 268a: Methyl 2-((4-bromobenzyl)amino)-2-methylpropanoate



(268a)

To a mixture of methyl 2-amino-2-methylpropanoate hydrochloride (0.538 g, 3.50 mmol) in ACN (10 mL) was added 1-bromo-4-(bromomethyl)benzene (0.875 g, 3.5 mmol) and DIEA (1.22 mL, 7.00 mmol) and the mixture was heated at 80°C for 3 h. The volatiles were then evaporated under reduced pressure and tert-butylmethyl ether (15 mL) and saturated aqueous sodium hydrogen carbonate (5 mL) were added to the residue. The aqueous phase was separated and re-extracted with tert-butylmethyl ether (10 mL), and the combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (12 g ISCO-type silica gel column, 0 to 10% EtOAc / hexane gradient) to afford the title compound (0.716 g, 2.50 mmol, 71% yield) as a clear, colorless oil. LC-MS (Method H): 0.96 min, $[M + H]^+$= 286.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.43 - 7.52 (m, 2 H), 7.24 - 7.33 (m, 2 H), 3.62 (s, 3 H), 3.54 (d, *J*=4.7 Hz, 2 H), 2.47 (br s, 1 H), 1.19 - 1.30 (m, 6 H).

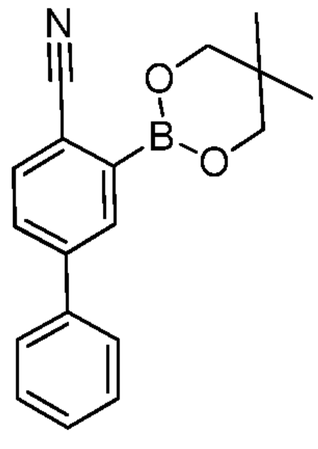
Intermediate 268b: Methyl 2-(N-(4-bromobenzyl)pentanamido)-2-methylpropanoate



(268b)

To a solution of **Intermediate 268a** (0.350 g, 1.22 mmol) in EtOAc (3.5 mL) was added DIEA (0.85 mL, 4.84 mmol) followed by pentanoyl chloride (0.22 mL, 1.84 mmol) and this mixture was heated at 65°C for 18 h. The cooled mixture was diluted with tert-butylmethyl ether (25 mL), washed (5 mL of 10% aqueous citric acid, then 5 mL of saturated aqueous sodium hydrogen carbonate), dried (anhydrous sodium sulfate), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (12 gram ISCO-type column using a 0 to 25% acetone / hexane gradient) to afford the title compound (0.716 g, 2.50 mmol, 71% yield) as an orange crystalline solid. LC-MS (Method H): 1.34 min, $[M + H]^+$= 370.0; ^{1}H NMR (DMSO-d_6) δ ppm 7.54 - 7.62 (m, 2H), 7.33 - 7.42 (m, J = 8.2 Hz, 2H), 4.64 (s, 2H), 3.58 (s, 3H), 2.11 - 2.23 (m, 2H), 1.35 - 1.49 (m, 2H), 1.26 (s, 6H), 1.18 (dq, J = 14.8, 7.3 Hz, 2H), 0.78 (t, J = 7.2 Hz, 3H).

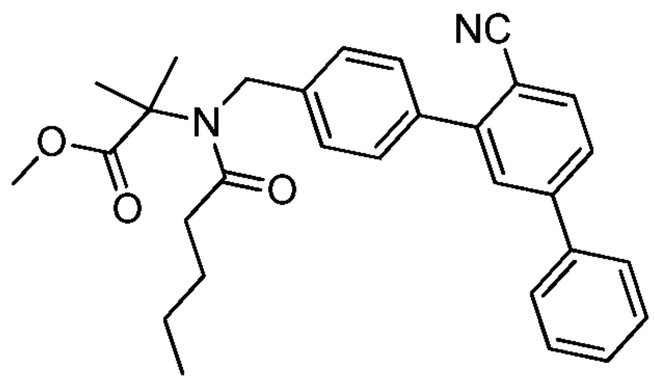
Intermediate 268c: 3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-[1,1'-biphenyl]-4-carbonitrile



(268c)

The title compound was prepared from [1,1'-biphenyl]-4-carbonitrile according to a literature procedure (*cf.* J. L. Kristensen, *et al. Journal of Organic Chemistry*, **2006**, *71*, 2518) to afford a white solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.04 - 8.08 (m, 1H), 7.88 - 7.91 (m, 2H), 7.67 - 7.74 (m, 2H), 7.47 - 7.54 (m, 2H), 7.41 - 7.47 (m, 1H), 3.82 (s, 4H), 0.99 (s, 6H).

Intermediate 268d: Methyl 2-(N-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-2-methylpropanoate



(268d)

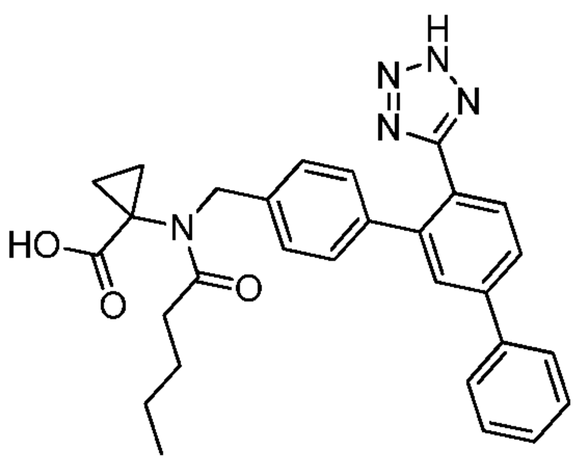
Intermediate 268d was prepared by the reaction of **Intermediate 268b** (0.075 g, 0.258 mmol) with **Intermediate 268c** (0.114 g, 0.309 mmol), according to the method described for the synthesis of **Intermediate 330b**. The title compound (0.100 g, 0.213 mmol, 83% yield) was isolated as a white solid. LC-MS (Method H): 1.45 min, [M-C_5H_9O+H]= 385.1; ^{1}H NMR (DMSO-d_6) δ ppm 8.03 (d, J = 7.8 Hz, 1H), 7.80 - 7.93 (m, 4H), 7.68 - 7.77 (m, 2H), 7.57 - 7.63 (m, 2H), 7.43 - 7.55 (m, 3H), 4.78 (s, 2H), 3.61 (s, 3H), 2.25 (t, J = 7.0 Hz, 2H), 1.37 - 1.55 (m, 2H), 1.32 (s, 6H), 1.10 - 1.29 (m, 2H), 0.73 - 0.89 (m, 3H).

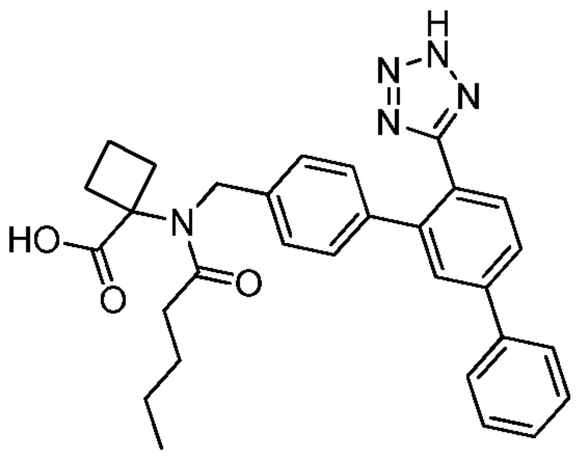
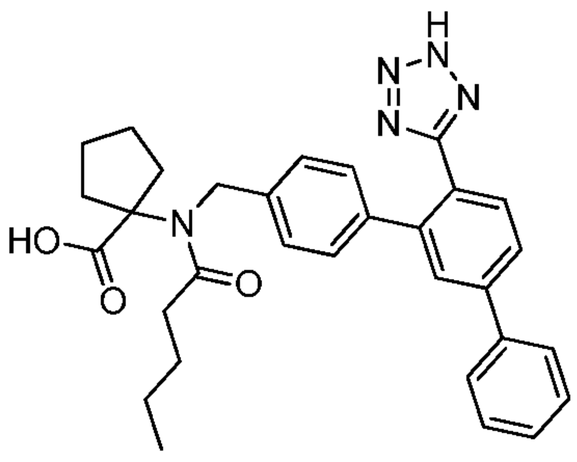
Example 268: 2-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-2-methylpropanoic acid

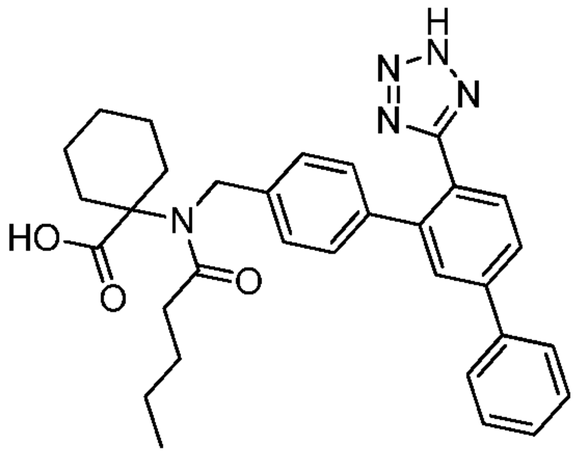
To a pressure vial containing **Intermediate 268d** (0.045 g, 0.096 mmol) was added toluene (6 mL), dibutyltin oxide (0.024 g, 0.096 mmol) and azidotrimethylsilane (0.064 mL, 0.48 mmol). The reaction vessel was sealed and the mixture was heated at 110°C for 18 h. The cooled mixture was then evaporated and the residue was taken up in DMSO (2.5 mL). To this mixture was added 2.5M NaOH (0.66 mL, 0.96 mmol) and the resulting

mixture was heated at 60°C for 3 days. To the cooled mixture was then added formic acid (0.072 mL, 1.92 mmol), the mixture was filtered and the filtrate was submitted to prep LC (Method F, TFA as modifier). This afforded the title compound (0.031 g, 0.062 mmol, 64% yield) as a white solid. LC-MS (Method H): 1.34 min, [M-H]= 496.1; ^{1}H NMR (DMSO-d_6) δ ppm 11.95 (br s, 2H), 7.79 - 7.91 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 7.48 - 7.57 (m, 2H), 7.41 - 7.48 (m, 1H), 7.36 - 7.41 (m, J = 8.2 Hz, 2H), 7.17 - 7.24 (m, 2H), 4.66 (s, 2H), 2.18 (t, J = 7.2 Hz, 2H), 1.43 (dt, J = 14.8, 7.3 Hz, 2H), 1.27 (s, 6H), 1.19 (dq, J = 15.0, 7.4 Hz, 2H), 0.79 (t, J = 7.2 Hz, 3H).

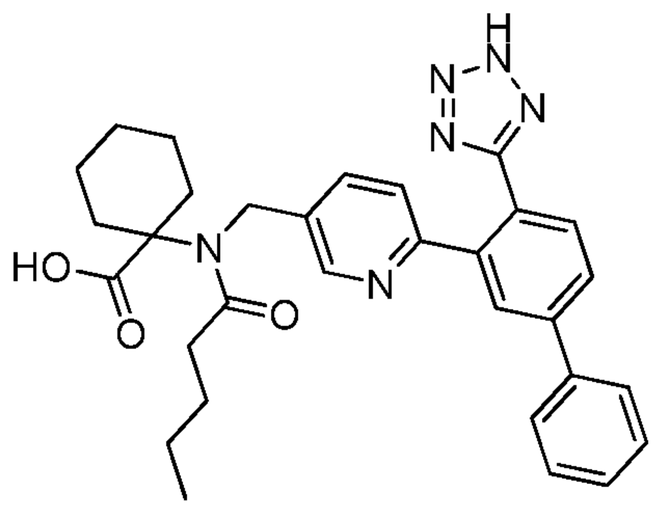
The following examples were similarly prepared from the corresponding amino ester or amino ester hydrochloride salt as described for the synthesis of **Example 268** above. Analytical LC-MS injections were used to determine the final purity and the retention time is reported for each compound and is referred as Method A1, Method A2 or Method H.

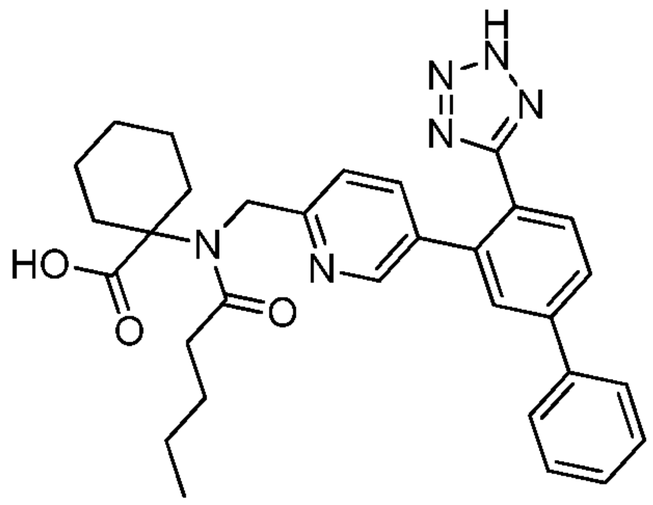
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
269		495.58	496.1; 1.29 min (Method H)	7.79 - 7.89 (m, 3H), 7.70 - 7.79 (m, 2H), 7.47 - 7.56 (m, 2H), 7.38 - 7.47 (m, 1H), 7.03 - 7.14 (m, 4H), 4.99 (d, J = 16.0 Hz, 1H), 4.10 (d, J = 16.0 Hz, 1H), 2.52 - 2.60 (m, 1H), 2.22 - 2.37 (m, 1H), 1.66 (m, 1H), 1.37 - 1.59 (m, 3H), 1.14 - 1.37 (m, 1H), 0.98 - 1.12 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H)

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
270		509.61	510.2; 1.31 min (Method H)	12.41 (br. s., 2H), 7.78 - 7.91 (m, 4H), 7.72 - 7.78 (m, 1H), 7.48 - 7.56 (m, 2H), 7.40 - 7.48 (m, 1H), 7.28 - 7.36 (m, 2H), 7.22 - 7.28 (m, 2H), 4.54 (s, 2H), 2.45 (d, J = 9.4 Hz, 1H), 2.03 - 2.26 (m, 3H), 1.84 - 2.03 (m, 1H), 1.67 (d, J = 10.2 Hz, 1H), 1.35 - 1.61 (m, 3H), 1.10 - 1.34 (m, 3H), 0.77 (t, J = 7.4 Hz, 3H).
271		523.63	524.1; 1.32 min (Method H)	12.05 (s, 2H), 7.78 - 7.90 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 7.48 - 7.55 (m, 2H), 7.40 - 7.48 (m, 1H), 7.31 - 7.39 (m, 2H), 7.17 - 7.24 (m, 2H), 4.64 (s, 2H), 2.21 - 2.32 (m, 2H), 2.16 (t, J = 7.2 Hz, 2H), 1.61 - 1.75 (m, 2H), 1.48 - 1.61 (m, 4H), 1.43 (dt, J = 14.9, 7.4 Hz, 2H), 1.18 (dq, J = 15.0, 7.3 Hz, 2H), 0.78 (t, J = 7.2 Hz, 3H).

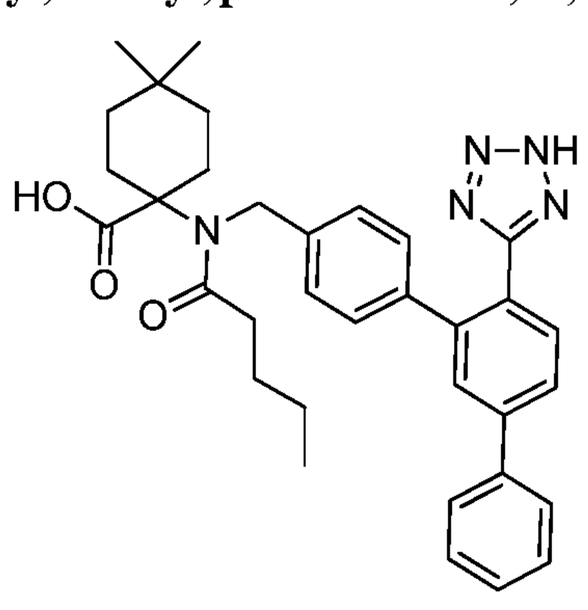
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
272		537.66	538.1; 1.34 min. (Method H)	11.93 (s, 2H), 7.78 - 7.90 (m, 4H), 7.74 (d, J = 8.2 Hz, 1H), 7.47 - 7.56 (m, 2H), 7.41 - 7.47 (m, 1H), 7.35 - 7.41 (m, 2H), 7.16 - 7.22 (m, 2H), 4.64 (m, 2H), 2.18 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 11.7 Hz, 2H), 1.51 - 1.68 (m, 4H), 1.36 - 1.51 (m, 6H), 1.15 - 1.26 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H).

5

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
273		538.65	539.2; 1.300 min (Method H)	12.01 (s, 2H), 8.50 (s, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.90 - 8.00 (m, 2H), 7.73 - 7.90 (m, 3H), 7.67 (d, J = 8.2 Hz, 1H), 7.49 - 7.57 (m, 2H), 7.40 - 7.49 (m, 1H), 4.76 (s, 2H), 2.20 (t, J = 6.8 Hz, 2H), 2.01 (d, J = 11.3 Hz, 2H), 1.38 - 1.70 (m, 9H), 1.06 - 1.33 (m, 3H), 0.80 (t, J = 7.4 Hz, 3H).

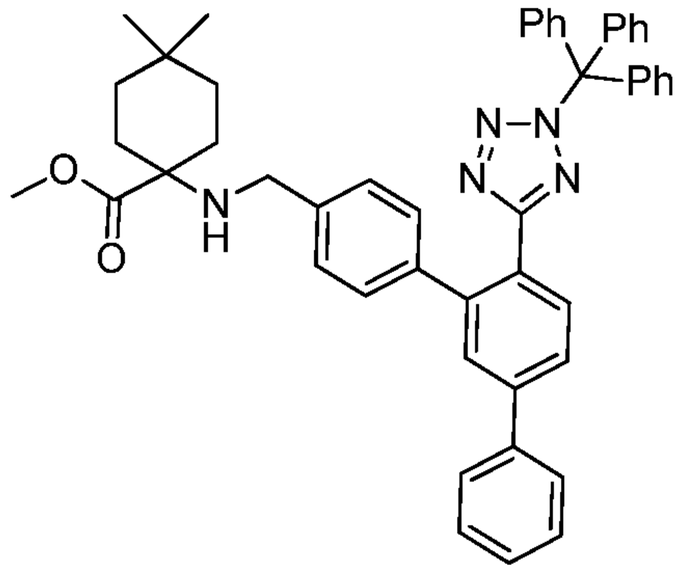
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
274		538.65	539.2; 1.290 min (Method H)	12.10 (s, 2H), 8.44 (d, J = 2.0 Hz, 1H), 7.92 - 7.99 (m, 1H), 7.81 - 7.92 (m, 4H), 7.72 (dd, J = 8.2, 2.3 Hz, 1H), 7.49 - 7.60 (m, 3H), 7.41 - 7.49 (m, 1H), 4.84 (s, 2H), 2.19 (t, J = 6.7 Hz, 1H), 2.06 (d, J = 9.8 Hz, 1H), 1.36 - 1.74 (m, 9H), 1.08 - 1.35 (m, 3H), 0.78 (t, J = 7.2 Hz, 3H).

Example 275: 1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-4,4-dimethylcyclohexanecarboxylic acid



(Ex. 275)

Intermediate 275a: Methyl 4,4-dimethyl-1-(((6'-(2-trityl-2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)amino)cyclohexanecarboxylate



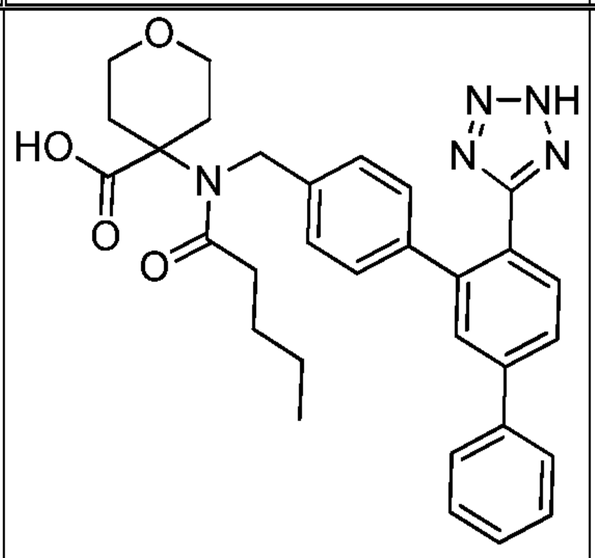
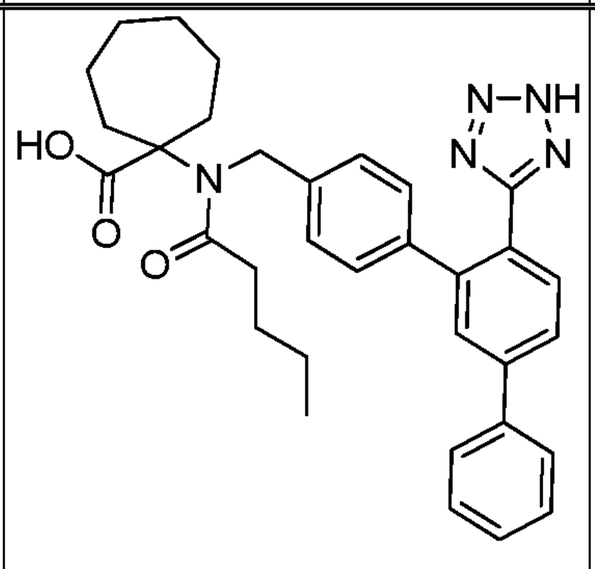
(275a)

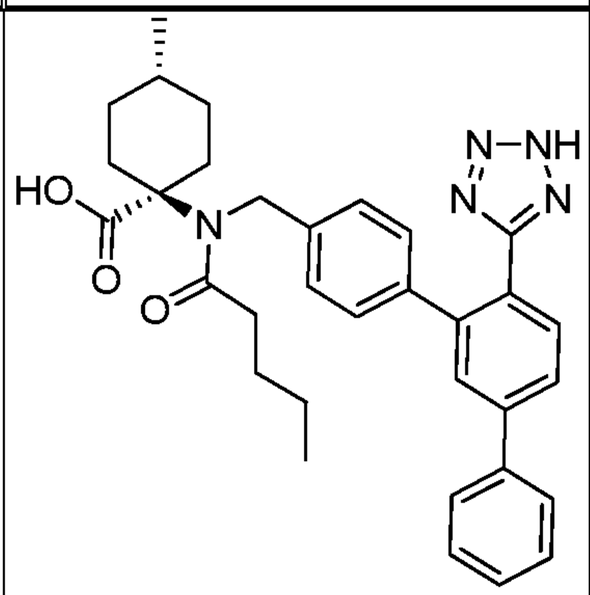
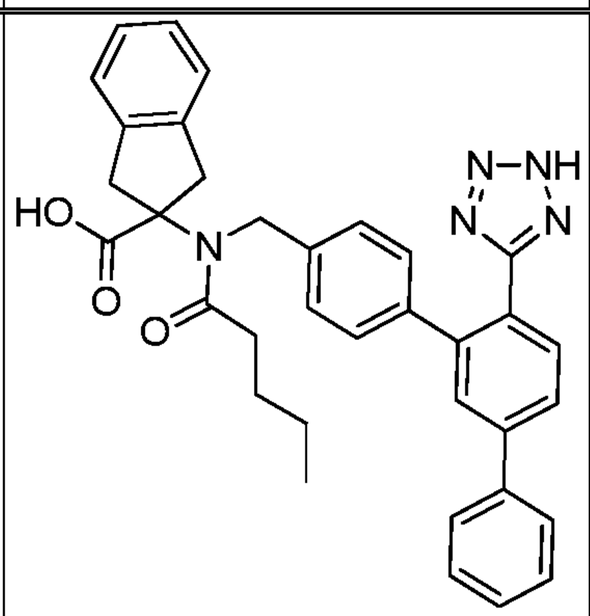
To a solution of **Intermediate I-004**, 0.110 g, 0.174 mmol) in ACN (2.5 mL) was added DIEA (0.121 mL, 0.694 mmol), followed by methyl 1-amino-4,4-dimethylcyclohexanecarboxylate hydrochloride (0.058 g, 0.260 mmol) and sodium iodide (0.130 g, 0.868 mmol) and the mixture was heated at 65°C for 5 h. To the cooled mixture was added H_2O (5 mL) and EtOAc (20 mL) and the organic layer was separated, washed (H_2O brine), dried (anhydrous sodium sulfate), filtered and evaporated. This afforded the title compound as a pale yellow foam (0.130 g) which was used as such in the next step without further purification or characterization.

Example 275: 1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-4,4-dimethylcyclohexanecarboxylic acid

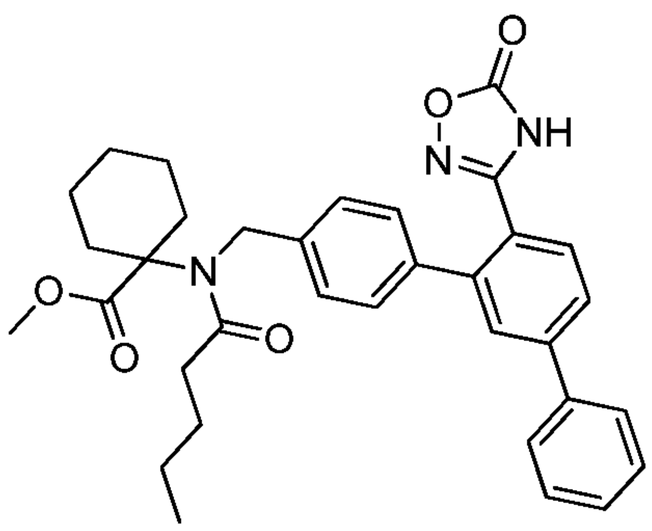
To a solution of **Intermediate 275a** (0.128 g, 0.174 mmol) in anhydrous THF (5 mL) was added sodium hydride (60% w/w in oil, 0.035 g, 0.870 mmol) in one portion and the mixture was stirred for 5 min. Pentanoyl chloride (0.103 mL, 0.870 mmol) was then added and the mixture was stirred at 50°C for 6 h and then at RT for a further 18 h. The resulting mixture was quenched with AcOH (0.100 mL, 1.75 mmol) and then the volatiles were evaporated and the residue was taken up in trifluoroacetic acid (1 ml) to give a clear yellow solution. Triisopropylsilane was then added in 10 µL portions until the color faded to give a pale yellow solution (required approximately 40 µL). The volatiles were again removed under reduced pressure and the residue taken up in DMSO (3 mL) and was submitted to prep LC purification (Method F, TFA as modifier). This afforded the title compound (0.005 g, 0.0083 mmol, 5% yield) as a white solid. LC-MS (Method H): 1.34 min, $[M + H]^+$= 566.1; ^{1}H NMR (DMSO-d_6) δ ppm 7.80 - 7.89 (m, 4H), 7.77 - 7.80 (m, 1H), 7.48 - 7.55 (m, 2H), 7.43 - 7.48 (m, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.68 (s, 2H), 2.21 (t, J = 7.2 Hz, 2H), 1.95 (m, 2H), 1.37 - 1.66 (m, 6H), 1.09 - 1.34 (m, 4H), 0.71 - 0.85 (m, 9H).

The following examples were similarly prepared from the corresponding amino ester or amino ester hydrochloride salt as described for the synthesis of **Example 275** above. Analytical LC-MS injections were used to determine the final purity and the retention time is reported for each compound and is referred as Method A1, Method A2 or Method H.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
276		539.63	540.1; 1.31 min (Method H)	12.29 (br s, 2H), 7.81 - 7.91 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 7.48 - 7.56 (m, 2H), 7.41 - 7.48 (m, 1H), 7.33 - 7.41 (m, 2H), 7.19 - 7.24 (m, 2H), 4.70 (s, 2H), 3.58 - 3.70 (m, 4H), 2.22 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 12.9 Hz, 2H), 1.62 - 1.79 (m, 2H), 1.45 (dt, J = 14.8, 7.3 Hz, 2H), 1.21 (dq, J = 14.8, 7.3 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H).
277		551.69	552.2; 1.41 min (Method H)	11.89 (br s, 2H), 7.76 - 7.87 (m, 4H), 7.73 (d, J = 8.2 Hz, 1H), 7.47 - 7.55 (m, 2H), 7.40 - 7.47 (m, 1H), 7.33 - 7.40 (m, 2H), 7.17 - 7.22 (m, 2H), 4.68 (s, 2H), 2.04 - 2.28 (m, 4H), 1.71 (dd, J = 14.5, 7.8 Hz, 2H), 1.33 - 1.55 (m, 10H), 1.17 (dq, J = 15.0, 7.4 Hz, 2H), 0.78 (t, J = 7.4 Hz, 3H).

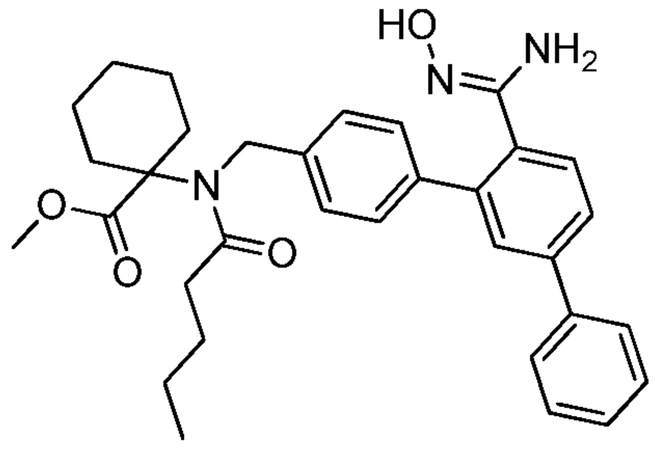
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
278		551.69	552.1; 1.41 min (Method H)	11.91 (br s, 2H), 7.80 - 7.86 (m, 3H), 7.77 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.47 - 7.55 (m, 2H), 7.39 - 7.46 (m, 1H), 7.32 - 7.38 (m, 2H), 7.15 - 7.23 (m, 2H), 4.64 (s, 2H), 2.18 (t, J = 7.0 Hz, 2H), 2.06 (d, J = 11.0 Hz, 2H), 1.38 - 1.52 (m, 6H), 1.31 (m, 3H), 1.12 - 1.25 (m, 2H), 0.72 - 0.86 (m, 6H).
279		571.68	572.1; 1.40 min. (Method H)	12.31 (br s, 2H), 7.77 - 7.85 (m, 3H), 7.68 - 7.77 (m, 2H), 7.46 - 7.55 (m, 2H), 7.38 - 7.46 (m, 1H), 7.27 - 7.36 (m, 2H), 7.16 - 7.23 (m, 2H), 7.07 - 7.16 (m, 4H), 4.60 (s, 2H), 3.62 (d, J = 16.8 Hz, 2H), 3.13 (d, J = 17.2 Hz, 2H), 2.19 (t, J = 7.0 Hz, 2H), 1.45 (dt, J = 14.8, 7.3 Hz, 2H), 1.12 - 1.27 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H).

Example 280: Methyl 1-(N-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(Ex. 280)

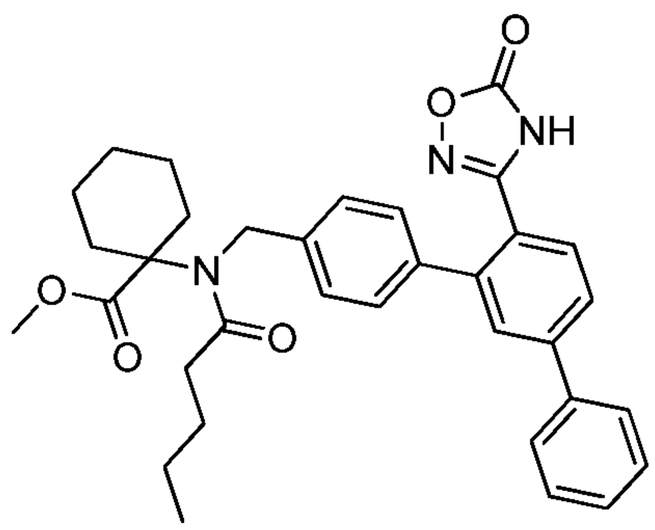
Intermediate 280a: (Z)-Methyl 1-(N-((6'-(N'-hydroxycarbamimidoyl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(280a)

To a solution of methyl 1-(N-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate (prepared from methyl 1-amino-4-cyclohexanecarboxylate according to the method described for the synthesis of **Intermediate 268d**) (0.100 g, 0.197 mmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (0.137 g, 1.97 mmol) and DIEA (0.342 mL, 1.97 mmol). The vessel was sealed and the mixture was heated at 85°C for 20 h. The cooled mixture was evaporated and to the residue was dissolved in dimethyl sulfoxide (2.5 mL) and filtered. The filtrate was submitted to purification by prep LC (Method F, TFA as modifier) to afford the title compound as a white solid (0.074 g, 0.113 mmol, 57% yield). LC-MS (Method H): 1.37 min, $[M + H]^+$= 542.2; ^{1}H NMR (DMSO-d_6) δ ppm 12.60 (br s, 1H), 11.15 (br s, 1H), 9.16 (br s, 1H), 8.98 (br s, 2H), 7.87 (dd, J = 8.0, 1.8 Hz, 1H), 7.78 - 7.85 (m, 3H), 7.70 (d, J = 8.2 Hz, 1H), 7.42 - 7.55 (m, 7H), 4.75 (s, 2H), 3.61 (s, 3H), 2.22 (t, J = 7.0 Hz, 2H), 1.95 - 2.11 (m, 2H), 1.32 - 1.62 (m, 9H), 1.05 - 1.28 (m, 3H), 0.81 (t, J = 7.2 Hz, 3H).

Example 280: Methyl 1-(N-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate

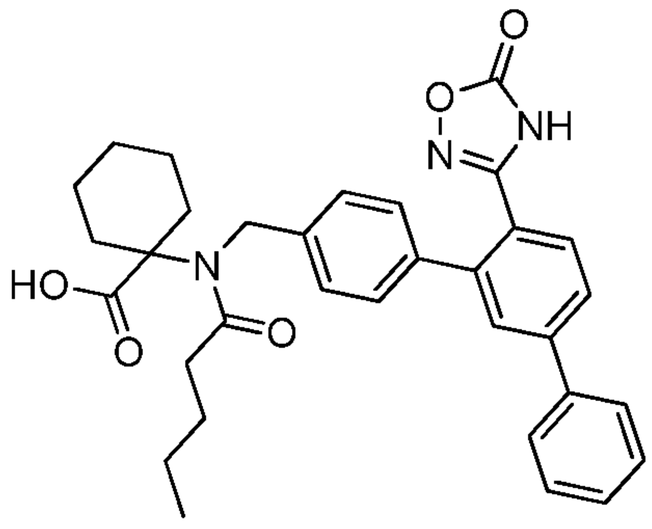


(Ex. 280)

To a solution of **Intermediate 280a** (0.072 g, 0.110 mmol) in THF (5 mL) was added DBU (0.084 g, 0.549 mmol) and N,N'-carbonyldiimidazole (0.089 g, 0.549 mmol) and the mixture was stirred at 50°C for 2 h. The cooled mixture was evaporated and the residue was taken up in DMSO (2.5 mL) and trifluoroacetic acid (0.100 mL) was added.

The solution was submitted to prep LC (Method F, TFA as modifier) to afford the title compound (0.074 g, 0.113 mmol, 57% yield) as a white solid. LC-MS (Method H): 1.46 min, $[M + H]^+$= 568.2; ^{1}H NMR (DMSO-d_6) δ ppm 12.41 (br s. 1H), 7.86 (dd, J = 8.0, 1.8 Hz, 1H), 7.82 (d, J = 7.4 Hz, 2H), 7.79 (d, J = 1.6 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.39 - 7.56 (m, 7H), 4.73 (s, 2H), 3.59 (s, 3H), 2.22 (t, J = 7.2 Hz, 2H), 2.03 (d, J = 7.4 Hz, 2H), 1.33 - 1.63 (m, 9H), 1.03 - 1.29 (m, 3H), 0.80 (t, J = 7.4 Hz, 3H).

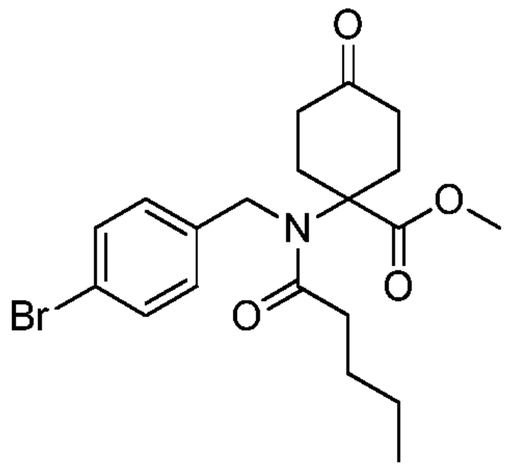
Example 281: 1-(N-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(Ex. 281)

To a solution of **Example 280** (0.025 g, 0.028 mmol) in DMSO (1 mL) was added 2.5M NaOH (0.225 mL, 0.564 mmol) and the mixture was stirred at 75°C for 18 h. To the cooled mixture was added trifluoroacetic acid (0.100 mL) and the solution was purified by prep LC (Method F, TFA as modifier) to afford the title compound (0.009 g, 0.016 mmol, 57% yield) as a white solid. LC-MS (Method H): 1.39 min, $[M + H]^+$= 554.2; ^{1}H NMR (DMSO-d_6) δ ppm 12.41 (s, 1H), 7.72 - 7.89 (m, 5H), 7.47 - 7.55 (m, 4H), 7.39 - 7.47 (m, 3H), 4.72 (s, 2H), 2.21 (t, J = 7.0 Hz, 2H), 1.96 - 2.14 (m, 2H), 1.32 - 1.71 (m, 9H), 1.00 - 1.28 (m, 3H), 0.79 (t, J = 7.4 Hz, 3H).

Intermediate 282a: Methyl 1-(N-(4-bromobenzyl)pentanamido)-4-oxocyclohexane-carboxylate

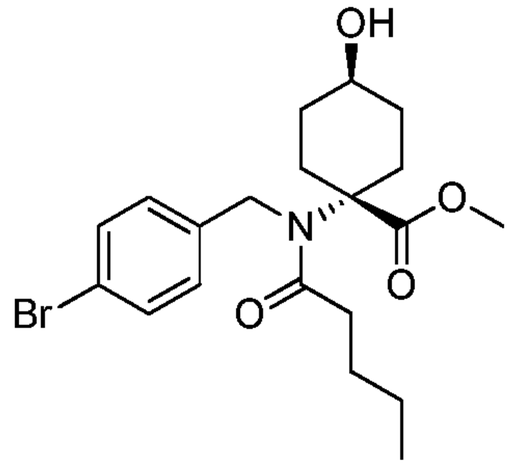


(282a)

The title compound was prepared as an orange crystalline solid from methyl 1-amino-4-oxocyclohexanecarboxylate, according to the method described for the synthesis of

Intermediate 268b. LC-MS (Method H): 1.31 min, $[M + H]^+$= 424.0; ^{1}H NMR ($CDCl_3$) δ ppm 7.50 - 7.56 (m, 2H), 7.29 (m, 2H), 4.56 (s, 2H), 3.82 (s, 3H), 2.70 (ddd, J = 16.0, 12.9, 6.3 Hz, 2H), 2.48 - 2.62 (m, 2H), 2.22 - 2.33 (m, 4H), 1.87 (td, J = 13.1, 5.5 Hz, 2H), 1.55 - 1.68 (m, 2H), 1.22 - 1.36 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H).

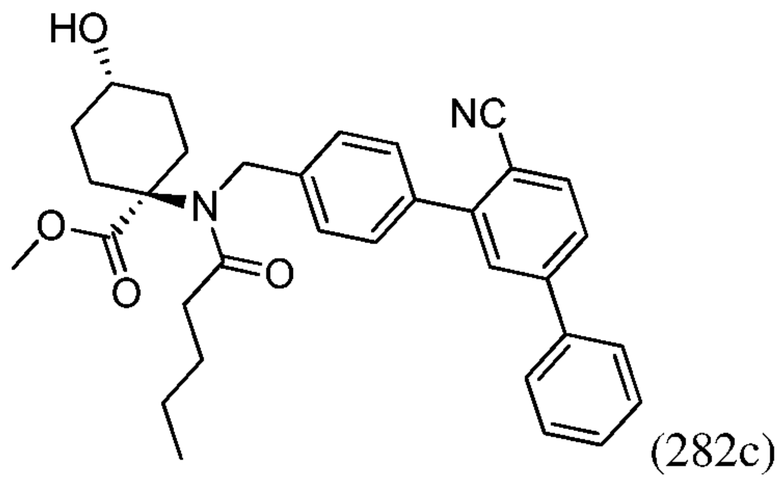
Intermediate 282b: (1R,4R)-Methyl 1-(N-(4-bromobenzyl)pentanamido)-4-hydroxycyclohexanecarboxylate



(282b)

To an ice-cold mixture of **Intermediate 282a** (0.300 g, 0.707 mmol) in ethanol (10 mL) was added sodium borohydride (0.080 g, 2.12 mmol) and the resulting mixture was stirred for 30 min. The reaction mixture was then quenched with H_2O (2 mL) and 2M HCl (2 mL) and stirring was continued for 5 min. The resulting mixture was partitioned with H_2O (50 mL) and tert-butylmethyl ether (50 mL) and the aqueous layer was separated and re-extracted with tert-butylmethyl ether (25 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography (25 g ISCO-type column, eluting with 0 to 35% acetone/hexane) to give the title compound (0.280 g, 0.657 mmol, 93% yield) as a clear, colorless gum. LC-MS (Method H): 1.30 min, $[M + H]^+$= 426.0; ^{1}H NMR ($CDCl_3$) δ ppm 7.48 - 7.55 (m, 2H), 7.29 (d, J = 8.6 Hz, 2H), 4.53 (s, 2H), 3.77 (s, 3H), 3.46 - 3.57 (m, 1H), 2.30 (d, J = 12.1 Hz, 2H), 2.23 (t, J = 7.2 Hz, 2H), 1.77 - 1.89 (m, 2H), 1.63 - 1.77 (m, 2H), 1.52 - 1.63 (m, 2H), 1.46 (dt, J = 13.3, 3.9 Hz, 3H), 1.19 - 1.33 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H).

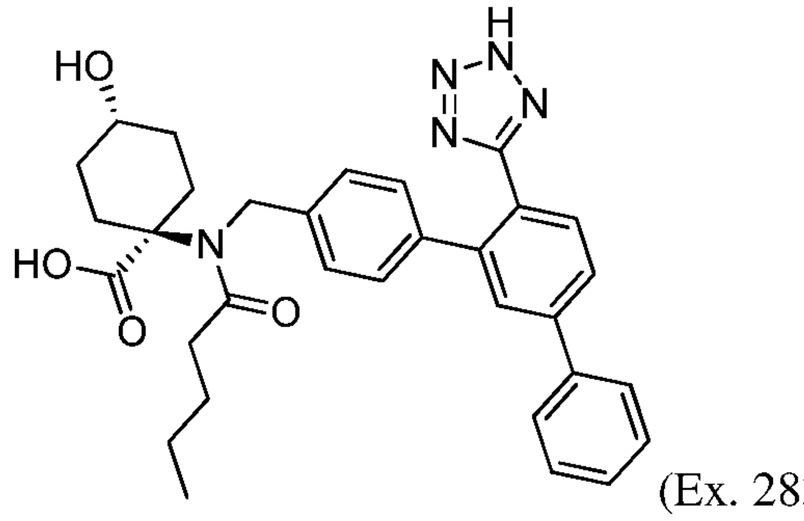
Intermediate 282c: (1R,4R)-Methyl 1-(N-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-hydroxycyclohexanecarboxylate



(282c)

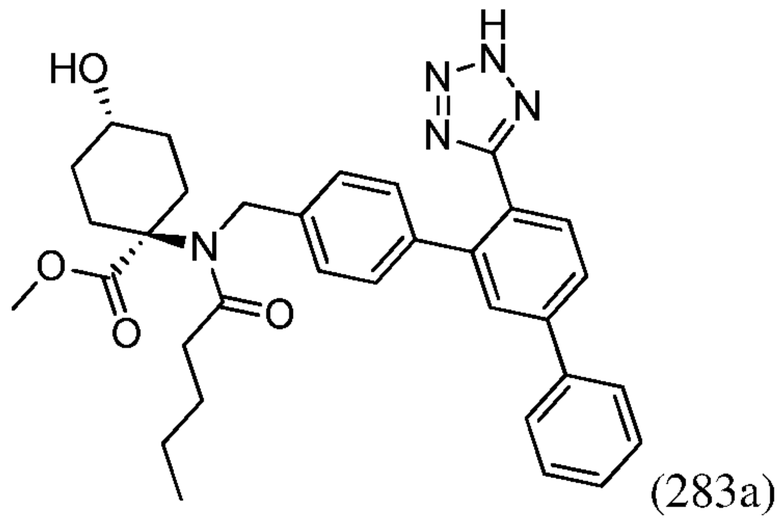
Intermediate 282c was prepared from **Intermediate 282b** as an off white solid, according to the procedure described for the synthesis of **Intermediate 268d**. LC-MS (Method H): 1.39 min, $[M + H]^+$= 525.2; ^{1}H NMR (DMSO-d_6) δ ppm 8.03 (d, J = 8.2 Hz, 1H), 7.81 - 7.92 (m, 3H), 7.72 (d, J = 8.2 Hz, 2H), 7.42 - 7.67 (m, 6H), 4.76 (s, 2H), 4.53 (d, J = 4.3 Hz, 1H), 3.62 (s, 3H), 3.34 - 3.47 (m, 1H), 2.23 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 11.3 Hz, 2H), 1.54 - 1.67 (m, 3H), 1.39 - 1.54 (m, 3H), 1.09 - 1.36 (m, 4H), 0.77 - 0.82 (m, 2H).

Example 283: (1R,4R)-1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-pentanamido)-4-hydroxycyclohexanecarboxylic acid



(Ex. 283)

Intermediate 283a: (1R,4R)-Methyl 1-(N-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-hydroxycyclohexanecarboxylate



(283a)

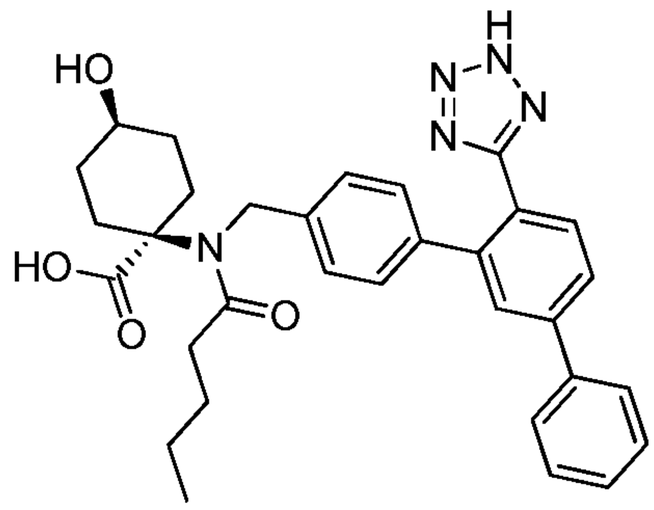
To a vial containing **Intermediate 282c** (0.080 g, 0.152 mmol) in toluene (3 mL) was added azidotrimethylsilane (0.161 mL, 1.22 mmol) and dibutyltin oxide (0.038 g, 0.152 mmol). The reaction vessel was sealed and the mixture was heated at 110°C for 18 h. The

cooled mixture was evaporated and the residue was taken up in a mixture of DMSO (2.5 mL) and trifluoroacetic acid (0.100 mL). Purification by prep LC (Method F, TFA as modifier) afforded the title compound (0.050 g, 0.088 mmol, 57% yield) as a white solid. LC-MS (Method H): 1.31 min, [M-H]= 566.2.

Example 283: (1R,4R)-1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-4-hydroxycyclohexanecarboxylic acid

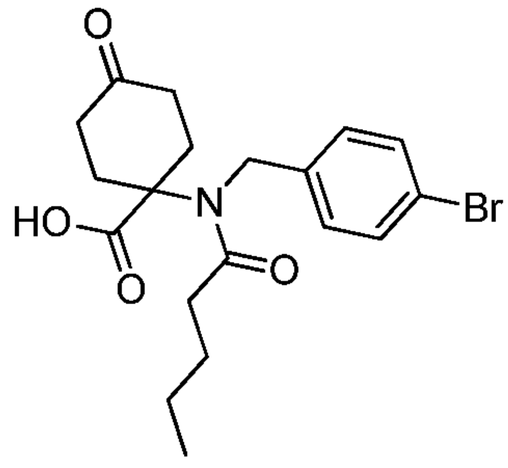
To a solution of **Intermediate 283a** (0.030 g, 0.053 mmol) in THF (3 mL) was added potassium trimethylsilanolate (0.068 g, 0.528 mmol) and the mixture was stirred at RT for 18 h. Formic acid (0.100 mL) was then added, the volatiles were evaporated and the residue was dissolved in DMSO (3 mL). Purification by prep LC (Method F, TFA as modifier) afforded the title compound (0.008 g, 0.014 mmol, 27% yield) as a white solid. LC-MS (Method H): 1.30 min, [M-H]= 554.2; ^{1}H NMR (15% v/v acetone-d_6 / $CDCl_3$) δ ppm 7.76 (d, J = 7.8 Hz, 1H), 7.49 - 7.64 (m, 3H), 7.30 - 7.38 (m, 2H), 7.20 - 7.30 (m, 4H), 7.09 (d, J = 7.0 Hz, 2H), 4.49 (s, 1H), 3.32 - 3.46 (m, 1H), 2.07 - 2.28 (m, 3H), 1.98 (d quint, J = 4.3, 2.2 Hz, 4H), 1.66 (m, 3H), 1.28 - 1.52 (m, 3H), 1.06 - 1.20 (m, 2H), 0.70 (t, J = 7.4 Hz, 3H).

Example 284: (1S,4S)-1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-hydroxycyclohexanecarboxylic acid



(Ex. 284)

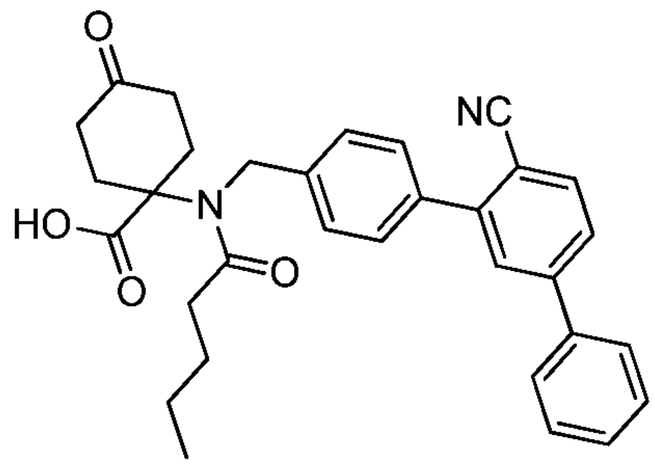
Intermediate 284a: 1-(N-(4-Bromobenzyl)pentanamido)-4-oxocyclohexanecarboxylic acid



(284a)

A solution of **Intermediate 282a** (0.300 g, 0.707 mmol) in DCM (10 mL) was cooled at 0°C and iodotrimethylsilane (0.300 mL, 2.12 ml) was added in one portion. The mixture was then allowed to warm to RT with stirring for 2 h. This mixture was then added to a well-stirred mixture of ACN (10 mL) and 1M HCl and stirring was continued for 30 min. The volatiles were then evaporated and the residue was taken up in DMSO (10 mL) and formic acid (0.200 mL) was added. Purification by prep LC (Method F, formic acid as modifier) afforded the title compound (0.251 g, 0.621 mmol, 87% yield) as a white solid. LC-MS (Method H): 1.29 min, [M-H]= 410.1.

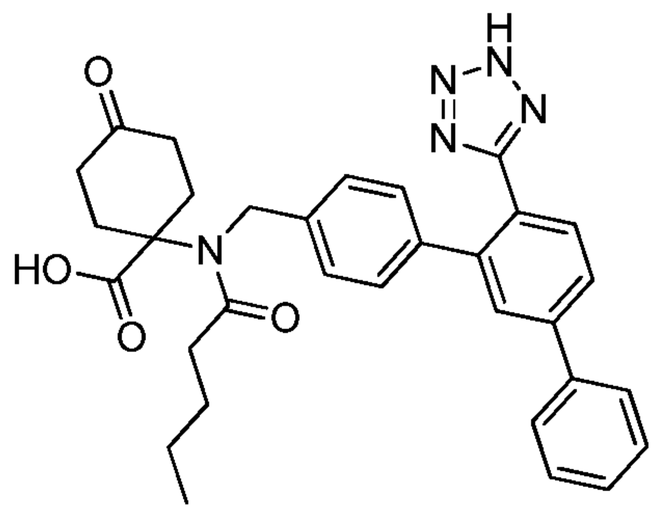
Intermediate 284b: 1-(N-((6'-Cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-oxocyclohexanecarboxylic acid



(284b)

The title compound was prepared from **Intermediate 284a**, according to the method described for the synthesis of **Intermediate 268d**, and was isolated as an off-white solid. LC-MS (Method H): 1.39 min, $[M + H]^+$= 509.2; ^{1}H NMR (DMSO-d_6) δ ppm 12.49 (br s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.80 - 7.92 (m, 4H), 7.72 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.41 - 7.56 (m, 3H), 4.82 (s, 2H), 2.43 - 2.57 (m, 2H), 2.15 - 2.36 (m, 6H), 1.96 - 2.15 (m, 2H), 1.48 (quint, J = 7.3 Hz, 2H), 1.23 (dq, J = 15.0, 7.4 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H).

Intermediate 284c: 1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-oxocyclohexanecarboxylic acid



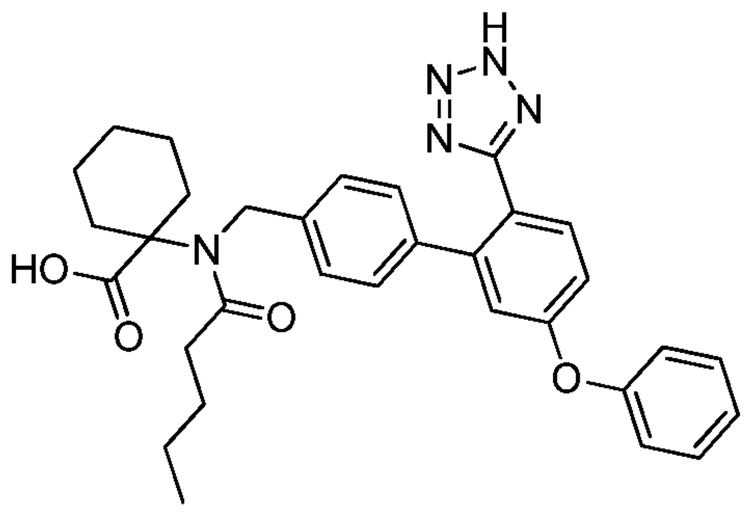
(284c)

The title compound was prepared from **Intermediate 284b** according to the method described for the synthesis of **Intermediate 283a** and was isolated as an off-white solid. LC-MS (Method H): 1.32 min, $[M + H]^+$= 552.2; ^{1}H NMR ($CDCl_3$) δ ppm 8.03 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.53 - 7.64 (m, 3H), 7.36 - 7.47 (m, 3H), 7.28 - 7.34 (m, 2H), 7.00 - 7.10 (m, 2H), 4.65 (br s, 2H), 2.79 (m, 2H), 2.53 (m, 2H), 2.22 - 2.44 (m, 4H), 1.96 (dd, J = 12.3, 8.0 Hz, 2H), 1.62 (dt, J = 15.2, 7.5 Hz, 2H), 1.20 - 1.37 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H).

Example 284: (1S,4S)-1-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-4-hydroxycyclohexanecarboxylic acid

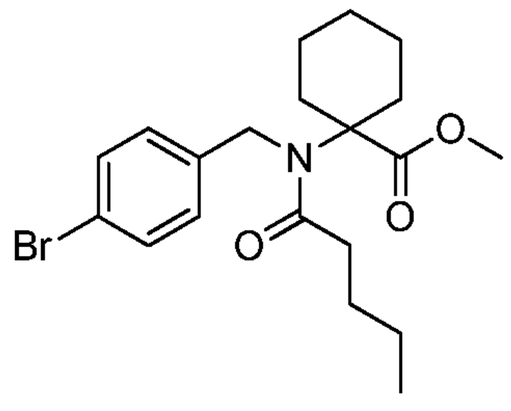
A solution of **Intermediate 284c** (0.030 g, 0.054 mmol) in dry THF (6 mL) was cooled at -78°C under N_2. To this mixture was added a solution of L-Selectride (1M in THF, 0.272 mL, 0.272 mmol) and stirring was continued at the same temperature for 30 min. The reaction was quenched by the addition of AcOH (0.100 mL) and the reaction was allowed to warm to RT. The volatiles were then removed under reduced pressure and the residue was taken up in DMSO (2 mL). This solution was submitted to purification by prep LC (Method F, formic acid as modifier) to afford the title compound (0.021 g, 0.038 mmol, 69% yield) as a white solid. LC-MS (Method H): 1.29 min, [M-H]= 554.1. ^{1}H NMR (DMSO-d_6) δ ppm 11.97 (br s, 2H), 7.76 - 7.86 (m, 3H), 7.67 - 7.76 (m, 2H), 7.46 - 7.55 (m, 2H), 7.30 - 7.46 (m, 3H), 7.20 (dd, J = 8.2, 2.7 Hz, 2H), 4.63 (d, J = 7.0 Hz, 2H), 4.49 (br s, 0.5H), 3.73 (br s, 0.5H), 2.11 - 2.25 (m, 2H), 1.95 - 2.11 (m, 1H), 1.67 - 1.90 (m, 2H), 1.38 - 1.67 (m, 7H), 1.08 - 1.32 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H).

Example 285: 1-(N-((5'-Phenoxy-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(Ex. 285)

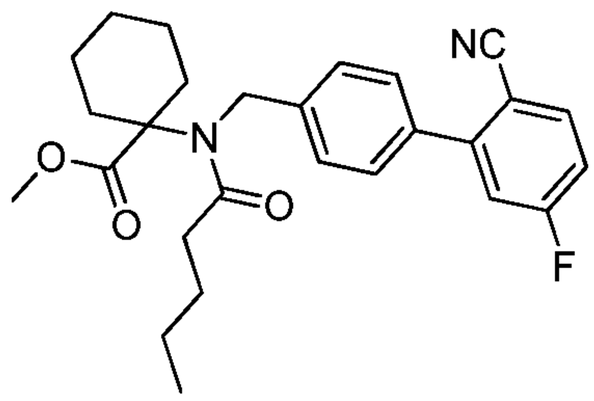
Intermediate 285a: Methyl 1-(N-(4-bromobenzyl)pentanamido)cyclohexanecarboxylate



(285a)

The title compound was prepared from methyl 1-amino-cyclohexanecarboxylate according to the method described for the synthesis of **Intermediate 268b** and was isolated as an orange crystalline solid. LC-MS (Method H): 1.43 min, $[M + H]^+$= 410.0; ^{1}H NMR (DMSO-d_6) δ ppm 7.50 - 7.64 (m, 2H), 7.27 - 7.42 (m, 2H), 4.64 (s, 2H), 3.58 (s, 3H), 2.17 (t, J = 7.0 Hz, 2H), 1.97 (d, J = 10.2 Hz, 2H), 1.32 - 1.61 (m, 8H), 1.17 (dt, J = 14.9, 7.4 Hz, 4H), 0.78 (t, J = 7.2 Hz, 3H).

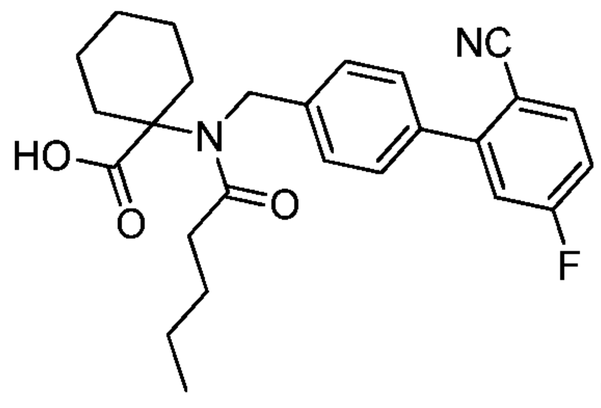
Intermediate 285b: Methyl 1-(N-((2'-cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(285b)

The title compound was prepared by the reaction **Intermediate 285a** (0.500 g, 1.22 mmol) with 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (0.602 g, 2.44 mmol), according to the method described for the synthesis of **Intermediate 330b**, to give a white solid (0.472 g, 1.05 mmol, 86% yield). HRMS (ESI): Calcd for $C_{27}H_{32}FN_2O_3$ $[M + H]^+$ *m/z* 451.2391; found 451.2416. ^{1}H NMR ($CDCl_3$) δ ppm 7.79 (dd, J = 8.6, 5.5 Hz, 1H), 7.52 - 7.62 (m, 4H), 7.23 - 7.27 (m, 1H), 7.17 (td, J = 8.2, 2.7 Hz, 1H), 4.69 (s, 2H), 3.78 (s, 3H), 2.18 - 2.35 (m, 4H), 1.51 - 1.80 (m, 8H), 1.43 (td, J = 12.8, 4.1 Hz, 2H), 1.29 (dq, J = 15.2, 7.5 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H).

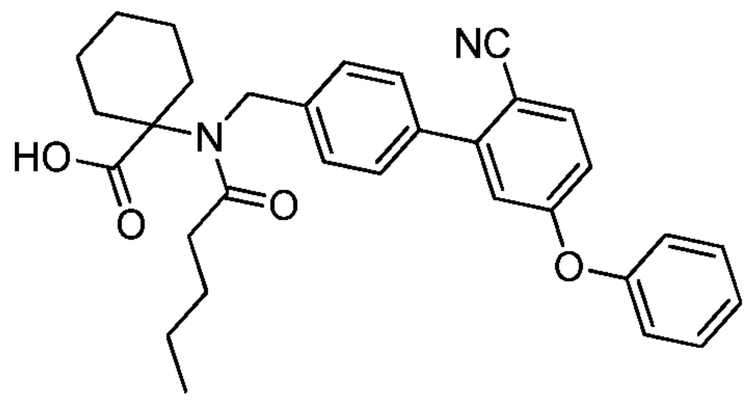
Intermediate 285c: 1-(N-((2'-Cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(285c)

The title compound was prepared from **Intermediate 285b** according to the method described for the synthesis of **Intermediate 284a** and was isolated as an off white solid. LC-MS (Method H): 1.37 min, [M-H]= 435.1; ^{1}H NMR (DMSO-d_6) δ ppm 12.01 (br s, 1H), 8.06 (dd, J = 8.6, 5.5 Hz, 1H), 7.54 - 7.68 (m, 5H), 7.46 (td, J = 8.4, 2.7 Hz, 1H), 4.75 (s, 2H), 2.21 (t, J = 7.0 Hz, 2H), 2.06 (d, J = 11.3 Hz, 2H), 1.35 - 1.61 (m, 8H), 1.02 - 1.27 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H).

Intermediate 285d: 1-(N-((2'-Cyano-5'-phenoxy-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(285d)

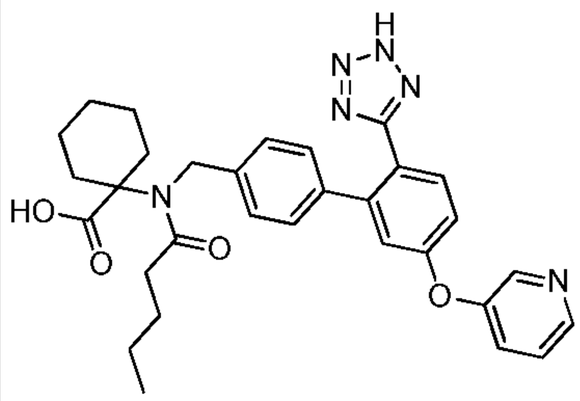
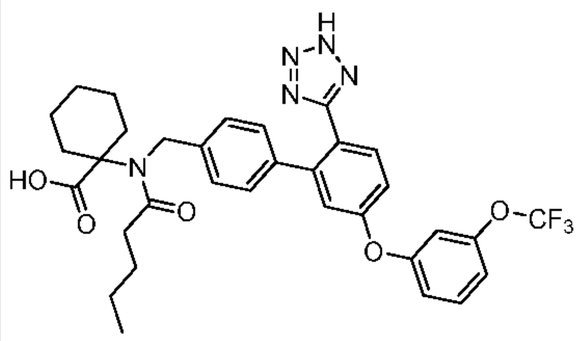
The title compound was prepared from **Intermediate 285c**, according to the method described for the synthesis of **Intermediate 330c** and was isolated as an off-white solid. LC-MS (Method H): 1.37 min, [M-H]= 509.1; ^{1}H NMR (DMSO-d_6) δ ppm 11.98 (br s, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.52 - 7.62 (m, 4H), 7.44 - 7.52 (m, 2H), 7.24 - 7.32 (m, 1H), 7.16 - 7.24 (m, 2H), 7.13 (d, J = 2.7 Hz, 1H), 7.06 (dd, J = 8.6, 2.3 Hz, 1H), 4.73 (s, 2H), 2.19 (t, J = 7.0 Hz, 2H), 2.05 (d, J = 11.7 Hz, 2H), 1.34 - 1.60 (m, 9H), 1.01 - 1.27 (m, 3H), 0.77 (t, J = 7.4 Hz, 3H).

Example 285: 1-(N-((5'-Phenoxy-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid

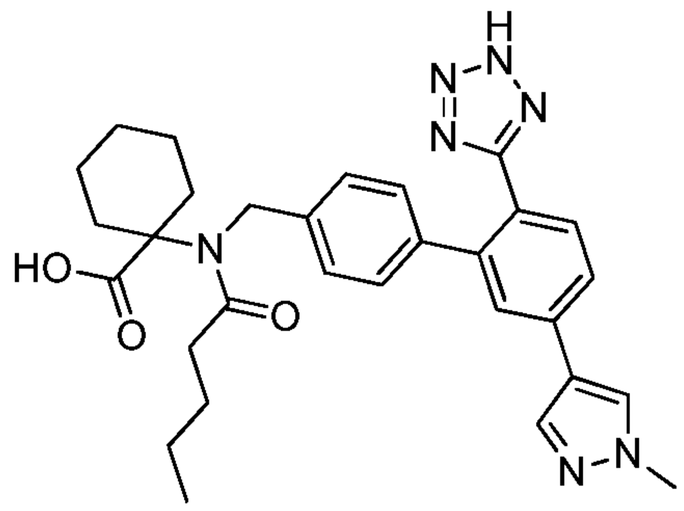
The title compound was prepared from **Intermediate 285d**, according to the method described for the synthesis of **Intermediate 283a** and was isolated as an off-white solid. LC-MS (Method H): 1.60 min, [M-H]= 552.1; ^{1}H NMR (DMSO-d_6) δ ppm 11.91 (br s, 2H), 7.65 (d, J = 8.6 Hz, 1H), 7.40 - 7.52 (m, 2H), 7.28 - 7.38 (m, 2H), 7.21 - 7.26 (m, 1H), 7.16 - 7.21 (m, 2H), 7.09 - 7.15 (m, 2H), 7.04 - 7.09 (m, 2H), 4.63 (s, 2H), 2.14 (t, J

= 7.0 Hz, 2H), 2.01 (d, J = 11.7 Hz, 2H), 1.34 - 1.64 (m, 9H), 0.98 - 1.24 (m, 3H), 0.76 (t, J = 7.4 Hz, 3H).

The following examples were similarly prepared from the appropriate phenol or hydroxypyridine, as described for the synthesis of **Example 285** above. Analytical LC-MS injections were used to determine the final purity and the retention time is reported for each compound and the method used is referred to as Method A1, Method A2 or Method H.

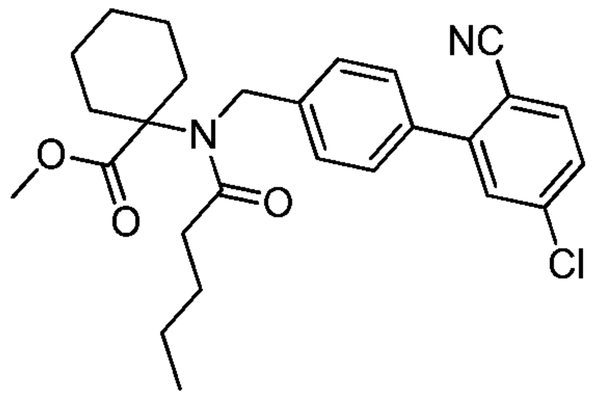
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
286		554.65	555.2; 1.29 min (Method H)	11.91 (br s, 2H), 8.53 (d, J = 2.7 Hz, 1H), 8.45 (dd, J = 4.7, 1.2 Hz, 1H), 7.58 - 7.73 (m, 2H), 7.50 (dd, J = 8.2, 4.7 Hz, 1H), 7.28 - 7.40 (m, 2H), 7.14 - 7.25 (m, 2H), 7.02 - 7.14 (m, 2H), 4.63 (s, 2H), 2.14 (t, J = 7.0 Hz, 2H), 2.01 (d, J = 11.3 Hz, 2H), 1.30 - 1.68 (m, 6H), 1.03 - 1.22 (m, 3H), 0.77 (t, J = 7.2 Hz, 3H).
287		637.66	638.1; 1.47 min (Method H)	11.92 (br s, 2H), 7.70 (d, J = 8.2 Hz, 1H), 7.54 - 7.62 (m, 1H), 7.31 - 7.38 (m, 2H), 7.16 - 7.26 (m, 5H), 7.04 - 7.11 (m, 2H), 4.63 (s, 2H), 2.14 (t, J = 7.2 Hz, 2H), 2.02 (d, J = 12.1 Hz, 2H), 1.31 - 1.67 (m, 9H), 1.00 - 1.22 (m, 3H), 0.77 (t, J = 7.2 Hz, 3H).

Example 288: 1-(N-((5'-(1-Methyl-1H-pyrazol-4-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(Ex. 288)

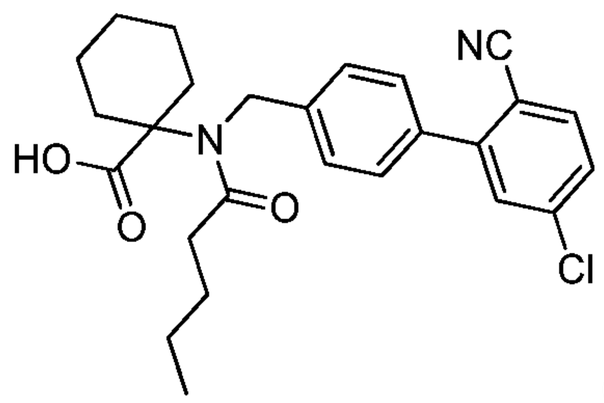
Intermediate 288a: Methyl 1-(N-((5'-chloro-2'-cyano-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(288a)

The title compound was prepared by the reaction of **Intermediate 285a** 0.800 g, 1.95 mmol) with 4-chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile (0.973 g, 3.90 mmol), according to the method described for the synthesis of **Intermediate 330b** and was isolated as a white solid (0.440 g, 0.942 mmol, 48% yield). HRMS (ESI): Calcd for $C_{27}H_{32}ClN_2O_3$ $[M + H]^+$ *m/z* 467.2096; found 467.2110. ^{1}H NMR ($CDCl_3$) δ ppm 7.72 (d, J = 8.2 Hz, 1H), 7.58 (m, 4H), 7.55 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 8.4, 2.2 Hz, 1H), 4.69 (s, 2H), 3.78 (s, 3H), 2.21 - 2.33 (m, 4H), 1.51 - 1.77 (m, 8H), 1.43 (td, J = 12.7, 4.3 Hz, 2H), 1.23 - 1.36 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H).

Intermediate 288b: 1-(N-((5'-Chloro-2'-cyano-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid

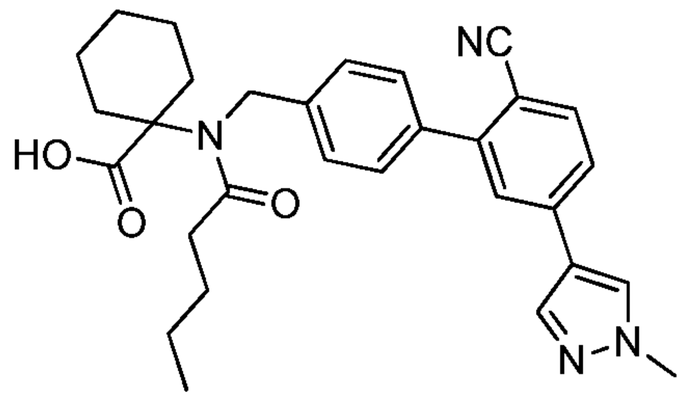


(288b)

The title compound was prepared from **Intermediate 288a** according to the method described for the synthesis of **Intermediate 284a** and was isolated as an off white solid. LC-MS (Method H): 1.37 min, [M-H]= 451.0; ^{1}H NMR (DMSO-d_6) δ ppm 11.99 (br s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.53 - 7.71 (m, 5H), 4.76 (s, 2H),

2.21 (t, J = 7.0 Hz, 2H), 2.06 (d, J = 11.3 Hz, 2H), 1.30 - 1.61 (m, 9H), 1.01 - 1.30 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H).

Intermediate 288c: 1-(N-((2'-Cyano-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(288c)

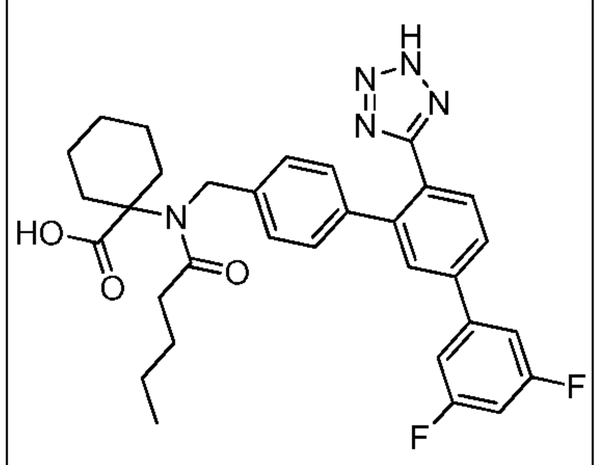
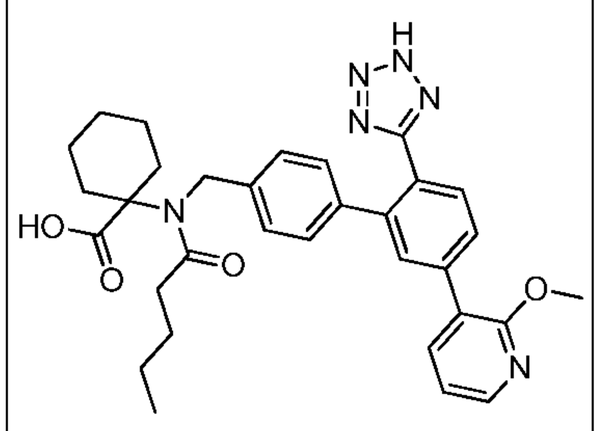
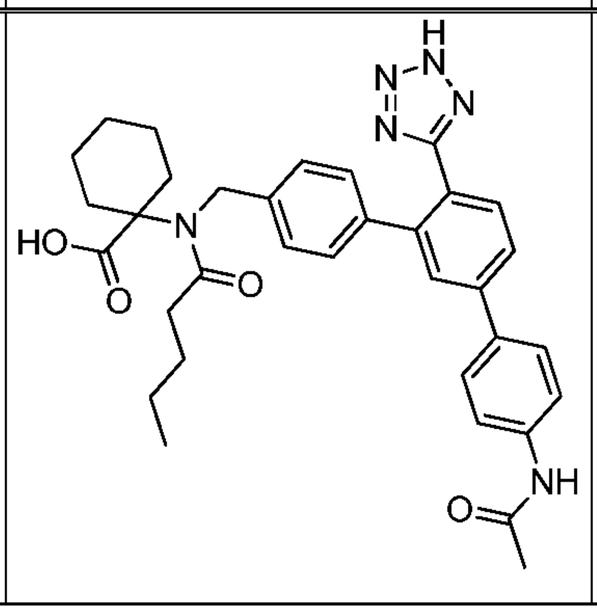
To a solution of **Intermediate 288b** (0.044 g, 0.088 mmol) in 10% v/v ethanol/toluene (3 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.055 g, 0.265 mmol) and 2M potassium phosphate (0.066 mL, 0.132 mmol). This stirred mixture was purged with a stream of N_2 for 15 min. Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.006 g, 0.0088 mmol) was then added and the mixture stirred at 100°C for 3 h. The cooled reaction mixture was evaporated, the residue was taken up in DMSO (3.5 mL) and the mixture was filtered and the filtrate purified by prep LC (Method F, formic acid as modifier) to afford the title compound as a white solid (0.037 g, 0.074 mmol, 84% yield). LC-MS (Method H): 1.29 min, [M-H]= 497.1; HRMS (ESI): Calcd for $C_{30}H_{35}N_4O_3$ $[M + H]^+$ *m/z* 499.2704; found 499.2707.

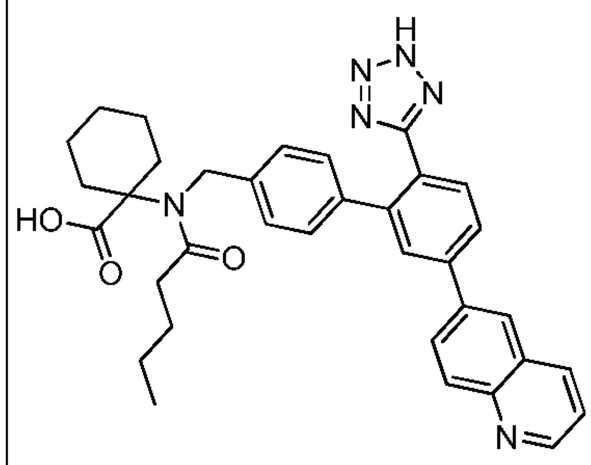
Example 288: 1-(N-((5'-(1-Methyl-1H-pyrazol-4-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid

The title compound was prepared from **Intermediate 288c** according to the method described for the synthesis of **Intermediate 283a** and was isolated as a white solid. LC-MS (Method H): 1.26 min, [M-H]= 540.1; ^{1}H NMR (DMSO-d_6) δ ppm 11.48 (s, 2H), 8.36 (s, 1H), 8.05 (s, 1H), 7.70 - 7.79 (m, 2H), 7.62 (d, J = 8.6 Hz, 1H), 7.31 - 7.42 (m, 2H), 7.08 - 7.19 (m, 2H), 4.66 (s, 2H), 3.88 (s, 3H), 2.18 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 12.1 Hz, 2H), 1.34 - 1.75 (m, 9H), 1.12 - 1.27 (m, 3H), 0.80 (t, J = 7.2 Hz, 3H).

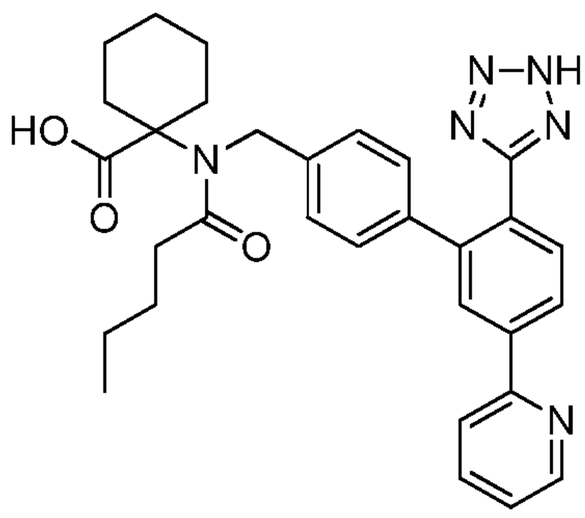
The following examples were similarly prepared from the appropriate boronic acids or boronate esters, as described for the synthesis of **Example 288** above. Analytical LC-MS

injections were used to determine the final purity, the retention time is reported for each compound and the method used is referred to as Method A1, Method A2 or Method H.

Ex	Structure	MW	LC-MS *m/z* [M-H]$^-$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
289		573.64	572.0; 1.41 min (Method H)	11.92 (br s, 2H), 7.91 - 7.96 (m, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.62 - 7.72 (m, 2H), 7.35 - 7.41 (m, 2H), 7.31 (tt, J = 9.3, 2.2 Hz, 1H), 7.17 - 7.24 (m, 2H), 4.66 (s, 2H), 2.18 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 11.7 Hz, 2H), 1.32 - 1.72 (m, 9H), 1.00 - 1.30 (m, 3H), 0.79 (t, J = 7.4 Hz, 3H).
290		568.67	567.2; 1.33 min (Method H)	11.92 (s, 2H), 8.24 (dd, J = 5.1, 2.0 Hz, 1H), 7.94 (dd, J = 7.2, 1.8 Hz, 1H), 7.73 - 7.78 (m, 1H), 7.66 - 7.73 (m, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.10 - 7.19 (m, 3H), 4.65 (s, 2H), 3.92 (s, 3H), 2.17 (t, J = 7.0 Hz, 2H), 2.03 (d, J = 12.1 Hz, 2H), 1.30 - 1.73 (m, 9H), 1.01 - 1.30 (m, 3H), 0.78 (t, J = 7.2 Hz, 3H).
291		594.71	593.1; 1.28 min (Method H)	11.92 (br s, 2H), 10.08 (s, 1H), 7.81 - 7.86 (m, 1H), 7.80 - 7.81 (m, 1H), 7.76 - 7.80 (m, 2H), 7.67 - 7.75 (m, 3H), 7.32 - 7.42 (m, 2H), 7.12 - 7.24 (m, 2H), 4.66 (s, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.07 (s, 3H), 2.03 (d, J = 12.1 Hz, 2H), 1.32 - 1.73 (m, 9H), 1.02 - 1.32 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H).

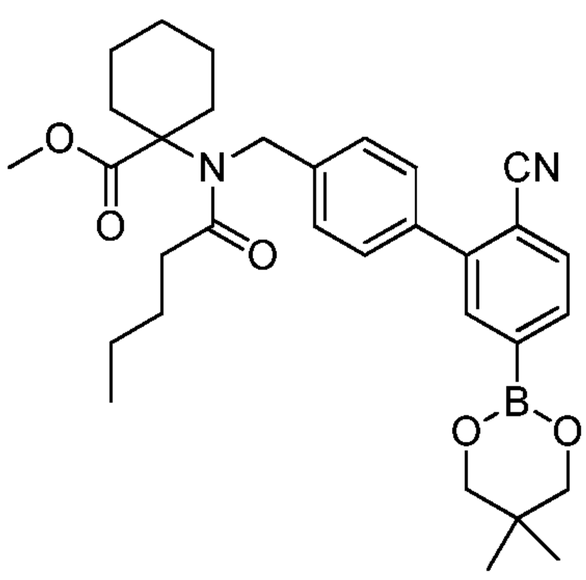
Ex	Structure	MW	LC-MS *m/z* [M-H]$^-$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
292			587.2; 1.340 min. (Method H)	11.94 (br s, 2H), 8.94 (dd, J = 4.3, 1.6 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.47 (d, J = 7.4 Hz, 1H), 8.27 (dd, J = 9.0, 2.0 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.03 (dd, J = 7.8, 1.6 Hz, 1H), 7.99 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 8.2, 3.9 Hz, 1H), 7.35 - 7.45 (m, 2H), 7.18 - 7.29 (m, 2H), 4.67 (s, 2H), 2.19 (t, J = 7.0 Hz, 2H), 2.03 (d, J = 12.1 Hz, 2H), 1.36 - 1.71 (m, 9H), 1.04 - 1.33 (m, 3H), 0.80 (t, J = 7.4 Hz, 3H).

Example 293: 1-(N-((5'-(Pyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(Ex. 293)

Intermediate 293a: Methyl 1-(N-((2'-cyano-5'-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate

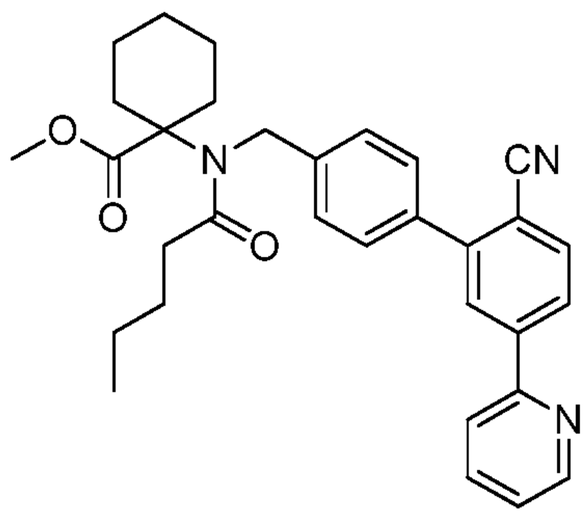


(293a)

In a 20 mL pressure vial containing **Intermediate 288a** (0.700 g, 1.50 mmol) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane (1.016 g, 4.50 mmol) was added 1,4-

dioxane (15 mL), KOAc (0.446 g, 4.50 mmol) and chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium (II) (0.236 g, 0.300 mmol). The stirred mixture was purged with a stream of N_2 for 15 min and then it was heated at 85°C for 1.5 h. The cooled mixture was partitioned with H_2O (25 mL) and EtOAc (50 mL) and the organic phase was separated, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography using a 12 g ISCO-type column and eluting with 20 to 50% EtOAc/hexane to give the title compound (0.620 g, 1.14 mmol, 76% yield) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ ppm 7.95 (s, 1H), 7.85 (dd, J = 7.6, 1.0 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.59 - 7.63 (m, 2H), 7.50 - 7.55 (m, 2H), 4.68 (s, 2H), 3.80 (s, 4H), 3.78 (s, 3H), 2.29 (m, 4H), 1.57 - 1.76 (m, 7H), 1.43 (td, J = 12.9, 3.9 Hz, 2H), 1.25 - 1.34 (m, 3H), 1.04 (s, 6H), 0.88 (t, J = 7.4 Hz, 3H).

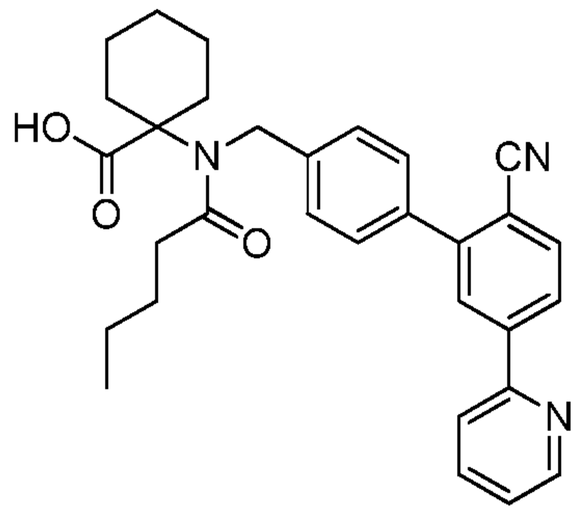
Intermediate 293b: Methyl 1-(N-((2'-cyano-5'-(pyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(293b)

To a mixture of **Intermediate 293a** (0.075 g, 0.138 mmol) in 20% v/v ethanol/toluene (3 mL) was added 2-bromopyridine (0.039 mL, 0.413 mmol) and 2M potassium phosphate (0.138 mL, 0.275 mmol). This stirred mixture was purged with a stream of N_2 for 15 min and then chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.011 g, 0.014 mmol) was added and the mixture was stirred at 100°C for 2 h. The cooled reaction mixture was evaporated and the residue was taken up in DMSO (3.5 mL). Purification by prep LC (Method F, formic acid as modifier) afforded the title compound (26 mg, 0.051 mmol, 37% yield) as a white solid. LC-MS (Method H): 1.40 min, $[M + H]^+$= 510.2; HRMS (ESI): Calcd for $C_{32}H_{36}N_3O_3$ $[M + H]^+$ *m/z* 510.2751; found 510.2765.

Intermediate 293c: 1-(N-((2'-Cyano-5'-(pyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(293c)

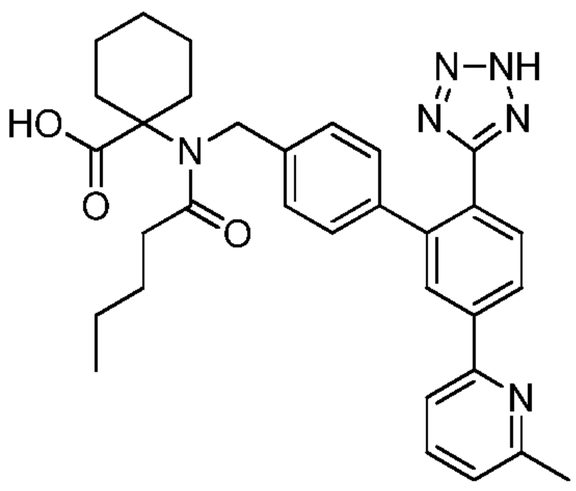
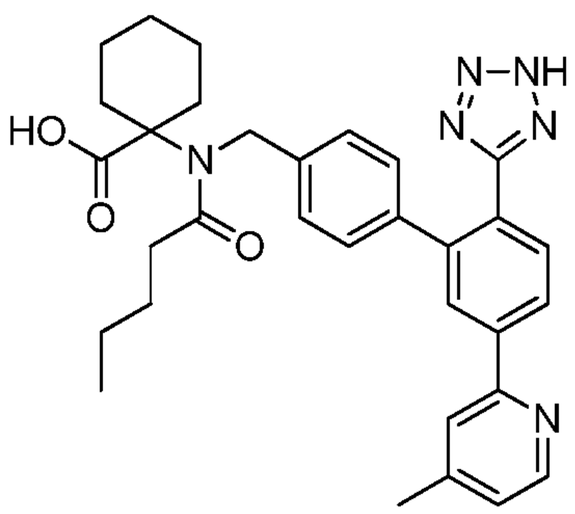
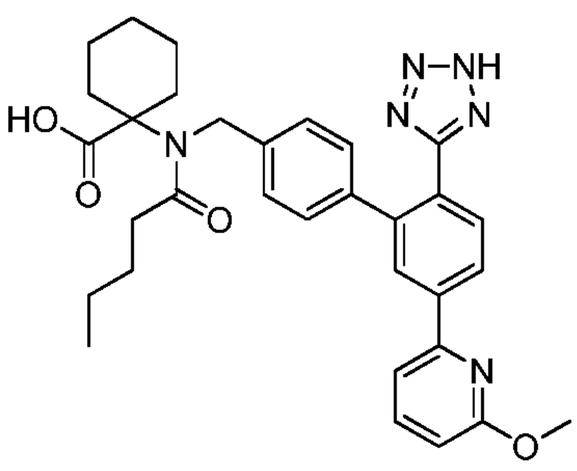
The title compound was prepared from **Intermediate 293b** according to the method described for the synthesis of **Intermediate 284a** and was isolated as an off-white solid. LC-MS (Method H): 1.37 min, $[M + H]^+$= 496.2; HRMS (ESI): Calcd for $C_{31}H_{34}N_3O_3$ [M + H]$^+$ *m/z* 496.2596; found 496.2606.

Example 293: 1-(N-((5'-(pyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid

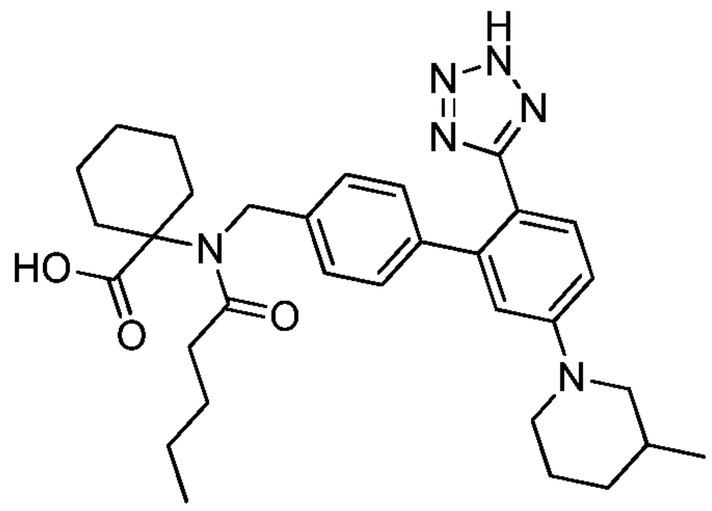
The title compound was prepared from **Intermediate 293c** according to the method described for the synthesis of **Intermediate 283a** and was isolated as an off-white solid. LC-MS (Method H): 1.30 min, $[M + H]^+$= 539.2; ^{1}H NMR (DMSO-d_6) δ ppm 11.93 (s, 2H), 8.73 (d, J = 4.7 Hz, 1H), 8.23 - 8.30 (m, 2H), 8.18 (d, J = 7.8 Hz, 1H), 7.95 (td, J = 7.8, 1.6 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.4, 4.7 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 4.67 (s, 2H), 2.19 (t, J = 7.0 Hz, 2H), 2.05 (d, J = 11.7 Hz, 2H), 1.37 - 1.67 (m, 9H), 1.07 - 1.25 (m, 3H), 0.80 (t, J = 7.2 Hz, 3H).

The following examples were similarly prepared from the corresponding 2-bromopyridine or 2-chloropyridine, as described for the synthesis of **Example 293** above. Analytical LC-MS injections were used to determine the final purity, the retention time is reported for each compound and the method used is referred to as Method A1, Method A2 or Method H.

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm

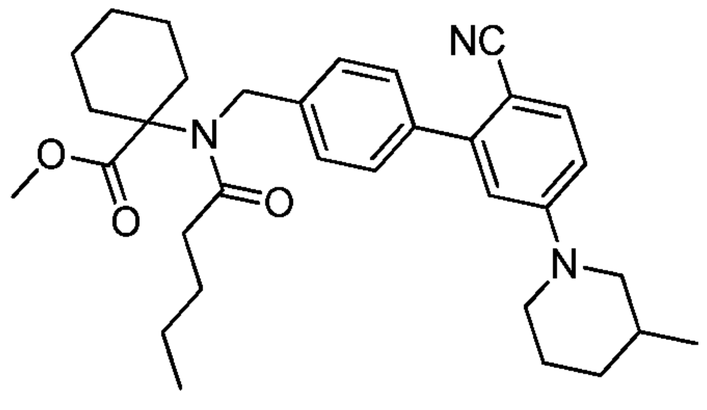
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
294		552.68	553.3; 1.33 min (Method H)	11.94 (s, 2H), 8.16 - 8.25 (m, 2H), 7.94 (d, J = 7.0 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.43 (br s, 2H), 7.29 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 4.67 (br s, 2H), 2.56 (s, 3H), 2.02 - 2.25 (m, 4H), 1.36 - 1.64 (m, 9H), 1.09 - 1.25 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H).
295		552.68	553.3; 1.32 min (Method H)	11.93 (s, 2H), 8.59 (d, J = 5.1 Hz, 1H), 8.27 (dd, J = 8.0, 1.8 Hz, 1H), 8.22 - 8.25 (m, 1H), 8.09 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.37 - 7.42 (m, 2H), 7.32 (d, J = 4.7 Hz, 1H), 7.16 - 7.21 (m, 2H), 4.67 (s, 2H), 2.44 (s, 3H), 2.19 (t, J = 7.2 Hz, 2H), 2.04 (d, J = 11.3 Hz, 2H),1.36 - 1.69 (m, 9H), 1.12 - 1.26 (m, 3H), 0.77 - 0.83 (m, 3H).
296		568.68	569.2; 1.39 min (Method H)	11.91 (s, 2H), 8.26 (dd, J = 8.0, 1.8 Hz, 1H), 8.17 - 8.23 (m, 1H), 7.79 - 7.86 (m, 1H), 7.76 (d, J = 7.4 Hz, 2H), 7.33 - 7.42 (m, 2H), 7.12 - 7.20 (m, 2H), 6.85 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 3.95 (s, 3H), 2.16 (t, J = 7.0 Hz, 2H), 1.96 - 2.09 (m, 2H), 1.35 - 1.65 (m, 9H), 1.02 - 1.23 (m, 3H), 0.77 (t, J = 7.4 Hz, 3H).

Example 297: 1-(N-((5'-(3-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(Ex. 297)

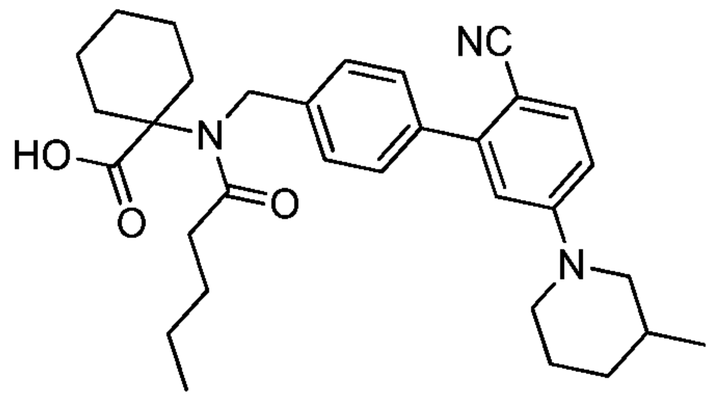
Intermediate 297a: Methyl 1-(N-((2'-cyano-5'-(3-methylpiperidin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylate



(297a)

To a solution of **Intermediate 288a** (0.077 g, 0.165 mmol) in dry THF (3 mL) were added 3-methylpiperidine (0.055 mL, 0.495 mmol), sodium 2-methylpropan-2-olate (0.095 g, 0.989 mmol) and chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium (II) (0.013 g, 0.016 mmol) and the mixture was stirred at 65°C for 3 h. The cooled mixture was then evaporated and the residue was taken up in DMSO (3.5 mL) and purified by prep LC (Method F, formic acid as modifier) to afford the title compound as a white solid (0.050 g, 0.094 mmol, 57% yield). LC-MS (Method H): 1.59 min, $[M + H]^+$= 530.3; HRMS (ESI): Calcd for $C_{33}H_{44}N_3O_3$ $[M + H]^+$ *m/z* 530.3377; found 530.3389.

Intermediate 297b: 1-(N-((2'-Cyano-5'-(3-methylpiperidin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid



(297b)

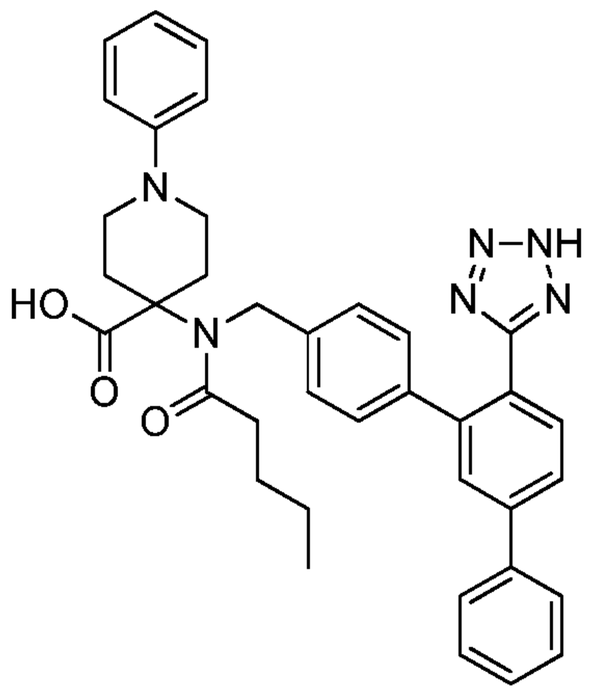
The title compound was prepared from **Intermediate 297a** according to the method described for the synthesis of **Intermediate 284a** and was isolated as an off-white solid.

LC-MS (Method H): 1.52 min, $[M + H]^+$= 516.3; HRMS (ESI): Calcd for $C_{32}H_{42}N_3O_3$ $[M + H]^+$ *m/z* 516.3221; found 516.3242.

Example 297: 1-(N-((5'-(3-Methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)pentanamido)cyclohexanecarboxylic acid

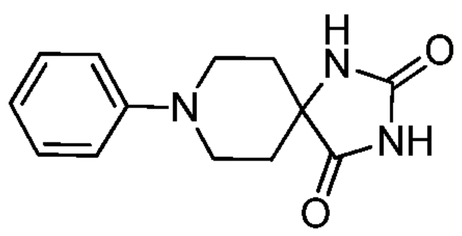
The title compound was prepared from **Intermediate 297b** according to the method described for the synthesis of **Intermediate 283a** and was isolated as an off-white solid. LC-MS (Method H): 1.41 min, $[M + H]^+$= 559.2; ^{1}H NMR (DMSO-d_6) δ ppm 11.92 (br s, 2H), 7.43 (d, J = 8.6 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.04 - 7.12 (m, 3H), 6.94 (d, J = 2.3 Hz, 1H), 4.64 (s, 2H), 3.75 - 3.90 (m, 2H), 2.75 (td, J = 12.1, 2.3 Hz, 1H), 2.44 (d, J = 12.1 Hz, 1H), 2.17 (t, J = 7.0 Hz, 2H), 2.04 (d, J = 12.1 Hz, 2H), 1.38 - 1.77 (m, 13H), 1.02 - 1.25 (m, 4H), 0.92 (d, J = 6.7 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H).

Example 298: 4-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-1-phenylpiperidine-4-carboxylic acid



(Ex. 298)

Intermediate 298a: 8-Phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione

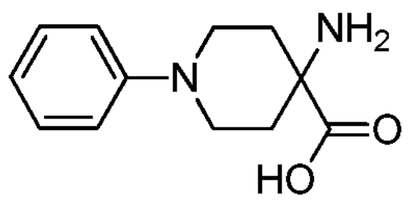


(298a)

To a solution of 1-phenylpiperidin-4-one (2.53 g, 14.46 mmol) in ethanol (75 mL) and H_2O (25 mL) was added ammonium carbonate (12.9 g, 134.3 mmol) and potassium cyanide (2.11 g, 32.5 mmol). The reaction vessel was sealed and the mixture was then heated at 80-90°C for 18 h. The cooled mixture was concentrated *in vacuo*, H_2O (200 mL) was added to the residue and the resulting suspension was briefly stirred at RT. This mixture was then filtered and the residue washed with H_2O to give the title compound as

a wet solid (*ca.* 3 g). The aqueous filtrate and washings were combined and extracted with EtOAc (3 x 100 mL) and the combined organic extract was washed (H_2O), dried (anhydrous sodium sulfate), filtered and evaporated to provide more of the title compound as an impure solid (*ca.* 2 g). The combined solids thus obtained were taken up in ethanol (200 mL) and the volatiles were removed under reduced pressure to give a brown solid. This solid was triturated a mixture of 20% v/v of ethanol/tert-butylmethyl ether (50 mL) and the resulting suspension was filtered and the filter-cake was washed with tert-butylmethyl ether. The solid thus obtained was air-dried to give the title compound (3.06 g, 12.5 mmol, 86% yield) as a brown solid which was used as such without further purification. ^{1}H NMR (DMSO-d_6) δ ppm 10.67 (br s, 1H), 8.53 (s, 1H), 7.21 (dd, J = 8.6, 7.4 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 3.63 (dt, J = 13.0, 3.9 Hz, 2H), 2.99 - 3.16 (m, 2H), 1.81 - 1.97 (m, 2H), 1.60 (d, J = 13.3 Hz, 2H).

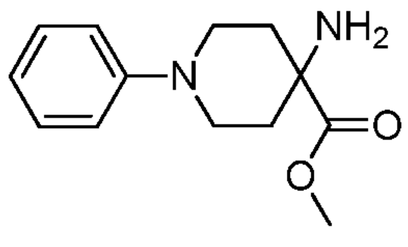
Intermediate 298b: 4-amino-1-phenylpiperidine-4-carboxylic acid



(298b)

A mixture of **Intermediate 298a** (3.06 g, 12.5 mmol) and 6M NaOH (100 mL, 600 mmol) were heated at 100°C in a sealed pressure bottle for 22 h. The reaction temperature was then increased to 130°C and stirring was continued for 24 h. The cooled mixture was neutralized (pH 6-7) by the slow addition of AcOH to give a beige precipitate. The resulting suspension was filtered and the filter-cake was washed with numerous small quantities of H_2O and then air-dried to give the title compound as a beige solid (2.64 g, 11.9 mmol, 96% yield). LC-MS (Method H): 0.34 min, $[M + H]^+$= 221.1; HRMS (ESI): Calcd for $C_{12}H_{17}N_2O_2$ $[M + H]^+$ *m/z* 221.1285; found 221.1284.

Intermediate 298c: Methyl 4-amino-1-phenylpiperidine-4-carboxylate

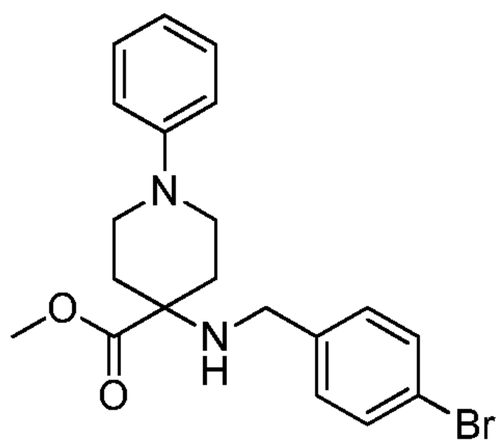


(298c)

To a suspension of **Intermediate 298b** (2.64 g, 11.9 mmol) in MeOH (60 mL) was slowly added thionyl chloride (2.61 mL, 36.0 mmol) and then the mixture was stirred at 65°C for 18 h. The cooled mixture was then evaporated under reduced pressure and the residue was taken up in H_2O (100 mL). This mixture was neutralized by the addition of

1M NaOH to give an off-white precipitate which was filtered and the filter-cake was washed with several small portions of wate. The resulting solid was air-dried to afford the title compound as an off-white solid (1.00 g, 4.27 mmol, 35% yield). LC-MS (Method H): 0.88 min, $[M + H]^+$= 235.2; ^{1}H NMR ($CDCl_3$) δ ppm 7.19 - 7.33 (m, 2H), 6.91 - 7.00 (m, 2H), 6.79 - 6.89 (m, 1H), 3.75 (s, 3H), 3.24 - 3.37 (m, 4H), 2.23 (ddd, J = 13.5, 8.2, 5.7 Hz, 2H), 1.62 - 1.73 (m, 2H), 1.56 (br s, 2H).

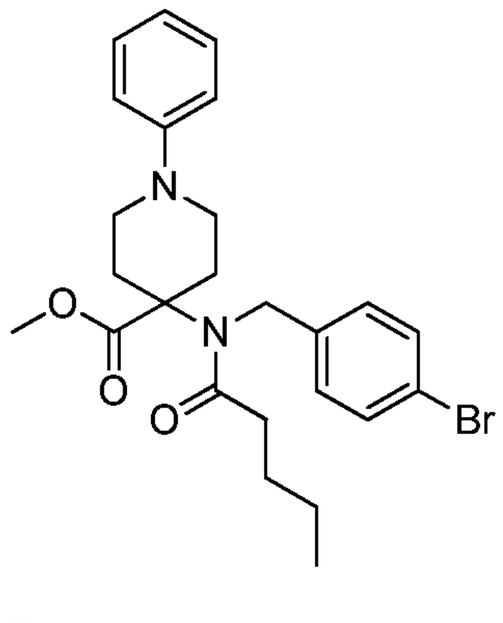
Intermediate 298d: Methyl 4-((4-bromobenzyl)amino)-1-phenylpiperidine-4-carboxylate



(298d)

To a mixture of **Intermediate 298c** (1.00 g, 4.27 mmol) in ACN (15 mL) was added 1-bromo-4-(bromomethyl)benzene (1.17 g, 4.69 mmol) and DIEA (0.97 mL, 5.55 mmol), the vessel was sealed and the mixture was heated at 80°C for 18 h. The cooled mixture was then evaporated under reduced pressure, the residue was taken up in tert-butylmethyl ether (100 mL) and saturated aqueous $NaHCO_3$ (25 mL) was added. The organic phase was separated and the aqueous phase was re-extracted with a further portion of tert-butylmethyl ether (20 mL). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue obtained was purified by flash chromatography using a 25 g ISCO-type column and eluting with a 0 to 10% acetone/hexane to give the title compound as a clear light yellow oil (1.60 g, 3.97 mmol, 93% yield). LC-MS (Method H): 1.28 min, $[M + H]^+$= 403.0. ^{1}H NMR ($CDCl_3$) δ ppm 7.40 - 7.48 (m, 2H), 7.19 - 7.30 (m, 4H), 6.92 - 6.99 (m, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 2H), 3.32 - 3.41 (m, 2H), 3.22 - 3.32 (m, 2H), 2.20 (ddd, J = 13.6, 9.5, 3.9 Hz, 2H), 1.81 - 1.93 (m, 2H).

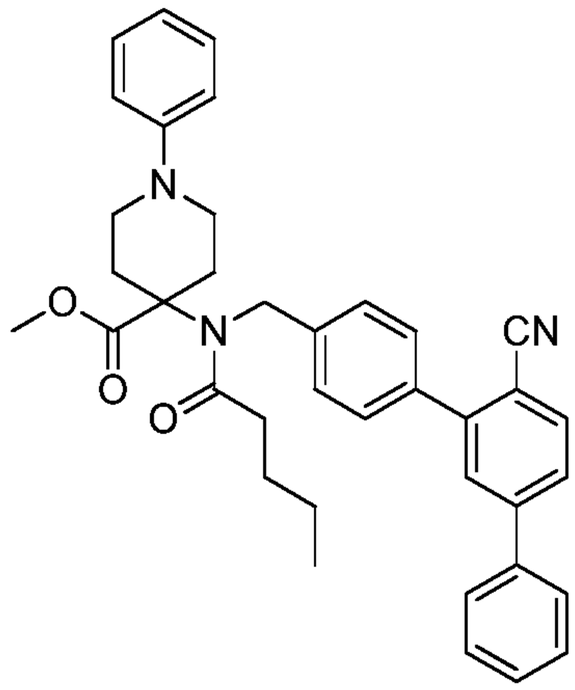
Intermediate 298e: Methyl 4-(N-(4-bromobenzyl)pentanamido)-1-phenylpiperidine-4-carboxylate



(298e)

To a mixture of **Intermediate 298d** (1.55 g, 3.84 mmol) in toluene (50 mL) was added DIEA (1.43 mL, 7.69 mmol) and pentanoyl chloride (0.69 mL, 5.76 mmol) and the resulting mixture was stirred at 65°C for 18 h. Additional portions of DIEA (1.43 mL, 7.69 mmol) and pentanoyl chloride (0.69 mL, 5.76 mmol) were then added and the mixture was stirred at the same temperature for 2 h. Additional portions of DIEA (1.43 mLl, 7.69 mmol) and pentanoyl chloride (0.69 mL, 5.76 mmol) were then added and the mixture was stirred at the same temperature for another 1 h. The cooled mixture was washed sequentially with 10% w/v aqueous citric acid (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), then dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography using a 40 g ISCO-type column with a 0 to 20% acetone/hexane gradient to afford the title compound as an orange gum (1.59 g, 3.26 mmol, 85% yield). LC-MS (Method H): 1.46 min, $[M + H]^+$= 487.1; ^1H NMR ($CDCl_3$) δ ppm 7.48 - 7.55 (m, 2H), 7.28 - 7.34 (m, 2H), 7.19 - 7.26 (m, 2H), 6.79 - 6.90 (m, 3H), 4.59 (s, 2H), 3.79 (s, 3H), 3.50 (d, J = 12.1 Hz, 2H), 3.10 (td, J = 12.3, 2.0 Hz, 2H), 2.30 - 2.38 (m, 2H), 2.27 (t, J = 7.2 Hz, 2H), 1.88 (td, J = 12.7, 5.1 Hz, 2H), 1.50 - 1.68 (m, 2H), 1.23 - 1.35 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).

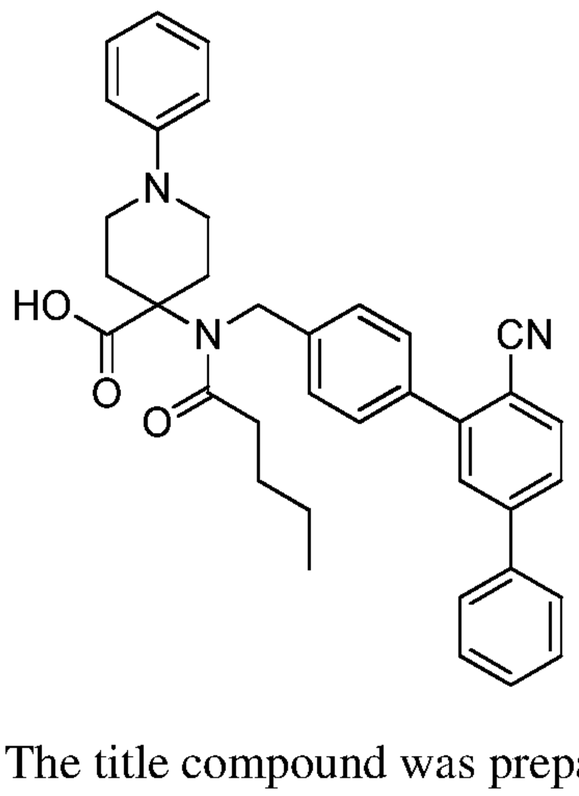
Intermediate 298f: Methyl 4-(N-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-1-phenylpiperidine-4-carboxylate



(298f)

The title compound was prepared by the reaction **Intermediate 298e** (0.078 g, 0.160 mmol) with **Intermediate 268c** (0.070 g, 0.240 mmol), according to the method described for the synthesis of **Intermediate 330b**, and was isolated as a white solid (0.090 g, 0.154 mmol, 96% yield).). LC-MS (Method H): 1.55 min, $[M + H]^+$= 586.2; ^1H NMR ($CDCl_3$) δ ppm 7.86 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.62 - 7.71 (m, 5H), 7.54 - 7.59 (m, 2H), 7.44 - 7.53 (m, 3H), 7.23 (dd, J = 8.6, 7.4 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 4.74 (s, 2H), 3.81 (s, 3H), 3.54 (d, J = 12.5 Hz, 2H), 3.13 (t, J = 11.7 Hz, 2H), 2.41 (d, J = 12.9 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.95 (td, J = 12.6, 4.9 Hz, 2H), 1.60 - 1.70 (m, 2H), 1.23 - 1.39 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

Intermediate 298g: 4-(N-((6'-Cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)pentanamido)-1-phenylpiperidine-4-carboxylic acid



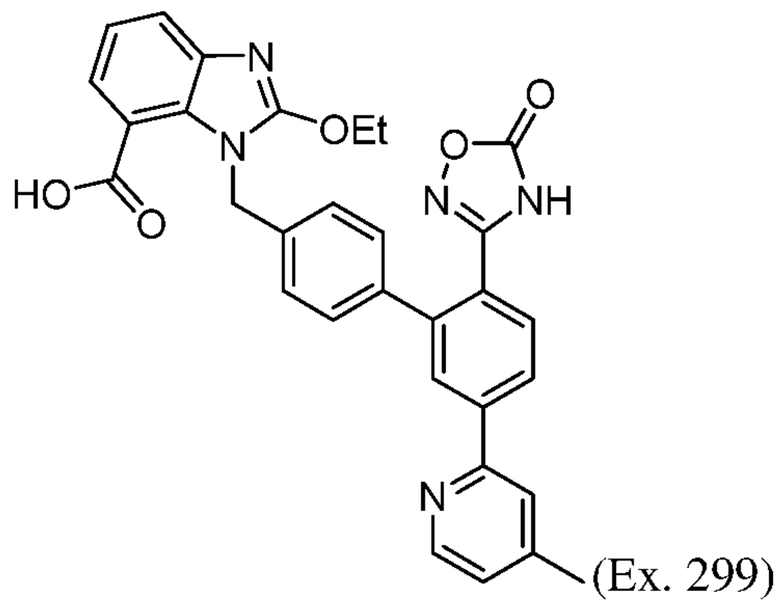
(298g)

The title compound was prepared from **Intermediate 298f** according to the method described for the synthesis of **Intermediate 284a** and was isolated as an off-white solid. LC-MS (Method H): 1.49 min, $[M + H]^+$= 572.2; HRMS (ESI): Calcd for $C_{37}H_{38}N_3O_3$ [M + H]$^+$ *m/z* 572.2908; found 572.2917.

Example 298: 4-(N-((6'-(2H-Tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)pentan-amido)-1-phenylpiperidine-4-carboxylic acid

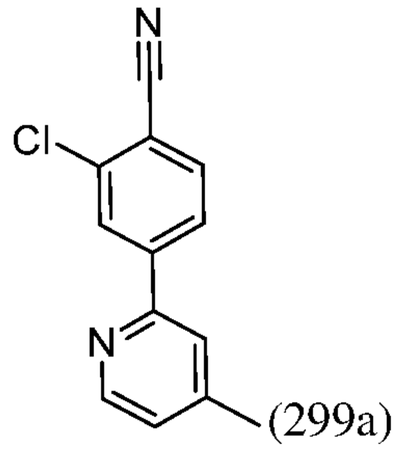
The title compound was prepared from **Intermediate 298g** according to the method described for the synthesis of **Intermediate 283a** and was isolated as an off-white solid. LC-MS (Method H): 1.39 min, $[M + H]^+$= 615.2; ^{1}H NMR (DMSO-d_6) δ ppm 12.28 (s, 2H), 7.78 - 7.90 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 7.48 - 7.55 (m, 2H), 7.41 - 7.48 (m, 1H), 7.35 - 7.41 (m, 2H), 7.13 - 7.25 (m, 4H), 6.85 - 6.96 (m, 2H), 6.75 (t, J = 7.0 Hz, 1H), 4.71 (s, 2H), 3.52 (d, J = 12.1 Hz, 2H), 3.02 (t, J = 11.3 Hz, 2H), 2.16 - 2.30 (m, 4H), 1.85 (dd, J = 12.1, 8.6 Hz, 2H), 1.42 - 1.51 (m, 2H), 1.16 - 1.26 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H).

Example 299: 2-ethoxy-1-((5'-(4-methylpyridin-2-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 299)

Intermediate 299a: 2-chloro-4-(4-methylpyridin-2-yl)benzonitrile

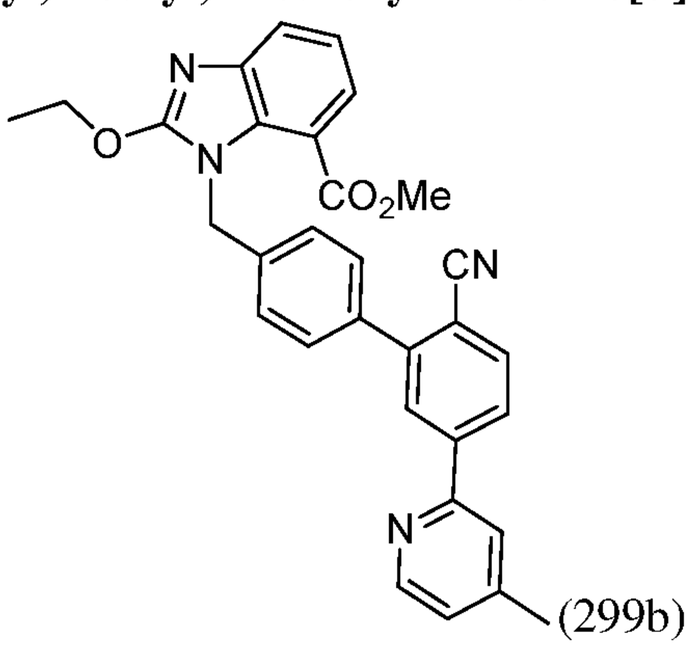


(299a)

To a solution of 2-bromo-4-methylpyridine (455 mg, 2.65 mmol) and (3-chloro-4-cyanophenyl)boronic acid (400 mg, 2.205 mmol) in 4:1 toluene/EtOH (10 mL) was added K_3PO_4 (2 M, aq) (2.205 mL, 4.41 mmol) followed by $PdCl_2$(dppf) (161 mg, 0.221 mmol). The resulting mixture was sparged with N_2 for 2 min before being sealed and heated at 120 °C for 45 min in the microwave. The reaction mixture was diluted with EtOAc, concentrated onto celite and purified by ISCO (0-100% EtOAc Hexanes) to afford the title compound (**299a**, 220 mg, 0.962 mmol, 43.6 % yield). LC-MS: MS (ESI) m/z: 229.0

$[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J=5.0 Hz, 1H), 8.22 (s, 1H), 8.01 (d, J=8.0 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.61 (s, 1H), 7.19 (d, J=5.1 Hz, 1H), 2.48 (s, 3H).

Intermediate 299b: methyl 1-((2'-cyano-5'-(4-methylpyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(299b)

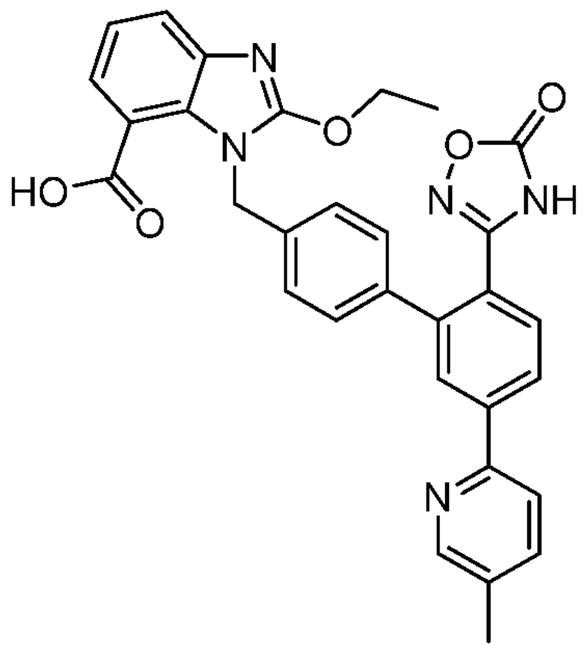
To a pressure-rated vial containing **I-005** (200 mg, 0.458 mmol), **Intermediate 299a** (115 mg, 0.504 mmol) and second generation xphos precatalyst (36.1 mg, 0.046 mmol) was added dioxane (2292 µl) followed by 2 M K_3PO_4 (2 M aq) (458 µl, 0.917 mmol). The reaction mixture was sparged with N_2 for 2 min before being sealed and heated at 85 °C for 18 h. The reaction mixture was then concentrated onto celite and purified by ISCO (0-100% EtOAc/Hexanes) to afford the title compound (159 mg, 0.316 mmol, 69.0 % yield). LC-MS (Method A2): 0.88 min, $[M + H]^+$=503.0.

Example 299: 2-ethoxy-1-((5'-(4-methylpyridin-2-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

Intermediate 299b (78 mg, 0.155 mmol) was dissolved in 1-butyl-3-methylimidazolium acetate (1.2 mL) along with hydroxylamine hydrochloride (270 mg, 3.88 mmol). The reaction mixture was sealed and allowed to stir at 65 °C for 24 h. The reaction mixture was diluted with H_2O and extracted with EtOAc 3x. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was dissolved in 5 mL of THF and DBU (0.234 mL, 1.552 mmol) was added followed by CDI (252 mg, 1.552 mmol). The reaction mixture was allowed to stir at RT for 30 minutes. The reaction mixture was concentrated and then re-dissolved in MeOH (5 mL). 1M NaOH (3.10 mL, 3.10 mmol) was added and the reaction mixture was allowed to stir at 65 °C for 3 h. The mixture was then acidified to pH 3-4 with 10% citric acid and extracted with EtOAc 3x. The combined organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by reverse phase

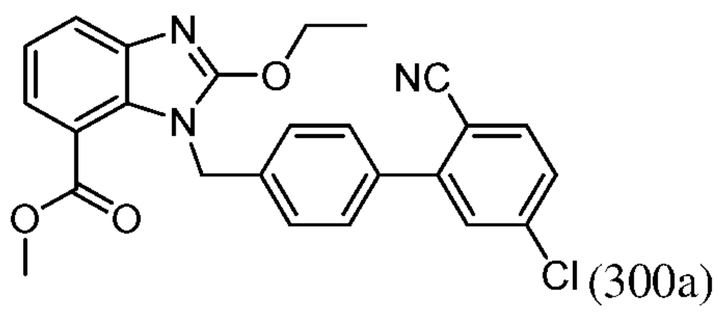
HPLC (Xbridge Prep Shield RP18, 15 min gradient of 20-100%B. A = H_2O/MeOH 10 mM NH_4OAc 90:10. B = H_2O/MeOH 10 mM NH_4OAc 10:90) to afford the title compound (**Example 299**, 7.9 mg, 0.014 mmol, 9.30 % yield). MS (ESI) *m/z* $[M + H]^+$ = 548.3. ^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (br d, *J*=4.9 Hz, 1H), 8.22 (br d, *J*=7.6 Hz, 1H), 8.09 (br s, 1H), 7.96 (br s, 1H), 7.75 (d, *J*=7.9 Hz, 1H), 7.66 (br d, *J*=7.0 Hz, 1H), 7.57 (br d, *J*=7.6 Hz, 1H), 7.31 (br d, *J*=7.3 Hz, 2H), 7.24 (br d, *J*=4.0 Hz, 1H), 7.18 (br s, 1H), 7.07 (br d, *J*=7.9 Hz, 2H), 5.73 (br s, 2H), 4.67 - 4.52 (m, *J*=6.7 Hz, 2H), 2.38 (s, 3H), 1.40 (br t, *J*=6.3 Hz, 3H). LC-MS retention time (Method A4): 1.298 min.

Example 300: 2-ethoxy-1-((5'-(5-methylpyridin-2-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 300)

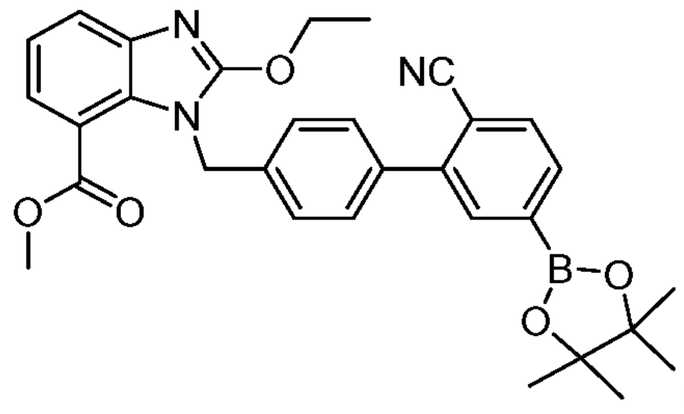
Intermediate 300a: methyl 1-((5'-chloro-2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(300a)

Intermediate 300a was synthesized from **I-005** and 4-chloro-2-iodobenzonitrile using the procedure described for **299b** to give the title compound (**Intermediate 300a**, 2.55 g, 5.6 mmol, 61 % yield). LC-MS (Method A2): 1.02 min, $[M + H]^+$=446.0. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J*=7.8, 1.0 Hz, 1H), 7.69 (d, *J*=8.3 Hz, 1H), 7.60 (dd, *J*=7.8, 1.0 Hz, 1H), 7.49 - 7.39 (m, 4H), 7.21 (t, *J*=7.8 Hz, 1H), 7.14 (d, *J*=8.3 Hz, 2H), 5.73 (s, 2H), 4.70 (q, *J*=7.1 Hz, 2H), 3.78 (s, 3H), 1.51 (t, *J*=7.2 Hz, 3H).

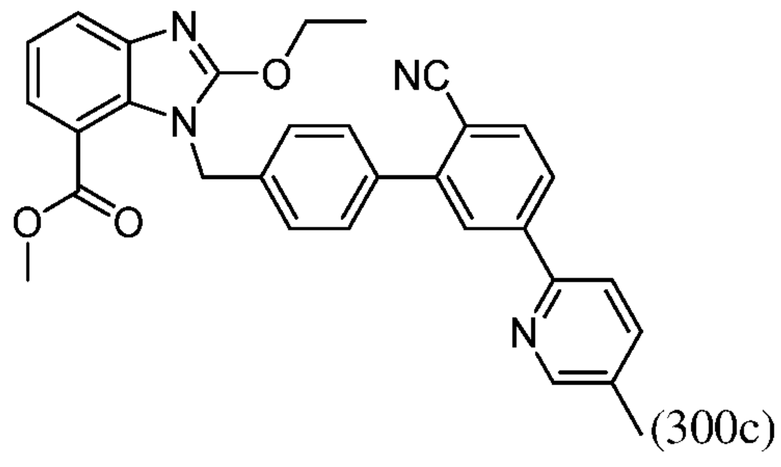
Intermediate 300b: methyl 1-((2'-cyano-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(300b)

To a flask containing **Intermediate 300a** (2100 mg, 4.71 mmol), bis(pinacolato)diborane (2392 mg, 9.42 mmol) and $Pd_2(dba)_3$ (431 mg, 0.471 mmol) was added dioxane (2.35E+04 µl) followed by KOAc (2311 mg, 23.55 mmol) and dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (225 mg, 0.471 mmol) (XPhos). The reaction mixture was evacuated and backfilled with N_2 (3x) and heated at 100 °C for 120 minutes. The reaction mixture was concentrated onto celite and purified by ISCO (0-60% EtOAc/DCM) to afford the title compound (**Intermediate 300b**, 2.2 g, 3.44 mmol, 73.0 % yield). LC-MS: MS (ESI) m/z: 538.1$(M+H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.84 (dd, *J*=7.7, 0.8 Hz, 1H), 7.79 - 7.70 (m, 2H), 7.59 (dd, *J*=7.8, 1.0 Hz, 1H), 7.47 (d, *J*=8.3 Hz, 2H), 7.21 (t, *J*=7.8 Hz, 1H), 7.10 (d, *J*=8.3 Hz, 2H), 5.71 (s, 2H), 4.70 (d, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 1.52 (t, *J*=7.2 Hz, 3H), 1.36 (s, 12H).

Intermediate 300c: methyl 1-((2'-cyano-5'-(5-methylpyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(300c)

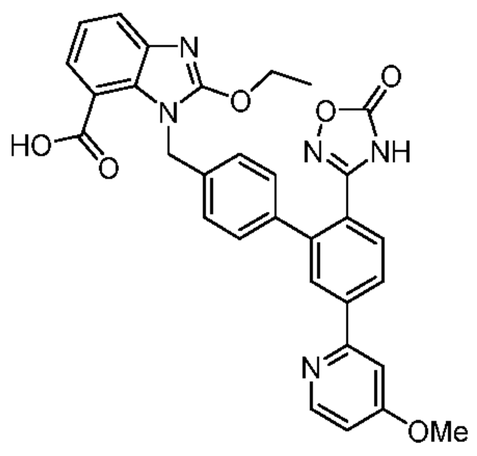
Intermediate 300b (128 mg, 0.200 mmol) was dissolved in 4:1 toluene/EtOH (2 mL) along with XPhos generation two pre-catalyst (31.5 mg, 0.040 mmol), K_3PO_4 (2 M, aq) (0.300 mL, 0.600 mmol) and 2-bromo-5-methylpyridine (68.8 mg, 0.400 mmol). The reaction mixture was evacuated and backfilled with N_2 (3x) then allowed to stir at 65 °C for 2 h. The reaction mixture was concentrated onto celite and purified by ISCO (0-100% DCM/EtOAc) to afford the title compound (**Intermediate 300c**, 68 mg, 0.135 mmol, 67.7 % yield). LC-MS: MS (ESI) m/z: 503.0 $(M+H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.10 (d, *J*=1.4 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.84 (d, *J*=8.3 Hz, 1H), 7.76 (d, *J*=7.8

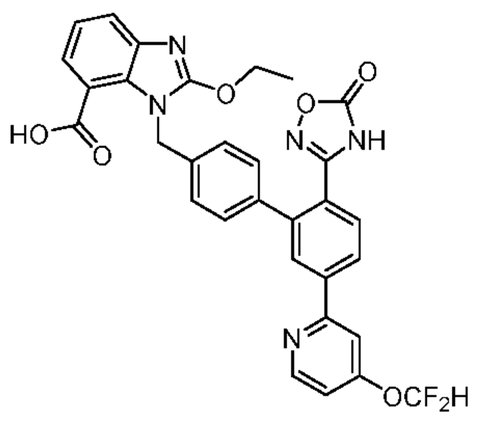
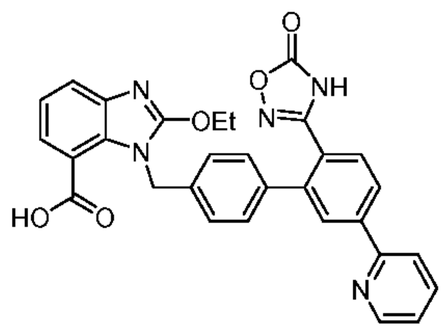
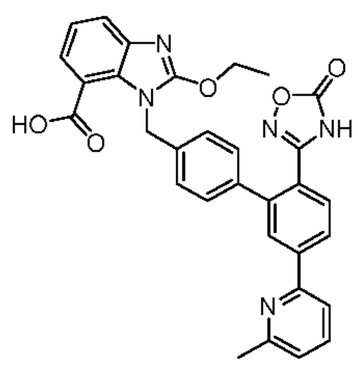
Hz, 1H), 7.69 (d, *J*=8.0 Hz, 1H), 7.60 (br d, *J*=8.0 Hz, 2H), 7.56 - 7.50 (m, *J*=8.3 Hz, 2H), 7.21 (t, *J*=7.8 Hz, 1H), 7.16 - 7.12 (m, *J*=8.3 Hz, 2H), 5.73 (s, 2H), 4.71 (d, *J*=6.9 Hz, 2H), 3.80 (s, 3H), 2.42 (s, 3H), 1.52 (t, *J*=7.0 Hz, 3H).

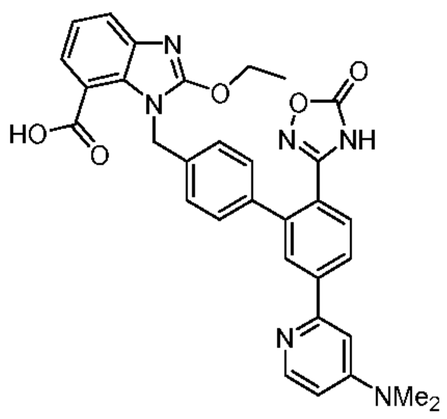
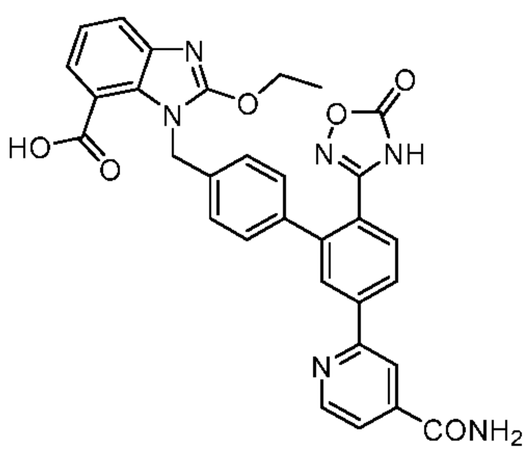
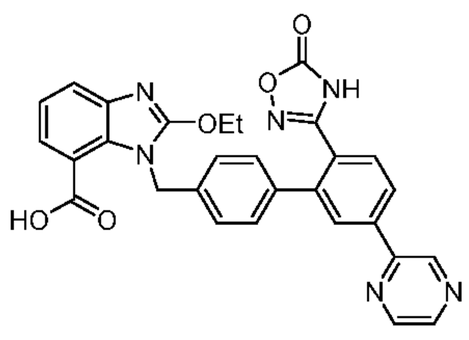
Example 300: 2-ethoxy-1-((5'-(5-methylpyridin-2-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

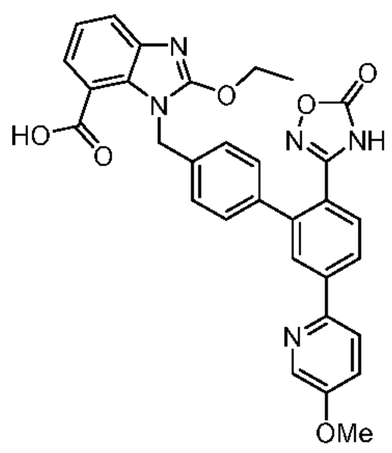
Example 300 was synthesized from **Intermediate 300c** according to the same procedure described for **Example 299** to give the title compound (**Example 300**, 2.9 mg, 5.30 µmol, 3.91 % yield). MS (ESI) *m/z* $[M + H]^+$ = 548.3. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 8.09 (br d, *J*=8.2 Hz, 1H), 8.02 - 7.90 (m, 2H), 7.70 (br d, *J*=7.0 Hz, 1H), 7.67 (br d, *J*=7.9 Hz, 1H), 7.60 (br d, *J*=7.9 Hz, 1H), 7.49 (br d, *J*=7.6 Hz, 1H), 7.27 (br d, *J*=7.6 Hz, 2H), 7.15 (br t, *J*=7.6 Hz, 1H), 7.02 (br d, *J*=7.6 Hz, 2H), 5.70 (br s, 2H), 4.59 (q, *J*=7.0 Hz, 2H), 2.34 (s, 3H), 1.41 (br t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.291 min.

The examples in the following table were prepared from the appropriate pyridyl bromide according to the sequence described for **Example 300**.

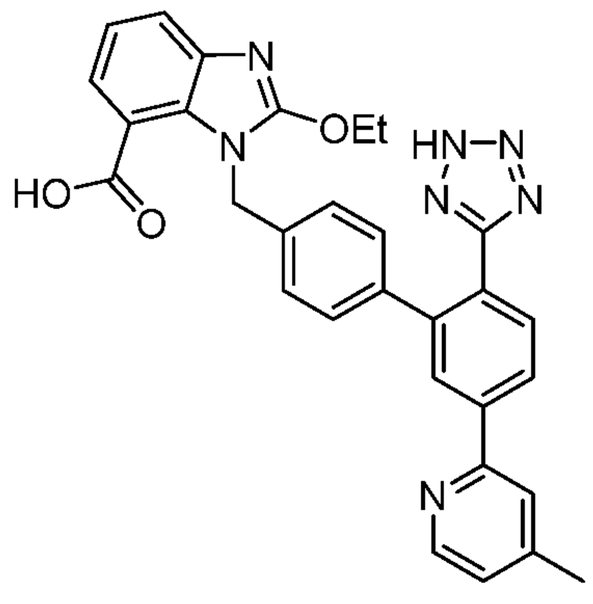
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
301		563.57	564.3; 1.213 min.	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, *J*=5.5 Hz, 1H), 8.20 (br d, *J*=8.2 Hz, 1H), 8.09 (s, 1H), 7.72 (d, *J*=7.9 Hz, 1H), 7.68 - 7.59 (m, 2H), 7.54 (br d, *J*=7.9 Hz, 1H), 7.30 (br d, *J*=7.6 Hz, 2H), 7.18 (t, *J*=7.8 Hz, 1H), 7.05 (br d, *J*=7.9 Hz, 2H), 6.98 (d, *J*=6.1 Hz, 1H), 5.69 (s, 2H), 4.60 (q, *J*=7.0 Hz, 2H), 3.90 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
302		599.55	600.0; 1.615 min.	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (d, *J*=5.6 Hz, 1H), 8.19 (dd, *J*=8.1, 1.4 Hz, 1H), 8.13 - 8.03 (m, 1H), 7.92 - 7.80 (m, 1H), 7.77 - 7.68 (m, 1H), 7.63 (d, *J*=7.8 Hz, 1H), 7.58 - 7.43 (m, 2H), 7.41 - 7.26 (m, *J*=8.1 Hz, 2H), 7.25 - 7.12 (m, 2H), 7.10 - 7.02 (m, *J*=8.1 Hz, 2H), 5.70 (s, 2H), 4.61 (q, *J*=7.1 Hz, 2H), 1.42 (t, *J*=7.0 Hz, 3H).
303		533.54	534.1; 1.319 min.	
304		547.57	548.0; 1.259 min.	

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
305		576.61	577.2; 1.247 min.	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (br d, *J*=6.7 Hz, 1H), 8.10 (br d, *J*=7.9 Hz, 1H), 8.00 (s, 1H), 7.84 (br d, *J*=7.9 Hz, 1H), 7.67 (br d, *J*=7.6 Hz, 1H), 7.56 (br d, *J*=7.9 Hz, 1H), 7.34 (br d, *J*=7.6 Hz, 2H), 7.28 (br s, 1H), 7.24 - 7.03 (m, 4H), 6.91 (br d, *J*=6.4 Hz, 1H), 5.70 (s, 2H), 4.60 (q, *J*=7.0 Hz, 2H), 3.25 - 3.14 (m, 6H), 1.40 (t, *J*=7.0 Hz, 3H).
306		576.57	578.4; 1.192 min	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, *J*=7.0 Hz, 1H), 8.07 (br d, *J*=8.2 Hz, 1H), 7.97 (s, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.67 (d, *J*=7.9 Hz, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.34 (br d, *J*=7.9 Hz, 3H), 7.28 (br d, *J*=2.4 Hz, 1H), 7.24 - 7.14 (m, 1H), 7.10 (br d, *J*=7.9 Hz, 2H), 7.03 - 6.87 (m, 2H), 5.69 (s, 2H), 4.59 (q, *J*=6.9 Hz, 2H), 1.40 (t, *J*=7.0 Hz, 3H).
307		534.53	535.2; 1.392 min.	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.73 (s, 1H), 8.64 (d, *J*=2.1 Hz, 1H), 8.19 (br d, *J*=9.2 Hz, 1H), 8.08 (s, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.31 (br d, *J*=7.9 Hz, 2H), 7.17 (t, *J*=7.8 Hz, 1H), 7.02 (br d, *J*=7.9 Hz, 2H), 5.69 (s, 2H), 4.60 (q, *J*=7.0 Hz, 2H), 1.42 (t, *J*=7.0 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
308		563.57	564.2; 1.458 min.	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (d, *J*=2.5 Hz, 1H), 8.08 - 7.94 (m, 3H), 7.67 (d, *J*=8.1 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.51 (d, *J*=7.8 Hz, 1H), 7.46 (d, *J*=8.5 Hz, 1H), 7.33 - 7.24 (m, *J*=7.9 Hz, 2H), 7.16 (t, *J*=7.7 Hz, 1H), 7.08 - 7.01 (m, *J*=7.9 Hz, 2H), 5.71 (s, 2H), 4.61 (q, *J*=7.0 Hz, 2H), 2.57 - 2.53 (m, 3H), 1.42 (t, *J*=7.0 Hz, 3H).

Example 309: 2-ethoxy-1-((5'-(4-methylpyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

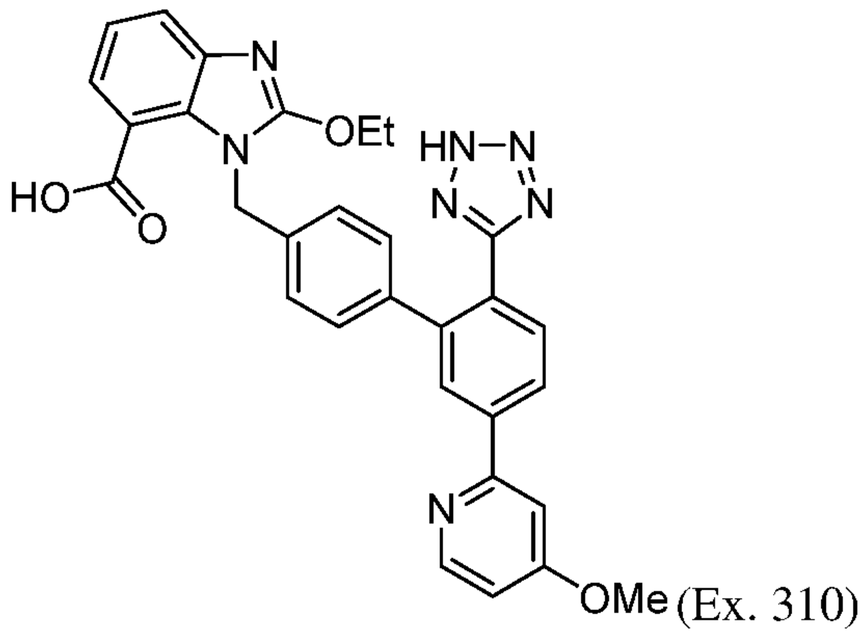


(Ex. 309)

Intermediate 299b (78 mg, 0.155 mmol) was dissolved in xylenes (1mL). Tributylchlorostannane (0.126 mL, 0.466 mmol) was added followed by sodium azide (30.3 mg, 0.466 mmol). The reaction mixture was stirred at 140 °C in a pressure-rated vial behind a blast shield for 18 h. The reaction mixture was diluted with EtOAc and the azide was quenched with 10% CAN (246 mg, 0.449 mmol). The reaction mixture was diluted with H_2O and extracted with EtOAc 3x. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was dissolved in 1:1 1M NaOH/MeOH (4 mL) and stirred at 65 °C for 1 h. The MeOH was evaporated off and the remaining aq. mixture was diluted with a small amount of H_2O and extracted (3x) with 1:1 EtOAc/hexanes. The aq. mixture was then acidified to pH 3-4 with 10% citric acid and extracted with EtOAc 3x. The combined organics were washed

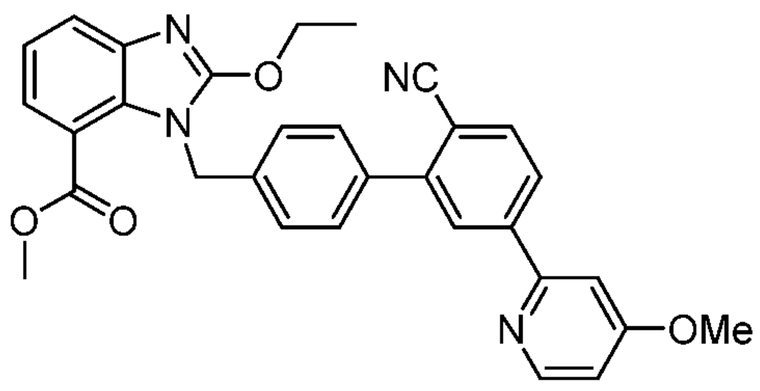
with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was dissolved in DMF, filtered and purified by reverse phase HPLC (Xbridge Prep Shield RP18, 15 min gradient of 20-100%B. A = H_2O/MeOH 10 mM NH_4OAc 90:10. B = H_2O/MeOH 10 mM NH_4OAc 10:90) to afford the title compound (**Example 309**, 4.3 mg, 8.09 µmol, 10.49 % yield). MS (ESI) *m/z* $[M + H]^+$ = 532.2. ^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (br d, *J*=4.3 Hz, 1H), 8.18 (br d, *J*=7.9 Hz, 1H), 8.07 (br s, 1H), 7.95 (br s, 1H), 7.74 (br d, *J*=7.6 Hz, 1H), 7.66 (br d, *J*=7.9 Hz, 1H), 7.53 (br d, *J*=7.6 Hz, 1H), 7.35 - 7.14 (m, 3H), 7.10 (br d, *J*=7.3 Hz, 2H), 6.93 (br d, *J*=7.3 Hz, 2H), 5.64 (br s, 2H), 4.60 (br d, *J*=6.7 Hz, 2H), 2.39 (br s, 3H), 1.47 - 1.37 (m, 3H). HPLC retention time (Method A4): 1.290min.

Example 310: 2-ethoxy-1-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 310)

Intermediate 310a: methyl 1-((2'-cyano-5'-(4-methoxypyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



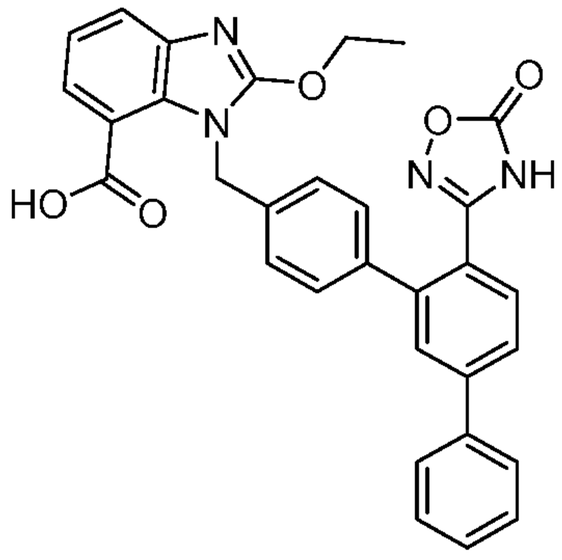
(310a)

Intermediate 310a was synthesized from 2-bromo-5-methoxypyridine according to the same procedure described for **Intermediate 300c** to give the title compound (**Intermediate 310a**, 21 mg, 0.040 mmol, 45.3 % yield). LC-MS (Method A2): 0.88 min, $[M + H]^+$=519.2.

Example 310: 2-ethoxy-1-((5'-(4-methoxypyridin-2-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

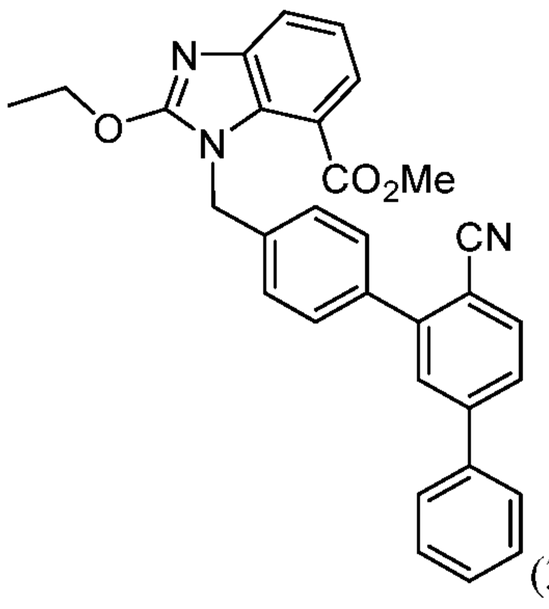
Example 310 was synthesized from **Intermediate 310a** using the procedure described for **Example 309** to give the title compound (**Example 310**, 9.6 mg, 0.018 mmol, 31.4 % yield). MS (ESI) *m/z* $[M + H]^+$ = 548.4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, *J*=5.7 Hz, 1H), 8.06 (br d, *J*=7.9 Hz, 1H), 7.98 (s, 1H), 7.71 (d, *J*=8.1 Hz, 1H), 7.60 (d, *J*=7.7 Hz, 1H), 7.56 - 7.45 (m, 2H), 7.20 - 7.05 (m, 3H), 6.97 - 6.87 (m, 3H), 4.60 (q, *J*=7.0 Hz, 2H), 3.91 (s, 3H), 1.92 (s, 3H), 1.42 (t, *J*=7.0 Hz, 3H. LC-MS retention time (Method A4): 1.066 min.

Example 311: 2-ethoxy-1-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 311)

Intermediate 311a: methyl 1-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(311a)

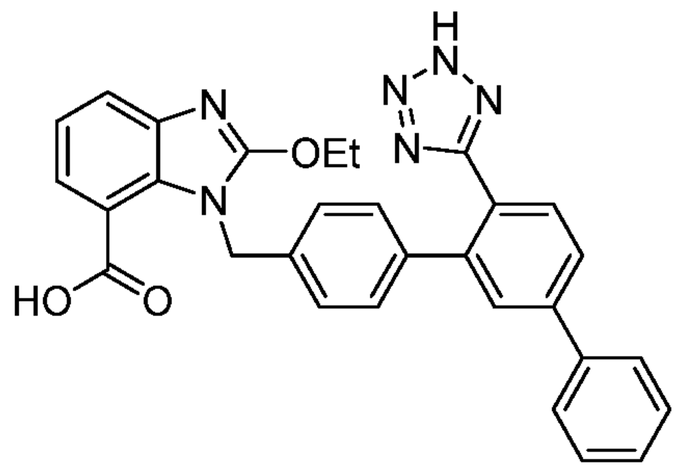
To a pressure-rated vial **I-005** (830 mg, 1.902 mmol), 3-chloro-[1,1'-biphenyl]-4-carbonitrile (488 mg, 2.283 mmol) and second generation XPHOS precatalyst (74.8 mg, 0.095 mmol) was added dioxane (9512 µl) followed by 2 M K_3PO_4 (2 M aq) (1902 µl, 3.80 mmol). The reaction mixture was sparged with N_2 for 2 min before being sealed and heated at 85 °C for 1 h. The reaction mixture was concentrated onto celite and purified by ISCO (0-100% EtOAc in hexane) to afford the title compound (**Intermediate 311a**, 900 mg, 1.846 mmol, 97 % yield). LC-MS: MS (ESI) m/z: 488.10 $(M+H)^+$. ^{1}H NMR

(500MHz, $CDCl_3$) δ 7.87 - 7.81 (m, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.68 - 7.57 (m, 5H), 7.54 - 7.40 (m, 5H), 7.24 - 7.18 (m, 1H), 7.15 (d, J=8.3 Hz, 2H), 5.73 (s, 2H), 4.71 (d, J=6.9 Hz, 2H), 3.79 (s, 3H), 1.52 (t, J=7.0 Hz, 3H).

Example 311: 2-ethoxy-1-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

Example 311 was synthesized from **Intermediate 311a** using the procedure described for **Example 299** to give the title compound (**Example 311**, 255 mg, 0.479 mmol, 61%). MS (ESI) *m/z* $[M + H]^+$ = 533.4. ^1H NMR (500MHz, DMSO-d_6) δ 7.82 (d, *J*=7.8 Hz, 1H), 7.77 (d, *J*=7.3 Hz, 2H), 7.73 - 7.64 (m, 3H), 7.54 (d, *J*=7.5 Hz, 1H), 7.51 - 7.45 (m, 2H), 7.42 (d, *J*=7.2 Hz, 1H), 7.33 (d, *J*=7.1 Hz, 2H), 7.18 (br. s., 1H), 7.06 (d, *J*=7.8 Hz, 2H), 5.69 (br. s., 2H), 4.59 (d, *J*=6.9 Hz, 2H), 1.40 (t, *J*=6.9 Hz, 3H). LC-MS retention time (method A4): 1.830 min.

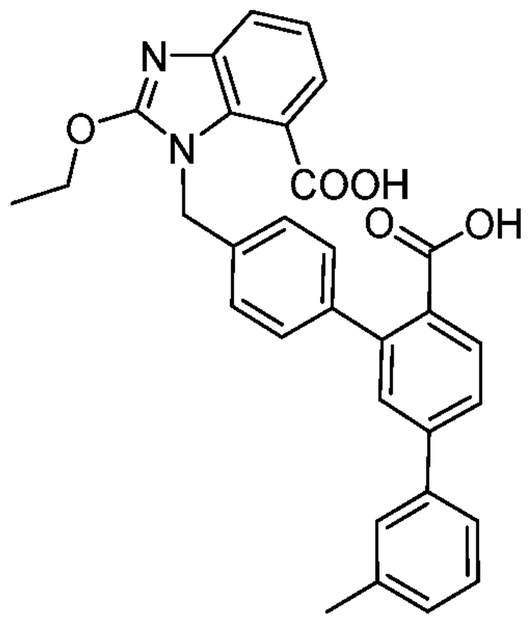
Example 312: 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 312)

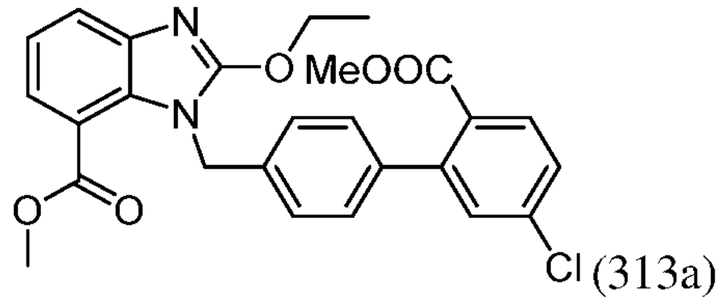
Example 312 was synthesized from **Intermediate 311a** using the same procedure used to synthesize **Example 309** to give the title compound (**Example 312**, 4 mg, 7.74 μmol, 7.61 % yield). MS (ESI) *m/z* $[M + H]^+$ = 517.2. ^1H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.73 (br d, *J*=7.3 Hz, 2H), 7.66 (s, 2H), 7.59 - 7.49 (m, 2H), 7.49 - 7.42 (m, 3H), 7.40 - 7.26 (m, *J*=7.0 Hz, 1H), 7.17 - 7.06 (m, 3H), 6.91 (br d, *J*=7.9 Hz, 2H), 5.66 (s, 2H), 4.58 (br d, *J*=7.0 Hz, 2H), 1.41 (br t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.7969 min.

Example 313: 1-((6'-carboxy-3''-methyl-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 313)

Intermediate 313a: methyl 1-((5'-chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(313a)

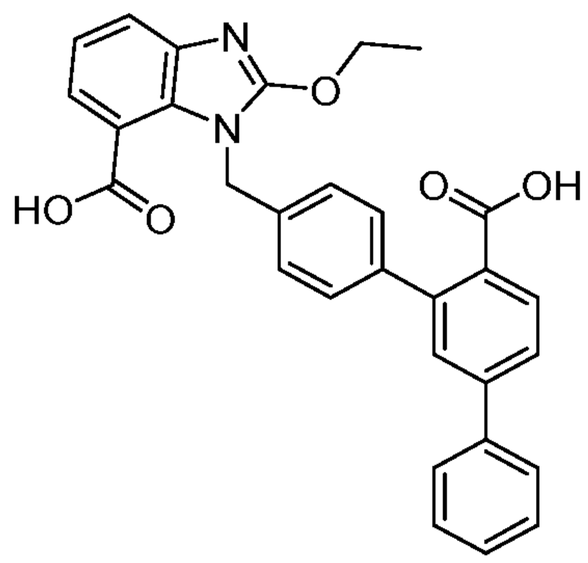
To a vial was added **I-005**(221 mg, 0.506 mmol), methyl 4-chloro-2-iodobenzoate (150 mg, 0.506 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (20.66 mg, 0.025 mmol). THF (3 mL) and 1.5 M Na_2CO_3 (1.012 mL, 1.518 mmol) were added. The mixture was bubbled with Ar for 3 min. The reaction mixture was sealed and irradiated in a microwave reactor at 100 °C for 30 min. The reaction mixture was diluted with EtOAc and H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude residue was purified by ISCO (0-100% EtOAc in Hexanes) to afford the title compound (**Example 313a**, 160mg, 0.334 mmol, 66.0 % yield). MS (ESI) (m/z) 479 $[M + H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 - 7.72 (m, 2H), 7.56 (dd, *J*=8.0, 0.8 Hz, 1H), 7.38 (dd, *J*=8.3, 2.2 Hz, 1H), 7.32 - 7.25 (m, 1H), 7.23 - 7.18 (m, 1H), 7.17 (d, *J*=8.3 Hz, 2H), 7.02 (d, *J*=8.3 Hz, 2H), 5.68 (s, 2H), 4.15 (q, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 3.57 (s, 3H), 1.52 (t, *J*=7.0 Hz, 3H).

Example 313: 1-((6'-carboxy-3''-methyl-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid

A solution of **Intermediate 313a** (25mg, 0.052 mmol), m-tolylboronic acid (21.29 mg, 0.157 mmol) and Pd-XPhos G3 (2.209 mg, 2.61 μmol) in THF (1 mL) and phosphoric acid, potassium salt (1.0 M aq.) (0.094 mL, 0.094 mmol) was degased with Ar for 1 min. The reaction mixture was sealed and heated at 140 °C in a microwave reactor for 30 min. 0.5 ml of MeOH was then added to the mixture followed by NaOH (0.157 mL, 0.313

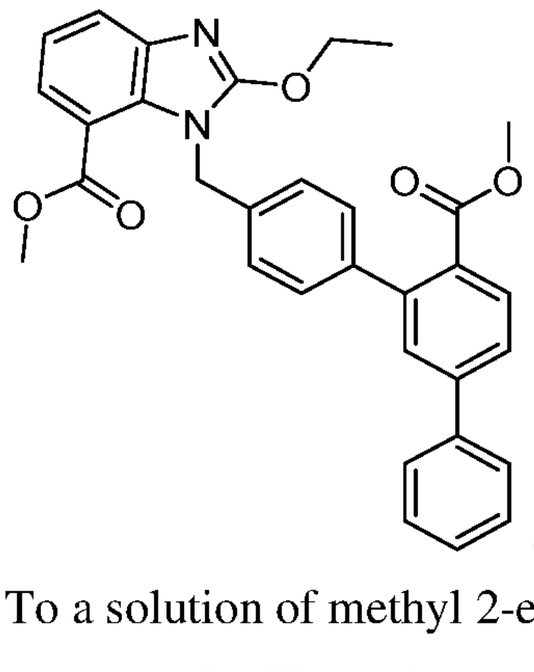
mmol). The mixture was heated up in microwave for 15 min at 100 °C. Additional NaOH (0.157 mL, 0.313 mmol) was added to the mixture and the mixture was stirred at 100 °C for 30 min. The mixture was filtrated and purified by via preparative LC-MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 10-50% B over 22 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min to afford the title compound (**Example 313**, 13.3 mg, 0.025 mol, 48%). MS (ESI) *m/z* $[M + H]^+$ = 507.4. ^1H NMR (500 MHz, DMSO-d_6) δ 7.74 - 7.61 (m, 2H), 7.54 (s, 1H), 7.52 - 7.45 (m, 3H), 7.40 (br d, *J*=7.3 Hz, 1H), 7.36 - 7.29 (m, 3H), 7.19 (br d, *J*=7.6 Hz, 1H), 7.15 - 7.04 (m, 3H), 5.76 (s, 2H), 4.58 (q, *J*=7.0 Hz, 2H), 2.36 (s, 3H), 1.42 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.986 min.

Example 314: 1-((6'-carboxy-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 314)

Intermediate 314a: methyl 2-ethoxy-1-((6'-(methoxycarbonyl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate

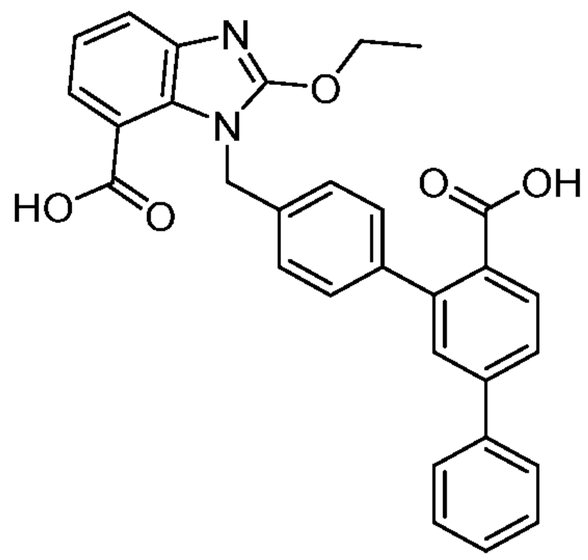


(314a)

To a solution of methyl 2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (55.5 mg, 0.252 mmol) in DMF (2 mL) was added sodium hydride (60%) (16.78 mg, 0.420 mmol) at RT. The reaction mixture was stirred for 10 min at RT before methyl 4''-(bromomethyl)-[1,1':3',1''-terphenyl]-4'-carboxylate (**Intermediate 400b**, 80 mg, 0.210 mmol) was added

in its own solution of DMF (1 mL). After 50 min of stirring at RT the reaction mixture was diluted with EtOAc and washed with 10% LiCl (aq). The organic phase was dried over MgSO4, filtered over celite, and concentrated. The residue was dissolved DMF and purified by ISCO (0-100% EtOAc/Hexanes) to afford the title compound (**Intermediate 314a**, 48 mg, 0.069 mmol, 33.0 % yield). LC-MS Retention time (Method A2) = 1.20 min. Found m/z: 520.1 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.89 (d, *J*=8.1 Hz, 1H), 7.66 - 7.57 (m, 4H), 7.55 - 7.49 (m, 2H), 7.49 - 7.31 (m, 4H), 7.22 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=8.1 Hz, 2H), 5.66 (s, 2H), 4.68 (q, *J*=7.1 Hz, 2H), 3.78 (s, 3H), 3.57 (s, 3H), 1.54 - 1.48 (m, 3H).

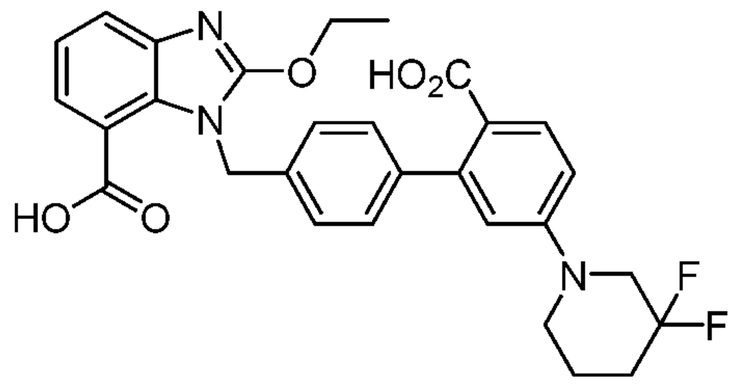
Example 314: 1-((6'-carboxy-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(314)

Intermediate 314a (36 mg, 0.069 mmol) was suspended in a solution of NaOH (1 M NaOH) (2.075 mL, 2.075 mmol) and THF (2 mL) and heated at 65 °C for 3h. The reaction mixture was diluted with EtOAc and washed with 1 M HCl. The aqueous phase was back extracted a second time with EtOAc and the organic phases were concentrated. The crude residue was retaken in DMF, filtered and purified by reverse phase HPLC Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 30-70% B over 20 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min) to afford the title compound (**Example 314**, 16 mg, 0.032 mmol, 46%). MS (ESI) *m/z* $[M + H]^+$ = 493.1. ^1H NMR (500MHz, DMSO-d_6) δ 7.79 (d, *J*=7.9 Hz, 1H), 7.75 - 7.68 (m, 3H), 7.65 (d, *J*=7.6 Hz, 1H), 7.56 - 7.51 (m, 2H), 7.49 - 7.43 (m, 2H), 7.42 - 7.36 (m, 1H), 7.32 (d, *J*=7.9 Hz, 2H), 7.18 (t, *J*=7.8 Hz, 1H), 7.05 (d, *J*=7.9 Hz, 2H), 5.69 (s, 2H), 4.61 (q, *J*=7.0 Hz, 2H), 1.42 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.846 min.

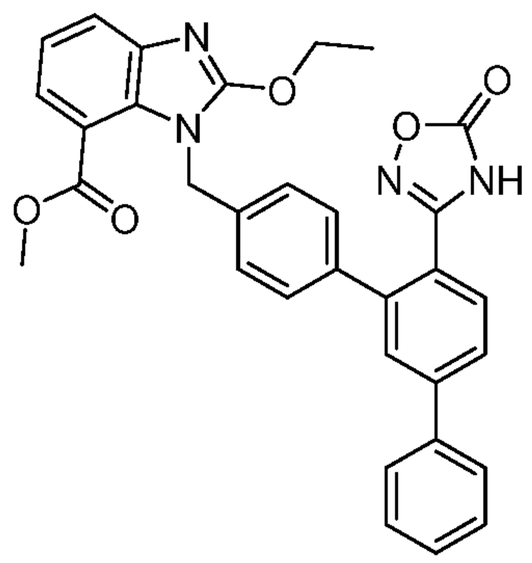
Example 315: 2-ethoxy-1-((6'-(methoxycarbonyl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate



(Ex. 315)

To a vial containing **Intermediate 313a** (18 mg, 0.038 mmol) was added 2nd generation ruphos precatalyst (5.84 mg, 7.52 µmol) followed sodium tert-butoxide (21.67 mg, 0.226 mmol). THF (1 mL) was then added followed by 3,3-difluoropiperidine, HCl (30 mg, 0.188mmol). The reaction was degassed with N_2. The reaction vial was sealed and heated at 65 °C for 18 h. The reaction mixture was then diluted with EtOAc and filtered through celite. The filtrate was concentrated. The crude residue was dissolved in MeOH (1 mL). 1M NaOH (0.752 mL, 0.752 mmol) was added and the reaction was allowed to stir at 65 °C for 1 h. The reaction mixture was then acidified to pH 3-4 with 5% citric acid and extracted (3x) with EtOAc. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was dissolved in DMF, filtered and purified by reverse phase HPLC (Xbridge Prep Shield RP18, 15 min gradient of 20-100%B. A = H_2O/MeOH 10 mM NH_4OAc 90:10. B = H_2O/MeOH 10 mM NH_4OAc 10:90) to afford the title compound (**Example 315**, 2.6 mg, 4.85 µmol, 12.92 % yield). MS (ESI) *m/z* $[M + H]^+$ = 536.0. ^1H NMR (500 MHz, DMSO-d_6) δ 7.65 (br s, 2H), 7.46 (br s, 1H), 7.42 (br s, 1H), 7.27 - 7.07 (m, 3H), 7.04 (br s, 2H), 6.97 (br s, 2H), 6.68 (br s, 1H), 5.75 (br s, 2H), 4.57 (br d, *J*=6.4 Hz, 2H), 2.05 (br d, *J*=16.8 Hz, 2H), 1.91 (br s, 2H), 1.73 (br s, 2H), 1.41 (br t, *J*=6.7 Hz, 3H), 1.00 (br d, *J*=6.4 Hz, 1H. LC-MS retention time (Method A4): 1.661 min.

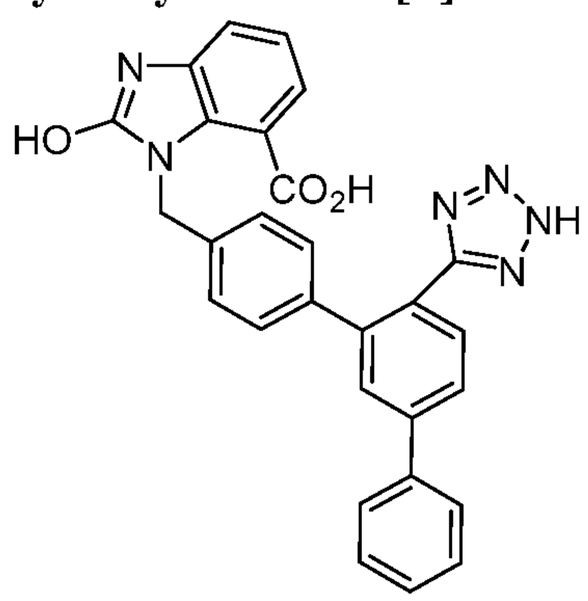
Example 316: methyl 2-ethoxy-1-((6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate



(Ex. 316)

Example 316 was synthesized from **Intermediate 311a** using the same procedure described for **Example 299**, however, the reaction sequence was stopped prior to the ester hydrolysis. The crude residue was purified by reverse phase HPLC (Xbridge Prep Shield RP18, 15 min gradient of 20-100%B. A = H_2O/MeOH 10 mM NH_4OAc 90:10. B = H_2O/MeOH 10 mM NH_4OAc 10:90) to afford the title compound (**Example 316**, 2.9 mg, 5.31 µmol, 19.33 % yield). MS (ESI) *m/z* $[M + H]^+$ = 547.1. ^1H NMR (500MHz, DMSO-d_6) δ 7.95 - 7.25 (m, 11H), 7.20 (t, *J*=7.9 Hz, 2H), 6.93 (br. s., 2H), 5.49 (br. s., 2H), 4.59 (q, *J*=6.8 Hz, 2H), 3.73 (br. s., 3H), 1.39 (t, *J*=6.9 Hz, 3H). LC-MS retention time (Method A4): 2.198 min.

Example 317: 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid

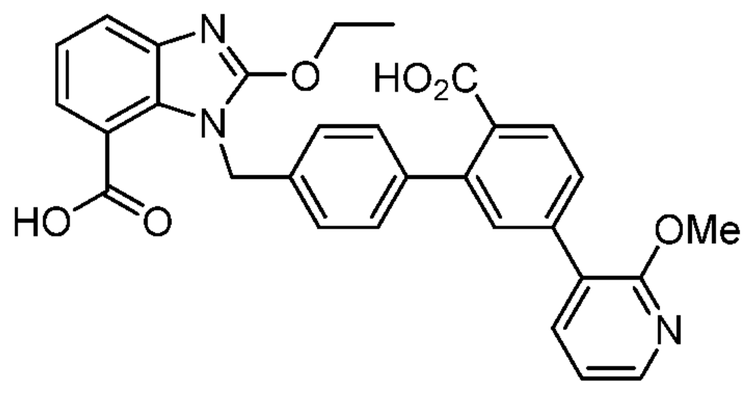


(Ex. 317)

To a small vial containing **Intermediate 311a** (30 mg, 0.062 mmol) was added dibutyltin oxide (15.32 mg, 0.062 mmol) and toluene (1 mL) followed by TMS-N_3 (0.041 mL, 0.308 mmol). The reaction mixture was sealed and heated at 100 °C behind a blast shield overnight. The reaction mixture was concentrated and the crude residue was dissolved in MeOH (2 mL). NaOH (170 mg, 4.24 mmol) was added followed by Water (2 mL). The reaction mixture was stirred at 75 °C for 45 minutes. The reaction mixture was diluted with MeOH and neutralized with AcOH. The reaction mixture was concentrated,

azeotroped with toluene 2x then re-dissolved in DMF filtered and purified by reverse phase HPLC (Xbridge Prep Shield RP18, 15 min gradient of 20-100%B. A = H_2O/MeOH 10 mM NH_4OAc 90:10. B = H_2O/MeOH 10 mM NH_4OAc 10:90) to afford the title compound (**Example 317**, 1.6 mg, 3.24 µmol, 5.73 % yield). MS (ESI) *m/z* $[M + H]^+$ = 489.1. ^1H NMR (500MHz, DMSO-d_6) δ 7.74 (d, *J*=7.5 Hz, 2H), 7.68 (br. s., 2H), 7.56 (s, 1H), 7.50 - 7.42 (m, 2H), 7.41 - 7.32 (m, 1H), 7.27 (d, *J*=6.8 Hz, 1H), 7.19 - 6.86 (m, 6H), 5.40 (br. s., 2H). LC-MS retention time (Method A4): 1.126 min.

Example 318: 1-((2'-carboxy-5'-(2-methoxypyridin-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid

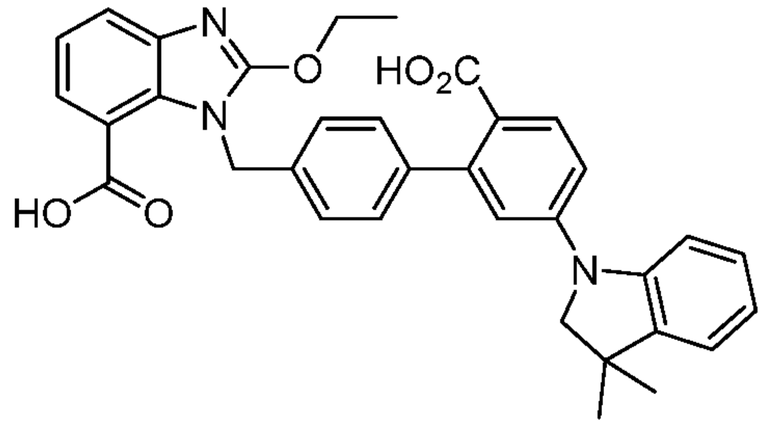


(Ex. 318)

To a pressure-rated vial containing **Intermediate 313a** (18 mg, 0.038 mmol), (2-methoxypyridin-3-yl)boronic acid (17.24 mg, 0.113 mmol) and second generation XPHOS precatalyst (8.87 mg, 0.011 mmol) was added dioxane (500 µl) followed by 2 M K_3PO_4 (2 M aq) (94 µl, 0.188 mmol). The reaction mixture was sparged with N_2 for 2 min before being sealed and heated at 65 °C. The reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated and the crude residue was dissolved in MeOH (1 mL). 1M NaOH (752 µl, 0.752 mmol) was added and the reaction was allowed to stir at 65 °C for 1 hour. The reaction mixture was then acidified to pH 3-4 with 5% citric acid and extracted (3x) with EtOAC. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was dissolved in DMF, filtered and purified by reverse phase HPLC (Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 ACN: H_2O with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 ACN: H_2O with 0.1% trifluoroacetic acid; Gradient: 20-60% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min) to afford the title compound (**Example 318**, 5.5 mg, 10.51 µmol, 28.0 % yield). MS (ESI) *m/z* $[M + H]^+$ = 524.2. ^1H NMR (500 MHz, DMSO-d_6) δ 8.20 (br d, *J*=3.7 Hz, 1H), 7.83 (br d, *J*=6.4 Hz, 1H), 7.75 (br d, *J*=7.9 Hz, 1H), 7.70 - 7.58 (m, 2H), 7.54 (br d, *J*=7.0 Hz, 1H), 7.45 (br s,

1H), 7.30 (br d, *J*=7.0 Hz, 2H), 7.18 (br s, 1H), 7.12 - 7.07 (m, 1H), 7.04 (br d, *J*=7.3 Hz, 2H), 5.69 (br s, 2H), 4.61 (q, *J*=7.0 Hz, 2H), 3.87 (s, 3H), 1.42 (br t, *J*=6.9 Hz, 3H. LC-MS retention time (Method A4): 1.661 min.

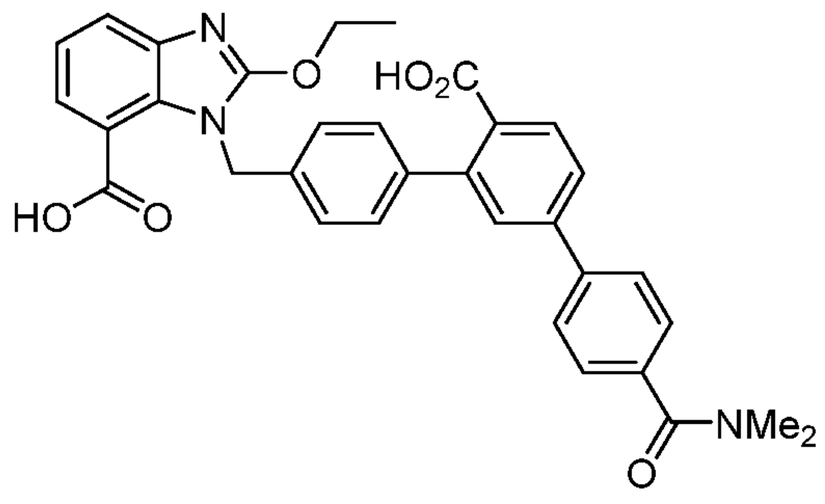
Example 319: 1-((2'-carboxy-5'-(3,3-dimethylindolin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(319)

Example 319 was synthesized from 3,3-dimethylindoline and **Intermediate 313a** according to the same procedure described for the synthesis of **Example 315** to give the title compound (**Example 319**, 0.6 mg, 1.068 µmol, 2.84 % yield). MS (ESI) *m/z* [M + H]$^+$ = 562.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76 (br s, 1H), 7.48 - 7.28 (m, 3H), 7.27 - 7.08 (m, 7H), 7.03 (br d, *J*=5.4 Hz, 1H), 6.90 (br s, 1H), 6.82 (br t, *J*=6.8 Hz, 1H), 5.82 (br s, 2H), 4.55 (br d, *J*=6.7 Hz, 2H), 3.73 (br s, 2H), 3.52 - 3.33 (m, 2H), 3.17 (s, 1H), 1.40 (br t, *J*=6.6 Hz, 3H), 1.28 (br s, 6H), 1.00 (br d, *J*=6.3 Hz, 1H. LC-MS retention time (Method A4): 2.137 min.

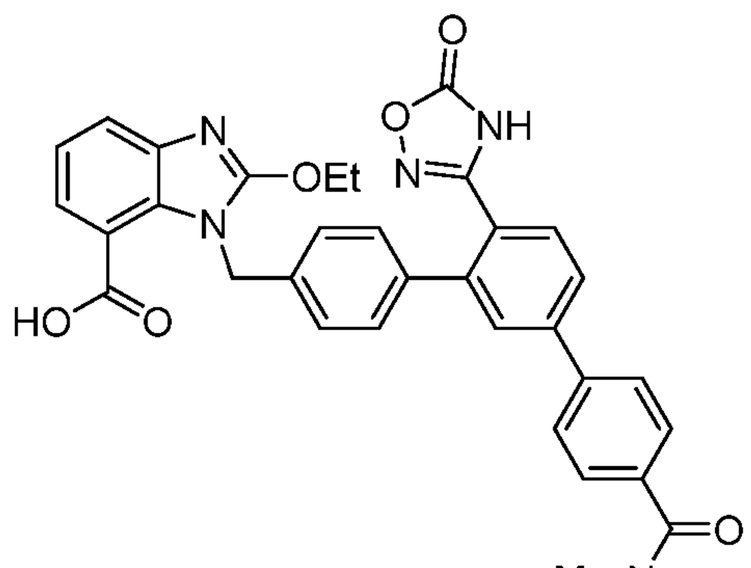
Example 320: 1-((6'-carboxy-4''-(dimethylcarbamoyl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 320)

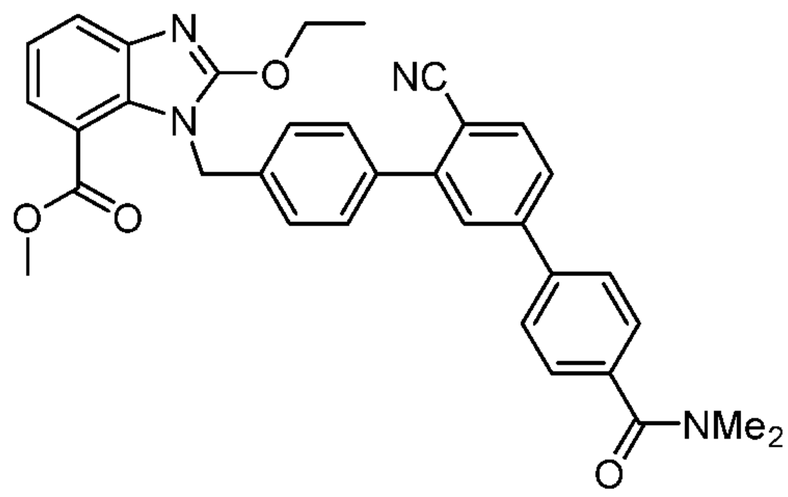
Example 320 was synthesized from **Intermediate 313a** and (4-(dimethylcarbamoyl)phenyl)boronic acid using the procedure that was described for **Example 299b** to give the title compound (**Example 320**, 5.9 mg, 10.47 µmol, 27.9 % yield). MS (ESI) *m/z* [M + H]$^+$ = 564.0. LC-MS retention time (Method A4): 1.533 min.

Example 321: 1-((4''-(dimethylcarbamoyl)-6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(321)

Intermediate 321a: methyl 1-((6'-cyano-4''-(dimethylcarbamoyl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



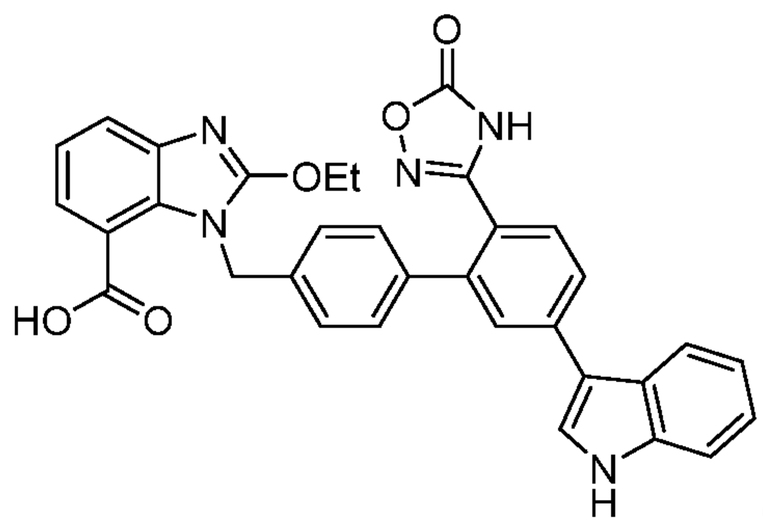
(321a)

Intermediate 321a was synthesized from **Intermediate 300a** and (4-(dimethylcarbamoyl)phenyl)boronic acid using the procedure that was used to synthesize **Intermediate 299b** to afford the title compound (**Intermediate 321a**, 40 mg, 0.072 mmol, 45.6 % yield). MS (ESI) *m/z* $[M + H]^+$ = 559.7. LC-MS retention time (Method A2): 0.97 min.

Example 321: 1-((4''-(dimethylcarbamoyl)-6'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid

Example 321 was synthesized from **Intermediate 321a** using the procedure described for **Example 299** to give the title compound (**Example 321**, 4.9 mg, 8.12 µmol, 11.34 % yield). MS (ESI) *m/z* $[M + H]^+$ = 604.5. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, *J*=8.2 Hz, 3H), 7.75 - 7.57 (m, 3H), 7.56 - 7.42 (m, 3H), 7.30 (br d, *J*=7.9 Hz, 2H), 7.17 (s, 1H), 7.05 (br d, *J*=8.2 Hz, 2H), 5.66 (s, 2H), 4.57 (br d, *J*=7.0 Hz, 2H), 2.99 (br s, 3H), 2.93 (br s, 3H), 1.38 (t, *J*=7.0 Hz, 3H. LC-MS retention time (Method A4): 1.479 min.

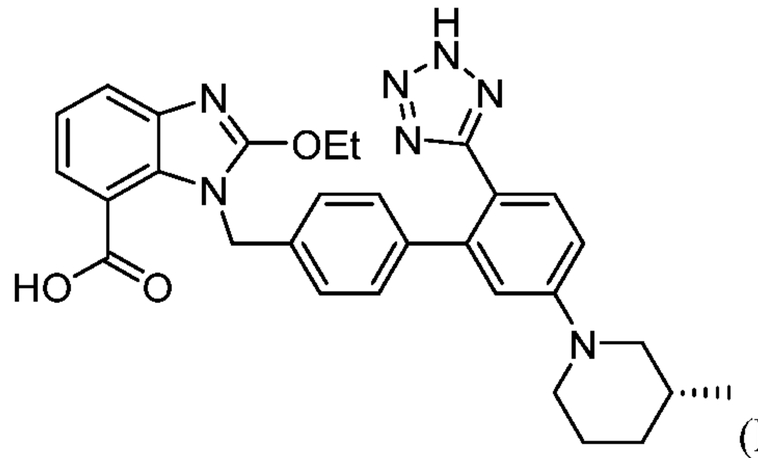
Example 322: 1-((5'-(1H-indol-3-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 322)

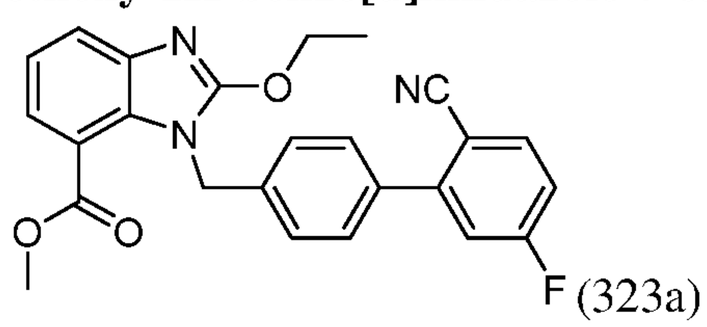
Example 322 was synthesized from **Intermediate 313a** and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole using the sequence described for **Example 321** to give the title compound (**Example 322**, 130 mg, 0.247 mmol, 73.2 % yield). MS (ESI) *m/z* [M + H]$^+$ = 572.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.57 (br s, 1H), 8.00 - 7.79 (m, 3H), 7.75 - 7.61 (m, 3H), 7.55 (br d, *J*=7.6 Hz, 1H), 7.47 (br d, *J*=8.0 Hz, 1H), 7.34 (br d, *J*=8.1 Hz, 2H), 7.25 - 7.11 (m, 3H), 7.08 (br d, *J*=8.0 Hz, 2H), 5.70 (s, 2H), 4.66 - 4.56 (m, 2H), 3.18 (s, 1H), 2.08 (s, 1H), 1.41 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.722 min.

Example 323: methyl (R)-1-((2'-cyano-5'-(3-methylpiperidin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(Ex. 323)

Intermediate 323a: methyl 1-((2'-cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate

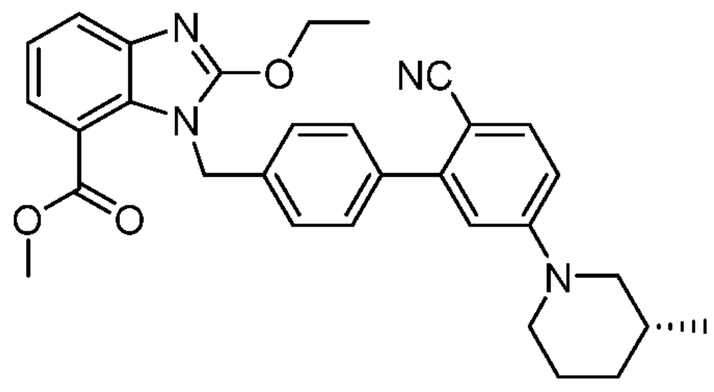


(323a)

To a solution of **I-005** (600 mg, 1.375 mmol) and 2-bromo-4-fluorobenzonitrile (330 mg, 1.650 mmol) in 4:1 toluene/EtOH (12 mL) was added K_3PO_4 (2 M, aq) (2.063 mL, 4.13 mmol) followed by $PdCl_2$(dppf) (101 mg, 0.138 mmol). The resulting mixture was sparged with N_2 for 2 min before being sealed and heated at 120 °C for 45 min in the microwave. Additional $PdCl_2$(dppf) (101 mg, 0.138 mmol) was added to the reaction

mixture which was then evacuated and backfilled with N_2 (3x) and stirred for an additional 45 min in the microwave at 120 °C. The reaction mixture was then concentrated onto celite and purified by ISCO (80 g column 0-100% EtOAc/Hexanes) to afford the title compound (**Intermediate 323a**, 400 mg, 0.931 mmol, 67.7 % yield). LC-MS: MS (ESI) m/z: 430.1 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=7.9 Hz, 2H), 7.59 (d, J=7.7 Hz, 1H), 7.45 (d, J=8.0 Hz, 2H), 7.23 - 7.09 (m, 5H), 5.73 (s, 2H), 4.73 - 4.67 (m, 2H), 3.78 (s, 3H), 1.51 (t, J=7.2 Hz, 3H).

Intermediate 323b: methyl (R)-1-((2'-cyano-5'-(3-methylpiperidin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



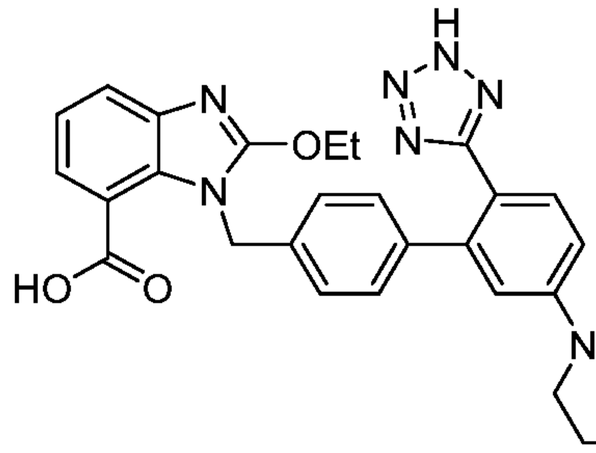
(323b)

Intermediate 323a (190 mg, 0.442 mmol) was dissolved in DMSO (1475 µl). Potassium carbonate (306 mg, 2.212 mmol) was added followed by (R)-3-methylpiperidine, HCl (132 mg, 0.973 mmol). The reaction was sealed and heated at 100 °C behind a blast shield for a total of 2 hours. The reaction mixture diluted with EtOAc and H_2O. The aqueous phase was extracted (3x) with EtOAc and the combined organic phases were washed with brine, dried with sodium sulfate, filtered and concentrated. The crude residue was purified by ISCO (0-100% EtOAc in hexane) to afford the title compound (**Intermediate 323b**, 140 mg, 0.275 mmol, 62.2 % yield). LC-MS (Method A2): 1.11 min, $[M + H]^+$=509.0.

Example 323: methyl (R)-1-((2'-cyano-5'-(3-methylpiperidin-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate

Example 323 was synthesized from **Intermediate 323b** using the same procedure as described for **Example 309** to give the title compound (**Example 323**, 3.6 mg, 6.70 µmol, 7.74 % yield). MS (ESI) *m/z* $[M + H]^+$ = 538.2. ^1H NMR (500 MHz, DMSO-d_6) δ 7.63 (d, *J*=7.9 Hz, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.41 (d, *J*=8.5 Hz, 1H), 7.16 (br t, *J*=7.6 Hz, 1H), 7.07 - 6.95 (m, 3H), 6.90 (br d, *J*=7.9 Hz, 2H), 6.85 - 6.66 (m, 1H), 5.62 (s, 2H), 4.59 (q, *J*=7.0 Hz, 2H), 3.73 (br s, 2H), 2.68 (br s, 1H), 2.48 - 2.36 (m, 1H), 1.80 - 1.53 (m, 5H), 1.41 (t, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.7 Hz, 3H). LC-MS retention time (Method A4): 1.559 min.

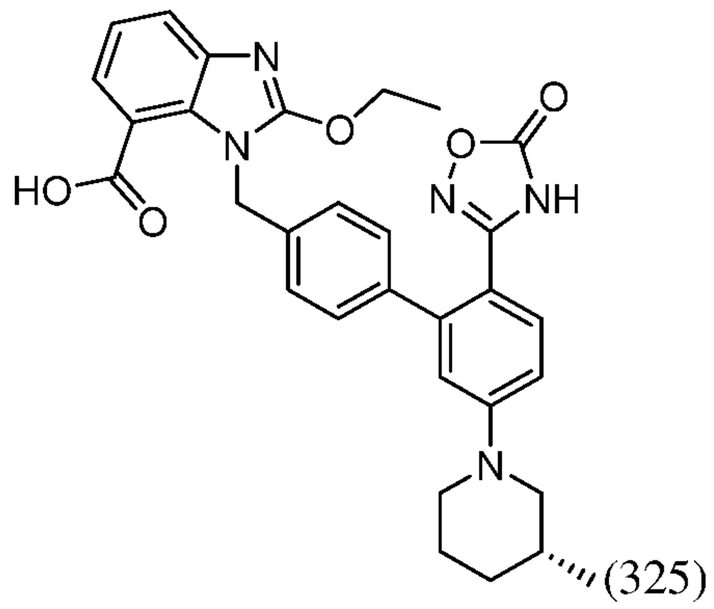
Example 324: (S)-2-ethoxy-1-((5'-(3-methylpiperidin-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(324)

Example 324 was synthesized from **I-005** and (S)-3-methylpiperidine, HCl according to the same sequence described for **Example 323**. MS (ESI) *m/z* $[M + H]^+$ = 538.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (d, *J*=7.8 Hz, 1H), 7.52 (br d, *J*=7.7 Hz, 1H), 7.42 (d, *J*=8.6 Hz, 1H), 7.16 (t, *J*=7.8 Hz, 2H), 7.07 - 6.98 (m, 3H), 6.93 (br d, *J*=8.1 Hz, 2H), 6.87 - 6.76 (m, 1H), 5.64 (s, 2H), 4.59 (q, *J*=7.0 Hz, 2H), 3.80 - 3.66 (m, 2H), 2.73 (br s, 1H), 2.48 - 2.34 (m, 1H), 1.76 (br d, *J*=12.7 Hz, 1H), 1.74 - 1.63 (m, 2H), 1.55 (br d, *J*=12.0 Hz, 1H), 1.40 (t, *J*=7.1 Hz, 3H), 1.17 - 1.01 (m, 1H), 0.91 (d, *J*=6.6 Hz, 3H). LC-MS retention time (Method A4): 1.561 min.

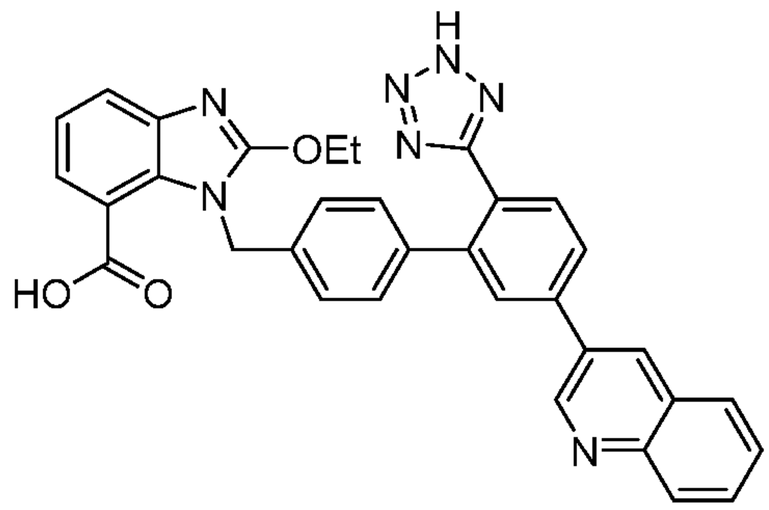
Example 325: (R)-2-ethoxy-1-((5'-(3-methylpiperidin-1-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(325)

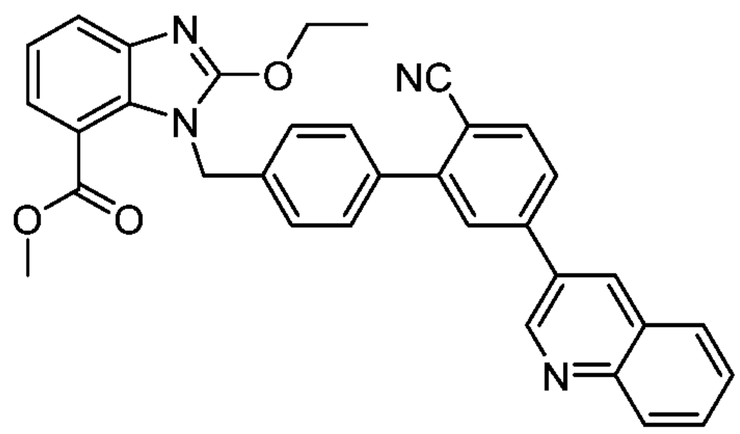
Example 325 was synthesized from **Intermediate 323b** according to the same procedure used to synthesize **Example 299** to give the title compound (**Example 325**, 3.4 mg, 6.14 µmol, 2.403 % yield). LC-MS (Method A4):1.745 min, $[M + H]^+$=554.3;

Example 326: 2-ethoxy-1-((5'-(quinolin-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 326)

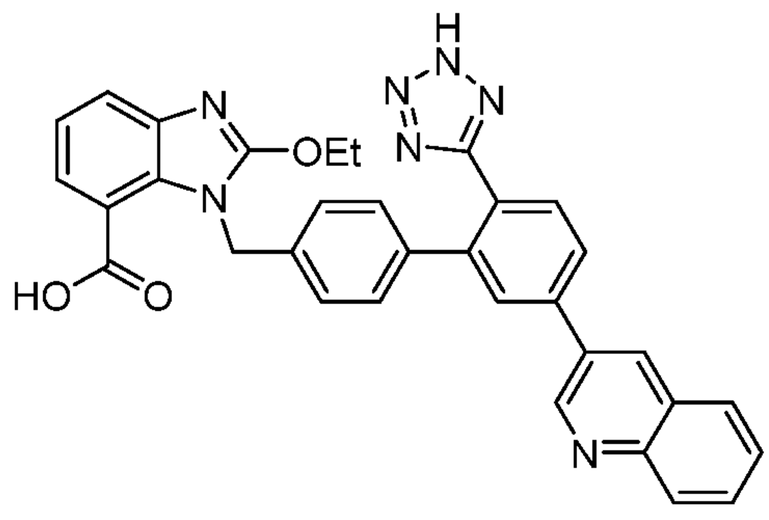
Intermediate 326a: methyl 1-((2'-cyano-5'-(quinolin-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(326a)

To a pressure-rated vial containing **Intermediate 300a** (75 mg, 0.168 m mol) and second generation XPHOS precatalyst (33.1 mg, 0.042 mmol) was added dioxane (2000 µl) followed by 2 M K_3PO_4 (2 M aq) (168 µl, 0.336 mmol). The reaction mixture was evacuated and backfilled with N_2 (3x) before being sealed and heated at 85 °C for 1 h. The reaction mixture was diluted with EtOAc, filtered and concentrated onto celite and purified by ISCO (0-100% EtOAc in hexanes) to afford the title compound (**Intermediate 326a**, 50 mg, 0.093 mmol, 55.2 % yield). LC-MS (Method A2): 0.91 min, $[M + H]^+$=539.0.

Example 326: 2-ethoxy-1-((5'-(quinolin-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

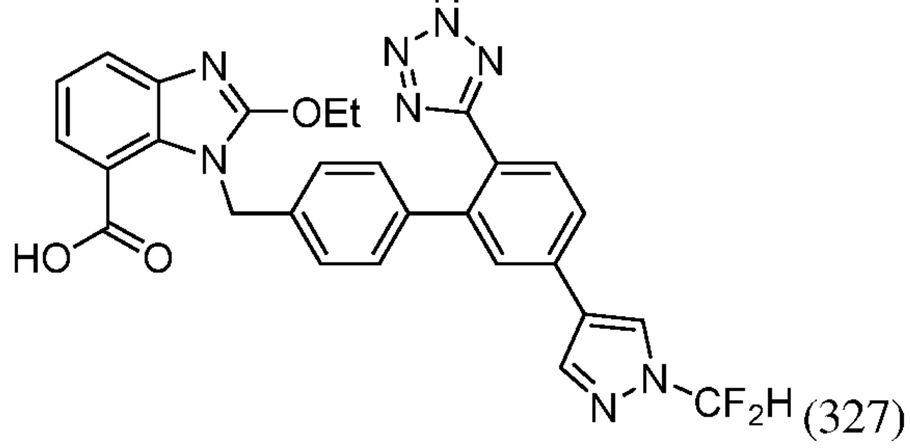


(326)

Example 326 was synthesized from **Intermediate 326a** according to the same procedure used to synthesize **Example 309** to give the title compound (**Example 326**, 18 mg, 0.032 mmol, 34.2 % yield). MS (ESI) *m/z* $[M + H]^+$ = 568.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ

9.38 (d, *J*=1.8 Hz, 1H), 8.91 - 8.77 (m, 1H), 8.13 - 8.04 (m, 3H), 7.98 (s, 1H), 7.87 - 7.78 (m, 2H), 7.72 - 7.63 (m, 2H), 7.56 (d, *J*=7.6 Hz, 1H), 7.25 - 7.11 (m, 3H), 6.99 (br d, *J*=7.9 Hz, 2H), 5.67 (s, 2H), 4.60 (q, *J*=7.0 Hz, 2H), 3.01 (s, 1H), 1.41 (t, *J*=7.2 Hz, 3H). LC-MS retention time (Method A4): 1.324 min.

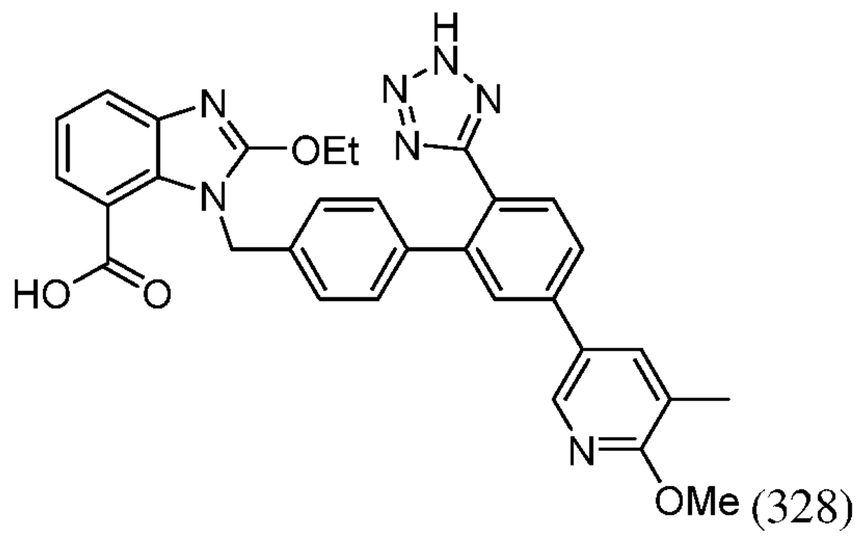
Example 327: 1-((5'-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(327)

Example 327 was synthesized from **Intermediate 300a** and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole according to the same sequence described for **Example 326** to give the title compound (**Example 327**, 20 mg, 0.036 mmol, 35.1 % yield). MS (ESI) *m/z* $[M + H]^+$ = 557.3. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.79 (s, 1H), 7.71 - 7.65 (m, 1H), 7.63 - 7.57 (m, 2H), 7.52 (br d, *J*=7.6 Hz, 1H), 7.42 (br d, *J*=7.6 Hz, 1H), 7.13 - 7.02 (m, 3H), 6.92 (br d, *J*=7.6 Hz, 2H), 5.68 (s, 2H), 4.58 (q, *J*=6.7 Hz, 2H), 1.42 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.490min.

Example 328: 2-ethoxy-1-((5'-(6-methoxy-5-methylpyridin-3-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

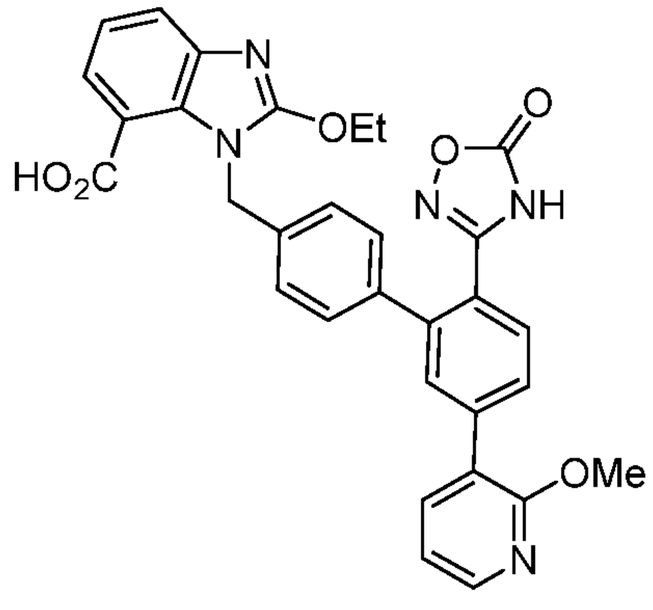


(328)

Example 328 was synthesized from **Intermediate 300a** and (6-methoxy-5-methylpyridin-3-yl)boronic acid according to the same sequence described for **Example 326** to give the title compound (**Example 328**, 0.8 mg, 0.0014 mmol, 1.6% yield). MS (ESI) *m/z* $[M + H]^+$ = 562.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 - 8.37 (m, 1H), 8.03 (s, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.75 - 7.65 (m, 3H), 7.55 (d, *J*=7.6 Hz, 1H), 7.19 (s, 1H),

7.11 (br d, *J*=8.2 Hz, 2H), 6.96 (br d, *J*=7.9 Hz, 2H), 5.65 (s, 2H), 4.59 (d, *J*=7.0 Hz, 2H), 3.93 (s, 3H), 2.21 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.814 min.

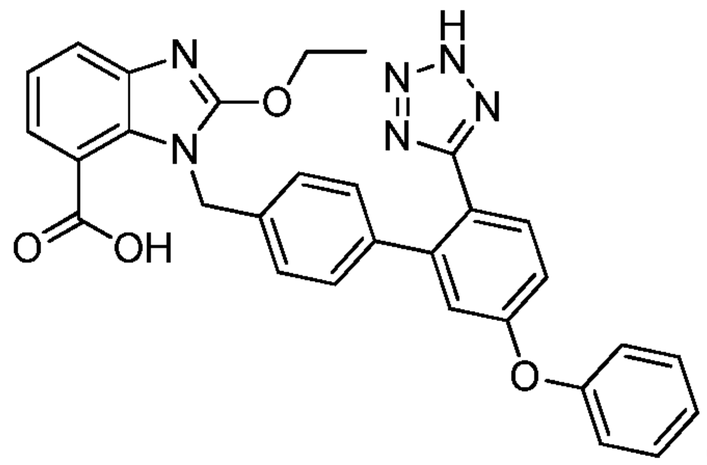
Example 329: 2-ethoxy-1-((5'-(2-methoxypyridin-3-yl)-2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(329)

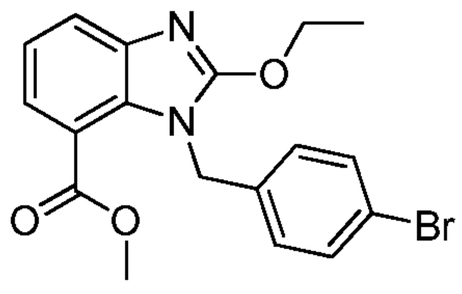
Example 329 was synthesized from **Intermediate 300a** and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine using the sequence described for **Example 321** to give the title compound (**Example 329**, 6.9 mg, 0.012 mmol, 17.3%). MS (ESI) *m/z* $[M + H]^+$ = 564.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.19 (br d, *J*=4.6 Hz, 1H), 7.83 (br d, *J*=7.3 Hz, 1H), 7.73 - 7.57 (m, 3H), 7.53 (s, 2H), 7.26 (br d, *J*=7.6 Hz, 2H), 7.17 (br s, 1H), 7.12 - 7.07 (m, 1H), 7.04 (br d, *J*=7.9 Hz, 2H), 5.66 (br s, 2H), 4.62 - 4.50 (m, 2H), 3.86 (s, 2H), 2.57 - 2.54 (m, 2H), 1.37 (t, *J*=7.0 Hz, 3H). LC-MS retention time (Method A4): 1.730 min.

Example 330: 2-Ethoxy-1-((5'-phenoxy-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



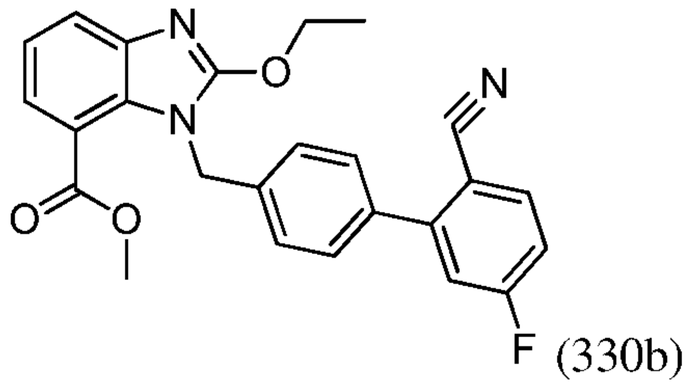
(Ex. 330)

Intermediate 330a: Methyl 1-(4-bromobenzyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate


(330a)

To a 50 mL pressure vessel containing methyl 2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (1.00 g, 4.54 mmol) was added 2-propanol (15 mL) and potassium carbonate (1.25 g, 9.08 mmol) and the mixture was stirred at 30°C for 5 min. To this mixture was added 1-bromo-4-(bromomethyl)benzene (1.19 g, 4.77 mmol) and tetrabutylammonium iodide (0.084 g, 0.23 mmol) and the temperature of the reaction was raised to 45°C. After 60 min an additional 15 mL of 2-propanol was added and the reaction was stirred at the same temperature for another 90 min. The cooled reaction mixture was diluted with EtOAc (200 mL) and H_2O (50 mL), the layers were separated and the organic phase was washed (brine), dried (anhydrous sodium sulfate), filtered and evaporated. The residue was dry-packed onto silica gel (15 g) and purified on a 40 gram column (ISCO/ 0-60% EtOAc-hexane) to provide the title compound as a pale yellow solid (1.50 g, 3.86 mmol, 85% yield). LC-MS (Method H): 1.38 min, $[M + H]^+$= 389.0; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (dd, *J*= 7.8, 1.2 Hz, 1H), 7.58 (dd, *J*= 7.8, 1.2 Hz, 1H), 7.33 - 7.39 (m, 2H), 7.18 (t, *J*= 8.0 Hz, 1H), 6.87 (m, *J*= 8.6 Hz, 2H), 5.58 (s, 2H), 4.65 (q, *J*= 7.2 Hz, 2H), 3.76 (s, 3H), 1.47 (t, *J*= 7.0 Hz, 3H).

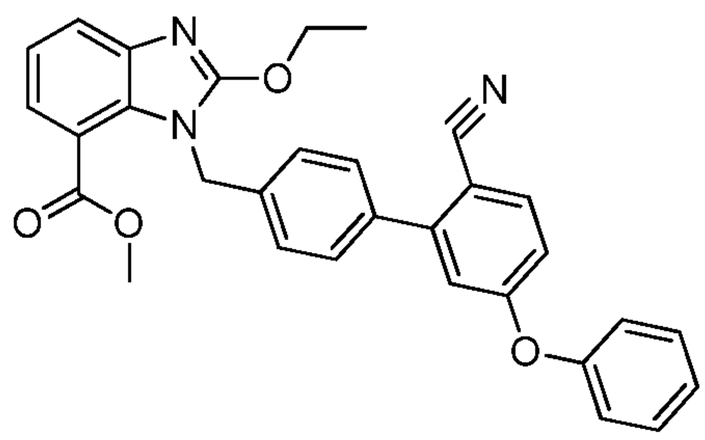
Intermediate 330b: Methyl 1-((2'-cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate


(330b)

In a 20 mL pressure vessel containing **Intermediate 330a** (0.750 g, 1.93 mmol) and 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (0.952 g, 3.85 mmol) was added ethanol/toluene (10 mL, 1:9) and 2M aqueous Na_2CO_3 (2.89 mL, 5.78 mmol). The mixture was purged with a stream of Ar for 10 min and then tetrakis(triphenylphosphine)palladium(0) (0.223 g, 0.193 mmol) was added, the vial was sealed and the mixture was stirred at 110°C for 3 h.

The cooled mixture was diluted with EtOAc (50 mL) and then it was washed (H_2O, brine), dried with anhydrous sodium sulfate, filtered and evaporated. The residue was dry-packed onto silica gel and purified by flash chromatography on a 25 gram column (ISCO/ 0 to 30% EtOAc / hexane) to provide the title compound as an off-white solid (0.800 g, 1.86 mmol, 97% yield). LC-MS (Method H): 1.36 min, $[M + H]^+$= 430.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (dd, *J*=8.6, 5.9 Hz, 1H), 7.71 (dd, *J*=7.8, 1.2 Hz, 1H), 7.53 (m, *J*=8.2 Hz, 2H), 7.40 - 7.51 (m, 3H), 7.20 (t, *J*=7.8 Hz, 1H), 7.09 (m, *J*=8.2 Hz, 2H), 5.58 (s, 2H), 4.62 (q, *J*=7.0 Hz, 2H), 3.70 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H).

Intermediate 330c: Methyl 1-((2'-cyano-5'-phenoxy-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(330c)

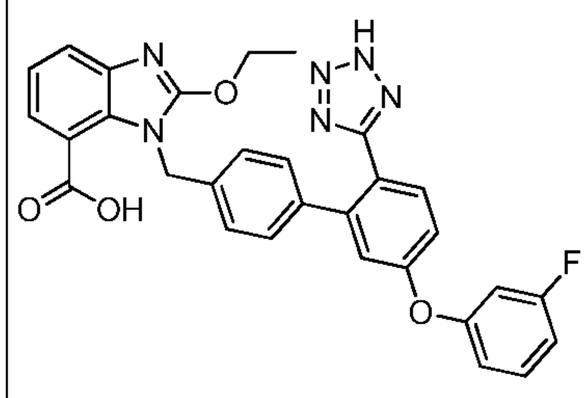
To a solution of **Intermediate 330b** (0.050 g, 0.116 mmol) in DMF (2 mL) was added phenol (0.022 g, 0.233 mmol) and cesium carbonate (0.114 g, 0.349 mmol) and the mixture was stirred at 100°C for 18 h. After cooling to RT, dimethyl sulfoxide (3.5 mL) and formic acid (0.044 mL, 1.16 mmol) were added and the mixture was filtered. The title compound was isolated by reverse phase HPLC (Method F, using formic acid as modifier) to afford a white solid (0.043 g, 0.085 mmol, 73% yield). LC-MS (Method H): 1.47 min, $[M + H]^+$= 504.1; HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O_4$ $[M + H]^+$ *m/z* 504.1918; found: 504.1909.

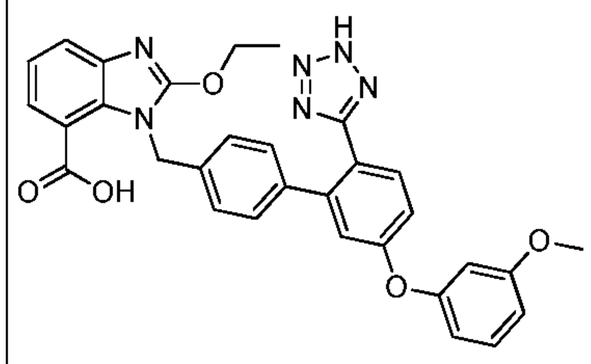
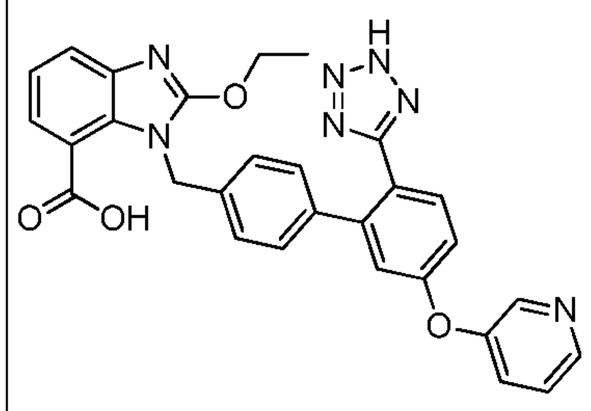
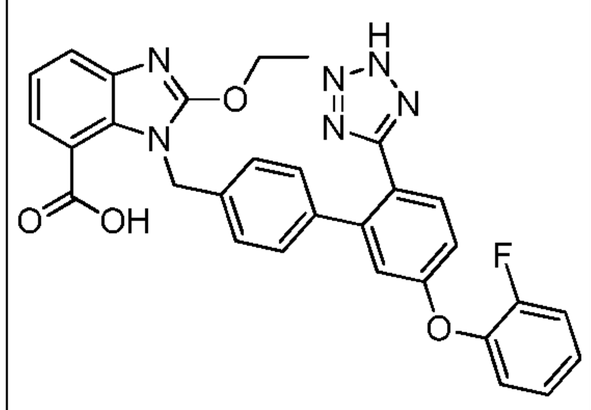
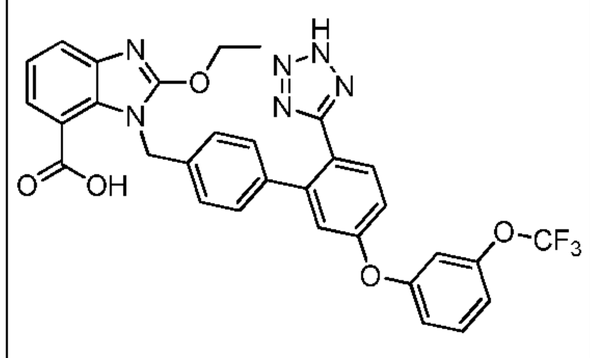
Example 330: 2-Ethoxy-1-((5'-phenoxy-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

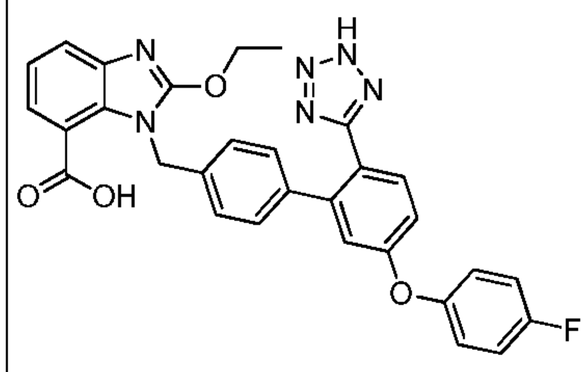
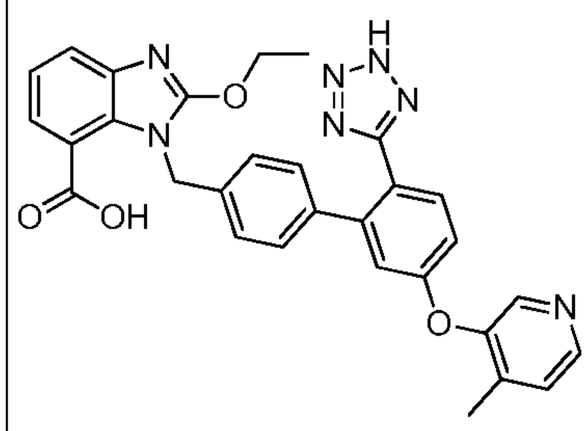
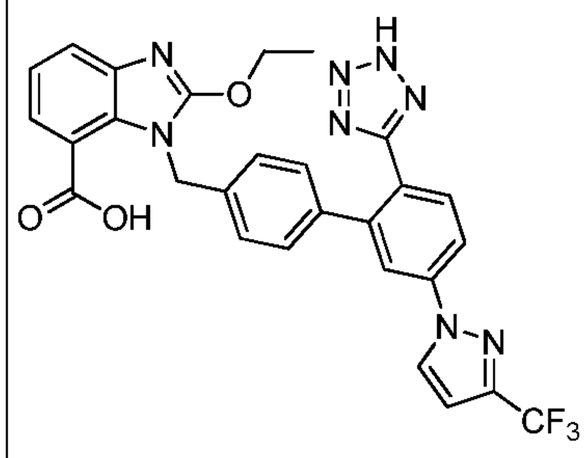
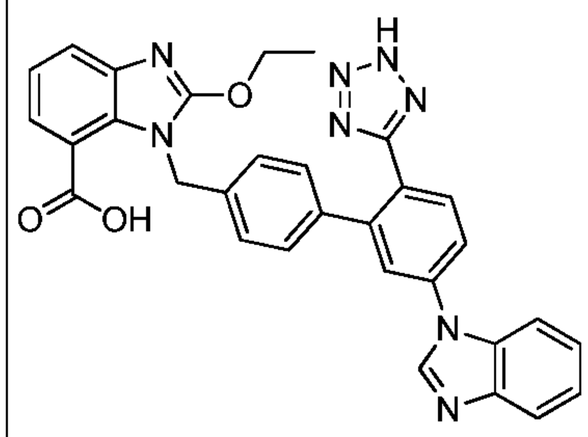
To a mixture of **Intermediate 330c** (0.033 g, 0.066 mmol) in *o*-xylene (3 mL) was added azidotributylstannane (0.054 mL, 0.197 mmol), the reaction vessel was sealed and the mixture was heated at 140°C for 6 days. The volatiles were then removed under reduced pressure and ethanol (3 mL) was added, followed by 2 M aqueous LiOH (0.492 mL, 0.963 mmol). The resulting mixture was stirred at RT for 20 h and then the volatiles were evaporated and EtOAc (3 mL) was added to give a biphasic mixture which was centrifuged at approximately 1000*g*. The supernatant was removed and the white residue

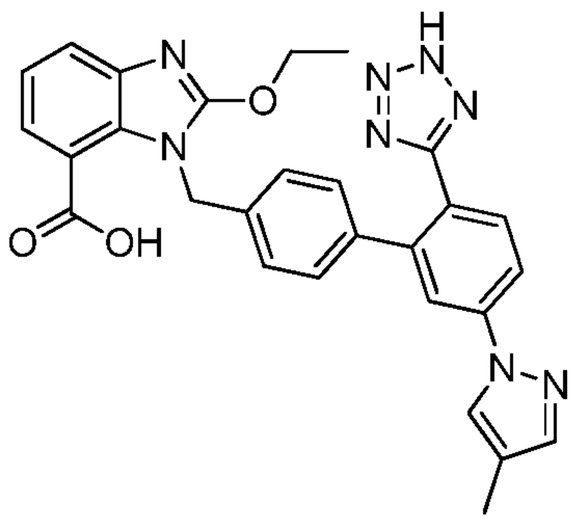
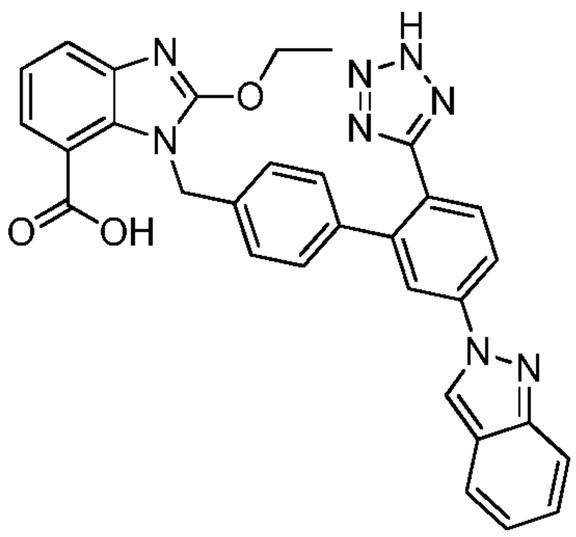
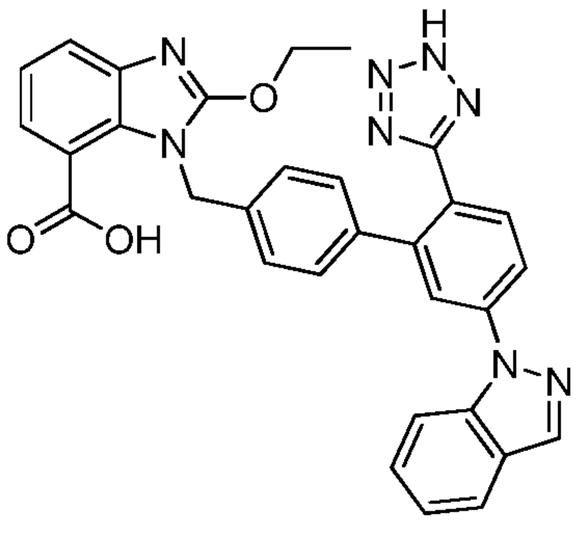
was dissolved in H_2O (3 mL) and AcOH (0.075 mL, 1.31 mmol) was added. The resulting suspension was centrifuged at approximately 1000*g* and then the supernatant was removed and the solid residue was taken up in DMSO (3 mL) and the solution was submitted to reverse phase HPLC purification (Method F, using formic acid as modifier) to afford the title compound as a white solid (0.025 g, 0.047 mmol, 71% yield). LC-MS (Method H): 1.44 min, $[M + H]^+$= 533.1; HRMS (ESI): Calcd. for $C_{30}H_{25}N_6O_4$ $[M + H]^+$ *m/z* 533.1932; found: 533.1931; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.25 (br s, 2H), 7.64 (dd, *J*=7.6, 6.1 Hz, 2H), 7.52 (d, *J*=7.8 Hz, 1H), 7.38 - 7.48 (m, 2H), 7.06 - 7.26 (m, 5H), 7.03 (br s, 1H), 6.99 (m, *J*=7.8 Hz, 2H), 6.91 (m, *J*=8.2 Hz, 2H), 5.61 (s, 2H), 4.56 (q, *J*=7.0 Hz, 2H), 1.36 (t, *J*=7.0 Hz, 3H).

The following examples have been similarly prepared from **Intermediate 330b** and the appropriate phenols, hydroxypyridines or azoles, using a method as described for the synthesis of **Example 330** above. Analytical LC-MS injections were used to determine the final purity and the retention time is reported for each compound, as determined by Method A1, Method A2 or Method H.

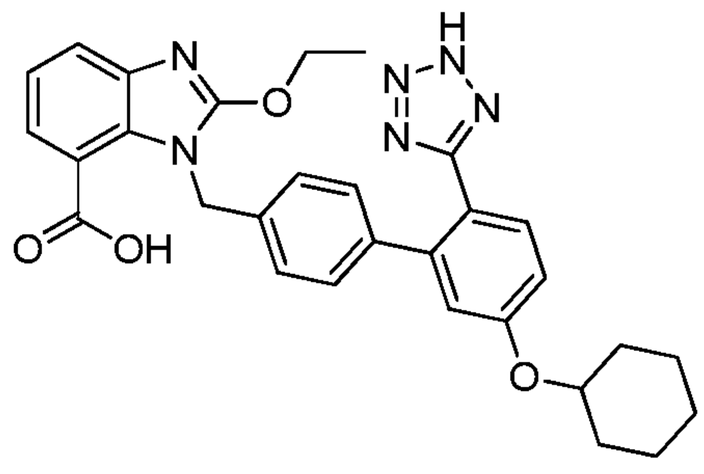
Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
331		550.54	551.1; 1.53 min (Method H)	13.13 (br s, 2H), 7.65 (dd, *J*=7.8, 5.5 Hz, 2 H), 7.52 (d, *J*=7.8 Hz, 1 H), 7.42 - 7.50 (m, 1 H), 7.13 - 7.20 (m, 2 H), 7.09 - 7.13 (m, 1 H), 6.94 - 7.09 (m, 5 H), 6.91 (d, *J*=8.2 Hz, 2 H), 5.61 (s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 1.36 (t, *J*=7.0 Hz, 3 H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
332		562.58	563.1; 1.37 min (Method H)	13.10 (br s, 2 H), 7.59 - 7.68 (m, 2 H), 7.52 (d, *J*=6.7 Hz, 1 H), 7.33 (t, *J*=8.2 Hz, 1 H), 7.16 (t, *J*=7.8 Hz, 1 H), 7.11 (dd, *J*=8.4, 2.5 Hz, 1 H), 7.04 (d, *J*=2.3 Hz, 1 H), 6.99 (m, *J*=8.2 Hz, 2 H), 6.91 (m, *J*=8.2 Hz, 2 H), 6.79 (dd, *J*=8.2, 2.0 Hz, 1 H), 6.72 (t, *J*=2.2 Hz, 1 H), 6.69 (dd, *J*=8.2, 2.0 Hz, 1 H), 5.61 (s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 3.75 (s, 3 H), 1.36 (t, *J*=7.0 Hz, 3 H).
333		533.54	534.1; 1.26 min (Method H)	13.16 (br s, 2 H), 8.49 (br s, 1 H), 8.43 (d, *J*=3.5 Hz, 1 H), 7.56 - 7.71 (m, 3 H), 7.42 - 7.56 (m, 2 H), 7.05 - 7.23 (m, 3 H), 6.85 - 7.05 (m, 4 H),5.61 (br s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 1.36 (t, *J*=6.8 Hz, 3 H).
334		550.54	551.1; 1.34 min (Method H)	13.12 (s, 2 H), 7.59 - 7.68 (m, 2 H), 7.52 (d, *J*=7.8 Hz, 1 H), 7.38 - 7.47 (m, 1 H), 7.22 - 7.38 (m, 3 H), 7.16 (t, *J*=7.8 Hz, 1 H), 7.01 - 7.09 (m, 2 H), 6.99 (m, *J*=7.8 Hz, 2 H), 6.91 (m, *J*=8.2 Hz, 2 H), 5.61 (s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 1.36 (t, *J*=7.0 Hz, 3 H).
335		616.55	617.1, 1.42 min (Method H)	13.12 (br s, 2 H), 7.60 - 7.72 (m, 2 H), 7.48 - 7.59 (m, 2 H), 7.09 - 7.24 (m, 6 H), 7.00 (m, *J*=8.2 Hz, 2 H), 6.91 (m, *J*=8.2 Hz, 2 H), 5.61 (s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 1.36 (t, *J*=7.0 Hz, 3 H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
336		550.54	551.1; 1.36 min (Method H)	13.14 (br s, 2 H), 7.64 (t, *J*=8.8 Hz, 2 H), 7.52 (d, *J*=7.4 Hz, 1 H), 7.12 - 7.32 (m, 5 H), 7.08 (dd, *J*=8.6, 2.7 Hz, 1 H), 6.94 - 7.04 (m, 3 H), 6.84 - 6.94 (m, 2 H), 5.61 (s, 2 H), 4.56 (q, *J*=6.8 Hz, 2 H), 1.36 (t, *J*=7.0 Hz, 3 H).
337		547.56	548.1; 1.27 min (Method H)	13.14 (br s, 2 H), 8.28 - 8.41 (m, 2 H), 7.62 (d, *J*=8.6 Hz, 1 H), 7.65 (d, *J*=7.8 Hz, 1 H), 7.52 (d, *J*=7.8 Hz, 1 H), 7.42 (d, *J*=4.7 Hz, 1 H), 7.16 (t, *J*=7.8 Hz, 1 H), 6.95 - 7.04 (m, 4 H), 6.85 - 6.95 (m, 2 H), 5.61 (s, 2 H), 4.56 (q, *J*=7.0 Hz, 2 H), 2.21 (s, 3 H), 1.36 (t, *J*=7.0 Hz, 3 H).
338		574.51	575.1; 1.34 min (Method H)	13.11 (br s, 2 H) 8.93 (br s, 1 H), 8.08 (dd, *J*=8.4, 2.2 Hz, 1 H), 7.94 - 8.01 (m, 1 H), 7.84 (d, *J*=8.2 Hz, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.54 (d, *J*=7.4 Hz, 1 H), 7.17 (t, *J*=7.8 Hz, 1 H), 7.05 - 7.14 (m, 3 H), 6.97 (d, *J*=7.8 Hz, 2 H), 5.65 (s, 2 H), 4.58 (q, *J*=7.0 Hz, 2 H), 1.39 (t, *J*=7.0 Hz, 3 H).
339		556.57	557.2; 1.29 min (Method H)	13.15 (br s, 2 H), 8.72 (s, 1 H), 7.84 - 7.94 (m, 2 H), 7.71 - 7.83 (m, 3 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.54 (d, *J*=7.8 Hz, 1 H), 7.28 - 7.40 (m, 2 H), 7.08 - 7.21 (m, 3 H), 6.97 (d, *J*=7.8 Hz, 2 H), 5.65 (s, 2 H), 4.58 (q, *J*=7.0 Hz, 2 H), 1.38 (t, *J*=7.0 Hz, 3 H).

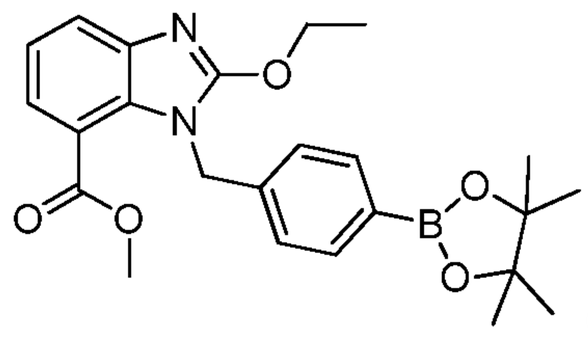
Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (Method)	^{1}H NMR (400MHz, DMSO-d_6) δ ppm
340		520.54	521.2; 1.26 min (Method H)	13.16 (br s, 2 H), 8.47 (s, 1 H), 7.97 (dd, *J*=8.4, 2.2 Hz, 1 H), 7.86 (d, *J*=2.0 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.62 (s, 1 H), 7.54 (d, *J*=7.8 Hz, 1 H), 7.18 (t, *J*=7.8 Hz, 1 H), 7.08 (m, *J*=8.2 Hz, 2 H), 6.95 (m, *J*=8.2 Hz, 2 H), 5.64 (s, 2 H), 4.58 (q, *J*=7.0 Hz, 2 H), 2.09 (s, 3 H), 1.39 (t, *J*=7.0 Hz, 3 H).
341		556.57	557.1; 1.31 min (Method H)	13.08 (br s, 2 H), 9.31 (s, 1 H), 8.28 (d, *J*=8.2 Hz, 1 H), 8.12 - 8.24 (m, 1 H), 7.87 (d, *J*=8.2 Hz, 1 H), 7.60 - 7.80 (m, 3 H), 7.54 (d, *J*=7.0 Hz, 1 H), 7.27 - 7.38 (m, 1 H), 7.06 - 7.23 (m, 4 H), 6.97 (d, *J*=8.2 Hz, 2 H), 5.66 (s, 2 H), 4.59 (q, *J*=6.8 Hz, 2 H), 1.40 (t, *J*=7.0 Hz, 3 H).
342		556.57	557.1; 1.32 min (Method H)	13.17 (br s, 2 H), 8.45 (s, 1 H), 8.00 (dt, *J*=8.3, 2.3 Hz, 2 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.80 - 7.90 (m, 2 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.48 - 7.58 (m, 2 H), 7.31 (t, *J*=7.4 Hz, 1 H), 7.10 - 7.21 (m, 3 H), 6.97 (d, *J*=7.8 Hz, 2 H), 5.64 (s, 2 H), 4.58 (q, *J*=7.0 Hz, 2 H), 1.38 (t, *J*=7.0 Hz, 3 H).

Example 343: 1-((5'-(Cyclohexyloxy)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 343)

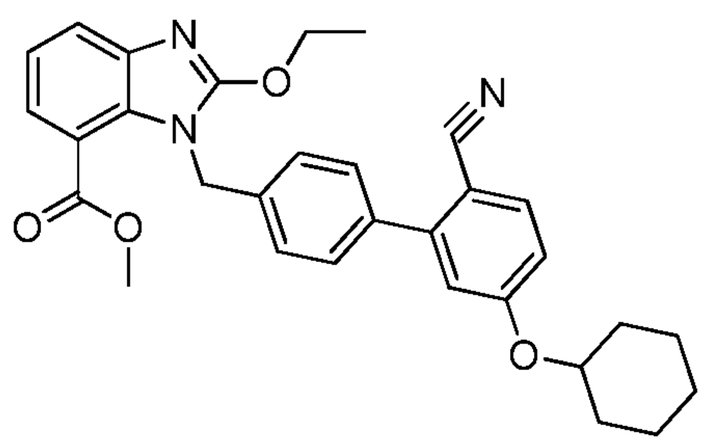
Intermediate 343a: Methyl 2-ethoxy-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-benzo[d]imidazole-7-carboxylate



(343a)

The title compound was prepared by the reaction of methyl 2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (1.00 g, 4.54 mmol) with 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.44 g, 4.77 mmol), in a similar fashion to that described for the synthesis of **Intermediate 330a**, and was obtained as a yellow solid (1.44 g, 3.31 mmol, 72% yield). LC-MS (Method H): 1.42 min, $[M + H]^+ = 437.2$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (dd, *J*=8.0, 1.0 Hz, 1 H), 7.67 (m, *J*=8.2 Hz, 2 H), 7.53 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.16 (t, *J*=7.8 Hz, 1 H), 6.96 (m, *J*=8.2 Hz, 2 H), 5.63 (s, 2 H), 4.65 (q, *J*=7.0 Hz, 2 H), 3.72 (s, 3 H), 1.46 (t, *J*=7.0 Hz, 3 H), 1.31 (s, 12 H).

Intermediate 343b: Methyl 1-((2'-cyano-5'-(cyclohexyloxy)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(343b)

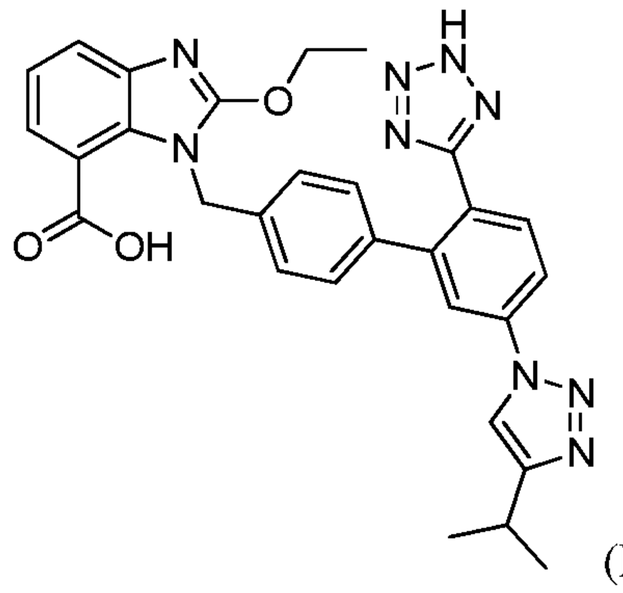
The title compound was prepared by the reaction of methyl 2-ethoxy-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-benzo[d]imidazole-7-carboxylate (**Intermediate 343a**, 0.100 g, 0.229 mmol) with 2-bromo-4-(cyclohexyloxy)benzonitrile (**Intermediate 209a**, 0.128 g, 0.458 mmol), in a similar fashion to that described for the synthesis of **Intermediate 330b,** and was obtained as an off-white solid (0.100 mg, 0.196

mmol, 86% yield).). LC-MS (Method H): 1.58 min, $[M + H]^+$= 510.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (d, *J*=8.6 Hz, 1 H), 7.68 - 7.74 (m, 1 H), 7.41 - 7.56 (m, 4 H), 7.32 - 7.40 (m, 1 H), 7.20 (t, *J*=7.8 Hz, 1 H), 7.03 - 7.12 (m, 3 H), 7.02 (d, *J*=2.3 Hz, 1 H), 5.57 (s, 2 H), 4.62 (q, *J*=7.0 Hz, 2 H), 4.55 (dt, *J*=8.3, 4.3 Hz, 1 H), 3.71 (s, 3 H), 1.86 - 1.97 (m, 2 H), 1.68 (dd, *J*=9.2, 3.3 Hz, 2 H), 1.41 (t, *J*=7.0 Hz, 3 H), 1.31 - 1.59 (m, 4 H), 1.14 - 1.30 (m, 2 H).

Example 343: 1-((5'-(Cyclohexyloxy)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid

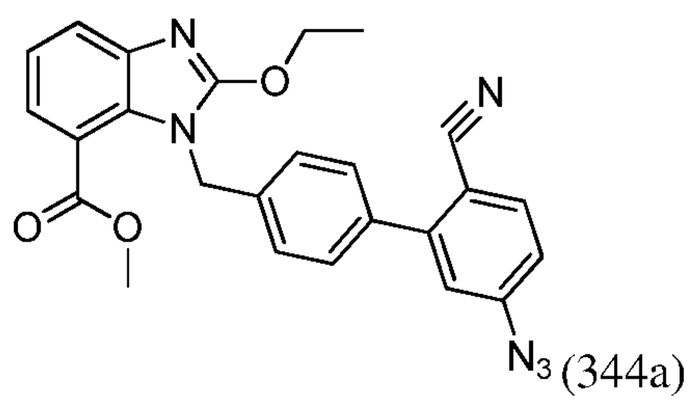
The title compound was prepared from **Intermediate 343b** (0.050 g, 0.098 mmol) according to the method described for the synthesis of **Example 330** and was obtained as a white solid (0.020 g, 0.037 mmol, 37% yield).). LC-MS (Method H): 1.36 min, $[M + H]^+$= 539.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.16 (br s, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.45 - 7.57 (m, 2 H), 7.17 (t, *J*=7.8 Hz, 1 H), 7.10 (dd, *J*=8.6, 2.3 Hz, 1 H), 6.98 - 7.04 (m, 2 H), 6.88 - 6.98 (m, 3 H), 5.62 (s, 2 H), 4.57 (q, *J*=7.0 Hz, 2 H), 4.46 - 4.54 (m, 1 H), 1.86 - 2.00 (m, 2 H), 1.62 - 1.77 (m, 2 H), 1.32 - 1.55 (m, 4 H), 1.38 (t, *J*=7.0 Hz, 3 H), 1.21 - 1.31 (m, 2 H).

Example 344: 2-Ethoxy-1-((5'-(4-isopropyl-1H-1,2,3-triazol-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid



(Ex. 344)

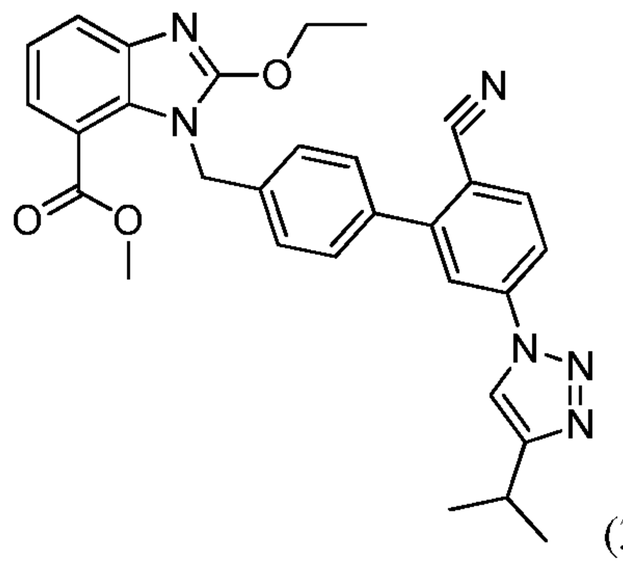
Intermediate 344a: Methyl 1-((5'-azido-2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(344a)

The title compound was prepared by the reaction of methyl 1-((2'-cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (**Intermediate 330b**, 0.100 g, 0.233 mmol) with sodium azide (0.030 g, 0.466 mmol), using conditions similar to those reported for the synthesis of **Intermediate 330c**, to afford a white solid (0.048 g, 0.11 mmol, 45% yield).). LC-MS (Method H): 1.36 min, $[M + H]^+$= 539.2; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.94 (d, *J*=8.2 Hz, 1 H), 7.71 (dd, *J*=8.0, 1.0 Hz, 1 H), 7.52 (m, *J*=8.2 Hz, 2 H), 7.47 (dd, *J*=7.8, 0.8 Hz, 1 H), 7.28 (dd, *J*=8.2, 2.3 Hz, 1 H), 7.24 (d, *J*=2.3 Hz, 1 H), 7.20 (t, *J*=7.8 Hz, 1 H), 7.09 (m, *J*=8.2 Hz, 2 H), 5.58 (s, 2 H), 4.62 (q, *J*=7.0 Hz, 2 H), 3.70 (s, 3 H), 1.41 (t, *J*=7.0 Hz, 3 H).

Intermediate 344b: Methyl 1-((2'-cyano-5'-(4-isopropyl-1H-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate



(344b)

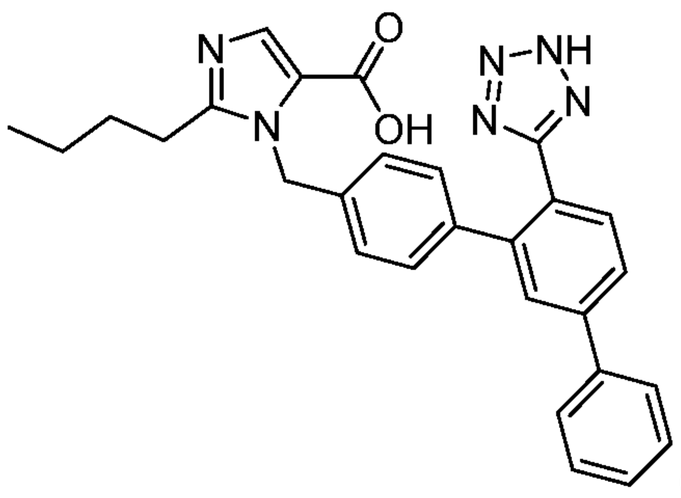
To a mixture of **Intermediate 344a** (0.044 g, 0.097 mmol) in 2-methylpropan-2-ol (2 mL) and H_2O (2 mL) was added 3-methylbut-1-yne (0.076 mL, 0.97 mmol), copper(II) sulfate pentahydrate (0.005 g, 0.019 mmol) and sodium (*R*)-5-((*S*)-1,2-dihydroxyethyl)-4-hydroxy-2-oxo-2,5-dihydrofuran-3-olate (0.004 g, 0.019 mmol) and the mixture was stirred at RT for 18 h and then at 65°C for 24 h. To the resulting mixture was added another portion of copper(II) sulfate pentahydrate (0.005 g, 0.019 mmol) and sodium (*R*)-5-((*S*)-1,2-dihydroxyethyl)-4-hydroxy-2-oxo-2,5-dihydrofuran-3-olate (0.004 g, 0.019 mmol) and heating was continued at 65°C for an additional 24 h. To the cooled mixture was added H_2O (3 mL), brine (2 mL) and tert-butylmethyl ether (10 mL). The organic phase was separated and the aqueous phase was re-extracted with tert-butylmethyl ether (5 mL). The combined organic extract was evaporated and residue was taken up in DMSO (3 mL) and the mixture was filtered. The filtrate was submitted to reverse phase HPLC purification (Method F, using formic acid as modifier) to afford the title compound as a white solid (0.035 g, 0.067 mmol, 69% yield). LC-MS (Method H): 1.37 min, [M +

H]$^+$= 521.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (s, 1 H), 8.11 - 8.20 (m, 2 H), 8.09 (d, *J*=1.6 Hz, 1 H), 7.72 (dd, *J*=7.8, 1.2 Hz, 1 H), 7.62 (m, *J*=8.2 Hz, 2 H), 7.48 (dd, *J*=7.8, 0.8 Hz, 1 H), 7.21 (t, *J*=7.8 Hz, 1 H), 7.13 (m, *J*=8.2 Hz, 2 H), 5.60 (s, 2 H), 4.63 (q, *J*=7.0 Hz, 2 H), 3.73 (s, 3 H), 3.06 (dt, *J*=13.9, 6.7 Hz, 1 H), 1.42 (t, *J*=7.0 Hz, 3 H), 1.29 (d, *J*=7.0 Hz, 6 H).

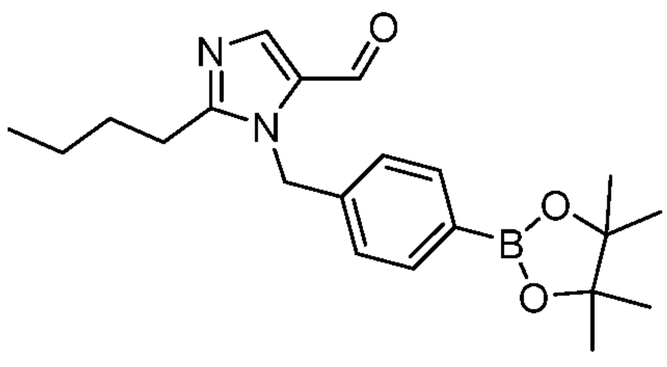
Example 344: 2-Ethoxy-1-((5'-(4-isopropyl-1H-1,2,3-triazol-1-yl)-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylic acid

The reaction of **Intermediate 344b** (0.035 g, 0.061 mmol) according to the method described for the synthesis of **Example 330** provided the title compound as a white solid (0.015 g, 0.027 mmol, 44% yield). LC-MS (Method H): 1.27 min, [M + H]$^+$= 550.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (s, 1 H), 8.10 (d, *J*=7.8 Hz, 1 H), 7.96 (br s, 1 H), 7.85 (d, *J*=8.6 Hz, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.54 (d, *J*=7.0 Hz, 1 H), 7.17 (t, *J*=7.8 Hz, 1 H), 7.11 (m, *J*=7.8 Hz, 2 H), 6.96 (m, *J*=7.4 Hz, 2 H), 5.65 (br s, 2 H), 4.58 (q, *J*=7.0 Hz, 2 H), 3.05 (tt, *J*=13.8, 6.7 Hz, 1 H), 1.39 (t, *J*=7.0 Hz, 3 H), 1.29 (d, *J*=7.0 Hz, 6 H).

Example 345: 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-1H-imidazole-5-carboxylic acid, TFA salt


(Ex. 345)

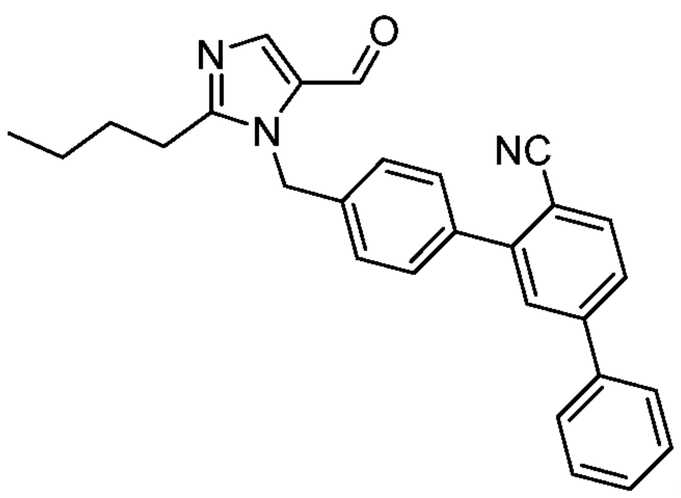
Intermediate 345a: 2-butyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-imidazole-5-carbaldehyde


(345a)

2-Butyl-4-chloro-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-imidazole-5-carbaldehyde (**035a** 2 g, 4.97 mmol) was dissolved in MeOH (100 mL). KOAc (0.585 g, 5.96 mmol) was added followed by Degussa Pd-C (0.264 g, 0.248 mmol). The reaction mixture was evacuated and backfilled with 1 atm of hydrogen and

was stirred at RT for 1 hour and 45 min. The reaction mixture was then evacuated and backfilled with N_2 and filtered through a celite pad which was washed with MeOH. The MeOH was concentrated *in vacuo*. The residue was then suspended in EtOAc and extracted with H_2O 2x, brine 1x, dried with sodium sulfate, filtered and concentrated to yield the title compound (**345a**, 3.8 g, 9.60 mmol, 97 % yield). LC-MS (Method A2): 0.84 min, $[M + H]^+$=369.15; ^1H NMR (500MHz, $CDCl_3$) δ 9.79 - 9.76 (m, 1H), 9.69 (s, 1H), 7.81 (s, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.02 (d, J=8.0 Hz, 2H), 5.62 (s, 2H), 5.60 - 5.59 (m, 1H), 2.68 - 2.63 (m, 2H), 1.76 - 1.65 (m, 2H), 1.40 - 1.37 (m, 2H), 1.37 - 1.33 (m, 12H), 0.94 - 0.85 (m, 3H).

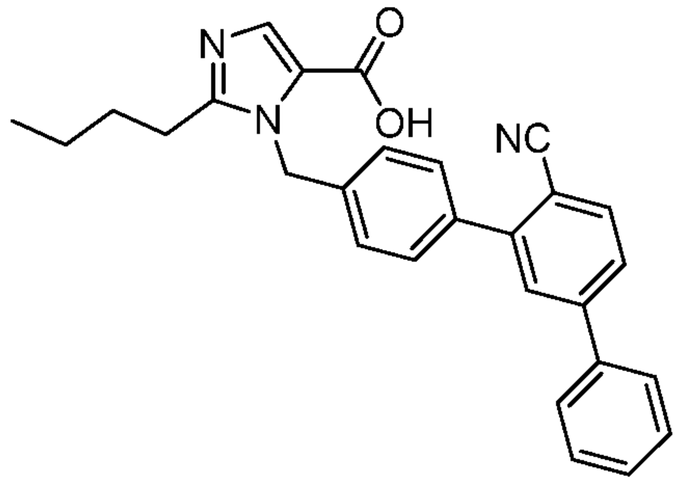
Intermediate 345b: 4''-((2-butyl-5-formyl-1H-imidazol-1-yl)methyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile



(345b)

2-butyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H-imidazole-5-carbaldehyde (**345a**, 1200 mg, 3.26 mmol), 3-chloro-[1,1'-biphenyl]-4-carbonitrile (766 mg, 3.58 mmol) and 2nd generation xphos precatalyst (128 mg, 0.163 mmol) were dissolved in dioxane (16 mL) followed by 2 M K_3PO_4 (2 M aq) (3.3 mL, 6.52 mmol). The reaction mixture was evacuated and backfilled with N_2 (3x) and then heated at 85 °C for 15 h. The reaction mixture was then concentrated onto celite and purified by ISCO (0-100% EtOAc/Hexanes) to afford the title compound (**345b**, 0.8 g, 1.907 mmol, 52.3 % yield). LC-MS: MS (ESI) m/z: 420.1(M+H)+; ^1H NMR (500MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.85 (t, J=4.0 Hz, 2H), 7.74 - 7.57 (m, 6H), 7.55 - 7.43 (m, 3H), 7.19 (d, J=8.3 Hz, 2H), 5.68 (s, 2H), 2.80 - 2.70 (m, 2H), 1.77 (t, J=7.7 Hz, 2H), 1.47 - 1.35 (m, 2H), 0.94 (t, J=7.4 Hz, 3H).

Intermediate 345c: 2-butyl-1-((6'-cyano-[1,1':3',1''-terphenyl]-4-yl)methyl)-1H-imidazole-5-carboxylic acid



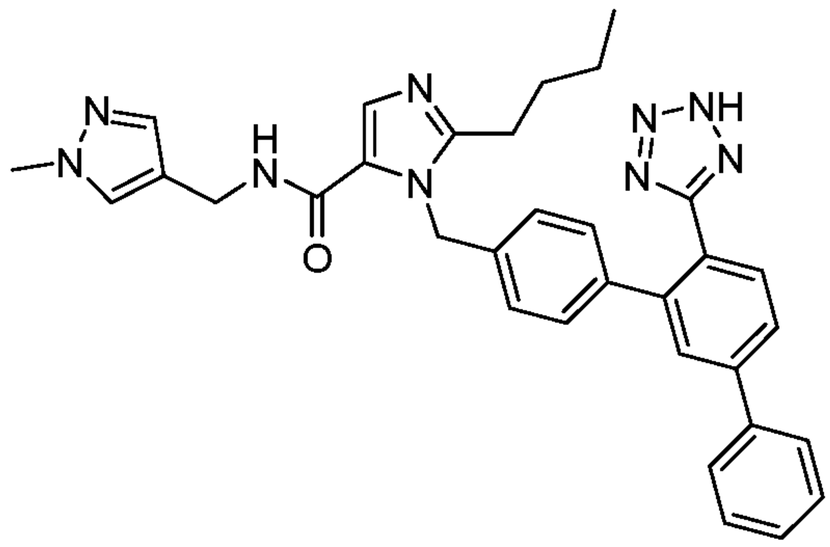
(345c)

4"-((2-butyl-5-formyl-1H-imidazol-1-yl)methyl)-[1,1':3',1"-terphenyl]-4'-carbonitrile (**345b**, 1.5 g, 3.58 mmol) and 2M 2-methylbut-2-ene in THF (7.15 mL, 14.30 mmol) were dissolved in 1-butanol (20 mL). Water (20 mL) was added followed by sodium dihydrogen phosphate (1.287 g, 10.73 mmol) and sodium chlorite (0.970 g, 10.73 mmol). The reaction mixture was allowed to stir at RT for 15 h. The reaction mixture was then cooled to 0 °C and quenched with 10% aq. sodium sulfite (31.5 g, 25.03 mmol). The reaction mixture was allowed to stir at RT for 10 min and was then extracted with EtOAc 3x. The combined organic layer was then washed with brine, dried with sodium sulfate, filtered and concentrated to yield 2-butyl-1-((6'-cyano-[1,1':3',1"-terphenyl]-4-yl)methyl)-1H-imidazole-5-carboxylic acid (**345c**, 1.17 g, 2.176 mmol, 60.9 % yield). LC-MS (Method A2): 0.84 min, $[M + H]^+$=436.10;

Example 345: 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1"-terphenyl]-4-yl)methyl)-2-butyl-1H-imidazole-5-carboxylic acid, TFA salt

To a small vial containing 2-butyl-1-((6'-cyano-[1,1':3',1"-terphenyl]-4-yl)methyl)-1H-imidazole-5-carboxylic acid (**345c**, 485 mg, 0.902 mmol) was added dibutyltin oxide (225 mg, 0.902 mmol) and toluene (20 mL) followed by TMS-N_3 (0.599 mL, 4.51 mmol). The reaction mixture was sealed and heated at 100 °C for 18 h. The reaction mixture was then diluted with hexanes and celite was added. The mixture was filtered and washed with hexanes. The celite was then purified using reverse phase ISCO (0-100% B. A = H_2O/ACN/TFA 90:10:0.1. B = ACN/H_2O/TFA 90:10:0.1) to afford the title compound (**Example 345**, 834 mg, 1.196 mmol, 66.3 % yield). LC-MS (Method A4): 1.599 min, $[M + H]^+$= 479.0; ^{1}H NMR (500MHz, DMSO-d_6) δ 7.75 (d, *J*=7.6 Hz, 2H), 7.69 (q, *J*=7.9 Hz, 2H), 7.58 (s, 2H), 7.48 (t, *J*=7.5 Hz, 2H), 7.42 - 7.35 (m, 1H), 7.16 (d, *J*=7.9 Hz, 2H), 6.89 (d, *J*=7.9 Hz, 2H), 5.59 (s, 2H), 2.58 (t, *J*=7.5 Hz, 2H), 1.54 (quin, *J*=7.5 Hz, 2H), 1.36 - 1.18 (m, 2H), 0.81 (t, *J*=7.3 Hz, 3H).

Example 346: 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1"-terphenyl]-4-yl)methyl)-2-butyl-N-((1-methyl-1H-pyrazol-4-yl)methyl)-1H-imidazole-5-carboxamide

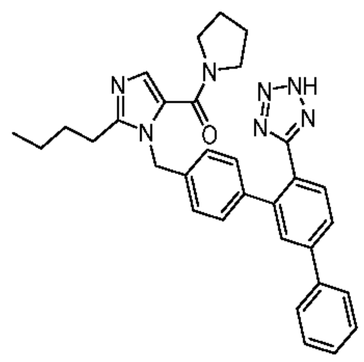
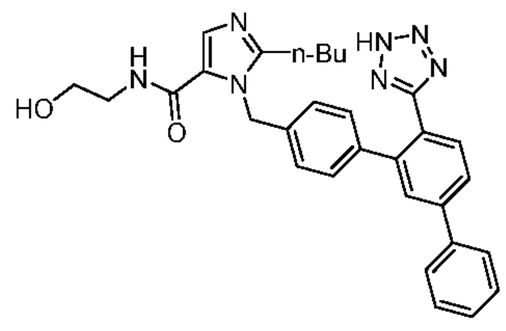
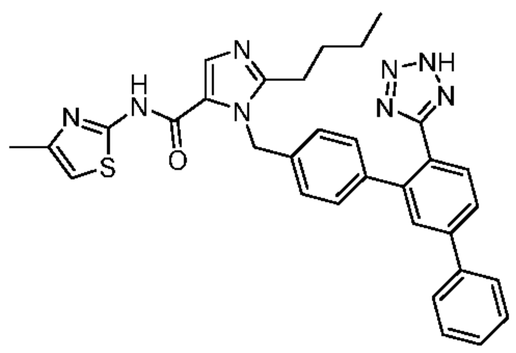


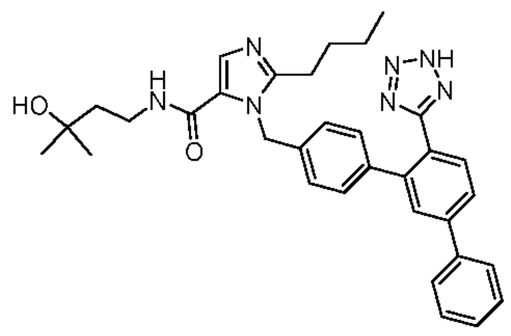
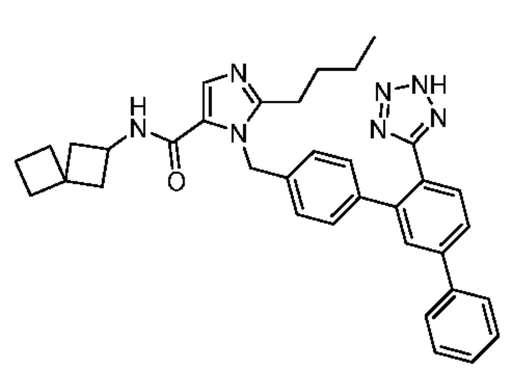
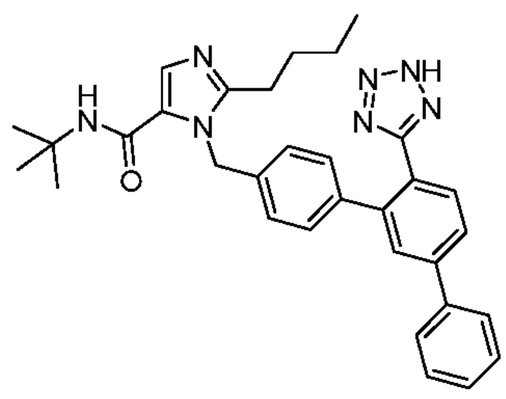
(Ex. 346)

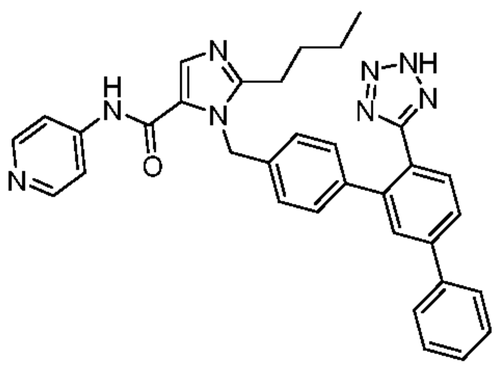
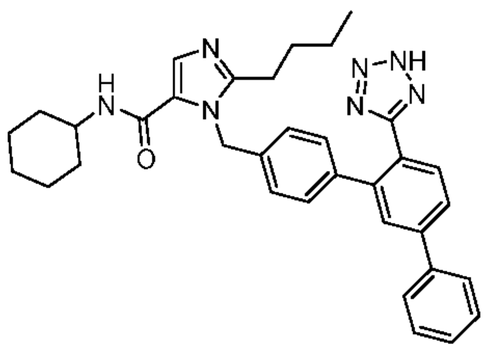
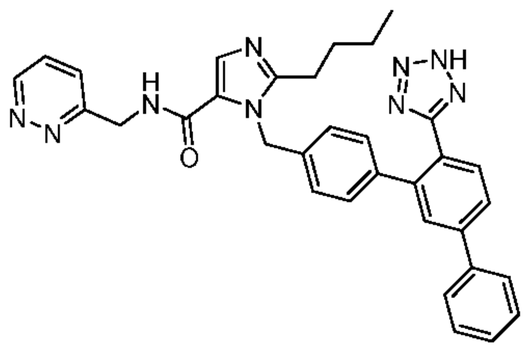
(1-methyl-1H-pyrazol-4-yl)methanamine (116 mg, 1.041 mmol), 1-((6'-(2H-tetrazol-5-yl)-[1,1':3',1''-terphenyl]-4-yl)methyl)-2-butyl-1H-imidazole-5-carboxylic acid (**Example 345**, 200 mg, 0.347 mmol), and Hunig's Base (224 mg, 1.734 mmol) were dissolved in DMF (5 mL). HATU (264 mg, 0.694 mmol) was added and the reaction mixture was allowed to stir at RT for 18 h. The reaction mixture was then filtered and purified via preparative HPLC (XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 ACN: H_2O with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN: H_2O with 10 mM NH_4OAc; Gradient: 13-53% B over 20 min, then a 6-minute hold at 100% B; Flow: 20 mL/min;) to afford the title compound (**Example 346**, 128.1 mg, 0.217 mmol, 62.7 % yield). LC-MS (Method A4): 1.542 min, $[M + H]^+$=572.4; ^1H NMR (500 MHz, DMSO-d_6) δ 8.46 (br t, *J*=5.7 Hz, 1H), 7.82 - 7.69 (m, 4H), 7.68 - 7.62 (m, 1H), 7.56 - 7.46 (m, 4H), 7.45 - 7.37 (m, 1H), 7.28 (s, 1H), 7.22 - 7.12 (m, *J*=8.1 Hz, 2H), 7.02 - 6.87 (m, *J*=8.1 Hz, 2H), 5.63 (s, 2H), 4.22 (d, *J*=5.8 Hz, 2H), 2.59 - 2.53 (m, 5H), 1.56 (quin, *J*=7.5 Hz, 2H), 1.34 - 1.23 (m, 2H), 0.84 (t, *J*=7.4 Hz, 3H).

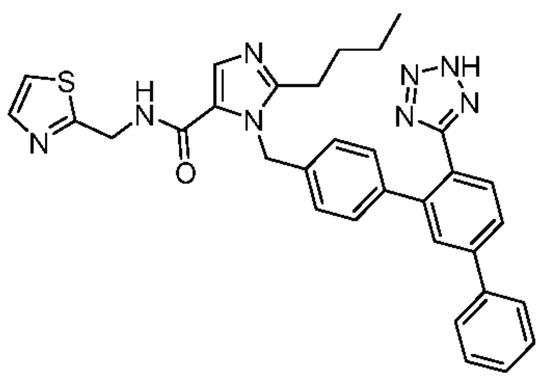
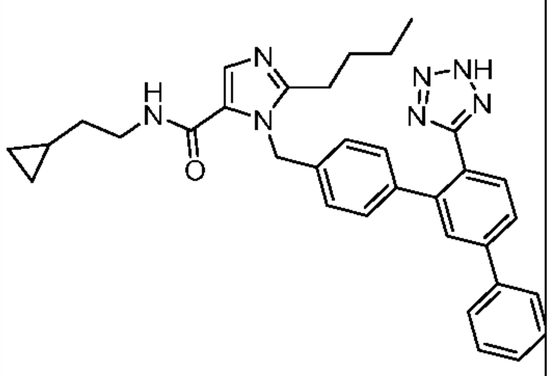
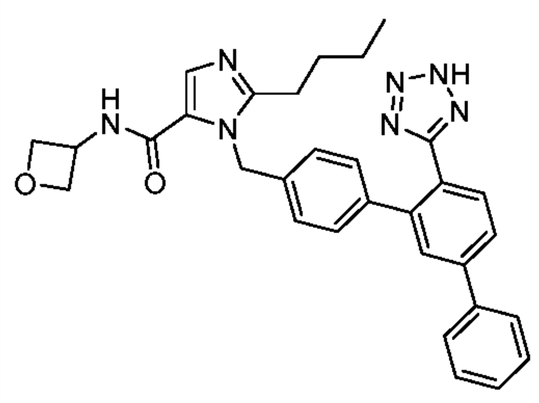
The following examples have been similarly prepared from **Example 345** as described above for **Example 346**.

Ex	Structure	MW	LC-MS *m/z* $[M + H]^+$; RT (min) (Method A4)	^1H NMR (500MHz, DMSO-d_6) δ ppm

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (min) (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
347		531.664	532.1; 1.71	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.33 (br d, *J*=2.4 Hz, 1H), 7.93 (br d, *J*=7.9 Hz, 1H), 7.84 (s, 1H), 7.81 - 7.73 (m, 2H), 7.27 - 7.11 (m, *J*=7.9 Hz, 2H), 7.04 - 6.94 (m, *J*=7.9 Hz, 2H), 5.60 (s, 2H), 3.92 (s, 3H), 2.69 - 2.57 (m, 2H), 1.59 - 1.44 (m, 2H), 1.33 - 1.15 (m, 2H), 0.81 (br t, *J*=7.2 Hz, 3H).
348		521.625	522.5; 1.424	^{1}H NMR (500MHz, DMSO-d_6) δ 8.25 (br. s., 1H), 7.82 - 7.72 (m, 3H), 7.67 (d, *J*=8.0 Hz, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.48 (t, *J*=7.6 Hz, 2H), 7.40 (d, *J*=7.4 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 1H), 6.91 (d, *J*=8.1 Hz, 1H), 5.60 (s, 2H), 3.44 (t, *J*=6.1 Hz, 2H), 3.23 (q, *J*=6.0 Hz, 2H), 2.53 (br. s., 2H), 1.57 - 1.45 (m, 2H), 1.29 - 1.15 (m, 2H), 0.79 (t, *J*=7.3 Hz, 3H).
349		574.71	575.5; 1.690	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (br s, 1H), 7.86 - 7.75 (m, 3H), 7.75 - 7.67 (m, 2H), 7.49 (br t, *J*=7.5 Hz, 2H), 7.45 - 7.38 (m, 1H), 7.15 (br d, *J*=7.7 Hz, 2H), 6.97 (br d, *J*=7.9 Hz, 2H), 6.75 (s, 1H), 5.68 (br s, 2H), 2.64 - 2.55 (m, 2H), 2.27 (s, 3H), 1.51 (br d, *J*=6.5 Hz, 2H), 1.25 (br d, *J*=6.9 Hz, 2H), 0.80 (br t, *J*=6.9 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (min) (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
350		563.706	564.5; 1.440	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (br s, 1H), 7.87 - 7.76 (m, 3H), 7.72 (br d, *J*=8.2 Hz, 2H), 7.55 - 7.46 (m, 3H), 7.46 - 7.39 (m, 1H), 7.13 (br d, *J*=8.0 Hz, 2H), 6.95 (br d, *J*=8.0 Hz, 2H), 5.62 (br s, 2H), 3.32 - 3.16 (m, 2H), 2.57 - 2.55 (m, 2H), 1.63 - 1.52 (m, 2H), 1.48 (br s, 2H), 1.23 (br d, *J*=7.2 Hz, 2H), 1.09 (s, 6H), 0.85 - 0.74 (m, 3H).
351		571.729	572.5; 1.901	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 - 8.36 (m, 1H), 7.84 (br d, *J*=8.0 Hz, 1H), 7.80 - 7.68 (m, 4H), 7.57 - 7.47 (m, 3H), 7.46 - 7.38 (m, 1H), 7.19 - 7.03 (m, *J*=8.0 Hz, 2H), 6.99 - 6.88 (m, *J*=8.0 Hz, 2H), 5.58 (s, 2H), 4.23 - 4.05 (m, 1H), 2.59 - 2.54 (m, 2H), 2.31 - 2.18 (m, 2H), 2.00 - 1.83 (m, 6H), 1.75 (q, *J*=7.7 Hz, 2H), 1.45 (quin, *J*=7.5 Hz, 2H), 1.28 - 1.13 (m, 2H), 0.77 (t, *J*=7.3 Hz, 3H).
352		533.68	534.6; 1.675	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 - 7.75 (m, 3H), 7.75 - 7.67 (m, 2H), 7.63 (br s, 1H), 7.54 - 7.45 (m, 3H), 7.45 - 7.39 (m, 1H), 7.17 - 7.09 (m, *J*=7.8 Hz, 2H), 7.05 - 6.94 (m, *J*=7.9 Hz, 2H), 5.55 (s, 2H), 2.58 - 2.52 (m, 2H), 1.46 (br d, *J*=7.0 Hz, 2H), 1.29 (s, 9H), 1.22 (br d, *J*=7.3 Hz, 2H), 0.78 (br t, *J*=7.3 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (min) (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
353		554.658	555; 1.496	[NEED NMR]
354		559.718	560; 1.520	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 - 8.30 (m, 1H), 7.84 (br d, *J*=8.0 Hz, 1H), 7.80 - 7.68 (m, 4H), 7.57 - 7.47 (m, 3H), 7.46 - 7.38 (m, 1H), 7.18 - 7.05 (m, *J*=8.0 Hz, 2H), 6.99 - 6.88 (m, *J*=8.0 Hz, 2H), 5.58 (s, 2H), 4.32 - 4.06 (m, *J*=7.9 Hz, 1H), 2.59 - 2.54 (m, 2H), 2.24 (br s, 2H), 2.04 - 1.89 (m, 4H), 1.85 (br d, *J*=7.5 Hz, 2H), 1.75 (br d, *J*=7.1 Hz, 2H), 1.45 (br d, *J*=7.4 Hz, 2H), 1.20 (br d, *J*=7.4 Hz, 2H), 0.77 (t, *J*=7.3 Hz, 3H).
355		569.673	570.1; 1.571	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (br d, *J*=4.6 Hz, 2H), 7.94 - 7.74 (m, 3H), 7.71 (br d, *J*=8.0 Hz, 1H), 7.68 - 7.61 (m, 3H), 7.54 - 7.46 (m, 3H), 7.46 - 7.37 (m, 1H), 7.13 (br d, *J*=7.7 Hz, 2H), 6.93 (br d, *J*=8.0 Hz, 2H), 5.60 (s, 2H), 4.66 (br d, *J*=5.7 Hz, 2H), 2.56 (br s, 2H), 1.57 - 1.44 (m, 2H), 1.31 - 1.19 (m, 2H), 0.80 (br t, *J*=7.3 Hz, 3H).

Ex	Structure	MW	LC-MS *m/z* [M + H]$^+$; RT (min) (Method A4)	^{1}H NMR (500MHz, DMSO-d_6) δ ppm
356		574.71	575.2; 1.676	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (br s, 1H), 7.78 (br d, *J*=8.6 Hz, 3H), 7.74 - 7.63 (m, 4H), 7.57 (br s, 1H), 7.53 - 7.40 (m, 3H), 7.21 - 7.06 (m, *J*=7.8 Hz, 2H), 7.01 - 6.91 (m, *J*=8.0 Hz, 2H), 5.64 (s, 2H), 4.66 (br d, *J*=5.9 Hz, 2H), 2.61 - 2.56 (m, 2H), 1.67 - 1.40 (m, 2H), 1.36 - 1.08 (m, *J*=7.2 Hz, 2H), 0.80 (br t, *J*=7.2 Hz, 3H).
357		545.29	546.1; 1.853	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (br s, 1H), 7.85 (br d, *J*=7.9 Hz, 1H), 7.79 (br d, *J*=7.4 Hz, 2H), 7.76 - 7.69 (m, 2H), 7.56 - 7.47 (m, 3H), 7.47 - 7.40 (m, 1H), 7.17 - 7.09 (m, *J*=7.9 Hz, 2H), 7.01 - 6.91 (m, *J*=7.9 Hz, 2H), 5.62 (s, 2H), 3.29 - 3.16 (m, 2H), 2.58 - 2.53 (m, 2H), 1.55 - 1.43 (m, 2H), 1.35 (q, *J*=6.8 Hz, 2H), 1.29 - 1.17 (m, 2H), 0.80 (br t, *J*=7.3 Hz, 3H), 0.65 (br s, 1H), 0.35 (br d, *J*=7.7 Hz, 2H), 0.00 (br d, *J*=3.6 Hz, 2H).
358		533.636	534; 1.622	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (br s, 1H), 7.79 - 7.63 (m, 6H), 7.59 (s, 1H), 7.48 (t, *J*=7.6 Hz, 2H), 7.44 - 7.35 (m, 1H), 7.22 - 7.05 (m, *J*=7.9 Hz, 2H), 6.97 - 6.80 (m, *J*=8.0 Hz, 2H), 5.58 (s, 2H), 5.02 - 4.85 (m, 1H), 4.72 (t, *J*=6.9 Hz, 2H), 4.52 (t, *J*=6.3 Hz, 2H), 2.57 - 2.53 (m, 2H), 1.60 - 1.44 (m, 2H), 1.32 - 1.18 (m, 2H), 0.81 (br t, *J*=7.3 Hz, 3H).

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 445

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 445

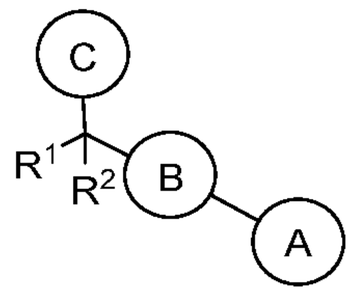
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

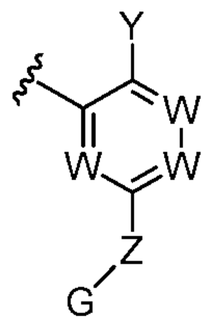
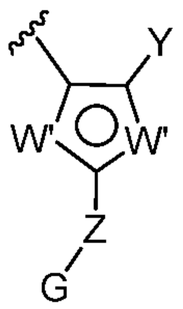
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or salt thereof:



(I)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring A is  or  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16}, wherein at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

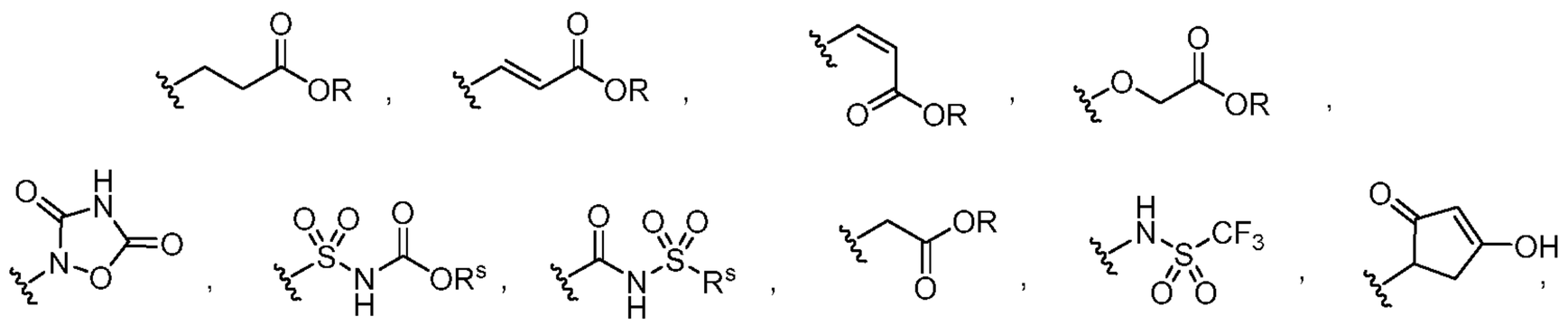
alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4 to 6 membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

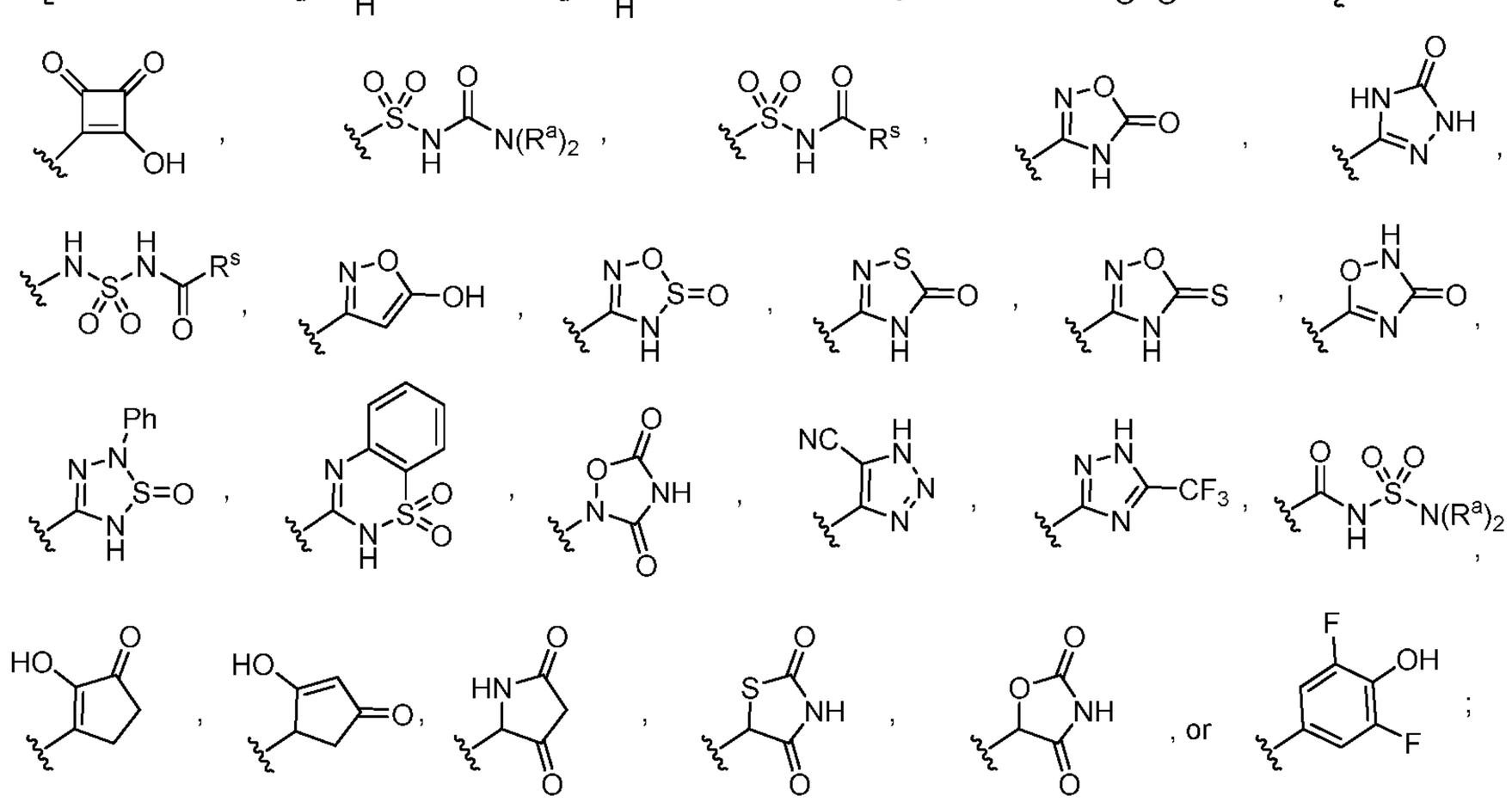
R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H , PO_3H_2, COOR,





R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_{6-10}-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_3 alkyl, C_{6-10} aryl, C_{6-10}-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl is a 5-10 membered group and the heterocycle is a 4-10 membered each having 1-3 heteroatoms selected from N, O, or S;

Z, at each occurrence, is independently selected from a bond, O, S, $N(R^z)$, $C(R^z)_2$, C=O, $C(=O)N(R^z)$, $N(R^z)C(=O)$, $C(R^z)_2C(R^z)_2$, $OC(R^z)_2$, $SC(R^z)_2$, $N(R^z)C(R^z)_2$, $C(R^z)_2O$, $C(R^z)_2S$, $C(R^z)_2N(R^z)$;

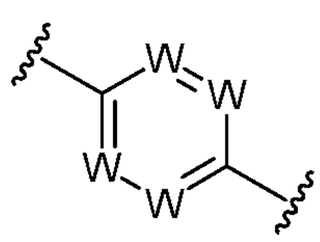
R^z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, two R^z groups either on the

same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ hydroxyalkyl, phenyl, CH_2-phenyl;

ring B is



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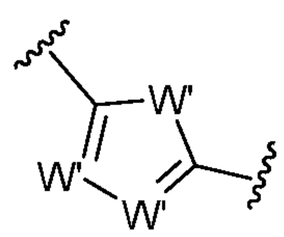

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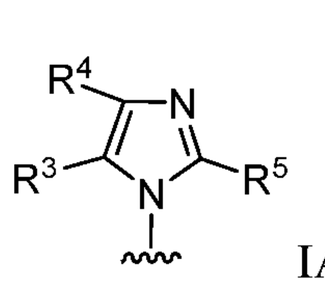
Group C is



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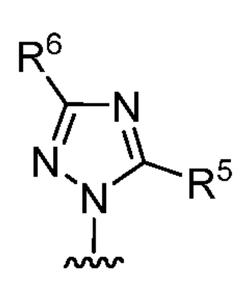

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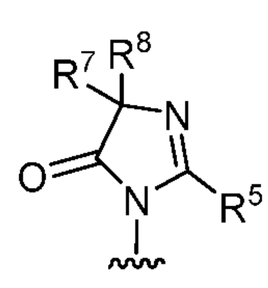

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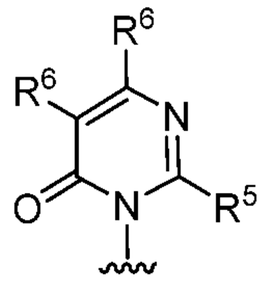

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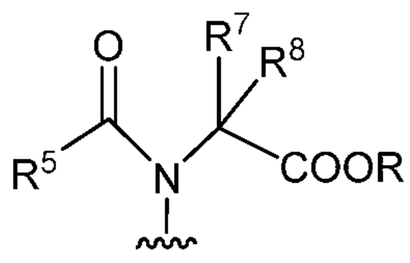

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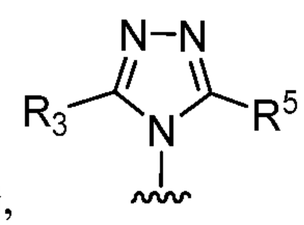

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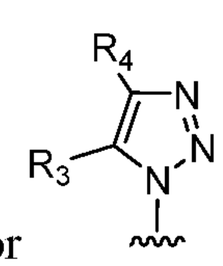
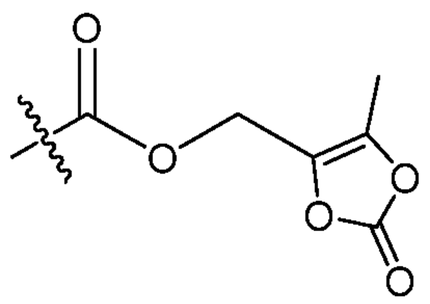
or


IJ

R^3 is $C_{1\text{-}4}$ hydroxyalkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}6}$–hydroxycycloalkyl, $C_{1\text{-}6}$–halocycloalkyl,



COOR, $CON(R^z)_2$, or ;

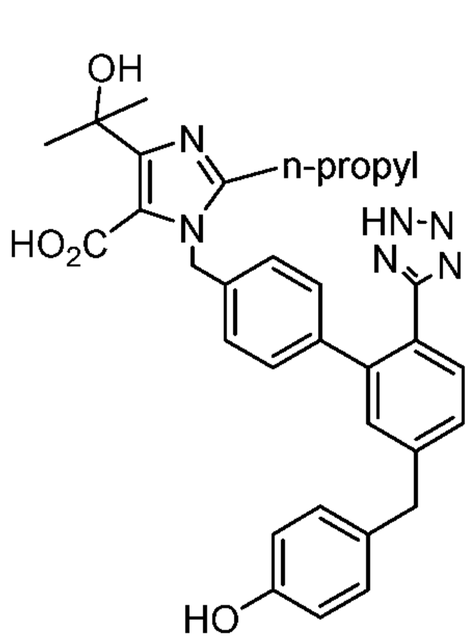
R^4 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ haloalkyl $C_{1\text{-}4}$ alkoxyalkyl, $C_{1\text{-}4}$ hydroxyalkyl, $C_{1\text{-}6}$–cycloalkyl, $C_{1\text{-}6}$–halocycloalkyl, $C_{1\text{-}6}$–alkoxycycloalkyl, or $C_{1\text{-}6}$–hydroxycycloalkyl;

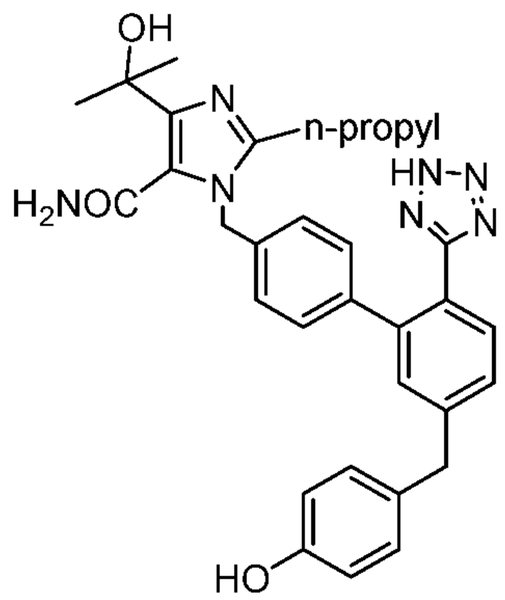
R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl; C_{1-6} alkoxyalkyl, C_{1-6}–cycloalkyl-C_{0-4}–alkyl which may be substituted with 1-3 halogens or a C_{1-3}-alkoxy group;

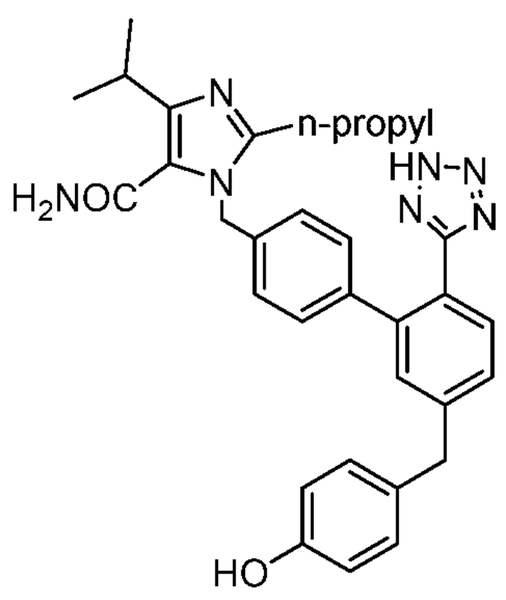
R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, C_{1-4}-alkyl, C_{1-4}-haloalkyl, C_{1-4}-alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{1-6}–cycloalkyl, C_{1-6}–halocycloalkyl, C_{1-6}–alkoxycycloalkyl, or C_{1-6}–hydroxycycloalkyl; and

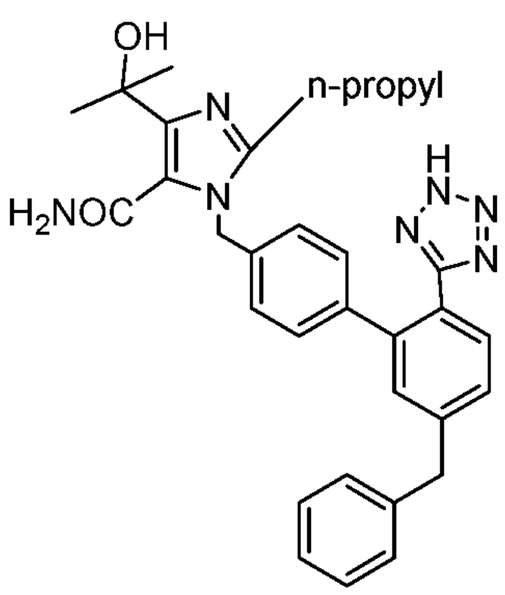
R^7 and R^8, are independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, R^7 and R^8, along with the atom to which they are attached, can join to form a C_3-C_6-cycloalkyl, a C_3-C_6-halocycloalkyl, a C_3-C_6-hydroxycycloalkyl or a 4 to 7 membered heterocycle having 1-2 heteroatoms selected from N, O, or S and the potential for further substitution with 1-4 F, OH, C_{1-4}-alkyl, C_{1-4}-haloalkyl C_{1-4}-alkoxyalkyl, C_{1-4}-hydroxyalkyl,

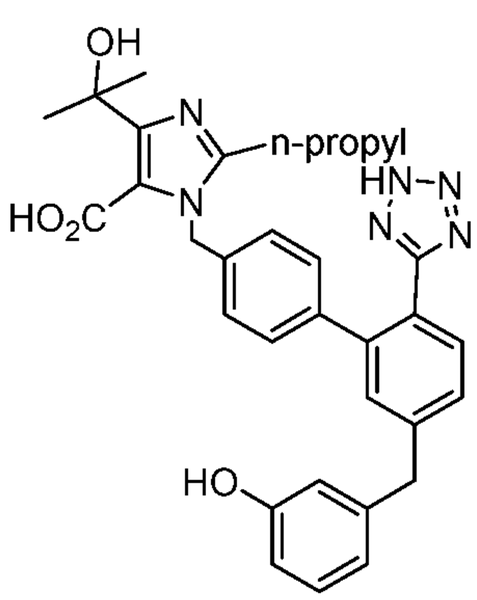
provided the compounds of Formula (I) are not

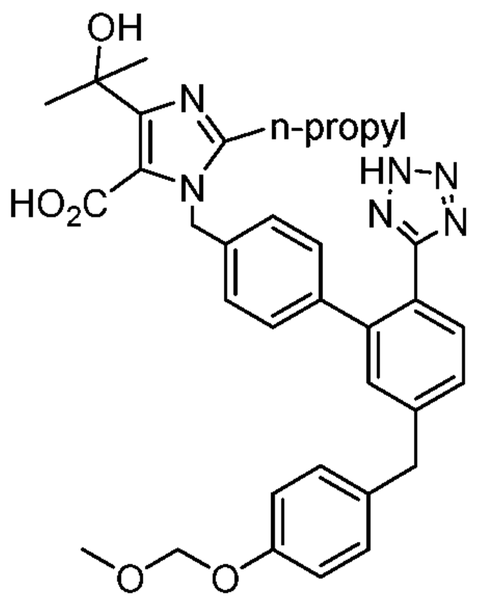


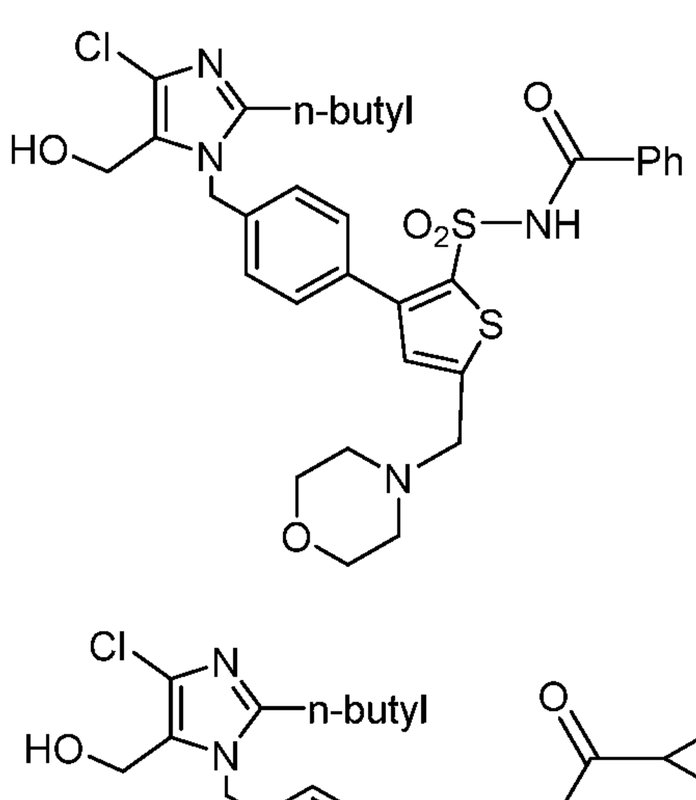


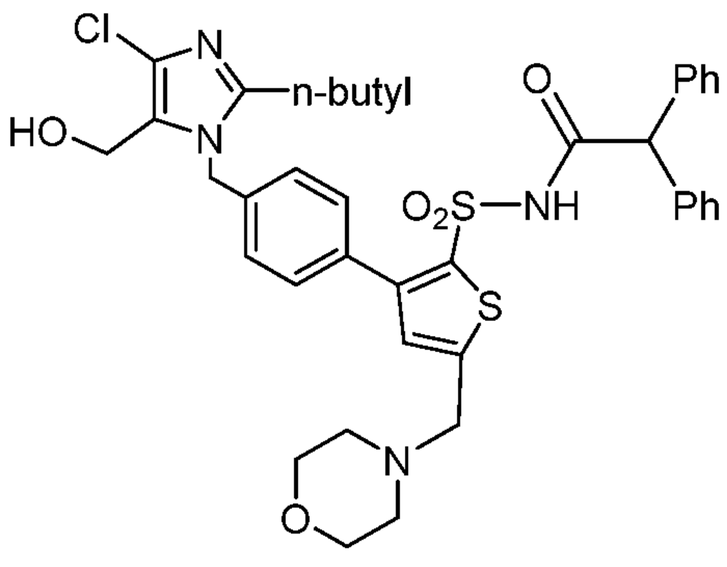


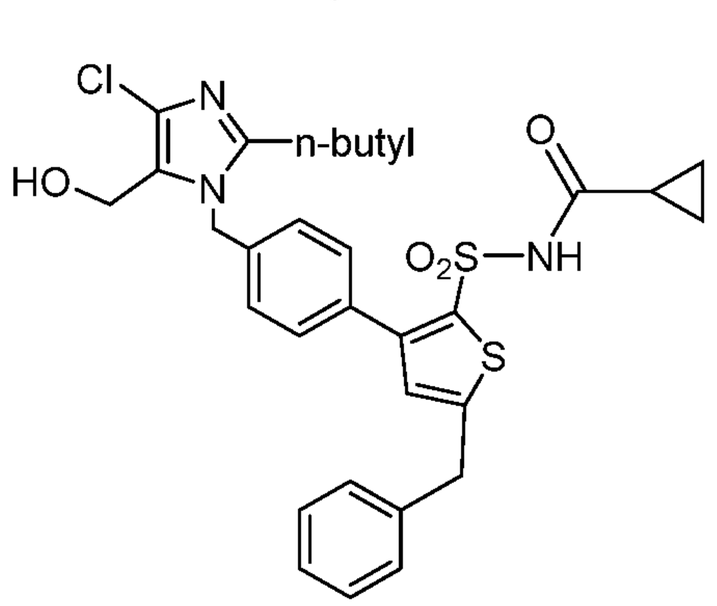


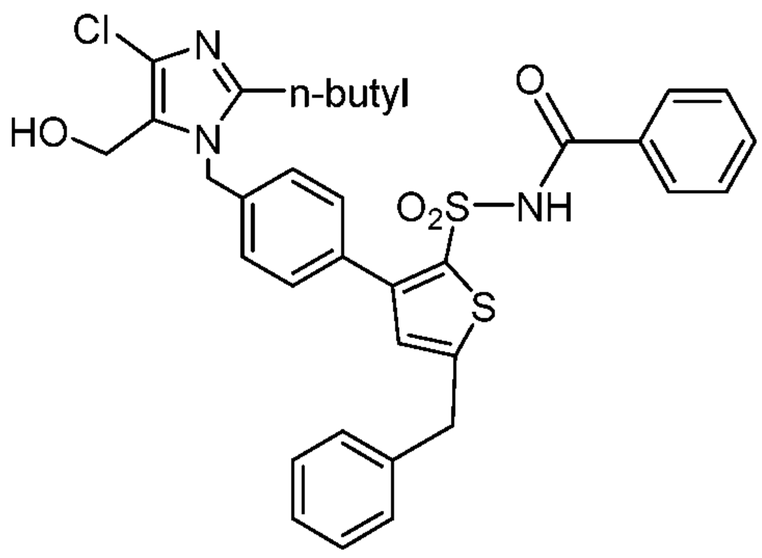








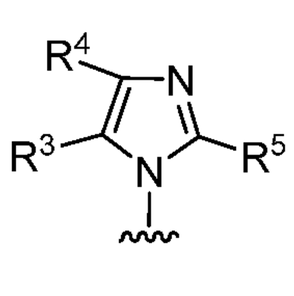
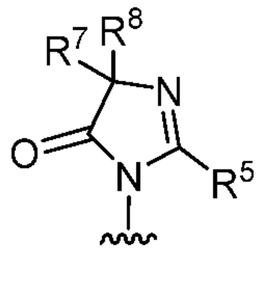
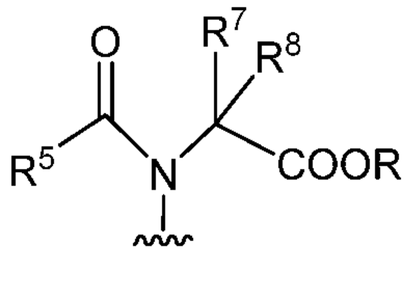




.

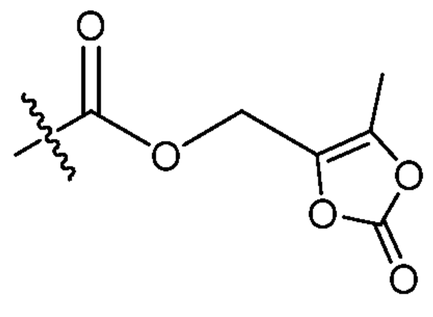
2. A compound of claim 1, or salt thereof, wherein

Group C is

 IA,  IC, or  IG.

3. A compound of claim 1, or salt thereof, wherein

R^1 and R^2 are H;

R^3 is H, C_{1-2} hydroxyalkyl, CO_2H, CO_2-C_{1-6} –alkyl, $CONH_2$, $CONH(C_{1-6}$ –alkyl), $CON(C_{1-6}$-alkyl$)_2$, or  ;

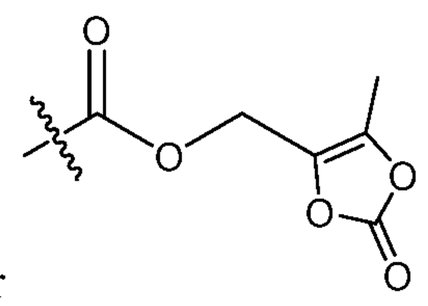
R^4 is H, F, Cl, Br, CF_3, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-2} hydroxyalkyl;-

R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl or $O(C_{1-6}$ alkyl);

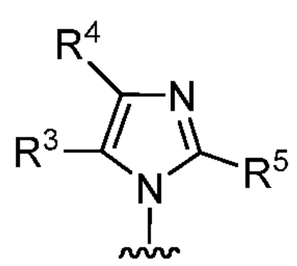
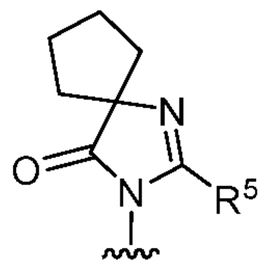
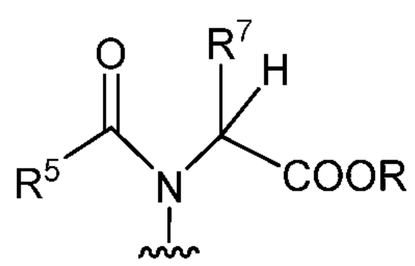
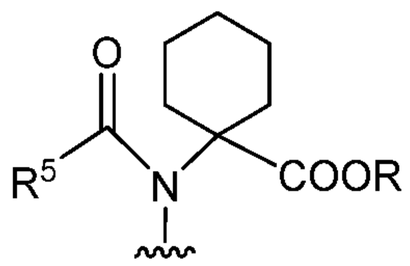
R^6 is hydrogen, or C_{1-4} alkyl;

R^7 and R^8 are H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-3} hydroxyalkyl

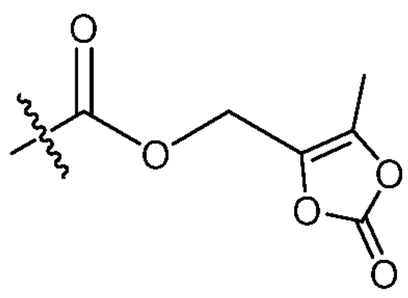
alternatively, R^7 and R^8, along with the atom to which they are attached, join to form a C_3-C_6-cycloalkyl or a C_4-C_7-heterocycle; and

R is H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, or  .

4. A compound of claims 1-3, or salt thereof, wherein

Group C is  ,  ,  , or  ;

R^1 and R^2 are H;



R^3 is hydroxyalkyl, CO_2H, or ;

R^4 is C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-3} hydroxyalkyl; and

R^5 is ethyl, n-propyl, or n-butyl.

5. A compound of claims 1-4, or salt thereof, wherein

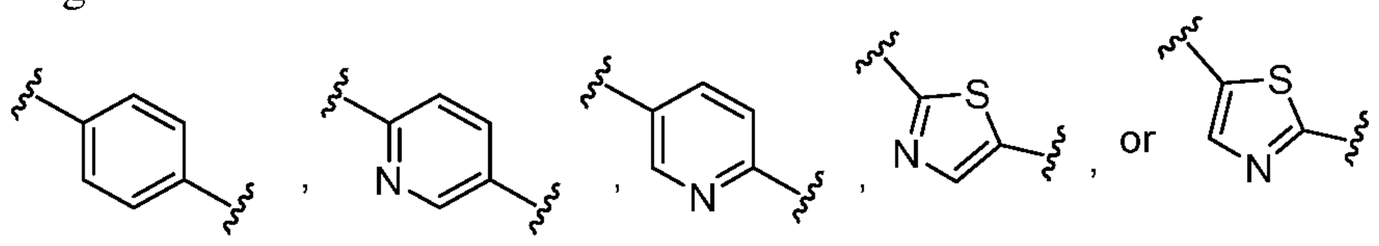
G is selected from a 5 to 10 membered heterocycle having 1-3 atoms selected from N, O, and S, phenyl or a C_6-C_{10}-heteroaryl having 1-3 atoms selected from N, O, and S; wherein the heterocycle, phenyl and heteroaryl are substituted with 0-3

substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkylthio, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2R^x$, $S(O)_2N(R^x)_2$, $N(R^x)S(O)_2(R^x)$, or $N(R^x)S(O)_2R^x$;

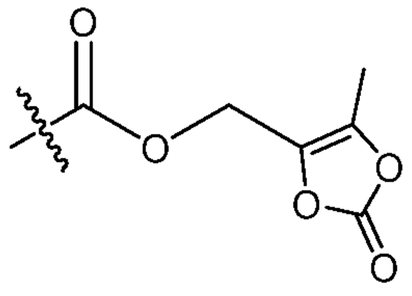
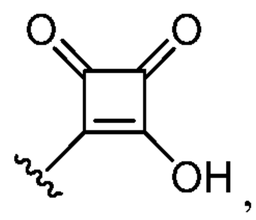
R^x is H, $C_{1\text{-}6}$ alkyl, CF_3, phenyl, CH_2phenyl.

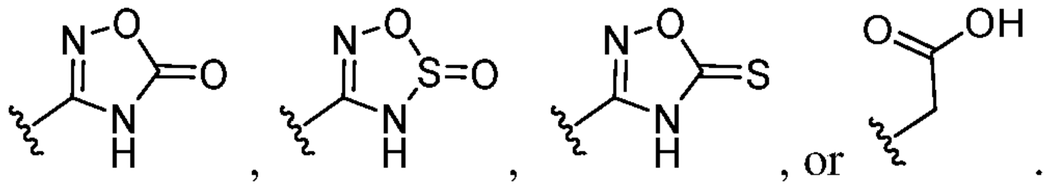
6. A compound of claims 1-5, or salt thereof, wherein

Ring B is



any of which are optionally substituted with 0-2 F,

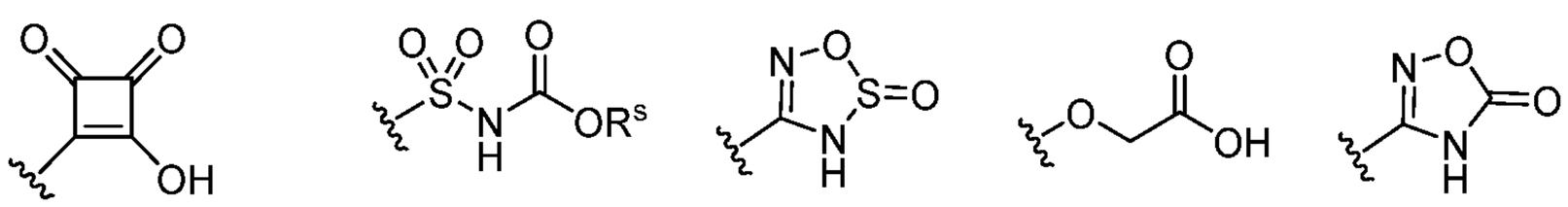
Y is COOH, COOMe, COOEt,  , 5-tetrazolyl, SO_3H,  ,



.

7. A compound of claims 1-4, or salt thereof,

wherein Y is COOH, 5-tetrazolyl, SO_3H,

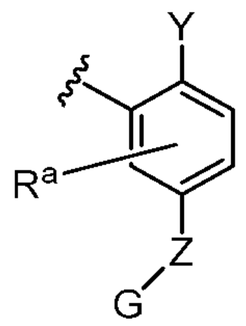
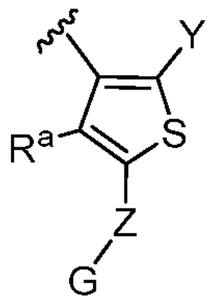


; and

R^s = $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$-aryl-C_1-C_6-alkyl or (CH_2Ph).

8. A compound of claims 1-7, or salt thereof, wherein

Ring A is


or 
; and

R^a is H or F.

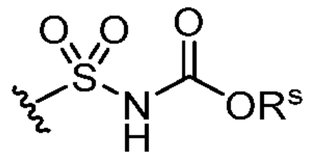
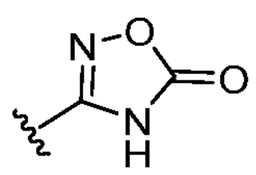
9. A compound of claims 1-8, or salt thereof, wherein

G is selected from a phenyl, thiophenyl, quinolinyl, isoquinolinyl, indolyl, pyrazolyl, pyrrolyl, pyridinyl, isoindolinyl, pyrrolidinyl; any of which are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2R^x$, $S(O)_2N(R^x)_2$, $N(R^x)S(O)_2(R^x)$, or $N(R^x)S(O)_2R^x$;

R^x is H, C_{1-3} alkyl, CF_3, phenyl, CH_2phenyl.

10. A compound of claims 1-9, or salt thereof, wherein

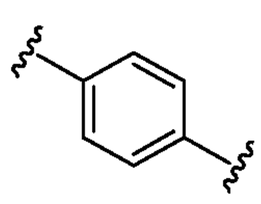
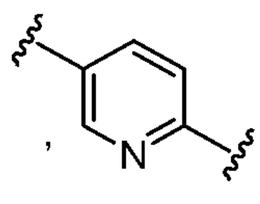
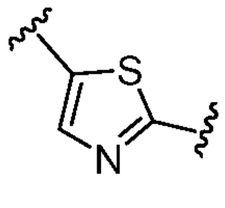
Y is COOH, 5-tetrazolyl,



; and

R^s is C_{1-6} alkyl.

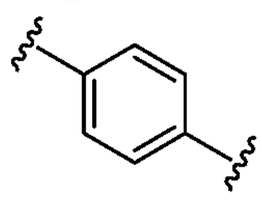
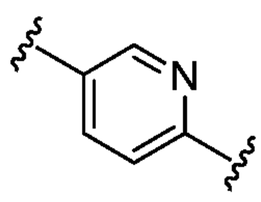
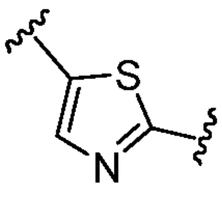
11. A compound of claims 1-10, or salt thereof, wherein

Ring B is

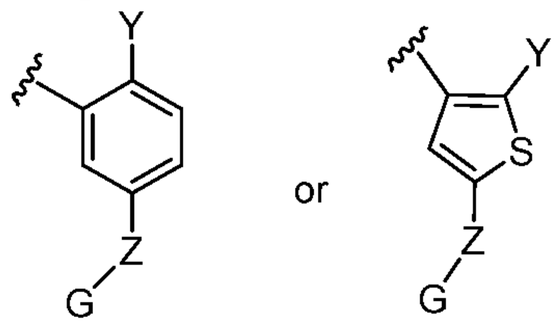

, 
, or 
, any of which are substituted with 0-2 F.

12. A compound of claims 1-11, or salt thereof, wherein

Ring B is


, 
, or 

Ring A is



Z is a bond or NR^a;

G is isoindolinyl-1,3-dione, pyrrolidine-2,5-dione, phenyl, thiazolyl, pyridinyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, any of which may be substituted with 0-3 substituents selected from =O, C_{1-4} alkyl, -O-R^x, C_{1-4} haloalkyl, -C(O)NR^x, -$N(R^x)_2$, and F;

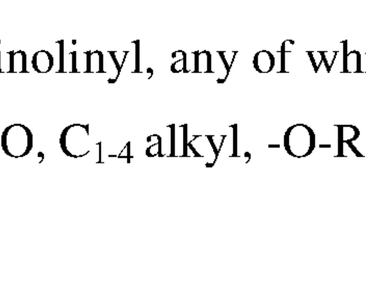
R^5 is C_{3-4} alkyl;

R^6 is C_{3-4} alkyl;

R^a is hydrogen, C_{1-4}alkyl, and C_{1-2} haloalkyl; and

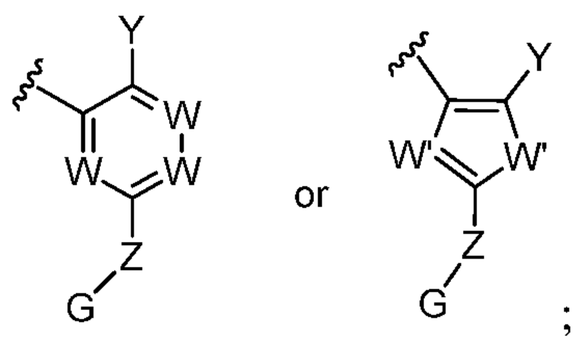
Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl.

13. A compound of formula (I), or salt thereof:



(I)

wherein

ring A is  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16} where at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4 to 6 membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2, COOR,

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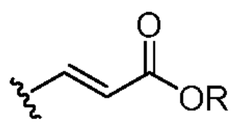
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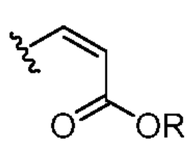
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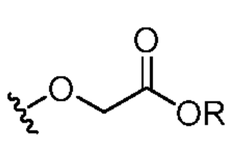
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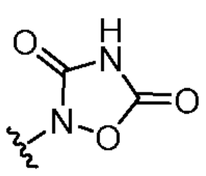
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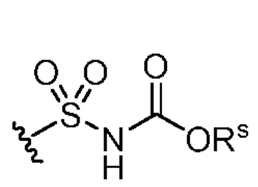
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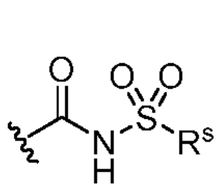
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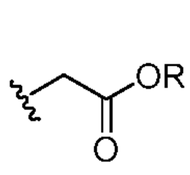
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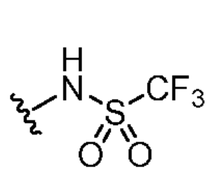
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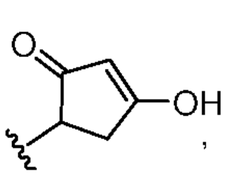
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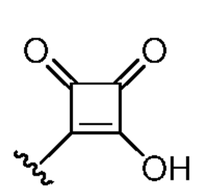
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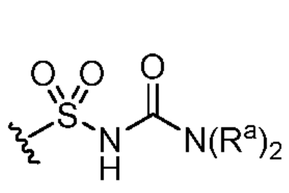
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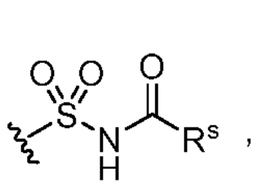
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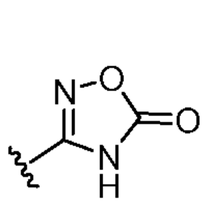
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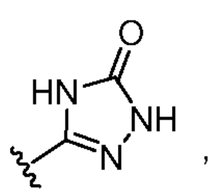
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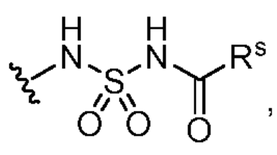
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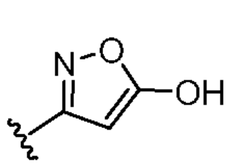
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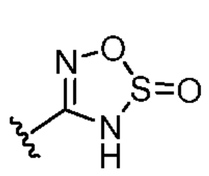
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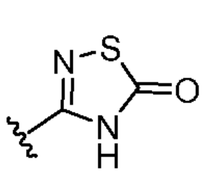
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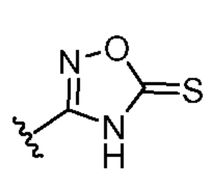
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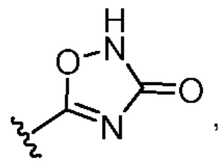
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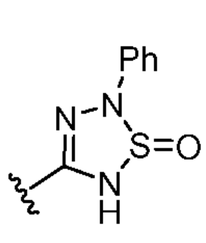
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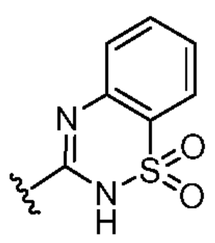
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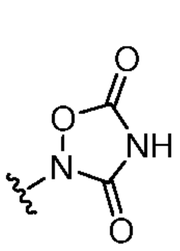
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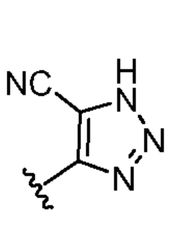
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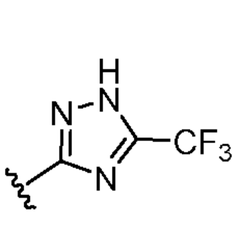
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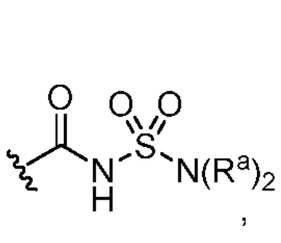
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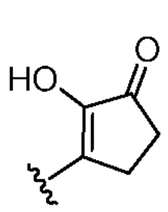
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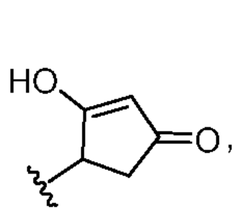
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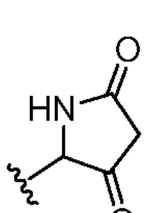
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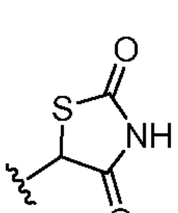
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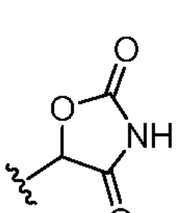
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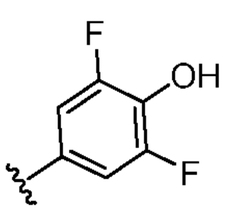

;

R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, $C_{6\text{-}10}$-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms

selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl-C_1-C_3 alkyl, C_{6-10} aryl, C_{6-10}-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl andheterocycle are each a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S;

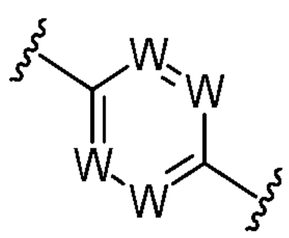
Z, at each occurrence, is independently selected from a bond, O, S, $N(R^z)$, $C(R^z)_2$, C=O, $C(=O)N(R^z)$, $N(R^z)C(=O)$, $C(R^z)_2C(R^z)_2$, $OC(R^z)_2$, $SC(R^z)_2$, $N(R^z)C(R^z)_2$, $C(R^z)_2O$, $C(R^z)_2S$, $C(R^z)_2N(R^z)$;

R^z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, two R^z groups either on the same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, phenyl, CH_2-phenyl;

ring B is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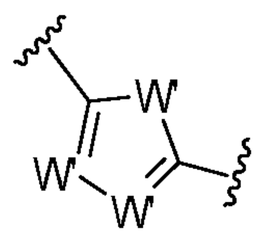
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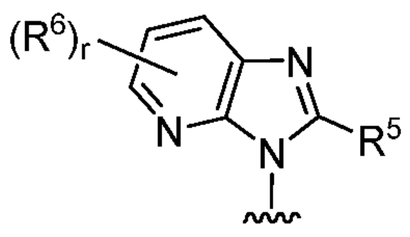
Group C is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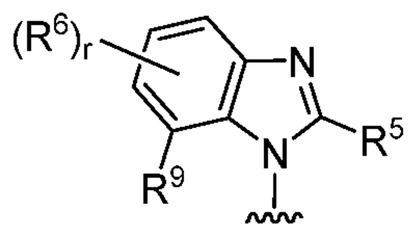

IF;

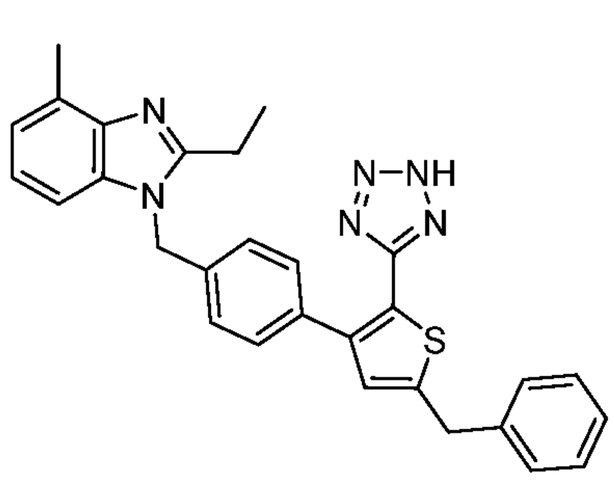
R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl C_{1-6} alkoxyalkyl, C_{3-6}–cycloalkylC_{0-4}–alkyl which may be substituted with 1-3 halogens or a C_{1-3}-alkoxy group;

R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{3-6}–cycloalkyl, C_{3-6}–halocycloalkyl, C_{3-6}–alkoxycycloalkyl, or C_{3-6}–hydroxycycloalkyl;

R^9 is COOR, $CON(R^z)_2$; and

r is 0 to 3;

provided that the compounds of Formula (I) are not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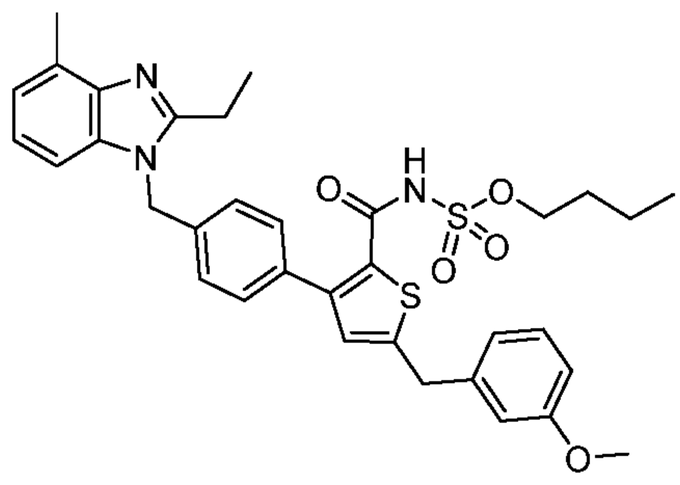
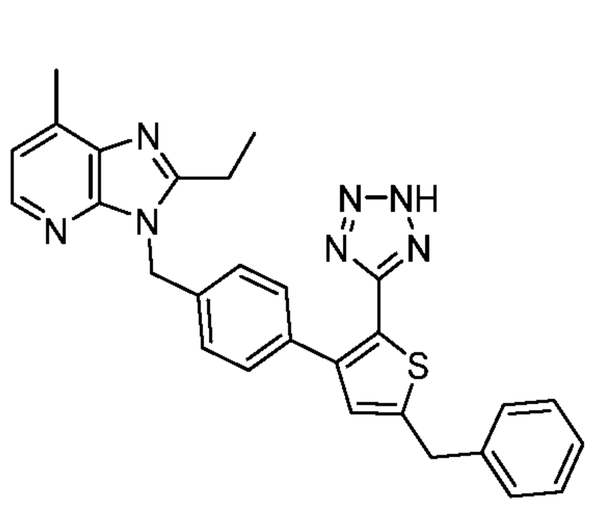
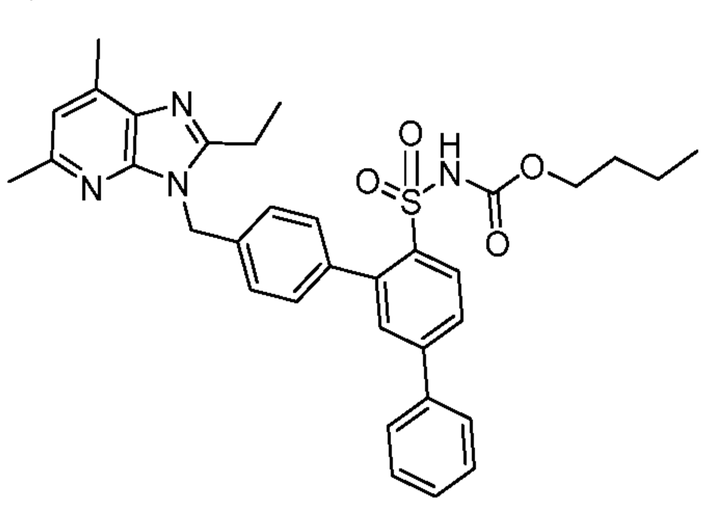
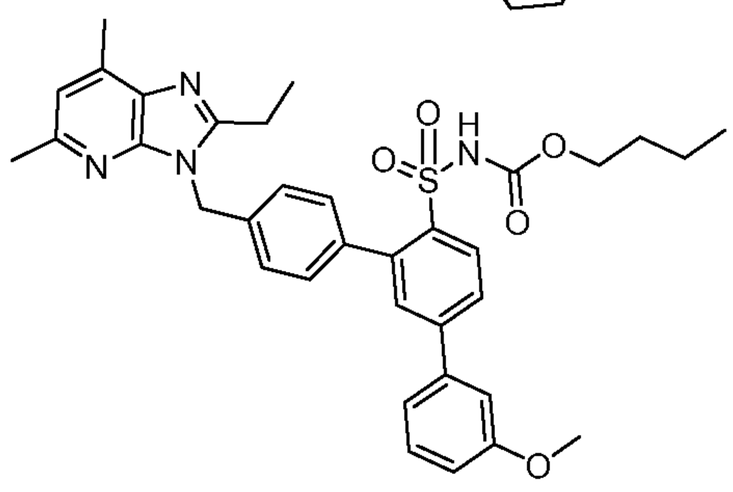
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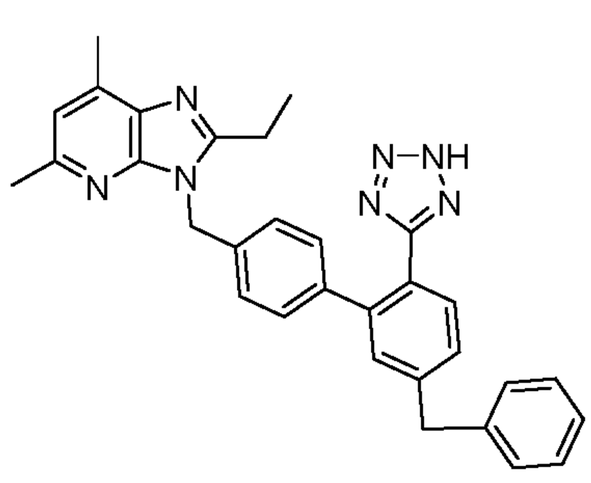
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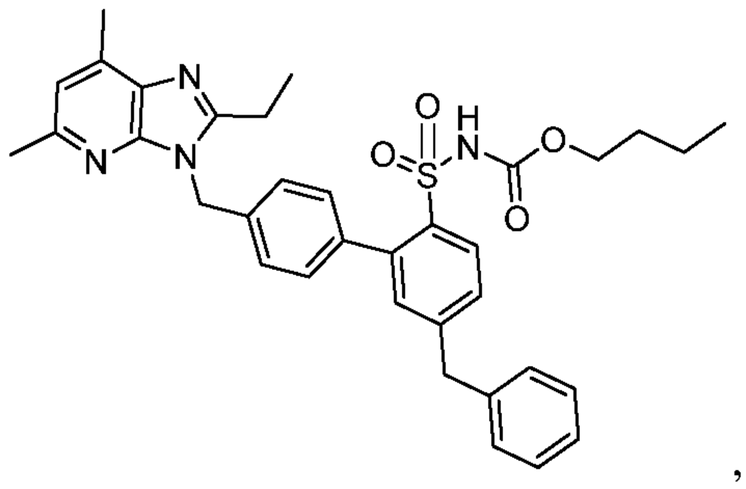
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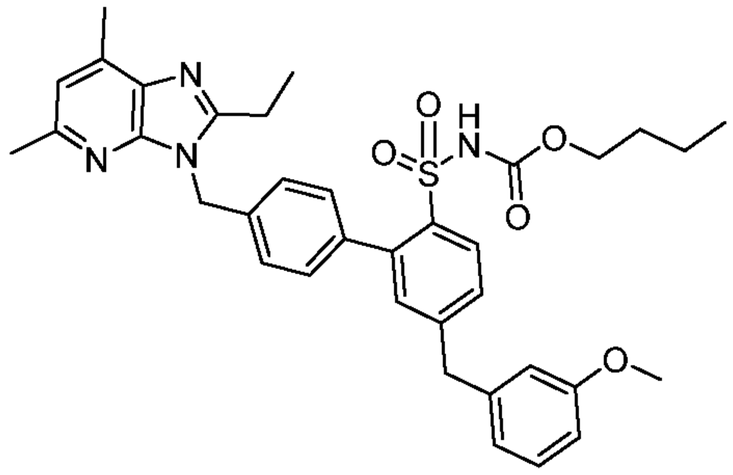

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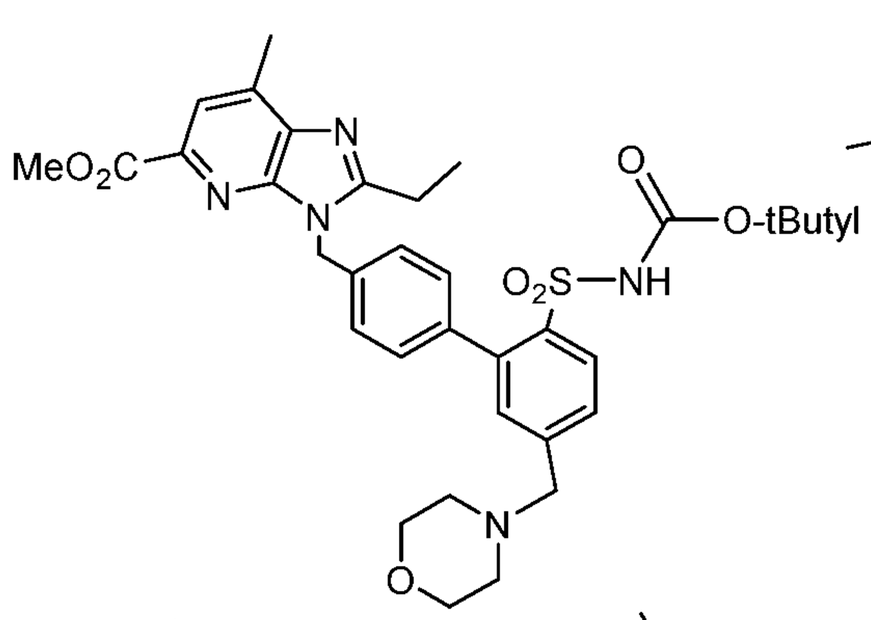
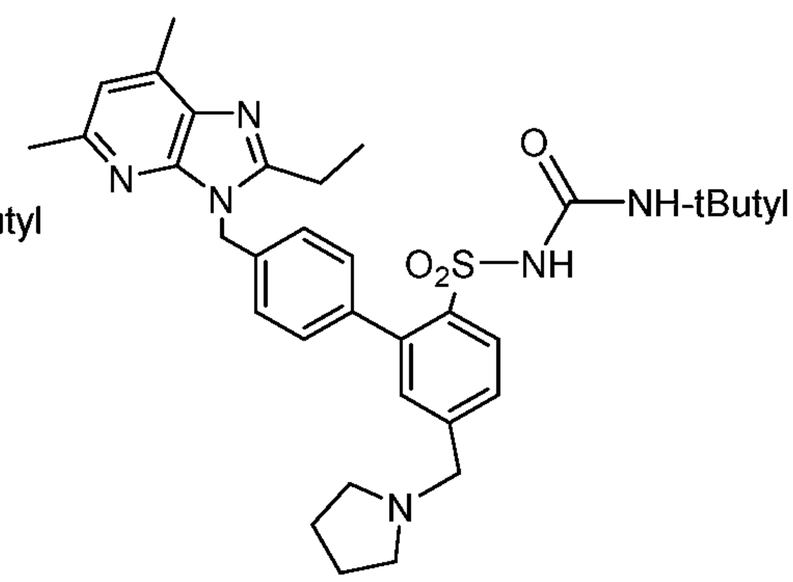
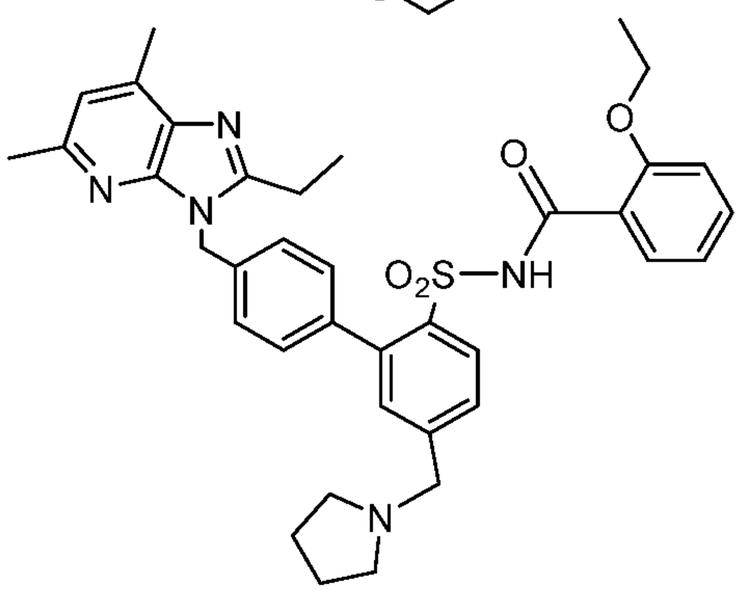
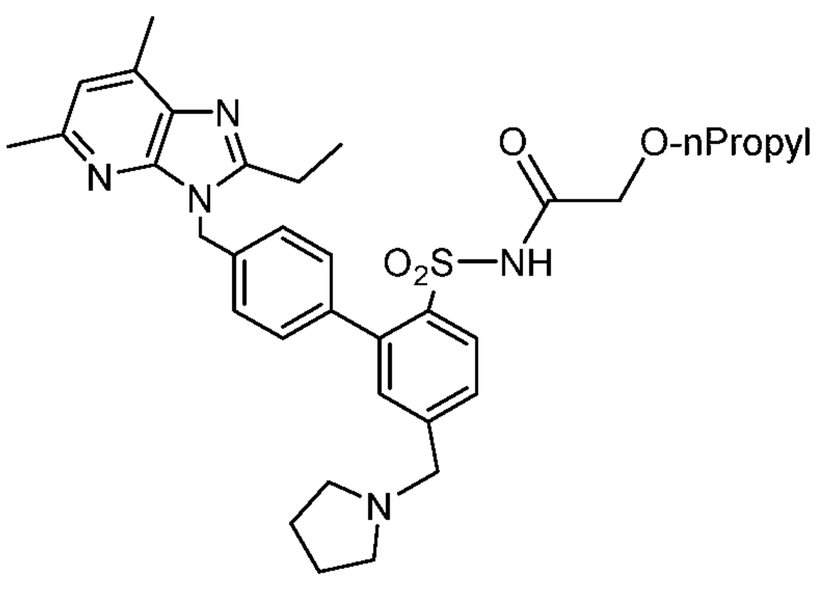
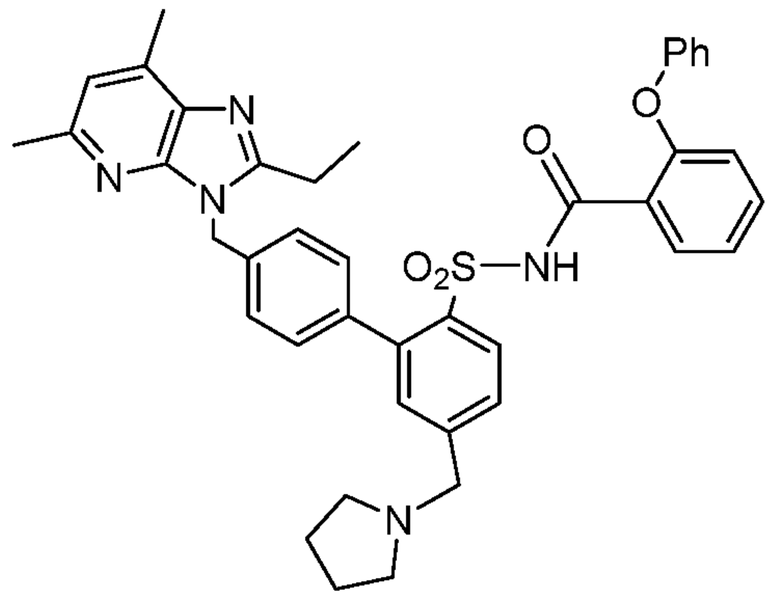
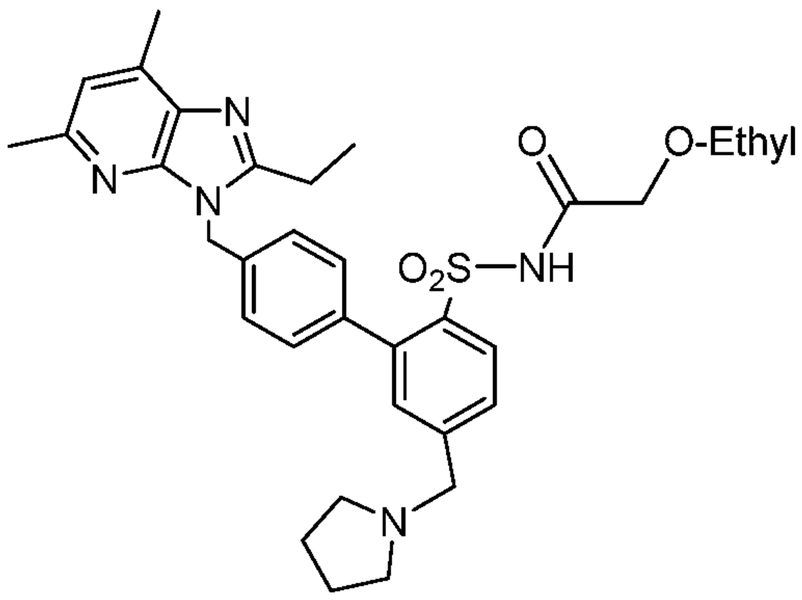
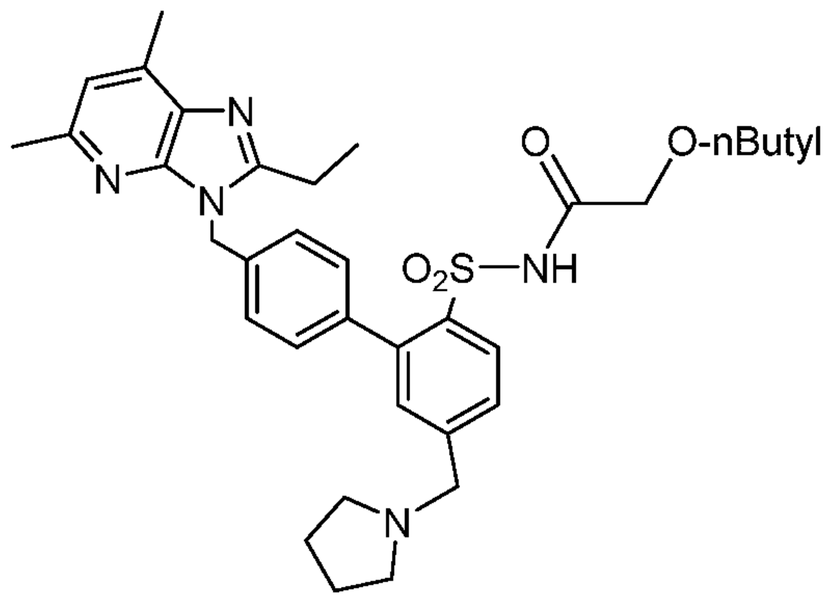
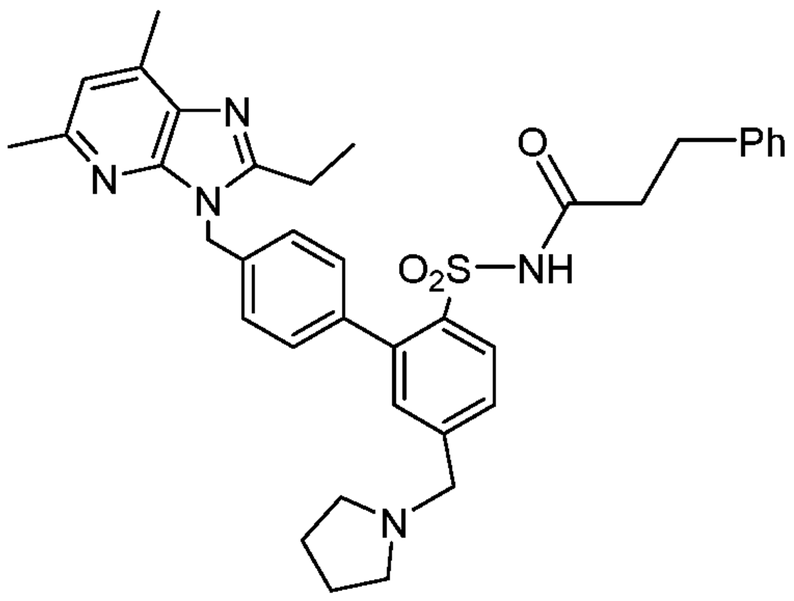
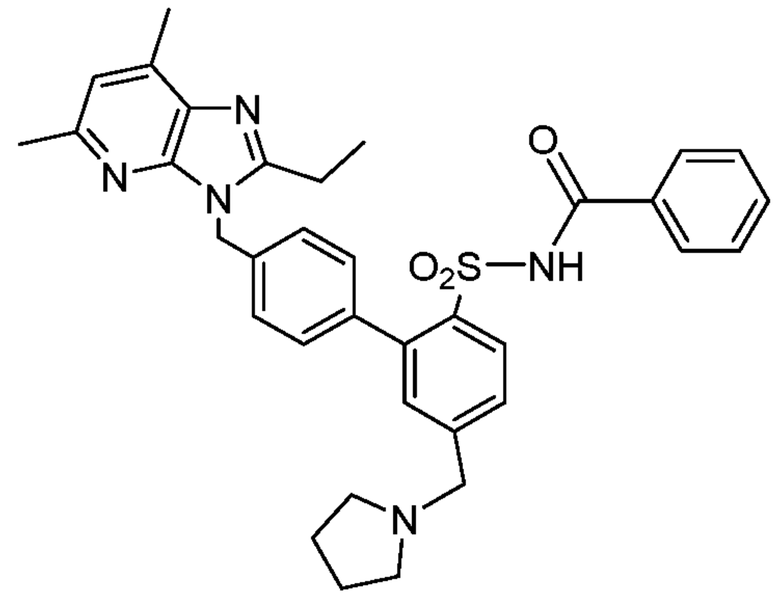





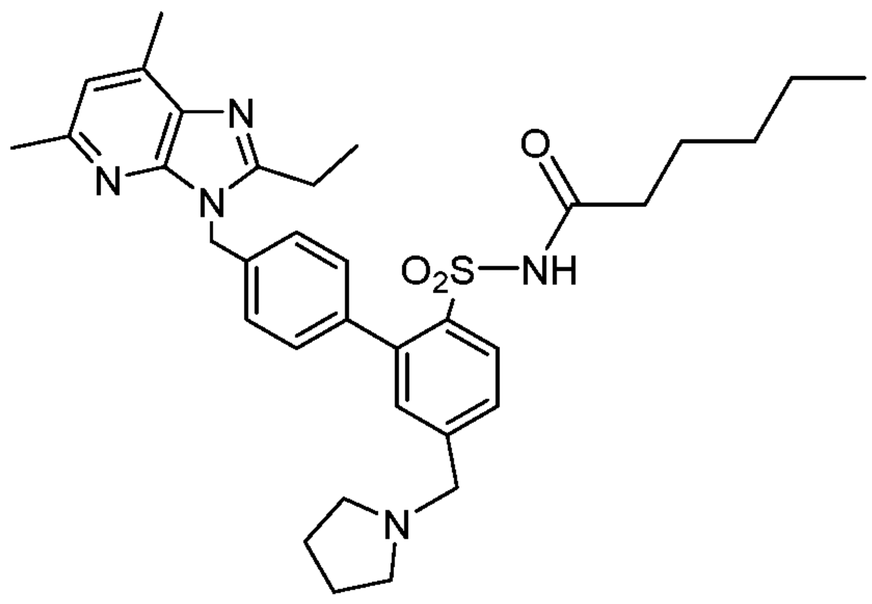

Ph
O
O
N
N
N
O_2S—NH
N

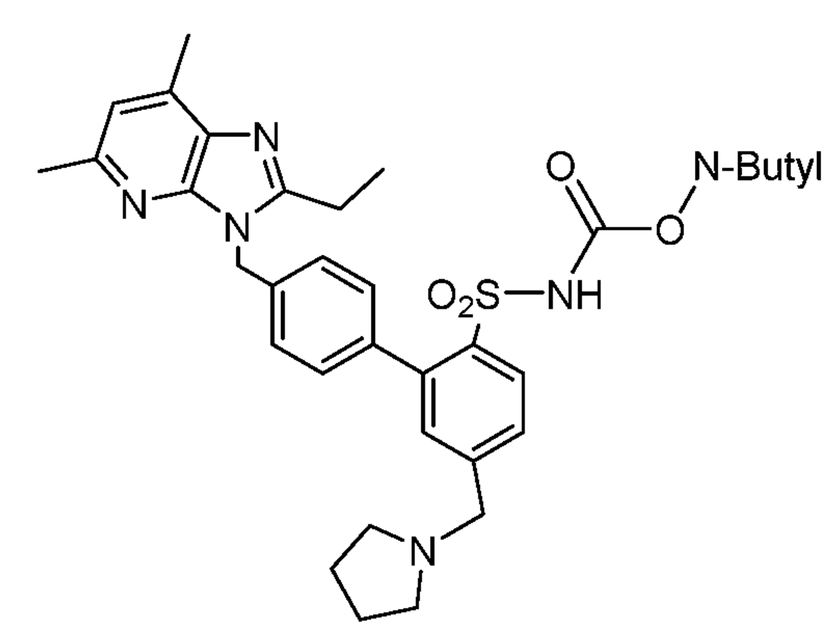

O
O-Ethyl
N
N
N
O_2S—NH
N

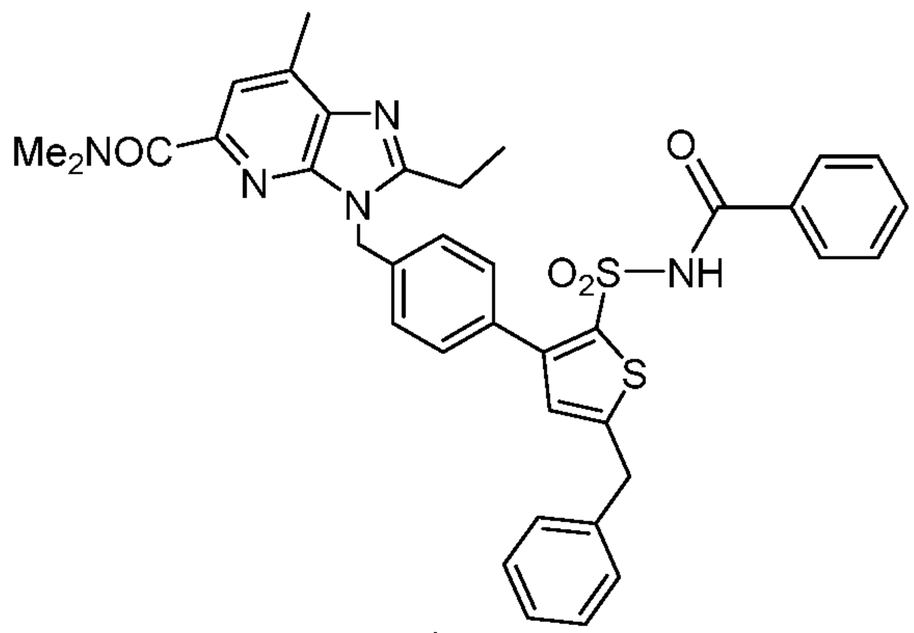

O
O-nButyl
N
N
N
O_2S—NH
N

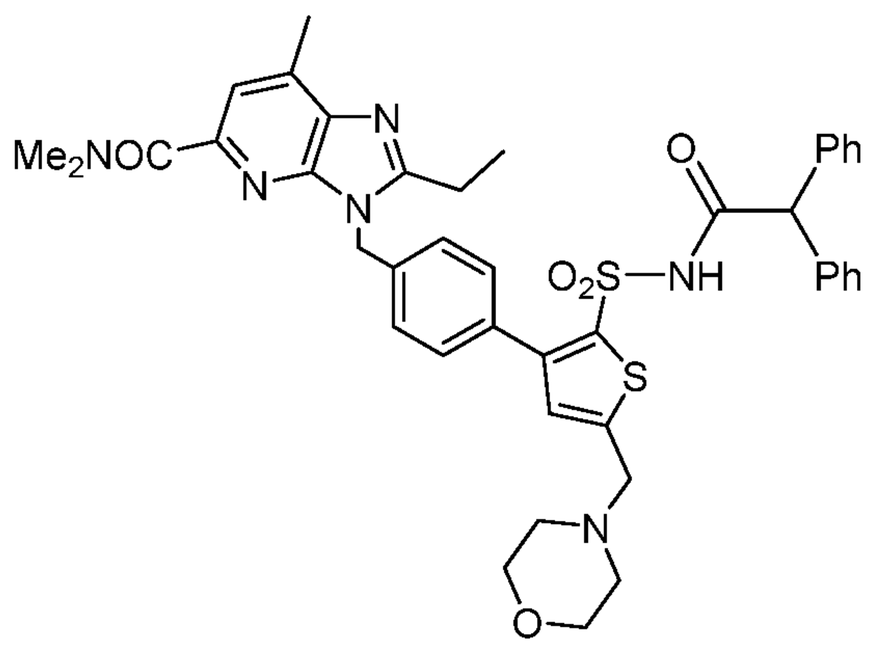

O
Ph
N
N
N
O_2S—NH
N

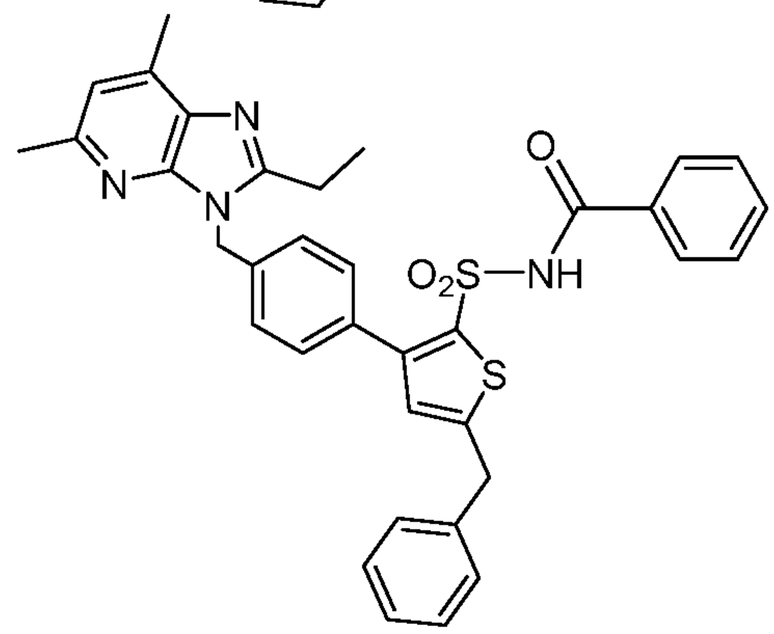

O
N
N
N
O_2S—NH
N

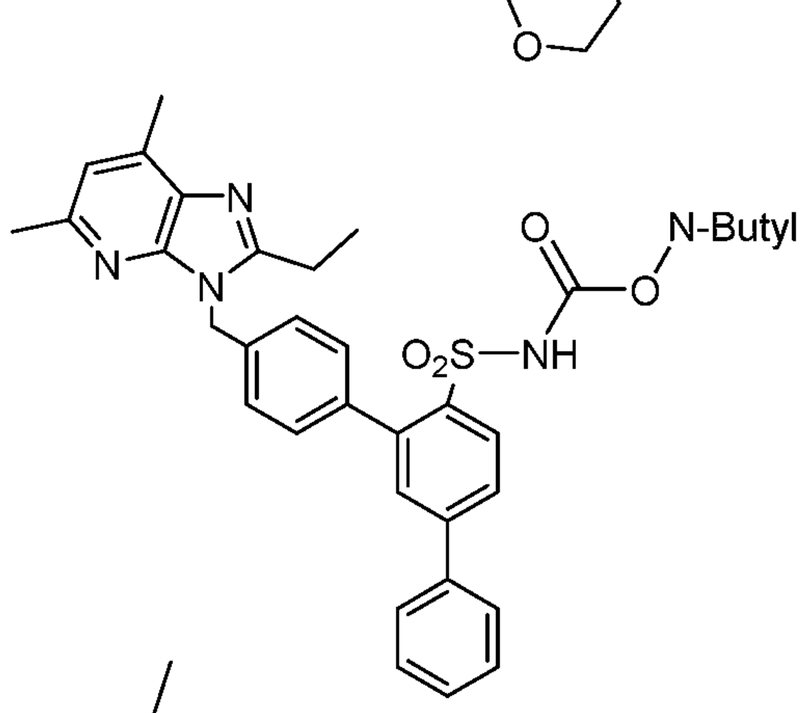

O
N
N
N
O_2S—NH
N

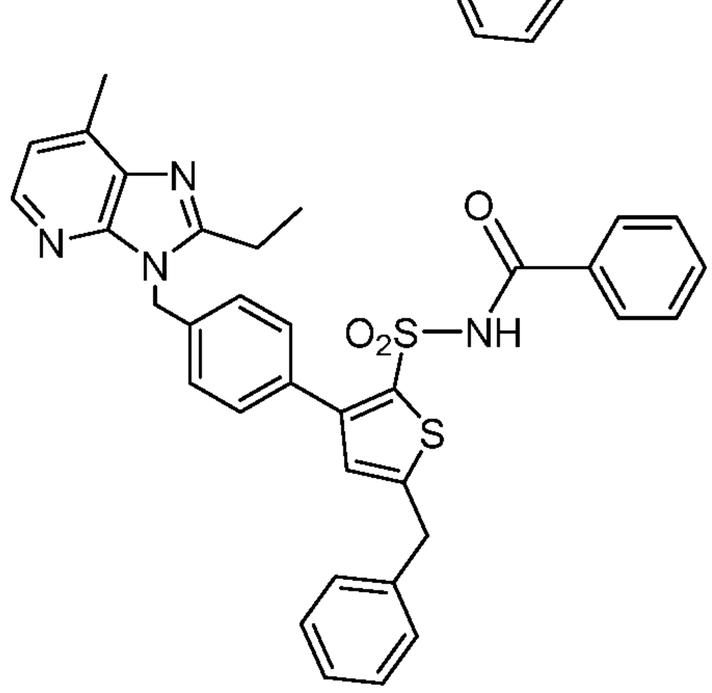


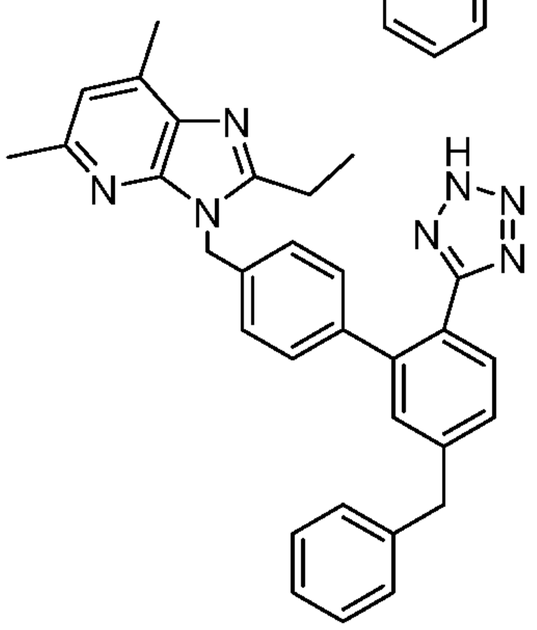


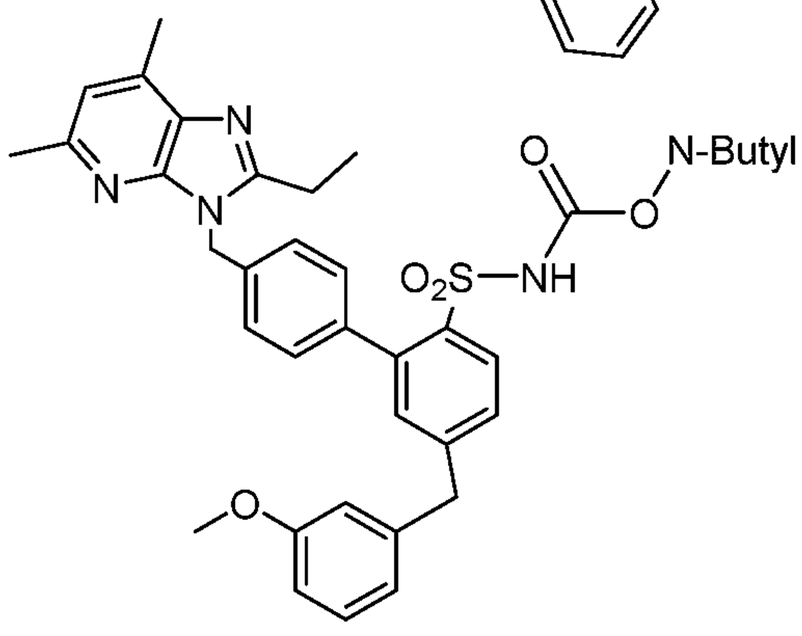


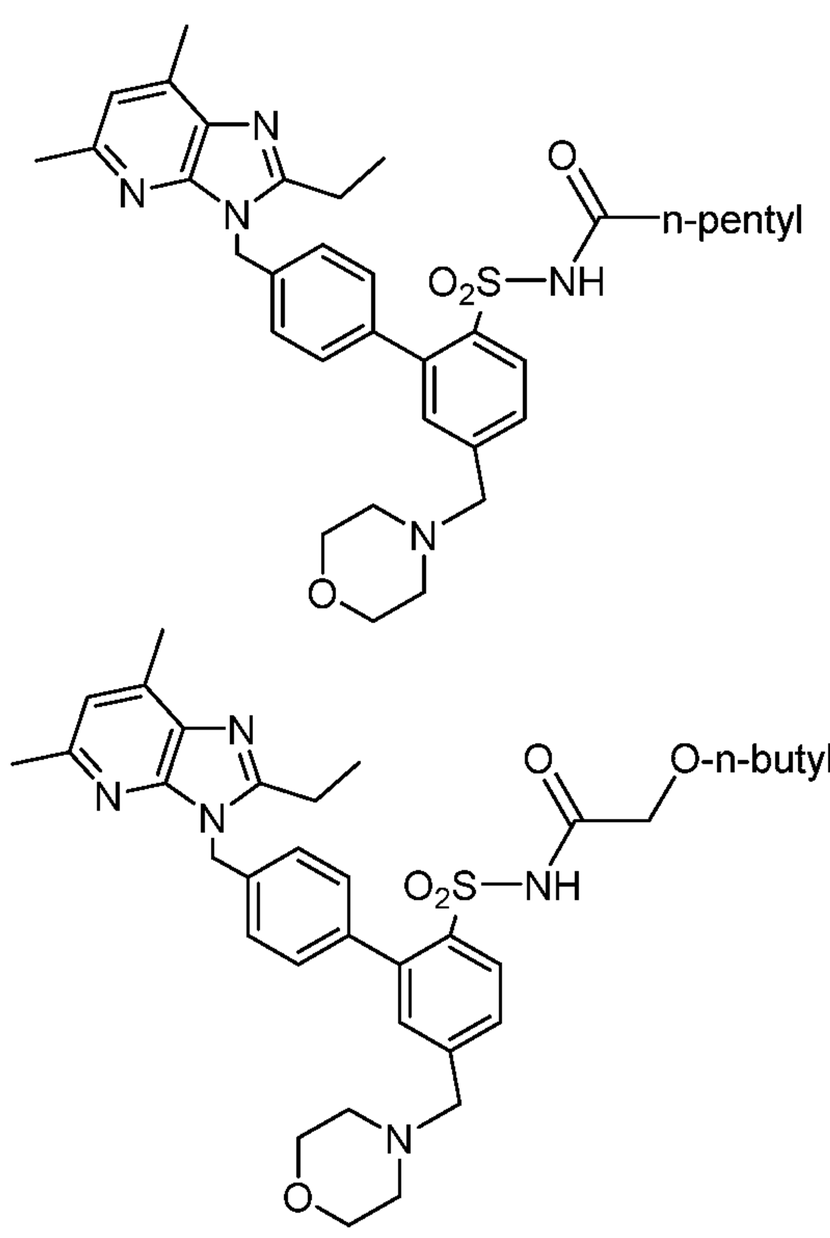


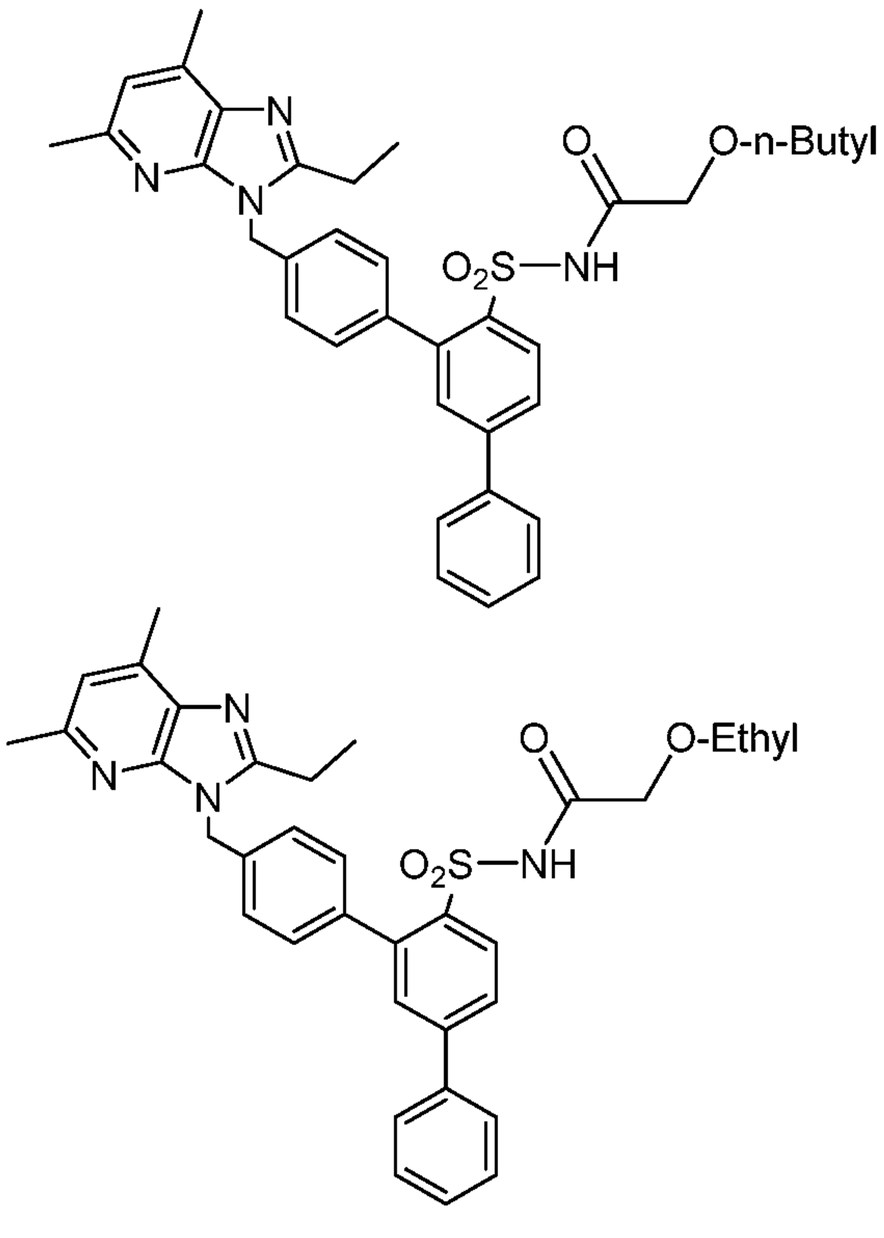


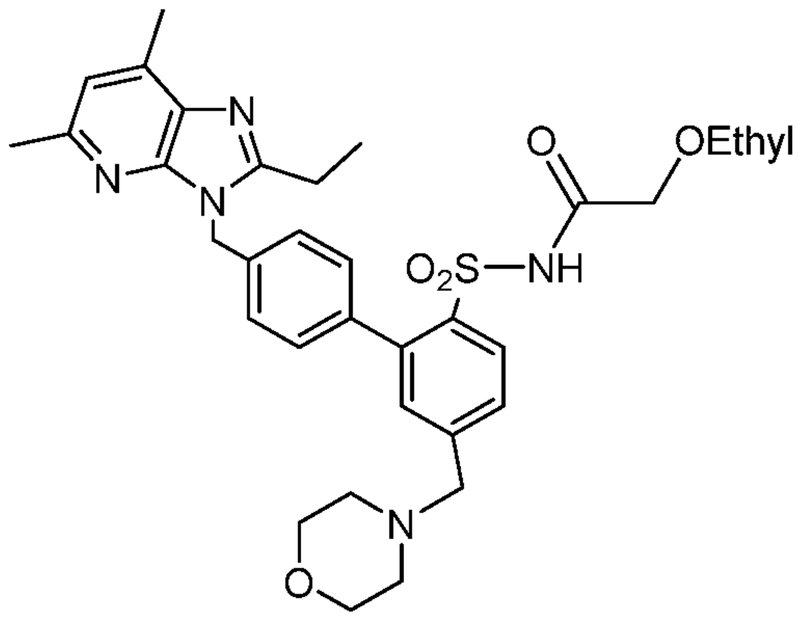


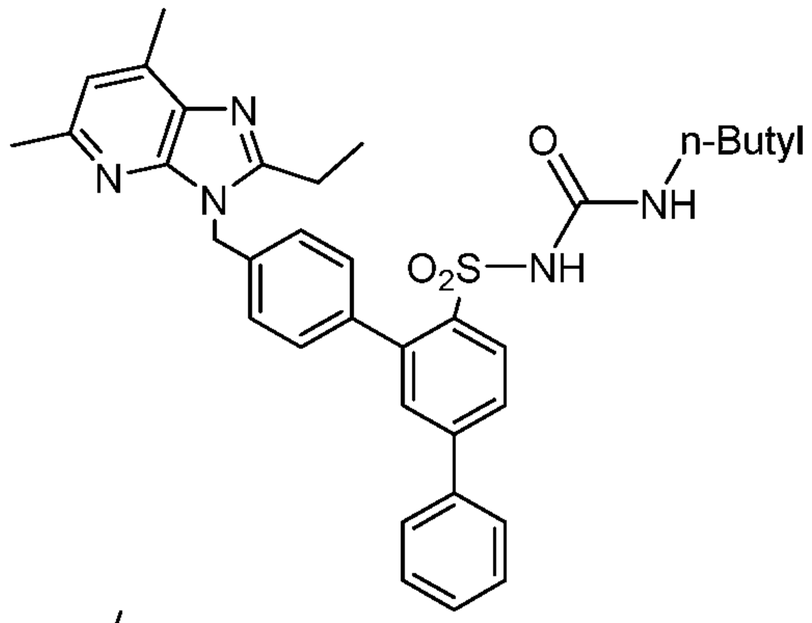


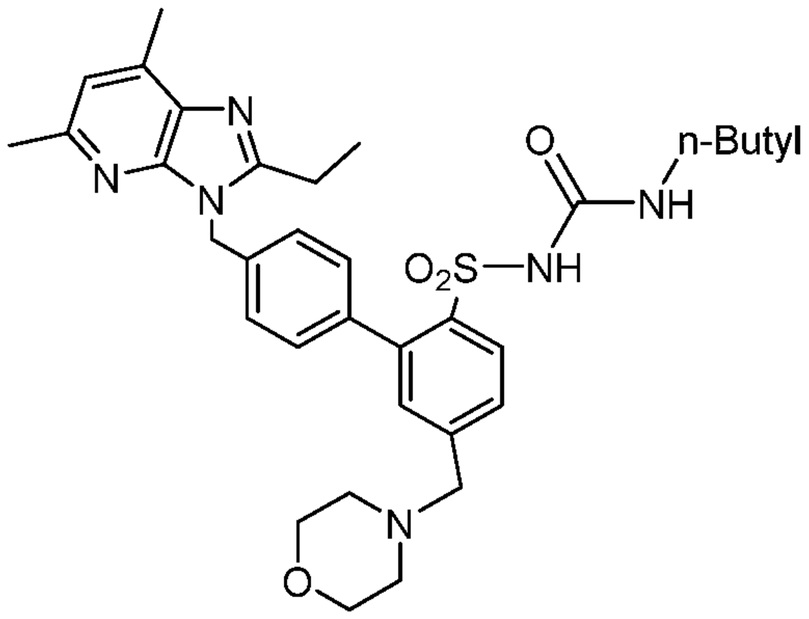


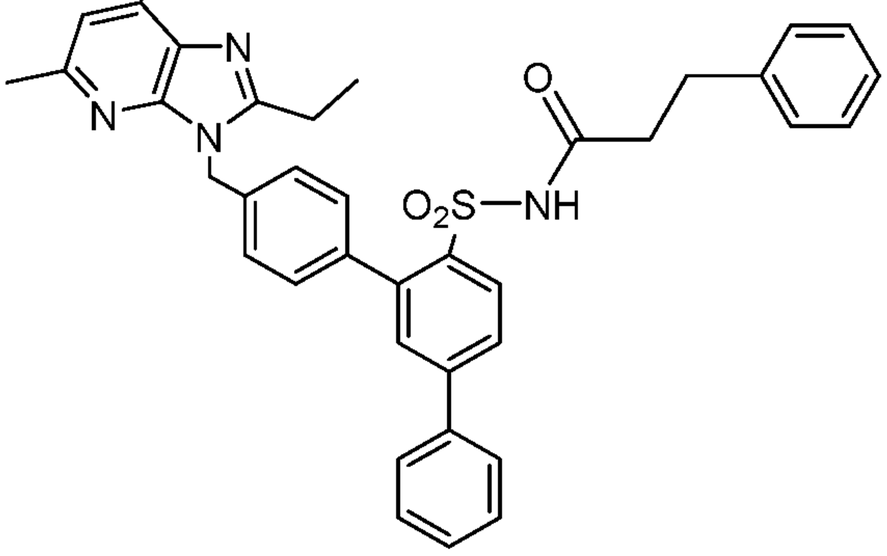

n-pentyl
O-n-butyl

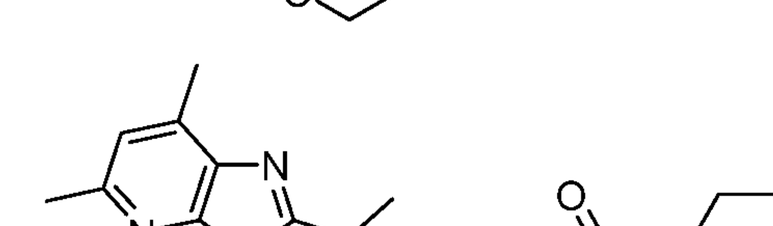

O-n-Butyl
O-Ethyl

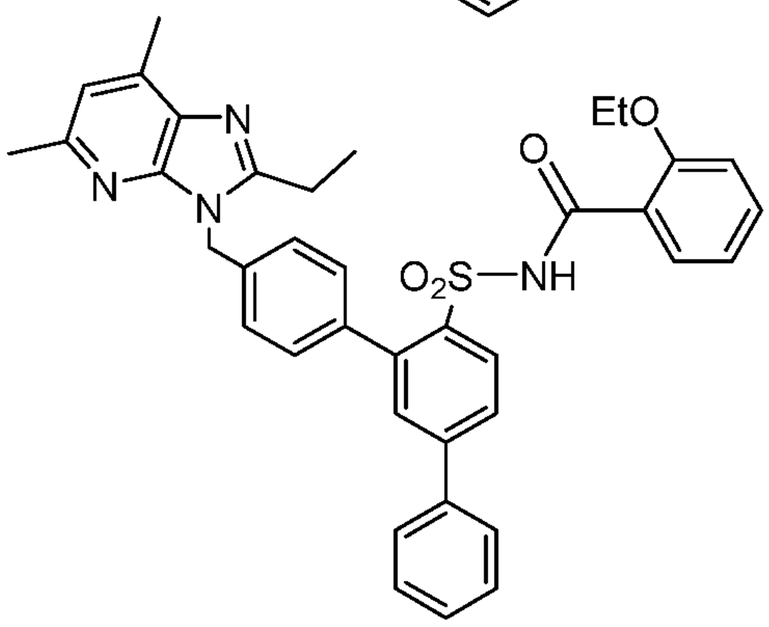


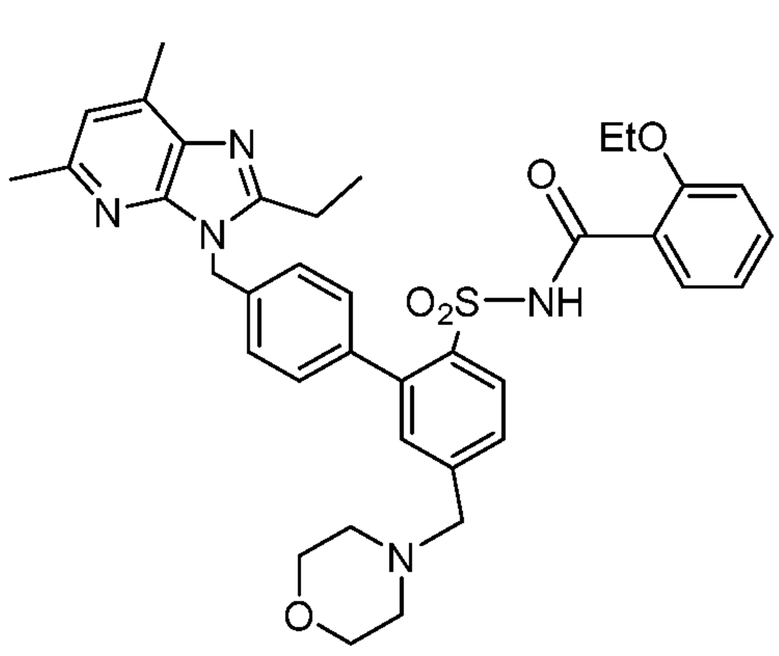


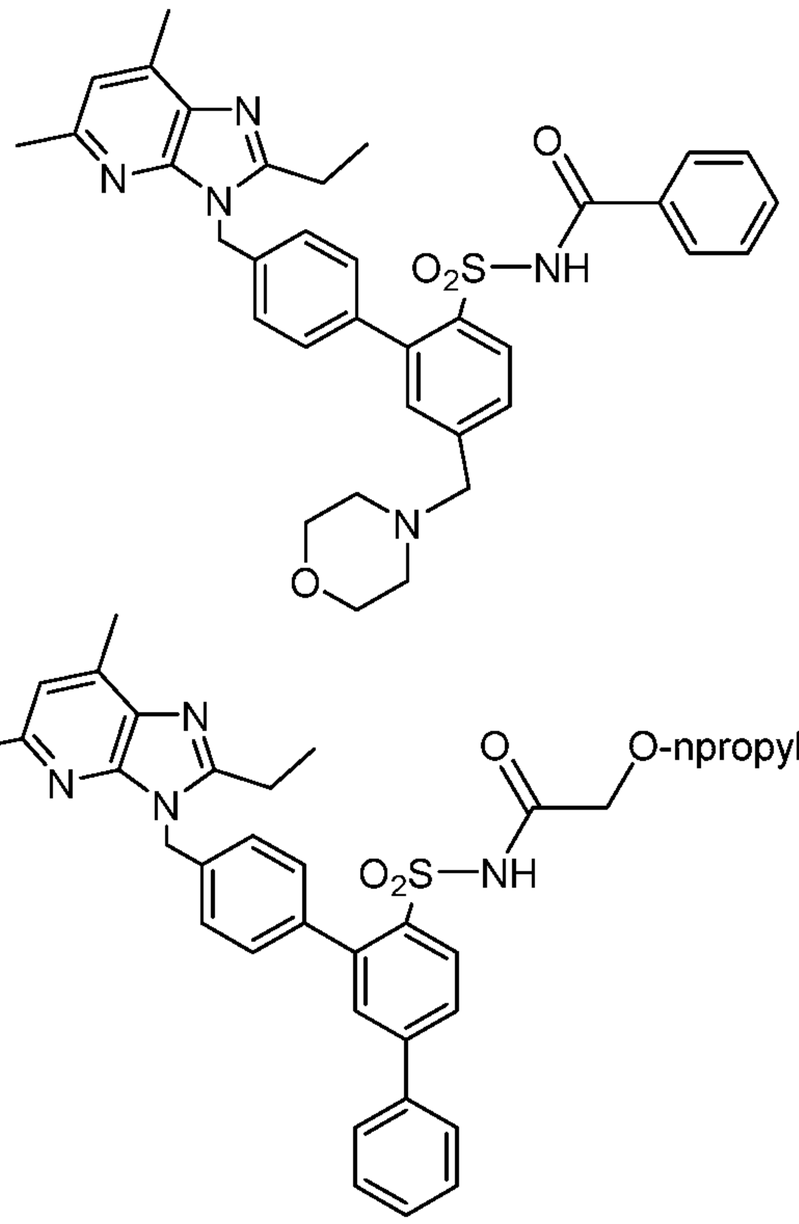


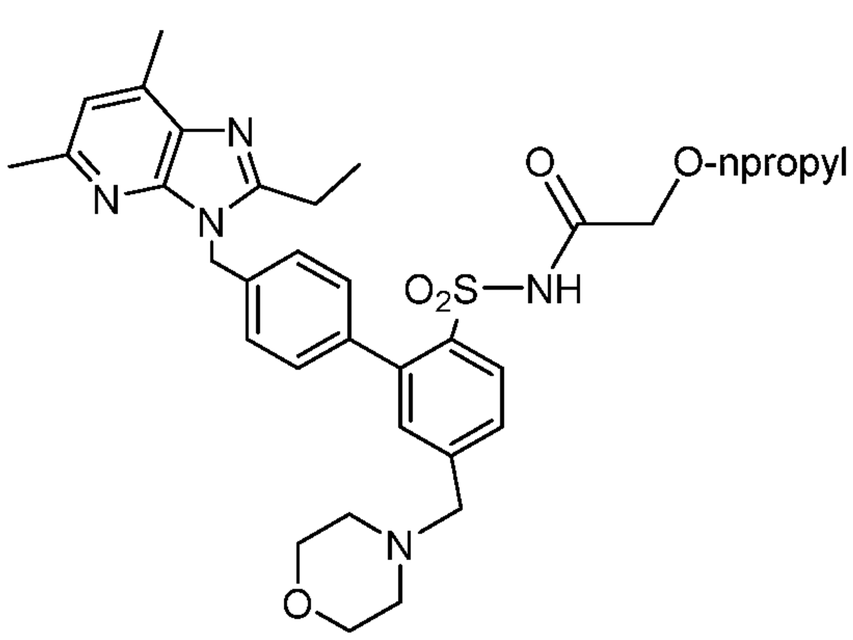


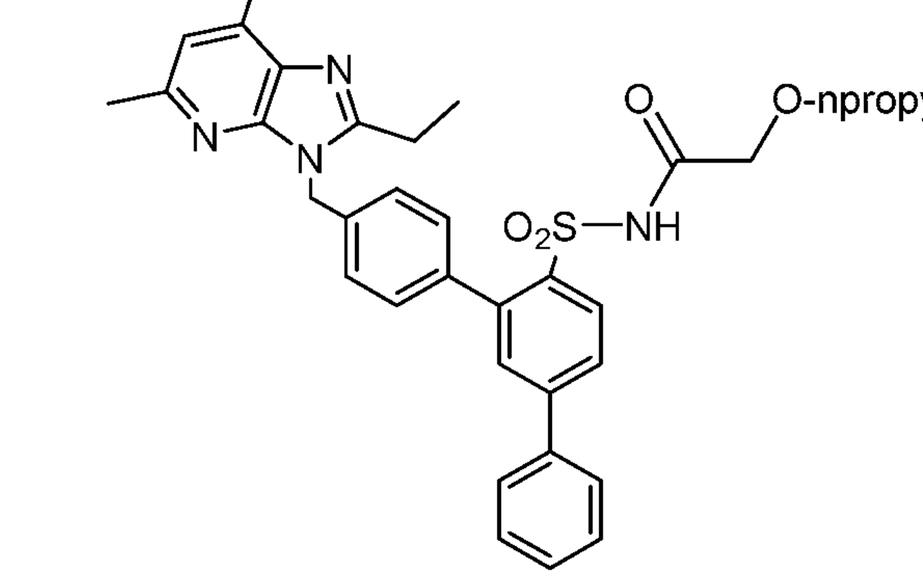


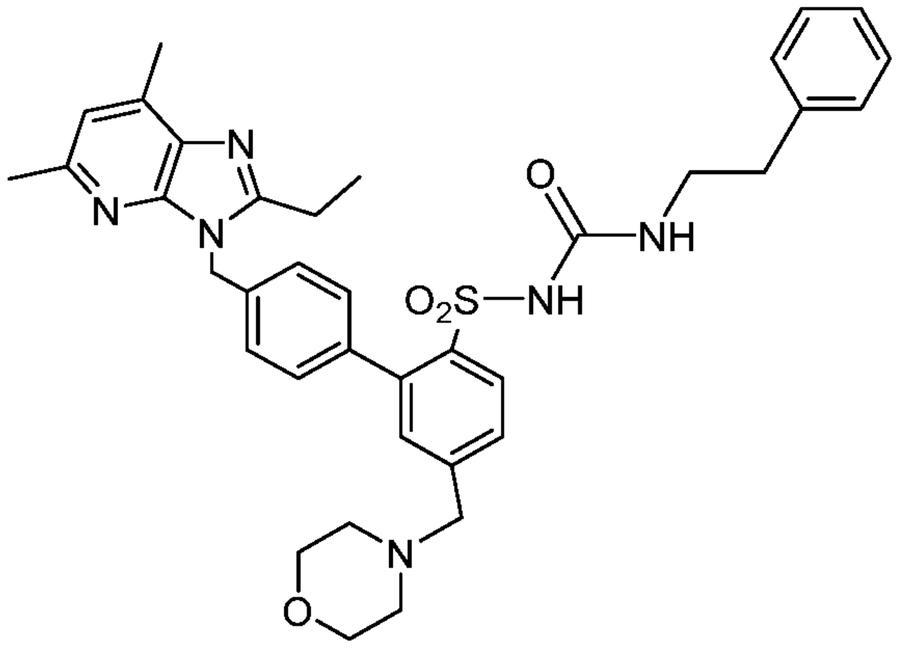


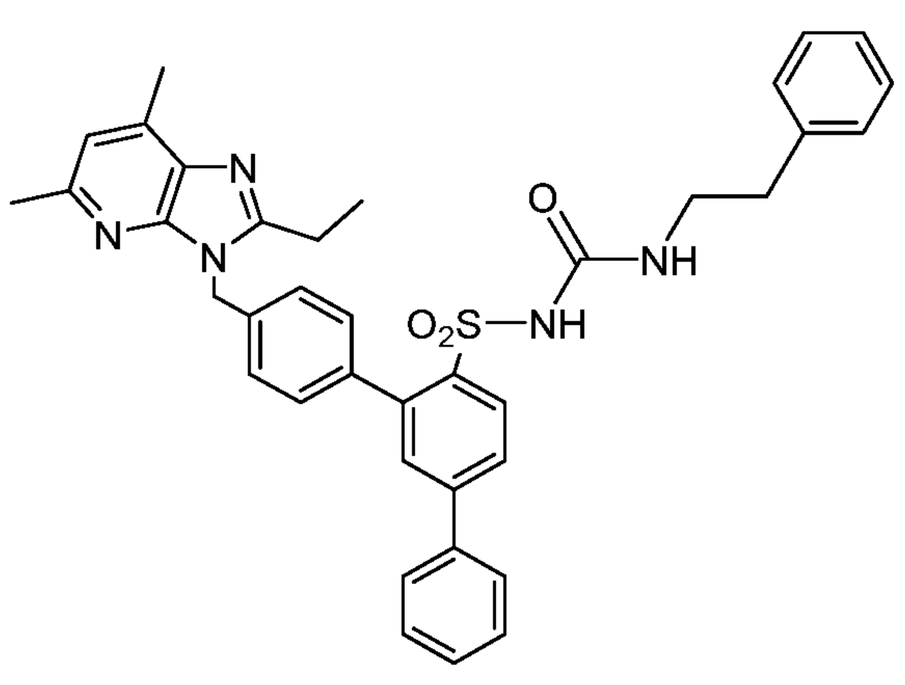

EtO
O
N
N
N
O_2S—NH
N
O

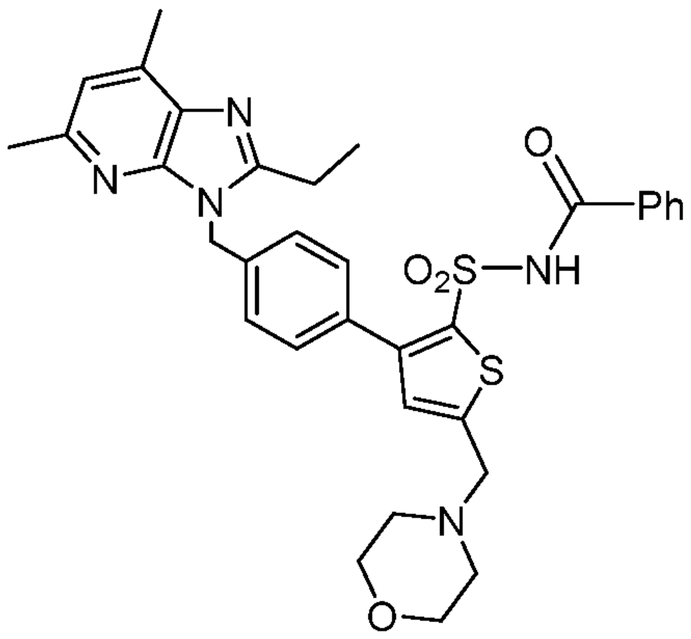

O
N
N
N
O_2S—NH
N
O

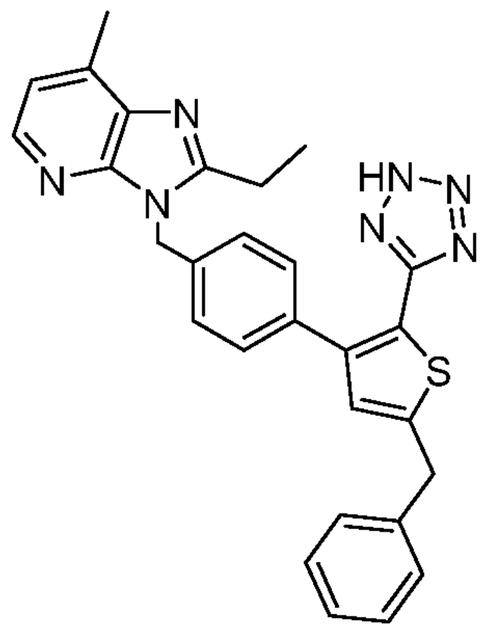

O
O-npropyl
N
N
N
O_2S—NH
N
O

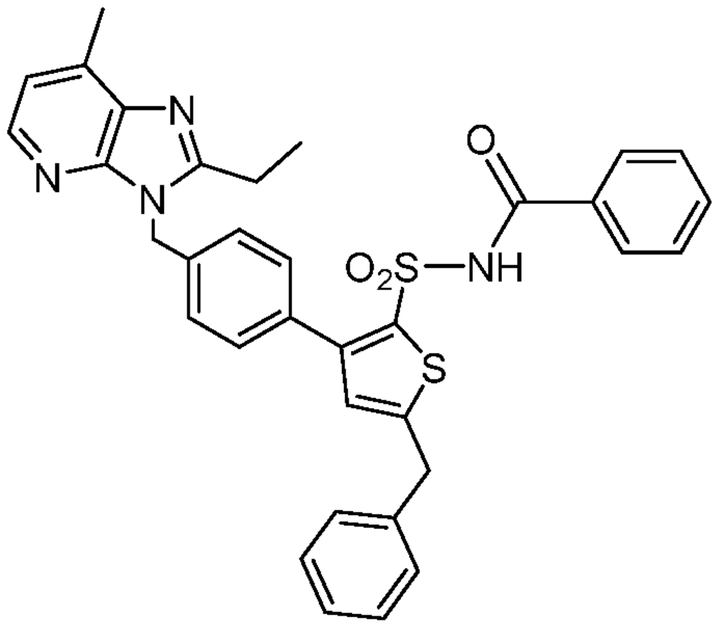

O
O-npropyl
N
N
N
O_2S—NH

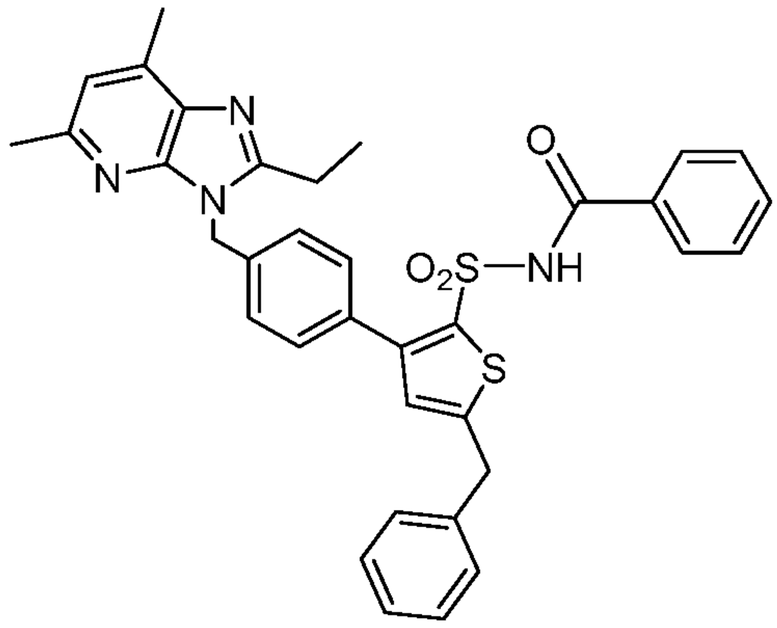

O
NH
N
N
N
O_2S—NH
N
O

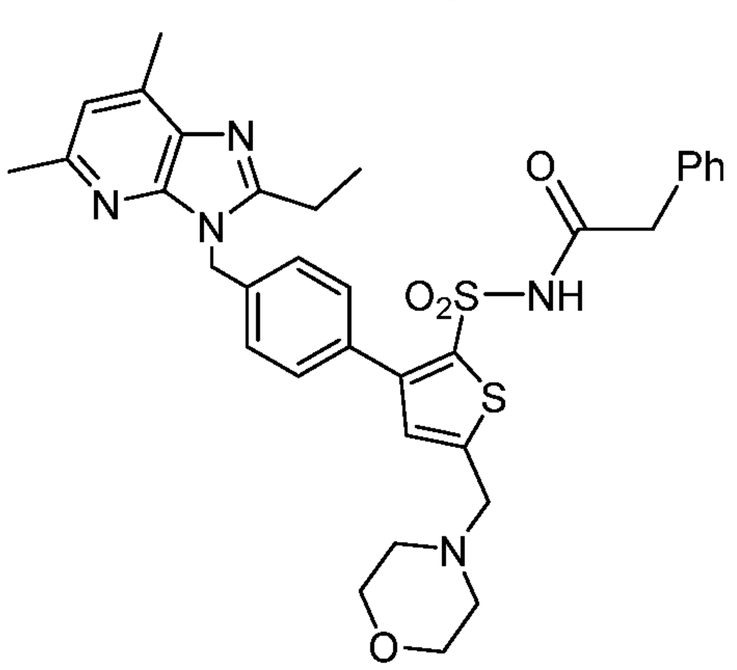

O
NH
N
N
N
O_2S—NH

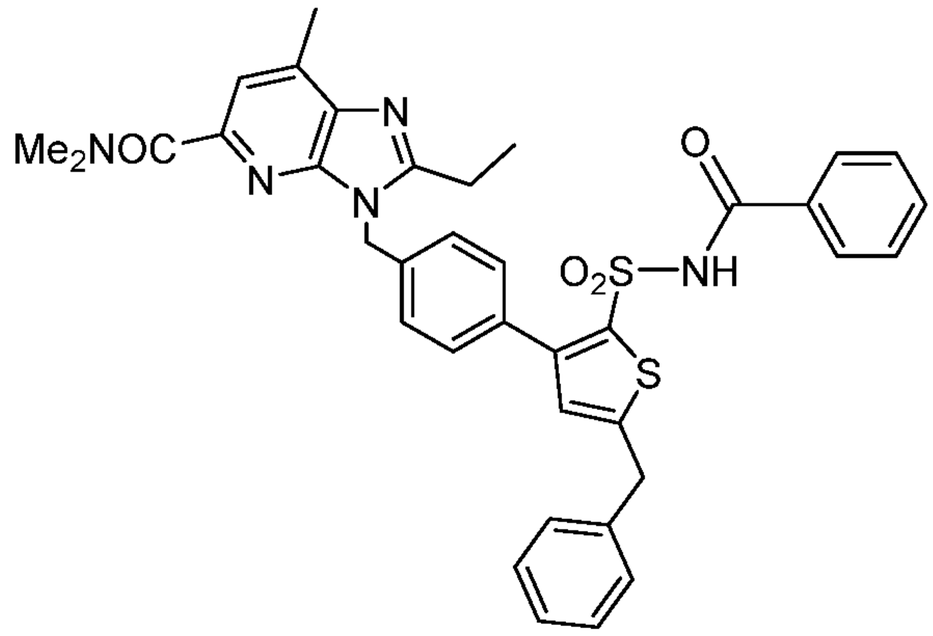


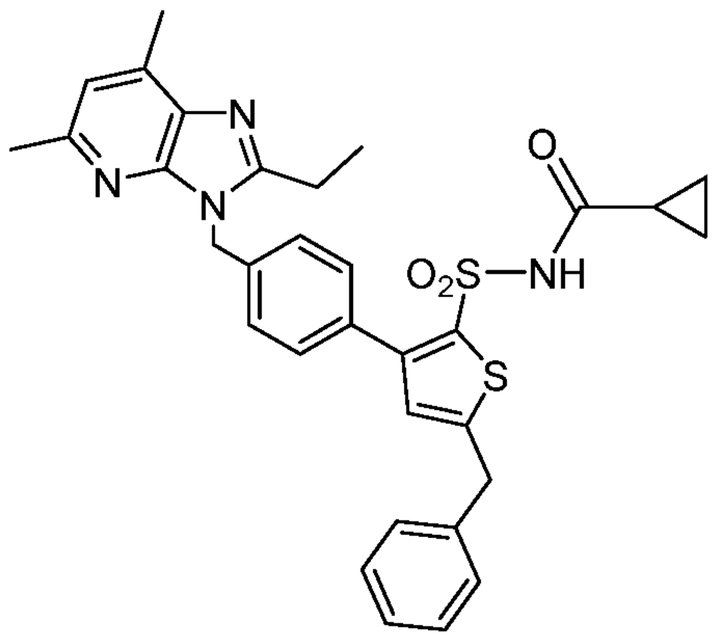


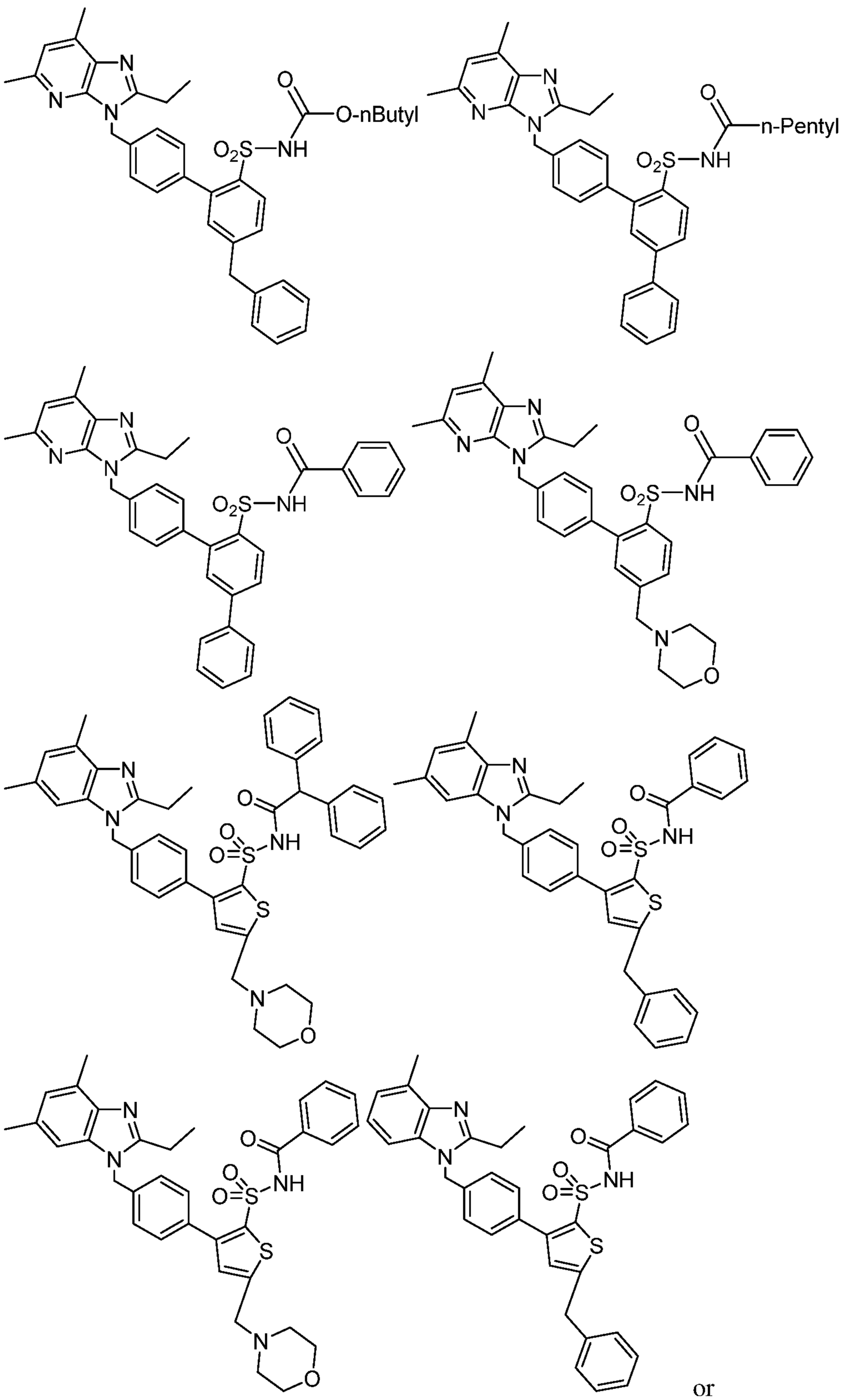




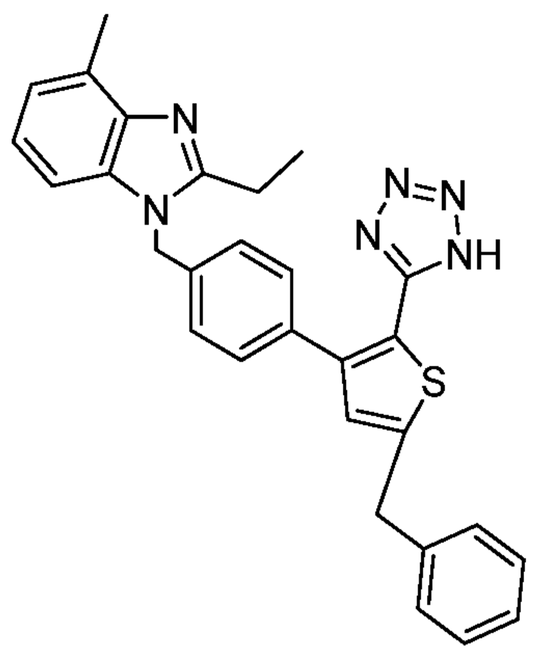








or



14. A compound of claim 13, or salt thereof, wherein

R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl or $O(C_{1-6}$ alkyl);

R^9 is CO_2H, CO_2- C_{1-6} –alkyl, CO_2NH_2, $CO_2NH(C_{1-6}$ –alkyl), $CO_2N(C_{1-6}$ –alkyl)$_2$.

and

R^6 is hydrogen, or C_{1-4} alkyl.

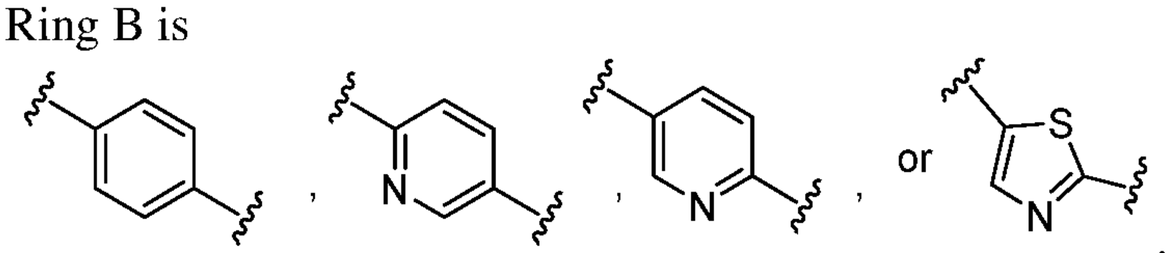
15. A compound of claims 13-14, or salt thereof, wherein

G is selected from a 5 to 10 membered heterocycle having 1-3 atoms selected from N, O, and S, phenyl or a C_6-C_{10}-heteroaryl having 1-3 atoms selected from N, O, and S; wherein the heterocycle, phenyl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkylthio, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2R^x$;

R^x is H, C_{1-6} alkyl, CF_3, phenyl, CH_2phenyl.

16. A compound of claims 13-15, or salt thereof, wherein

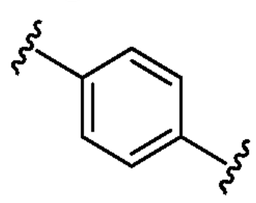
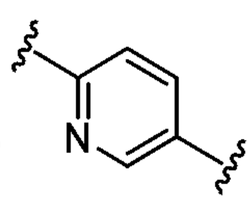
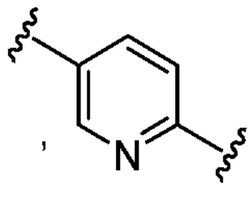
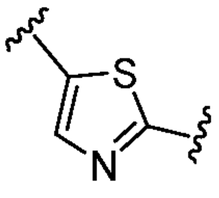
Ring B is



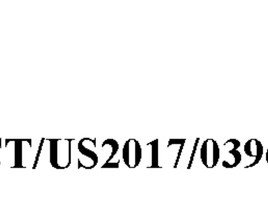
any of which are optionally substituted with 0-2 F,

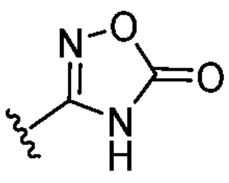
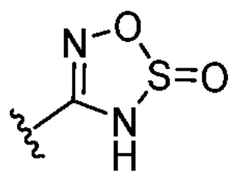
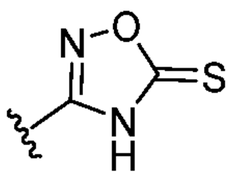
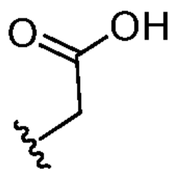
17. A compound of claims 13-15, or salt thereof, wherein

Ring B is


, 
, 
, or 
,

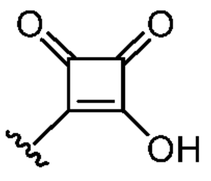
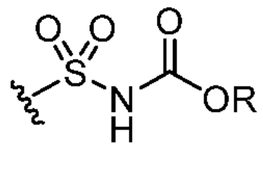
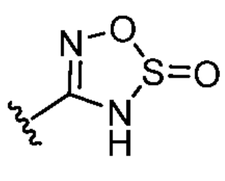
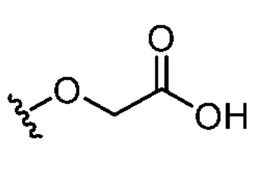
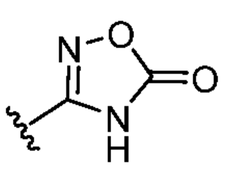
any of which are optionally substituted with 0-2 F,

Y is COOH, COOMe, COOEt,
, 5-tetrazolyl, SO_3H, 
,


, 
, 
, or 
.

18. A compound of claims 13-15, or salt thereof, wherein

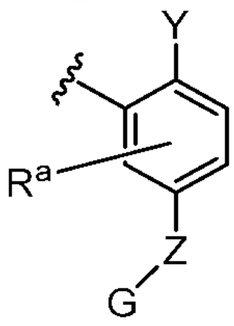
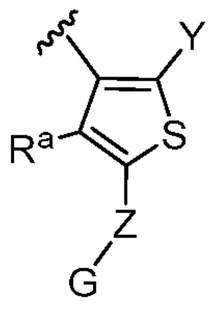
wherein Y is COOH, 5-tetrazolyl, SO_3H,






; and

$R = C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$-aryl-C_1-C_6-alkyl , or (CH_2Ph).

19. A compound of claims 13-18, or salt thereof, wherein

Ring A is


or 
; and

R^a is H or F.

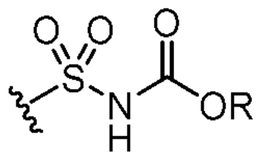
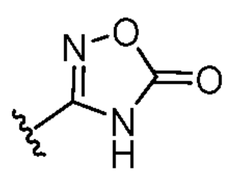
20. A compound of claims 13-19, or salt thereof, wherein

G is selected from a phenyl, thiophenyl, quinolinyl, isoquinolinyl, indolyl, pyrazolyl, pyrrolyl, pyridinyl, isoindolinyl, pyrrolidinyl; ; any of which are substituted with 0-3 substituents independently selected from the group consisting of =O, Cl, Br, I, F, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, OH, OR^x, $N(R^x)_2$, $CO(R^x)$,

$CON(R^X)_2$, CO_2R^X, $N(R^X)CO_2(R^X)$, $N(R^X)CO(R^X)$, $N(R^X)CON(R^X)_2$, $S(O)_2(R^X)$, $S(O)_2N(R^X)_2$, or $N(R^X)S(O)_2R^X$;

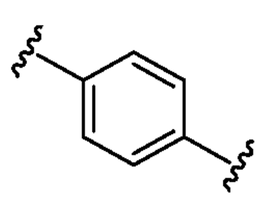
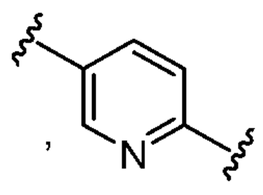
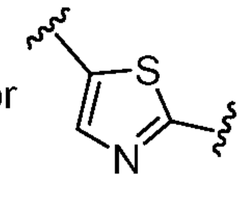
R^X is H, C_{1-3} alkyl, CF_3, phenyl, CH_2phenyl.

21. A compound of claims 13-19, or salt thereof, wherein
Y is carboxyl, 5-tetrazolyl,



; and

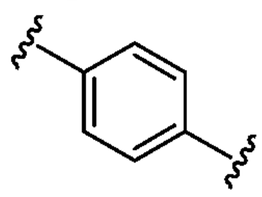
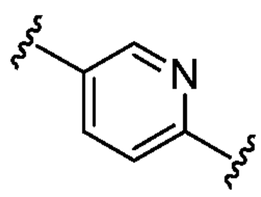
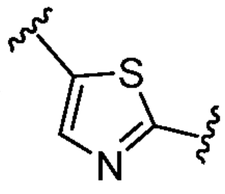
R is C_{1-6} alkyl.

22. A compound of claims 13-20, or salt thereof, wherein
Ring B is

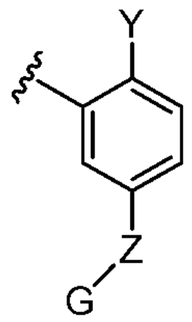
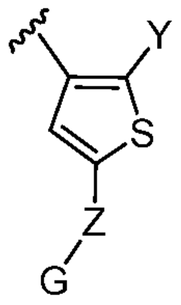


, or

, any of which are substituted with 0-2 F.

23. A compound of claim 13, or salt thereof wherein

Ring B is


,

, or


Ring A is


or


Z is a bond or NR^a;

G is isoindolinyl-1,3-dione, pyrrolidine-2,5-dione, phenyl, thiazolyl, pyridinyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, any of which may be substituted with 0-3 substituents selected from =O, C_{1-4} alkyl, -O-R^X, C_{1-4} haloalkyl, -$C(O)NR^X$, -$N(R^X)_2$, and F;

R^5 is C_{3-4} alkyl;

R^6 is C_{3-4} alkyl;

R^a is hydrogen, C_{1-4}alkyl, and C_{1-2} haloalkyl; and

Y is tetrazolyl, COOH, 1,2,4-oxadiazol-5(4H)-one, or -SO_2NHCOO-nbutyl.

24. A compound according to claim 1, or salt thereof, where the compound is selected from Examples 1-462.

25. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof.

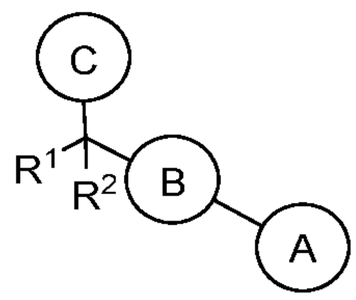
26. A method for the treatment or prophylaxis of diseases or disorders which can be modulated by biased agonism or β-Arrestin agonism of the angiotensin II receptor, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of at least one of the compounds of claims 1-23, wherein the disease or disorder is preserved injection fraction heart failure, reduced injection heart failure, and/or renal disease.

27. A method for the treatment or prophylaxis of diseases or disorders which can be modulated by biased agonism or β-Arrestin agonism of the angiotensin II receptor of claim 23, wherein the compound is administered in combination with at least one other type of therapeutic agent.

28. A method for the treatment or prophylaxis of diseases or disorders, comprising administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of at least one of the compounds of claims 1-23, wherein the disease or disorder is preserved injection fraction heart failure, reduced injection heart failure, and/or renal disease.

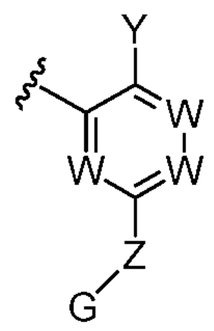
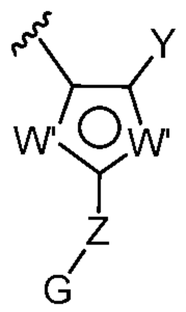
29. A method for the treatment or prophylaxis of diseases or of claim 27, wherein the compound is administered in combination with at least one other type of therapeutic agent.

30. A compound of formula (X), or salt thereof:



(X)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring A is  or  ;

W is N, or CR^{16};

W', at each occurrence, is independently selected from N, O, S and CR^{16}, wherein at least one W' is not CR^{16}, and at most only one W' is selected as O or S;

R^1 and R^2 are independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyalkyl, and C_3-C_6 cycloalkyl;

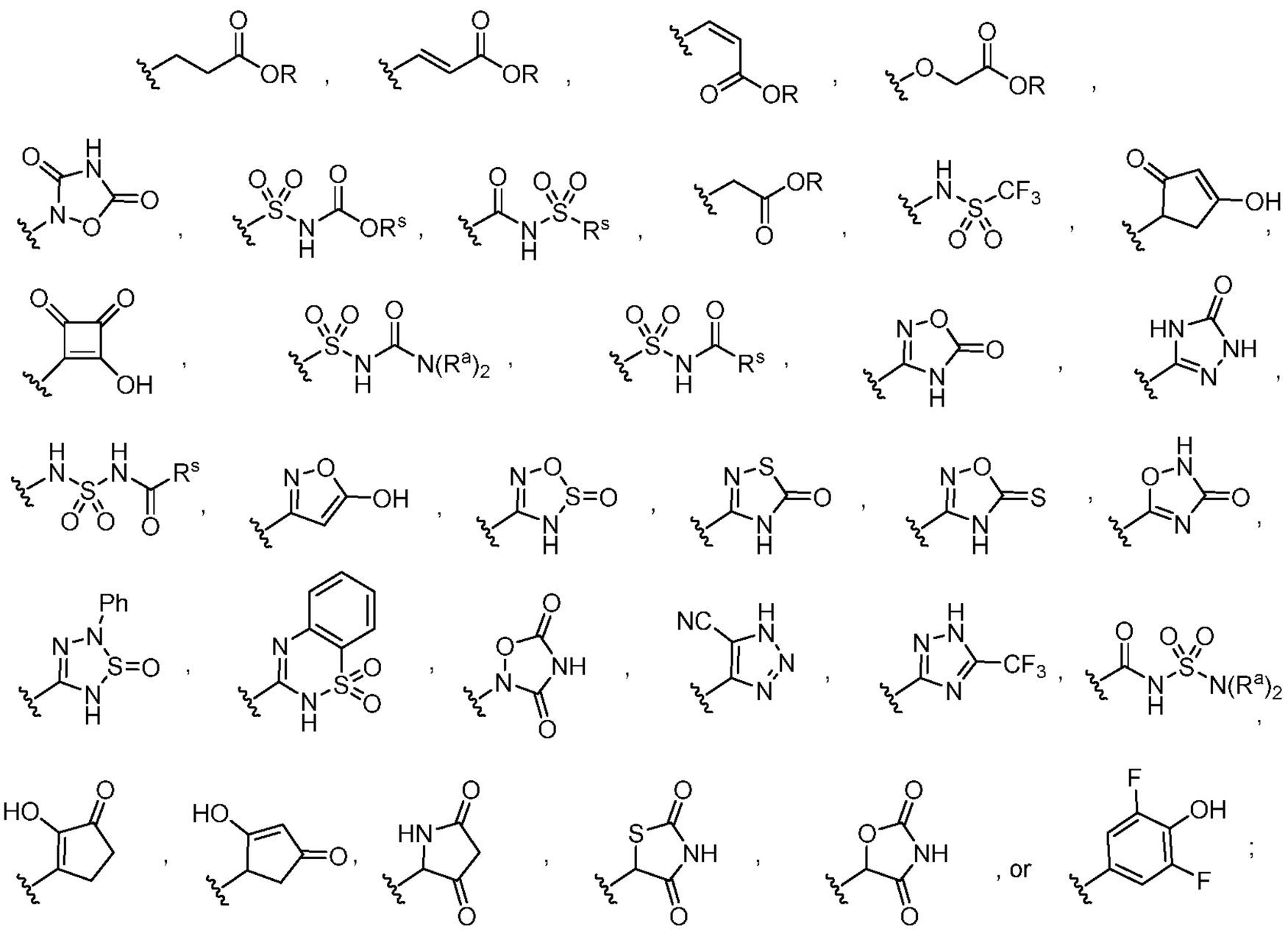
alternatively, R^1 and R^2, together with the atom to which they are attached, join together to form a C_3-C_6 cycloalkyl, or a 4 to 6 membered heterocycle having 1-2 heteroatoms, the cycloalkyl or heterocycle is substituted with 0-4 F and 0-1 OH;

R^{16}, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, OH, $N(R^a)_2$, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_4-hydroxyalkyl, C_1-C_3-haloalkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-halocycloalkyl

R^a is, at each occurrence, independently selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, and C_3-C_6-cycloalkyl;

or two R^a, along with the nitrogen atom to which they are attached, join to form a 5 to 6 membered heterocycle containing 0-2 additional heteroatoms selected from N, O and S;

Y is 5-tetrazolyl, SO_3H, PO_2H , PO_3H_2, COOR,



R, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_{6-10}-aryl-C_1-C_6 alkyl, heterocycle-C_1-C_6 alkyl, wherein said heterocycle is a 4-10 membered group having 1-3 heteroatoms selected from N, O, or S, said aryl and heterocycle are each substituted with 0-3 groups chosen from C_1-C_3 alkyl, halo, OH, or C_1-C_3 fluoroalkyl;

R^s at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_3 alkyl, C_{6-10} aryl, C_{6-10}-aryl-C_1-C_6-alkyl , heteroaryl, heteroaryl-C_1-C_6-alkyl, heterocyclyl, heterocycle-C_1-C_6-alkyl, wherein the heteroaryl is a 5-10 membered group and the heterocycle is a 4-10 membered each having 1-3 heteroatoms selected from N, O, or S;

Z, at each occurrence, is independently selected from a bond, O, S, $N(R^z)$, $C(R^z)_2$, C=O, $C(=O)N(R^z)$, $N(R^z)C(=O)$, $C(R^z)_2C(R^z)_2$, $OC(R^z)_2$, $SC(R^z)_2$, $N(R^z)C(R^z)_2$, $C(R^z)_2O$, $C(R^z)_2S$, $C(R^z)_2N(R^z)$;

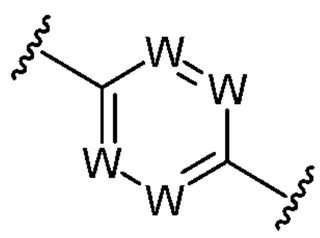
R^z is at each occurrence independently selected from H, C_1-C_4-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxyalkyl, C_1-C_4-haloalkyl, C_3-C_{10}-cycloalkyl, 5-10-membered heterocycle-C_1-C_6-alkyl, 5-10-membered heterocycle, C_3-C_{10}- cycloalkyl-C_1-C_6-

alkyl, 4 to 7 membered heterocyclyl having 1-2 heteroatoms selected from N, O, or S, or, alternatively, two R^z groups either on the same atom or on adjacent atoms can join to form a C_3-C_6-cycloalkyl or a 4 to 7 membered heterocycle containing 1-2 heteroatoms selected from N, O and S;

G is selected from a 4 to 11 membered heterocycle having 1-4 atoms selected from N, O, and S, a C_3-C_8-cycloalkyl, C_6-C_{10}-aryl or a 5 to 10 membered heteroaryl having 1-4 atoms selected from N, O, and S; wherein the heterocycle, cycloalkyl, aryl and heteroaryl are substituted with 0-3 substituents independently selected from the group consisting of =O, F, Cl, Br, I, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, CH_2-phenyl, OH, OR^x, SR^x, $N(R^x)_2$, $CO(R^x)$, $CON(R^x)_2$, CO_2R^x, $N(R^x)CO_2(R^x)$, $N(R^x)CO(R^x)$, $N(R^x)CON(R^x)_2$, $S(O)_2(R^x)$, $S(O)_2N(R^x)_2$, or $N(R^x)S(O)_2(R^x)$;

R^x is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ hydroxyalkyl, phenyl, CH_2-phenyl;

ring B is



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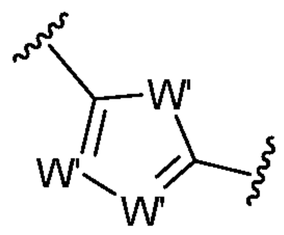
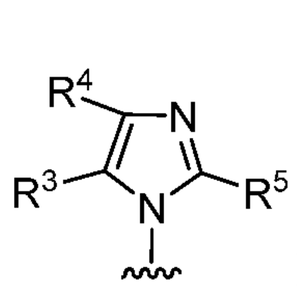


;

Group C is



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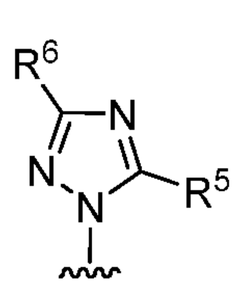

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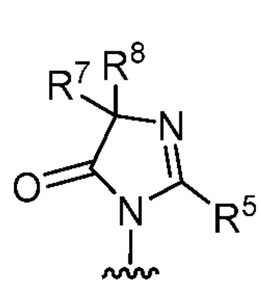

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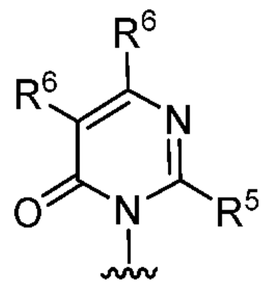

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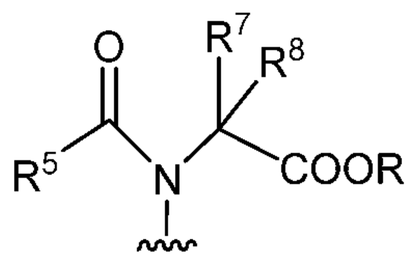

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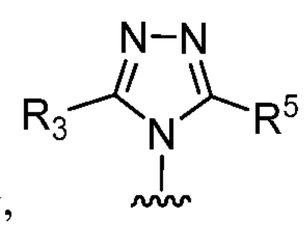

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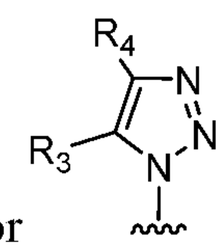
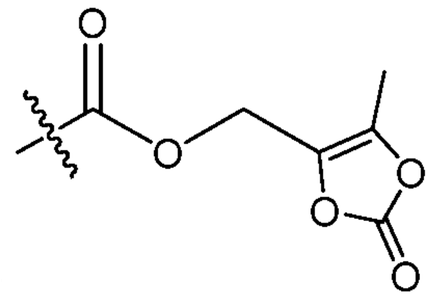


IJ

R^3 is $C_{1\text{-}4}$ hydroxyalkyl, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}6}$–hydroxycycloalkyl, $C_{1\text{-}6}$–halocycloalkyl, COOR, $CON(R^z)_2$, 5-6 membered heteroaryl or



;

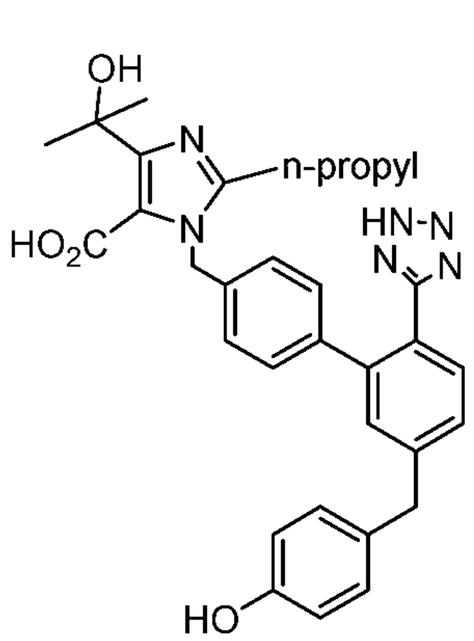
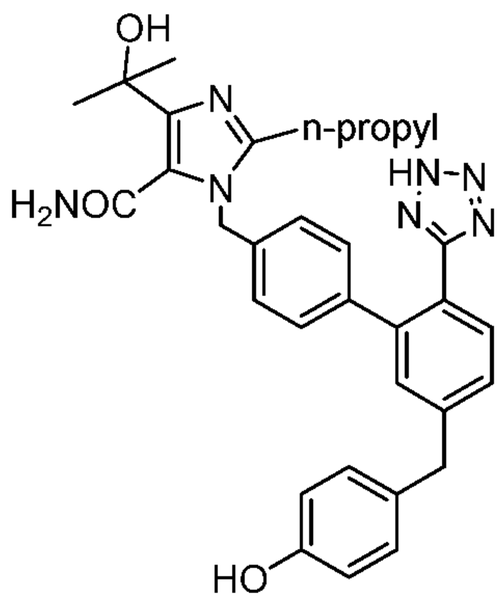
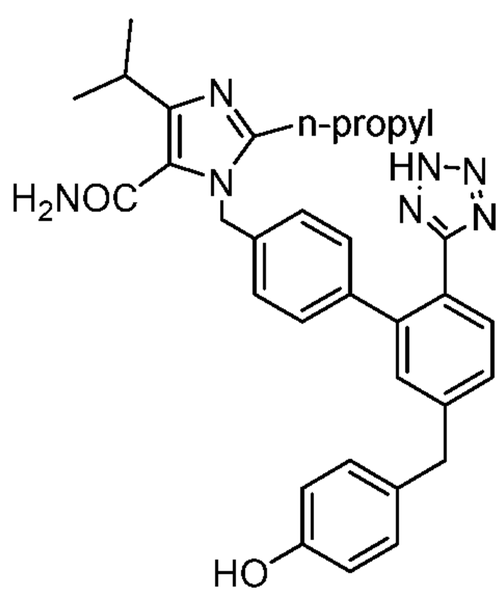
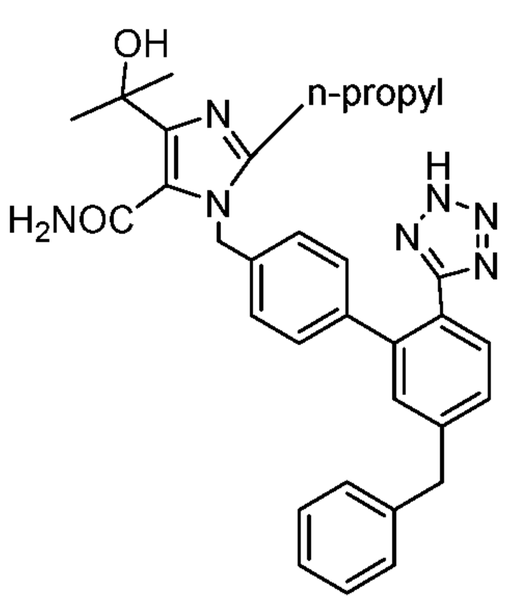
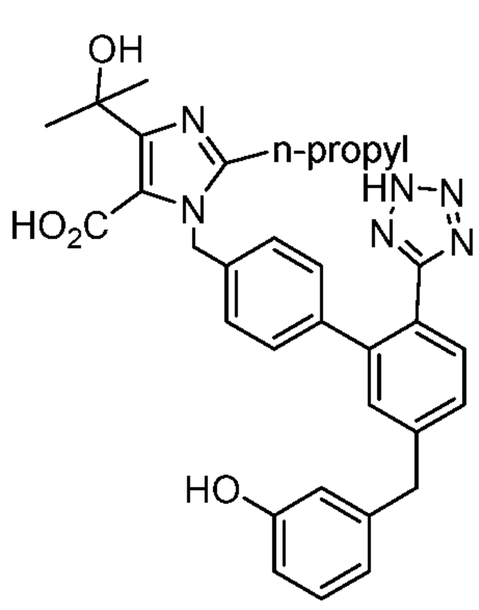
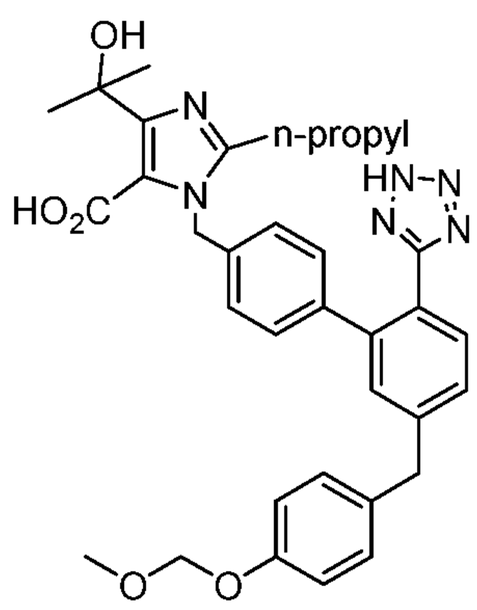
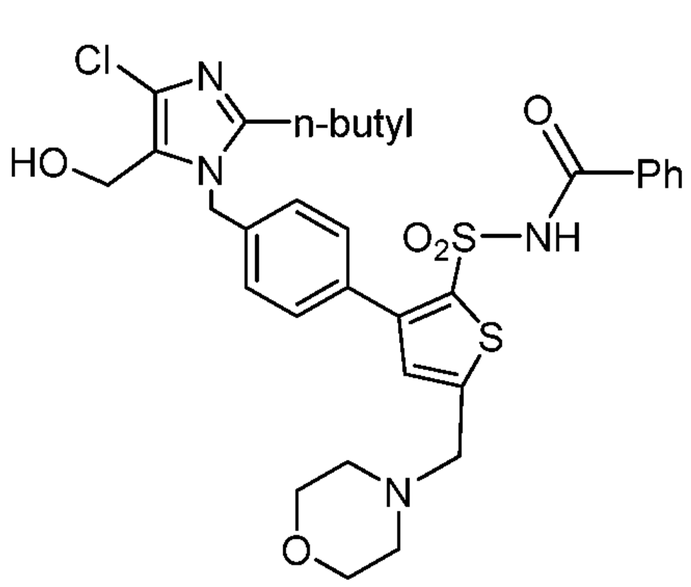
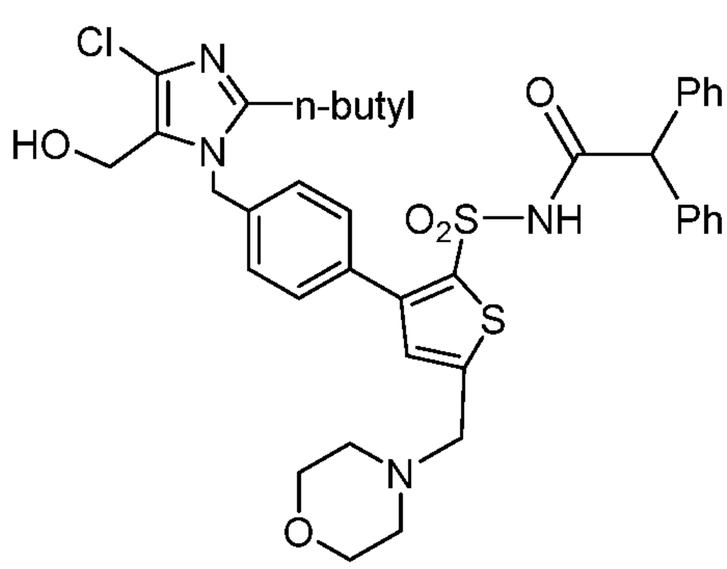
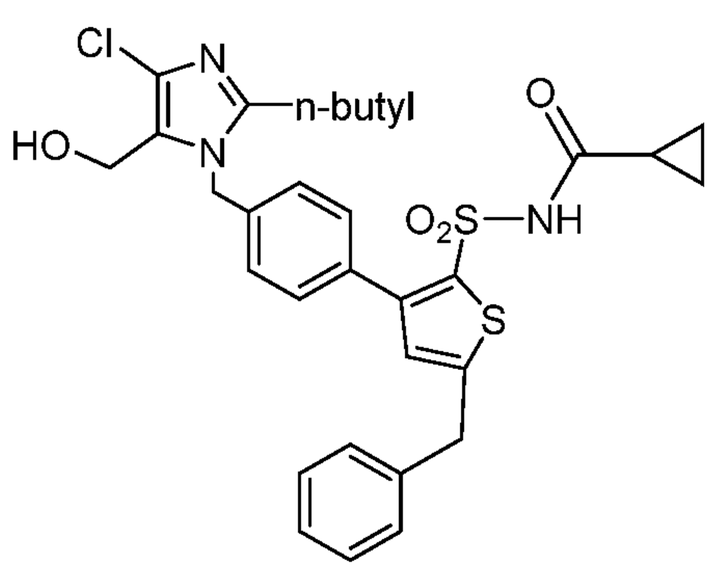
R^4 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$,C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{3-6}–cycloalkyl, C_{3-6}–halocycloalkyl, C_{3-6}–alkoxycycloalkyl, C_3-C_6-cycloalkyl-C_1-C_6-alkyl, or C_{3-6}–hydroxycycloalkyl;

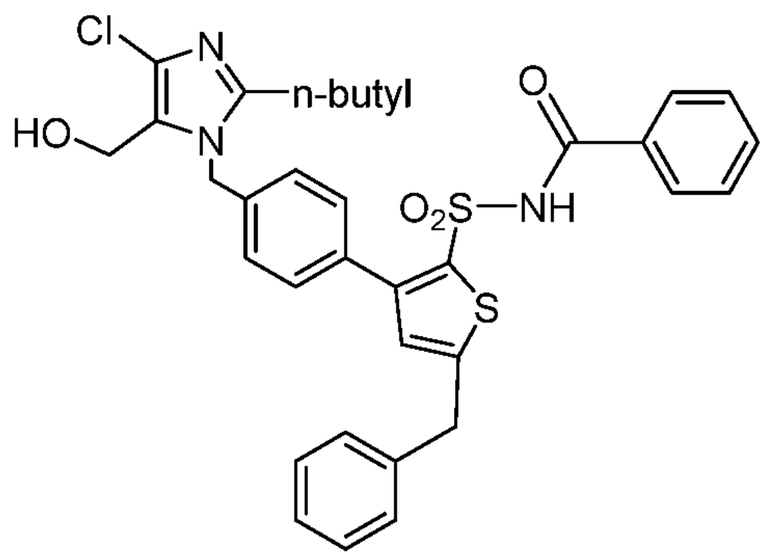
R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl; C_{1-6} alkoxyalkyl, C_{3-6}–cycloalkyl-C_{0-4}–alkyl which may be substituted with 1-3 halogens or a C_{1-3}-alkoxy group;

R^6 is H, F, Cl, Br, CF_3, CN, $N(R^z)_2$, $CON(R^z)_2$, C_{1-4}-alkyl, C_{1-4}-haloalkyl, C_{1-4}-alkoxyalkyl, C_{1-4} hydroxyalkyl, C_{3-6}–cycloalkyl, C_{3-6}–halocycloalkyl, C_{1-6}–alkoxy-C~~3~~-C_6-cycloalkyl, or C_{3-6}–hydroxycycloalkyl; and

R^7 and R^8, are independently selected from H, C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_3-C_6-cycloalkyl or, alternatively, R^7 and R^8, along with the atom to which they are attached, can join to form a C_3-C_9 cycloalkyl, a C_3-C_9-halocycloalkyl, a C_3-C_9-hydroxycycloalkyl or a 4 to 7 membered heterocycle having 1-2 heteroatoms selected from N, O, or S each of said cycloalkyl and heterocycle being optionally substituted with 1-4 F, OH, C_{1-4} alkyl, C_{1-4} haloalkyl C_{1-4} alkoxyalkyl, or C_{1-4} hydroxyalkyl, and may be fused with a 6-membered aryl or 5-6 membered heteroaryl ring,

provided the compounds of Formula (X) are not



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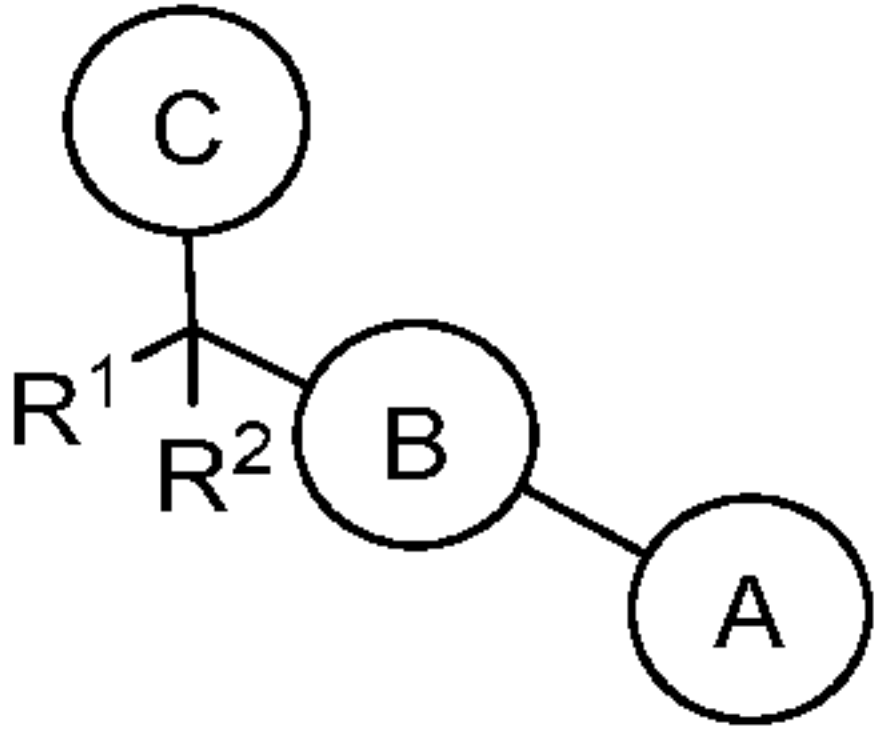

(I)