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(71) Applicant: **CARDIO THERAPEUTICS PTY LTD** [AU/AU]; PO Box 824, Turramurra, New South Wales 2074 (AU).

(72) Inventors: **TREUTLEIN, Herbert**; c/- PO Box 824, Turramurra, New South Wales 2074 (AU). **ZENG, Jun**; c/- PO Box 824, Turramurra, New South Wales 2074 (AU). **DIXON, Ian**; c/- PO Box 824, Turramurra, New South Wales 2074 (AU). **JAMES, Ian**; c/- PO Box 824, Turramurra, New South Wales 2074 (AU). **PALMER, James T**; c/- PO Box 824, Turramurra, New South Wales 2074 (AU).

(74) Agent: **FPA PATENT ATTORNEYS PTY LTD**; Level 43, 101 Collins Street, Melbourne, Victoria 3000 (AU).

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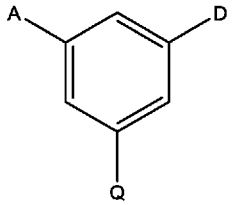
(54) Title: HETEROCYCLIC INHIBITORS OF PCSK9



(I)

(57) Abstract: This application relates to chemical compounds which may act as inhibitors of, or which may otherwise modulate the activity of, PCSK9, or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and to compositions and formulations comprising such compounds, and methods of using and making such compounds. Compounds include compounds of Formula (I): (I) wherein A, D and Q are described herein.

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Heterocyclic Inhibitors of PCSK9

Field of the invention

The present disclosure relates to compounds for the treatment of LDL related disorders, to their compositions and methods for their use, and to PCSK9 inhibition.

Background of the invention

Cardiovascular diseases are said to cause an estimated 17.5 million (over 30%) of all deaths as of 2012 (E. Corey, The Pharmaceutical Journal, 2015). A particular risk factor, atherosclerosis, results from high levels of circulating low-density lipoprotein (LDL-C, a.k.a. "bad" cholesterol) in the blood. LDL-C accumulation in the inner walls of arteries results in atherosclerosis and can provoke an inflammatory response, which in turn can lead to cardiovascular events such as heart attack and stroke. Thus, LDL-C measurement is an effective surrogate marker for the risk of cardiovascular events.

Proprotein convertase subtilisin kexin type 9 (PCSK9) was discovered in 2003 (Seidah, N.G. et al, PNAS, 2003), is a serine protease, and is highly expressed in the liver. It is a genetically validated target for hypercholesterolemia (Abifadel, M. et al, Nature Genetics, 2003). Loss-of-function mutations of the PCSK9 gene have been linked to lower levels of LDL-C and a reduction of cardiovascular risk (Cohen, J.C. et al, NEJM, 2006). Its regulatory mechanisms have been reviewed (Lagace, T.A, Curr. Opin. Lipidol. (2014), 387-393). PCSK9 is synthesized as an enzyme precursor. Following synthesis, PCSK9 undergoes autocatalytic cleavage, which is required for secretion from the cell. The cleaved prodomain remains with PCSK9, blocking access to the active site of the enzyme. While LDL-C normally binds to the LDL receptor (LDL-R), which are together internalized and degraded intracellularly, PCSK9 attaches to the LDL-R/LDL complex for internalization/degradation. As a result, recirculation of LDL-R is reduced, resulting in increased circulatory LDL. Inhibition of PCSK9 or prevention of LDL-R attachment thereto results in increased cell surface expression of LDL-R, lowering circulatory LDL.

Because PCSK9's only substrate is itself, targeting circulating PCSK9 by small molecule inhibitors is unlikely to represent an option for LDL reduction because the mechanism of action of PCSK9 in reducing cellular LDLR does not involve proteolytic

activity. However, small cell-permeable molecules targeting the catalytic site of PCSK9 pro-enzyme could theoretically inhibit the auto-processing of PCSK9, thereby promoting its degradation in the ER. However, cross-reactivity associated with such inhibitors raises concern that PCSK9 pro-enzyme inhibition could co-inhibit other proprotein convertases. (Mousavi, S.A.et al., J. Int. Med. (2009) **266**, 517-519).

Despite the discovery of PCSK9 and its role in LDL regulation, statins have served as the primary therapy used to prevent cardiovascular events. By inhibiting the rate-limiting enzyme HMG-CoA reductase, which has a vital role in internal (hepatic) cholesterol production through the reduction of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid, various statins can reduce LDL-C levels from 10-60% and have been shown to reduce the risk of heart attack and stroke.

Familial hypercholesterolemia (FH) is a hereditary disorder of LDL cholesterol metabolism, affects 1 in 250 persons and is characterized by greatly increased levels of LDL-C (Besseling, J. et al., J. Am. Coll. Cardiol. (2016) **68**, 252-268). Patients with heterozygous FH are at 3- to 4-fold higher risk for coronary artery disease (CAD) and tend to develop CAD on average 10 years earlier in life than unaffected persons. Statins lower LDL cholesterol in patients with heterozygous FH, approximately to the same extent as in the general population while the average relative risk reduction of statins for CAD is estimated to be 22% per mmol/l among the general population it was unknown whether there is a comparable risk reduction in the setting of heterozygous FH because it would be unethical to withhold treatment from these patients. In the Besseling study to estimate the relative risk reduction for CAD and mortality by statins in heterozygous FH patients, the authors concluded that moderate- to high-intensity statin therapy lowered the risk for CAD and mortality by 44%. However, reduction in LDL-C is not considered sufficient in many cases. One mechanism by which statins display a countervailing mechanism is in the upregulation of sterol regulatory element binding protein 2 (SREBP-2, see Wong, J. et al., Biochem. J. (2006), **400**, 485-491.). This increased activity results in the activation of both LDL receptors (LDLR) and PCSK9. Increased expression and secretion binds LDLR, resulting in higher LDLC. Thus, while statins reduce LDL via HMGCoA inhibition, their effect on SREPB acts as a counterbalance. Adding PCSK9 inhibitors to therapy can help override this mechanism.

While statins have been on the market for almost 30 years, some patients find statins to be ineffective or are burdened by intolerable side effects such as muscle pain (Abd, T.T., Jacobson, T. A., Expert Opinion on Drug Safety, p 373-387, 2011). Observationally, up to 10-15% of statin users develop muscle side effects ranging from mild myalgia to more severe symptoms. Furthermore, it has been reported that statin therapy is associated with a slightly higher risk of diabetes (2-17%, Sattar, N. et al., Lancet, (2010) **375**, 735-742.) Given that familial hypercholesterolemia patients may not sufficiently benefit from statin therapy even in the absence of adverse side effects, there exists a need for alternative therapy avenues such as PCSK9 inhibition.

To date, there are no marketed small molecule inhibitors of PCSK9. Monoclonal antibody based drugs alirocumab and evolocumab have shown evidence of large improvements in lipid levels. These drugs are administered by injection, for instance biweekly. Alirocumab, when delivered every 2 weeks, showed greatest effect in heterozygous FH patients at cardiovascular risk who had not achieved LCL-C goals with statin therapy alone. Alirocumab also showed a moderate increase in "good" cholesterol (HDL-C) of 6-12% over this period. However, legal disputes over the intellectual property surrounding alirocumab have resulted in an injunction from its marketing in some jurisdictions. These issues, together with the substantially higher costs typically associated with monoclonal antibody production over small molecule inhibitors, clearly illustrates the very high need for competitive small molecule inhibitors of PCSK9.

Small molecule approaches have been described in the following: See WO2014170786, (Pfizer), WO2014150395, WO2014150326 (Shifa), WO2011051961, WO2014002106 (Cadila Healthcare) and US20120004223 (CVI), none of which have progressed beyond the discovery stage. Additional reported approaches include RNAi and gene-silencing oligonucleotides.

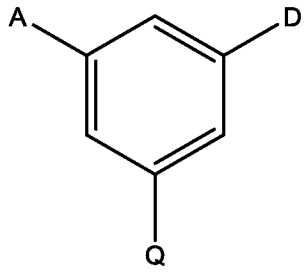
The present invention seeks to provide small molecule inhibitors of PCSK9.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood,

regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

Summary of the invention

As discussed above, the present invention seeks to provide small molecule inhibitors of PCSK9. In one aspect, therefore, the invention provides a compound according to Formula (I):



(I)

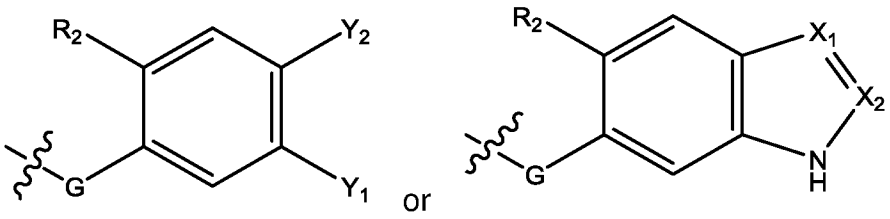
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

A is H or an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group;

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

wherein D is



wherein G is selected from the group consisting of $–NR_1C(O)-$, $–C(O)NR_1-$, $-S(O)_2NR_1-$, and $–NR_1S(O)_2-$;

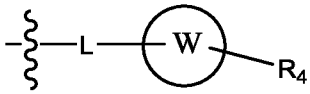
wherein R_1 is H or methyl and R_2 is H,

or wherein G is $–NR_1C(O)-$ and R_1 and R_2, together with the atoms between them, form an optionally substituted C_3-C_6 heterocyclic ring, thereby creating a bicyclic or tricyclic ring; and

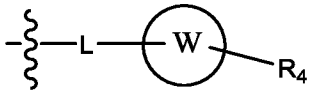
wherein X_1 is CR_3 and X_2 is N, or X_1 is N and X_2 is CR_3, or both X_1 and X_2 are CR_3;

wherein R_3 is H, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy or C_1-C_2 alkylamino; and

wherein Y_1 is H or methyl and Y_2 is



or Y_2 is H or methyl and Y_1 is



or both Y_1 and Y_2 are independently selected from H or methyl;

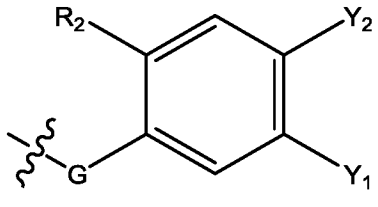
wherein L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

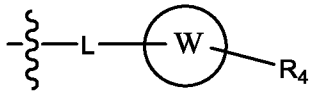
where m is 1 or 2; and

wherein 

is aryl or heteroaryl; and

wherein R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

Typically, when A is methyl-substituted imidazole, Q is 

$-CF_3$, and D is wherein G is $-NR_1C(O)-$ where R_1 is H and Y_2 is methyl, Y_1 is not 

wherein L is –NH- and 

is substituted pyrimidinyl where the substituent is 3-pyridinyl.

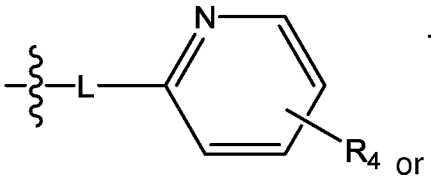
Typically, 

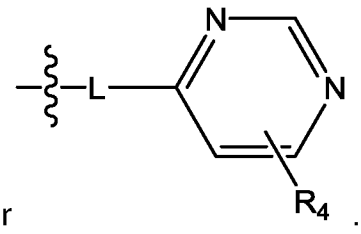
is named relative to the position of attachment to L.

Typically, 

is not pyrazolopyridinyl, ortho-substituted pyridine, 4-pyrimidinyl or imidazole. Accordingly, when 

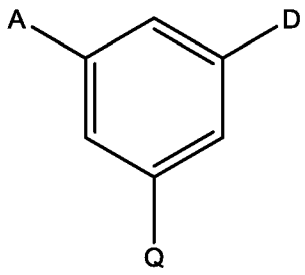
is not ortho-substituted pyridine, 4-pyrimidinyl, Y_1 or Y_2 is not



or 

.

In one aspect, therefore, the invention provides a compound according to Formula (I):



(I)

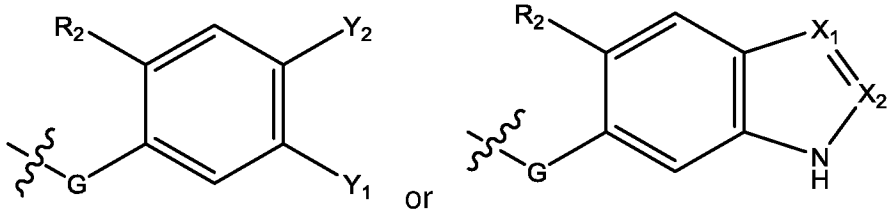
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

A is H or an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group;

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

wherein D is



wherein G is selected from the group consisting of $–NR_1C(O)-$, $–C(O)NR_1-$, $-S(O)_2NR_1-$, and $–NR_1S(O)_2-$;

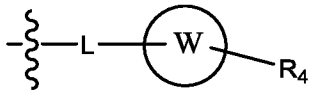
wherein R_1 is H or methyl and R_2 is H,

or wherein G is $–NR_1C(O)-$ and R_1 and R_2, together with the atoms between them, form an optionally substituted C_3-C_6 heterocyclic ring, thereby creating a bicyclic or tricyclic ring; and

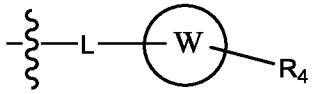
wherein X_1 is CR_3 and X_2 is N, or X_1 is N and X_2 is CR_3, or both X_1 and X_2 are CR_3;

wherein R_3 is H, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy or C_1-C_2 alkylamino; and

wherein Y_1 is H or methyl and Y_2 is



or Y_2 is H or methyl and Y_1 is



or both Y_1 and Y_2 are independently selected from H or methyl;

wherein L is selected from the group consisting of –O–, –NH–, –C(O)–, –NH$(CH_2)_m$–, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

where m is 1 or 2; and

wherein 

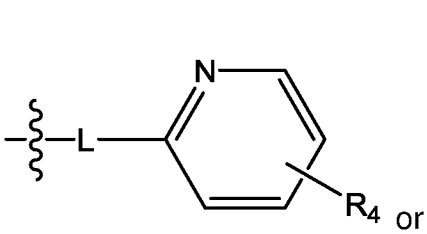
is aryl or heteroaryl; and

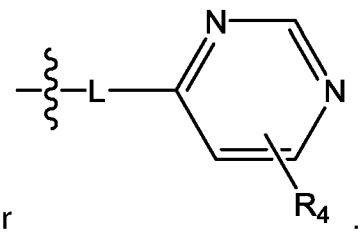
wherein R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

Typically, 

is not pyrazolopyridinyl, ortho-substituted pyridine, 4-pyrimidinyl or imidazole. Accordingly, when 

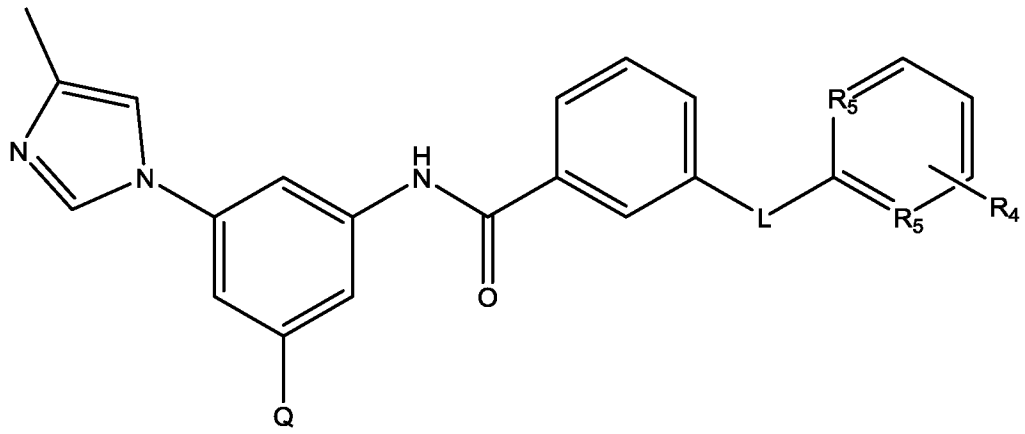
is not ortho-substituted pyridine, 4-pyrimidinyl, Y_1 or Y_2 is not



or


.

In one aspect, the invention provides a compound of formula II:



(II)

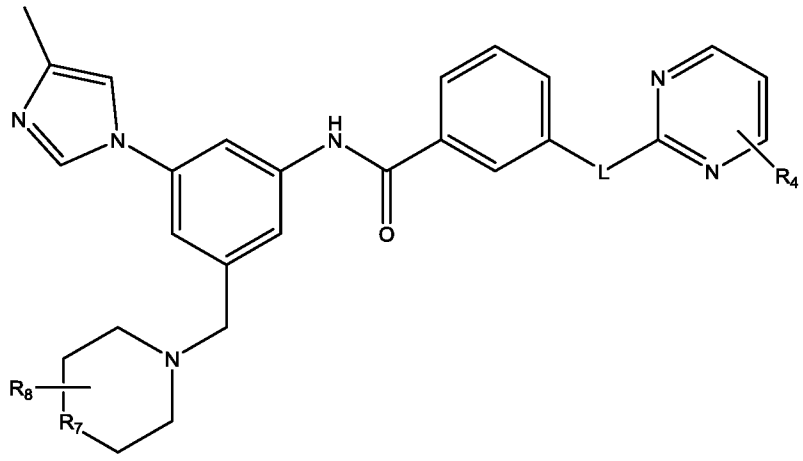
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

L , R_4 and Q are as defined above; and

each R_5 is independently CH or N.

In one aspect, the invention provides a compound of formula III:



(III)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

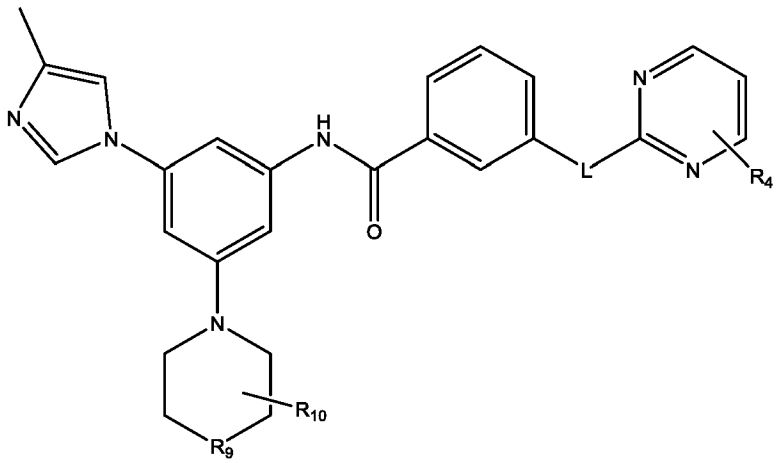
wherein

L and R_4 are as defined above;

R_7 is O, CHR_6 or NR_6; wherein R_6 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkylamino, C_1-C_3 alkyl, –OH; and

R_8 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_3 alkyl, C_1-C_4 alkylamino, C_1-C_3 alkoxy, –OH.

In one aspect, the invention provides a compound of formula IV:



(IV)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

L and R_4 are as defined above;

R_9 is O, CHR_{11} or NR_{11}; wherein R_{11} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_3 alkyl, C_1-C_4 alkylamino, C_1-C_3 alkoxy, –OH; and

R_{10} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkylamino, C_1-C_3 alkoxy, C_1-C_3 alkyl, –OH;

In one aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and a pharmaceutically acceptable excipient.

In one aspect, there is provided a method for inhibiting PCSK9 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for inhibiting PCSK9 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a therapeutically effective amount of a compound according to formula (I), formula (II), formula (III) and/or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof to a subject.

In one aspect, there is provided a method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a therapeutically effective amount of a composition comprising a compound according to

formula (I), formula (II), formula (III) and/or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof to a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the inhibition of PCSK9 in a subject.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the inhibition of PCSK9 in a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the reduction of LDL in a subject.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the reduction of LDL in a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the inhibition of PCSK9.

In another aspect, there is provided use of a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for inhibiting PCSK9.

In another aspect, there is provided use of a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the reduction of LDL.

In another aspect, there is provided use of a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the reduction of LDL.

In another aspect, there is provided use of a compound Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a composition comprising a compound Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in inhibiting PCSK9.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in inhibiting PCSK9.

In another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in reducing LDL.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in reducing LDL.

In another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for inhibiting PCSK9.

In yet another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for inhibiting PCSK9.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for reducing LDL.

In yet another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for reducing LDL.

In yet another aspect, there is provided a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

Any embodiment herein shall be taken to apply *mutatis mutandis* to any other embodiment unless specifically stated otherwise.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

Figure 1: Mechanism of LDL uptake following PCSK9-LDLR binding.

Figure 2: Fluorescence LDL uptake in HepG2 cells.

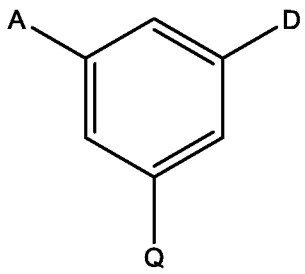
Figure 3: Promotion of LDL uptake in HepG2 cells by PCSK9 inhibitors.

Figure 4: a) Sequence alignment of sequences for existing PCSK9 structures and key species from NCBI database; b) lack of sequence conservation across the PCSK family (PCSK1 to PCSK7 and PCSK9); and c) PCSK9 conservation mapped to structure, illustrating several relevant amino acids for compound binding. The sequences and alignments in the Figures and provided in SEQ ID 1 are based on a particular UNIPROT sequence database.

Detailed description of the embodiments

The inventors have designed the compounds described herein as being applicable to LDL related conditions, potentially as small molecule inhibitors of PCSK9. Without wishing to be bound to any theory and on the basis of these molecular modelling studies, these compounds may target extracellular PCSK9, thereby preventing the PCSK9 from interacting with the LDLR.

In one aspect, therefore, the invention provides a compound according to Formula (I):



(I)

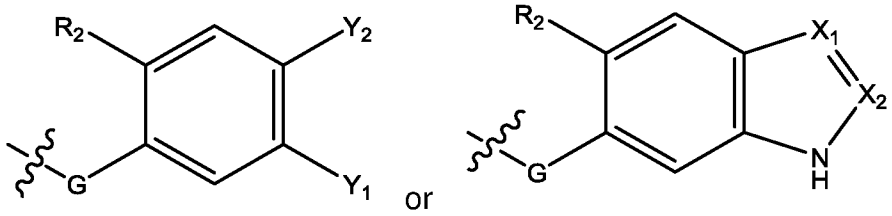
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

A is H or an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group;

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

wherein D is



wherein G is selected from the group consisting of $–NR_1C(O)$-, $–C(O)NR_1$-, $-S(O)_2NR_1$-, and $–NR_1S(O)_2$-;

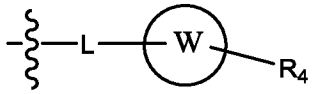
wherein R_1 is H or methyl and R_2 is H,

or wherein G is $–NR_1C(O)$- and R_1 and R_2, together with the atoms between them, form an optionally substituted C_3-C_6 heterocyclic ring, thereby creating a bicyclic or tricyclic ring; and

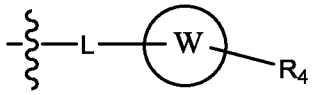
wherein X_1 is CR_3 and X_2 is N, or X_1 is N and X_2 is CR_3, or both X_1 and X_2 are CR_3;

wherein R_3 is H, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy or C_1-C_2 alkylamino; and

wherein Y_1 is H or methyl and Y_2 is



or Y_2 is H or methyl and Y_1 is



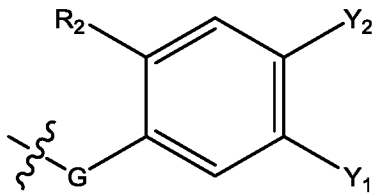
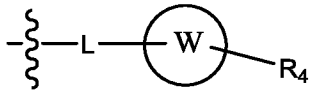
or both Y_1 and Y_2 are independently selected from H or methyl;

wherein L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

where m is 1 or 2; and

wherein  is aryl or heteroaryl; and

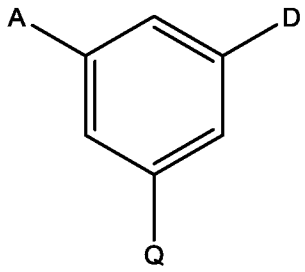
wherein R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

In one embodiment, when A is methyl-substituted imidazole, Q is $–CF_3$, and D is  wherein G is $–NR_1C(O)-$ where R_1 is H and Y_2 is methyl, Y_1 is not  wherein L is –NH- and  is substituted pyrimidinyl where the substituent is 3-pyridinyl.

Typically,  is named relative to the position of attachment to L.

In another embodiment,  is not pyrazolopyridinyl, ortho-substituted pyridine, 4-pyrimidinyl or imidazole.

In one embodiment therefore, the invention provides a compound according to Formula (I):



(I)

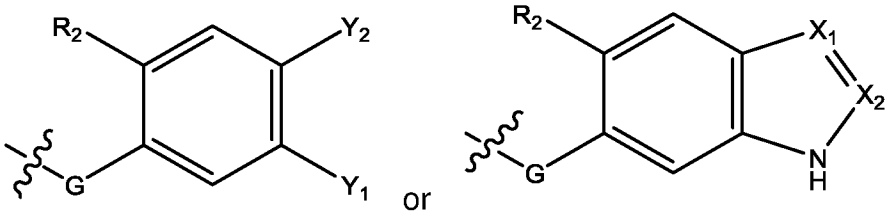
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

A is H or an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group;

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

wherein D is



wherein G is selected from the group consisting of $–NR_1C(O)-$, $–C(O)NR_1-$, $-S(O)_2NR_1-$, and $–NR_1S(O)_2-$;

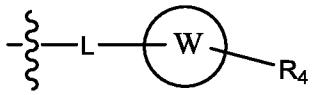
wherein R_1 is H or methyl and R_2 is H,

or wherein G is $–NR_1C(O)-$ and R_1 and R_2, together with the atoms between them, form an optionally substituted C_3-C_6 heterocyclic ring, thereby creating a bicyclic or tricyclic ring; and

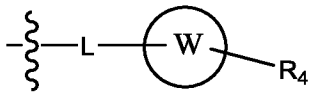
wherein X_1 is CR_3 and X_2 is N, or X_1 is N and X_2 is CR_3, or both X_1 and X_2 are CR_3;

wherein R_3 is H, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy or C_1-C_2 alkylamino; and

wherein Y_1 is H or methyl and Y_2 is



or Y_2 is H or methyl and Y_1 is



or both Y_1 and Y_2 are independently selected from H or methyl;

wherein L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

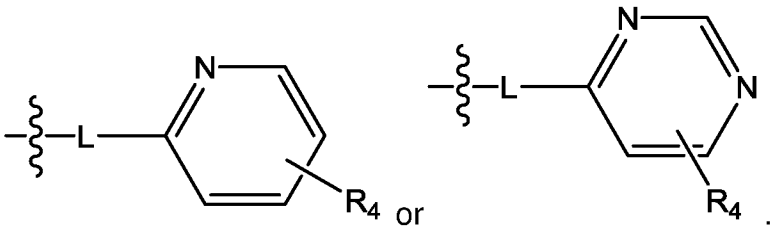
where m is 1 or 2; and

wherein 

is aryl or heteroaryl; and

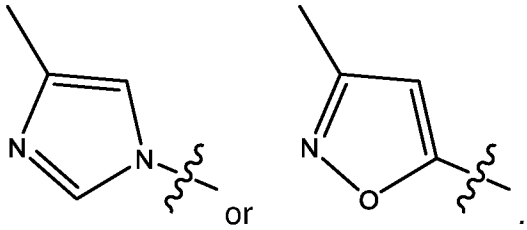
wherein R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

In another embodiment typically,  is not pyrazolopyridinyl, ortho-substituted pyridine, 4-pyrimidinyl or imidazole. Accordingly, when  is not ortho-substituted pyridine, 4-pyrimidinyl, Y_1 or Y_2 is not

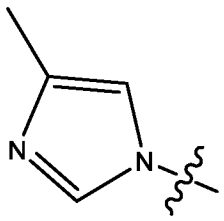


In one embodiment A is an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group.

In one embodiment, A is hydrogen,



Preferably, A is

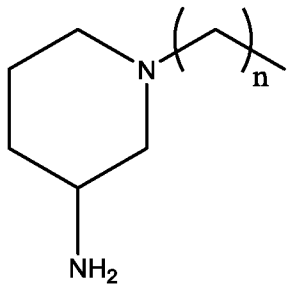


In one embodiment, Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6

alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl.

In preferred embodiments, Q is optionally substituted C_4-C_7 heterocyclyl or (C_1-C_3 alkyl)C_3-C_7 heterocyclyl and more preferably, the C_4-C_7 heterocyclyl is a C_6 heterocyclyl group. Even more preferably, the C_6 heterocyclyl group of C_4-C_7 heterocyclyl or (C_1-C_3 alkyl)C_3-C_7 heterocyclyl is a substituted or unsubstituted morpholino, piperidinyl or piperazinyl group. More preferably, the C_6 heterocyclyl group of C_4-C_7 heterocyclyl or (C_1-C_3 alkyl)C_3-C_7 heterocyclyl is selected from the groups consisting of piperazinyl, morpholino, 4-methyl piperazinyl, 4-(C_3 alkoxy)piperazinyl, (C_1-C_3 alkyl)(amino-substituted piperidinyl), (C_1-C_3 alkyl)(hydroxy-substituted piperidinyl) and optionally substituted (C_1-C_3 alkyl)piperidinyl preferably where the piperidinyl group is mono or bis-substituted with substituents independently selected from the group consisting of methyl, amino and hydroxyl.

In one particularly preferred embodiment, Q is:

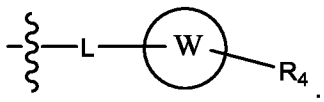


where n is 1-2. Preferably n is 1.

Where substituents on any of the heterocyclic rings are chiral, the compound may be racemic, predominantly one enantiomer, or completely one enantiomer.

In a preferred embodiment, G is –$NR_1C(O)$- . More preferably G is –$NR_1C(O)$- and R_1 is H.

In another preferred embodiment, Y_2 is H or methyl and Y_1 is



In one embodiment, 

is aryl and R_4 is H or optionally substituted aryl, preferably halo-substituted aryl.

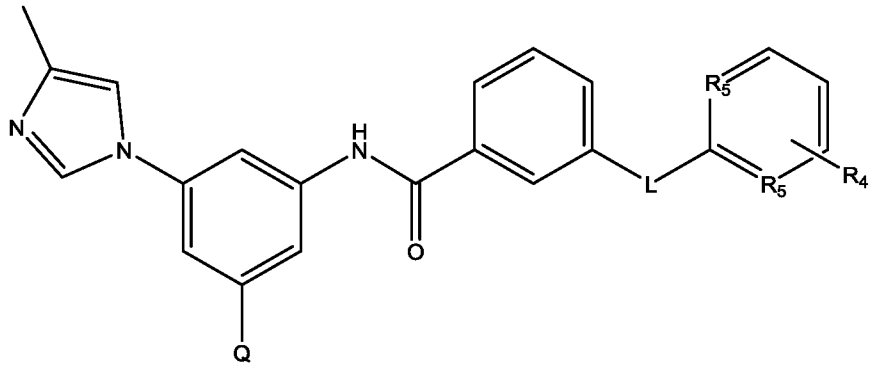
In another embodiment, 

is heteroaryl wherein the heteroaryl group is 2-pyrimidinyl, wherein 2-pyrimidinyl refers to the positon of attachment to L.

In yet another embodiment, 

is heteroaryl wherein the heteroaryl group is a bicyclic heteroaryl group and R_4 is H, preferably isoquinolinyl,

In one aspect, the invention provides a compound of formula II:



(II)

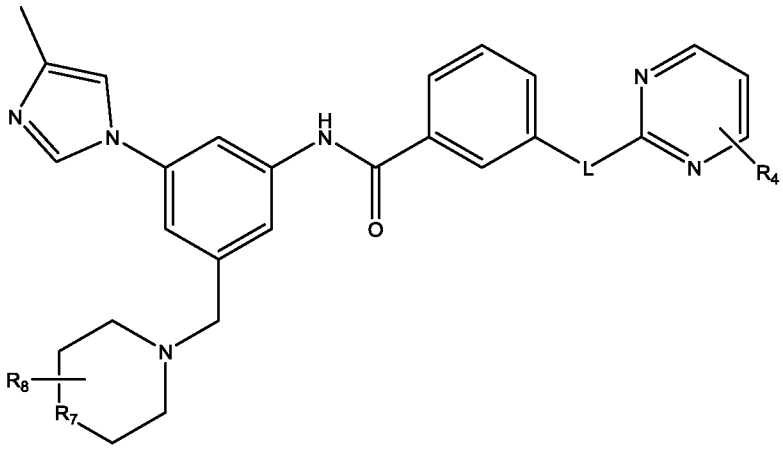
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

L , R_4 and Q are as defined above; and

each R_5 is independently CH or N.

In one aspect, the invention provides a compound of formula III:



(III)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

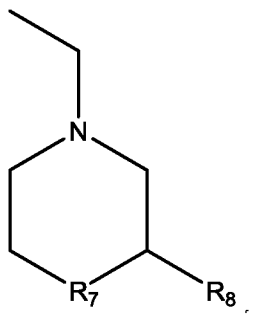
L and R_4 are as defined above;

R_7 is O, CHR_6 or NR_6; wherein R_6 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH; and

R_8 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH.

In a preferred embodiment, R_7 is CHR_6 or NR_6.

Preferably R_8 is positioned as shown:



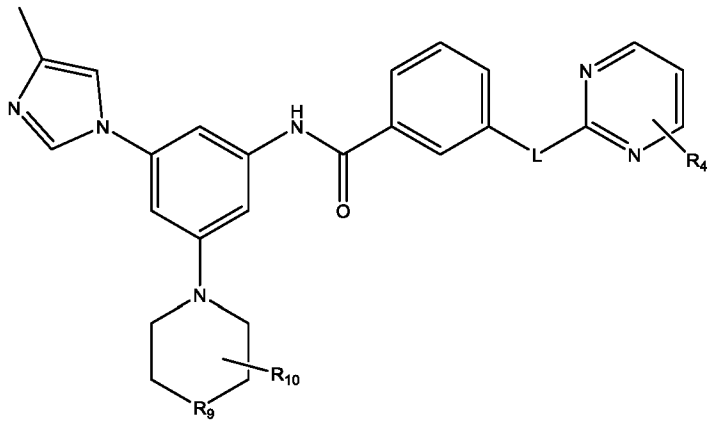
In one embodiment, R_7 is NR_6 wherein R_6 is H or methyl, preferably methyl.

In another embodiment, R_7 is CHR_6 and R_6 is –OH or $–NH_2$.

Preferably, R_8 is H, $–NH_2$ or methyl.

In one preferred embodiment, R_7 is CHR_6 and R_6 is H, and R_8 is $–NH_2$.

In one aspect, the invention provides a compound of formula IV:



(IV)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

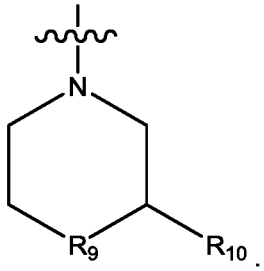
wherein

L and R_4 are as defined above;

R_9 is O, CHR_{11} or NR_{11}; wherein R_{11} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH; and

R_{10} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH.

Preferably R_{10} is positioned as shown:



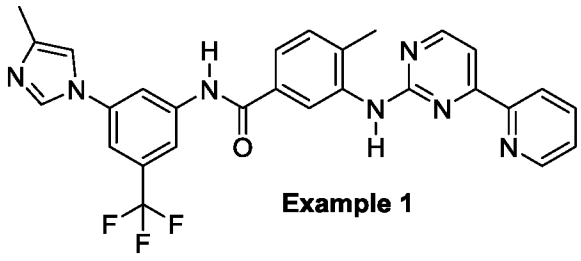
In one preferred embodiment, R_9 is CHR_{11} or NR_{11};

In another preferred embodiment, R_9 is NR_{11} wherein R_{11} is H or methyl.

Preferably R_{10} is H, $–NH_2$ or methyl.

In one particularly preferred embodiment, R_9 is CHR_{11} and R_{11} is H, and R_{10} is $–NH_2$.

In particular embodiments of the invention, the compound of formula I has a structure selected from any one of the following:



Example 1

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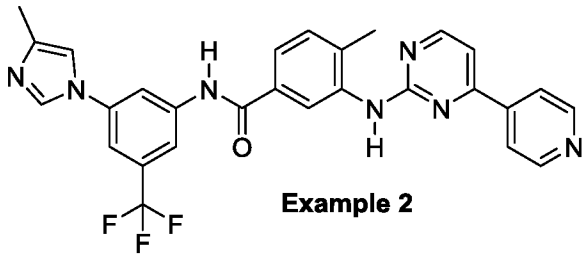

Example 2

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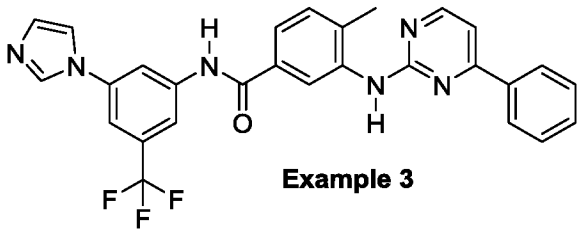

Example 3

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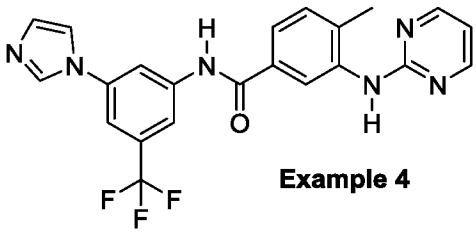

Example 4

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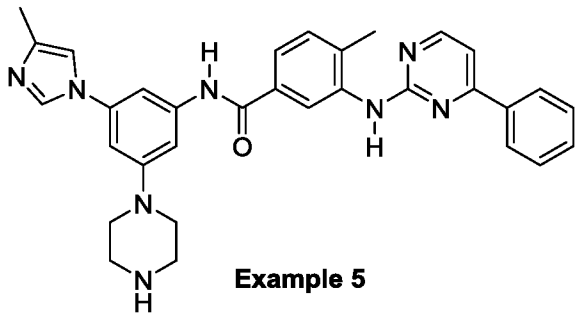

Example 5

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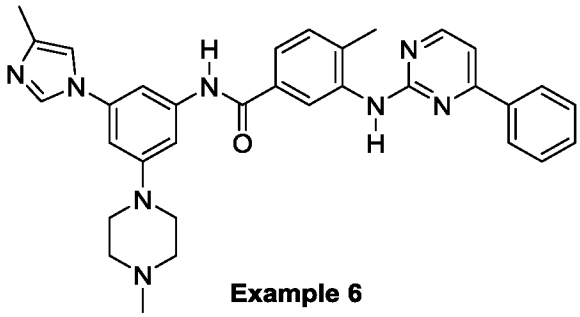

Example 6

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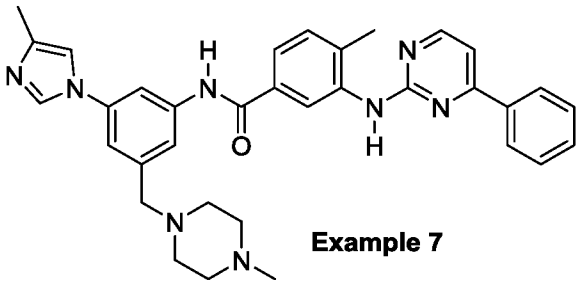
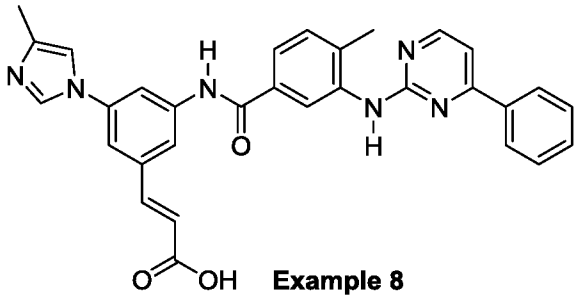
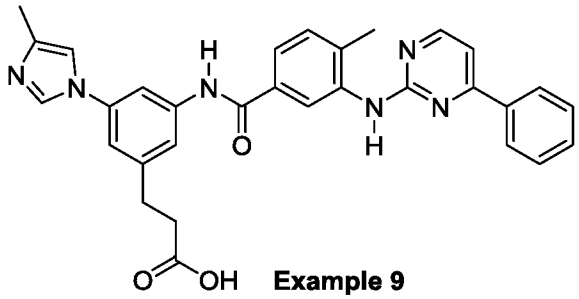


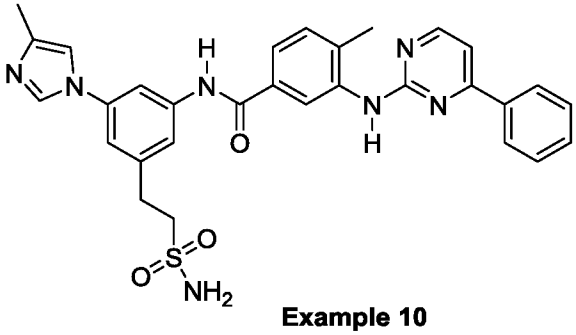
Example 7 ,



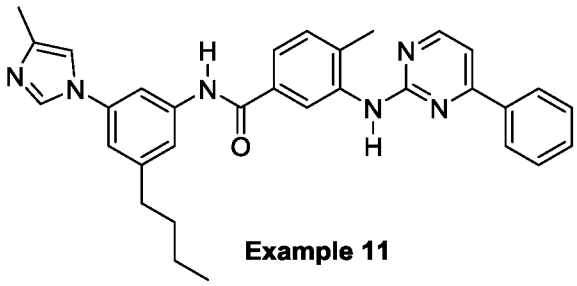
Example 8 ,



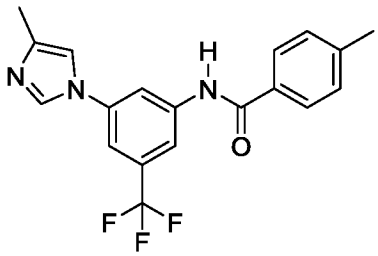
Example 9 ,



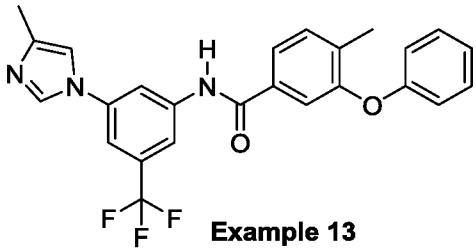
Example 10 ,



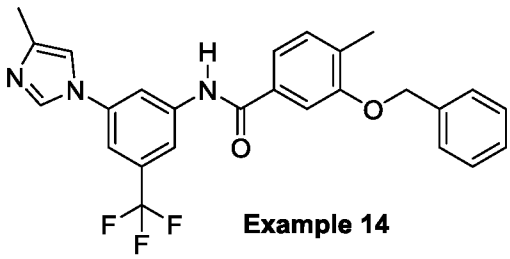
Example 11 ,



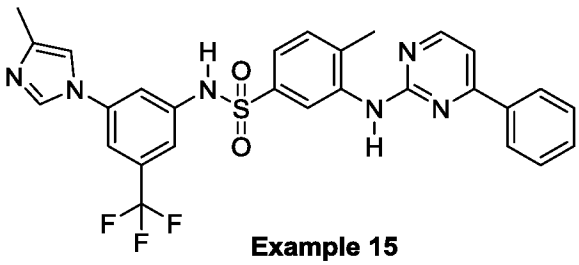
Example 12 ,



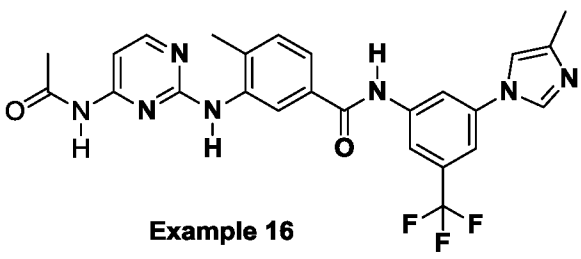
Example 13 ,



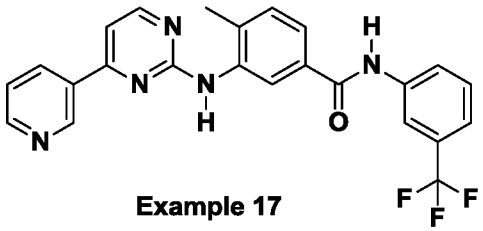
Example 14 ,



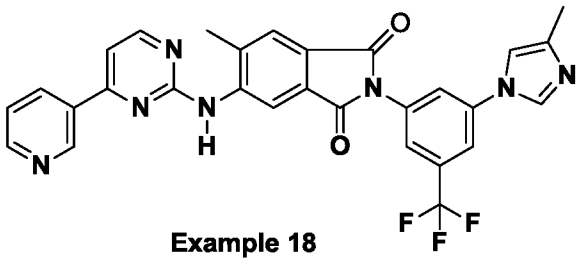
Example 15 ,



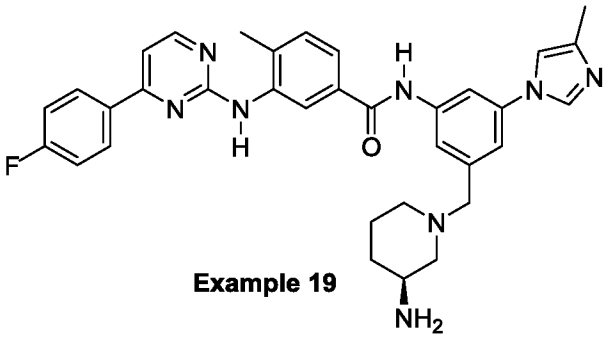
Example 16 ,



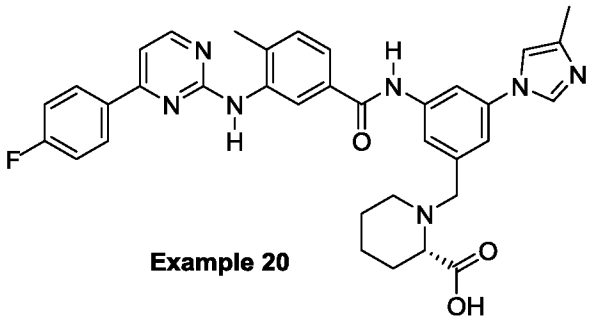
Example 17 ,



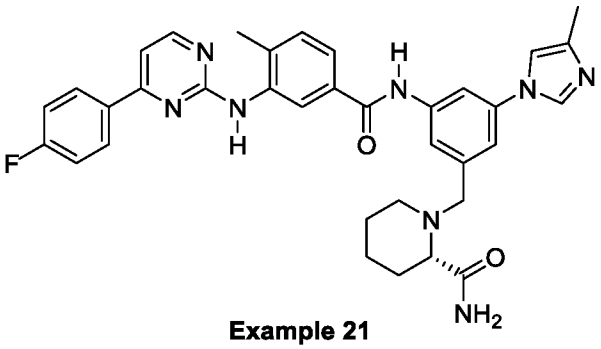
Example 18 ,



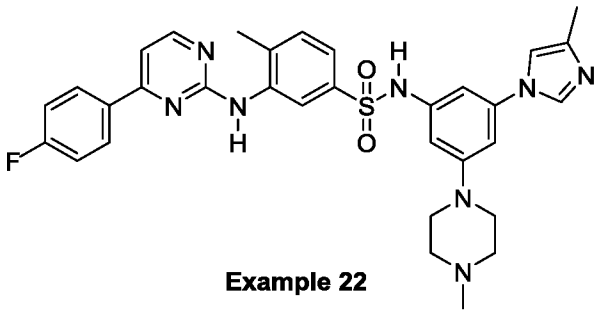
Example 19 ,



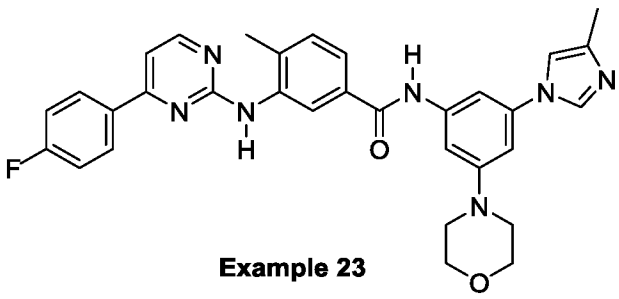
Example 20 ,



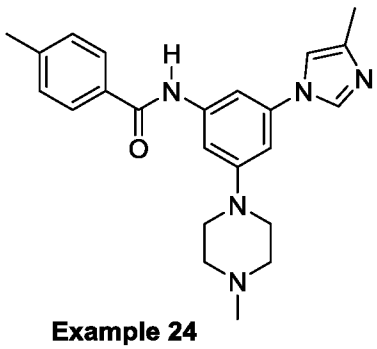
Example 21 ,



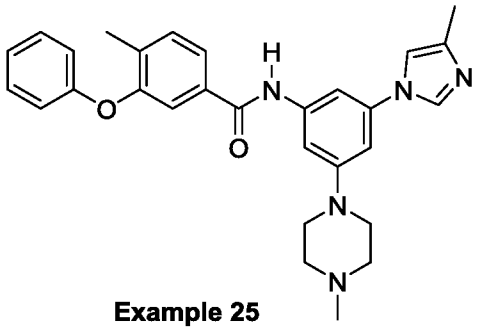
Example 22 ,



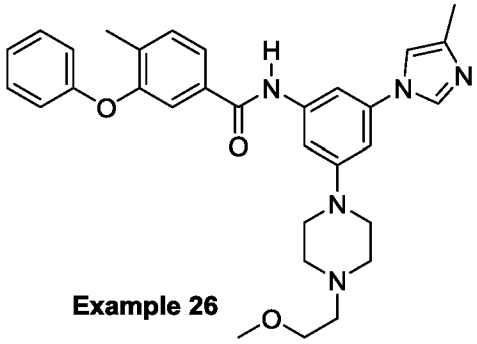
Example 23 ,



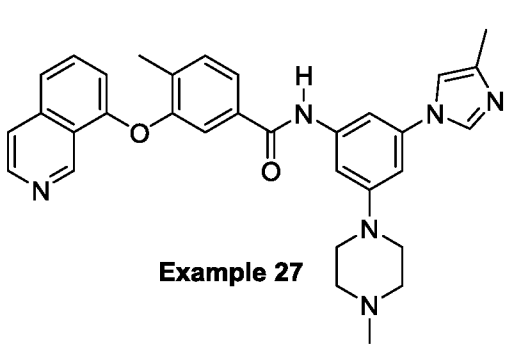
Example 24 ,



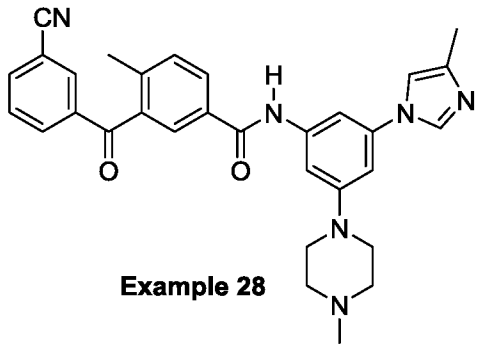
Example 25 ,



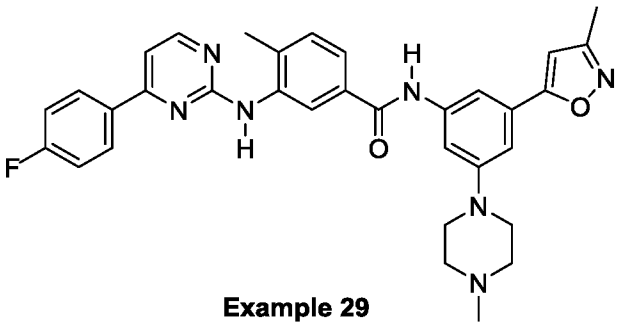
Example 26 ,



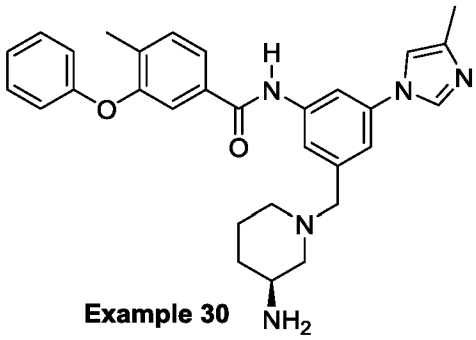
Example 27 ,



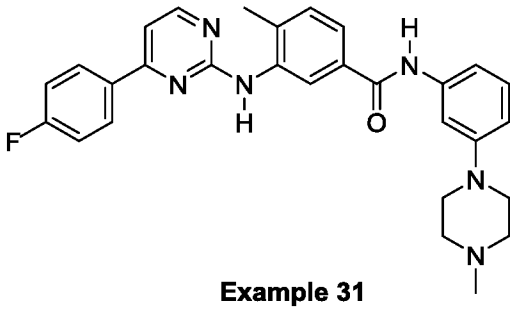
Example 28 ,



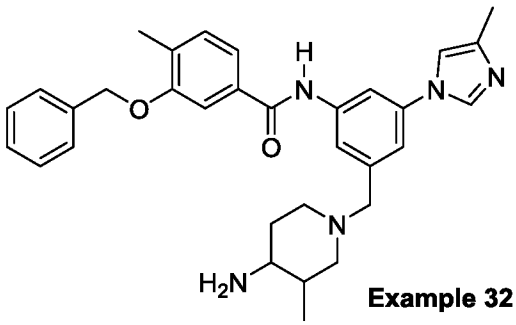
Example 29 ,



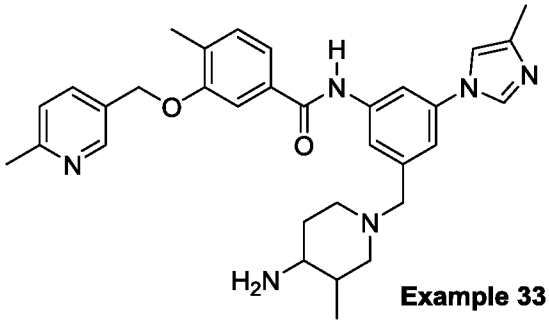
Example 30 ,



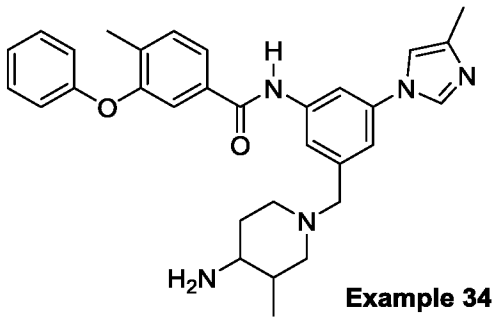
Example 31 ,



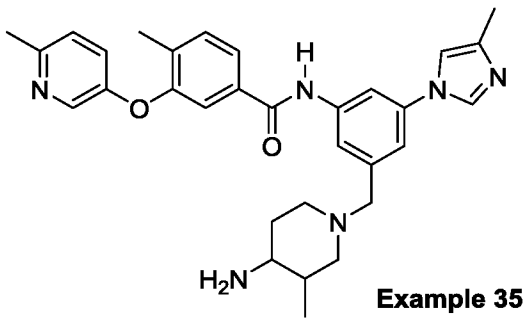
Example 32 ,



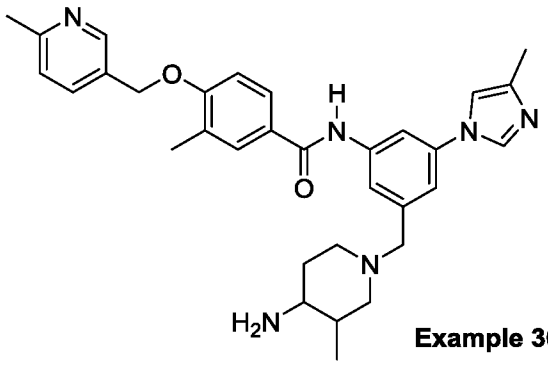
Example 33 ,



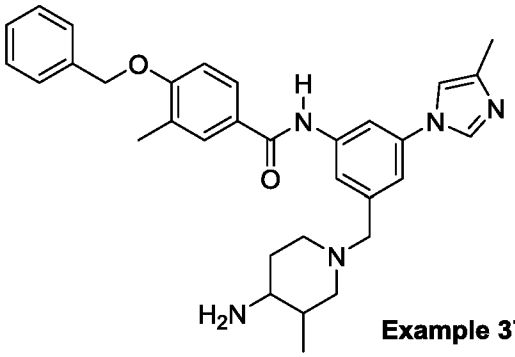
Example 34 ,



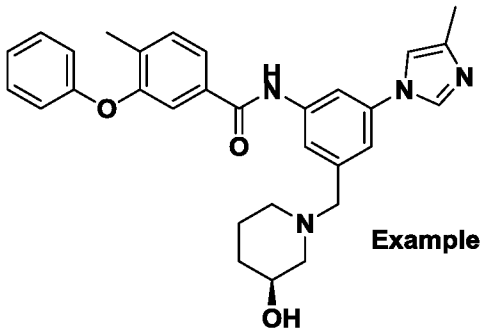
Example 35,



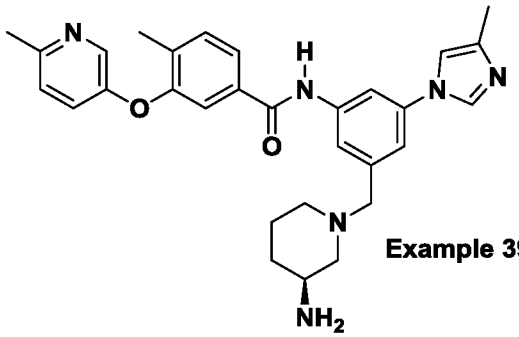
Example 36,



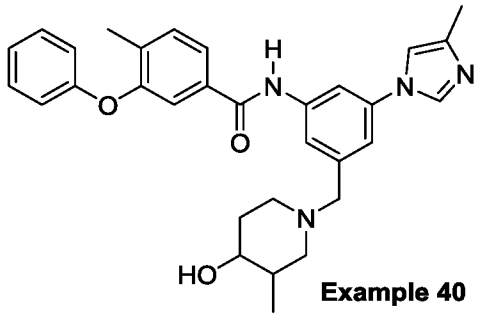
Example 37,



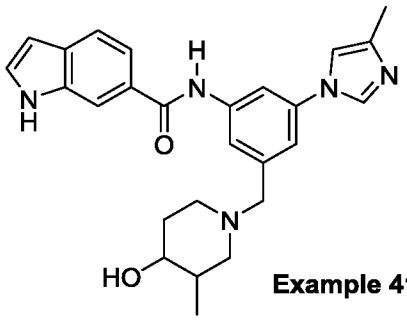
Example 38,



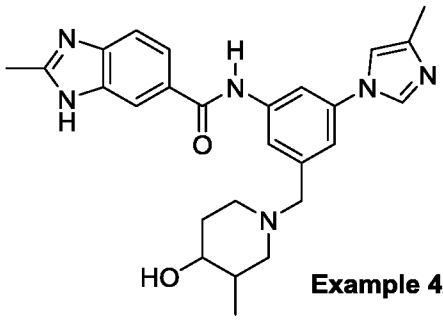
Example 39,



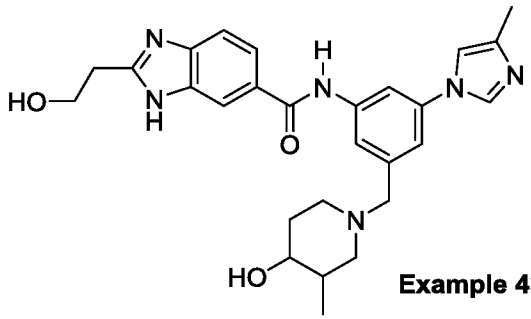
Example 40,



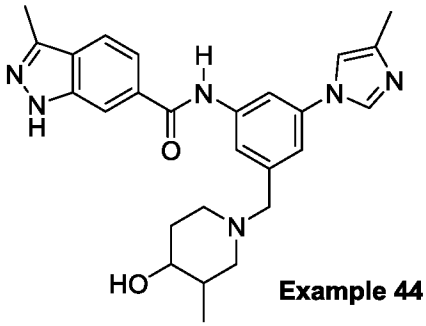
Example 41,



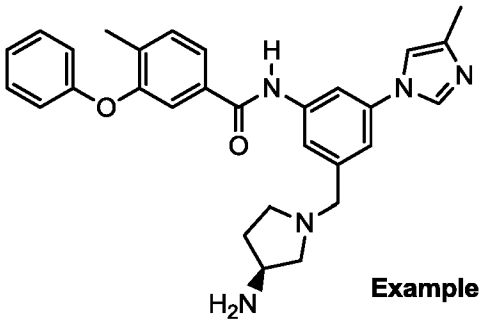
Example 42,



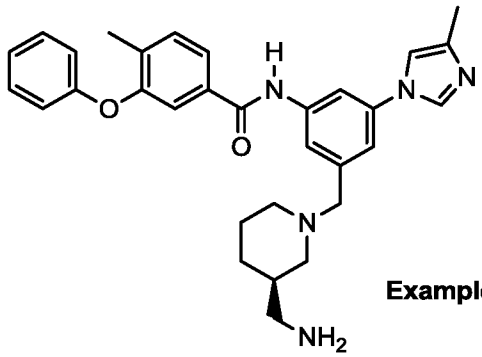
Example 43,



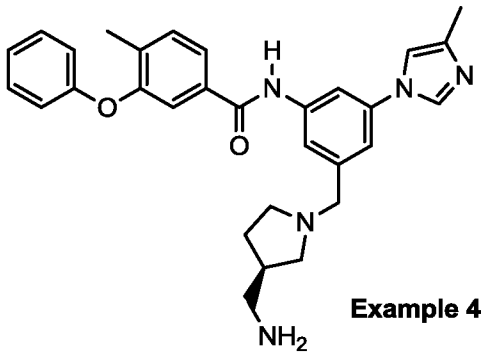
Example 44,



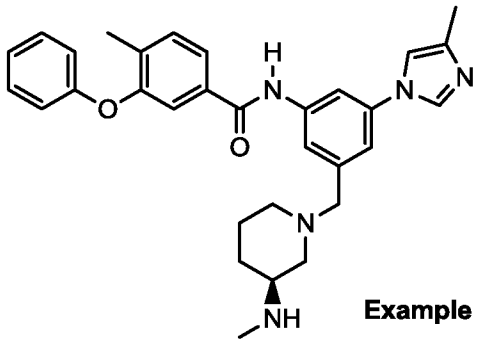
Example 45,



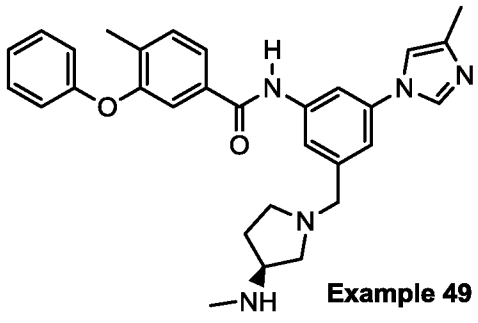
Example 46



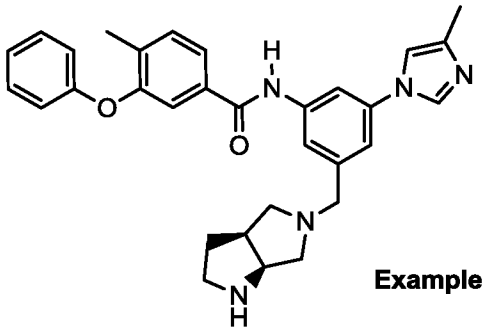
Example 47,



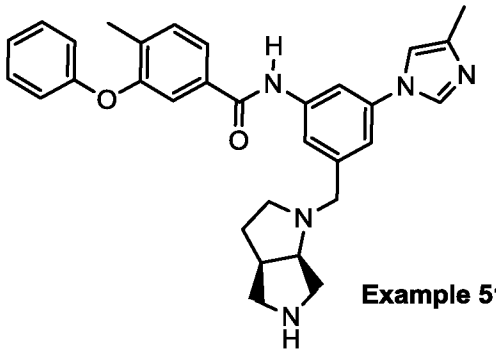
Example 48,



Example 49,



Example 50,



Example 51

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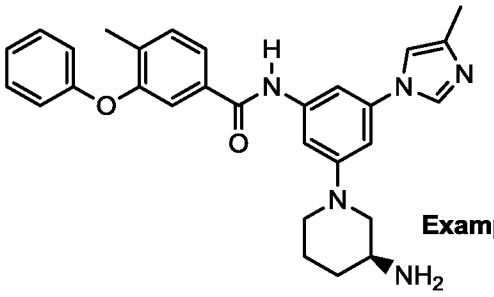

Example 52

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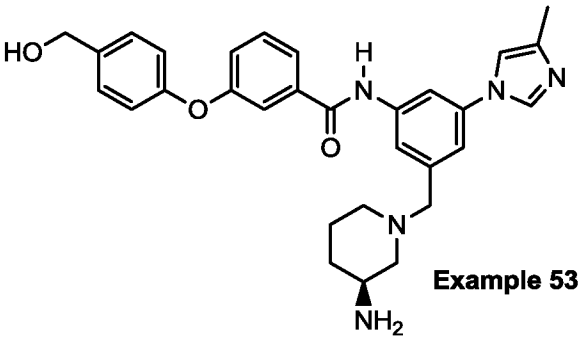

Example 53

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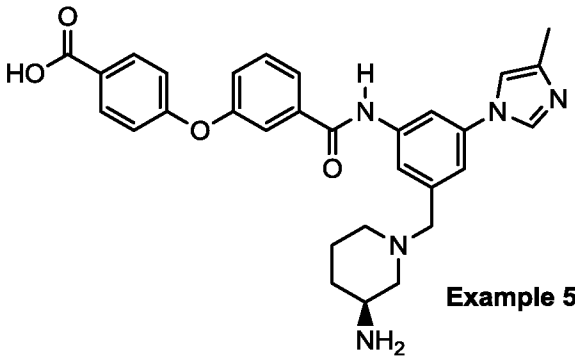

Example 54

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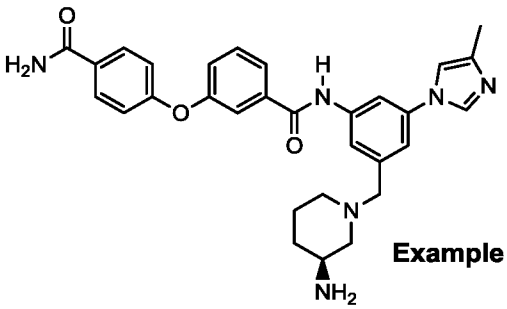

Example 55

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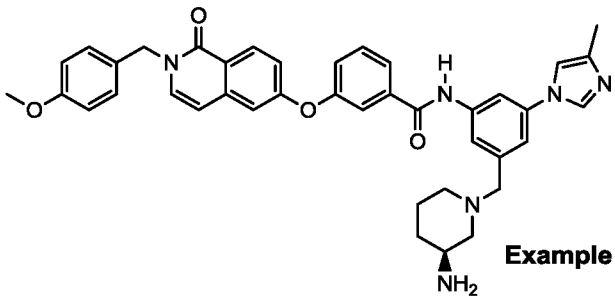

Example 56

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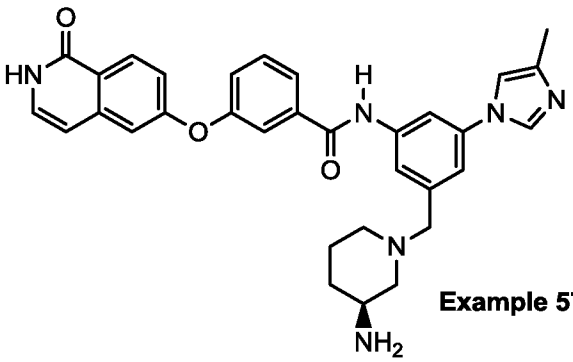

Example 57

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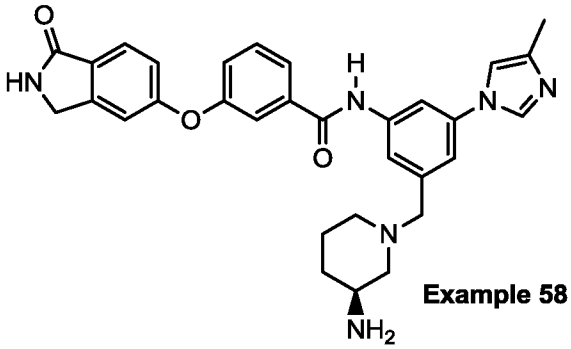

Example 58

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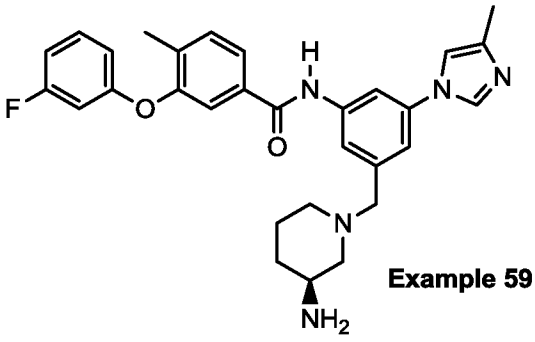

Example 59

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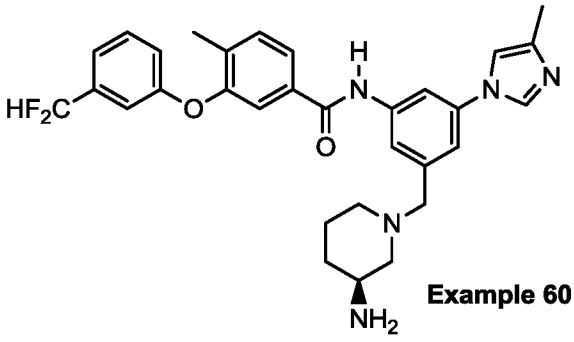
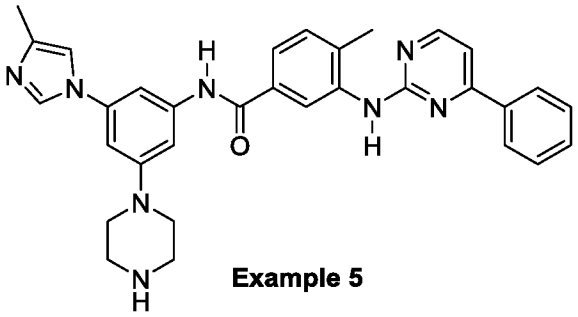


Example 60

.or a salt, solvate, prodrug or polymorph thereof.

In particular embodiments of the invention, the compound of formula I has a structure selected from any one of the following:



Example 5

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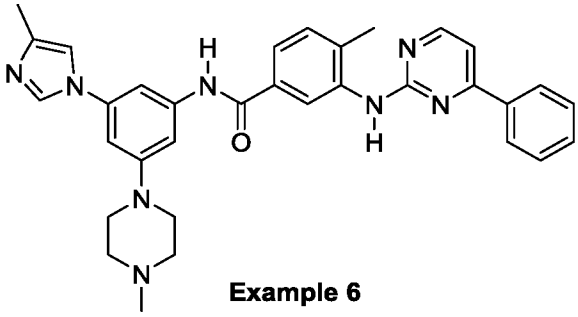

Example 6

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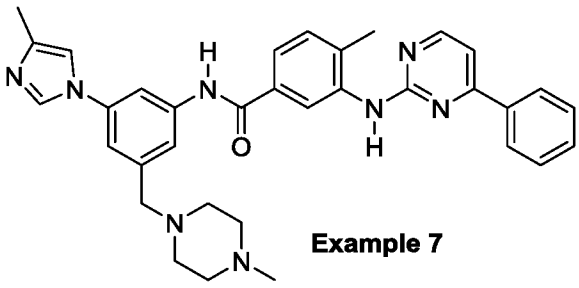

Example 7

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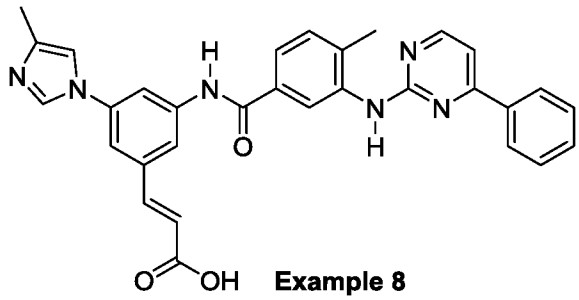

Example 8

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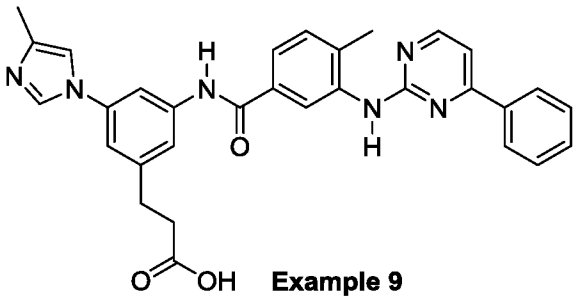

Example 9

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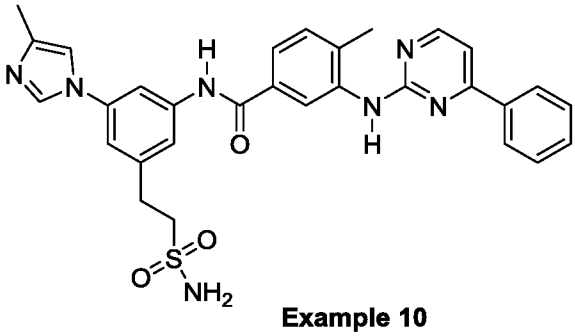

Example 10

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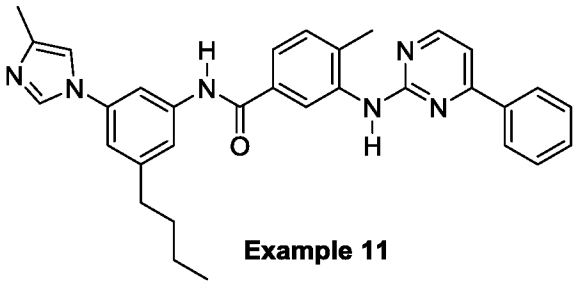
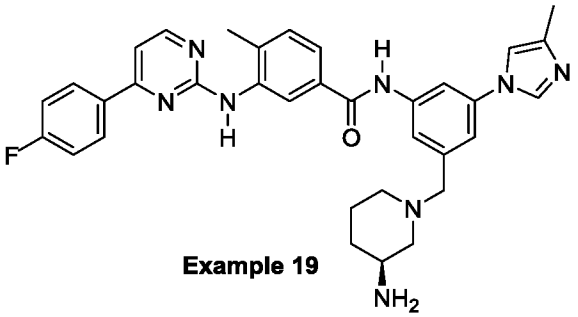
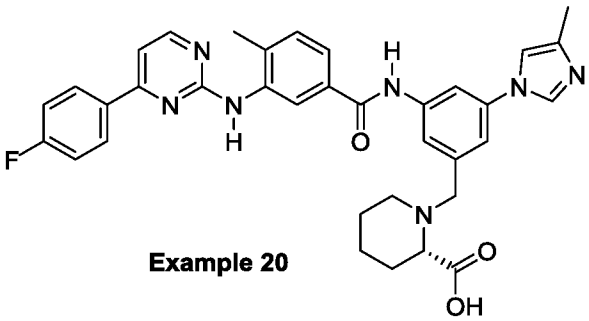


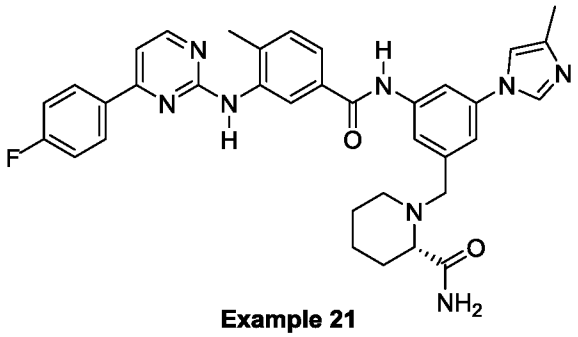
Example 11 ,



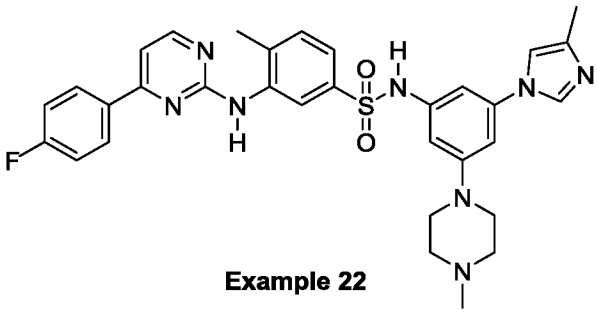
Example 19 ,



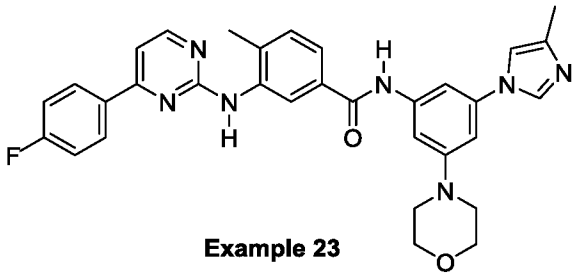
Example 20 ,



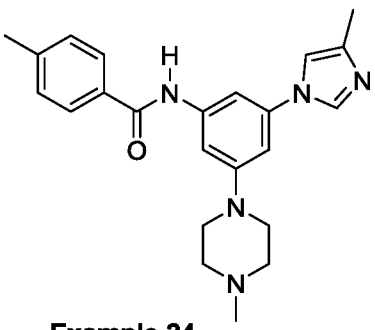
Example 21 ,



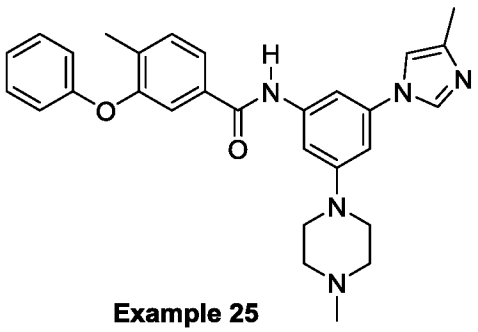
Example 22 ,



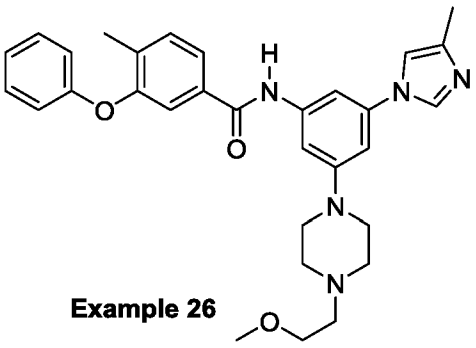
Example 23 ,



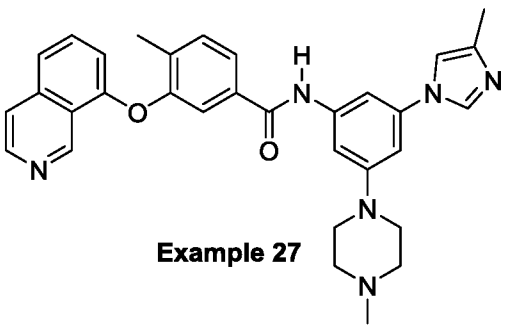
Example 24 ,



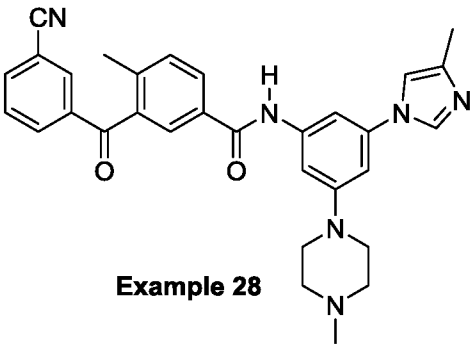
Example 25 ,



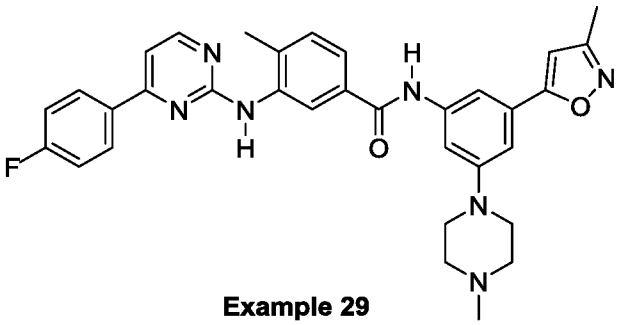
Example 26 ,



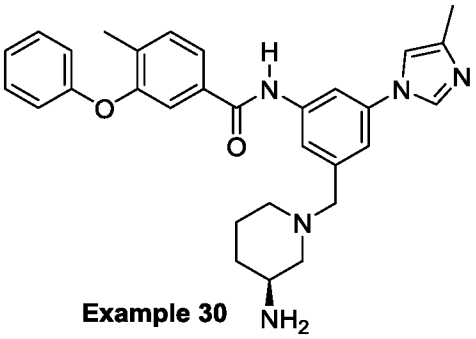
Example 27 ,



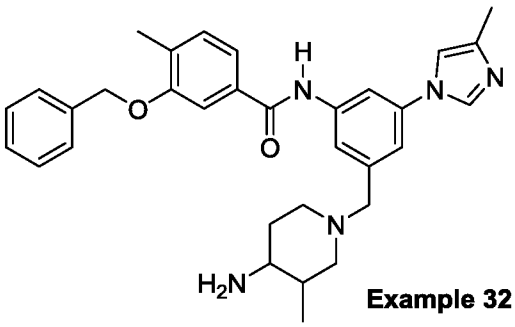
Example 28,



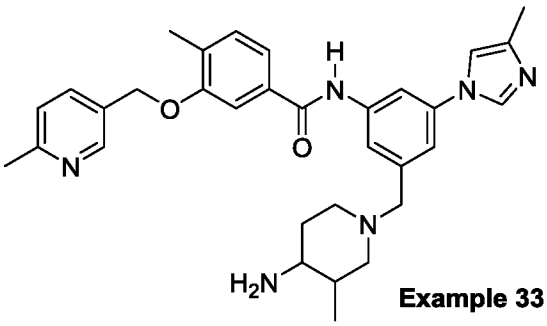
Example 29,



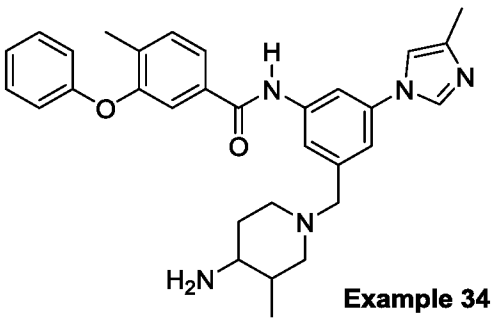
Example 30,



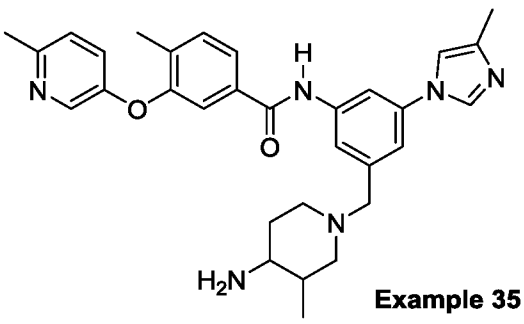
Example 32,



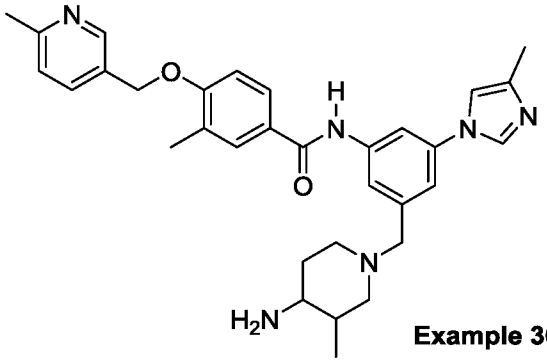
Example 33,



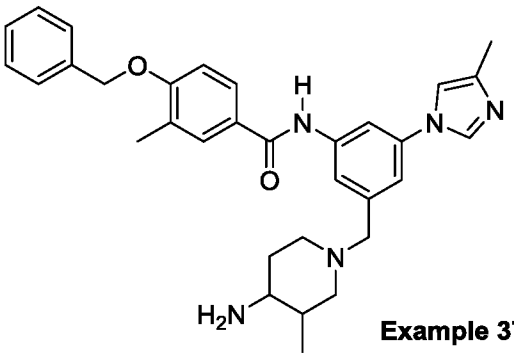
Example 34,



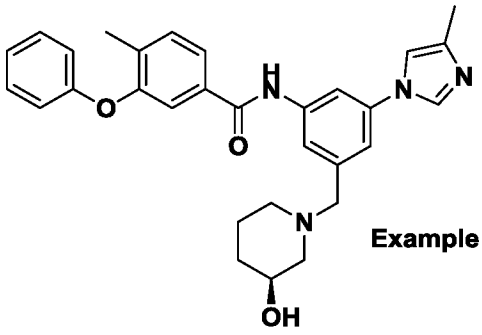
Example 35,



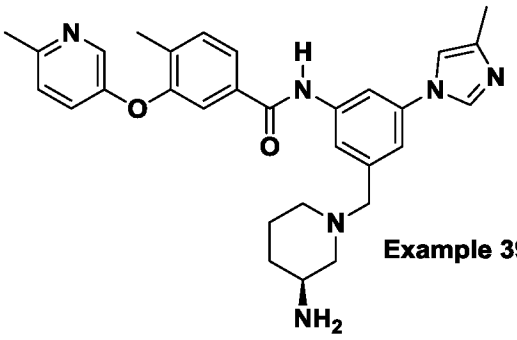
Example 36,



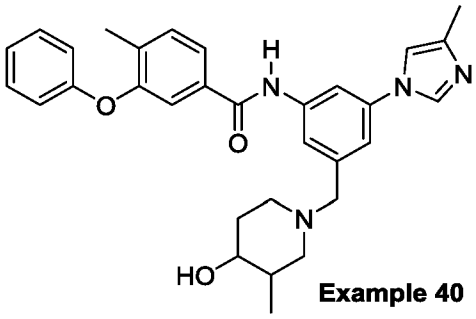
Example 37,



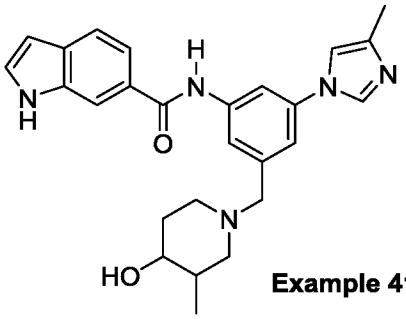
Example 38,



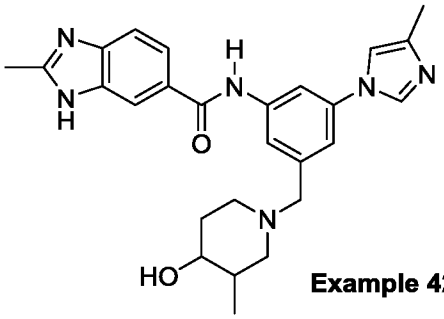
Example 39,



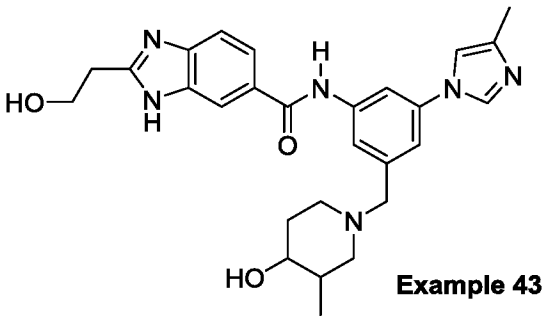
Example 40,



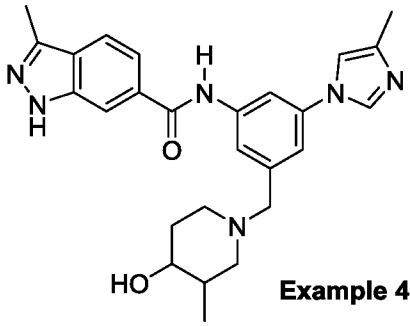
Example 41,



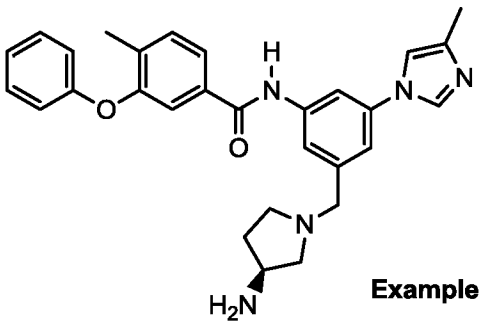
Example 42,



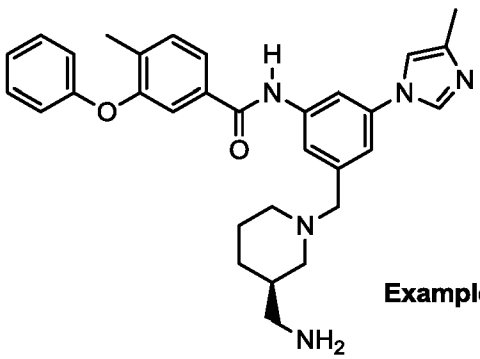
Example 43 and



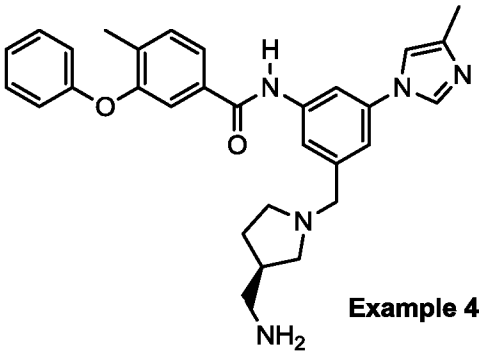
Example 44,



Example 45,



Example 46,



Example 47

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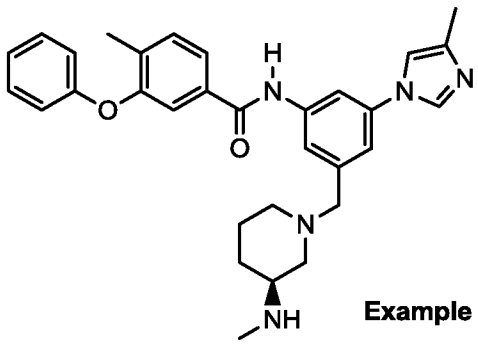

Example 48

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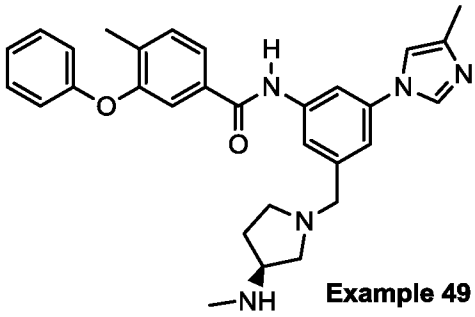

Example 49

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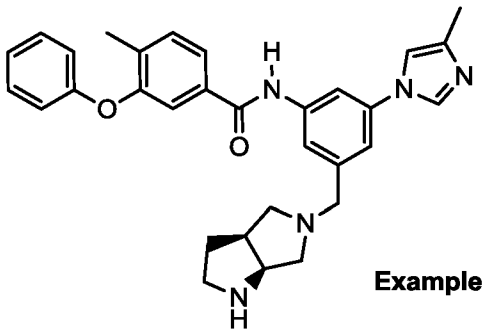

Example 50

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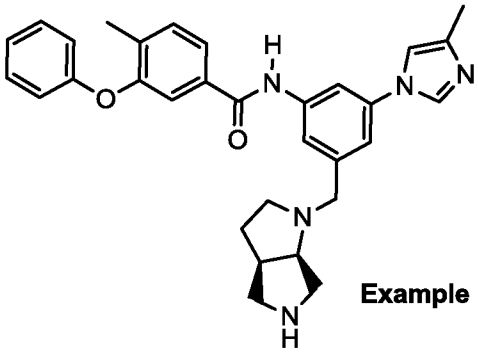

Example 51

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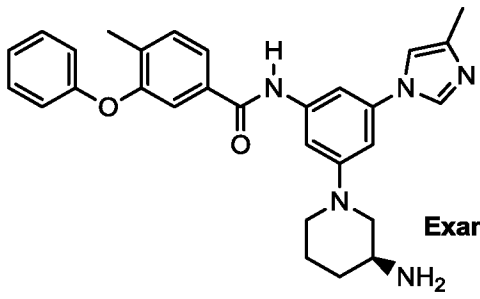

Example 52

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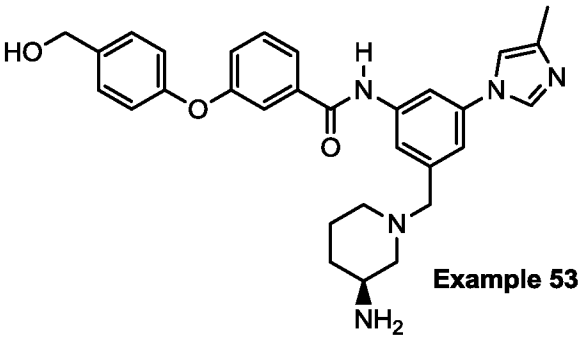

Example 53

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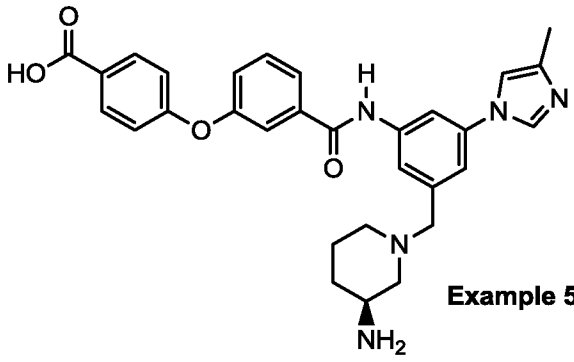

Example 54

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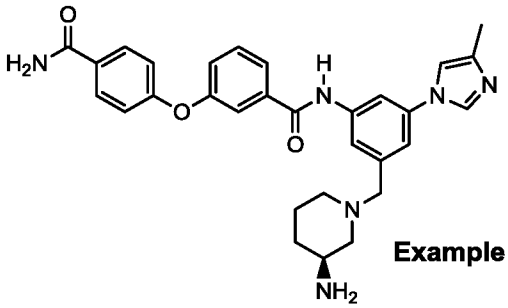
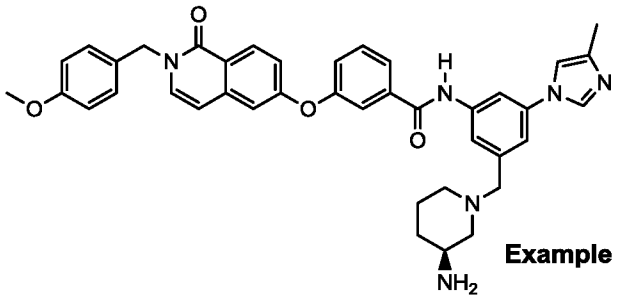
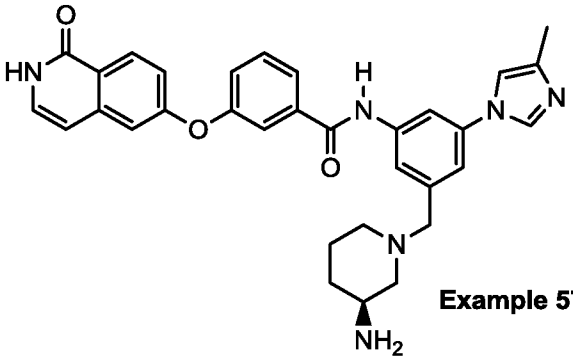


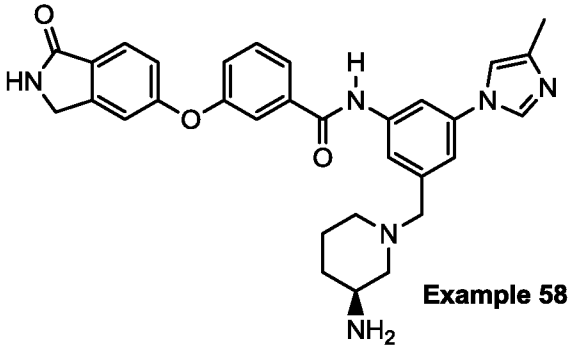
Example 55 ,



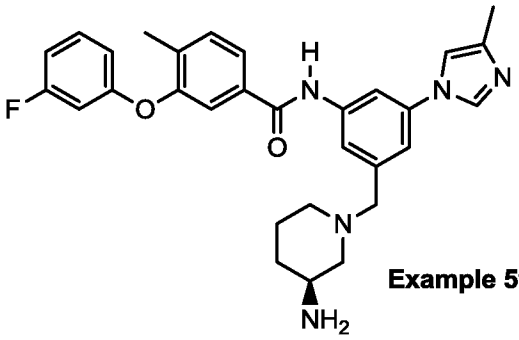
Example 56 ,



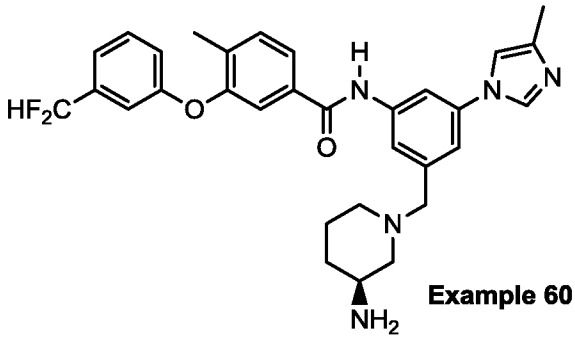
Example 57 ,



Example 58 ,



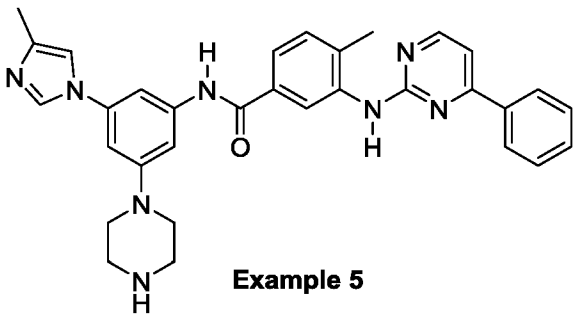
Example 59 , and



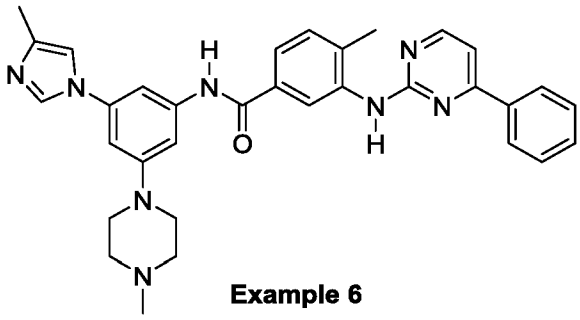
Example 60 .

or a salt, solvate, prodrug or polymorph thereof.

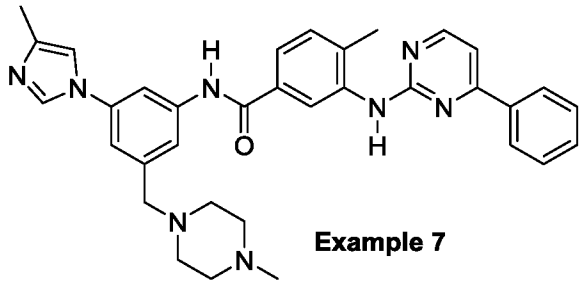
Preferably, the compound has a structure selected from any one of the following:



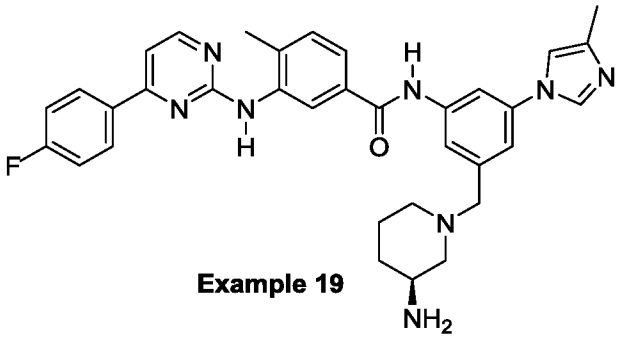
Example 5 ,



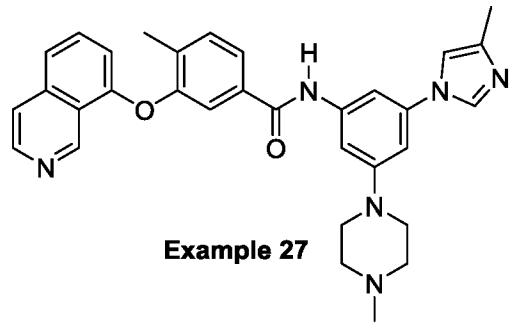
Example 6 ,



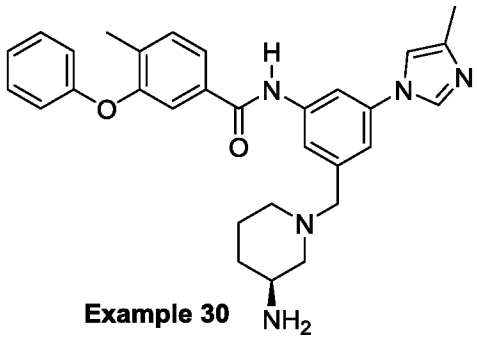
Example 7 ,



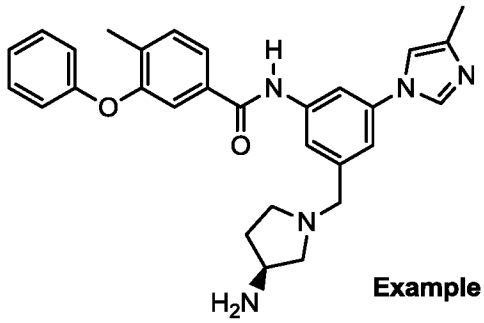
Example 19 ,



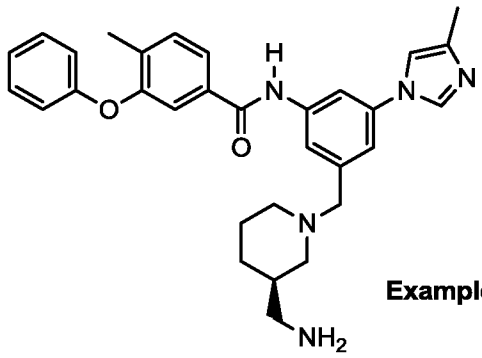
Example 27 ,



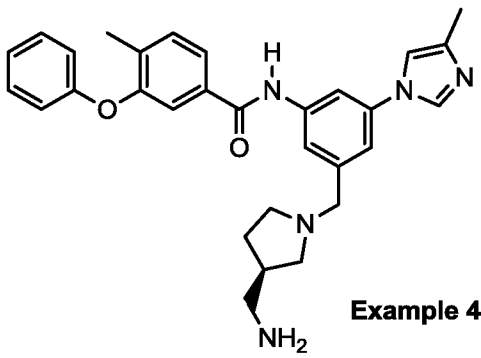
Example 30 ,



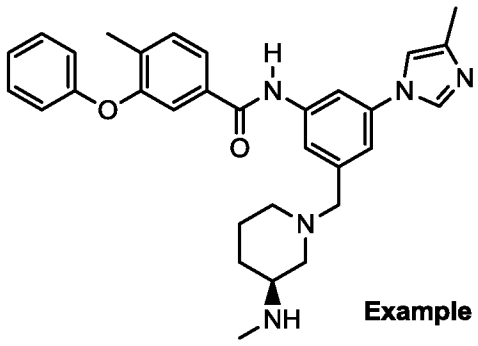
Example 45 ,



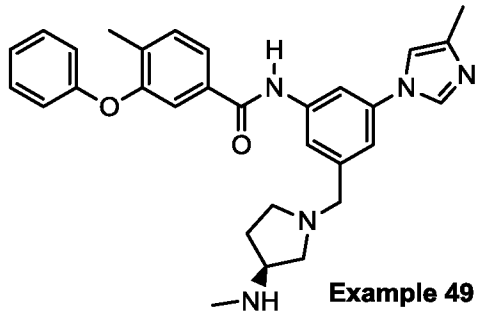
Example 46



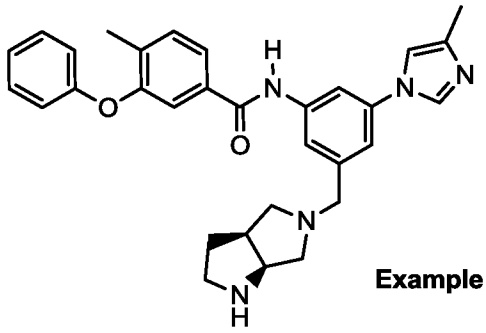
Example 47 ,



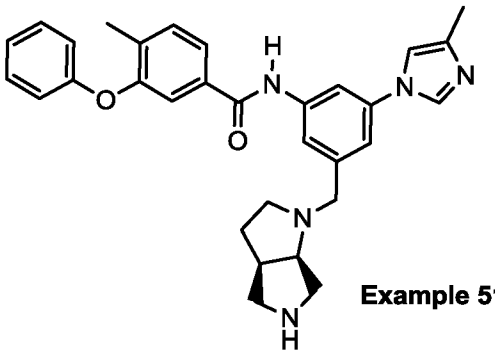
Example 48 ,



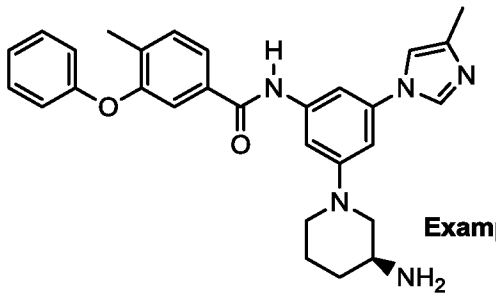
Example 49,



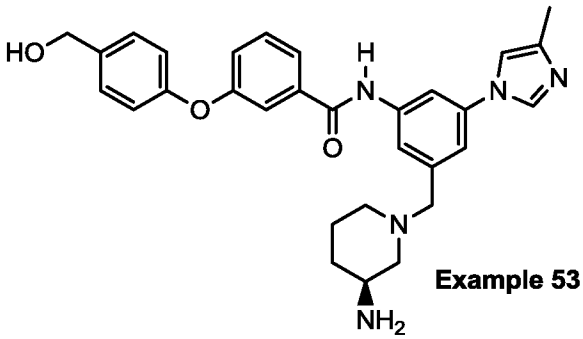
Example 50



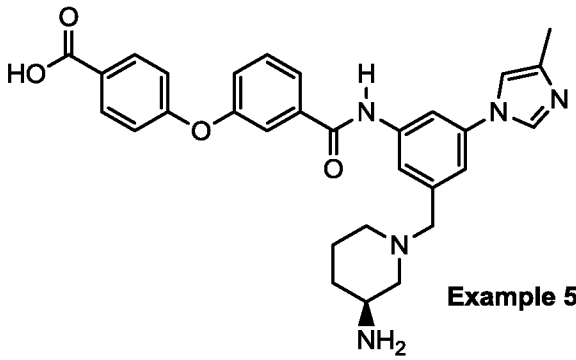
Example 51,



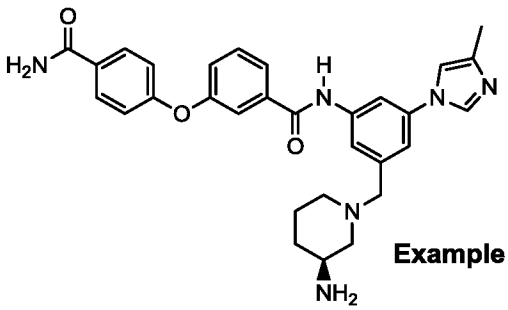
Example 52



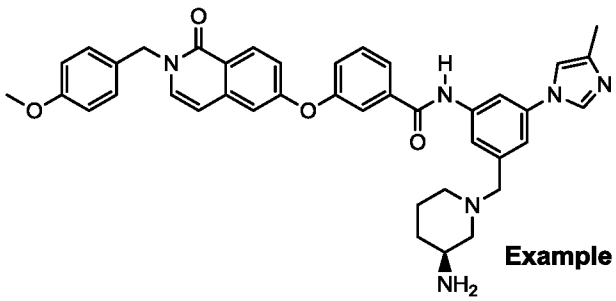
Example 53,



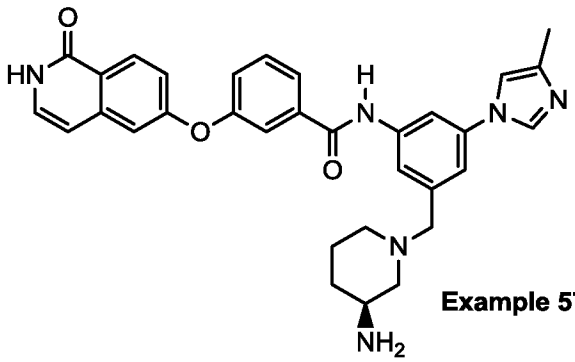
Example 54



Example 55,



Example 56



Example 57

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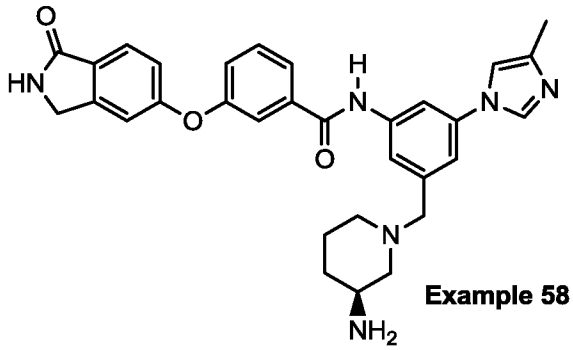

Example 58

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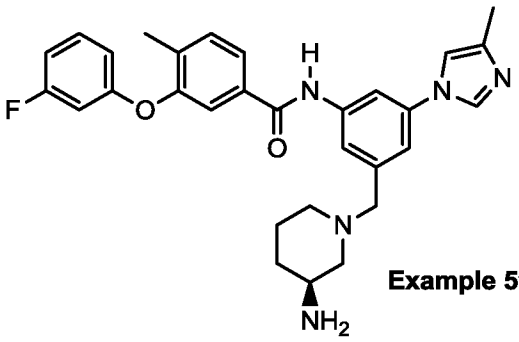
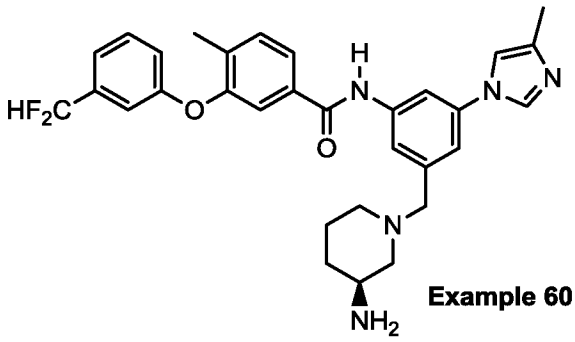


Example 59

, and

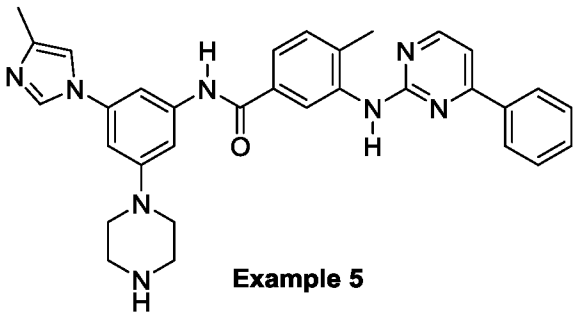


Example 60

,

or a salt, solvate, prodrug or polymorph thereof.

Preferably, the compound has a structure selected from any one of the following:



Example 5

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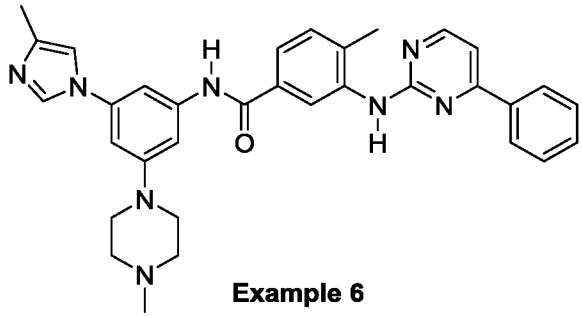

Example 6

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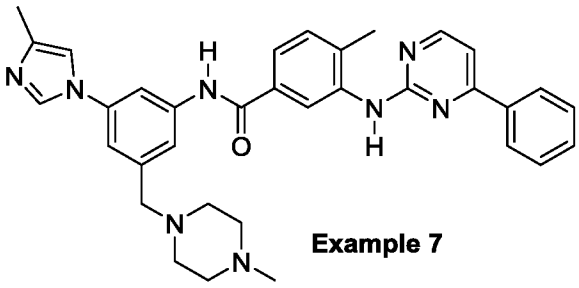

Example 7

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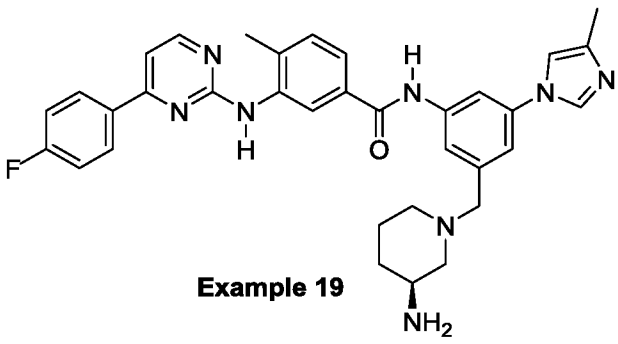

Example 19

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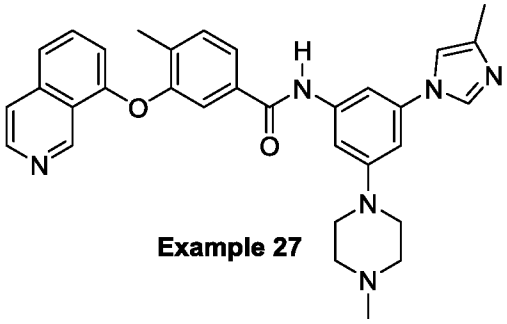
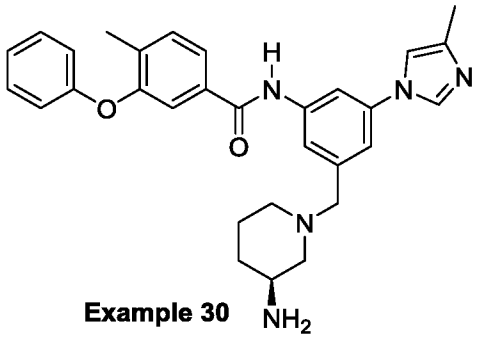


Example 27

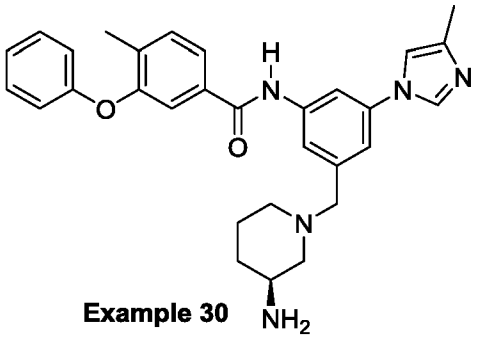
and



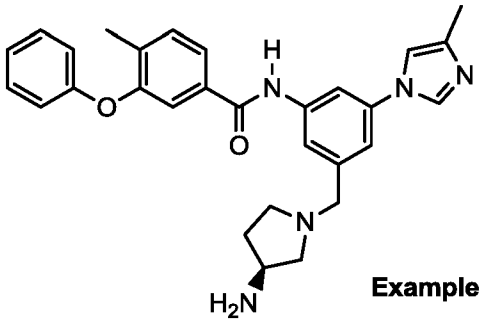
Example 30 ,

or a salt, solvate, prodrug or polymorph thereof.

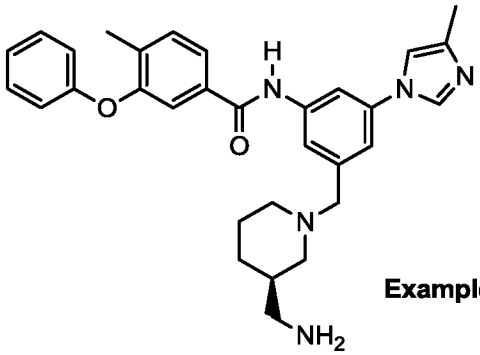
Preferably, the compound has a structure selected from any one of the following:



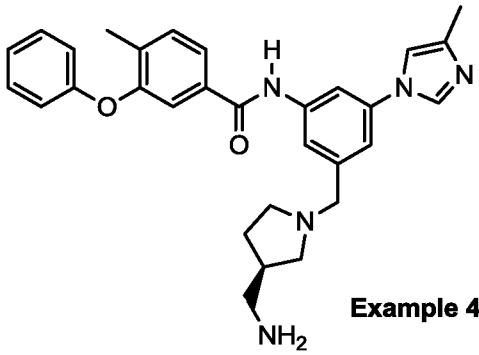
Example 30 ,



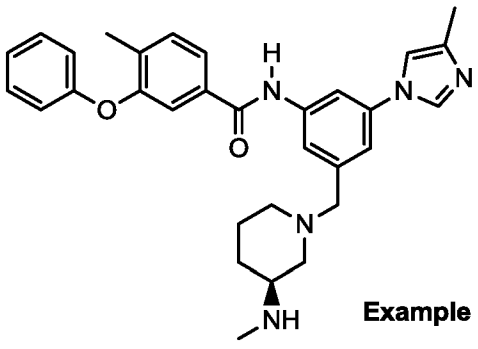
Example 45 ,



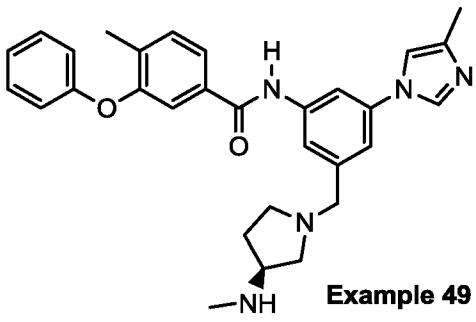
Example 46 ,



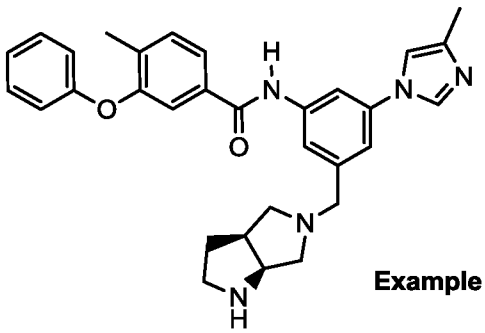
Example 47 ,



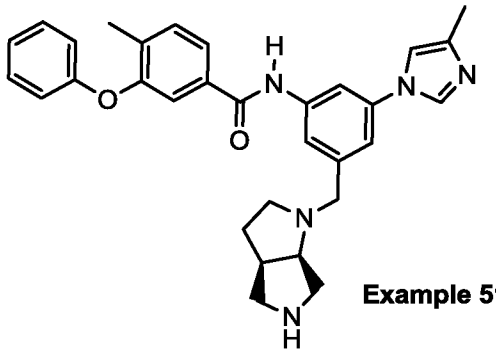
Example 48 ,



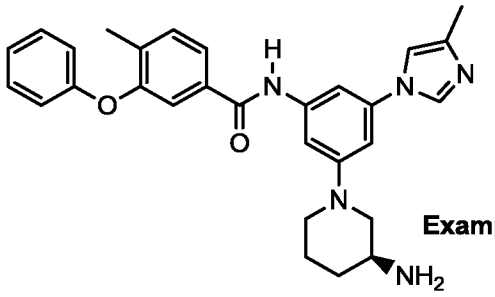
Example 49 ,



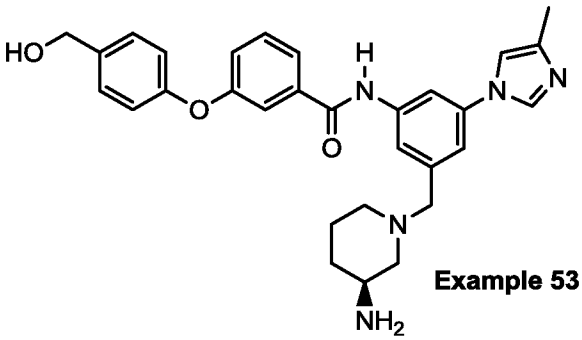
Example 50 ,



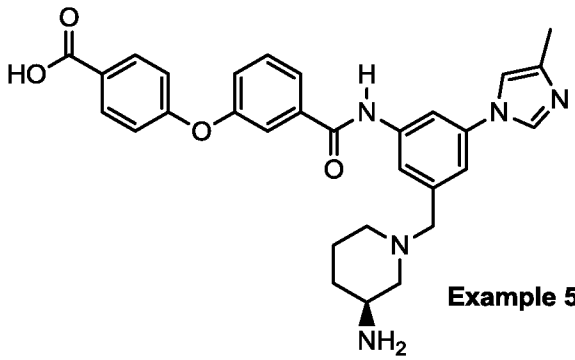
Example 51 ,



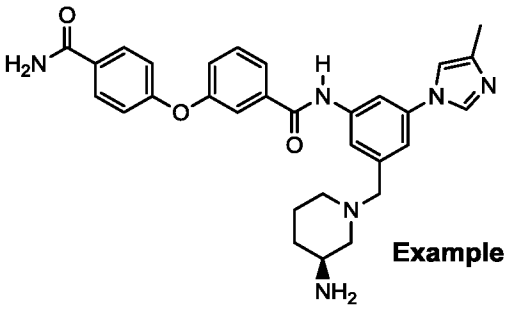
Example 52 ,



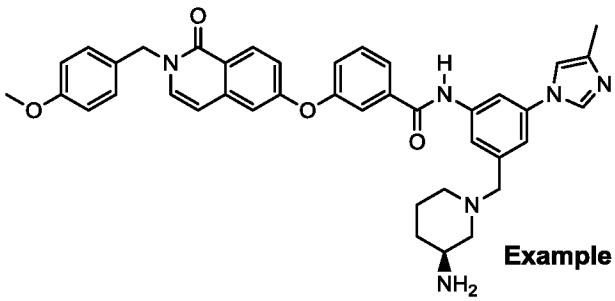
Example 53 ,



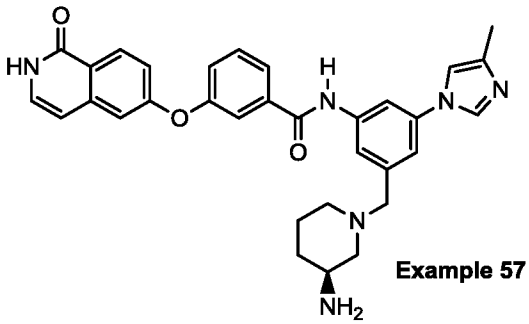
Example 54 ,



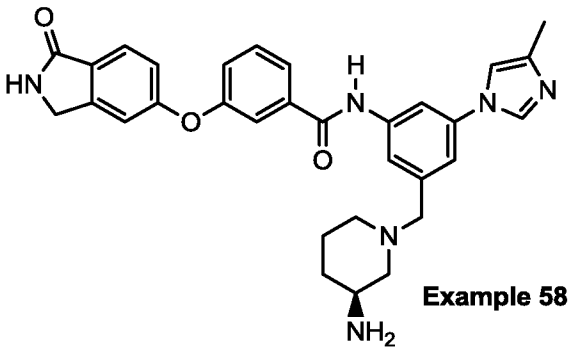
Example 55 ,



Example 56 ,



Example 57 ,



Example 58

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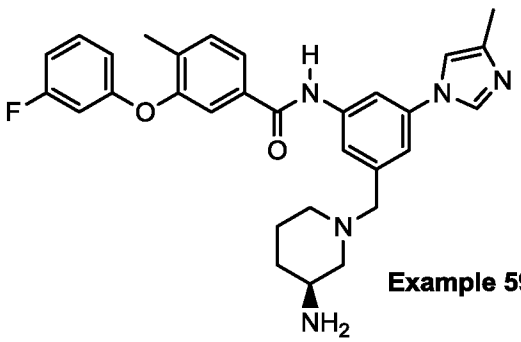
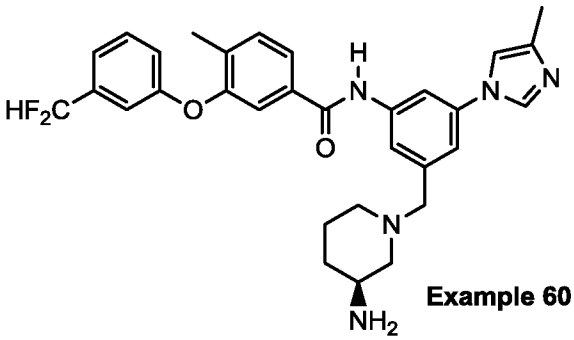


Example 59

, and

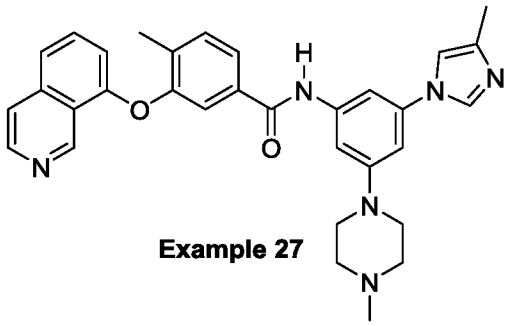


Example 60

,

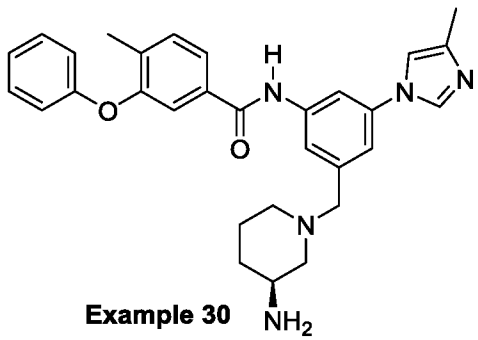
or a salt, solvate, prodrug or polymorph thereof.

Most preferably, the compound has the structure:



Example 27

, or

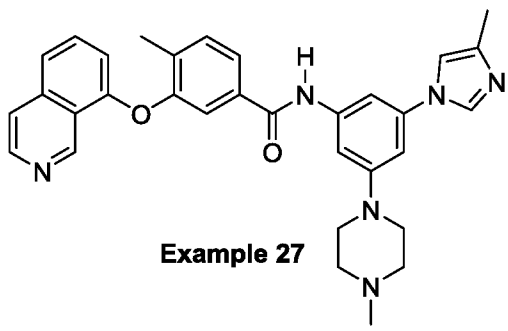


Example 30

,

or a salt, solvate, prodrug or polymorph thereof.

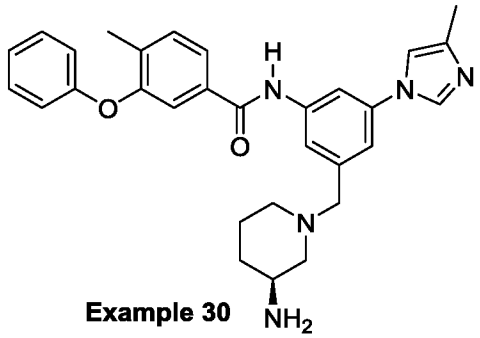
In a particularly preferred embodiment, the compound has the structure



Example 27

or a salt, solvate, prodrug or polymorph thereof.

In another particularly preferred embodiment, the compound has the structure



Example 30

or a salt, solvate, prodrug or polymorph thereof.

In some embodiments, the compounds may not inhibit kinase activity at physiologically relevant concentrations, particularly c-KIT, SRC, ABL and PDGFR kinases.

In one aspect, therefore, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and a pharmaceutically acceptable excipient.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

As used herein the term "alkyl" refers to a straight or branched chain hydrocarbon radical having from one to twelve carbon atoms, or any range between, i.e. it contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. The alkyl group is optionally substituted with substituents, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the terms "C_1-C_2 alkyl", "C_1-C_4 alkyl" and "C_1-C_6 alkyl" refer to an alkyl group, as defined above, containing at least 1, and at most 2, 4 or 6 carbon atoms

respectively, or any range in between (e.g. alkyl groups containing 2-5 carbon atoms are also within the range of C_1-C_6).

As used herein the term "alkenyl" refers to an alkyl group containing a double bond. It may also be optionally substituted with substituents, multiple degrees of substitution being allowed.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I). Preferably, 'halo' is fluoro or chloro.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring. In a like manner the term "C_3-C_7 cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from five to eight carbon atoms, or any range in between. For example, the C_3-C_7 cycloalkyl group would also include cycloalkyl groups containing 6 to 7 carbon atoms. The alkyl group is as defined above, and may be substituted. The cycloalkyl group refers to a nonaromatic cyclic ring, being saturated or having one or more degrees of unsaturation. Exemplary "C_3-C_7 cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the terms "heterocyclic" or "heterocyclyl" refer to a nonaromatic heterocyclic ring, being saturated or having one or more degrees of unsaturation, containing one or more heteroatom substitutions selected from S, S(O), $S(O)_2$, O, N, $Si(R_aR_b)$, P, $P(O)R_aR_b$, or $B(OR_c)$, wherein R_a and R_b are C_1-C_6 alkyl or aryl, or together with the atom between them form a 5- or 6- membered heterocyclyl ring, and R_c is hydrogen or C_1-C_6 alkyl. The term "C_3-C_7 heterocyclyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms containing one or more heteroatom substitutions as referred to herein. The heterocyclic moiety may be substituted, multiple degrees of substitution being allowed. The term "C_3-C_7 heterocyclyl" also includes heterocyclyl groups containing C_4-C_5, C_5-C_7, C_6-C_7, C_4-C_7, C_4-C_6 and C_5-C_6 carbon atoms. Preferably, the heterocyclic ring contains four to six carbon atoms and one or two heteroatoms. More preferably, the heterocyclic ring contains five carbon atoms and one heteroatom, or four carbon atoms and two heteroatom substitutions, or five carbon atoms and one heteroatom. Such a ring may be

optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, oxetane, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, *N*-methylpiperazinyl, 2,4-piperazinedione, pyrrolidine, imidazolidine, pyrazolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As an example of substituted heterocyclic groups, the term "(C_1-C_3 alkyl)C_3-C_7 heterocyclyl" includes heterocyclyl groups containing an alkyl group of one to three carbons in length as a linker between the compound and the heterocycle, (e.g. -CH_2-heterocycle or –CH_2CH_2-heterocycle). These heterocycles may be further substituted.

Substituted cycloalkyl and heterocyclyl groups may be substituted with any suitable substituent as described below.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or napthalene ring systems. Examples of "aryl" groups include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof. Preferred aryl groups include arylamino, aralkyl and aralkoxy groups.

As used herein, the term "heteroaryl" refers to a monocyclic five, six or seven membered aromatic ring, or to a fused bicyclic or tricyclic aromatic ring system comprising at least one monocyclic five, six or seven membered aromatic ring. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen heteroatoms, where N-oxides and sulfur oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, cinnolyl, phthalazyl, naphthyridinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, benzimidazolyl, and substituted versions thereof. Preferred heteroaryl groups include isoquinolinyl, imidazolyl and oxazolyl groups.

A "substituent" as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may

be a moiety such as a halogen, alkyl group, or other substituent described herein that is covalently bonded to an atom, preferably a carbon or nitrogen atom, that is a ring member. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated substituents, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound, i.e., a compound that can be isolated, characterized and tested for biological activity.

The terms "optionally substituted" or “may be substituted” and the like, as used throughout the specification, denotes that the group may or may not be further substituted or fused (so as to form a polycyclic system), with one or more non-hydrogen substituent groups. Suitable chemically viable substituents for a particular functional group will be apparent to those skilled in the art.

Examples of substituents include but are not limited to:

C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkyl, C_3-C_7 heterocyclyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, arylsulfonoamino, alkylcarboxy, alkylcarboxyamide, oxo, hydroxy, mercapto, amino, acyl, carboxy, carbamoyl, aryl, aryloxy, heteroaryl, aminosulfonyl, aroyl, aroylamino, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, ureido, C_1-C_6 perfluoroalkyl or phosphorus containing groups such as phosphine oxides, $P(O)R_a$, $P(O)OR_aOR_b$, $P(O)R_aR_b$, C_1-C_6 alkyl-$P(O)R_aR_b$ or the like, wherein R_a and R_b are C_1-C_6 alkyl or aryl, or together with the atom between them form a 5- or 6- membered heterocyclyl ring.

Any of these groups may be further substituted by any of the above-mentioned groups, where appropriate. For example, alkylamino, or dialkylamino, C_1-C_6 alkoxy, etc.

Unless specified otherwise, the compounds disclosed herein refer to compounds of formula (I), formula (II), formula (III) and/or formula (IV) or pharmaceutically acceptable salts, solvates, prodrugs or polymorphs thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers, and isotopically labelled compounds (including deuterium substitutions), as well as inherently formed moieties (e.g., polymorphs and/or solvates).

Where the compounds are chiral, the compound may exist as a racemic mixture, predominantly one enantiomer, or only one enantiomer.

In one embodiment of the invention, in a compound of formula I described herein, A may be selected to interact with Ser221 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

In one embodiment of the invention, in a compound of formula I and/or formula II described herein, Q may be selected to interact with Asp212 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

In one embodiment of the invention, in a compound of formula I and/or formula II described herein, Q may be selected to interact with Lys223 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

In one embodiment, the invention provides compounds of the present invention as described herein, wherein D is selected to interact with the Lys258 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

In one embodiment, the invention provides compounds of the present invention as described herein, wherein A may be selected to interact with Ser221, Q may be selected to interact with the Asp212 and D may be selected to interact with the Lys258 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

See Figure 4c for the PCSK9 conservation mapped to structure, illustrating several relevant amino acids for compound binding.

The activity of the compounds of the invention was measured first in a binding assay wherein the compounds interfered with the above-mentioned protein-protein interaction between the LDLR and PCSK9. Selected compounds were then subjected to a functional, cell-based assay wherein positive activity was recorded as a measure of increase of LDL uptake in cells. This assay therefore demonstrated the link between the targeted molecular interaction and the intended consequence, namely, to reduce circulatory, or plasma LDL by increasing its cellular uptake through inhibition of PCSK9.

The compounds have demonstrated efficacy and the levels of LDL have been decreased with their use. Accordingly, the present invention also provides for the use of

these compounds in inhibiting PCSK9, preventing the protein-protein interaction between PCSK9 and LDLR, and in reducing LDL levels.

The targeted site is specific to the PCSK9 protein and the homology of this region is conserved across species. For example, it is conserved between humans, mice, rats, guinea pigs, pigs, elephants and killer whales (see Figure 4a).

The PCSK family show very low levels of sequence identity. Cross-reactivity of the compounds with other PCSK molecules is therefore unlikely (See Figure 4b).

In one aspect, therefore, there is provided a method for inhibiting PCSK9 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for inhibiting PCSK9 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof of Formula (I), Formula (II), Formula (III) and/or Formula (IV) to a subject.

In one aspect, there is provided a method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a

therapeutically effective amount of a compound according to formula (I), formula (II), formula (III) and/or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof to a subject.

In one aspect, there is provided a method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a therapeutically effective amount of a composition comprising a compound according to formula (I), formula (II), formula (III) and/or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof to a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the inhibition of PCSK9 in a subject.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the inhibition of PCSK9 in a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the reduction of LDL in a subject.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, in the preparation of a medicament for the reduction of LDL in a subject.

In another aspect, there is provided use of a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the

following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the inhibition of PCSK9.

In another aspect, there is provided use of a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for inhibiting PCSK9.

In another aspect, there is provided use of a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the reduction of LDL.

In another aspect, there is provided use of a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the reduction of LDL.

In another aspect, there is provided use of a compound Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided use of a composition comprising a compound Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically

acceptable salt, solvate, prodrug or polymorph thereof, for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in inhibiting PCSK9.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in inhibiting PCSK9.

In another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in reducing LDL.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in reducing LDL.

In another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for inhibiting PCSK9.

In yet another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for inhibiting PCSK9.

In yet another aspect, there is provided a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for reducing LDL.

In yet another aspect, there is provided a composition comprising a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for reducing LDL.

In yet another aspect, there is provided a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In yet another aspect, there is provided a composition comprising a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

The term “pharmaceutically acceptable” may be used to describe any pharmaceutically acceptable salt, hydrate or prodrug, or any other compound which upon administration to a subject, is capable of providing (directly or indirectly) a

compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or an active metabolite or residue thereof.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, zinc, ammonium, alkylammonium such as salts formed from triethylamine, alkoxyammonium such as those formed with ethanolamine and salts formed from ethylenediamine, choline or amino acids such as arginine, lysine or histidine. General information on types of pharmaceutically acceptable salts and their formation is known to those skilled in the art and is as described in general texts such as "*Handbook of Pharmaceutical salts*" P.H.Stahl, C.G.Wermuth, 1st edition, 2002, Wiley-VCH.

In the case of compounds that are solids, it will be understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

The term "polymorph" includes any crystalline form of compounds of Formula (I), Formula (II), Formula (III) and/or Formula (IV), such as anhydrous forms, hydrous forms, solvate forms and mixed solvate forms.

Formula (I), Formula (II), Formula (III) and Formula (IV) are intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, Formula (I), Formula (II), Formula (III) and/or Formula (IV) include compounds having the indicated structures, including the hydrated or solvated forms, as well as the non-hydrated and non-solvated forms.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I), Formula (II), Formula (III) and/or Formula (IV) or a salt, prodrug or polymorph thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

Basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified in vivo, following administration to a subject or patient, to produce a compound of formula (I) provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, carboxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, carboxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved in vivo to generate the parent compounds.

Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (eg, two, three or four) amino acid residues which are covalently joined to free amino, and amido groups of compounds of Formula (I). The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are

covalently bonded to the above substituents of Formula (I), Formula (II), Formula (III) and/or Formula (IV) through the carbonyl carbon prodrug sidechain.

The compounds of Formula (I), Formula (II), Formula (III) and/or Formula (IV) and prodrugs thereof may be covalent irreversible or covalent reversible inhibitors of the active site of a protein.

Pharmaceutical compositions may be formulated from compounds according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) for any appropriate route of administration including, for example, topical (for example, transdermal or ocular), oral, buccal, nasal, vaginal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (for example, intravenous), intramuscular, spinal, intracranial, intrathecal, intraocular, periocular, intraorbital, intrasynovial and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use or parenteral use are preferred. Suitable oral forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. For intravenous, intramuscular, subcutaneous, or intraperitoneal administration, one or more compounds may be combined with a sterile aqueous solution which is preferably isotonic with the blood of the recipient. Such formulations may be prepared by dissolving solid active ingredient in water containing physiologically compatible substances such as sodium chloride or glycine, and having a buffered pH compatible with physiological conditions to produce an aqueous solution, and rendering said solution sterile. The formulations may be present in unit or multi-dose containers such as sealed ampoules or vials. Examples of components are described in Martindale – The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences.

In the context of this specification the term “administering” and variations of that term including “administer” and “administration”, includes contacting, applying, delivering or providing a compound or composition of the invention to an organism, or a surface by any appropriate means.

For the inhibition of PCSK9, the dose of the biologically active compound according to the invention may vary within wide limits and may be adjusted to individual

requirements. Active compounds according to the present invention are generally administered in a therapeutically effective amount. Preferred doses range 5 from about 0.1 mg to about 140 mg per kilogram of body weight per day (e.g. about 0.5 mg to about 7 g per patient per day). The daily dose may be administered as a single dose or in a plurality of doses. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. Dosage unit forms will generally contain between about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular subject and will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i.e. other drugs being used to treat the subject), and the severity of the particular disorder undergoing therapy. The dosage will generally be lower if the compounds are administered locally rather than systemically, and for prevention rather than for treatment. Such treatments may be administered as often as necessary and for the period of time judged necessary by the treating physician. A person skilled in the art will appreciate that the dosage regime or therapeutically effective amount of the compound of formula (I) to be administered may need to be optimized for each individual. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

It will also be appreciated that different dosages may be required for treating different disorders. An effective amount of an agent is that amount which causes a statistically significant decrease in LDL levels.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in

improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

The terms “treating”, “treatment” and “therapy” are used herein to refer to curative therapy, prophylactic therapy and preventative therapy. Thus, in the context of the present disclosure the term “treating” encompasses reducing the severity of elevated LDL levels, thereby resulting in the treatment or a reduced risk of cardiovascular diseases such as stroke, heart attack, coronary artery disease, hypercholesterolemia, and/or cerebrovascular diseases, atherosclerosis and/or associated diseases or their symptoms.

“Preventing” or "prevention" means preventing the occurrence of, or tempering the severity of, the above-mentioned diseases or conditions.

“Subject” includes any human or non-human animal. Thus, in addition to being useful for human treatment, the compounds of the present invention may also be useful for veterinary treatment of mammals, including companion animals and farm animals, such as, but not limited to dogs, cats, horses, cows, sheep, and pigs.

The term “inhibit” is used to describe any form of inhibition of PCSK9 that results in prevention, reduction or otherwise amelioration of the above-mentioned diseases or conditions, including complete and partial inhibition of PCSK9.

The compounds of the present invention may be administered along with a pharmaceutical carrier, diluent or excipient as described above.

The methods of the present disclosure can be used to prevent or treat elevated LDL levels, which may or not have been diagnosed as one of the diseases or conditions referred to above.

Generally, the optimal level of LDL in a human adult is less than 100 mg/dL. LDL levels in the range of 100-129mg/dL are considered as slightly elevated, 130-159mg/dL are considered as borderline high, 160-189mg/dL is considered as high and over 190mg/dL as very high.

Accordingly, in one aspect of the invention, the patients receiving treatment have an LDL level greater than 100mg/dL. In another embodiment, the patients receiving treatment will have an LDL level above 130mg/dL. In another embodiment, the patients receiving treatment will have an LDL level above 160mg/dL. In yet embodiment, the patients receiving treatment will have an LDL level above 190mg/dL.

In another aspect, the compounds of the present invention may be used to treat patients with a high diastolic blood pressure. In one embodiment of the invention, the patient receiving the treatment may have a diastolic blood pressure greater than 80. In another embodiment, the patient receiving the treatment may have a diastolic blood pressure greater than 90.

Diabetes can be associated with hypercholesterolemia, both in terms of a potential risk due to hypercholesterolemia or as a result of previous treatments, such as statin treatment. Accordingly, a high blood glucose level may represent a cohort of patients for which treatment using the compounds of the invention may be appropriate. For example, it may be beneficial to treat patients with high blood glucose levels who may or may not be considered to be diabetic with compounds of the present invention rather than with medication that can further increase the risk of diabetes and/or an even higher blood glucose level. Alternatively, such patients may benefit from a lower dose of the other treatment in combination with the compounds of the present invention, as discussed below.

Accordingly, in one aspect, the compounds of the present invention may be used to treat patients with a high blood glucose level. For the majority of healthy individuals, normal blood sugar levels are below 6.1 mmol/L (108mg/dL) when fasting, and up to 7.8 mmol/L (140 mg/dL) two hours after eating. For patients with pre-diabetes, blood sugar levels are increased from between 6.1-6.9 mmol/L (108-125 mg/dL) or more when fasting, and between 7.8-11.0 mmol/L (140-199 mg/dL) or more two hours after eating. For patients with diabetes, blood sugar levels are increased to 7 mmol/L (126 mg/dL) or more when fasting, and 11.1 mmol/L (200 mg/dL) or more two hours after eating. In one aspect, therefore, the compounds of the present invention are particularly suited for patients with pre-diabetes or diabetes.

Combination therapy

As discussed above, the compounds of the present invention are useful in reducing LDL. The compounds provide this result by inhibiting PCSK9, which is a different mechanism of action to that of the statins. Consequently, these compounds may provide treatment for the diseases or conditions listed above for patients who do not want or who are unable to take statins. This may be due, for example, to the side effects of the statins, or simply that the statins will be (or have been) ineffective at (sufficiently) treating the disease or condition, such as some forms of hypercholesterolemia.

Statins inhibit the synthesis of cholesterol being produced by the liver, thereby decreasing the amount of LDL. They increase activity of sterol regulatory element-binding protein 2 (SREBP-2), resulting in activation of both LDL receptor (LDLR) and PCSK9. Increased expression and secretion of PCSK9 binds LDLR, resulting in higher LDL-C. Thus, while statins reduce LDL, as HMGcoA inhibitors, their effect on SREBP-2 acts as a counterbalance.

The addition of PCKS9 inhibitors to statin therapies may therefore help override this mechanism. Accordingly, the compounds of the present invention may therefore also be used together with statins to provide a more effective reduction in LDL than the statins alone, or to enable a lower dose of the statins to be used to reach a similar efficacy. This could then result in more effective treatments and/or fewer side effects for the patient than treatment or prophylaxis with statins alone.

Accordingly, in one aspect, the invention also provides a composition comprising:

- a compound of the present invention, or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and

- a statin.

In another aspect, the present invention provides a method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising:

- compound of formula (I), formula (II), formula (III) or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin.

In one aspect, there is provided a method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a therapeutically effective amount of a composition comprising:

- a compound according to formula (I), formula (II), formula (III) and/or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin.

In another aspect, the present invention provides use of a composition comprising:

- compound of formula (I), formula (II), formula (III) or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin

in the preparation of a medicament for reducing LDL in a subject.

In another aspect, there is provided use of a composition comprising:

- a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin

in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, the present invention provides use of a composition comprising:

- compound of formula (I), formula (II), formula (III) or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin

for reducing LDL.

In another aspect, there is provided use of a composition comprising:

- a compound Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and
- a statin

for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, the present invention provides use of a composition comprising:

- compound of formula (I), formula (II), formula (III) or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and
- a statin

for use in reducing LDL.

In another aspect, there is provided a composition comprising:

- a compound according to Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and
- a statin

for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

In another aspect, the present invention provides use of a composition comprising:

- compound of formula (I), formula (II), formula (III) or formula (IV), or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and

- a statin

when used for reducing LDL.

In yet another aspect, there is provided a composition comprising:

- a compound of Formula (I), Formula (II), Formula (III) and/or Formula (IV) or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof, and
- a statin

when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

The statins referred to in these aspects of the invention can include any statin that is approved for medical use. For example, the following statins may be used: atorvastatin (Lipitor), fluvastatin (Lescol, Lescol XL), lovastatin (Mevacor, Altoprev), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor), and pitavastatin (Livalo).

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

The methods and compounds described herein are described by the following illustrative and non-limiting examples.

Examples

Definitions:

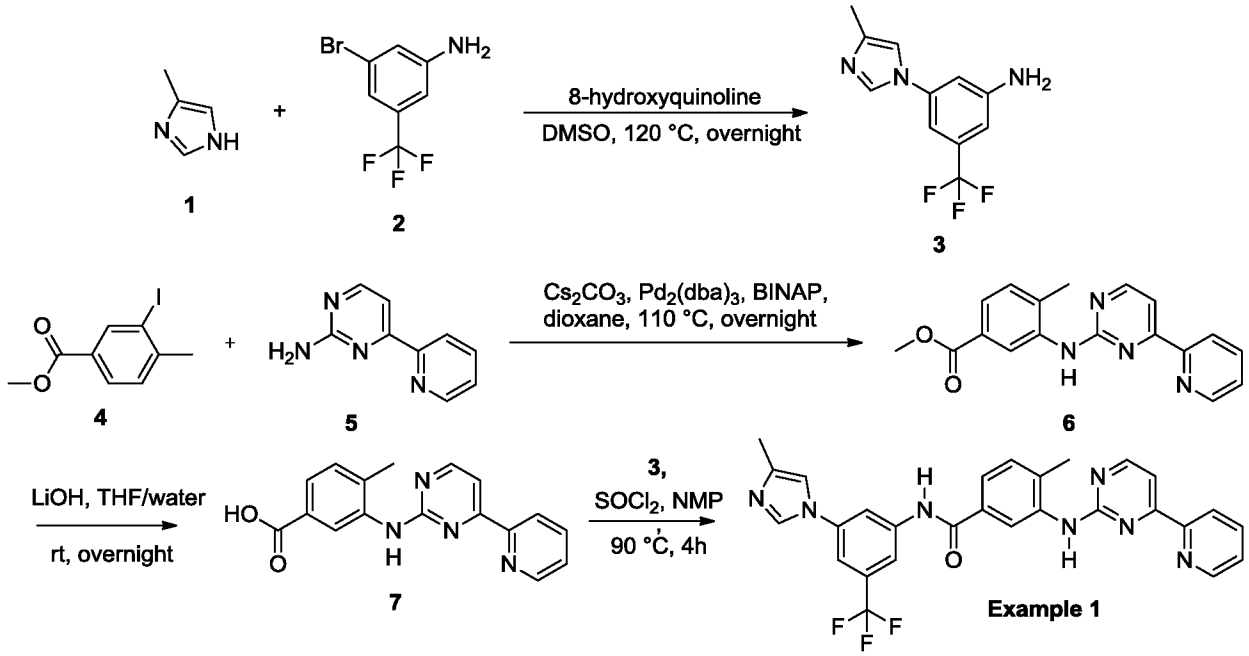
TLC	Thin layer chromatography
Prep-TLC	Preparative thin layer chromatography
DIPEA	Diisopropyl ethyl amine
TPP	Triphenylphosphine
DIAD	Diisopropyl azodicarboxylate
NBS	N-bromosuccinimide
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
TFA	Trifluoroacetic acid
DMF	Dimethylformamide
mL	milliliter(s)
mmol	millimole(s)
h	hour or hours
min	minute or minutes
g	gram(s)
mg	milligram(s)
µL	microlitres
eq	equivalent(s
rt or RT	room temperature, ambient, about 25°C
MS	mass spectrometry

Experimental procedure:

Yields reported herein refer to purified products (unless specified) and are not optimized. Analytical TLC was performed on Merck silica gel 60 F_{254} aluminium-backed plates. Compounds were visualised by UV light and/or stained with either I_2 or potassium permanganate solution followed by heating. Flash column chromatography was performed on silica gel. ^{1}H-NMR spectra were recorded on a 400 MHz spectrometer with a BBO (Broad Band Observe) and BBFO (Broad Band Fluorine Observe) probe. Chemical shifts (δ) are expressed in parts per million (ppm) downfield by reference to tetramethylsilane as the internal standard. Splitting patterns are

designated as s (singlet), d (doublet), triplet (t) m (multiplet). The abbreviation br (broad) may be included with any of these. A partially obscured or merged signal is represented by an asterisk (e.g. d* (merged doublet). Coupling constants (*J*) are given in Hertz (Hz). LCMS analysis was performed using the Electrospray Ionisation (ESI) technique. The following solvents, reagents or scientific terminology may be referred to by their abbreviations as defined above:

Example 1. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-2-yl)pyrimidin-2-yl)amino)benzamide.



A suspension of **1** (3.0 g, 36 mmol), **2** (4.8 g, 20 mmol), K_2CO_3 (4.5 g, 33 mmol), CuI (1.14 g, 6 mmol) and 8-hydroxyquinoline (0.56 g, 4 mmol) in DMSO (20 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **3** (2.8 g, 58%) as a yellow solid. LCMS (m/z: m+1): 242.2.

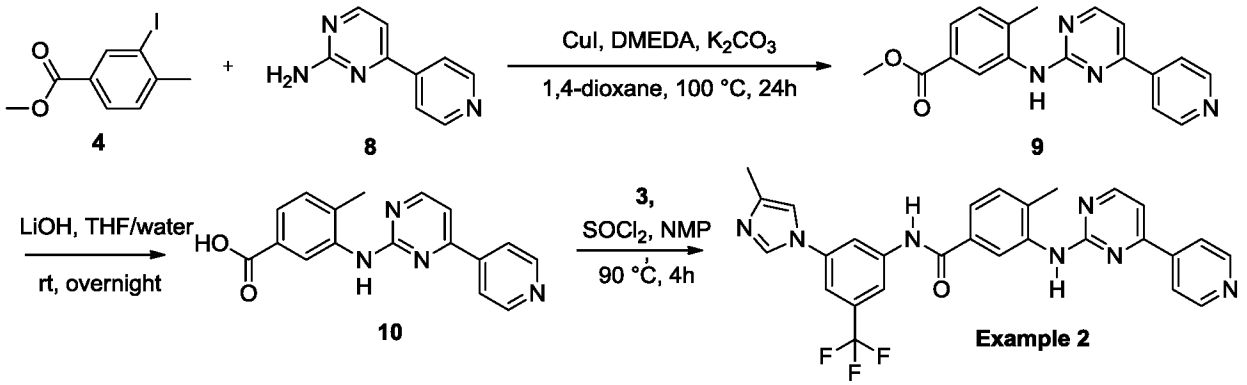
A mixture of **4** (321 mg, 1.16 mmol), **5** (100 mg, 0.58 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), $Pd_2(dba)_3$ (45 mg) and BINAP (63 mg) in 2 ml of dioxane was stirred at 110 °C under N_2 overnight. The mixture was filtered, concentrated and purified by column

chromatography to give **6** (82 mg, 44%) as a slightly yellow solid. LCMS (m/z: m+1): 321.1.

To a solution of **6** (200 mg, 0.624 mmol) in THF/H_2O (10/5 mL) was added LiOH (45 mg, 1.87 mmol). The reaction was stirred at room temperature overnight, concentrated. To the residue water (10 ml) was added and then acidified to pH 4 with aqueous $KHSO_4$. The precipitate was filtered and washed with water. The cake was collected and dried to give **7** (160 mg, 84%) as a white solid. LCMS (m/z: m+1): 308.3.

To a solution of **7** (100 mg, 0.33 mmol) in NMP (2 mL) was added $SOCl_2$ (58 mg, 0.49 mmol). The reaction was heated at 90 °C for 1 hour before **3** (80 mg, 0.33 mmol) was added. The resulting mixture was stirred at 90 °C for 3 hours. The reaction was quenched with water and basified with aqueous NaOH. The mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-2-yl)pyrimidin-2-yl)amino)benzamide (23 mg, 13%) as a gray solid.

Example 2. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-4-yl)pyrimidin-2-yl)amino)benzamide.

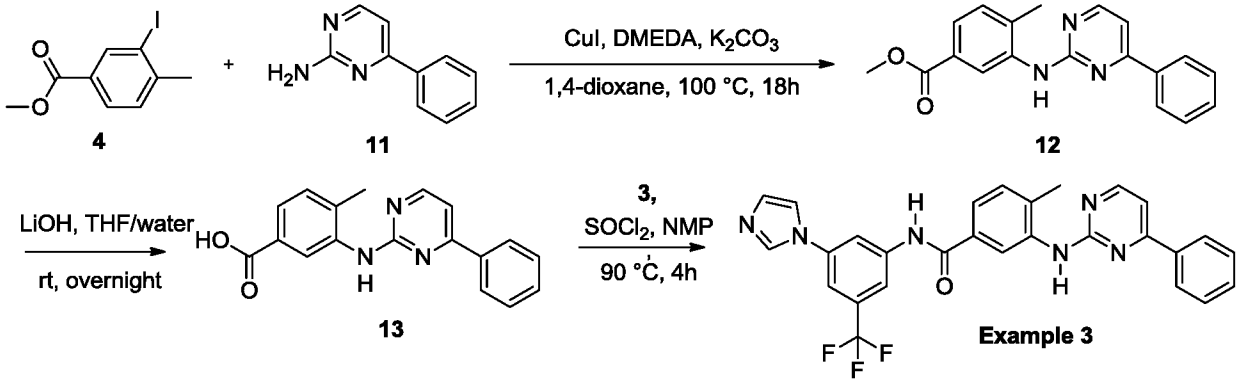


A mixture of **4** (1443 mg, 5.23 mmol), **8** (600 mg, 3.48 mmol), K_2CO_3 (963 mg, 6.97 mmol), DMEDA (77 mg, 0.871 mmol) and CuI (166 mg, 0.871 mmol) in 18 ml of dioxane was stirred at 100 °C under N_2 for 24h. The mixture was filtered, concentrated and purified by column chromatography to give **9** (918 mg, 82%) as a slightly yellow solid. LCMS (m/z: m+1): 321.1.

To a solution of **9** (500 mg, 1.56 mmol) in THF/H_2O (20/10 mL) was added LiOH (112 mg, 4.68 mmol). The reaction was stirred at room temperature overnight, concentrated. To the residue water (30 ml) was added and then acidified to pH 4 with aqueous $KHSO_4$. The precipitate was filtered and washed with water and EtOAc. The cake was collected and dried to give **10** (320 mg, 67%) as a white solid.

To a solution of **10** (150 mg, 0.49 mmol) in NMP (3 mL) was added $SOCl_2$ (87 mg, 0.73 mmol). The reaction was heated at 90 °C for 1 hour before **3** (118 mg, 0.49 mmol) was added. The resulting mixture was stirred at 90 °C for 3 hours. The reaction was quenched with water and basified with aqueous NaOH. The mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-4-yl)pyrimidin-2-yl)amino)benzamide (30 mg, 12%) as a yellow solid.

Example 3. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



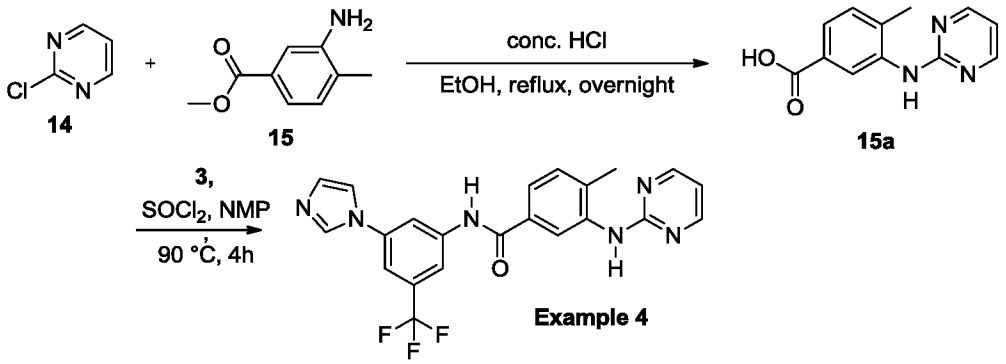
A mixture of **4** (7.26 g, 26.3 mmol), **11** (3.0 g, 17.5 mmol), K_2CO_3 (4.84 g, 35.0 mmol), DMEDA (386 mg, 4.38 mmol) and CuI (834 mg, 0.871 mmol) in 90 ml of dioxane was stirred at 100 °C under N_2 for 18h. The mixture was filtered, concentrated and purified by column chromatography to give **12** (2.2 g, 39%) as a slightly yellow solid. LCMS (m/z: m+1): 320.2.

To a solution of **12** (2.2 g, 6.89 mmol) in THF/water (60/30 mL) was added LiOH (496 mg, 20.7 mmol). The reaction was stirred at room temperature overnight,

concentrated. To the residue water (30 ml) was added and then acidified to pH 4 with aqueous $KHSO_4$. The precipitate was filtered and washed with water and EtOAc. The cake was collected and dried to give **13** (1.4 g, 67%) as a white solid. LCMS (m/z: M+1): 306.2

To a solution of **13** (100 mg, 0.33 mmol) in NMP (2 mL) was added $SOCl_2$ (58 mg, 0.49 mmol). The reaction was heated at 90 °C for 1 hour before **3** (80 mg, 0.33 mmol) was added. The resulting mixture was stirred at 90 °C for 3 hours. The reaction was quenched with water and basified with aqueous NaOH. The mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide (22 mg, 13%) as a white solid.

Example 4. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(pyrimidin-2-ylamino)benzamide.

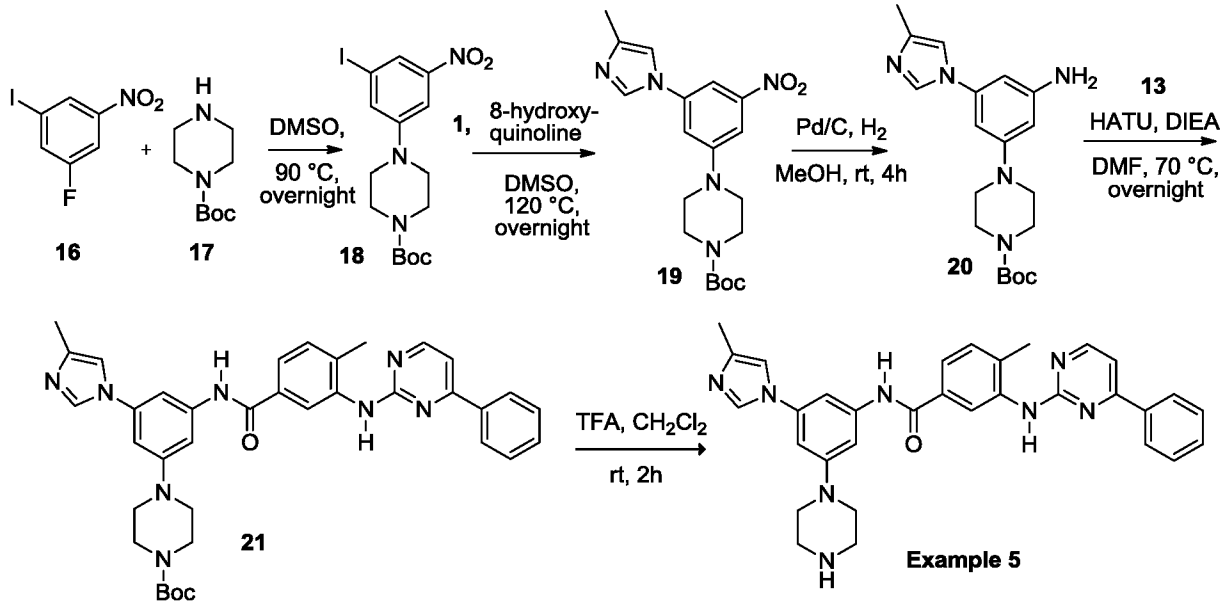


To a solution of **14** (347 mg, 3.03 mmol) and **15** (500 mg, 3.03 mmol) in EtOH (10 mL) was added conc. HCl (1 mL). The reaction was heated to reflux overnight before being concentrated. The residue was purified by silica gel column chromatography and then reverse prep-HPLC to give **15a** (80 mg, 12%) as a white solid. LCMS (m/z: m+1): 230.2.

To a solution of **15a** (80 mg, 0.35 mmol) in NMP (2 mL) was added $SOCl_2$ (62 mg, 0.52 mmol). The reaction was heated at 90 °C for 1 hour before **3** (84 mg, 0.35 mmol) was added. The resulting mixture was stirred at 90 °C for 3 hours. The reaction was quenched with water and basified with aqueous NaOH. The mixture was extracted

with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(pyrimidin-2-ylamino)benzamide (12 mg, 7.6%) as a slightly yellow solid.

Example 5. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(piperazin-1-yl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



A mixture of **16** (0.24 g, 0.9 mmol) and **17** (0.5 g, 2.7 mmol) in DMSO (1.5 mL) was heated at 90 °C overnight. After cooling, water was added and the resulting yellow precipitate was collected by filtration. The cake was dried to give **18** (0.35 g, 90%) as a yellow solid.

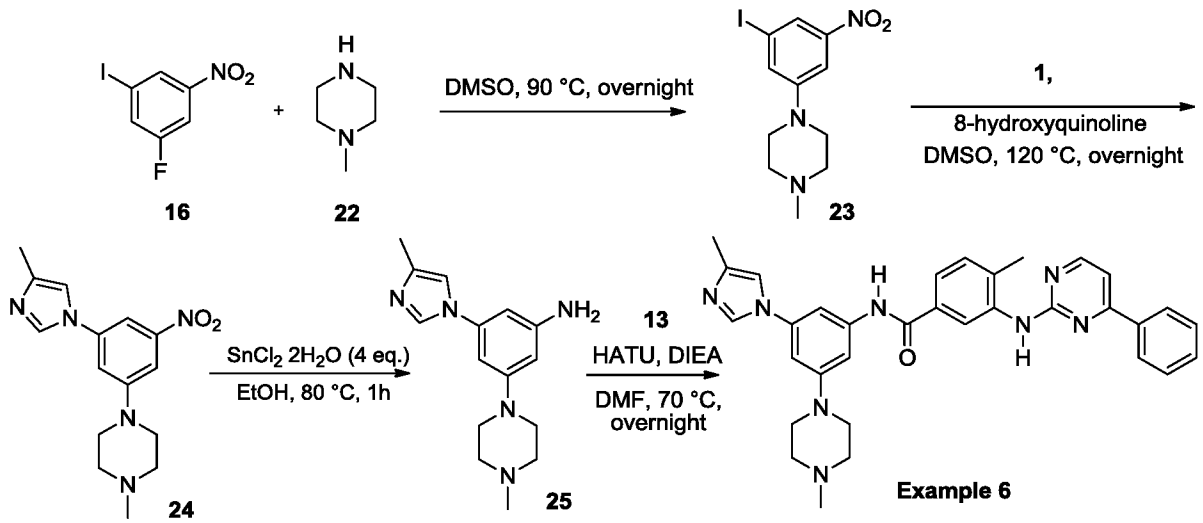
A suspension of **18** (0.86 g, 2 mmol), **1,** (0.32 g, 4 mmol), K_2CO_3(0.55 g, 4 mmol), CuI (0.12 g, 0.6 mmol), and 8-hydroxyquinoline (0.05 g, 0.4 mmol) in DMSO(4 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **19** (0.5 g, 65%) as a yellow solid. LCMS (m/z: m+1): 388.3.

A mixture of **19** (0.5 g, 1.3 mmol) and Pd/C (100 mg) in MeOH (10 mL) was stirred at room temperature under hydrogen atmosphere for 4 hours. The reaction mixture was filtered and concentrated. The crude product was purified by silica gel column chromatography to give **20** (0.4 g, 79%) as a slightly yellow oil. LCMS (m/z: M+1): 358.3.

A mixture of **13** (60 mg, 0.20 mmol), **20** (80 mg, 0.22 mmol), HATU (152 mg, 0.40 mmol) and DIEA (103 mg, 0.80 mmol) in DMF (1.5 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give **21** (43 mg, 34%) as a slightly yellow solid. LCMS (m/z: m+Na): 667.3.

To a solution of **21** (43 mg, 0.067 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.5 mL). The reaction was stirred at room temperature for 2 hours before evaporated under reduced pressure. The residue was treated with water and basified with aqueous NaOH. The precipitate was filtered and washed with water. The cake was collected and dried to give **Example 5** (35 mg, 96%) as a yellow solid.

Example 6. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



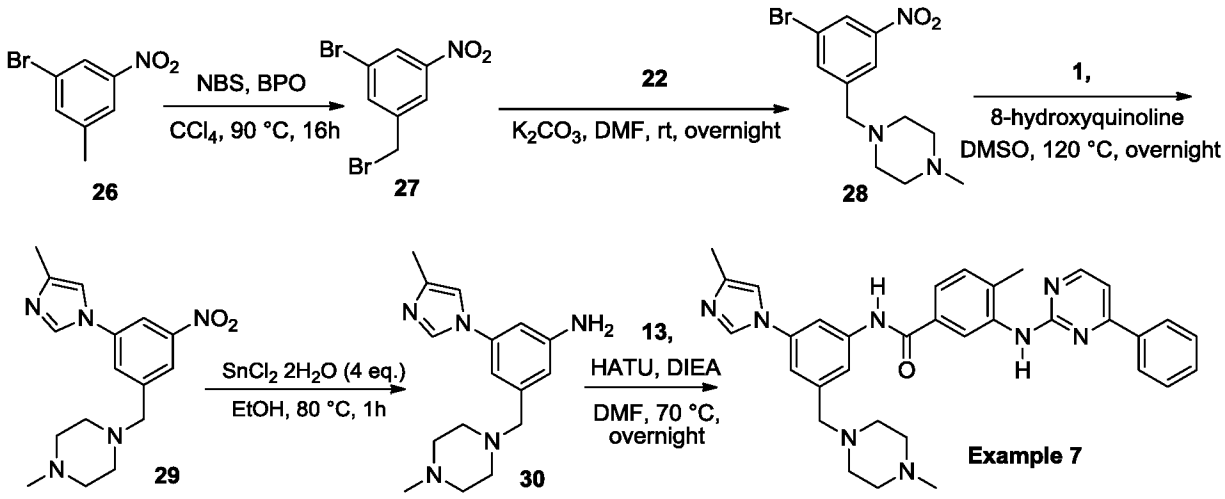
A solution of **16** (0.97 g, 3.6 mmol) and **22** (4.02 ml, 36 mmol) in DMSO (3 mL) was heated at 90 °C for 4 h. overnight. After cooling, water was added and the resulting yellow precipitate was collected by filtration. The cake was collected and dried to give **23** (1.1 g, 88%) as a yellow solid. LCMS (m/z: m+1): 348.1.

A suspension of **23** (0.7 g, 2 mmol), **1** (0.32 g, 4 mmol), K_2CO_3 (0.55 g, 4 mmol), CuI (0.12 g, 0.6 mmol) and 8-hydroxyquinoline (0.05 g, 0.4 mmol) in DMSO (4 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **24** (0.4 g, 66%) as a yellow solid. LCMS (m/z: m+1): 302.1.

A mixture of **24** (100 mg, 0.33 mmol) and $SnCl_22H_2O$ (250 mg, 1.33 mmol) in EtOH (3 ml) was heated at 80 °C for 1 hour. After cooling, silica gel was added to the reaction and the mixture was concentrated to dryness. The residue was purified by silica gel column chromatography to give **25** (80 mg, 89%) as a yellow solid.

A mixture of **13** (90 mg, 0.29 mmol), **25** (80 mg, 0.29 mmol), HATU (220 mg, 0.58 mmol) and DIEA (150 mg, 1.16 mmol) in DMF (2 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide (64 mg, 40%) as a slight yellow solid.

Example 7. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-((4-methylpiperazin-1-yl)methyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



A mixture of **26** (2.16 g, 10 mmol), N-bromosuccinimide (1.78 g, 10 mmol) and benzoyl peroxide (0.24 g, 1 mmol) in CCl_4 (30 mL) was heated at 90 °C for 16 h. After

cooling, the precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to give **27** (3.3 g, 100%) as yellow solid which was used for the next step without purification.

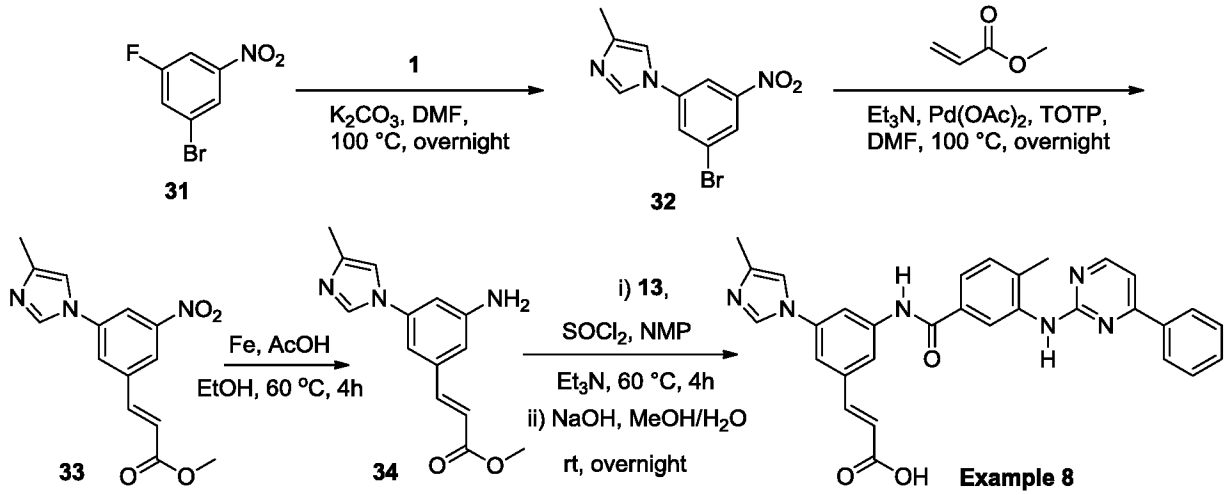
A mixture of **27** (1.0 g, 3.4 mmol), N-methylpiperazine (**22**; 0.7 g, 7 mmol) and K_2CO_3 (0.9 g, 7 mmol) in DMF (10 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **28** (0.64 g, 60%) as a yellow solid. LCMS (m/z: m+1): 314.1, 316.1.

A suspension of **28** (0.63 g, 2 mmol), **1,** (0.49 g, 6 mmol), K_2CO_3 (0.55 g, 4 mmol), CuI (0.12 g, 0.6 mmol) and 8-hydroxyquinoline (0.05 g, 0.4 mmol) in DMSO (4 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **29** (0.30 g, 48%) as a yellow solid. LCMS (m/z: m+1): 316.3.

A mixture of **29** (250 mg, 0.79 mmol) and $SnCl_2$ $2H_2O$ (720 mg, 3.2 mmol) in EtOH (5 ml) was heated at 80 °C for 1 hour. After cooling, silica gel was added to the reaction and concentrated to dryness. The residue was purified by silica gel column chromatography to give **30** (205 mg, 82%) as a yellow solid. LCMS (m/z: m+1): 286.4.

A mixture of **13** (107 mg, 0.35 mmol), **30** (100 mg, 0.35 mmol), HATU (266 mg, 0.70 mmol) and DIEA (181 mg, 1.4 mmol) in DMF (2 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-((4-methylpiperazin-1-yl)methyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide (25 mg, 12%) as a slightly yellow solid.

Example 8. Synthesis of (E)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamido)phenyl)acrylic acid.



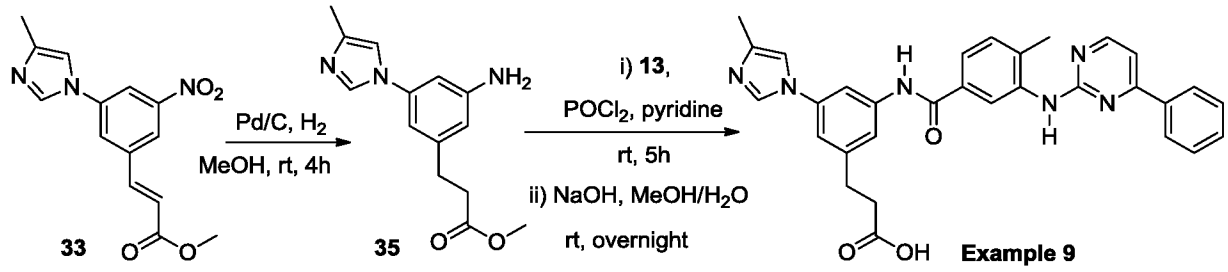
A mixture of **31** (0.66 g, 3 mmol), **1** (0.8 g, 10 mmol) and K_2CO_3 (0.8 g, 6 mmol) in DMF (5 mL) was heated at 100 °C overnight. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **32** (0.76 g, 90%) as a yellow solid. LCMS (m/z: m+1): 282.0, 284.0.

A mixture of **32** (1 g, 3.5 mmol), methyl acrylate (0.45 g, 5.25 mmol), Et_3N (0.7 g, 7 mmol), $Pd(OAc)_2$ (0.07 g, 0.35 mmol) and TOTP (0.2 g, 0.7 mmol) in DMF (5 mL) was heated at 100 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **33** (0.8 g, 80%) as a yellow solid. LCMS (m/z: m+1): 288.2.

A mixture of **33** (200 mg, 0.70 mmol) and Fe (195 mg, 3.5 mmol) in EtOH (3 mL) and AcOH (1 mL) was heated at 60 °C for 4 h. After cooling, water was added, basified with aqueous $NaHCO_3$ and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **34** (150 mg, 84%) as a yellow oil. LCMS (m/z: m+1): 258.2.

To a solution of **13** (119 mg, 0.39 mmol) in NMP (2 mL) was added $SOCl_2$ (70 mg, 0.59 mmol). The reaction was heated at 60 °C for 1 hour before **34** (100 mg, 0.39 mmol) and Et_3N (158 mg, 1.6 mmol) was added. The resulting mixture was stirred at 60 °C for 3 hours. The reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give the methyl ester of Example 8 (80 mg, 38%) as a slight yellow solid. LCMS (m/z, m+1): 545.3. This material (80 mg, 0.15 mmol) was dissolved in MeOH/H_2O (3/1 mL) and was treated with NaOH (18 mg, 0.45 mmol). The mixture was stirred at room temperature overnight. The reaction was diluted with water and acidified with aqueous $KHSO_4$. The precipitate was filtered and washed with water. The cake was collected and dried to give (E)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamido)phenyl)acrylic acid (62 mg, 80%) as a slightly yellow solid.

Example 9. Synthesis of 3-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamido)phenyl)propanoic acid.

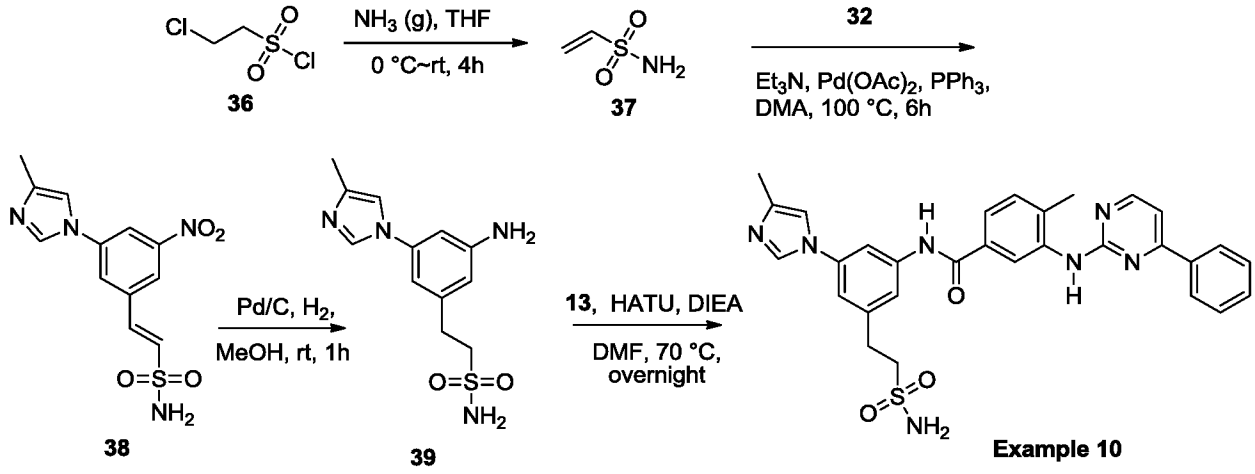


A mixture of **33** (300 mg, 1.05 mmol) and Pd/C (100 mg) in MeOH (10 mL) was stirred at room temperature under hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **35** (300 mg, 100%) as a yellow oil that was used in next step without purification. LCMS (m/z: m+1): 260.2.

To a solution of **13** (122 mg, 0.40 mmol) and **35** (130 mg, 0.50 mmol) in pyridine (1.5 mL) was added $POCl_3$ (123 mg, 0.80 mmol) dropwise. The reaction was stirred at room temperature for 5 hours. The reaction was poured in ice-water and the precipitate was collected by filtration. The solid was further purified by silica gel prep-TLC to give the methyl ester of Example 9 (60 mg, 27%) as a slightly yellow solid. LCMS (m/z: m+1): 547.3. To a solution of this material (60 mg, 0.11 mmol) in MeOH/H_2O (3/1 mL) was added NaOH (13 mg, 0.33 mmol). The mixture was stirred at room temperature

overnight. The reaction was diluted with water and acidified with aqueous $KHSO_4$. The precipitate was filtered and washed with water. The cake was collected, dried and washed with CH_2Cl_2 to give Synthesis of 3-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamido)phenyl)propanoic acid (25 mg, 43%) as a slightly yellow solid.

Example 10. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(2-sulfamoylethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



36 37 38 39 Example 10

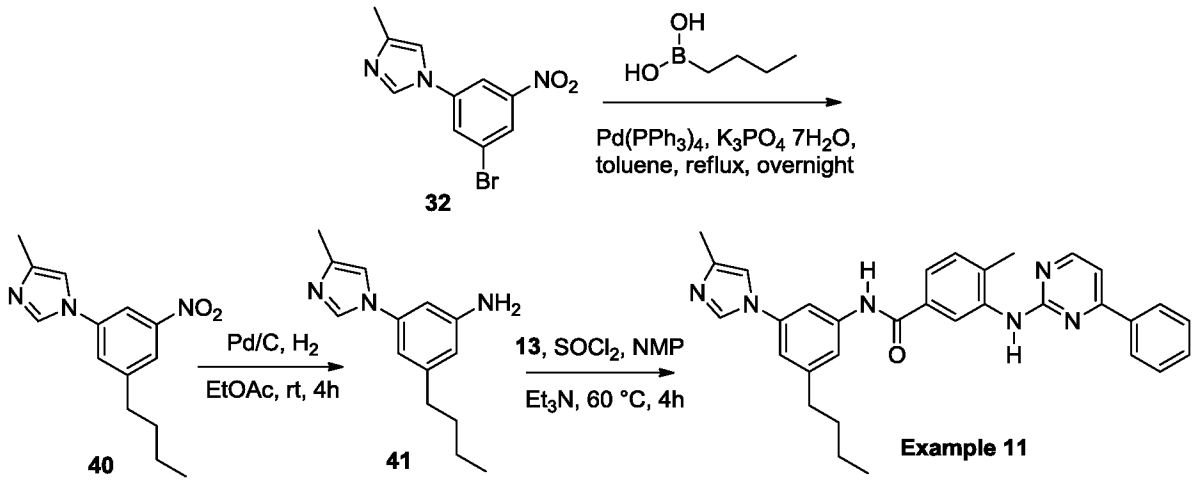
To a solution of **36** (1.0 g, 6.13 mmol) in THF (10 mL) was bubbled NH_3 (gas) slowly at 0 °C for 2 hours. The reaction was then stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **37** (300 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.05 (br s, 2H); 6.78 (dd, J = 16.4, 10 Hz, 1H); 6.00 (d, J=16.4 Hz, 1H); 5.82 (d, J=10 Hz, 1H).

A mixture of **32** (350 mg, 1.25 mmol), **37** (200 mg, 1.87 mmol), Et_3N (253 mg, 2.5 mmol), $Pd(OAc)_2$ (28 mg, 0.125 mmol) and PPh_3 (63 mg, 0.25 mmol) in DMF (3 mL) was heated at 100 °C for 6 hours under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **38** (220 mg, 57%) as a yellow solid. LCMS (m/z: m+1): 309.1.

A mixture of **38** (80 mg, 0.26 mmol) and Pd/C (80 mg) in MeOH (5 mL) was stirred at room temperature under hydrogen atmosphere for 1 hour. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **39** (72 mg, 99%) as a yellow solid which was used in next step without purification. LCMS (m/z: m+1): 281.2.

A mixture of **13** (78 mg, 0.26 mmol), **39** (72 mg, 0.26 mmol), HATU (198 mg, 0.52 mmol) and DIEA (134 mg, 1.04 mmol) in DMF (1.5 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(2-sulfamoylethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzamide (13 mg, 8.9%) as an off-white solid.

Example 11. Synthesis of N-(3-butyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamide.



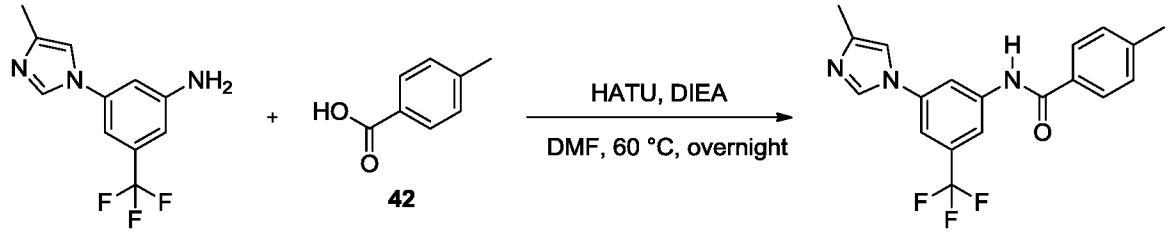
A mixture of **32** (200 mg, 0.7 mmol), butylboronic acid (289 mg, 2.8 mmol), K_3PO_4 $7H_2O$ (720 mg, 2.1 mmol) and $Pd(PPh_3)_4$ (243 mg, 0.21 mmol) in toluene (5 mL) was refluxed overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **40** (53 mg, 29%) as a slightly yellow solid. LCMS (m/z: m+1): 260.2.

A mixture of **40** (53 mg, 0.2 mmol) and Pd/C (50 mg) in EtOAc (5 mL) was stirred at room temperature under hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **41** (50 mg,

100%) as a slightly yellow solid that was used in next step without further purification. LCMS (m/z: m+1): 230.3.

To a solution of **13** (67 mg, 0.22 mmol) in NMP (1 mL) was added $SOCl_2$ (39 mg, 0.33 mmol). The reaction was heated at 60 °C for 1 hour before **41** (50 mg, 0.22 mmol) and Et_3N (89 mg, 0.88 mmol) was added. The resulting mixture was stirred at 60 °C for 3 hours. The reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give N-(3-butyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((4-phenylpyrimidin-2-yl)amino)benzamide (23 mg, 20%) as a slightly yellow solid.

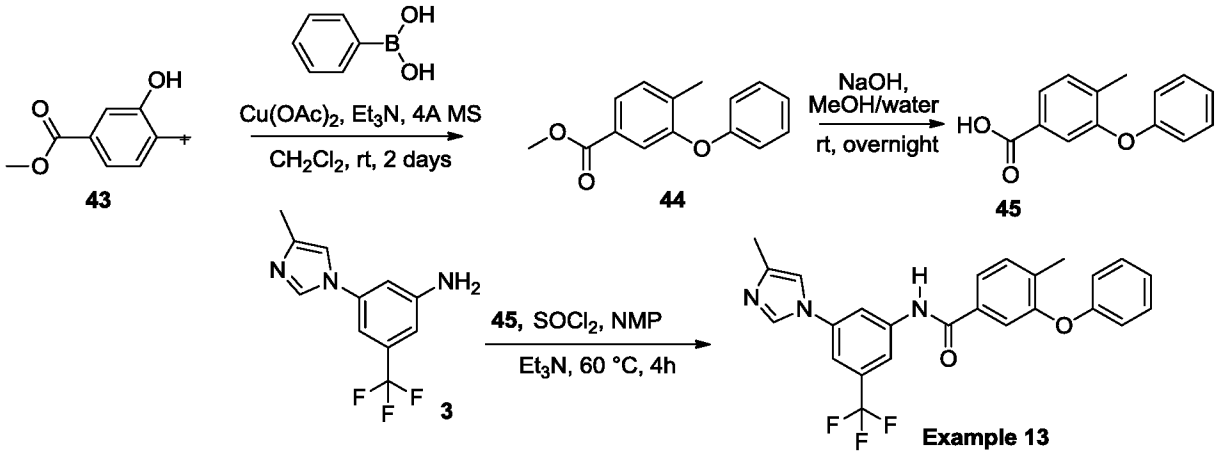
Example 12. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide



3 + **42** → **Example 12**

A mixture of **3** (100 mg, 0.41 mmol), p-toluic acid (**42**) (56 mg, 0.41 mmol), HATU (312 mg, 0.82 mmol) and DIEA (207 mg, 1.6 mmol) in DMF (2 mL) was heated at 60 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide (21 mg, 14%) as an off-white solid.

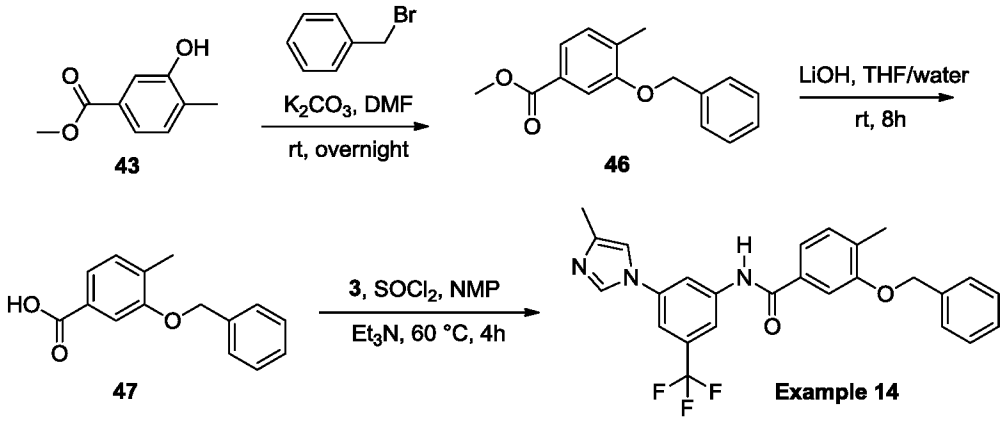
Example 13. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-phenoxybenzamide.



A mixture of **43** (2.0 g, 12 mmol), phenylboronic acid (7.4 g, 60 mmol), $Cu(OAc)_2$ (3.2 g, 18 mmol), Et_3N (6.0 g, 60 mmol) and 4A MS (10.0 g) in CH_2Cl_2 (100 mL) was stirred at room temperature under air for 2 days. The reaction mixture was filtered and washed with CH_2Cl_2. The filtrate was concentrated. The residue was purified by silica gel column chromatography to give **44** (2.3 g, 79%) as a colorless oil. LCMS (m/z: m+1): 243.1.

A mixture of **44** (2.3 g, 9.5 mmol) and NaOH (759 mg, 19 mmol) in $MeOH/H_2O$ (20/5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated. The residue dissolved in water, acidified to pH 3 with aqueous HCl and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give **45** (1.9 g, 88%) as a white solid. To a solution of this material (48 mg, 0.21 mmol) in NMP (1 mL) was added $SOCl_2$ (38 mg, 0.32 mmol). The reaction was heated at 60 °C for 1 hour before **3** (50 mg, 0.21 mmol) and Et_3N (85 mg, 0.84 mmol) was added. The resulting mixture was stirred at 60 °C for 3 hours. The reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-phenoxybenzamide (27 mg, 29%) as a slightly yellow solid.

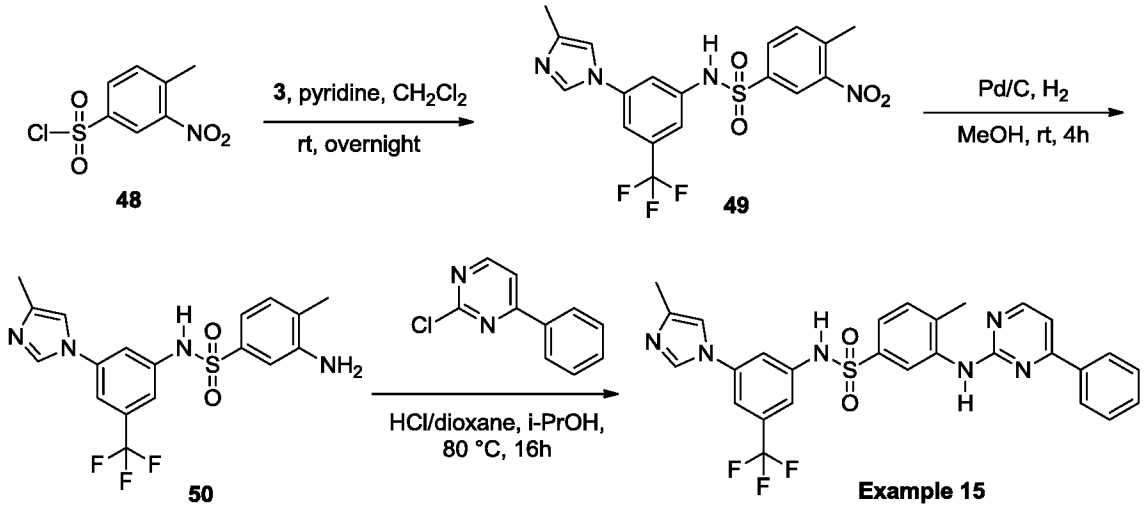
Example 14. Synthesis of 3-(benzyloxy)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide.



A mixture of **43** (100 mg, 0.6 mmol), benzyl bromide (103 mg, 0.6 mmol), and K_2CO_3 (166 mg, 1.2 mmol) in DMF (1 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc twice. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel prep-TLC to give **46** (100 mg, 65%) as a white solid. LCMS (m/z: m+1): 257.2.

A mixture of **46** (100 mg, 0.39 mmol) and LiOH (28 mg, 1.17 mmol) in THF/H_2O (2/1 mL) was stirred at room temperature for 8 hours. TLC indicated the reaction was complete. The reaction mixture was diluted with water and acidified to pH 3 with aqueous HCl. The resulting precipitate was filtered washed with water and dried to give **47** (90 mg, 95%) as a white solid. To a solution of **47** (100 mg, 0.41 mmol) in NMP (1.5 mL) was added $SOCl_2$ (74 mg, 0.62 mmol). The reaction was heated at 60 °C for 1 hour before **3** (100 mg, 0.41 mmol) and Et_3N (166 mg, 1.64 mmol) were added. The resulting mixture was stirred at 60 °C for 3 hours. The reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give 3-(benzyloxy)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide (25 mg, 13%) as a white solid.

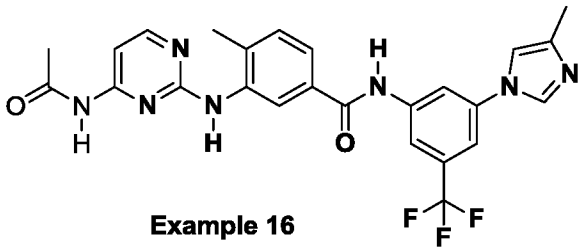
Example 15. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzenesulfonamide.



To a solution of **3** (500 mg, 2.1 mmol) and **48** (489 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) was added pyridine (242 mg, 3.1 mmol), dropwise. The reaction was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **49** (180 mg, 20%) as a slightly yellow solid. LCMS (m/z: m+1): 441.1.

A mixture of **49** (180 mg, 0.41 mmol) and Pd/C (60 mg) in MeOH (10 mL) was stirred at room temperature under hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **50** (170 mg, 100%) as a yellow solid, which was used in next step without further purification. This material (170 mg, 0.41 mmol) and 2-chloro-4-phenylpyrimidine (158 mg, 0.83 mmol) in i-PrOH (3 mL) was added a saturated solution of HCl in dioxane (0.5 mL). The reaction was heated at 80 °C for 16 hours before being concentrated under reduced pressure. The residue was dissolved in CH_3CN and basified with Et_3N. The resulting solution was concentrated, then purified by reverse prep-HPLC and then silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-phenylpyrimidin-2-yl)amino)benzenesulfonamide (20 mg, 8.5%) as a white solid.

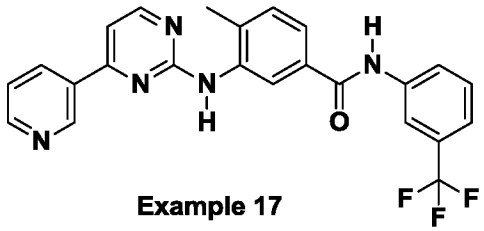
Example 16. 3-((4-acetamidopyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide.



Example 16

This compound was prepared by treating methyl 3-((4-acetamidopyrimidin-2-yl)amino)-4-methylbenzoate with **3** in the presence of trimethylaluminum (2.0M in THF) followed by purification by HPLC to give 3-((4-acetamidopyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide in 3% isolated yield as an off white solid. Analytical data are summarized in Table 1.

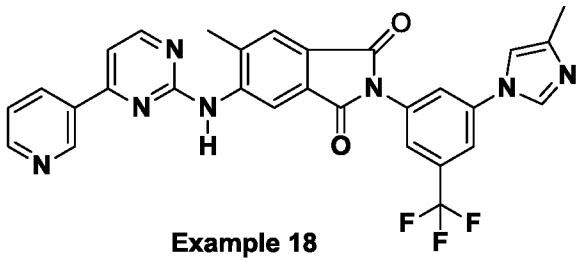
Example 17. 4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)-N-(3-(trifluoromethyl)phenyl)benzamide.



Example 17

This compound was prepared similarly to Example 16 using methyl 4-methyl-3-((4-(pyridin-3-yl)-pyrimidin-2-yl)amino)benzoate, 3-trifluoromethylaniline, and trimethylaluminum (2.0 M in THF) followed by column chromatography to yield 4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)-N-(3-(trifluoromethyl)phenyl)benzamide in 48% yield as an off-white solid. Analytical data are summarized in Table 1.

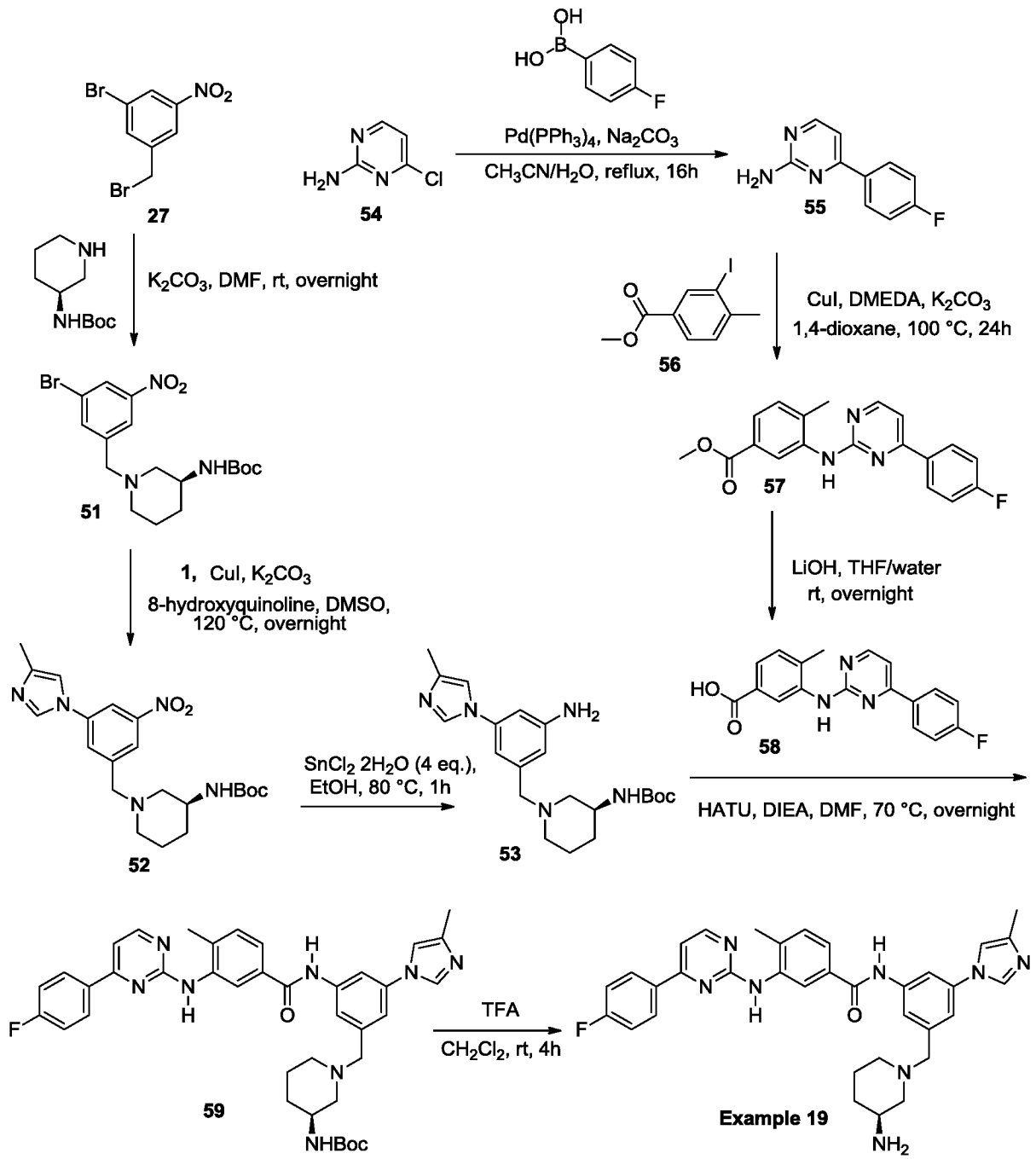
Example 18. 5-methyl-2-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-6-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)isoindoline-1,3-dione.



Example 18

3 was combined with protected 5-amino-6-methylisobenzofuran-1,3-dione to form 5-amino-6-methyl-2-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-isoindoline-1,3-dione, which was then coupled with 2-chloro-4-(pyridin-3-yl)pyrimidine in the presence of BINAP (0.1 eq.), palladium diacetate (0.02 eq.) sodium carbonate (4 eq.) in dioxane followed by HPLC purification to yield . 5-methyl-2-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-6-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)isoindoline-1,3-dione (38 mg, 43%) as a yellow solid. Analytical data are summarized in Table 1.

Example 19. Synthesis of (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamide.



A mixture of **27** (1366 mg, 4.63 mmol), (S)-tert-butyl piperidin-3-ylcarbamate (1020 mg, 4.63 mmol) and K_2CO_3 (768 mg, 5.56 mmol) in DMF (8 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4

and concentrated. The residue was purified by silica gel column chromatography to give **51** (870 mg, 45%) as a slightly yellow solid. LCMS (m/z: m+1): 414.0, 116.1.

A suspension of **51** (870 mg, 2.1 mmol), **1** (517 mg, 6.3 mmol), K_2CO_3 (580 mg, 4.2 mmol), CuI (120 mg, 0.63 mmol) and 8-hydroxyquinoline (61 mg, 0.42 mmol) in DMSO (8 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **52** (630 mg, 72%) as a slightly yellow solid. LCMS (m/z: m+1): 416.3.

A mixture of **52** (630 mg, 1.52 mmol) and $SnCl_2\,2H_2O$ (1369 mg, 6.06 mmol) in EtOH (13 ml) was heated at 80 °C for 1 hour. After cooling, silica gel was added to the reaction and concentrated to dryness. The residue was purified by silica gel column chromatography to give **53** (430 mg, 74%) as a slightly yellow solid. LCMS (m/z: m+1): 386.4.

A mixture of **54** (9.5 g, 73.3 mmol), 4-fluorophenylboronic acid (10.3 g, 73.3 mmol), Na_2CO_3 (15.5 g, 147 mmol), and $Pd(PPh_3)_4$ (1.5 g) in CH_3CN/H_2O (2/1, 200 mL) was refluxed under N_2 for 16 hours. After cooling, the mixture was diluted with water and extracted with EtOAc twice. The combined organic layers were washed with brine, fried over Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography to give **55** (5.1 g, 37%) as a slightly yellow solid. LCMS (m/z: m+1): 190.2.

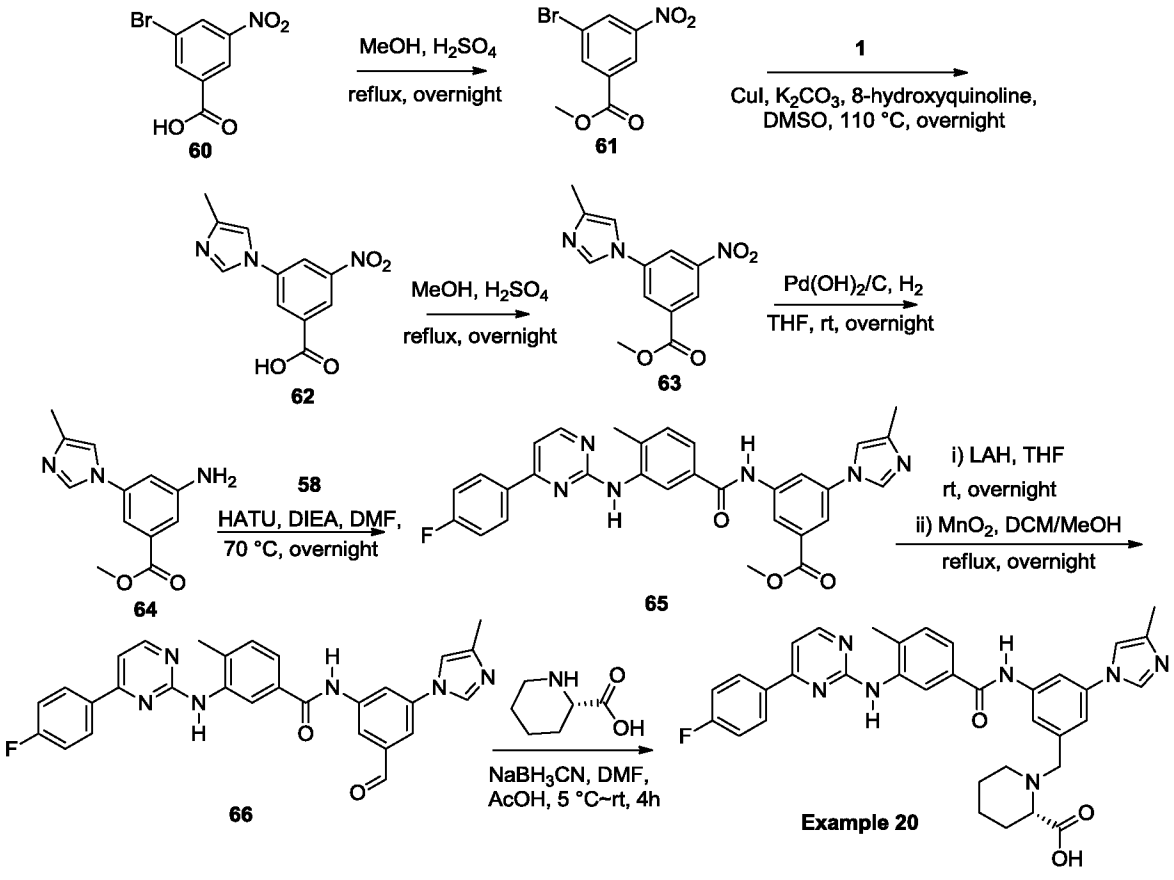
A mixture of **56** (11.2 g, 40.4 mmol), **55** (5.1 g, 27.0 mmol), K_2CO_3 (7.5 g, 54.0 mmol), DMEDA (476 mg, 5.4 mmol) and CuI (1.28 g, 6.7 mmol) in 100 ml of dioxane was stirred at 100 °C under N_2 for 24 hours. The mixture was filtered, concentrated and purified by column chromatography to give **57** (1.6 g, 18%) as a slightly yellow solid. LCMS (m/z: m+1): 338.3.

To a solution of **57** (1.6 g, 4.74 mmol) in THF/H_2O (32/16 mL) was added LiOH (341 mg, 14.2 mmol). The reaction was stirred at room temperature overnight, concentrated. To the residue water was added and then acidified to pH 4 with aqueous $KHSO_4$. The precipitate was filtered and washed with water and EtOAc. The cake was collected and dried to give **58** (1.3 g, 85%) as an off-white solid. LCMS (m/z: m+1): 324.1.

A mixture of **53**(130 mg, 0.34 mmol), **58** (109 mg, 0.34 mmol), HATU (257 mg, 0.68 mmol) and DIEA (218 mg, 1.69 mmol) in DMF (2 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give **59** (33 mg, 14%) as a slightly yellow solid. LCMS (m/z: m+1): 691.3

To a solution of **59** (33 mg, 0.048 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL) and the reaction was stirred at room temperature for 4 hours before concentrated under reduced pressure. The residue was treated with water, basified with 0.5 N NaOH and extracted with CH_2Cl_2/MeOH (15/1) 3 times. The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by reverse prep-HPLC to give (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamide (14 mg, 50%) as an off-white solid.

Example 20. Synthesis of (S)-1-(3-(3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamido)-5-(4-methyl-1H-imidazol-1-yl)benzyl)piperidine-2-carboxylic acid.



To a solution of **60** (1.0 g, 4.1 mmol) in MeOH (30 mL) was added dropwise H_2SO_4 (5 mL). The reaction was refluxed overnight before concentrated. The residue was treated with water and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give **61** (1.1 g, 100%) as an off-white solid. A suspension of **61** (900 mg, 3.46 mmol), **1** (853 mg, 10.4 mmol), K_2CO_3 (955 mg, 6.92 mmol), CuI (198 mg, 1.04 mmol) and 8-hydroxyquinoline (100 mg, 0.69 mmol) in DMSO (9 mL) was heated at 110 °C overnight under nitrogen. After cooling, water was added and the mixture was acidified by aqueous $KHSO_4$, and extracted with EtOAc 3 times. The product was in the water phase. The water layer was directly purified by reverse prep-HPLC to give **62** (310 mg, 36%) as a white solid. LCMS (m/z: m+1): 248.1.

To a mixture of **62** (310 mg, 1.26 mmol) in MeOH (30 mL) was added dropwise H_2SO_4 (2 mL). The reaction was refluxed overnight before concentrated. The residue treated with water, basified by 2N NaOH under ice-water bath and extracted with CH_2Cl_2 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give **63** (260 mg, 79%) as a slightly yellow solid. LCMS (m/z: m+1): 262.1.

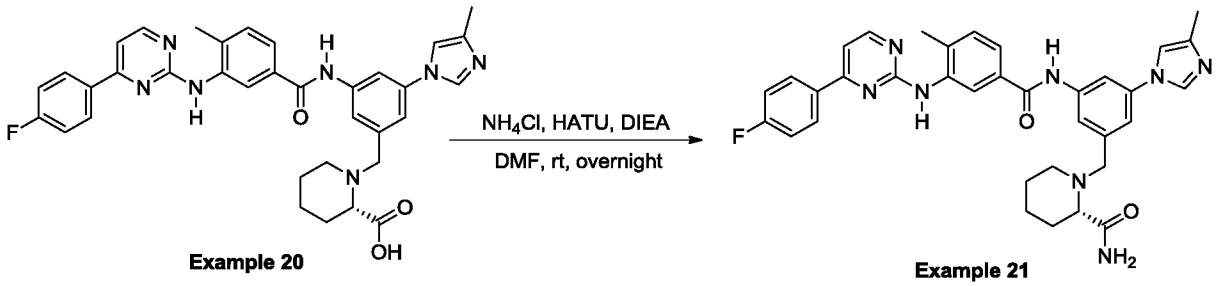
A mixture of **63** (260 mg, 1.0 mmol) and Pd/C (80 mg) in THF (10 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give **64** (231 mg, 100%) as a slightly yellow oil. LCMS (m/z: m+1): 232.3.

A mixture of **64** (231 mg, 1.0 mmol), **58** (323 mg, 1.0 mmol), HATU (760 mg, 2.0 mmol) and DIEA (646 mg, 5.0 mmol) in DMF (3 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give **65** (148 mg, 28%) as a slightly yellow solid. LCMS (m/z: m+1): 537.3.

To a solution of **65** (148 mg, 0.28 mmol) in THF (5 mL) was added LAH (42 mg, 1.10 mmol). The mixture was stirred at room temperature overnight before quenched with water (100 mg). The resulting mixture was filtered through Celite and washed with CH_2Cl_2/MeOH (10/1). The filtrate was evaporated under reduced pressure to give the fully reduced benzylic alcohol (145 mg, 100%) as a slightly yellow solid which was used in next step without purification. A mixture of this material (125 mg, 0.25 mmol) and

MnO_2 (427 mg, 4.9 mmol) in CH_2Cl_2/MeOH (20/1, 30 mL) was refluxed overnight. The reaction mixture was filtered and washed with CH_2Cl_2/MeOH (20/1, 60 mL). The filtrate was evaporated under reduced pressure to give aldehyde **66** (123 mg, 99%) as a slightly yellow solid. This material was also used in the next step without intermediate purification. To a solution of **66** (103 mg, 0.20 mmol) and (S)-piperidine-2-carboxylic acid (129 mg, 1.0 mmol) in DMF (2 mL) was added AcOH (2 drops) and then $NaBH_3CN$ (63 mg, 1.0 mmol) at 5 °C. The mixture was stirred at room temperature for 4 hours. The reaction mixture was directly purified by reverse prep-HPLC to give crude product (48 mg, ~60% purity). 23 mg of the crude product was further purified by silica gel prep-TLC to give pure (S)-1-(3-(3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamido)-5-(4-methyl-1H-imidazol-1-yl)benzyl)piperidine-2-carboxylic acid (12 mg, 20%) as a white solid.

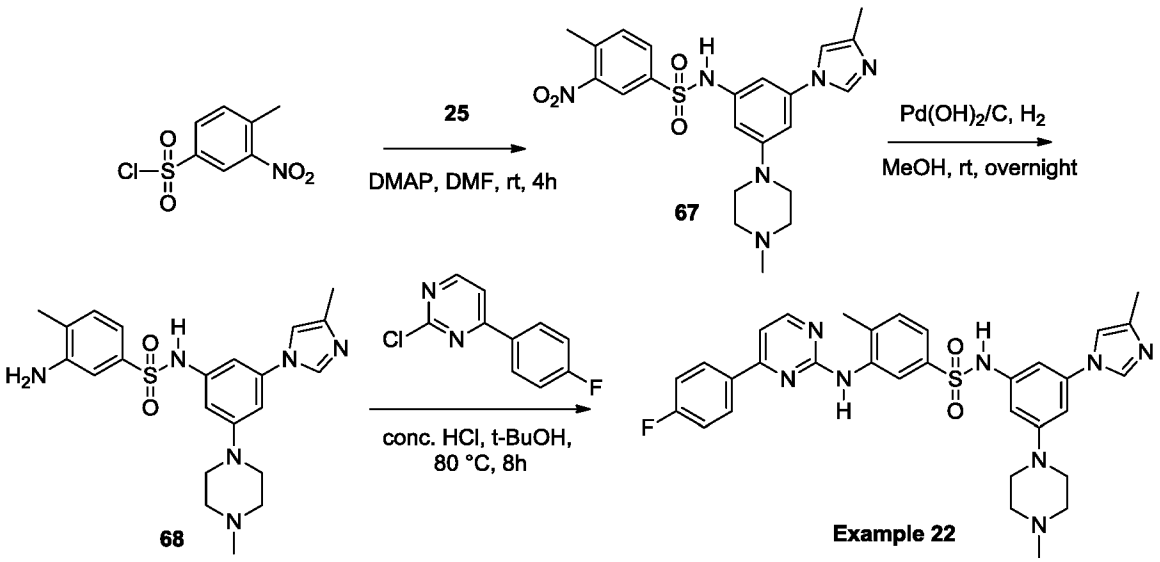
Example 21. Synthesis of (S)-1-(3-(3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamido)-5-(4-methyl-1H-imidazol-1-yl)benzyl)piperidine-2-carboxamide.



Example 20 Example 21

A mixture of crude (S)-1-(3-(3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamido)-5-(4-methyl-1H-imidazol-1-yl)benzyl)piperidine-2-carboxylic acid (25 mg, 0.040 mmol), NH_4Cl (10.8 mg, 0.20 mmol), HATU (46 mg, 0.12 mmol) and DIEA (41 mg, 0.32 mmol) in DMF (1 mL) was stirred at room temperature overnight. The reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give (S)-1-(3-(3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methylbenzamido)-5-(4-methyl-1H-imidazol-1-yl)benzyl)piperidine-2-carboxamide (13.5 mg, 54%) as a white solid.

Example 22. Synthesis of 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzenesulfonamide.

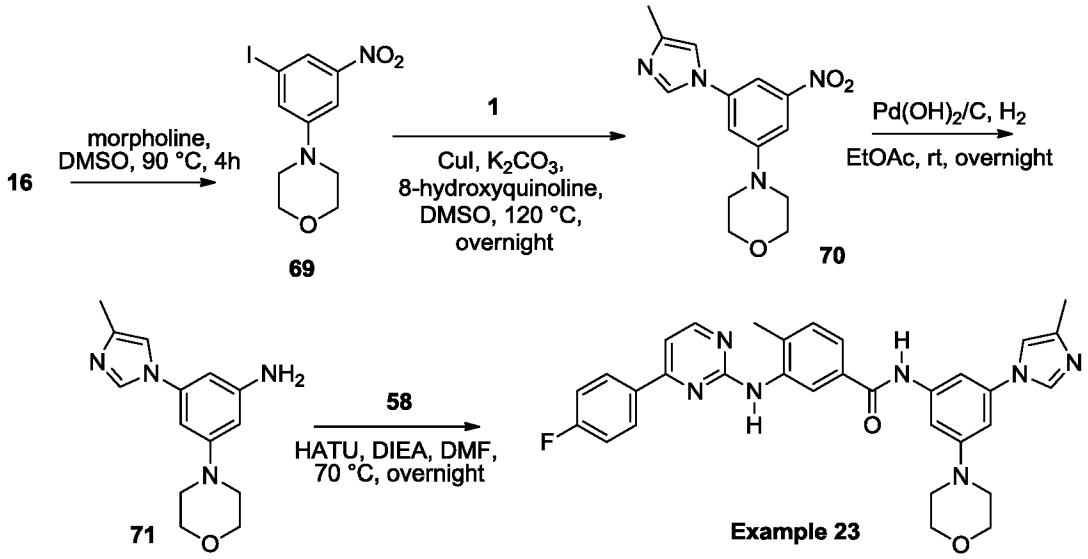


To a solution of **25** (500 mg, 1.84 mmol) and 4-methyl-3-nitrobenzenesulfonyl chloride (651 mg, 2.76 mmol) in DMF (5 ml) was added DMAP (449 mg, 3.68 mmol) in portions. The reaction was stirred at room temperature overnight and directly purified by reverse prep-HPLC to give **67** (310 mg, 36%) as a slightly yellow solid. LCMS (m/z: m+1): 471.3.

A mixture of **67** (310 mg, 0.66 mmol) and $Pd(OH)_2/C$ (60 mg) in MeOH (15 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give **68** (291 mg, 100%) as a slightly yellow solid. LCMS (m/z: m+1): 441.3.

To a solution of **68** (109 mg, 0.25 mmol) and 2-chloro-4-phenylpyrimidine (77 mg, 0.37 mmol) in t-BuOH (3 mL) was added conc. HCl (0.25 mL). The reaction was heated at 80 °C for 8 hours before concentrated under reduced pressure. The residue was dissolved in CH_3CN and basified with Et_3N. The resulting solution was purified by reverse prep-HPLC and then silica gel prep-TLC to give 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzenesulfonamide (21 mg, 14%) as an off-white solid.

Example 23. Synthesis of 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-morpholinophenyl)benzamide.



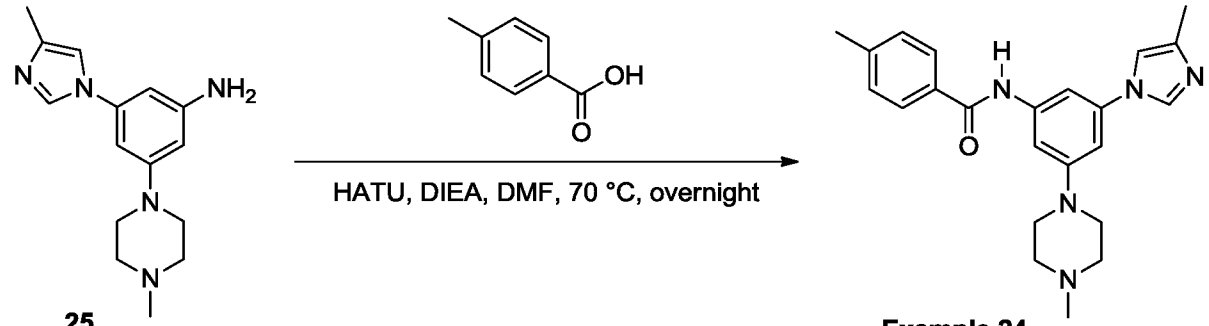
A solution of **16** (200 mg, 0.75 mmol) and morpholine (326 mg, 3.75 mmol) in DMSO (2 mL) was heated at 90 °C for 4 hours before poured into water with stirring. The precipitate was filtered and washed with water. The cake was collected and dried to give **69** (220 mg, 88%) as a yellow solid. This material (220 mg, 0.658 mmol), **1** (162 mg, 1.98 mmol), K_2CO_3 (182 mg, 1.32 mmol), CuI (38 mg, 0.198 mmol) and 8-hydroxyquinoline (19 mg, 0.132 mmol) in DMSO (2.5 mL) were combined and heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **70** (152 mg, 80%) as a yellow solid. LCMS (m/z: m+1): 289.2.

A mixture of **70** (150 mg, 0.52 mmol) and $Pd(OH)_2/C$ (200 mg) in EtOAc (75 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give **71** (135 mg, 100%) as a colorless oil. LCMS (m/z: m+1): 259.2.

A mixture of **71** (134 mg, 0.519 mmol), **58** (201 mg, 0.622 mmol), HATU (394 mg, 1.04 mmol) and DIEA (335 mg, 2.59 mmol) in DMF (2.5 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC to afford the crude product which was rinsed with $MeOH/H_2O$ (3/1) to give 3-((4-(4-

fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-morpholinophenyl)benzamide (82 mg, 28%) as a slightly yellow solid.

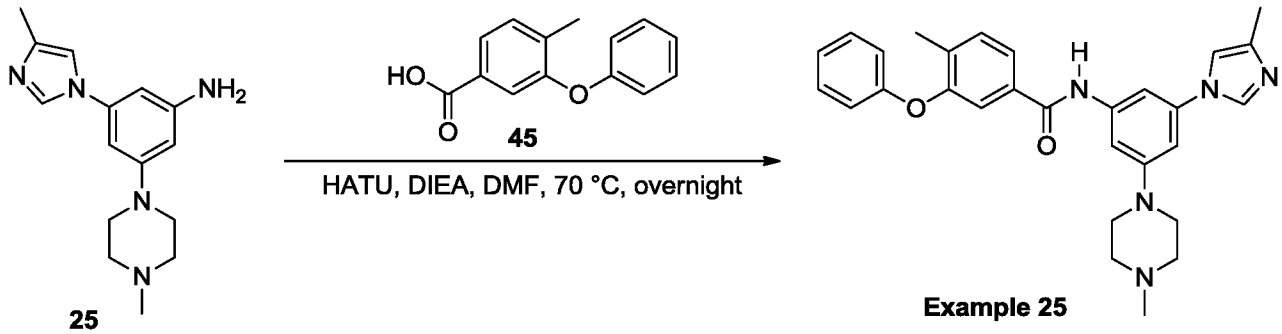
Example 24. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide.



25 **Example 24**

A mixture of **25** (200 mg, 0.74 mmol), 4-methylbenzoic acid (151 mg, 1.11 mmol), HATU (562 mg, 1.48 mmol) and DIEA (478 mg, 3.7 mmol) in DMF (4 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide (64 mg, 22%) as a white solid.

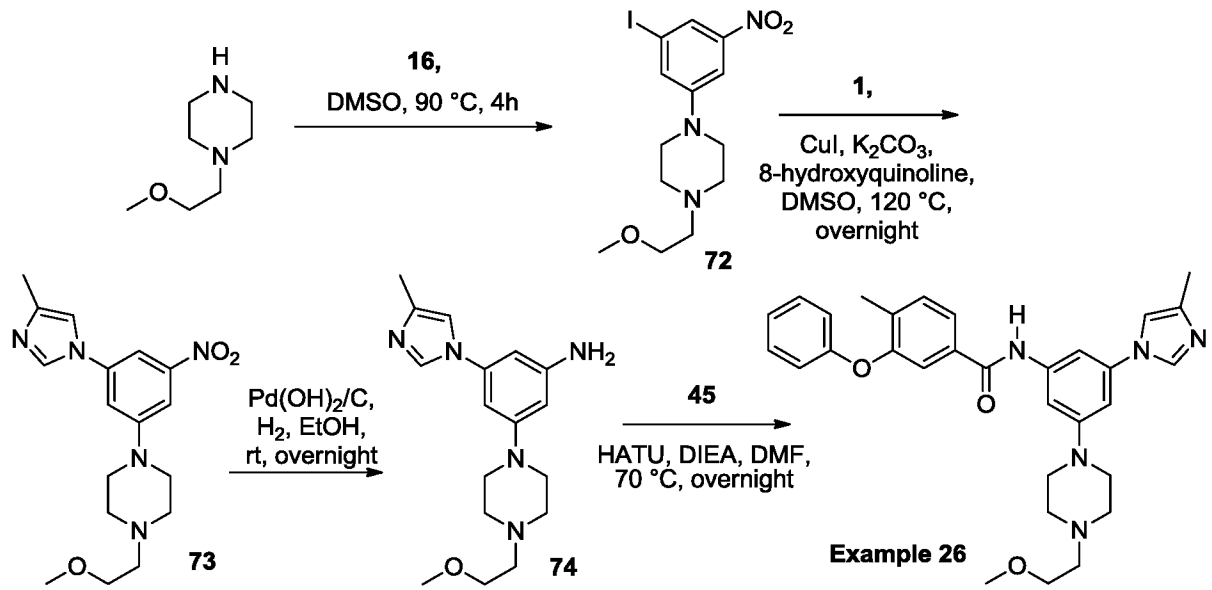
Example 25. Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)-3-phenoxybenzamide.



25 **Example 25**

A mixture of **25** (119 mg, 0.44 mmol), **45** (100 mg, 0.44 mmol), HATU (333 mg, 0.88 mmol) and DIEA (283 mg, 2.19 mmol) in DMF (2 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC to give 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)-3-phenoxybenzamide (22 mg, 10%) as a white solid.

Example 26. Synthesis of N-(3-(4-(2-methoxyethyl)piperazin-1-yl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



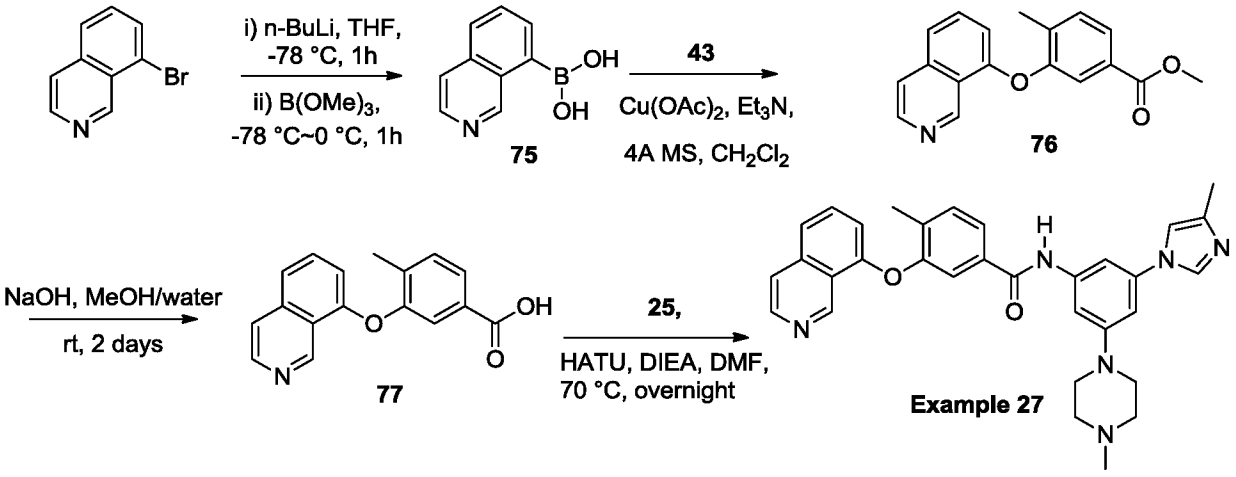
A solution of **16** (200 mg, 0.75 mmol) and 1-(2-methoxyethyl)piperazine (324 mg, 2.25 mmol) in DMSO (2 mL) was heated at 90 °C for 4 hours before poured into water with stirring. The mixture was stood at room temperature overnight. The precipitate was filtered and washed with water. The cake was collected and dried to give **72** (278 mg, 95%) as a yellow solid. A suspension of this material (278 mg, 0.711 mmol), **1** (175 mg, 2.13 mmol), K_2CO_3 (196 mg, 1.42 mmol), CuI (41 mg, 0.213 mmol) and 8-hydroxyquinoline (21 mg, 0.142 mmol) in DMSO (2.5 mL) was heated at 120 °C overnight under nitrogen. After cooling, water was added and the mixture was extracted with CH_2Cl_2/MeOH twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **73** (208 mg, 85%) as a yellow solid. LCMS (m/z: m+1): 346.2.

A mixture of **73** (200 mg, 0.56 mmol) and $Pd(OH)_2/C$ (100 mg) in EtOH (10 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **74** (183 mg, 100%) as a slightly yellow solid which was used in next step without purification. LCMS (m/z: m+1): 316.3.

A mixture of **74** (90 mg, 0.286 mmol), **45** (85 mg, 0.371 mmol), HATU (217 mg, 0.571 mmol) and DIEA (184 mg, 1.43 mmol) in DMF (1.5 mL) was heated at 70 °C

overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC to give **Example 26** (15 mg, 10%) as a slightly yellow solid.

Example 27. Synthesis of 3-(isoquinolin-8-yloxy)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide.



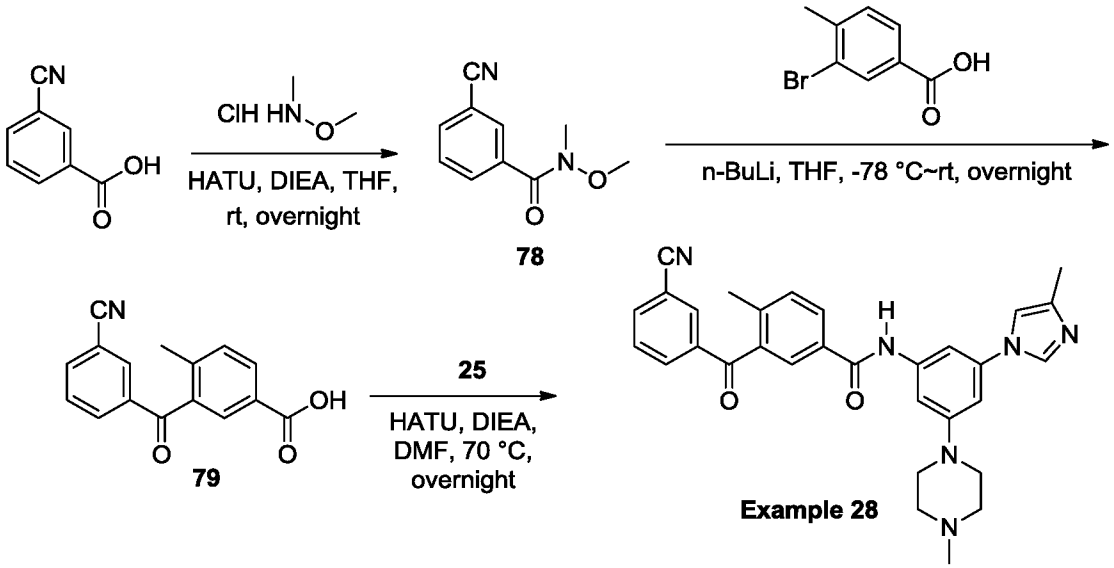
To a solution of 8-bromoisoquinoline (2.0 g, 9.6 mmol) in THF (40 mL) was added dropwise n-BuLi (2.5 M, 4.2 mL, 10.6 mmol) at -78 °C under nitrogen. After 1 hour, $B(OMe)_3$ (2.0 g, 19.2 mmol) was added to the reaction and the mixture was warmed to 0 °C for 1 hour. The reaction was quenched by aqueous $NaHCO_3$ and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **75** (680 mg, 41%) as a slightly yellow solid. LCMS (m/z: m+1): 174.1.

A mixture of **75** (680 mg, 3.93 mmol), **43** (1306 mg, 7.86 mmol), $Cu(OAc)_2$ (2142 mg, 11.8 mmol), Et_3N (2387 mg, 23.6 mmol) and 4A MS (5.0 g) in CH_2Cl_2 (50 mL) was stirred at room temperature under air for 3 days. The reaction was filtered and washed with CH_2Cl_2. The filtrate was concentrated and purified by silica gel column chromatography (CH_2Cl_2/MeOH) and then silica gel prep-TLC (petroleum ether/EtOAc) to give **76** (230 mg, 20%) as a slightly yellow solid. LCMS (m/z: m+1): 294.2.

To a solution of this material (230 mg, 0.784 mmol) in MeOH/H_2O (3/0.5 mL) was added NaOH (63 mg, 1.57 mmol). The reaction was stirred at room temperature for 2 days. Water (3 mL) was added to the reaction and then acidified by 1M HCl. The resulting solution was concentrated under reduced pressure to give **77** as a slightly

yellow solid that was used in next step without further purification. LCMS (m/z: m+1): 280.1. A mixture of this material (218 mg, 0.784 mmol theoretical amount from previous step), **32** (255 mg, 0.941 mmol), HATU (596 mg, 1.57 mmol) and DIEA (607 mg, 4.70 mmol) in DMF (3 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC to give 3-(isoquinolin-8-yloxy)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide (113 mg, 27% over two steps) as a yellow solid.

Example 28. Synthesis of 3-(3-cyanobenzoyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide.



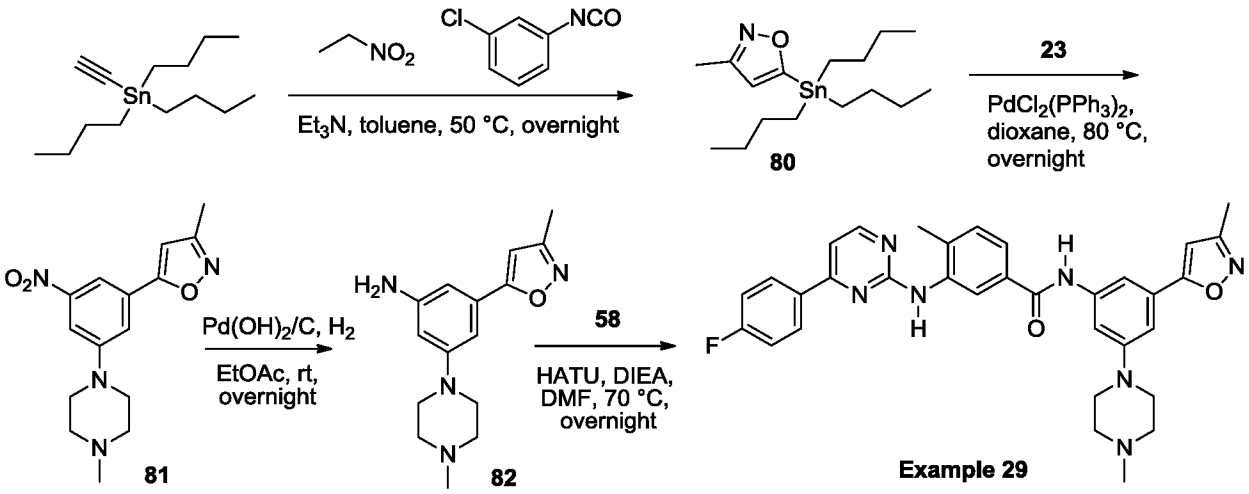
A mixture of 3-cyanobenzoic acid (5.0 g, 34 mmol), N,O-dimethylhydroxylamine hydrochloride (5.0 g, 51 mmol), HATU (19.4 g, 51 mmol) and DIEA (17.5 g, 136 mmol) in THF (80 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **86** (6.9 g, 100%) as a colorless oil. LCMS (m/z: m+1): 191.2.

To a solution of 3-bromo-4-methylbenzoic acid (565 mg, 2.63 mmol) in THF (20 mL) was added dropwise n-BuLi (2.5 M, 2.31 mL, 5.78 mmol) at -78 °C under nitrogen. After 1 hour, a THF solution of **78** (500 mg, 2.63 mmol) was added one portion. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by water and acidified with 1M HCl. The mixture was extracted with EtOAc

twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **79** (500 mg, 72%) as an off-white solid. LCMS (m/z: m+1): 266.1.

A mixture of **79** (100 mg, 0.377 mmol), **25** (123 mg, 0.452 mmol), HATU (287 mg, 0.754 mmol) and DIEA (243 mg, 1.88 mmol) in DMF (1.5 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC to give 3-(3-cyanobenzoyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide (35 mg, 18%) as a slightly yellow solid.

Example 29. Synthesis of 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(3-methylisoxazol-5-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide.



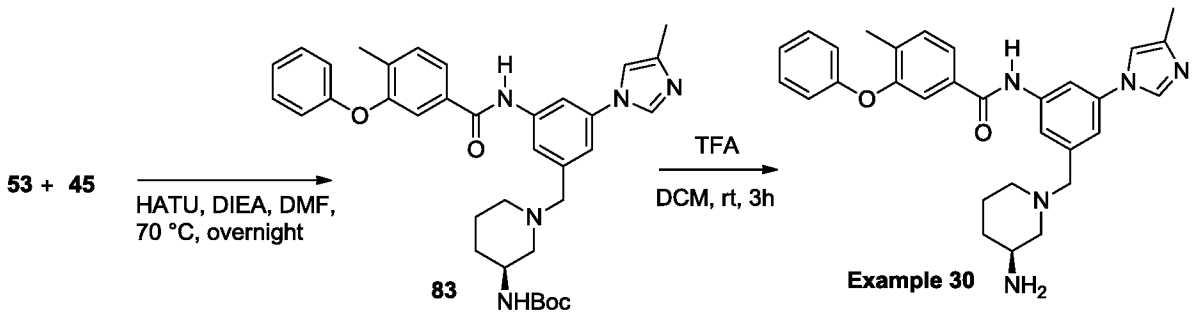
To a solution of nitroethane (300 mg, 4.0 mmol) in toluene (12 mL) was added 1-chloro-3-isocyanatobenzene (1226 mg, 8.0 mmol). The mixture was stirred at 50 °C for 10 min before Et_3N (20 mg, 0.2 mmol) and tributylethynylstannane (1195 mg, 3.8 mmol) were added. The mixture was stirred at 50 °C overnight. Water was added to the reaction mixture and the suspension was filtered. The filtrate was extracted with toluene twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give **80** (960 mg, 68%) as a slightly yellow oil. LCMS (m/z: m+1): 371.2, 372.2, 374.1.

A mixture of **80** (960 mg, 2.58 mmol), **23** (896 mg, 2.58 mmol) and $PdCl_2(PPh_3)_2$ (130 mg) in dioxane (10 mL) was heated at 80 °C overnight under nitrogen. The reaction mixture was concentrated and the residue was purified by silica gel column

chromatography to give **81** (310 mg, 40%) as a yellow solid. LCMS (m/z: m+1): 303.1. ^{1}H NMR (400 MHz, $CDCl_3$): □ 7.94 (t, J=1 Hz, 1H); 7.74 (m, 1H); 7.65 (d, J=1 Hz); 6.49 (s, 1H); 3.38 (m, 4H); 2.61 (m, 4H); 2.39 (s, 3H); 2.38 (s, 3H).

A mixture of **81** (100 mg, 0.33 mmol) and $Pd(OH)_2/C$ (50 mg) in EtOAc (10 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give **82** (90 mg, 100%) as a slightly yellow oil that was used in next step without purification. LCMS (m/z: m+1): 273.2. A mixture of this material (90 mg, 0.330 mmol), **58** (128 mg, 0.397 mmol), HATU (251 mg, 0.661 mmol) and DIEA (213 mg, 1.65 mmol) in DMF (2 mL) was heated at 70 °C overnight. After cooling, the reaction was directly purified by reverse prep-HPLC and silica gel prep-TLC and reverse prep-HPLC once more to give 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(3-methylisoxazol-5-yl)-5-(4-methylpiperazin-1-yl)phenyl)benzamide (23 mg, 12%) as an off-white solid and at the same time a by-product, 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)benzamide resulting from an incomplete Stille coupling between **80** and **23**.

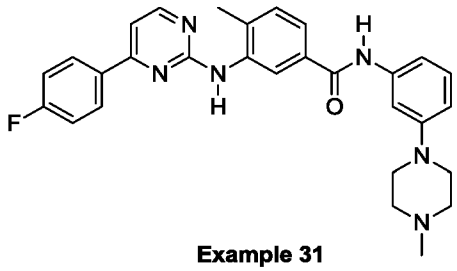
Example 30. Synthesis of (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



A mixture of **53** (150 mg, 0.39 mmol), **45** (107 mg, 0.47 mmol), HATU (296 mg, 0.78 mmol) and DIEA (251 mg, 0.95 mmol) in DMF (2 mL) was heated at 70 °C overnight. Alternatively, the reaction was performed in the same solvent at room temperature. After cooling, the reaction was directly purified by reverse prep-HPLC and then silica gel prep-TLC to give **83** (65 mg, 28%) as a slightly yellow solid. To a solution of **83** (65 mg, 0.109 mmol) in CH_2Cl_2 (3 mL) was added TFA (1.5 mL) and the reaction was stirred at room temperature for 3 hours before concentrated under reduced

pressure. The residue was treated with water, basified with 0.5 N NaOH and extracted with CH_2Cl_2/MeOH (15/1) 3 times. The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by silica gel prep-TLC to give (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide (50 mg, 93%) as a white solid.

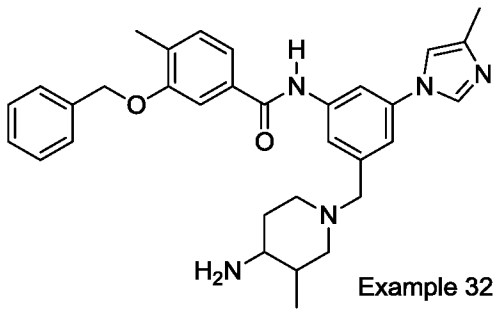
Example 31. 3-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)-4-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)benzamide.



Example 31

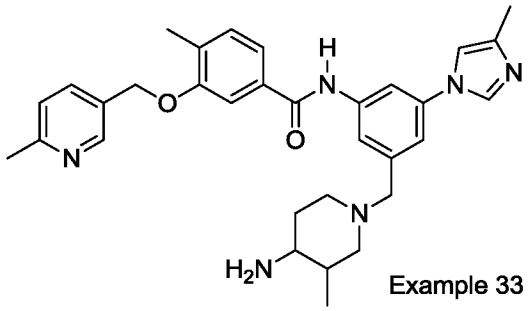
This material was isolated as a by-product from the coupling between **80** and **23** and subsequent processing through the reduction and coupling steps described for Example 29.

Example 32. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-(benzyloxy)-4-methylbenzamide.



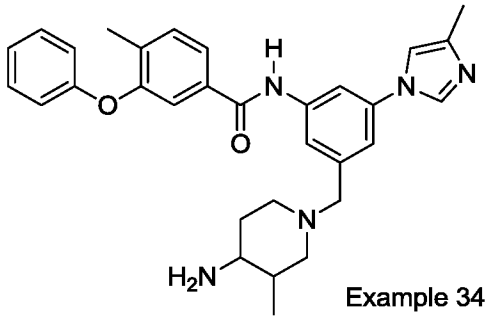
Example 32

Example 33. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((6-methylpyridin-3-yl)methoxy)benzamide.



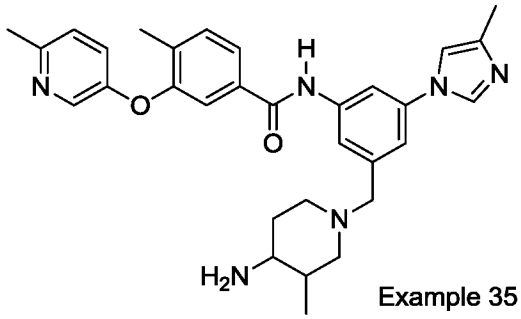
Example 33

Example 34. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



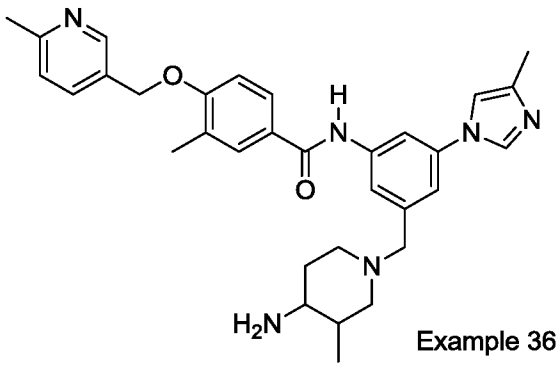
Example 34

Example 35. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((6-methylpyridin-3-yl)oxy)benzamide.



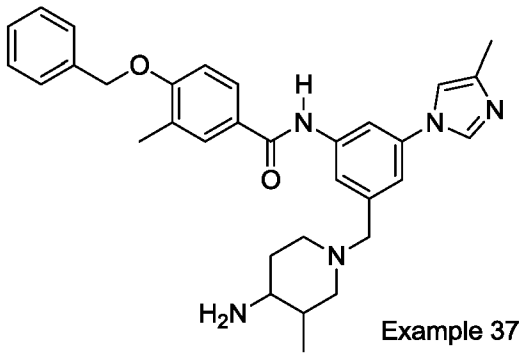
Example 35

Example 36. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-methyl-4-((6-methylpyridin-3-yl)methoxy)benzamide.



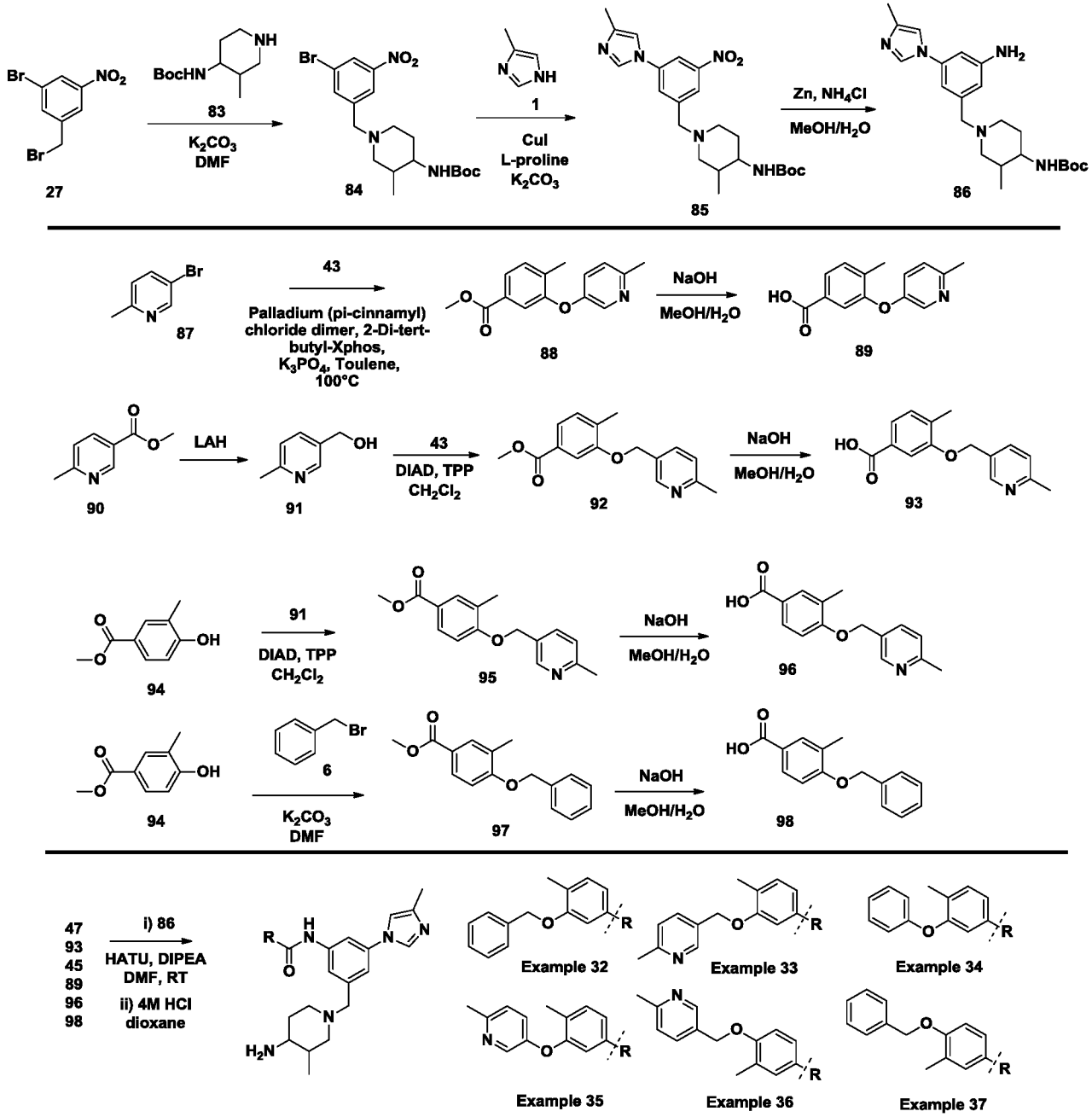
Example 36

Example 37. N-(3-((4-amino-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-(benzyloxy)-3-methylbenzamide.



Example 37

Examples 32-37 were prepared using the following general schematic.



Intermediate **84** was prepared from **27** and **83** in similar manner as described for Example 19. To a solution of **84** (1.0 eq) in DMSO was added K_2CO_3 (2.5 eq), **1** (3.5 eq), CuI (0.8 eq) and L-proline (0.5 eq) under N_2. The resulting reaction mass was heated at 120°C for 16h. After completion of reaction (TLC monitoring), the reaction mass was diluted with water and extracted with EtOAc (3 times). The combined organics were washed with ice-cold water and brine respectively. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via flash chromatography, eluting with 5% MeOH in DCM to

get desired product **85** (1.0 g, 68%) as an off white solid. To a solution of **85** (1.0 eq) in MeOH: H_2O (2:1) was added zinc powder (2.5 eq) and NH_4Cl (3.0 eq). The resulting reaction mass was heated at 90°C for 3h. After completion of reaction, the mixture was filtered through Celite, washed with 10% MeOH in DCM (2 times). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via flash chromatography, elution with 8% MeOH in DCM to yield **86** (0.9 g, 96%) as a brown solid.

To a solution of **43** (1.0 g, 6.02 mmol) in toluene (15 mL) was added **87**(1.5 g, 9.03 mmol), K_3PO_4 (2.5 g, 12.04 mmol), bis[cinnamyl palladium(II) chloride] (0.25 g, 0.48 mmol) and 2-di-tert-butyl Xphos (0.61 g, 1.44 mmol) under nitrogen degassing. The resulting reaction mass was heated at 100°C for 16h. After completion of reaction (TLC monitoring), the mixture was diluted with water (100 mL) and extracted with EtOAc (3 times). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via Combiflash ® chromatography, eluting with 20% EtOAc in hexanes to yield **88** (0.7 g, 45%) as a light yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.48 (s, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.11 (s, 2H), 3.85 (s, 3H), 2.54 (s, 3H) and 2.32 (s, 3H). LC-MS: 258.36 (M+H). To an ice-cold solution of **88** (1.0 eq) in methanol was added aqueous NaOH (3.0 eq). The resulting mixture was stirred at RT for 3-4h. After completion of reaction the mixture was concentrated under reduced pressure, the crude was diluted with water and washed with EtOAc (2 times) for removal of organic impurities. The aqueous part was acidified with 2M-HCl (adjust pH ~4-5), to yield **89** as a solid white precipitate, which was filtered and dried under vacuum. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 8.88 (s, 1H), 8.55 (s, 1H), 7.76-7.77 (m, 1H), 7.54 (s, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 5.17 (s, 2H), 2.47 (s, 3H) and 2.22 (s, 3H). LC-MS: 258.14 (M+H).

To a solution of **90** (5.0 g, 3.31 mmol) in THF was cooled to -78°C, followed by addition of LAH solution (2M in THF, 4.13 mL, 8.27 mmol) slowly. The resulting mixture was stirred at -78°C for 1h. After completion of reaction (TLC monitoring), water (4.0 mL) and 15% NaOH solution (4 mL) were added slowly. The resulting reaction mixture was filtered through Celite and washed with EtOAc (2 times). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure to yield

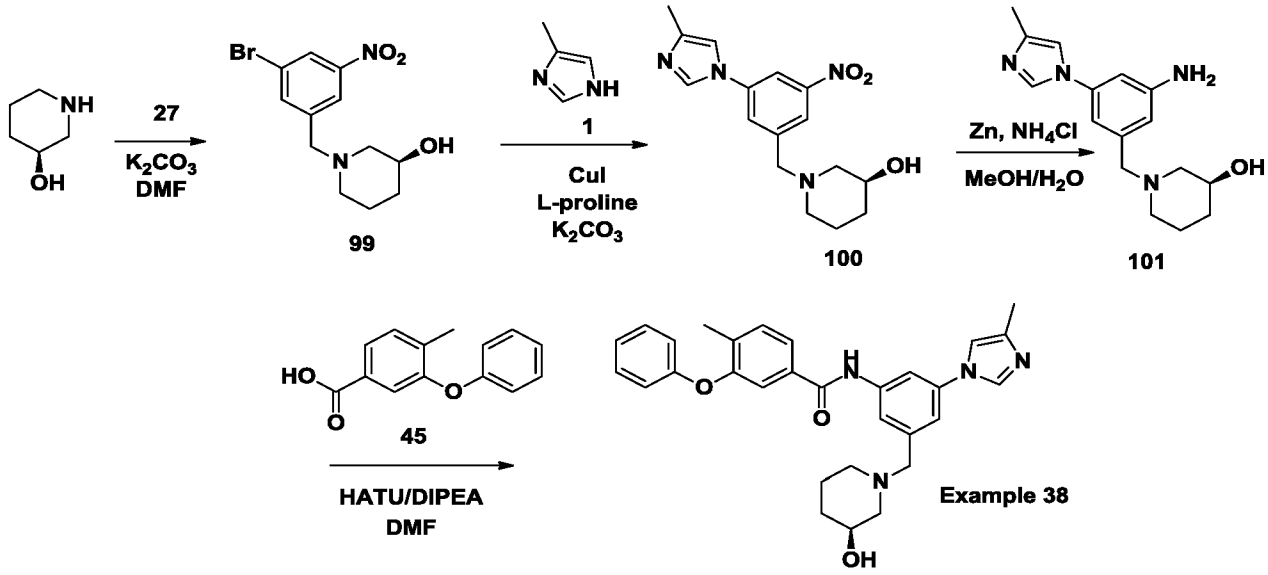
91 (3.5 g, 87%) as a light yellowish liquid. ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.36 (s, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.18 (d, J=8.0 Hz, 1H), 5.21 (t, J= 5.6 Hz, 1H), 4.46 (d, J=5.6 Hz, 2H) and 2.45 (s, 3H). LC-MS: 124.06 (M-H). To an ice-cold solution of **43** (1.0 eq) and **91** (1.5 eq) in DCM was added DIAD (3.0 eq) and TPP (3.0 eq). The mixture was stirred at RT for 16h. After completion of reaction, the mixture was diluted with water and extracted with DCM (3 times). The combined organics was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified over silica gel column chromatography, eluting with 10% EtOAc in hexanes to yield **92** (1.3 g, 31%) as a light yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.64-7.68 (m, 2H), 7.46-7.47 (m, 1H), 7.14-7.18 (m, 2H), 5.10 (s, 2H), 3.85 (s, 3H), 2.58 (s, 3H) and 2.34 (s, 3H). MS: 272.16 (M+H). This material was then converted to **93** using the same conditions as described for **89**. Analtyical data for **93**: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 8.88 (s, 1H), 8.55 (s, 1H), 7.76-7.77 (m, 1H), 7.54 (s, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 5.17 (s, 2H), 2.47 (s, 3H) and 2.22 (s, 3H). LC-MS: 258.14 (M+H).

Likewise, intermediate **96** was prepared from **94** in two steps following similar experimental conditions as described for **92** and **93** (TPP/DIAD followed by NaOH saponification in MeOH/H_2O). Analytical data for intermediate **95**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.85-7.88 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.07 (s, 2H), 3.87 (s, 3H), 2.56 (s, 3H) and 2.26 (s, 3H). LC-MS: 272.10 (M+H). Analytical data for **96:** ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 8.55 (s, 1H), 7.75-7.78 (m, 3H), 7.28 (d, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 5.28 (s, 2H), 2.47 (s, 3H) and 2.19 (s, 3H). LC-MS: 258.11 (M+H).

Likewise, intermediate **98** was prepared from **94** in two steps following similar experimental conditions as described for the preparation of **47**. Analytical data for intermediate **98**: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.51 (br s, 1H), 7.75-7.77 (m, 2H), 7.46-7.48 (m, 2H), 7.38-7.42 (m, 2H), 7.33-7.35 (m, 1H), 7.08 (d, *J*=8.0 Hz, 1H), 5.20 (s, 2H) and 2.22 (s, 3H). LC-MS: 241.05 (M-H).

The synthesis of Examples 32-37 were conducted via the methods described for Example 30 (two steps: HATU/DIPEA/DMF coupling, performed at room temperature or 70°C overnight) followed by acid-based cleavage (HCl/dioxane or TFA/DCM). For analytical data see Table 1.

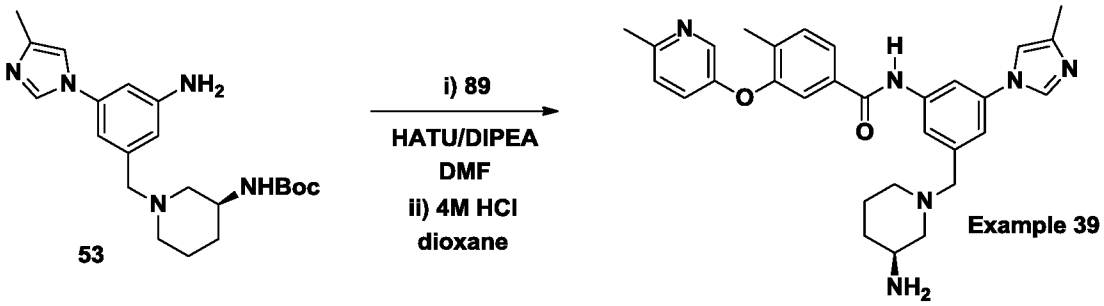
Example 38. Synthesis of (S)-N-(3-((3-hydroxypiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



99 was prepared from (S)-3-hydroxypiperidine and **27** using the same method as described for Example 19. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 4.62 (d, *J* = 4.8 Hz, 1H), 3.61-3.64 (m, 2H), 3.48-3.54 (m, 1H), 2.49-2.66 (m, 6H) and 1.90-1.95 (m, 2H). LC-MS: 315.01 (M+H). **99** was then converted to **100** using the same procedure as described for intermediate **85**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.32-8.34 (m, 2H), 8.07 (s, 1H), 8.01 (s, 1H), 7.64 (s, 1H), 4.61 (d, *J* = 4.0 Hz, 1H), 3.65-3.68 (m, 2H), 3.58-3.62 (m, 1H), 2.63-2.66 (m, 2H), 2.17 (s, 3H), 1.90-1.97 (m, 2H), 1.77-1.82 (m, 2H) and 1.43-1.46 (m, 2H). MS: 317.13 (M+H). **100** was then reduced to **101** using the same procedure as described for **86**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.79 (s, 1H), 7.26 (s, 1H), 6.55-6.59 (m, 2H), 6.49 (s, 1H), 5.35 (br s, 2H), 4.57 (d, *J* = 4.0 Hz, 1H), 3.43-3.45 (m, 1H), 2.78-2.80 (m, 1H), 2.63-2.65 (m, 1H), 2.15 (s, 3H), 1.80-1.83 (m, 3H), 1.58-1.64 (m, 3H) and 1.40-1.45 (m, 2H). LC-MS: 288.31 (M+H).

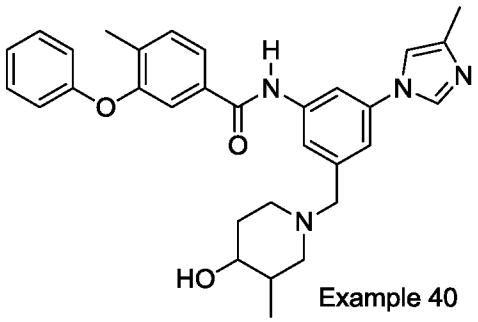
101 and **45** were then coupled in the same manner as described for Example 30. Analytical data for the product, (S)-N-(3-((3-hydroxypiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide, is summarized in Table 1.

Example 39. Synthesis of (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((6-methylpyridin-3-yl)oxy)benzamide.

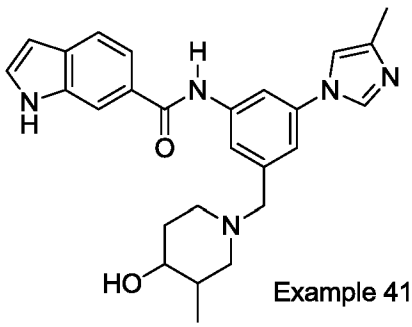


53 and **89** were coupled using the same method as described for Examples 32-37. The intermediate was then deprotected using 4M HCL in dioxane according to the same method as described for Examples 32-37, the final product being purified by preparative HPLC. Analytical data for the product, (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-((6-methylpyridin-3-yl)oxy)benzamide, is summarized in Table 1.

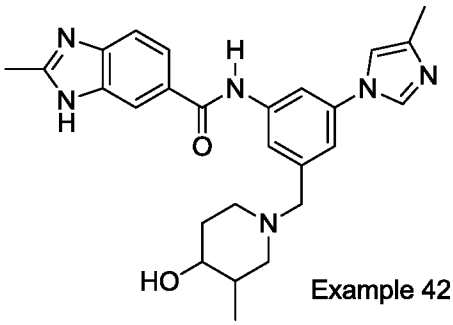
Example 40. N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



Example 41. N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-1H-indole-6-carboxamide.

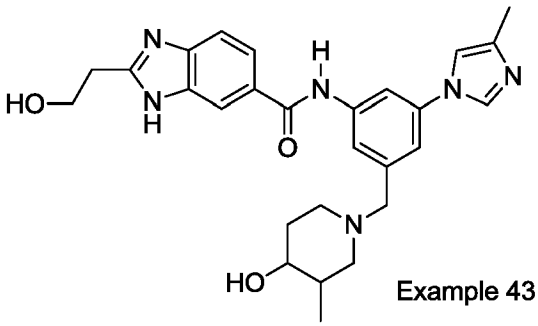


Example 42. N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methyl-1H-benzo[d]imidazole-6-carboxamide.



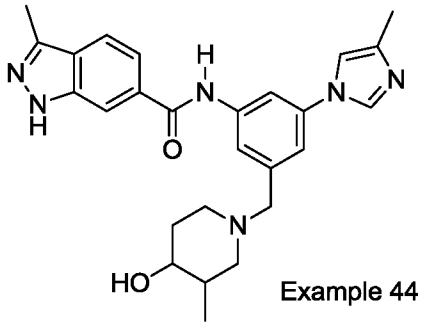
Example 42

Example 43. N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-2-(2-hydroxyethyl)-1H-benzo[d]imidazole-6-carboxamide.



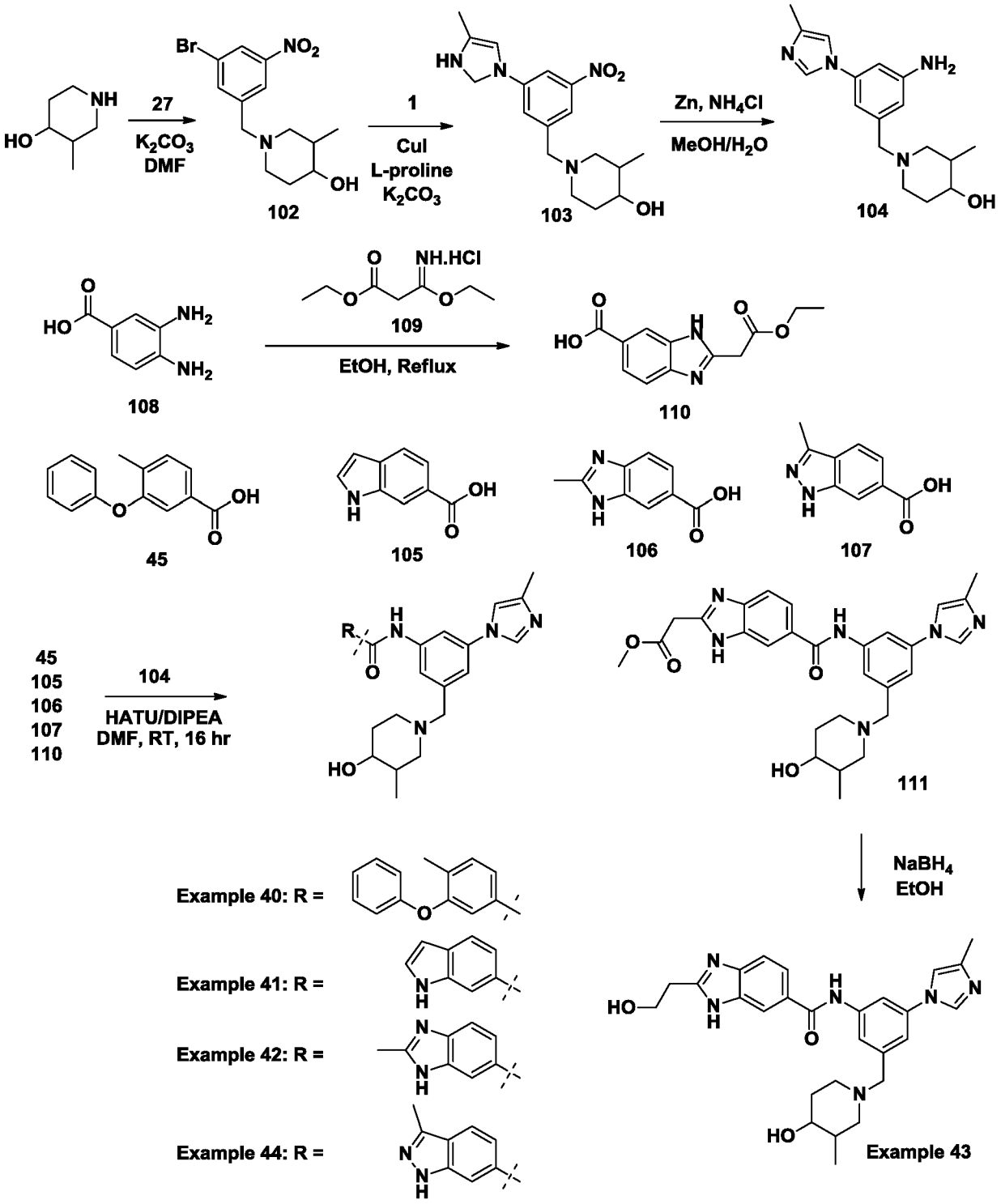
Example 43

Example 44. N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-methyl-1H-indazole-6-carboxamide.



Example 44

Examples 40-44 were prepared according to the following general schematic:



102 was prepared from **27** and 3-methylpiperidin-4-ol according to the method described in Example 19. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 4.53 (d, *J* = 5.2 Hz, 1H), 3.56 (s, 2H), 2.92 (d, *J* = 4.8 Hz, 1H), 2.66-2.68 (m, 1H), 1.90-1.98 (m, 2H), 1.67-1.73 (m, 2H), 1.38-1.45 (m, 2H) and 0.84 (d, *J* = 6.4 Hz, 3H). MS: 329.02 (M+H). This material was converted to **103** by the same method as described for intermediate **85.** ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.31-8.33 (m, 2H),

8.07 (s, 1H), 7.98 (s, 1H), 7.63 (s, 1H), 4.55 (d, *J* = 5.2 Hz, 1H), 3.59 (s, 2H), 2.93-2.95 (m, 1H), 2.70-2.78 (m, 3H), 2.16 (s, 3H), 2.00-2.06 (m, 1H), 1.69-1.74 (m, 1H), 1.41-1.46 (m, 2H) and 0.86 (d, *J* = 6.8 Hz, 3H). LC-MS: 331.13 (M+H). Subsequent reduction of **103** to intermediate **104** by zinc/ammonium chloride was facilitated in similar fashion to that described for intermediate **86**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.80 (s, 1H), 7.21 (s, 1H), 6.53 (s, 2H), 6.49 (s, 1H), 5.32 (s, 2H), 4.51 (d, *J* = 5.2 Hz, 1H), 3.28 (s, 2H), 2.87-2.89 (m, 1H), 2.68-2.74 (m, 1H), 2.13 (s, 3H), 1.91-1.98 (m, 1H), 1.88-1.91 (m, 1H), 1.71-1.74 (m, 1H), 1.52-1.59 (m, 1H), 1.38-1.43 (m, 2H) and 0.83 (d, *J* = 6.8 Hz, 3H). LC-MS: 301.22 (M+H).

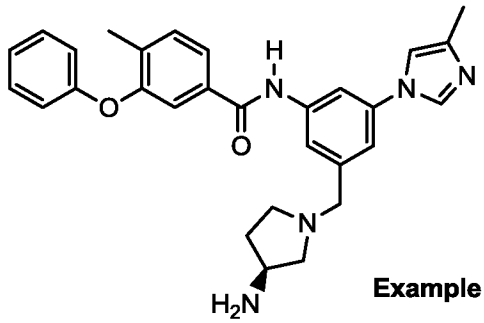
To a solution of 3,4-diaminobenzoic acid **108** (2.5 g, 12.82 mmol) in EtOH (20 mL) was added ethyl 3-ethoxy-3-iminopropanoate hydrochloride **109** (1.55 g, 10.25 mmol). The resulting mixture was heated at 80°C for 16h. After completion of reaction, the mixture was concentrated under reduced pressure. The crude product was dissolved in water and extracted with EtOAc (3 times). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get desired product **110** (0.4 g, 13%) as a light yellowish liquid. The material was used in the next step without further purification. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.69 (br s, 1H), 8.08-8.14 (m, 1H), 7.80-7.81 (m, 1H), 7.53-7.59 (m, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 4.02 (s, 2H) and 1.19 (t, *J*= 6.8 Hz, 3H). MS: 249.07 (M+H).

Couplings of **104** with **45, 105**, **106**, and **107** according to the method described for Example 30, using HATU/DIPEA in DMF at room temperature, followed by HPLC purification, to yield N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide, N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-1H-indole-6-carboxamide, N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methyl-1H-benzo[d]imidazole-6-carboxamide, and N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-methyl-1H-indazole-6-carboxamide respectively. Furthermore, the same coupling conditions were used to combine **104** with intermediate **110**, to give intermediate **111**.

To an ice-cold solution of **111** (160 mg, 0.31 mmol) in ethanol (10 mL) was added $NaBH_4$ (57 mg, 1.51 mmol). The resulting reaction mixture was heated at 80°C for 6h. After completion of reaction, the mixture was cooled to RT and water (2-3 mL) was

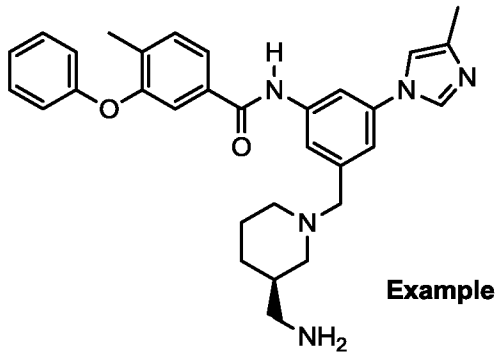
added. The mixture was concentrated was under reduced pressure. The crude residue was purified over prep-HPLC to yield N-(3-((4-hydroxy-3-methylpiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-2-(2-hydroxyethyl)-1H-benzo[d]imidazole-6-carboxamide (30 mg, 20%) as an off-white solid. Analytical data for Examples 40-44 are summarized in Table 1.

Example 45. (S)-N-(3-((3-aminopyrrolidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



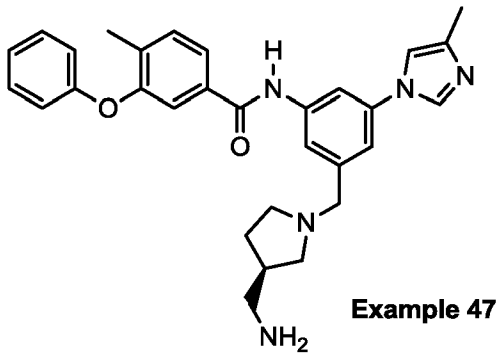
Example 45

Example 46. (R)-N-(3-((3-(aminomethyl)piperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



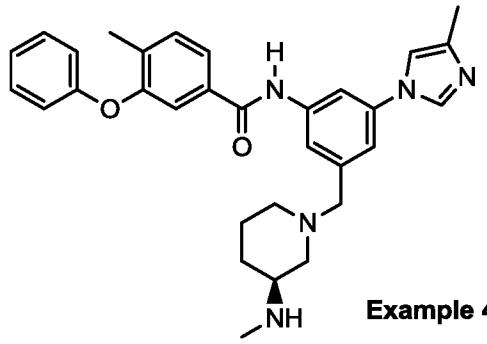
Example 46

Example 47. (R)-N-(3-((3-(aminomethyl)pyrrolidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



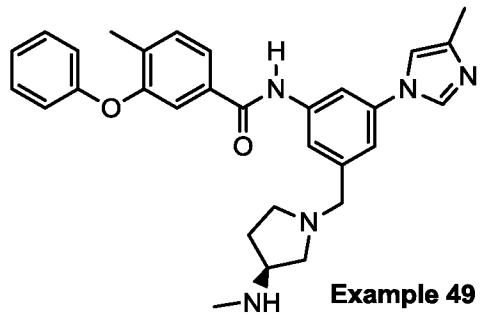
Example 47

Example 48. (S)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-((3-(methylamino)-piperidin-1-yl)methyl)phenyl)-3-phenoxybenzamide.



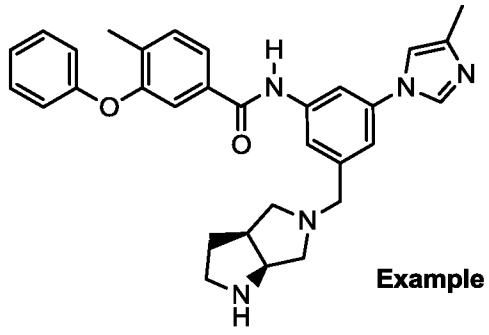
Example 48

Example 49. (S)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-((3-(methylamino)-pyrrolidin-1-yl)methyl)phenyl)-3-phenoxybenzamide.



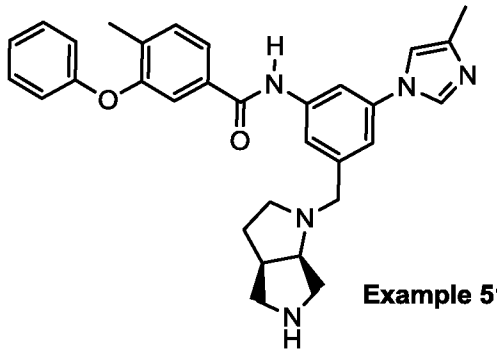
Example 49

Example 50. N-(3-(((3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



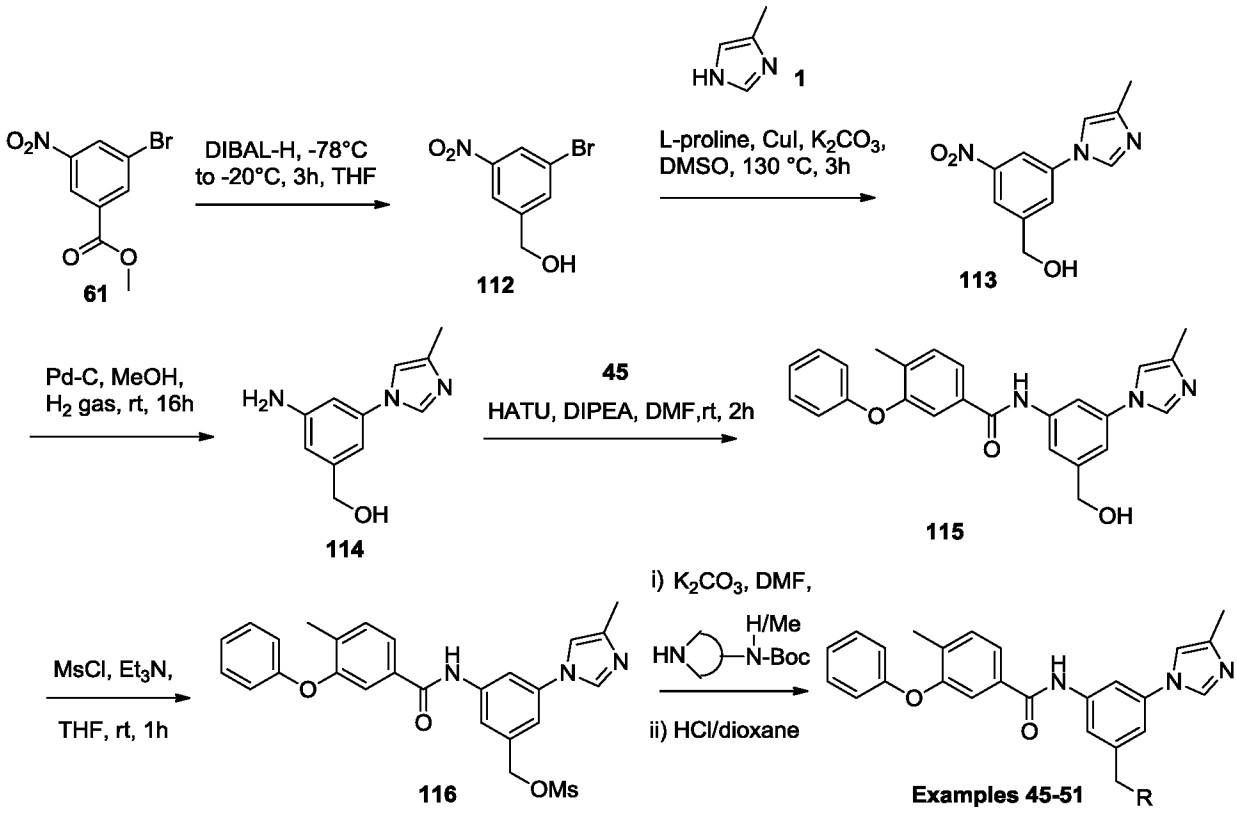
Example 50

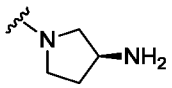
Example 51. N-(3-(((3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.

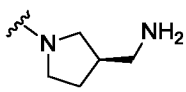


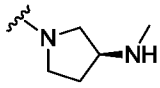
Example 51

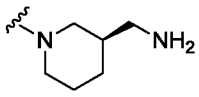
Examples 45-51 were prepared according to the following general schematic:

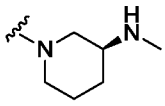


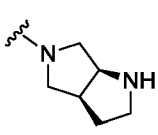
Example 45: R = 

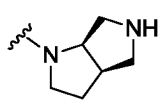
Example 47: R = 

Example 49: R = 

Example 46: R = 

Example 48: R = 

Example 50: R = 

Example 51: R = 

To a solution of **61** (20 g, 76.92 mmol) in dry DCM (400 mL), DIBAL-H (1M in Toluene, 154 mL, 153.8 mmol) was slowly added at -78 °C and the temperature was increased to -20°C. The resulting was stirred for another 3 hr at the same temperature. After consumption of starting material, the reaction was quenched with MeOH (160 mL) followed by water (160 mL) and stirred for 30 min. This white suspension was filtered through a pad of Celite and thoroughly washed with DCM (3 x 200 mL). The mother liquor was concentrated *in vacuo* to give **112 (**17.4 g, 98%) as a yellow solid. ^{1}H-NMR (400 MHz; *DMSO-d*$_6$): δ 8.24 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 5.64 (t, J = 5.7 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H).

To a solution of **112** (14 g, 60.34 mmol) in DMSO (200 mL), **1** (17 g, 211.18 mmol), L-proline (3.47 g, 30.17 mmol), CuI (9.2 g, 48.27 mmol) and K_2CO_3 (20.8 g, 150.8 mmol) were sequentially added at room temperature under N_2. The reaction mixture was heated at 130 °C for 3 h. After cooling at room temperature, water (200 mL) was added and reaction mixture was filtered through a pad of Celite, washed with EtOAc (3 x 50 mL). The filtrate was extracted with ethyl acetate (2 x 100 mL). The organic layer washed with brine solution (200 mL) and dried (Na_2SO_4), concentrated *in vacuo* to give the crude residue. This material was triturated with diethyl ether to give **113 (**8 g, 57%) as a light brown solid. MS (ESI +ve): 234.21. ^{1}H-NMR (400 MHz; DMSO-*d*$_6$): *δ* 8.34 - 8.30 (m, 2H), 8.12 (s, 1H), 8.01 (s, 1H), 7.64 (bs, 1H), 5.64 (t, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 5.6 Hz, 2H), 2.17 (s, 3H).

To a solution of **113** (10.0 g, 42.91 mmol) in MeOH (200 mL), 10 mol% Pd on carbon (50% wet, 2.0 g) was added and the reaction mixture was stirred at room temperature under H_2 (125 psi) for 16 h. After completion, the reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo* to give **114** (8 g, 92%) as a yellow waxy mass. MS (ESI +ve): 204.01. ^{1}H-NMR (400 MHz; DMSO-*d*$_6$): *δ* 7.89 (s, 1H), 7.21 (s, 1H), 6.58 (s, 1H), 6.53 - 6.51 (m, 2H), 5.32 (bs, 2H), 5.12 (bs, 1H), 4.38 (bs, 2H), 2.14 (s, 3H)

To a suspension of 4-methyl-3-phenoxybenzoic acid (**45,** 2.25 g, 9.84 mmol) in dry DMF (50 mL), HATU (4.9 g, 12.79 mmol) and DIPEA (3.18 g, 24.6 mmol) were added at room temperature. After 15 min stirring, **114** (2.0 g, 9.84 mmol) was added and reaction was continued at room temperature for 2 h. After completion, the reaction mixture was diluted with water (200 mL) and the yellow suspension obtained was collected by filtration, washed with water, and dried *in vacuo* to give **115** (2 g, 50 %) as a white solid. MS (ESI +ve): 414.04. ^{1}H-NMR (400 MHz; DMSO-*d*$_6$): *δ* 10.33 (bs, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 - 7.37 (m, 2H), 7.31 (s, 1H), 7.23 (s, 1H),

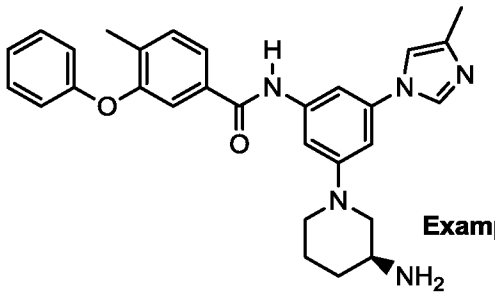
7.15 - 7.11 (m, 1H), 6.97 - 6.95 (m, 2H), 5.35 (t, *J* = 5.4 Hz, 1H), 4.53 (d, *J* = 5.0 Hz, 2H), 2.26 (s, 3H), 2.16 (s, 3H).

To a solution of **115** (500 mg, 1.21 mmol) in THF (50 mL), Et_3N (0.85 mL, 6.05 mmol) was added dropwise. After 15 min stirring, methanesulfonyl chloride (0.19 mL, 2.42 mmol) was slowly added at 0 °C and the reaction was continued at the room temperature for another 1 h. After consumption of starting material, the reaction mixture was diluted with water (70 mL), and extracted with EtOAc (3 x 50 mL). The organic layers were combined and washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **116 (**550 mg, 90%) as a brown gummy liquid. This material was used in the next steps without further purification.

To a solution of the corresponding Boc-protected amines, 0.8 eq) in dry DMF (5 mL/mmol), K_2CO_3 (2.5 eq) was added, stirred for 10 min, whereupon **116** (1 eq) was added at room temperature. The reaction was stirred at room temperature for 16 h. After completion of the reaction, the mixture was poured into water (5 mL/mmol) and the solid suspension was filtered and dried *in vacuo* to give the Boc-protected coupled intermediates, which were used in the next step without further purification.

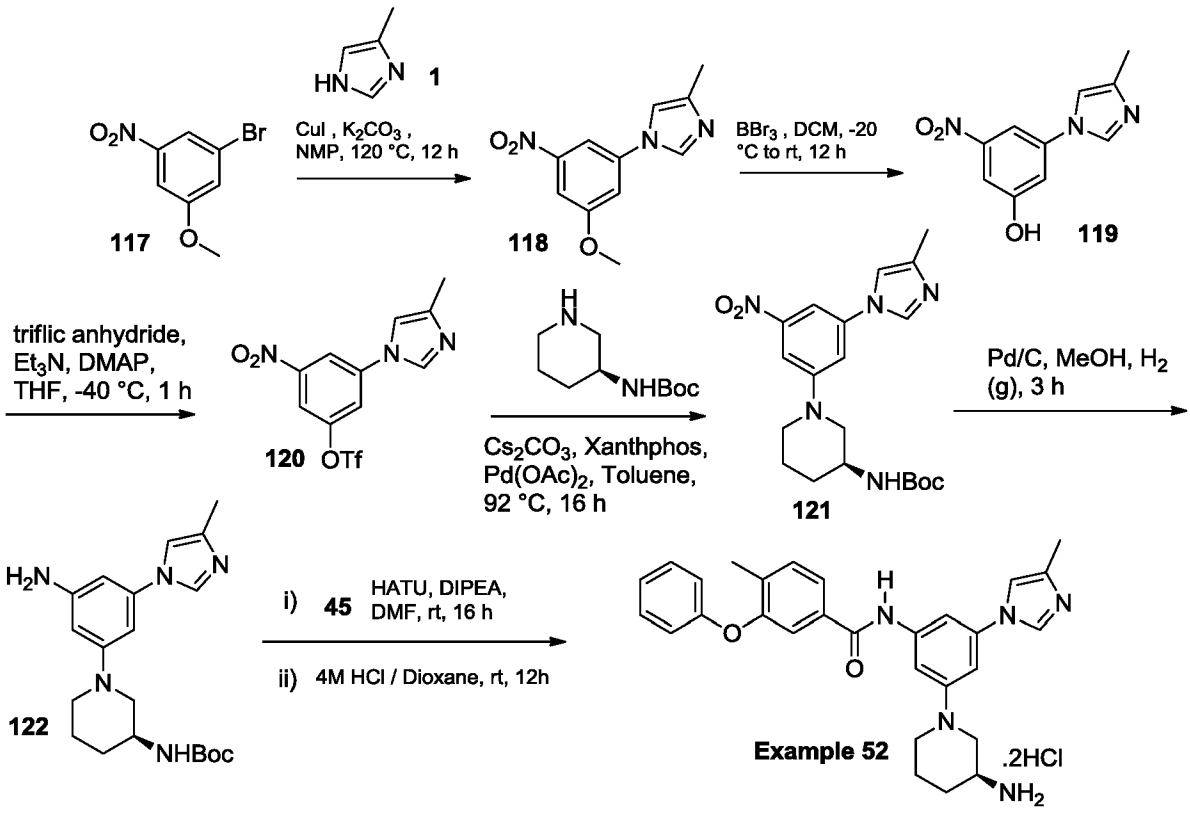
To a solution of the coupled intermediates (1 eq.) in DCM (20 mL), 4 N HCl in dioxane (4.8 mL) was added at 0 °C and stirred at room temperature for 3 h. The reaction mixtures were concentrated *in vacuo* to give **Examples 45-51**, which were purified through prep HPLC or by flash column chromatography. Analytical data for Examples 45-51 are summarized in Table 1.

Example 52. (S)-N-(3-(3-aminopiperidin-1-yl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-phenoxybenzamide.



Example 52

This compound was prepared according to the following schematic:



To a mixture of **117** (5.0 g, 21.6 mmol) and 4-methyl-1H-imidazole (**1**, 2.13 g, 25.9 mmol) under N_2, K_2CO_3 (8.9 g, 64.9 mmol) and CuI (2.05 g, 10.8 mmol) were added. The reaction mixture was stirred at 120 ºC for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature. The residue was partitioned between EtOAc (3 x 200 mL) and water (150 mL) and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was triturated with diethyl ether and pentane to give **118** (2.82g, 56% yield) as an off-white solid. MS (ESI + ve): 234.08. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 8.46 (bs, 1H), 8.04 (s, 1H), 7.59-7.54 (m, 3H), 3.94 (s, 3H), 2.61 (s, 3H).

To a stirred solution of **118** (2.5 g, 10.7 mmol) in DCM (60 mL), BBr_3 (3.0 mL, 32.1 mmol) was added under N_2 at -20 °C. The reaction mixture was stirred at 20 ºC for 16 h. After completion, the reaction mixture was poured into sat. NH_4Cl (200 mL) and extracted with EtOAc (2 x 300 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 3% MeOH in DCM] to give **119** (1.21 g, 67% yield) as white solid. MS (ESI + ve): 220.06. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 10.86 (s, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.43 (s, 3H), 2.15 (s, 1H).

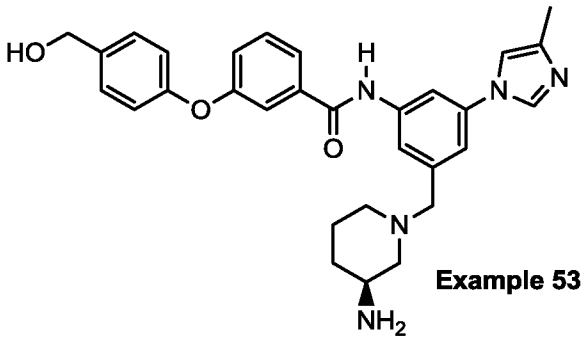
To a stirred solution of **119** (1.2 g, 5.47 mmol) in THF (50 mL), Et_3N (2.2 g, 21.8 mmol), DMAP (0.3 g, 2.73 mmol), and triflic anhydride (1.54 g, 5.47 mmol) were added under N_2 at -40 °C. The reaction mixture was stirred at -40 ºC for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (2 x 300 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 3% MeOH in DCM] to give **120** (1.23 g, 38% yield) as a white solid. MS (ESI - ve): 350.01. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.29 (s, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 7.10 (s, 1H), 7.62 (s, 1H), 2.29 (s, 3H).

To a solution of **120** (1.0 g, 2.9 mmol) in toluene (50 mL), (S)-tert-butylpiperidin-3-yl carbamate, (0.58 g, 2.9 mmol), Xantphos (0.1 g, 0.3 mmol), and $Pd(OAc)_2$ (0.3 g, 0.01 mmol), were added and the reaction mixture was heated to 90 °C for 16 h. After completion, the reaction mixture was concentrated, diluted with water (80 mL) and extracted with EtOAc (2 x 120 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to give **121** (0.19 g, 16% yield) as a yellow solid. MS (ESI + ve): 402.21. 0.15 g (0.37 mmol) of this material was dissolved in MeOH (25 mL), Pd/C (0.3 g) was added, and the reaction mixture was stirred under H_2 at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was filtered through Celite and the filtrate was concentrated to give **122** as a light brown solid. This material was used for the next step without further purification. MS (ESI + ve): 372.5.

To a stirred solution of **45** (0.60 g, 0.2 mmol) in DMF (5 mL), **122** (0.8 g, 0.2 mmol), HATU (0.25 g, 0.65 mmol), and DIPEA (0.18 mL, 1.0 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness, diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 4% MeOH in DCM] to give the Boc-protected amine (0.46 g, 42% yield) as an off white solid. MS (ESI + ve): 582.3. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 10.16 (s, 1H), 8.29 (d, J = 5.3 Hz, 1H), 7.76 (d, J = 5.3 Hz, 1H), 7.53-7.48 (m, 3H), 7.45 (s, 1H), 7.41-7.37 (m, 2H), 7.24 (s, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.3 Hz, 3H), 6.87 (s, 1H), 3.69-3.61 (m, 1H), 3.49-3.41 (m, 1H), 2.71-2.76 (m, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.86-1.82 (m, 1H), 1.77-1.75 (m, 1H), 1.56-1.51

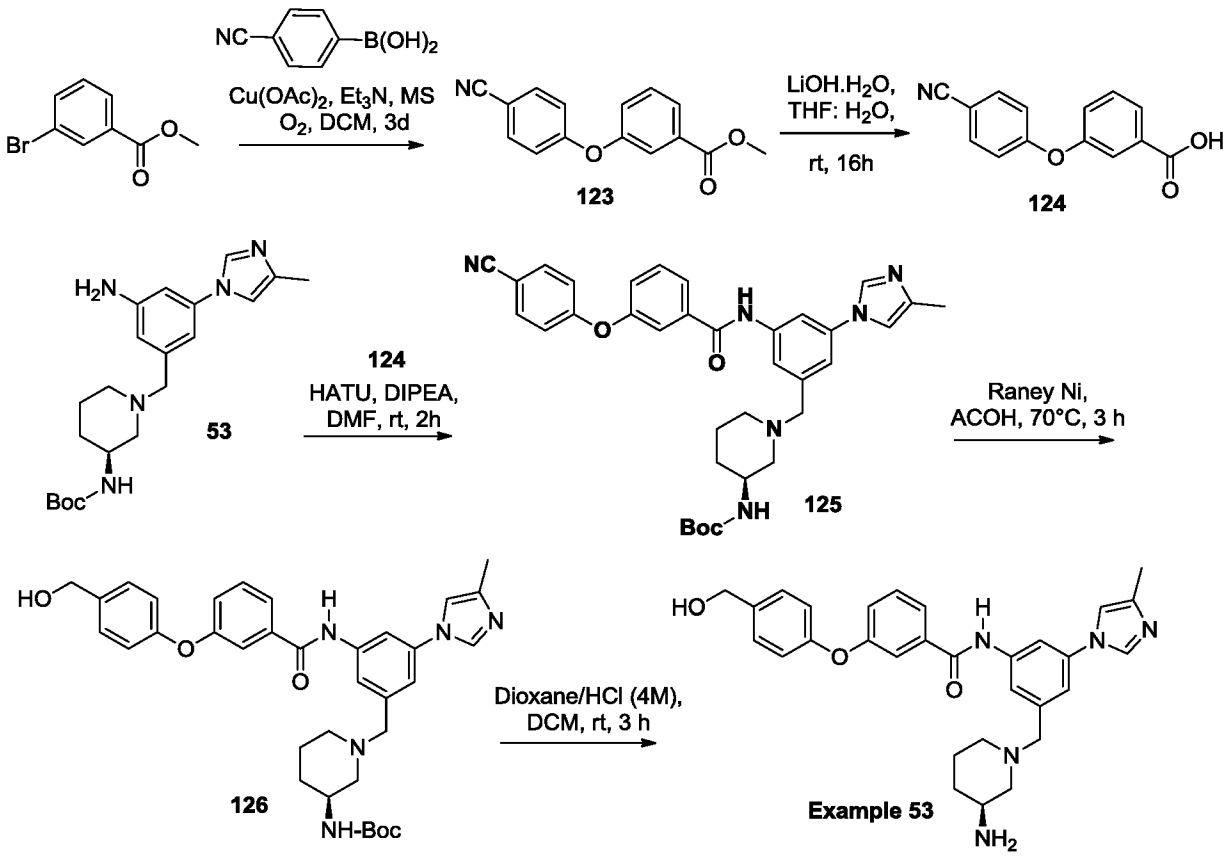
(m, 1H), 1.38 (s, 9H), 1.37-1.32 (m, 2H). To a stirred solution of this material)0.2 g, 0.32 mmol) in 1,4-dioxane (1 mL), 4M HCl in dioxane (4 mL), was added at 0 °C and the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness. The residue was purified by trituration with ethyl acetate and diethyl ether to give **Example 52** (39 mg) as an off white solid. Analytical data for Example 52 are summarized in Table 1.

Example 53. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-(4-(hydroxymethyl)phenoxy)benzamide.



Example 53

This compound was prepared according to the following schematic:



To a solution of methyl 3-bromobenzoate (8 g, 52.58 mmol) in DCM (100 mL), (4-cyanophenyl)boronic acid (9.27 g, 63.10 mmol), Et_3N (22.2 mL, 157.2 mmol) and $Cu(OAc)_2$ (19.1g, 105.1mmol) were added. The reaction mixture was stirred at room temperature under O_2 for 2 days. After consumption of starting material, the reaction mixture was filtered through a pad of Celite, washed with DCM (2 x 50 mL). The filtrate was diluted with water (50 mL) and extracted with DCM (2 X 50 mL). The combined organic layer was dried with anhydrous Na_2SO_4, concentrated *in vacuo* to give **123** (3.0 g, 23%) as a white solid. 2.0 g, 7.90 mmol of **123** in THF : H_2O (8:2, 20 mL) was treated with $LiOH.H_2O$ (1.66 mg, 39.49 mmol) at room temperature. The reaction mixture was stirred for another 16h. After consumption of starting material, the reaction mixture was concentrated *in vacuo* to dryness. The residue was dissolved in water (20 mL) and neutralized by 1M HCl, a white solid was precipitated out, filtered, washed with water, and dried *in vacuo* to give **124 (**1.5 g, 79%) as a white solid. MS (ESI -ve): 238.08. ^{1}H-NMR (400 MHz; *DMSO-d_6*): δ 13.27 (bs, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.61 - 7.56 (m, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 6.7 Hz, 2H).

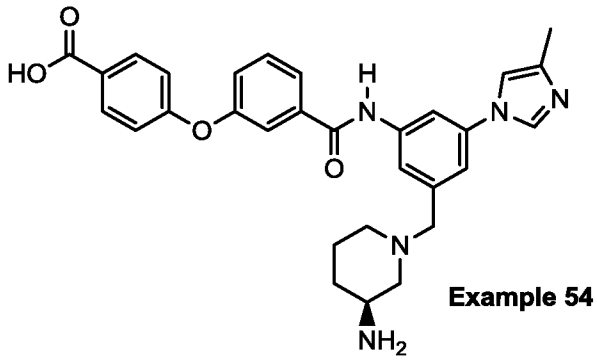
To a suspended solution of **124** (2.25 g, 9.84 mmol) in dry DMF (20 mL), HATU (1.28 g, 3.37 mmol) and DIPEA (1.1 mL, 6.49 mmol) were sequentially added at room temperature. After 15 min stirring, **53** (1.0 g, 2.59 mmol) was added and stirring was continued at the same temperature for 2 h. After completion, the reaction mixture was diluted with water (100 mL), white solid precipitates were obtained, which were collected through filtration, washed with water, and dried *in vacuo* to give **125** (1.0 g, 64%) as a white solid. MS (ESI +ve): 607.20. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 10.44 (bs, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.92 - 7.85 (m, 3H), 7.76 (s, 1H), 7.70 - 7.60 (m, 2H), 7.45 - 7.40 (m, 1H), 7.34 (s, 1H), 7.24 (s, 1H), 7.17 (d, *J* = 4.9 Hz, 2H), 3.52 - 3.36 (m, 3H), 2.82 - 2.72 (m, 1H), 2.70 - 2.60 (m, 1H), 2.16 (s, 3H), 2.00 - 1.90 (m, 1H), 1.82 - 1.76 (m, 1H), 1.72 - 1.60 (m, 3H), 1.45 - 1.40 (m, 1H), 1.34 (s, 9H).

To a solution of **125** (300 mg, 0.49 mmol) in AcOH (50 mL), Raney Ni (50 mg) was added and the reaction mixture was stirred at 70° C under H_2 (125 psi) for 3 h. After completion, the reaction mixture was filtered through a pad of Celite and washed with EtOAc (2 X 20 mL). The filtrate was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried with anhydrous Na_2SO_4, and concentrated *in vacuo* to give **126** (300 mg) as a yellow solid. MS (ESI +ve): 612.23.

This material was dissolved in DCM : MeOH (8:2, 10 mL) and treated with 4M HCl in dioxane (2 mL) at 0 °C and the reaction mixture was stirred at that temperature for 3 h. After

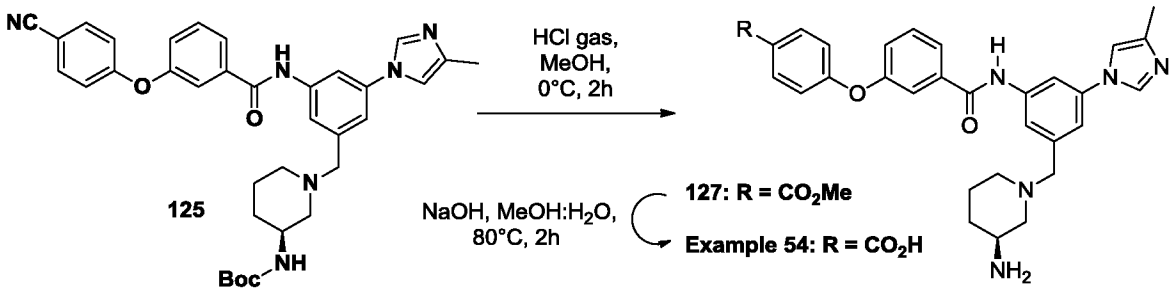
completion, the reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by prep-HPLC (reverse phase, Sunfire C18 (19 x 250 mm) 10µ, gradient 10-25 % ACN in 13 min containing 0.1% TFA in water, RT: 11.77 min, wavelength 214 nm) to give **Example 53** (55 mg, 22%) as a white solid. Analytical data for Example 53 are summarized in Table 1.

Example 54. (S)-4-(3-((3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)phenyl)carbamoyl)phenoxy)benzoic acid.



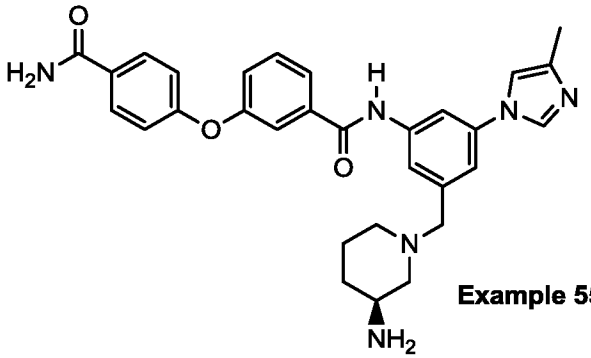
Example 54

This compound was prepared according to the following schematic:



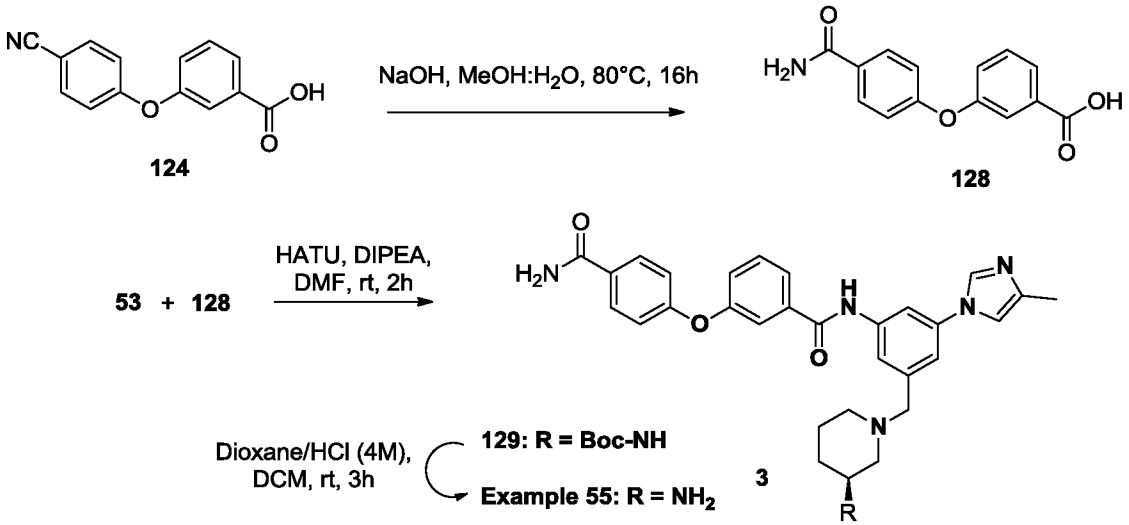
To a solution of **125** (300 mg, 0.49 mmol) in MeOH (20 mL), HCl gas was purged at 0 °C and the reaction mixture was stirred at same temperature for 2h. After consumption of starting material, the reaction mixture was concentrated *in vacuo* to give **127** (300 mg, crude) as a white solid. LCMS: m/z 540.48 (M+1). To a solution of this material in MeOH : H_2O (8:2, 10 mL), NaOH (47 mg, 1.17 mmol) was added at room temperature. The reaction was stirred at 80°C for 2 h. After consumption of starting material, the reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by prep-HPLC (reverse phase, X-Select Hexyl Phenyl (19-250 mm) 15µ, gradient 10-52 % ACN in 11 mins containing 0.1% TFA in water, RT: 10.5 min, wavelength 214 nm) to give **Example 54 (**50 mg, 17%, bis-TFA salt) as a white solid. Analytical data for Example 54 are summarized in Table 1.

Example 55. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-(4-carbamoylphenoxy)benzamide.



Example 55

This compound was prepared according to the following schematic:



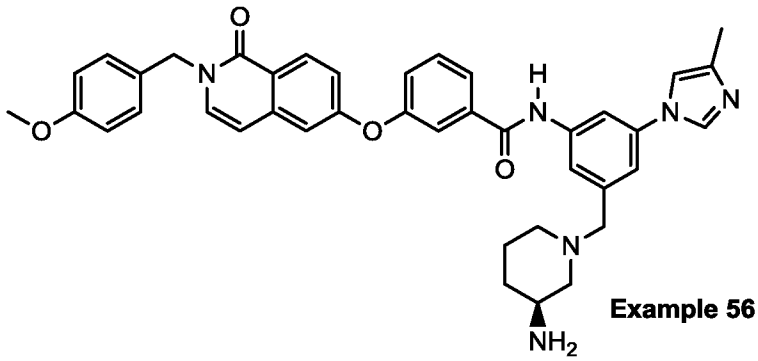
To a solution of **124** (300 mg, 1.25 mmol) in MeOH : H_2O (8:2, 20 mL), NaOH (251 g, 6.27 mmol) was added at room temperature. The reaction was stirred at 80°C for 16h. After consumption of starting material, the reaction mixture was concentrated *in vacuo* to dryness. The residue was dissolved in water (20 mL) and neutralized by 1N aqueous HCl, and a white solid precipitated out. The precipitate was filtered, washed with water, and dried *in vacuo* to give **128** (300 mg) as a white solid. **MS (ESI +ve):** 258.21.

To a suspended solution of **128** (267 mg, 1.04 mmol) in dry DMF (20 mL), HATU (513 mg, 1.35 mmol) and DIPEA (400 mg, 3.11 mmol) were added at room temperature. After 15 min stirring, **53** (400 mg 1.04 mmol) was added and the reaction was continued at the same temperature for 2h. After consumption of starting material, the reaction mixture was diluted

with water (100 mL), and a yellow solid precipitated out which was filtered, washed with water and dried *in vacuo* to give crude **129 (**600 mg). MS (ESI +ve): 625.19.

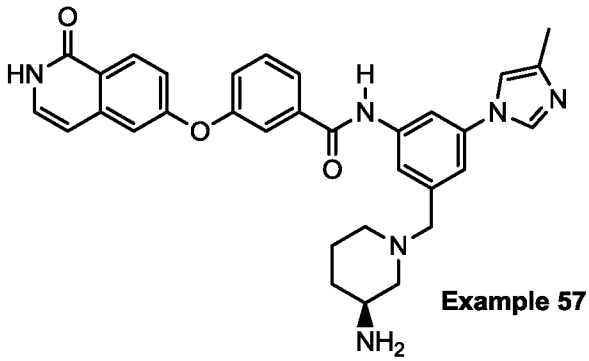
To a solution of **129** (400 mg, 0.64 mmol) in DCM (20 mL), 4M HCl in dioxane (5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 3h. After consumption of starting material, the reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by prep-HPLC (reverse phase, Sunfire C18 (19 x 250 mm) 10µ, gradient 10-25 % ACN in 15 mins containing 0.1% TFA in Water, RT: 10.7 min, wavelength 214 nm) to give **Example 55** (85 mg, 25% as bis-TFA salt) as a white solid. Analytical data for Example 55 are summarized in Table 1.

Example 56. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl-)phenyl)-3-((2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinolin-6-yl)oxy)benzamide.



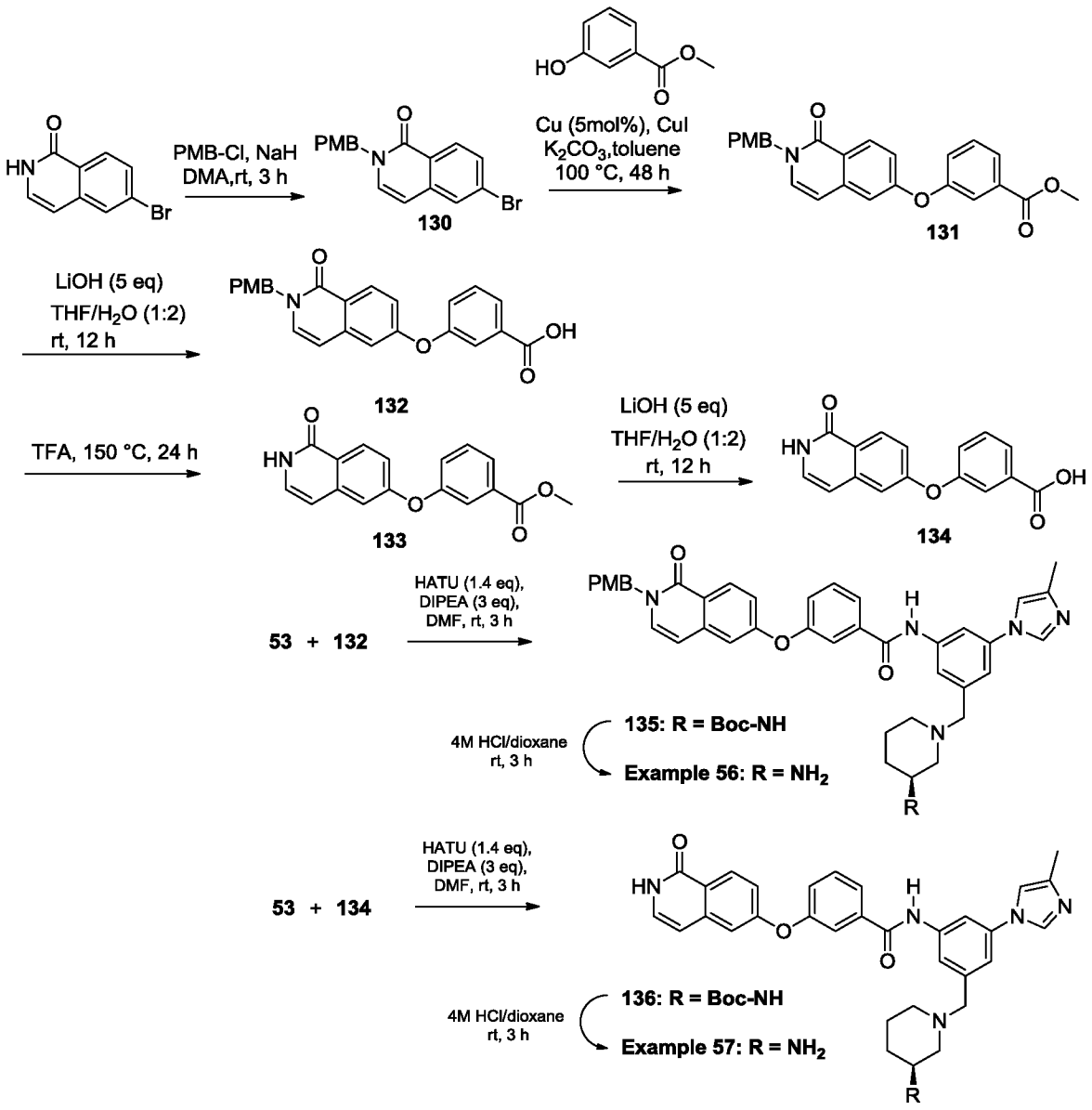
Example 56

Example 57. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-((1-oxo-1,2-dihydroisoquinolin-6-yl)oxy)benzamide.



Example 57

These compounds were prepared according to the following schematic:



To a solution of 6-bromoisoquinolin-1(2H)-one (0.5 g, 2.23 mmol) in DMA (10 mL), was added NaH (60%, 0.13 g, 3.34 mmol) at room temperature and the mixture was stirred for 30 min. 4-methoxybenzyl chloride (0.52 g, 3.34 mmol) was added to the reaction mixture at room temperature. The reaction mixture was stirred at rt for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were separated, dried (Na_2SO_4), filtered and concentrated to afford **130** (1.02 g, crude) as a brown semisolid. This material was used for the next step without further purification. MS (ESI + ve): 344.04. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 8.12 (d, *J*

= 8.56 Hz, 1H), 7.94 (s, 1H), 7.65-7.62 (m, 2H), 7.30-7.26 (m, 2H), 6.91-6.87 (m, 2H), 6.61 (d, *J* = 7.32 Hz, 1H), 5.08 (s, 2H), 3.72 (s, 3H).

To a stirred solution of **130** (1 g, 2.91 mmol) in toluene (20 mL), were added methyl 3-hydroxybenzoate (0.53 g, 3.49 mmol), Cu (0.09 g, 1.45 mmol), CuI (0.27 g, 1.45 mmol) and K_2CO_3 (1.2 g, 8.76 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 48 h. Progress of the reaction was monitored by TLC. The reaction mixture was filtered through a Celite bed and washed with EtOAc. The filtrate was evaporated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 30% EtOAC in hexane] to afford **131** (0.58 g, 47% yield) as an off white solid. This material was used in the next step without further purification. MS (ESI + ve): 416.13.

To a solution of **131** (0.25 g, 0.60 mmol) in THF/H_2O (2:1), was added LiOH (0.12 g, 3.01 mmol) at room temperature. The reaction mixture was stirred at rt for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (80 mL) and washed with EtOAc (2 x 50 mL) to remove non-polar impurities. The aqueous layer was acidified with 1N HCl and extracted with EtOAc (3 x 60 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated to afford **132** (0.22 g, crude) as a white solid. This material was used for the next step without further purification. MS (ESI + ve): 402.09.

To a stirred solution of **132** (0.18 g, 0.46 mmol) in DMF (5 mL), **53** (0.15 g, 0.38 mmol), HATU (0.21 g, 0.54 mmol), and DIPEA (0.2 mL, 1.16 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, diluted with water (50 mL) and extracted with EtOAc (2 x 80 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to afford **135** (0.13 g, 44%) as an off white solid. MS (ESI + ve): 769.32. ^{1}H-NMR (400 MHz; DMSO-d_6): δ10.4 (s, 1H), 8.26 (d, *J* = 8.72 Hz, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.87 (d, *J* = 7.64 Hz, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 8.32 Hz, 2H), 7.54 (d, *J* = 7.28 Hz, 1H), 7.39 (d, *J* = 9.4 Hz, 1H), 7.33 (s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.24-7.21 (m, 2H), 7.15 (s, 1H), 6.88 (d, *J* = 8.32 Hz, 2H), 6.69-6.66 (m, 1H), 6.58 (d, *J* = 7.68 Hz, 1H), 5.08 (s, 2H), 3.71 (s, 3H), 3.53-3.49 (m, 3H), 2.79-2.76 (m, 1H), 2.75-2.71 (m, 2H), 2.16 (s, 3H), 1.93-1.89 (m, 2H),1.84-1.80 (m, 1H), 1.69-1.62 (m, 2H), 1.33 (s, 9H).

To a solution of **135 (**0.05 g, 0.06 mmol) in 1, 4-dioxane (1 mL), 4M HCl in dioxane (0.5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 5 h.

Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness. The residue was triturated with EtOAc and pentane to afford **Example 56** (0.04 g) as a brown solid.

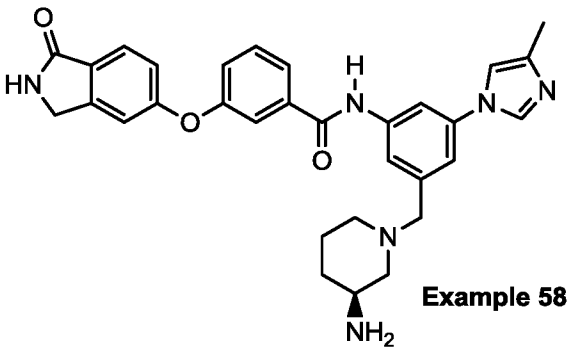
A solution of **131** (0.58 g, 1.39 mmol) in TFA (5 mL) was stirred at 150 °C for 24 h. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with ice cold saturated aq. $NaHCO_3$ solution (80 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layer was dried (Na_2SO_4), concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 30% EtOAC in hexane] to afford **133 (**0.21 g, 50%) as an off white solid. This material was used for the next step without further purification. MS (ESI + ve): 295.96. This material was dissolved in THF/H_2O (2:1) to which was added LiOH (0.15 g, 3.55 mmol) at room temperature. The reaction mixture was stirred at rt for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (80 mL) and washed with EtOAc (2 x 50 mL) to remove non-polar impurities. The aqueous layer was acidified with 1N HCl and extracted with EtOAc (3 x 60 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated to afford **134** (0.19 g, crude) as an off white solid. MS (ESI +ve): 281.92.

To a stirred solution of **134** (0.19 g, 0.67 mmol) in DMF (5 mL), **53** (0.2 g, 0.51 mmol), HATU (0.28 g, 0.75 mmol), and DIPEA (0.26 mL, 1.55 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness, diluted with ice cold water (50 mL) and extracted with EtOAc (2 x 500 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to afford **136** (0.08 g, 23%) as a brown solid. MS (ESI + ve): 649.29. ^{1}H-NMR (400 MHz; DMSO-d_6): δ10.4 (s, 1H), 8.21 (d, J = 8.16 Hz, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.66-7.61 (m, 2H), 7.40 (d, J = 8.44 Hz, 1H), 7.35 (s, 1H), 7.24 (s, 1H), 7.20-7.16 (m, 3H), 6.73 (bs, 1H), 6.49 (d, J = 7.28 Hz, 1H), 3.48 (s, 3H), 2.16 (s, 3H), 2.0-1.98 (m, 1H), 1.88-1.85 (m, 2H) 1.66-1.61 (m, 3H), 1.45-1.43 (m, 2H),1.33 (s, 9H).

To a stirred solution of **136** (0.08 g, 0.12 mmol) in 1, 4-dioxane (2 mL), 4M HCl in dioxane (1 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 5 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to

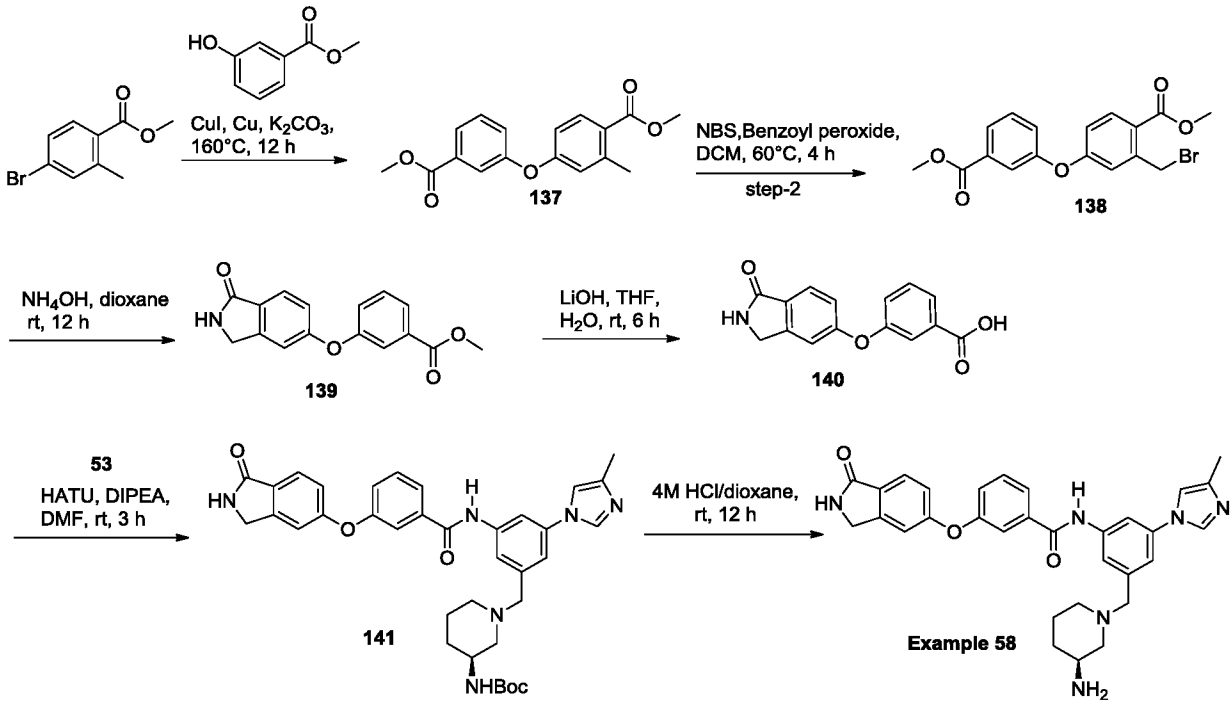
dryness. The residue was triturated with EtOAc and pentane to afford **Example 57** 0.04 g, 23% yield) as a white solid. Analytical data for Examples 56 and 57 are summarized in Table 1.

Example 58. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-((1-oxoisoindolin-5-yl)oxy)benzamide.



Example 58

This compound was prepared according to the following schematic:



To a mixture of methyl 4-bromo-2-methylbenzoate (5.0 g, 22.1 mmol) and methyl 3-hydroxybenzoate (3.36 g, 22.1 mmol) under N_2, K_2CO_3 (15.2 g, 110 mmol), CuI (0.84 g, 4.42 mmol) and Cu powder (0.28 g, 4.42 mmol) were added. The reaction mixture was stirred at 160 °C for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature. The residue was partitioned between EtOAc (2 x 300 mL) and water (120 mL) and the aqueous layer was separated and extracted with EtOAc (100 mL). The

combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 4% ethyl acetate in hexane] to **137** (2.7 g, 41%) as an off white solid. MS (ESI + ve): 300.92. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 7.89 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.53 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H) 2.50 (s, 3H).

To a solution of **137 (**2.5 g, 8.3 mmol) in dry DCM (30 mL), NBS (1.48 g, 8.3 mmol) and benzoyl peroxide (2.5 g, 8.3 mmol) were added and the mixture was heated at 60 °C for 4 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine solution (50 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 5% ethyl acetate in hexane] to give **138** (1.5 g, 48%) as a yellowish semi-solid. MS (ESI + ve): 378.8. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 7.92 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 8.0 (Hz, 1H), 7.28 (s, 1H), 7.04 (d, J = 8.5 Hz, 1H), 5.01 (s, 2H), 3.85 (s, 6H).

To a solution of **138** (0.8 g, 2.11 mmol) in 1,4-dioxane (10 mL), aq. NH_4OH (5 mL) was added at room temperature and the reaction mixture was stirred at room temperature for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, diluted with water (50 mL) and extracted with DCM (2 x 100 mL). The organic layers were washed with brine solution (50 mL) and dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 60% ethyl acetate in hexane] to give **139** (0.51 g, 85%) as an off-white solid. MS (ESI + ve): 283.97. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 8.48 (bs, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.60 (t, J =8.0 Hz, 1H), 7.53 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.13 (d, J = 8.2 Hz, 1H), 4.33 (s, 2H), 3.83 (s, 3H).

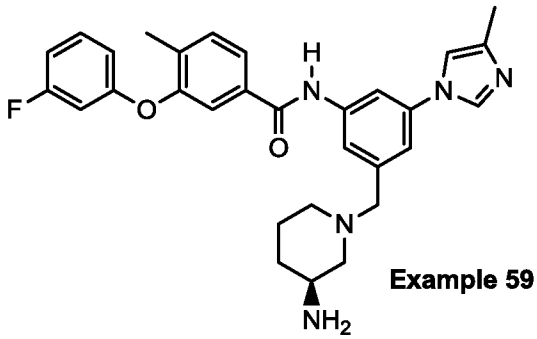
To a solution of **139** (0.5 g, 1.76 mmol) in THF (10 mL), aq. LiOH (0.13 g, 5.3 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, diluted with water (50 mL) and extracted with EtOAc (30 mL). The aqueous layer was acidified with 1N HCl and extracted by DCM (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated to dryness to give **140** (0.36 g, 77%) as an off-white solid. MS (ESI + ve): 270.10. ^{1}H-NMR (400 MHz; DMSO-d_6): δ

13.1 (bs, 1H), 8.47 (bs, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.18 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.33 (s, 2H).

To a stirred solution of **140** (0.2 g, 0.77 mmol) in DMF (20 mL), **53** (0.3 g, 0.77 mmol), HATU (0.88 g, 2.31 mmol), and DIPEA (1 mL, 3.85 mmol), were added and the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 5% MeOH in DCM] to give **141** (0.16 g, 32%) as a yellow solid. MS (ESI + ve): 637.30. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 10.4 (s, 1H), 8.47 (s, 1H), 8.3 (s, 1H), 7.93 (s, 1H), 7.84 (d, *J* = 7.0 Hz, 1H), 7.70-7.60 (m, 4H), 7.36-7.34 (m, 2H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.19 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.72 (bs, 1H), 4.33 (s, 2H), 3.41 (s, 2H), 2.69-2.65 (m, 1H), 2.16 (m, 3H), 1.94-1.90 (m, 2H), 1.68-1.61 (m, 4H), 1.47-1.44 (m, 2H), 1.34 (s, 9H).

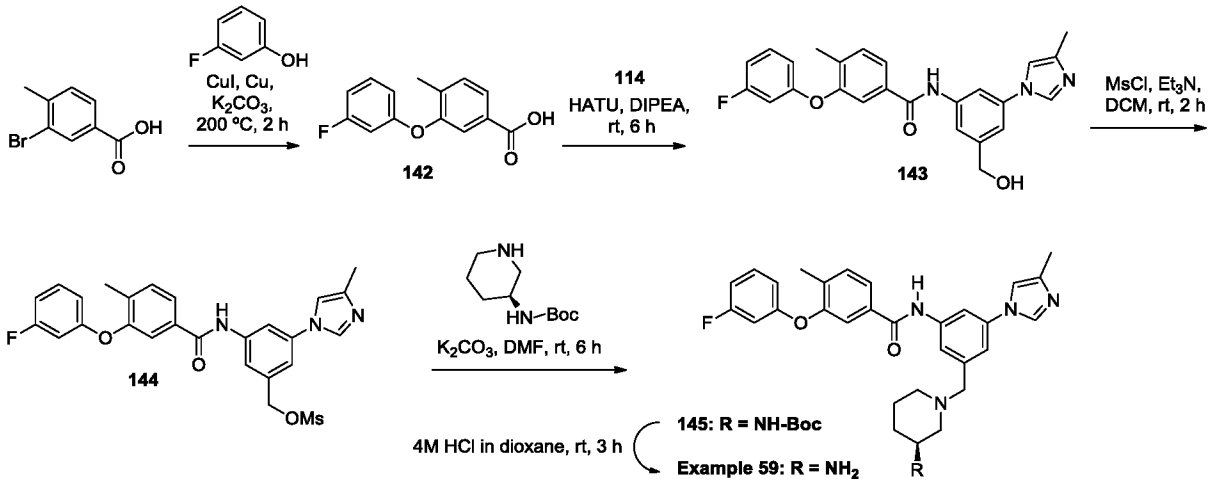
To a stirred solution of **141** (0.15 g, 0.23 mmol) in 1,4-dioxane (5 mL), 4M HCl in dioxane (3 mL), was added at 0 °C and the reaction mixture was stirred at room temperature for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness. The residue was purified by Prep-HPLC using 0.1% TFA as buffer to afford **Example 58**, 0.12 g as bis-TFA salt) as an off-white solid. Analytical data for Example 58 are summarized in Table 1.

Example 59. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-(3-fluorophenoxy)-4-methylbenzamide.



Example 59

This compound was prepared according to the following schematic:



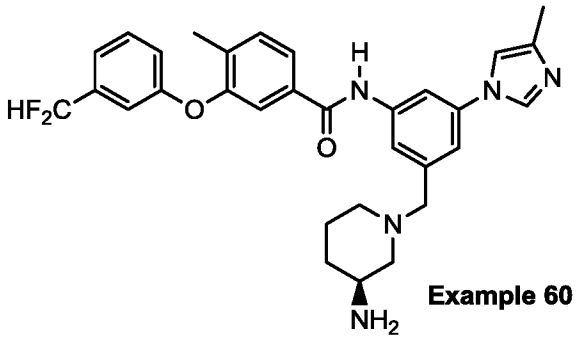
To a mixture of 3-fluorophenol (1, 27.0 g, 242 mmol) and 3-bromo-4-methylbenzoic acid (2, 4 g, 18.6 mmol) under N_2, K_2CO_3 (12.8 g, 93.4 mmol), CuI (1.77 g, 9.34 mmol) and Cu powder (0.58 g, 9.34 mmol) were added. The reaction mixture was stirred at 200 °C for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature. The residue was partitioned between EtOAc (2 x 200 mL) and water (120 mL) and the aqueous layer was separated. The aqueous layer was acidified with 1N HCl and extracted by DCM (2 x 200 mL), the DCM layer dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to give **142** (3.5 g, 77%) as a white solid. MS (ESI - ve): 245.0. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 13.0 (s, 1H), 7.70 (d, J = 6.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.38 (s, 1H), 6.98 (t, J = 6.4 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 2.25 (s, 3H).

To a solution of **142** (1.8 g, 7.3 mmol) in DMF (30 mL), **114** (1.0 g, 4.9 mmol), HATU (5.6 g, 14.7 mmol), and DIPEA (4.5 mL, 24.6 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, diluted with water (80 mL) and extracted with EtOAc (2 x 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 6% MeOH in DCM] to give **143** (0.55 g, 26%) as a yellow solid. MS (ESI + ve): 432.01. ^{1}H-NMR (400 MHz; DMSO-d_6): δ10.3 (s, 1H), 8.04 (s, 1H), 7.88-7.82 (m, 2H), 7.67-7.63 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.18 (s, 1H), 6.98-6.94 (m, 1H), 6.84-6.75 (m, 2H), 5.33 (bs, 1H), 4.54 (d, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.16 (s, 3H).

To a stirred solution of **143** (0.45 g, 1.04 mmol) in DCM (25 mL), Et_3N (0.21 mL, 1.56 mmol) and MsCl (0.12 mL, 1.56 mmol) were added at 0 °C and the reaction mixture was stirred at room temperature for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with ice cold water (20 mL) and extracted with DCM (3 x 30 mL). The organic layer was washed with brine solution (20 mL), dried with anhyd. Na_2SO_4, concentrated *in vacuo* to give **144 (**0.41 g, crude) as a yellow gummy liquid. This material was used in the next step without further purification. MS (ESI + ve): 510.02. Similarly to the procedure described for the coupling of **116** to Boc-protected amines (**Examples 45-51**), (S)-tert-butylpiperidin-3-yl carbamate was combined with **144** in the presence of HATU and DIPEA in DMF to yield **145.**

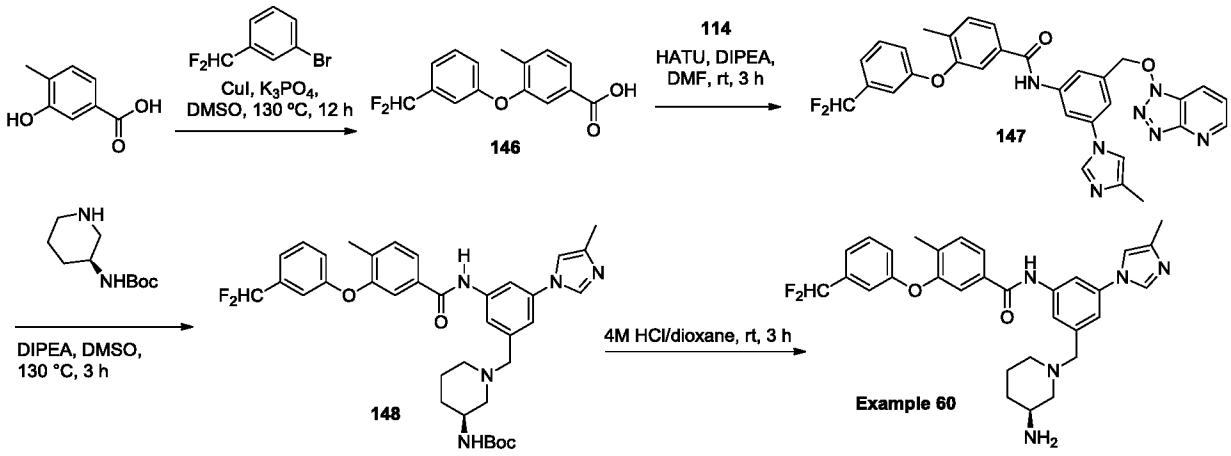
To a stirred solution of **145** (0.2 g, 0.32 mmol) in 1,4-dioxane (5 mL), 4M HCl in dioxane (3 mL), was added at 0 °C and the reaction mixture was stirred at room temperature for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness. The residue was purified by Prep-HPLC using 0.1% TFA as a buffer to yield **Example 59** (0.12 g, bis-TFA salt) as an off white solid. Analytical data for Example 59 are summarized in Table 1.

Example 60. (S)-N-(3-((3-aminopiperidin-1-yl)methyl)-5-(4-methyl-1H-imidazol-1-yl)-phenyl)-3-(3-(difluoromethyl)phenoxy)-4-methylbenzamide



Example 60

This compound was prepared according to the following schematic:



To a stirred solution of 1-bromo-3-(difluoromethyl)benzene (1, 1 g, 4.83 mmol) in DMSO (10 mL), 3-hydroxy-4-methylbenzoic acid (2, 0.95 g, 6.2 mmol), K_3PO_4 (3.07 g, 14.4 mmol) and CuI (0.5 g, 2.4 mmol) were added at room temperature. The reaction mixture was stirred at 130 °C for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt, diluted with water (100 mL) and washed with EtOAc (2 x 50 mL) to remove non-polar impurities. The aqueous layer was acidified with 1N HCl and extracted with EtOAc (3 x 120 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient only DCM] to afford **146** (1.12 g, 83%) as a white solid. MS (ESI - ve): 277.02. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 13.0 (s, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.52-7.49 (m, 2H), 7.30-3.37 (m, 2H), 7.12 (s, 2H), 7.01 (s, 1H), 2.26 (s, 3H).

To a stirred solution of **146** (0.86 g, 3.11 mmol) in DMF (15 mL), **114** (1.0 g, 2.59 mmol), HATU (1.38 g, 3.6 mmol), and DIPEA (1.3 mL, 7.79 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness, diluted with water (80 mL) and extracted with EtOAc (2 x 200 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to afford **147** (0.75 g, 50% yield) as a brown solid. MS (ESI + ve): 582.06. ^{1}H-NMR (400 MHz; DMSO-d_6): δ10.5 (s, 1H), 8.80 (d, *J* = 4.16 Hz, 1H), 8.69 (s, 1H), 8.61 (d, *J* = 8.36 Hz, 1H), 8.17 (s, 1H), 7.90 (s, 1H), 7.84 (d, *J* = 7.76 Hz, 1H), 7.62-7.57 (m, 6H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.16-7.12 (m, 2H), 7.02 (s, 1H), 5.70 (s, 2H), 2.26 (s, 6H).

To a solution of **147** (0.29 g, 1.45 mmol) in DMSO, DIPEA (0.43 g, 3.35 mmol) was added and the reaction mixture was stirred at 130 °C for 3 h. Progress of the reaction was monitored

by TLC. The reaction mixture was concentrated to dryness, diluted with water (50 mL) and extracted with EtOAc (2 x 80 mL). The organic layers were separated, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM] to afford **148** (0.45 g, 62%) as an off-white solid. MS (ESI + ve): 646.37. ^{1}H-NMR (400 MHz; DMSO-d_6): δ10.3 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 6.92 Hz, 1H), 7.61 (s, 2H), 7.55-7.52 (m, 2H), 7.32 (d, *J* = 6.32 Hz, 2H), 7.22 (s, 1H), 7.16-7.11 (m, 2H), 6.69 (d, *J* = 8.36 Hz, 1H), 3.49-3.43 (m, 3H), 2.88 (s, 1H), 2.75 (s, 1H), 2.73 (s, 1H), 2.25 (s, 3H), 2.16 (s, 3H), 1.90 (s, 1H), 1.79 (s, 1H), 1.67-1.63 (m, 2H), 1.46-1.43 (m, 2H), 1.33 (s, 9H).

To a stirred solution of **148** (0.35 g, 0.54 mmol) in 1,4-dioxane (5 mL), 4M HCl in dioxane (3.5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated to dryness. The residue purified by prep HPLC by Prep-HPLC using 0.1% TFA as buffer to afford **Example 60** (0.22 g, 74%, bis-TFA salt) as an off-white solid. Analytical data for Example 60 are summarized in Table 1.

Table 1. Analytical Data for Examples 1-60

Example	LCMS	NMR
1	m/z (M+1) = 530.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H); 9.16 (s, 1H); 8.73 (dd, J=3.6, 1.6 Hz, 1H); 8.59 (d, J= 5.2 Hz, 1H); 8.35 (s, 1H); 8.30 (s, 1H); 8.28 (d*, 1H); 8.20 (d, J=1.2 Hz, 1H); 8.15 (s, 1H); 7.91 (dd, J=9.2, 7.6 Hz, 1H); 7.77 (dd, J=7.6, 1.6 Hz, 1H); 7.71 (m, 2H); 7.51 (dd, J=7.6, 4.4 Hz, 1H); 7.48 (s, 1H); 7.46 (d, J=8.4 Hz, 1H); 2.37 (s, 3H); 2.18 (s, 3H).
2	m/z (M+1) = 530.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H); 9.25 (s, 1H); 8.71 (d, J=1.6 Hz, 1H); 8.70 (d, J=1.6 Hz, 1H); 8.61 (d, J= 5.2 Hz, 1H); 8.32 (dd, J=6.4, 1.6 Hz, 1H); 8.21 (d, J=1.2 Hz, 1H); 8.16 (s, 1H); 8.04 (d, J=1.6 Hz, 1H); 7.77 (dd, J=8, 1.6 Hz, 1H); 7.73 (s, 1H); 7.51 (d, J=5.2 Hz, 1H); 7.49-7.45 (m, 2H); 2.36 (s, 3H); 2.18 (s, 3H).
3	m/z (M+1) = 529.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.71 (s, 1H); 9.07 (s, 1H); 8.92 (br s, H); 8.49 (d, J=5.6 Hz, 1H); 8.46 (s, 1H); 8.37 (s, 1H); 8.19 (s, 1H); 8.12 (d, J= 6.4 Hz, 2H); 7.82 (s, 1H); 7.76 (s*, 1H); 7.75 (m*, 1H); 7.41-7.50 (m*, 4H); 7.40 (d, J= 1.2 Hz, 1H); 2.33 (s, 3H); 2.27 (s, 3H).

4	m/z (M+1) = 453.1	^{1}H NMR (400 MHz, DMSO-d6): δ 10.59 (s, 1H); 9.00 (s, 1H); 8.40 (d, J=4.4 Hz, 2H); 8.30 (s, 1H); 8.20 (d, J=0.8 Hz, 1H); 8.15 (m, 1H); 7.74 (d*, 1H); 7.72 (s*, 1H); 7.49 (s, 1H); 7.41 (d, J=8 Hz, 1H); 6.79 (t, J= 4.8 Hz, 1H); 2.31 (s, 3H); 2.18 (s, 3H).
5	m/z (M+1) = 545.4	^{1}H NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H); 9.03 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.31 (d, J=1.2 Hz, 1H); 8.11 (dd, J= 7.6, 1.6 Hz, 2H); 8.01 (d, J=1.2 Hz, 1H); 7.70 (dd, J=7.6, 1.6 Hz, 1H); 7.39-7.49 (m*, 6H); 7.33 (s, 1H); 6.82 (s, 1H); 3.32 (m, 4H); 2.83 (m, 4H); 2.35 (s, 3H); 2.16 (s, 3H).
6	m/z (M+1) = 559.4	^{1}H NMR (400 MHz, DMSO-d6): δ 10.15 (s, 1H); 9.03 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.32 (d, J=1.2 Hz, 1H); 8.12 (dd, J= 7.6, 1.6 Hz, 2H); 8.02 (d, J=1.2 Hz, 1H); 7.71 (dd, J=7.6, 1.6 Hz, 1H); 7.45-7.50 (m, 4H); 7.39-7.42 (m, 2H); 7.33 (d, J=1.2 Hz, 1H); 6.85 (s, 1H); 3.21 (m, 4H); 2.47 (m, 4H); 2.35 (s, 3H); 2.23 (s, 3H); 2.16 (s, 3H).
7	m/z (M+1) = 573.4	^{1}H NMR (400 MHz, DMSO-d6): δ 10.34 (s, 1H); 9.03 (s, 1H); 8.50 (d, J=5.2 Hz, 1H); 8.35 (d, J=1.2 Hz, 1H); 8.13 (dd, J= 7.6, 1.6 Hz, 2H); 8.01 (d, J=1.2 Hz, 1H); 7.95 (t, J=1.6 Hz, 1H); 7.72 (m*, 1H); 7.71 (m*, 1H); 7.39-7.48 (m, 5H); 7.33 (s, 1H); 7.21 (s, 1H); 3.49 (s, 2H); 2.49 (m*, 2H); 2.33-2.49 (m+s, 9H); 2.17 (s, 6H).
8	m/z (M+1) = 531.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.53 (s, 1H); 9.07 (s, 1H); 8.99 (br s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.34 (d, J=1.2 Hz, 1H); 8.24 (s, 1H); 8.13 (d, J=1.6 Hz, 1H); 8.11 (d, J=2 Hz, 2H); 7.97 (s, 1H); 7.84 (s, 1H); 7.73-7.79 (m, 2H); 7.58 (d, J= 16 Hz, 1H); 7.40-7.49 (m, 5H); 6.64 (d, J=16 Hz, 1H); 2.36 (s, 3H); 2.29 (s, 3H).
9	m/z (M+1) = 533.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.48 (s, 1H); 9.46 (s, 1H); 9.05 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.32 (d, J=1.2 Hz, 1H); 8.18 (s, 1H); 8.12 (dd, J=7.6, 1.6 Hz, 1H); 7.93 (s, 1H); 7.71 (d, J=1.2Hz, 1H); 7.67 (s, 1H); 7.38-7.49 (m, 6H); 2.91 (t, J=7.4 Hz, 2H); 2.64 (t, J=7.4 Hz, 2H); 2.36 (s, 3H); 2.35 (s, 3H).
10	m/z (M+1) = 568.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.33 (s, 1H); 9.05 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.32 (s, 1H); 8.12 (d, J=2.4 Hz, 2H); 8.06 (s, 1H); 7.88 (s, 1H); 7.72 (d, J=7.6 Hz, 1H); 7.66 (s, 1H); 7.39-7.49 (m, 5H); 7.36 (s, 1H); 7.30 (s, 1H); 6.94 (s, 2H); 3.33 (m*, 2H); 3.06 (m, 2H); 2.35 (s, 3H), 2.17 (s, 3H).
11	m/z (M+1) = 517.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.27 (s, 1H); 9.03 (s, 1H); 8.50 (d, J=5.2 Hz, 1H); 8.33 (s, 1H); 8.12 (dd, J=7.6, 1.2 Hz, 2H); 8.03 (s, 1H); 7.85 (s, 1H); 7.72 (dd, J=7.6, 1.2 Hz, 1H); 7.58 (s, 1H); 7.39-7.50 (m, 5H); 7.34 (s, 1H); 7.17 (s, 1H); 2.62 (t, J= 6 Hz, 2H); 2.35 (s, 3H); 2.16 (s, 3H); 1.61 (m, 2H); 1.33 (m, 2H); 0.91 (t, J=7.6 Hz, 3H).
12	m/z (M+1) = 360.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.61 (s, 1H); 8.30 (s, 1H); 8.21 (d, J=1.2 Hz, 1H); 8.16 (s, 1H); 7.93 (d, J=8 Hz, 2H); 7.73 (s, 1H); 7.49 (s, 1H); 7.38 (d, J=8 Hz, 2H); 2.41 (s, 3H); 2.18 (s, 3H).

13	m/z (M+1) = 452.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H); 8.26 (s, 1H); 8.19 (s, 1H); 8.10 (s, 1H); 7.80 (d, J=7.2 Hz, 1H); 7.72 (s, 1H); 7.54 (s+d*, J=8 Hz, 2H); 7.43 (s, 1H); 7.39 (t, J=4 Hz, 2H); 7.14 (t, J=7.6 Hz, 1H); 6.96 (d, J=8 Hz, 1H); 2.28 (s, 3H); 2.17 (s, 3H).
14	m/z (M+1) = 466.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.59 (s, 1H); 8.30 (s, 1H); 8.21 (d, J=1.2 Hz, 1H); 8.14 (s, 1H); 7.73 (s, 1H); 7.63 (s, 1H); 7.57 (dd, J=5.6, 1.2 Hz, 1H); 7.35-7.52 (m, 8H); 5.24 (s, 2H); 2.29 (s, 3H); 2.18 (s, 3H).
15	m/z (M+1) = 565.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.97 (br s, 1H); 8.96 (s, 1H); 8.47 (d, J=4.8 Hz, 1H); 8.43 (s, 1H); 8.16 (dd, J= 7.2, 1.2 Hz, 2H); 8.05 (s, 1H); 7.38-7.52 (m*, 8H); 7.27 (s, 2H); 2.31 (s, 3H); 2.08 (s, 3H).
16	m/z (M+1) = 510.12	^{1}H NMR (400 MHz, DMSO-d6): δ 10.56 (s, 1H); 10.36 (s, 1H); 9.16 (s, 1H); 8.76 (s, 1H); 8.28 (d, J= 12 Hz, 2H); 8.19 (d, J=10.8 Hz, 2H); 8.09 (s, 1H); 7.73 (s, 2H); 7.49 (s, 1H); 7.42 (br s, 2H); 2.29 (s, 3H); 2.18 (s, 3H); 2.07 (s, 3H).
17	m/z (M+1) = 450.09	^{1}H NMR (400 MHz, DMSO-d6): δ 10.46 (s, 1H); 9.27 (s, 1H); 9.13 (s, 1H); 8.68 (d, J= 4 Hz, 1H); 8.54 (d, J=5.2 Hz, 1H); 8.44 (d, J=8 Hz, 1H); 8.29 (s, 1H); 8.24 (s, 1H); 8.07 (d, J=8 Hz, 1H); 7.74 (d, J=8 Hz, 1H); 7.59 (t, J=8 Hz, 1H); 7.50 (m, 4H); 7.57 (m*, 1H); 2.35 (s, 3H).
18	m/z (M+1) = 556.1	^{1}H NMR (400 MHz, DMSO-d6): δ 9.34 (d, J= 3 Hz, 1H); 8.73 (d, J= 4 Hz, 1H); 8.69 (d, J=5.2 Hz, 1H); 8.57 (s, 1H); 8.49 (d, J= 8 Hz, 1H); 8.31 (s, 1H); 8.12 (s, 2H); 7.93 (s, 1H); 7.85 (s, 1H); 7.65 (d, J=5.2 Hz, 1H); 7.60 (s*, 1H); 7.57 (m*, 1H); 2.55 (s, 3H); 2.18 (s, 3H).
19	m/z (M+1) = 591.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.34 (s, 1H); 9.06 (s, 1H); 8.49 (d, J=5.6 Hz, 1H); 8.31 (d, J=1.2 Hz, 1H); 8.19 (dd, J= 5.6, 2 Hz, 2H); 8.02 (d, J=1.2 Hz, 1H); 7.95 (s, 1H); 7.73 (dd, J=7.6, 1.2 Hz, 1H); 7.68 (s, 1H); 7.40 (m, 2H); 7.31 (m, 3H); 7.22 (s, 1H); 3.48 (AB pattern, J=13.6, 13.2 Hz, 2H); 2.67 (m, 2H); 2.33 (s, 3H); 2.17 (s, 3H); 1.99 (m, 1H); 1.73 (m, 2H); 1.61 (m, 1H); 1.45 (m, 1H); 1.02 (m, 1H).
20	m/z (M+1) = 620.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.37 (s, 1H); 9.04 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.32 (s, 1H); 8.18 (dd, J= 3.6, 3.2 Hz, 2H); 8.00 (d, J=1.2 Hz, 1H); 7.95 (s, 1H); 7.73 (dd*, J=7.2, 1.6 Hz, 1H); 7.71 (s*, 1H); 7.40 (m, 2H); 7.32 (m, 3H); 7.23 (s, 1H); 3.89 (d, J=13 Hz, 1H); 3.48 (d, J=13 Hz, 1H); 3.12 (m, 1H); 2.91 (m, 1H); 2.67 (t, J=2 Hz, 1H); 2.42 (s*, 3H); 2.41 (m*, 1H); 2.33 (s, 3H); 1.76 (m, 2H); 1.36-1.46 (m*, 4H).
21	m/z (M+1) = 619.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.33 (s, 1H); 9.05 (s, 1H); 8.49 (d, J=4.8 Hz, 1H); 8.32 (s, 1H); 8.19 (dd, J= 5.6, 1.6 Hz, 2H); 8.05 (d, J=1.2 Hz, 1H); 7.96 (s, 1H); 7.73 (dd, J=7.6, 1.6 Hz, 1H); 7.64 (s, 1H); 7.28-7.42 (m, 7H); 7.07 (s, 1H); 3.83 (d, J=13.6 Hz, 1H); 3.15 (d, J=13.6 Hz, 1H); 2.83 (d, J= 11.6 Hz, 1H); 2.70 (m, 1H); 2.34 (s, 3H); 2.18 (s, 3H); 1.94 (t, J=9.6 Hz, 1H); 1.78 (m, 1H); 1.76 (m, 1H); 1.65 (m, 1H); 1.54 (m, 1H); 1.39 (m, 1H).

22	m/z (M+1) = 613.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.32 (br s, 1H); 9.00 (s, 1H); 8.49 (d, J=4.8 Hz, 1H); 8.46 (d, J=1.2 Hz, 1H); 8.24 (dd, J= 5.6, 2 Hz, 2H); 7.88 (d, J=1.2 Hz, 1H); 7.40-7.48 (m, 3H); 7.32 (t, J=8.4 Hz, 2H); 7.14 (s, 1H); 6.68 (s, 1H); 6.59 (s, 1H); 6.56 (s, 1H); 3.03 (m, 4H); 2.32 (s*, 3H); 2.30 (m*, 4H); 2.14 (s, 3H); 2.07 (s, 3H).
23	m/z (M+1) = 564.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.19 (s, 1H); 9.03 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.29 (d, J=2 Hz, 1H); 8.20 (dd, J= 5.6, 2.4 Hz, 2H); 8.04 (d, J=1.2 Hz, 1H); 7.71 (dd, J=8, 1.6 Hz, 1H); 7.52 (s, 1H); 7.39-7.43 (m, 2H); 7.29-7.34 (m, 4H); 6.88 (s, 1H); 3.76 (m, 4H); 3.18 (m, 4H); 2.34 (s, 3H); 2.16 (s, 3H).
24	m/z (M+1) = 390.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H); 8.02 (d, J=1.2 Hz, 1H); 7.87 (m, 2H); 7.48 (s, 1H); 7.35 (dd, J=8.4, 4.4 Hz, 4H); 6.85 (s, 1H); 3.23 (m, 4H); 2.47 (m*, 4H); 2.39 (s, 3H); 2.24 (s, 3H); 2.16 (s, 3H).
25	m/z (M+1) = 482.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.16 (s, 1H); 8.02 (d, J=1.2 Hz, 1H); 7.77 (dd, J=7.6, 1.2 Hz, 1H); 7.52 (s*, 1H); 7.51 (d*, J=7.6 Hz, 1H); 7.38-7.43 (m, 3H); 7.33 (s, 1H); 7.29 (s, 1H); 7.14 (t, J=5.6 Hz, 1H); 6.96 (d, J=7.6 Hz, 1H); 6.85 (s, 1H); 3.21 (m, 4H); 2.47 (m*, 4H); 2.27 (s, 3H); 2.23 (s, 3H); 2.15 (s, 3H).
26	m/z (M+1) = 526.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.16 (s, 1H); 8.02 (d, J=1.2 Hz, 1H); 7.77 (dd, J=8, 1.6 Hz, 1H); 7.52 (s*, 1H); 7.51 (d*, 1H); 7.38-7.43 (m, 3H); 7.33 (s, 1H); 7.28 (s, 1H); 7.14 (t, J=5.6 Hz, 1H); 6.96 (d, J=8 Hz, 1H); 6.84 (s, 1H); 3.47 (t, J=6 Hz, 2H); 3.25 (s, 3H); 3.20 (m, 4H); 2.56 (m, 4H); 2.52 (m*, 2H); 2.27 (s, 3H); 2.23 (s, 3H); 2.15 (s, 3H).
27	m/z (M+1) = 533.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.16 (s, 1H); 9.67 (s, 1H); 8.62 (d, J=6 Hz, 1H); 8.00 (d, J=1.6 Hz, 1H); 7.91 (m, 1H); 7.88 (m, 1H); 7.71 (m, 3H); 7.60 (d, J=8 Hz, 1H); 7.42 (s, 1H); 7.32 (s, 1H); 7.28 (s, 1H); 6.84 (d, J=1.6 Hz, 1H); 6.82 (m, 1H); 3.19 (m, 4H); 2.46 (m, 4H); 2.32 (s, 3H); 2.22 (s, 3H); 2.14 (s, 3H).
28	m/z (M+1) = 519.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H); 8.10-8.20 (m, 3H); 8.02 (m, 2H); 7.94 (d, J=1.6 Hz, 1H); 7.79 (t, J=7.8 Hz, 1H); 7.59 (d, J=7.8 Hz, 1H); 7.42 (s, 1H); 7.33 (s, 1H); 7.28 (s, 1H); 6.85 (t, J=1.6 Hz, 1H); 3.21 (m, 4H); 2.46 (m, 4H); 2.35 (s, 3H); 2.23 (s, 3H); 2.15 (s, 3H).
29	m/z (M+1) = 578.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.17 (s, 1H); 9.04 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.31 (s, 1H); 8.19 (dd, J= 5.6, 3.2 Hz, 2H); 7.78 (s, 1H); 7.72 (dd, J=8, 1.6 Hz, 1H); 7.52 (s, 1H); 7.38-7.42 (m, 2H); 7.30 (t, J=8.8 Hz, 2H); 7.12 (s, 1H); 6.84 (s, 1H); 3.21 (m, 4H); 2.48 (m*, 4H); 2.34 (s, 3H); 2.28 (s, 3H) 2.23 (s, 3H).

30	m/z (M+1) = 496.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.34 (s, 1H); 8.01 (d, J=1.2 Hz, 1H); 7.92 (s, 1H); 7.79 (m, 1H); 7.62 (s, 1H); 7.55 (d, J= 1.6 Hz, 1H); 7.52 (d, J=8.4 Hz, 1H); 7.40 (m, 2H); 7.33 (s, 1H); 7.21 (s, 1H); 7.13 (t, J=7.6 Hz, 1H); 6.95 (dd, J=8.4, 1.2 Hz, 2H); 3.47 (AB pattern, J= 13.6 Hz, 2H); 2.63-2.72 (m, 3H); 2.27 (s, 3H); 2.16 (s, 3H); 1.96 (m, 1H); 1.71 (m, 2H); 1.62 (m, 1H); 1.49 (m, 1H); 1.00 (m, 1H).
31	m/z (M+1) = 497.3	^{1}H NMR (400 MHz, DMSO-d6): δ 10.00 (s, 1H); 9.03 (s, 1H); 8.49 (d, J=5.2 Hz, 1H); 8.28 (d, J= 1.2 Hz, 1H); 8.19 (dd, J= 5.6, 3.2 Hz, 2H); 7.67 (dd, J=7.6,1.6 Hz, 1H); 7.39 (m, 3H); 7.29 (m, 3H); 7.16 (t, J=8 Hz, 1H); 6.68 (dd, J=8, 2Hz, 1H); 3.12 (m, 4H); 2.49 (m*, 4H); 2.33 (s, 3H); 2.22 (s, 3H).
32	m/z (M+1) = 524.46	^{1}H NMR (partial: isomer mix, 400 MHz, DMSO-d6): δ 10.31 (s, 1H); 8.03 (m, 1H); 7.95 (m, 1H); 7.65 (m, 1H); 7.62 (m, 2H); 7.56 (m, 1H); 7.50 (m, 2H); 7.42 (t, J = 7.3 Hz, 2H); 7.35 (m, 3H); 7.21 (m, 1H); 5.21 (s, 2H); 3.43 (m, 2H); 2.72 (m, 2H); 2.33 (s, 3H); 2.16 (s, 3H); 1.33-1.94 (m*, 7 H); 1.21 (m, 3H), 0.84 (m, 3H).
33	m/z (M+1) = 539.22	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 10.31 (s, 1H); 8.58 (s, 1H); 8.02 (s, 1H); 7.95 (m, 1H); 7.79 (m, 1H); 7.65 (s, 2H); 7.56 (d, J = 7 Hz, 1H); 7.35 (s, 1H); 7.32 (m, 2H); 7.21 (s, 1H); 5.22 (s, 2H); 3.44 (m, 3H); 2.81 (m, 1H); 2.73 (m, 1H); 2.72 (m, 2H); 2.25 (s, 3H); 2.17 (s, 3H); 2.06 (m, 1H); 1.50-1.7 (m*, 4H); 1.26 (m*), 0.84 (m*, 3H).
34	m/z (M+1) = 510.41	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 9.93 (br s, 1H); 8.00 (s, 1H); 7.92 (s, 1H); 7.79 (dd, J=7.8, 1.4 Hz, 1H); 7.63 (s, 1H); 7.54 (d, J=2.3 Hz, 1H); 7.50 (d, J=8 Hz, 1H); 7.40 (t, J= 8 Hz, 2H); 7.32 (s, 1H); 7.13 (t, J=7.4 Hz, 1H); 6.96 (d, J=7.9 Hz, 2H); 4.55 (d, 1H); 3.48 (br s, 2H); 2.92 (m, 1H); 2.81 (d, J= 10.4 Hz, 1H); 2.73 (d, J= 8.5 Hz, 1H); 2.60 (m*, 1H); 2.27 (s, 3H); 2.16 (s, 3H); 2.00 (m, 1H); 1.69 (m, 2H); 1.44 (m, 2H); 0.84 (d, J= 6.5 Hz, 3H).
35	m/z (M+1) = 525.42	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 10.32 (s, 1H); 8.22 (s, 1H); 7.99 (s, 1H); 7.86 (s, 1H); 7.77 (d, J=7.8 Hz, 1H); 7.62 (s, 1H); 7.49 (d, J=8 Hz, 1H); 7.47 (s, 1H); 7.29 (d, J= 7.5 Hz, 1H); 7.28 (s*, 2H); 7.18 (s, 1H); 3.45 (m*); 2.81 (d, J= 8.1 Hz, 1H); 2.74 (d, J= 8.9 Hz, 1H); 2.45 (s, 3H); 2.28 (s, 3H); 2.14 (s, 3H); 2.81 (d, J= 10.4 Hz, 1H); 2.73 (d, J= 8.5 Hz, 1H); 2.60 (m*, 1H); 2.27 (s, 3H); 2.16 (s, 3H); 1.96 (dd, J=12, 10.6 Hz, 1H); 1.78 (d, J=10.4 Hz, 1H); 1.67 (t, J= 11 Hz, 1H); 1.56 (m, 1H); 1.42 (m, 2H) 0.85 (d, J= 6.4 Hz, 3H).
36	m/z (M+1) = 539.23	^{1}H NMR (partial, isomer mix, 400 MHz, DMSO-d6 with D_2O): δ 10.55 (s, 1H); 9.18 (br m, 1H); 8.63 (s, 1H); 8.07 (m, 2H); 7.96 (m, 1H); 7.82 (m, 3H); 7.55 (d, J= 7.5 Hz, 2H); 7.18 (d, J=8.8 Hz, 1H); 5.27 (s, 2H); 2.33 (s, 3H); 2.25 (s, 3H); 0.98 (m, 3H).
37	m/z (M+1) = 524.43	^{1}H NMR (partial, isomer mix, 400 MHz, DMSO-d6 with D_2O): δ 10.21 (s, 1H); 8.02. 8.01 (~3:1, 2xs, 1H); 7.74-7.84 (m, 3H); 7.66, 7.64 (~1:3, 2xs, 1H); 7.47 (m, 2H); 7.40 (t, J=7.4 Hz, 2H); 7.32 (m, 2H); 7.19 (s, 1H); 7.12 (d, J=9.3 Hz, 1H); 5.20 (s, 2H); 3.46 (m, 2H); 2.7-2.8 (m*, 2H) 2.33 (s, 3H); 2.25 (s, 3H); 1.4-1.96 (m*, 6H); 0.89, 0.93 (~1:3, 2xd, J = 6.5 Hz, 3H).

38	m/z (M+1) = 497.35	^{1}H NMR (400 MHz, DMSO-d6): δ 10.33 (s, 1H); 8.01 (d, J= 0.9 Hz, 1H); 7.92 (br t, 1H); 7.79 (dd, J= 7.8, 1.5 Hz, 1H); 7.61 (s, 1H); 7.54 (d, J= 1.3 Hz, 1H); 7.50 (d, J=8 Hz, 1H); 7.40 (m, 2H); 7.33 (s, 1H); 7.21 (s, 1H); 7.13 (t, J=7.4 Hz, 1H); 4.57 (m, 1H); 3.47 (m, 4H); 2.80 (m, 1H); 2.66 (m, 1H); 2.27 (s, 3H); 2.17 (s, 3H); 1.90 (m, 1H); 1.70-1.76 (m, 2H); 1.62 (m, 1H); 1.42 (m, 1H); 1.09 (m, 1H).
39	m/z (M+1) = 511.39	^{1}H NMR (400 MHz, DMSO-d6): δ 10.40 (s, 1H); 8.24 (d, J=1.8 Hz, 1H); 8.04 (s, 1H); 7.91 (br s, 1H); 7.82 (m, 1H); 7.66 (s, 1H); 7.51 (d, J=8.2 Hz, 1H); 7.49 (s, 1H); 7.34 (s, 1H); 7.30 (m, 3H); 6.95 (dd, J=8.4, 1.2 Hz, 2H); 3.57 (d, J= 13.6 Hz, 1H); 3.52 (d, J=10.8 Hz, 1H); 3.16 (br s, 1H); 2.72 (br d, J= 8 Hz, 1H); 2.43 (s, 3H); 2.30 (s, 3H); 2.16 (s, 3H); 1.80 (m, 1H); 1.72 (m, 1H); 1.44-1.55 (m, 3H); 1.29 (m*, 2H).
40	m/z (M+1) = 511.37	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 10.33 (s, 1H); 8.00 (s, 1H); 7.92 (s, 1H); 7.79 (dd, J=7.8, 1.4 Hz, 1H); 7.63 (s, 1H); 7.54 (d, J=2.3 Hz, 1H); 7.50 (d, J=8 Hz, 1H); 7.40 (t, J= 8 Hz, 2H); 7.32 (s, 1H); 7.13 (t, J=7.4 Hz, 1H); 6.96 (d, J=7.9 Hz, 2H); 4.55 (d, 1H); 3.48 (br s, 2H); 2.92 (m, 1H); 2.81 (d, J= 10.4 Hz, 1H); 2.73 (d, J= 8.5 Hz, 1H); 2.60 (m*, 1H); 2.27 (s, 3H); 2.16 (s, 3H); 2.00 (m, 1H); 1.69 (m, 2H); 1.44 (m, 2H); 0.84 (d, J= 6.5 Hz, 3H).
41	m/z (M+1) = 444.12	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 11.49 (s, 1H); 10.32 (s, 1H); 8.10 (s, 1H); 8.02 (s, 1H); 7.99 (s, 1H); 7.76 (s, 1H); 7.66 (m, 2H); 7.57 (t, J=2.5 Hz, 1H); 7.35 (s, 1H); 7.18 (s, 1H); 6.53 (s, 1H); 4.55 (d, J=5 Hz, 1H); 3.47 (s, 2H); 2.95 (m, 1H); 2.80 (d, J= 9.9 Hz, 1H); 2.74 (d, J= 10.3 Hz, 1H); 2.17 (s, 3H); 1.99 (t, J= 10.7 Hz, 1H); 1.75 (d, J= 9.4 Hz, 1H); 1.67 (t, J = 10.7 Hz, 1H); 1.47 (m, 2H); 0.86 (d, J= 6.6 Hz, 3H).
42	m/z (M+1) = 459.15	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 10.34 (s, 1H); 8.17 (s, 1H); 8.02 (s, 1H); 7.99 (s, 1H); 7.81 (d, J= 8.4 Hz, 1H); 7.71 (s, 1H); 7.55 (s, J=8.4 Hz, 1H); 7.35 (s, 1H); 7.19 (s, 1H); 6.53 (s, 1H); 4.55 (br s, 1H); 3.47 (s, 2H); 2.93 (m, 1H); 2.79 (d, J= 10.8 Hz, 1H); 2.74 (d, J= 11 Hz, 1H); 2.18 (s, 3H); 1.99 (t, J= 12.2 Hz, 1H); 1.89 (s, 3H); 1.75 (d, J= 9.2 Hz, 1H); 1.67 (t, J = 11.1 Hz, 1H); 1.45 (m, 2H); 0.86 (d, J= 6.4 Hz, 3H).
43	m/z (M+1) = 489.2	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 12.47 (m, 1H); 10.34 (s, 1H); 8.02 (s, 1H); 7.99 (s, 1H); 7.83 (m*, 1H); 7.81 (s*, 1H); 7.71 (s, 1H); 7.55-7.61 (br m, 1H); 7.34 (s, 1H); 7.19 (s, 1H); 4.89 (br s, 1H); 4.55 (d, J=5.2 Hz, 1H); 3.86 (br t, 2H); 3.23 (s, 2H); 3.00 (t, J= 6.6 Hz, 2H); 2.93 (m, 1H); 2.79 (d, J= 10.4 Hz, 1H); 2.74 (d, J= 9.8 Hz, 1H); 2.18 (s, 3H); 1.96 (t, J= 10.3 Hz, 1H); 1.90 (s, 3H); 1.75 (br d, J= 10 Hz, 1H); 1.64 (t, J = 11 Hz, 1H); 1.45 (m, 2H); 0.86 (d, J= 6.4 Hz, 3H).
44	m/z (M+1) = 459.09	^{1}H NMR (isomer mix, 400 MHz, DMSO-d6): δ 13.03 (br s, 1H); 10.51 (br s, 1H); 8.12 (s, 1H); 8.03 (s, 1H); 7.98 (s, 1H); 7.83 (d, J= 8.3 Hz, 1H); 7.70 (s*, 1H); 7.67 (d, J=8.4 Hz, 1H); 7.35 (s, 1H); 7.21 (s, 1H); 4.56 (br s, 1H); 3.47-3.50 (d* + s*, 3H); 2.93 (m, 2H); 2.79 (d, J= 11 Hz, 1H); 2.74 (d, J= 14 Hz, 1H); 2.33 (s, 1H); 2.18 (s, 3H); 2.00 (br t, 1H); 1.75 (br d, J= 9.4 Hz, 1H); 1.67 (t, J = 11 Hz, 1H); 1.47 (m, 2H); 0.84 (d, J= 6.4 Hz, 3H* (signal obscured))

45	m/z (M+1) = 482.2	^{1}H NMR (400 MHz, DMSO-d6): δ 10.32 (s, 1H); 8.01 (s, 1H); 7.88 (s, 1H); 7.79 (d, J=7.7 Hz, 1H); 7.65 (s, 1H); 7.54 (s, 1H); 7.50 (d, J=7.9 Hz, 1H); 7.40 (t, J=7.7 Hz, 2H); 7.33 (s, 1H); 7.24 (s, 1H); 7.13 (t, J=7.3 Hz, 1H); 6.97 (d, J=8 Hz, 2H); 4.16 (br s, 2H); 3.56 (AB pattern, J= 14 Hz, 2H); 3.44 (m, 1H). (400 MHz, MeOH-d4): δ 2.87 (m, 1H); 2.74 (m, 1H); 2.53 (m, 2H); 2.32 (s, 3H); 2.25 (s*+m*, 4H); 1.64 (m, 1H).
46	m/z (M+1) = 510.26	^{1}H NMR (partial, 400 MHz, DMSO-d6+TFA-D): δ 9.57 (s, 1H); 8.22 (s, 1H); 8.08 (s, 1H); 7.86 (s, 1H); 7.77 (d, J=8 Hz, 1H); 7.56 (s, 1H); 7.54 (s, 1H); 7.46 (d, J=7.9 Hz, 1H); 7.34 (t, J=7.7 Hz, 2H); 7.07 (t, J=7.6 Hz, 1H); 6.92 (d, J=8.1 Hz, 2H); 4.34 (AB pattern, 2H); 3.46 (m, 2H). (partial, 400 MHz, MeOH-d4): δ 2.94-2.98 (m, 2H); 2.82-2.90 (m, 3H); 2.43 (s, 3H); 2.33 (s, 3H); 2.27 (m*, 2H); 2.01 (m, 2H);); 1.86 (m, 1H); 1.32 (m, 1H).
47	m/z (M+1) = 496.19	^{1}H NMR (400 MHz, MeOH-d4): δ 9.00 (s, 1H); 8.06 (s, 1H); 8.01 (s, 1H); 7.71 (d, J=8 Hz, 1H); 7.65 (s, 1H); 7.57 (s, 1H); 7.47-7.50 (m, 2H); 7.36 (t, J= 8 Hz, 2H); 7.07 (t, J=7.6 Hz, 1H); 6.95 (d, J=8 Hz, 2H); 4.50 (m, 2H); 3.57 (m, 1H); 3.13 (m*, 2H); 2.78 (m, 1H); 2.41 (s+m*, 4H); 2.33 (s+m*, 4H); 2.27 (m*, 2H); 1.90 (m, 1H).
48	m/z (M+1) = 510.23	^{1}H NMR (400 MHz, DMSO-d6+ TFA-d): δ 9.53 (s, 1H); 8.19 (s, 1H); 8.13 (s, 1H); 7.77 (s, 1H); 7.74 (d, J=8.1 Hz, 1H); 7.56 (s, 1H); 7.53 (s, 1H); 7.40 (d, J=7.9 Hz, 1H); 7.29 (t, J=7.9 Hz, 2H); 7.03 (t, J=7.3 Hz, 1H); 6.88 (d, J=8 Hz, 2H); 4.45 (AB pattern, J= 13 Hz, 2H); 3.69 (m, 1H); 3.41 (m, 2H); 2.97 (m, 2H); 2.56 (s, 3H); 2.30 (s, 3H); 2.22 (s, 3H); 2.10 (m, 1H); 1.92 (m, 1H); 1.73 (m, 1H); 1.48 (m, 1H).
49	m/z (M+1) = 496.22	^{1}H NMR (partial, 400 MHz, DMSO-d6+ TFA-d): δ 9.58 (s, 1H); 8.17 (s, 1H); 8.12 (s, 1H); 7.88 (s, 1H); 7.78 (d, J=9 Hz, 1H); 7.61 (s, 1H); 7.54 (s, 1H); 7.49 (d, J=8.5 Hz, 1H); 7.36 (t, J=7.8 Hz, 2H); 7.10 (t, J=7.3 Hz, 1H); 6.94 (d, J=8.3 Hz, 2H); 4.50 (s, 2H). 1H NMR (partial, 400 MHz, MeOH-d4): δ 4.13 (br s, 2H); 3.90 (m, 1H); 3.23 (m*, 2H); 2.90 (m, 2H); 2.72 (s, 3H); 2.48 (m, 1H); 2.45 (s, 3H); 2.33 (s, 3H); 2.07 (m, 1H).
50	m/z (M+1) = 508.25	^{1}H NMR (400 MHz, MeOH-d4): δ 9.32 (s, 1H); 8.00 (s, 1H); 7.92 (s, 1H); 7.77 (s, 1H); 7.71 (d, J=8 Hz, 1H); 7.46-7.49 (m, 3H); 7.36 (t, J=7.9 Hz, 2H); 7.11 (t, J=7.4 Hz, 1H); 6.94 (d, J=8 Hz, 2H); 4.23 (m, 1H); 3.87 (AB pattern, J= 13 Hz, 2H); 3.50 (m, 1H); 3.25 (m*, 2H); 3.11 (m, 1H); 2.95 (d, J=10 Hz, 1H); 2.78 (dd, J= 11.5, 5.8 Hz, 1H); 2.64 (t, J=8.5 Hz, 1H); 2.45 (s, 3H); 2.33 (s, 3H); 2.22 (m, 1H); 1.99 (m, 1H).
51	m/z (M+1) = 508.24	^{1}H NMR (400 MHz, MeOH-d4): δ 9.33 (s, 1H); 8.02 (s, 1H); 7.91 (s, 1H); 7.77 (s, 1H); 7.72 (d, J=7.8 Hz, 1H); 7.55 (s, 1H); 7.49 (s*, 1H); 7.47 (d*, J=8.1 Hz, 1H); 7.36 (t, J=7.8 Hz, 2H); 7.11 (t, J=7.2 Hz, 1H); 6.94 (d, J=8.1 Hz, 2H); 4.22 (d, 1H); 3.82 (m, 1H); 3.72 (m, 1H); 3.50 (m, 1H); 3.31 (m*, 2H); 3.19-3.23 (m, 3H); 2.57 (m, 1H); 2.56 (s, 3H); 2.33 (s, 3H); 2.31 (m*, 1H); 1.70 (m, 1H).
52	m/z (M+1) = 482.23	^{1}H NMR (400 MHz, DMSO-d6+ TFA-d): δ 9.48 (s, 1H); 7.79 (s, 1H); 7.73 (d, J=7.9 Hz, 1H); 7.61 (s, 1H); 7.51 (s, 2H); 7.38 (d, J=7.9 Hz, 1H); 7.30 (t, J=7.7 Hz, 2H); 7.04 (t, J=7.2 Hz, 1H); 6.99 (s, 1H); 6.88 (d, J=7.7 Hz, 2H); 3.69 (m*, 1H); 3.47 (m, 1H); 3.27 (m, 1H); 3.03 (m, 2H); 2.29 (s, 3H); 2.21 (s, 3H); 1.96 (m, 1H); 1.80 (m, 1H); 1.59 (m, 2H).

53	m/z (M+1) = 512.22	^{1}H NMR (400 MHz, MeOH-d4): δ 9.32 (s, 1H); 8.07 (s, 1H); 7.92 (s, 1H); 7.78 (s, 1H); 7.70 (d, J=7.9 Hz, 1H); 7.53-7.57 (m, 3H); 7.40 (t, J=8.3 Hz, 2H); 7.23 (d, J=7.5 Hz, 1H); 7.03 (d, J=8.3 Hz, 2H); 4.61 (d, 2H); 3.91 (s, 2H); 3.46 (m, 1H); 3.02 (m, 1H); 2.85 (m, 1H); 2.65 (m, 2H); 2.45 (s, 3H); 1.91-2.01 (m, 2H); 1.76 (m, 1H); 1.63 (m, 1H).
54	m/z (M+1) = 526.23	^{1}H NMR (400 MHz, DMSO-d6): δ 10.68 (s, 1H); 8.04 (s, 1H); 7.99 (s, 1H); 7.85 (d, J=8.4 Hz, 2H); 7.80 (d, J=7.8 Hz, 1H); 7.68 (s, 2H); 7.56 (t, J=7.9 Hz, 1H); 7.34 (s, 1H); 7.28 (d, J=8.1 Hz, 1H); 7.24 (s, 1H); 6.93 (d, J=8.5 Hz, 2H); 3.52 (AB pattern, J= 13.7 Hz, 2H); 3.05 (m, 1H); 2.73 (d, J=8.3 Hz, 1H); 2.58 (m, 1H); 2.08-2.15 (m*+s, 4H); 1.80 (m, 1H); 1.73 (m, 1H); 1.49 (m, 1H); 1.33 (m, 1H).
55	m/z (M+1) = 525.25	^{1}H NMR (400 MHz, MeOH-d4): δ 9.32 (s, 1H); 8.08 (s, 1H); 7.94 (s, 1H); 7.91 (s, 1H); 7.81 (d, J=8.1 Hz, 1H); 7.78 (s, 1H); 7.66 (s, 1H); 7.60 (t, J= 7.9 Hz, 1H); 7.53 (s, 1H); 7.34 (d, J=8.8 Hz, 1H); 7.09 (d, J=8.6 Hz, 2H); 3.95 (s, 2H); 3.31 (m, 1H); 3.08 (m, 1H); 2.88 (m, 1H); 2.68 (m, 2H); 2.45 (s, 3H); 1.92-2.01 (m, 2H); 1.78 (m, 1H); 1.63 (m, 1H).
56	m/z (M+1) = 669.30	^{1}H NMR (400 MHz, DMSO-d6+ TFA-d): δ 9.59 (s, 1H); 8.27 (d, J=8.7 Hz, 1H); 8.21 (s, 1H); 8.12 (s, 1H); 7.89 (s, 1H); 7.87 (d*, J=8.7 Hz, 1H); 7.73 (s, 1H); 7.65 (m, 2H); 7.54 (d, J=7.4 Hz, 1H); 7.41 (d, J=8.2 Hz, 1H); 7.28 (d, J=8.5 Hz, 2H); 7.16-7.20 (m*, 1H); 6.87 (d, J=8.6 Hz, 2H); 6.55 (d, J=7.4 Hz, 1H); 5.08 (s, 2H); 4.52 (br s, 2H); 3.70 (s, 3H); 3.44-3.56 (m, 3H); 2.97 (m, 2H); 2.33 (s, 3H); 2.02 (m, 1H); 1.95 (m, 1H); 1.74 (m, 1H); 1.49 (m, 1H).
57	m/z (M+1) = 549.26	^{1}H NMR (400 MHz, MeOH-d4): δ 9.41 (d, J=1.1 Hz, 1H); 8.32 (d, J=8.8 Hz, 1H); 8.26 (s, 1H); 8.07 (s, 1H); 7.88 (d*+s, 2H); 7.83 (s, 1H); 7.73 (s, 1H); 7.64 (t, J=7.9 Hz, 1H); 7.40 (dd, J=8.1, 1.7 Hz, 1H); 7.22 (dd, J=8.9, 2.2 Hz, 1H); 7.19 (d*+s, 2H); 6.58 (d, J=7.1 Hz, 1H); 4.49 (s, 2H); 3.72 (m, 1H); 3.65 (m, 1H); 3.48 (m, 1H); 3.12 (m, 2H); 2.46 (s, 3H); 2.10-2.18 (m, 2H); 2.01 (m, 1H); 1.71 (m, 1H).
58	m/z (M+1) = 537.25	^{1}H NMR (400 MHz, MeOH-d4): δ 9.31 (s, 1H); 8.08 (s, 1H); 7.91 (s, 1H); 7.78-7.83 (m, 3H); 7.67 (br t, 1H); 7.61 (t, J=8 Hz, 1H); 7.51 (s, 1H); 7.36 (dd, J=8.1, 2.1 Hz, 1H); 7.22 (s, 1H); 7.17 (dd, J=8.4, 1.8 Hz, 1H); 4.44 (s, 2H); 3.87 (s, 2H); 3.45 (m, 1H); 3.02 (m, 1H); 2.81 (m, 1H); 2.62 (m, 2H); 2.46 (s, 3H); 1.99 (m, 1H); 1.90 (m, 1H); 1.75 (m, 1H); 1.63 (m, 1H).
59	m/z (M+1) = 514.23	^{1}H NMR (400 MHz, MeOH-d4): δ 9.28 (s, 1H); 8.03 (s, 1H); 7.89 (s, 1H); 7.77 (d*+s, 2H); 7.57 (s, 1H); 7.50 (d*+s, 2H); 7.35 (q, J=8.1 Hz, 1H); 6.85 (m, 1H); 6.75 (d, J=8.2 Hz, 1H); 6.67 (d, J=10.4 Hz, 1H); 3.85 (s, 2H); 3.46 (m, 1H); 2.97 (m, 1H); 2.78 (m, 1H); 2.61 (d, J=7.7 Hz, 2H); 2.46 (s, 3H); 2.31 (s, 3H); 1.97 (m, 1H); 1.89 (m, 1H); 1.75 (m, 1H); 1.62 (m, 1H).
60	m/z (M+1) = 546.26	^{1}H NMR (400 MHz, MeOH-d4): δ 9.30 (s, 1H); 8.04 (s, 1H); 7.90 (s, 1H); 7.77 (d*+s, 2H); 7.47-7.55 (m*, 4H); 7.28 (d, J=7.5 Hz, 1H); 7.09 (m, 2H); 6.74 (t, J= 56 Hz (CHF_2), 1H); 3.88 (s, 2H); 3.44 (m*, 1H); 3.01 (m, 1H); 2.80 (m, 1H); 2.63 (d, J=7.1 Hz, 2H); 2.45 (s, 3H); 2.32 (s, 3H); 1.90-1.97 (m, 2H); 1.75 (m, 1H); 1.62 (m, 1H).

Example 61. Inhibition of PCSK9-LDLR binding by selected compounds of the invention

Compounds were assayed for their ability to inhibit the binding between PCSK9 and the LDL receptor using a CircuLex PCSK9-LDLR *in vitro* binding assay kit (Catalog # CY-8150. The procedure employed the reagents and buffers included in the kit as follows.

88 µL of 1X reaction buffer were placed into each well. 5 µL of test compounds in 20% DMSO were added into each well. 10mM solutions of test compounds in DMSO were diluted by 3-fold series to give 8 point concentration curves. The compounds were then diluted 20-fold with the reaction buffer. To each well was then added 7 µL of His-tagged PCSK9 wild type solution (1000ng/mL) into each well. The plate was then covered with a plate sealer and incubated at room temperature for 3 hours, shaking at 300 rpm on an orbital microplate shaker. The test solutions were washed 4 times with 350 µL wash buffer. 100 µL of biotinylated anti-His-tag monoclonal antibody was added to each well. The plate was covered with a plate sealer, and incubated at room temperature for 1 hour, shaking at 300 rpm. The test solutions were washed 4 times with 350 µL wash buffer. 100 µL of HRP-conjugated streptavidin was added to each well. The plate was covered with a plate sealer, and incubated at room temperature for 20 min, shaking at 300 rpm. The test solutions were washed 4 times with 350 µL wash buffer. 100 µL of substrate reagent were added into each well. The plate was covered with a plate sealer, and incubated at room temperature for 15 min, shaking at 300 rpm. Finally, 100 µL of the stop solution was added to each well in the same order as the previously added substrate reagent. Absorbance was measured at 450 nm and 540nm and IC_{50} curves were plotted.

Table 2. Inhibition of PCSK9-LDLR binding: Values in table for inhibition ranges are as follows: >100 µM: - ; 10-100 µM: + ; 1-10 µM: ++ ; 0.1-1 µM: +++ ; <0.1 µM: ++++. Starred values refer to levels of inhibition of binding by less than 35% at the

highest concentration tested, due either to solubility limitations or dynamic range limitations of the assay.

Example	Inhibition	Example	Inhibition	Example	Inhibition
1	+	2	++	3	++
4	+	5	+++	6	+++
7	+++	8	+	9	++
10	+	11	++	12	+
13	+	14	+	15	+
16	+	17	-	18	++
19	+++	20	+	21	++
22	*	23	+	24	+
25	*	26	*	27	++++
28	++	29	+	30	+++
31	++				

Example 62. Inhibition of LDL uptake in a cell-based assay.

Human liver cells (hepG2) express the LDL receptor, which can take up fluorescent-labeled LDL into the cell. PCSK9 binds to LDL receptor, wherein the complex is internalized and degraded in the lysosome, resulting in lowered LDL uptake in hepG2 cells. Inhibition of PCSK9 inhibition lowers plasma (circulating) LDL-C by increasing LDL incorporation into the cell. See **Figure 1**.

The cell-based assay was conducted as follows, according to the procedure outlined in Xu and Liu, J Bioequiv Availab 2013, **5**, 7. In this assay the dynamic range of measuring LDL uptake is enhanced by adding a gain-of-function mutant of PCSK9, which significantly reduces LDL uptake via increased LDLR binding, and whose inhibition indicates functional activity against the target, enabling a high-throughput format to be used. Human liver HepG2 cells were seeded in a 96 well plate at 2×105 cells /ml and incubated overnight. PCSK9-D374Y (2 µg/ml) was added, along with test compounds. The wells were incubated for 16 hours, whereupon the medium was replaced with fresh medium containing 10 µg/ml Bodipy FL LDL, and the wells were incubated for a further 4 hours. The wells were washed using warm PBS and then the

LDL uptake was quantified on a fluorescent plate reader at excitation/emission wavelengths of 485 and 530 nm respectively.

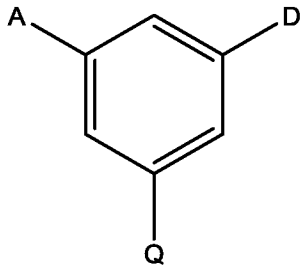
Figure 2 indicates the decrease in LDL update in HepG2 cells comparing untreated and PCSK9-D374Y gain-of-function treated cells. Test compounds were measured at their ability to increase LDL uptake at concentrations of 0.1 and 1 µM and the results shown in **Figure 3**. The positive control (from WO2014150326, catalogue number AMB-657286 (Ambinter, France) was included. Significant increases in LDL uptake equivalent to untreated cells, to which no PCSK9-D374Y had been added, were observed at both 0.1 and 1 µM concentrations for Examples 27 and 30.

SEQ ID No 1 (homo sapien):

MGTVSSRRSWWPLPLLLLLLLLLGPAGARAQEDEDGDYEELVLALRSEEDGLAEAPEH
GTTATFHRCAKDPWRLPGTYVVVLKEETHLSQSERTARRLQAQAARRGYLTKILHVFH
GLLPGFLVKMSGDLLELALKLPHVDYIEEDSSVFAQSIPWNLERITPPRYRADEYQPPD
GGSLVEVYLLDTSIQSDHREIEGRVMVTDFENVPEED^{212}GTRFHRQAS^{221}KC^{223}DSHGT
HLAGVVSGRDAGVAKGASMRSLRVLNCQGK^{258}GTVSG^{263}TLIGLEFIRKSQLVQPVGP
LVVLLPLAGGYSRVLNAACQRLARAGVVLVTAAGNFRDDACLYSPASAPEVITVGATN
AQDQPVTLGTLGTNFGRCVDLFAPGEDIIGASSDCSTCFSQSGTSQAAAHVAGIAAMM
LSAEPELTLAELRQRLIHFSAKDVINEAWFPEDQRVLTPNLVAALPPSTHGAGWQLFCR
TVWSAHSGPTRMATAVARCAPDEELLSCSSFSRSGKRRGERMEAQGGKLVCRAHNA
FGGEGVYAIARCCLLPQANCSVHTAPPAEASMGTRVHCHQQGHVLTGCSSHWEVED
LGTHKPPVLRPRGQPNQCVGHREASIHASCCHAPGLECKVKEHGIPAPQEQVTVACE
EGWTLTGCSALPGTSHVLGAYAVDNTCVVRSRDVSTTGSTSEGAVTAVAICCRSRHL
AQASQELQ

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound according to Formula (I):



(I)

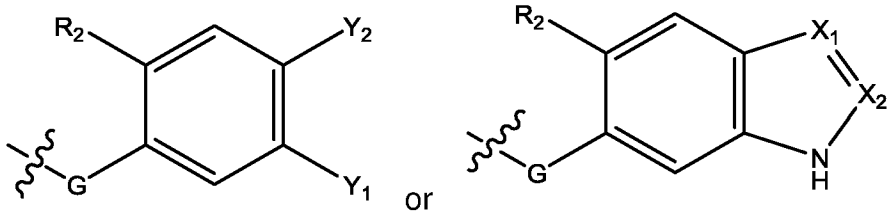
or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

A is an optionally substituted 5-membered heteroaryl ring, wherein the substituent is a methyl group;

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

wherein D is



wherein G is selected from the group consisting of $–NR_1C(O)$-, $–C(O)NR_1$-, $-S(O)_2NR_1$-, and –NR1$S(O)_2$-;

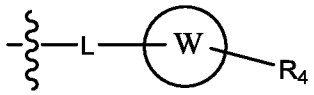
wherein R_1 is H or methyl and R_2 is H,

or wherein G is $–NR_1C(O)-$ and R_1 and R_2, together with the atoms between them, form an optionally substituted C_3-C_6 heterocyclic ring, thereby creating a bicyclic or tricyclic ring; and

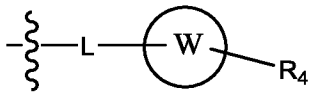
wherein X_1 is CR_3 and X_2 is N, or X_1 is N and X_2 is CR_3, or both X_1 and X_2 are CR_3;

wherein R_3 is H, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy or C_1-C_2 alkylamino; and

wherein Y_1 is H or methyl and Y_2 is



or Y_2 is H or methyl and Y_1 is



or both Y_1 and Y_2 are independently selected from H or methyl;

wherein L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

where m is 1 or 2; and

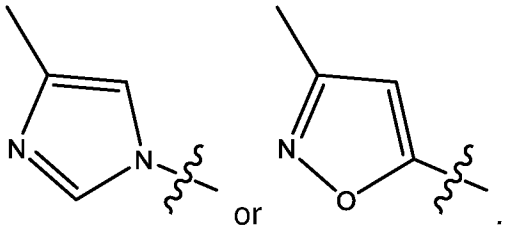
wherein 

is aryl or heteroaryl with the proviso that 

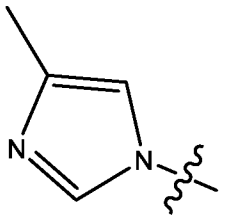
, named relative to the position of attachment to L, is not pyrazolopyridinyl, ortho-substituted pyridine, 4-pyrimidinyl or imidazole; and

wherein R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

2. A compound according to claim 1, wherein A is selected from



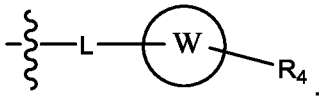
3. A compound according to claim 2, wherein A is



4. A compound according to any one of claims 1 to 3, wherein G is $-NR_1C(O)-$.

5. A compound according to claim 4 wherein R_1 is H.

6. A compound according to any one of claims 1 to 5, wherein Y_2 is H or methyl and Y_1 is



7. A compound according to any one of claims 1 to 6, wherein 

is aryl.

8. A compound according to any one of claims 1 to 6, wherein 

is heteroaryl wherein the heteroaryl group is 2-pyrimidinyl, wherein 2-pyrimidinyl refers to the position of attachment to L.

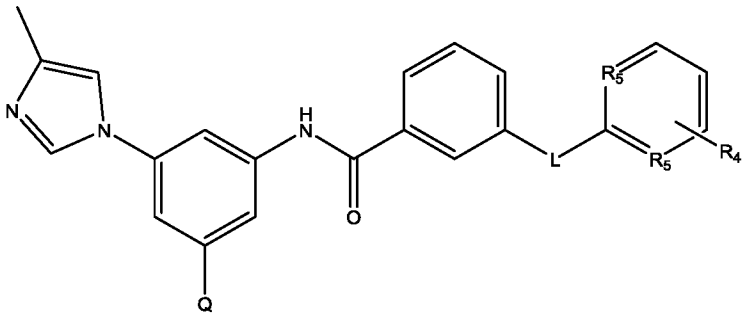
9. A compound according to any one of claims 1 to 6, wherein 

is heteroaryl wherein the heteroaryl group is a bicyclic heteroaryl group.

10. A compound according to claim 9, wherein 

is isoquinolinyl.

11. A compound according to formula II:



(II)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

Q is selected from the group consisting of optionally substituted: C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_1-C_6 alkyloxy, C_2-C_6 alkenyloxy, C_1-C_6 alkylamino, C_2-C_6 alkenylamino, C_1-C_6 alkylcarboxy, C_2-C_6 alkenylcarboxy, C_1-C_6 haloalkoxy, C_2-C_6 haloalkenyloxy, C_1-C_6 hydroxyalkyl, C_2-C_6 hydroxyalkenyl, C_1-C_6 alkylcarboxyamide, C_2-C_6 alkenylcarboxyamide, C_1-C_6 alkylsulfanyl, C_2-C_6 alkenylsulfanyl, C_1-C_6 alkylsulfenyl, C_2-C_6 alkenylsulfenyl, C_1-C_6 alkylsulfonyl, C_2-C_6 alkenylsulfonyl, C_1-C_6 alkylsulfonylamino, C_2-C_6 alkenylsulfonylamino, C_4-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 heterocyclyl, (C_1-C_3 alkyl)C_3-C_7 cycloalkyl and C_3-C_7 cycloalkyl;

L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

wherein m is 1 or 2;

R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; and

each R_5 is independently CH or N.

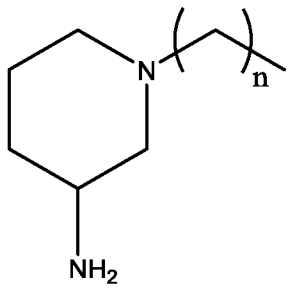
12. A compound accordingly to any one of claims 1 to 11, wherein Q is optionally substituted C_4-C_7 heterocyclyl or (C_1-C_3 alkyl)C_3-C_7 heterocyclyl.

13. A compound according to claim 12 wherein the C_4-C_7 heterocyclyl is a C_6 heterocyclyl group selected from a substituted or unsubstituted morpholino, piperidinyl or piperazinyl group.

14. A compound according to claim 12 wherein the C_4-C_7 heterocyclyl or (C_1-C_3 alkyl)C_3-C_7 heterocyclyl is selected from the groups consisting of piperazinyl, morpholino, 4-methyl piperazinyl, 4-(C_3 alkoxy)piperazinyl, (C_1-C_3 alkyl)(amino-substituted piperidinyl), (C_1-C_3 alkyl)(hydroxy-substituted piperidinyl) and optionally substituted (C_1-C_3 alkyl)piperidinyl.

15. A compound according to claim 13, wherein the piperidinyl group is mono or bis-substituted with substituents independently selected from the group consisting of methyl, amino and hydroxyl.

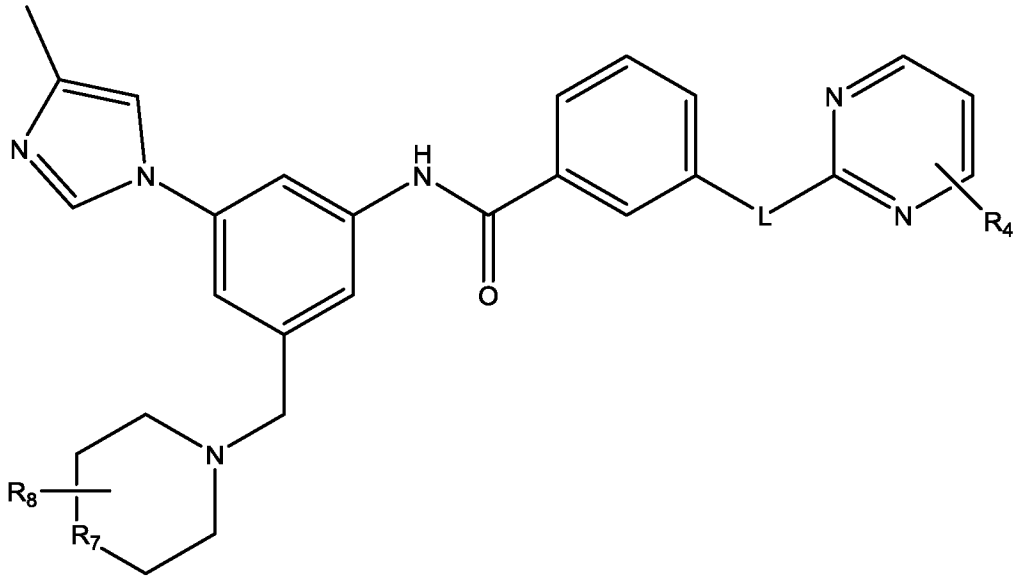
16. A compound according to claim 12, wherein Q is:



where n is 1-2.

17. A compound according to claim 16, wherein n is 1.

18. A compound according to formula III:



(III)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

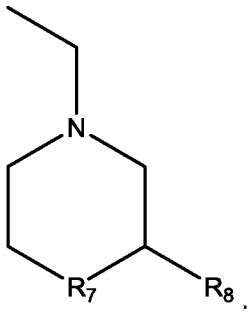
wherein m is 1 or 2;

R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R_7 is O, CHR_6 or NR_6; wherein R_6 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH; and

R_8 is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH.

19. A compound according to claim 18, wherein R_8 is positioned as shown:



20. A compound according to claim 18 or claim 19, wherein R_7 is CHR_6 or NR_6.

21. A compound according to claim 20, wherein R_7 is NR_6, wherein R_6 is H or methyl.

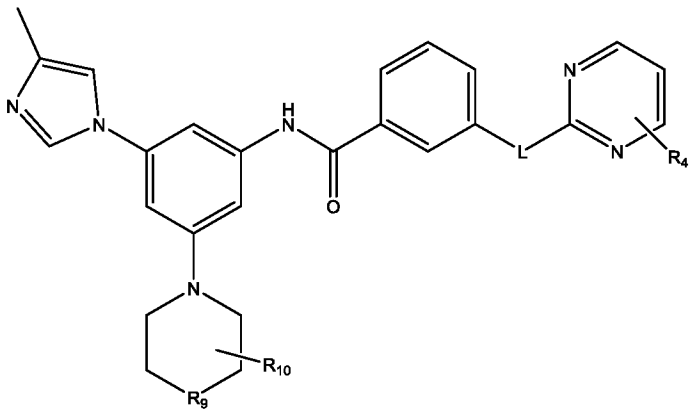
22. A compound according to claim 21, wherein R_6 is methyl.

23. A compound according to claim 20, wherein R_7 is CHR_6 and R_6 is –OH or $–NH_2$.

24. A compound according to any one of claims 18 to 23, wherein R_8 is selected from any one of H, $–NH_2$ or methyl.

25. A compound according to claim 18, wherein R_7 is CHR_6, R_6 is H, and R_8 is $–NH_2$.

26. A compound according to formula IV:



(IV)

or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof,

wherein

L is selected from the group consisting of –O–, –NH–, –C(O)–, $–NH(CH_2)_m–$, C_1-C_3 alkoxy, C_1-C_3 alkylamino;

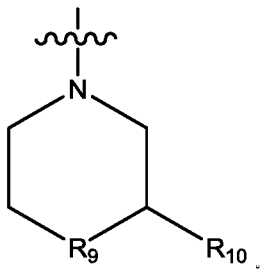
wherein m is 1 or 2;

R_4 is H, $NHC(O)CH_3$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R_9 is O, CHR_{11} or NR_{11}; wherein R_{11} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH; and

R_{10} is independently selected from the group consisting of H, –COOH, $–CONH_2$, $–NH_2$, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy and –OH.

27. A compound according to claim 26, wherein R_{10} is positioned as shown:



28. A compound according to claim 26 or claim 27, wherein R_9 is CHR_{11} or NR_{11};

29. A compound according to claim 26 or claim 27, wherein R_9 is NR_{11} and R_{11} is H or methyl.

30. A compound according to any one of claims 26 to 29, wherein R_{10} is selected from the group consisting of H, $–NH_2$ or methyl.

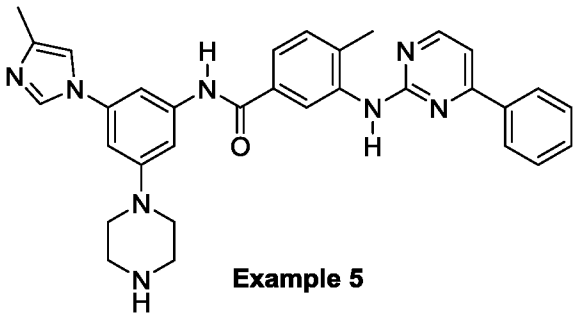
31. A compound according to claim 26, wherein R_9 is CHR_{11}, R_{11} is H, and R_{10} is $–NH_2$.

32. A compound according to any one of claims 1 to 31, wherein R_4 is H or optionally substituted aryl.

33. A compound according to claim 32, wherein the substituted aryl is halo-substituted aryl.

34. A compound according to any one of claims 1 to 33, wherein L is –O– or –NH–.

35. A compound selected from the group consisting of:



Example 5

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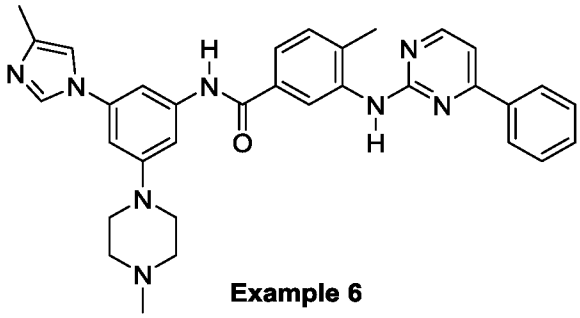

Example 6

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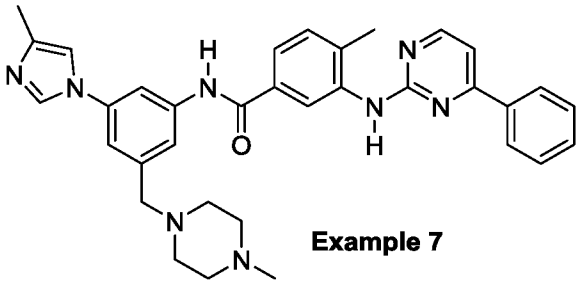

Example 7

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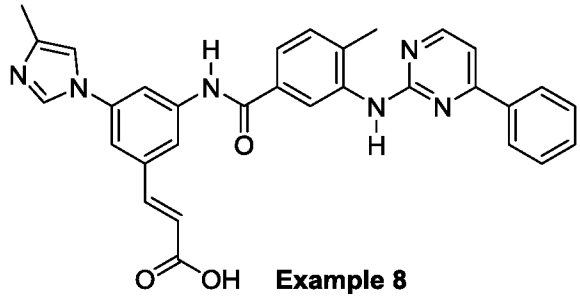

Example 8

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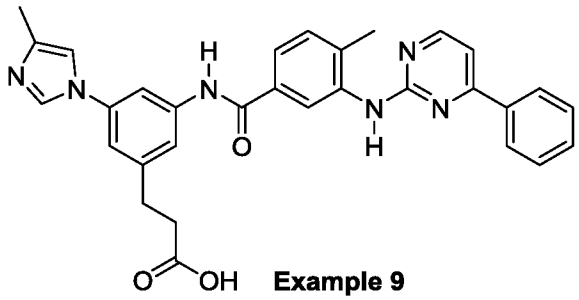

Example 9

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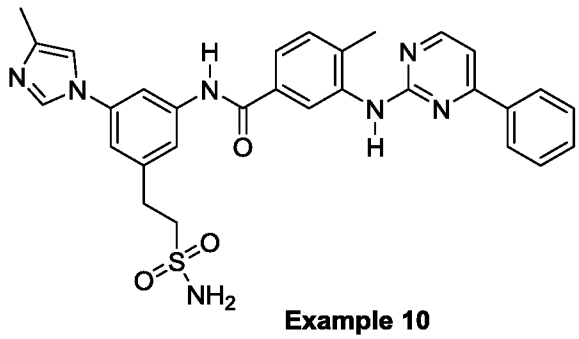

Example 10

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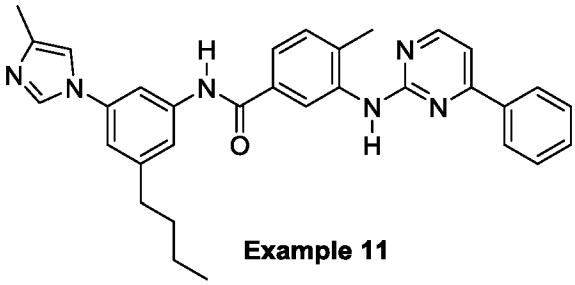

Example 11

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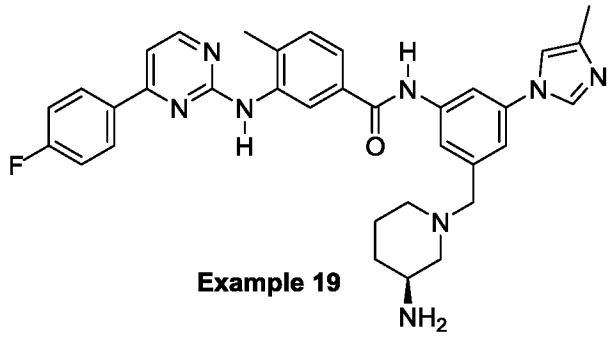
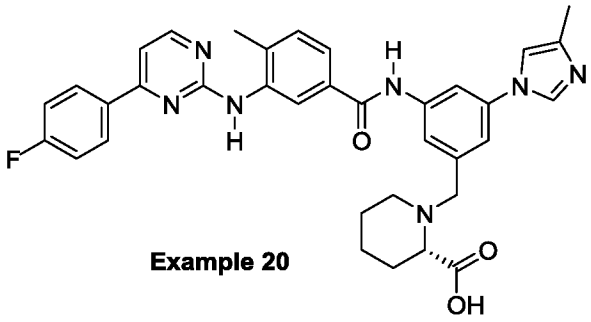
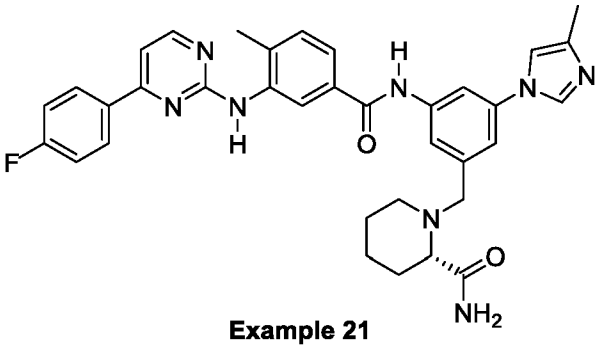


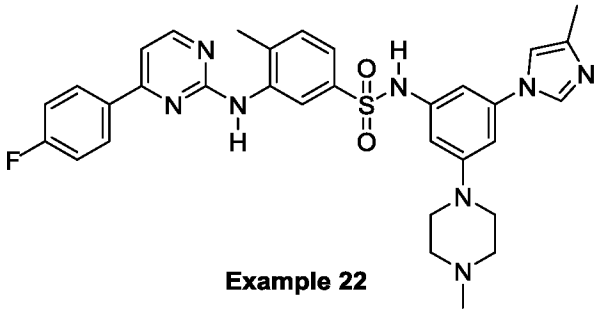
Example 19 ,



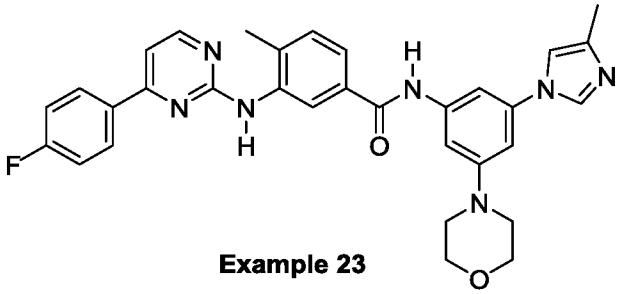
Example 20 ,



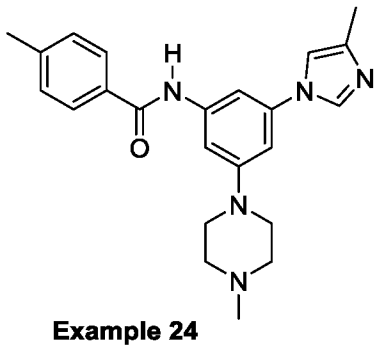
Example 21 ,



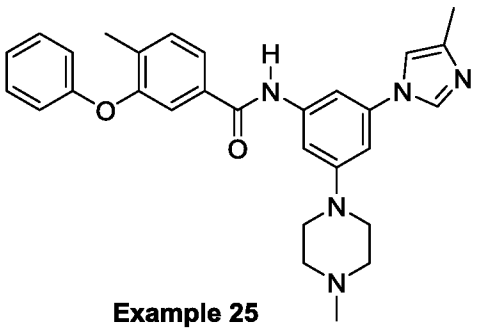
Example 22 ,



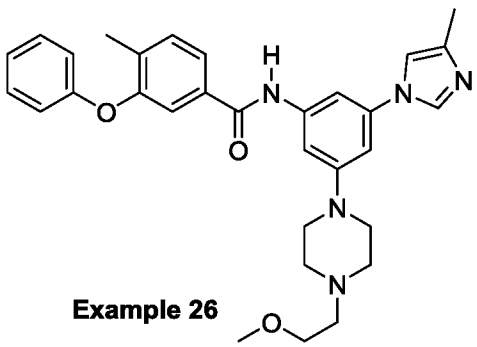
Example 23 ,



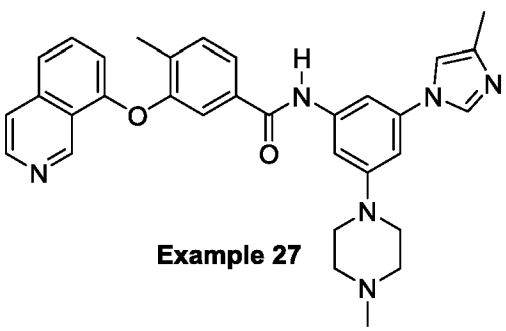
Example 24 ,



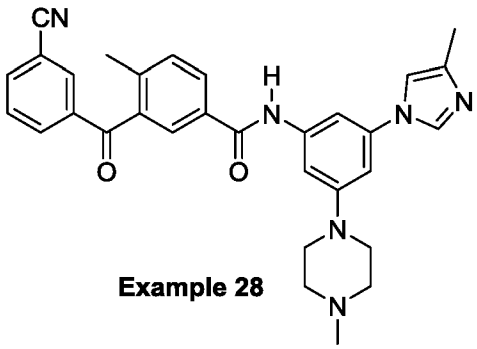
Example 25 ,



Example 26 ,



Example 27 ,



Example 28 ,

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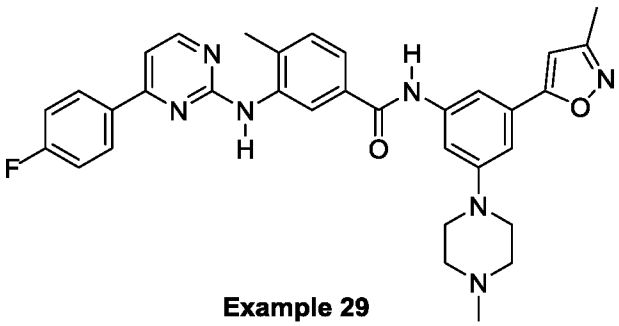
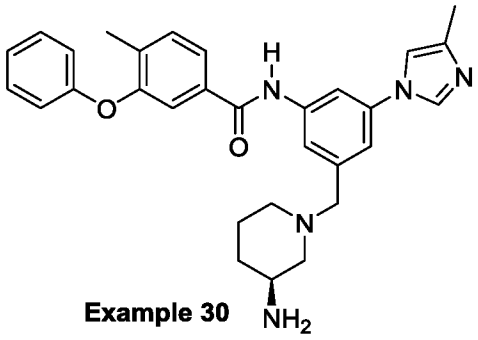
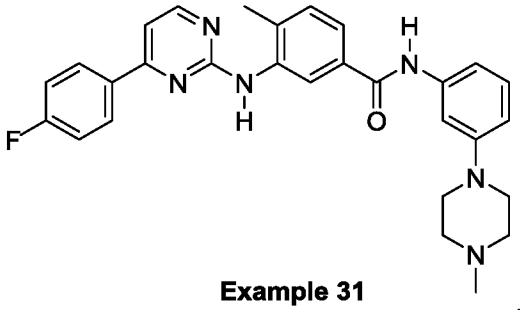


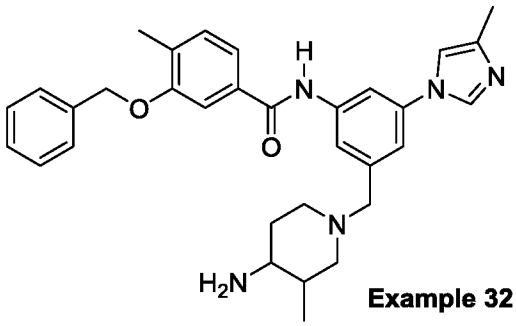
Example 29,



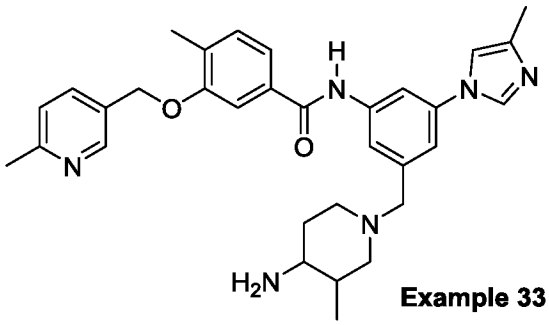
Example 30,



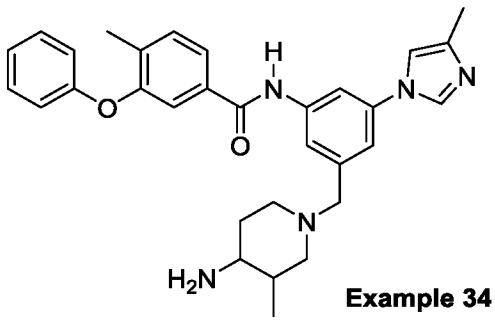
Example 31,



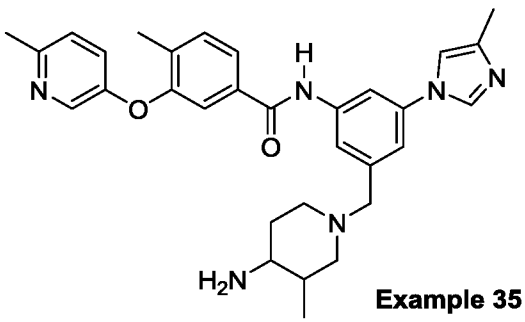
Example 32,



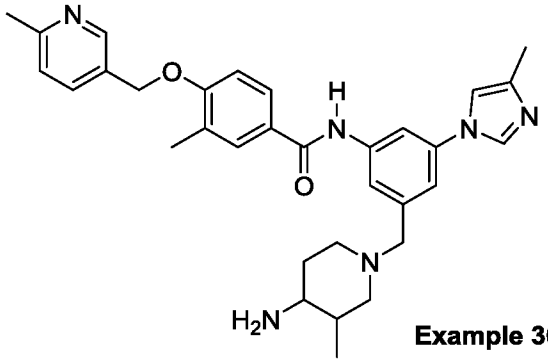
Example 33,



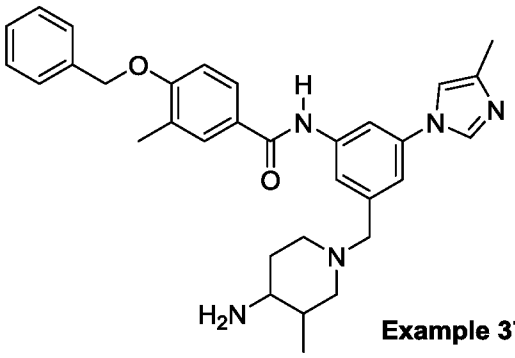
Example 34,



Example 35,



Example 36,



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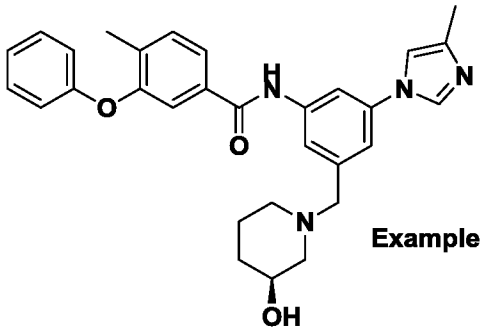

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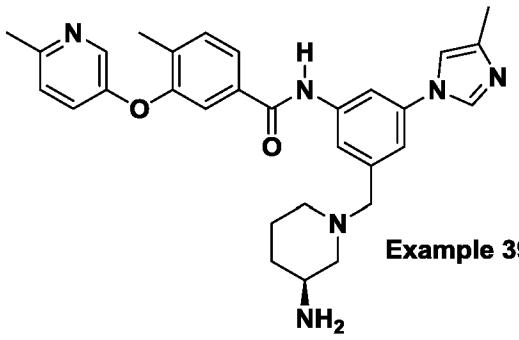

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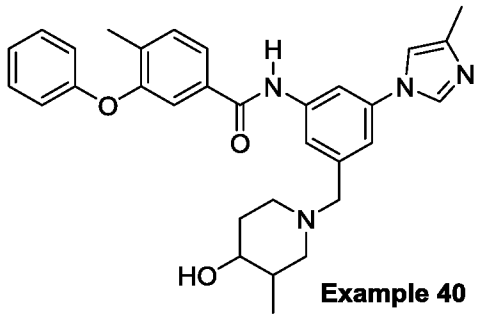

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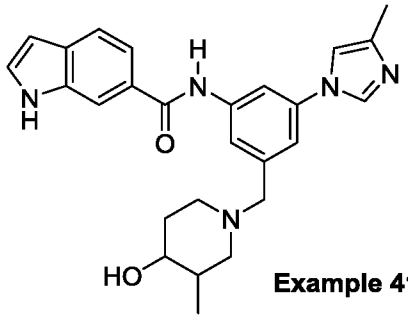

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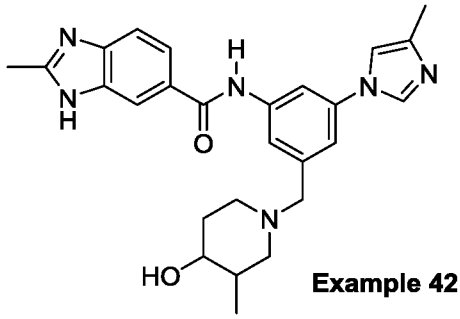

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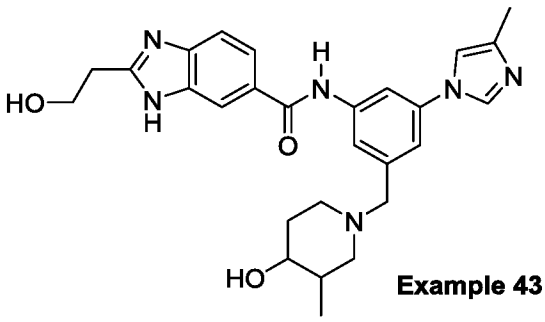

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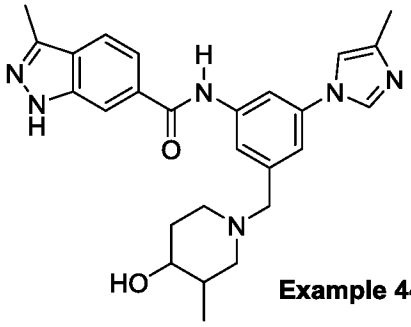

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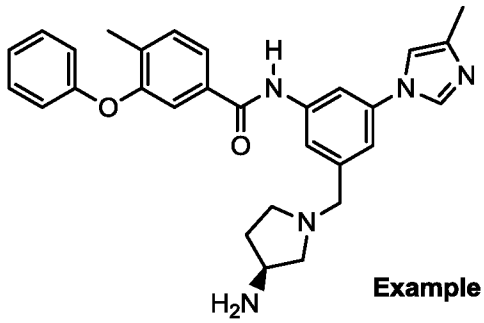
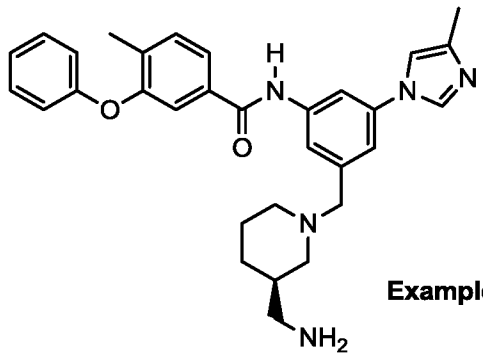
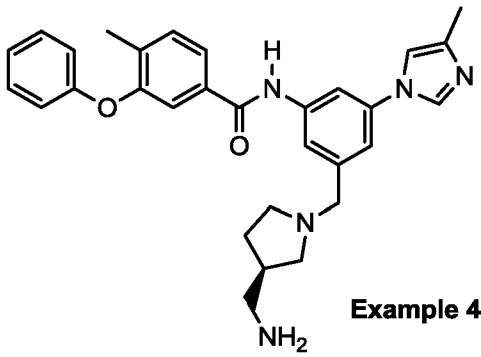


Example 45 ,



Example 46 ,



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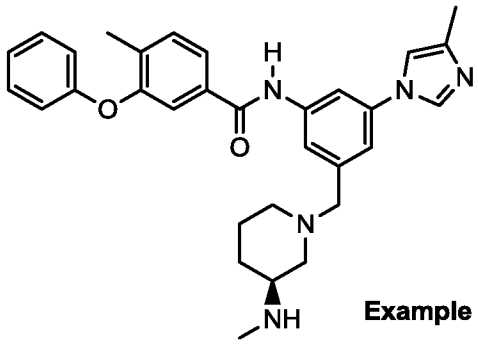

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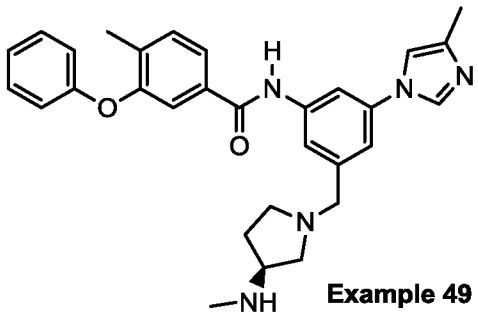

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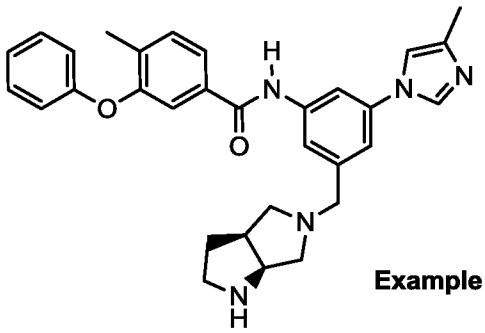

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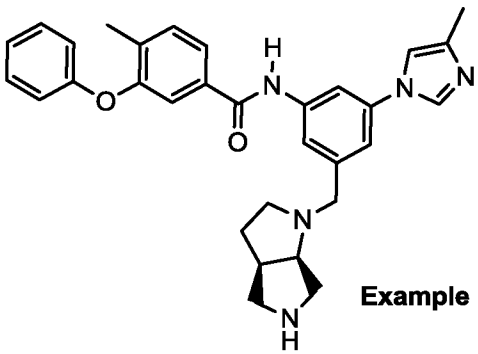
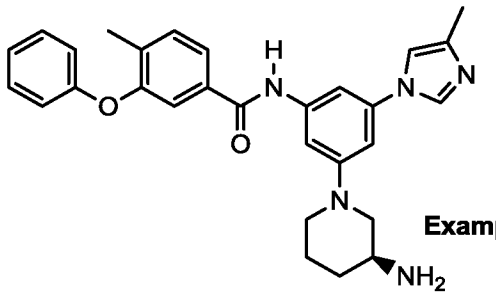


Example 51 ,



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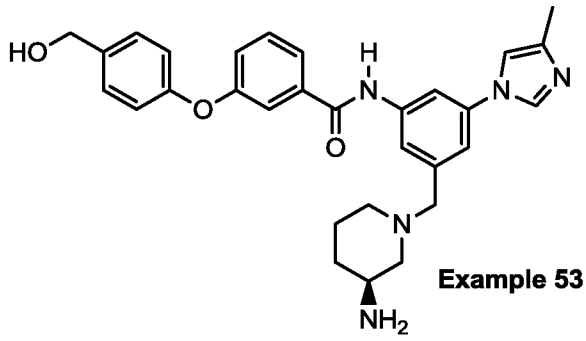

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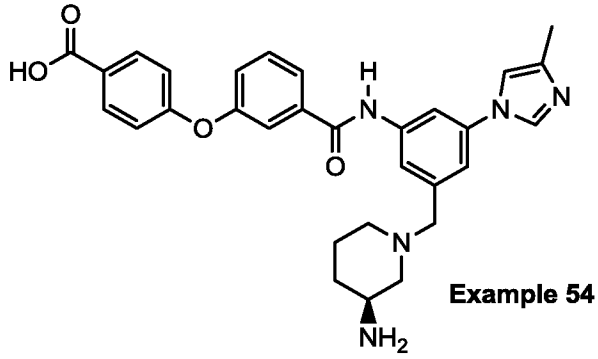
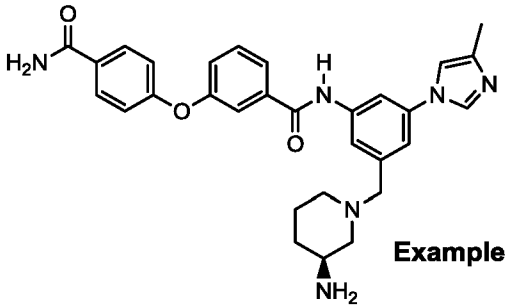


Example 54 ,



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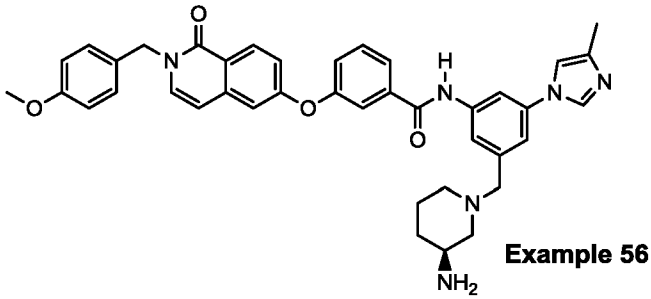
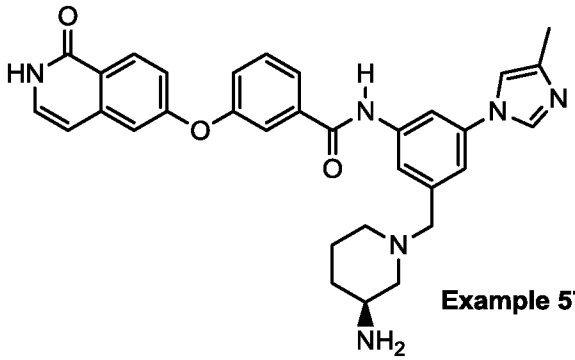


Example 56 ,



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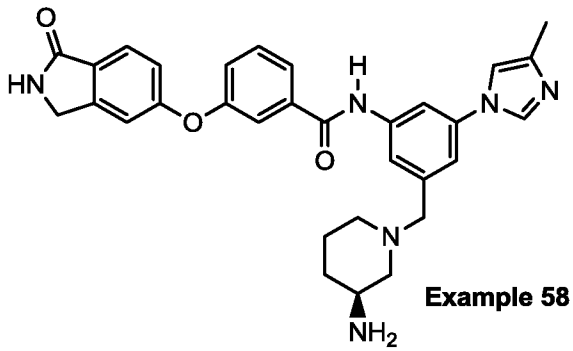
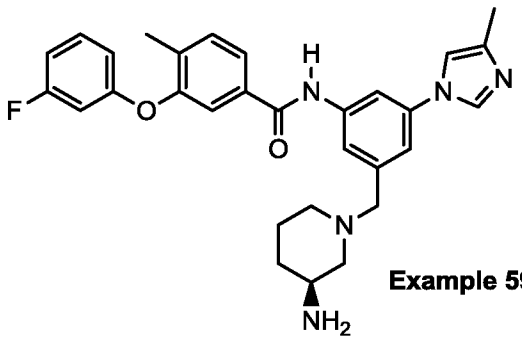
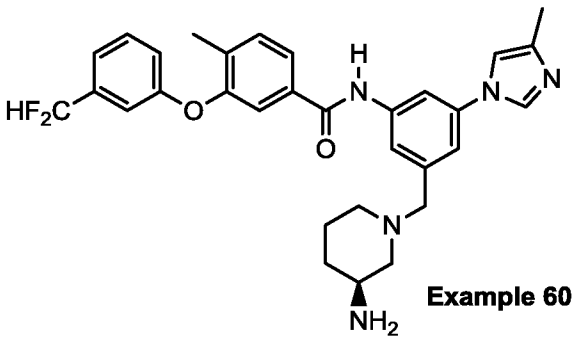


Example 58 ,



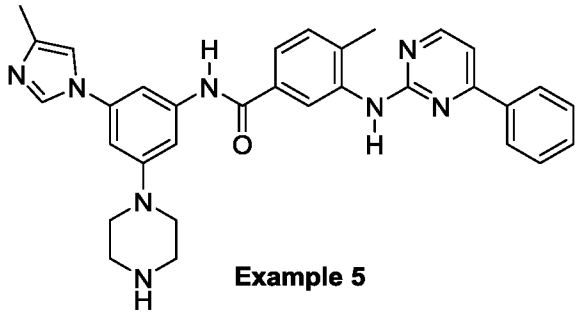
Example 59 , and



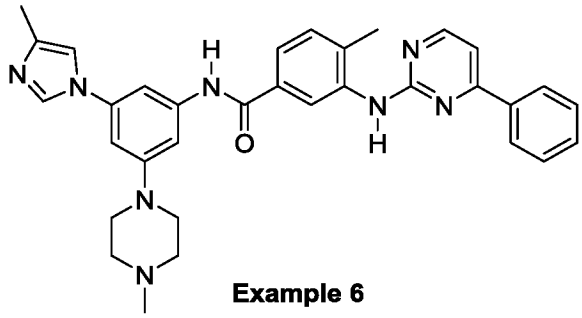
Example 60 .

or a salt, solvate, prodrug or polymorph thereof.

36. A compound selected from the group consisting of:



Example 5 ,



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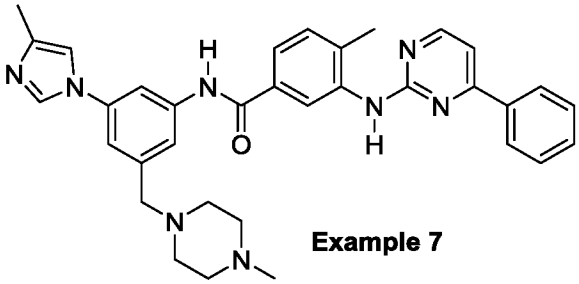
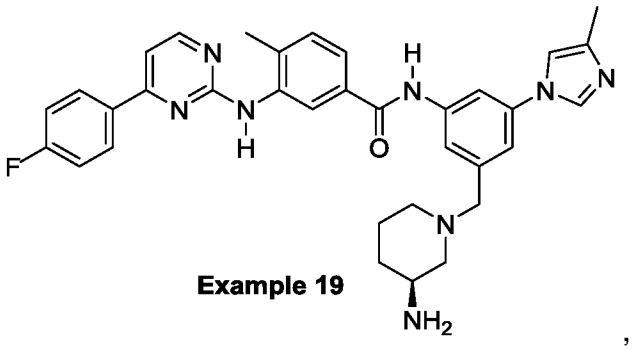
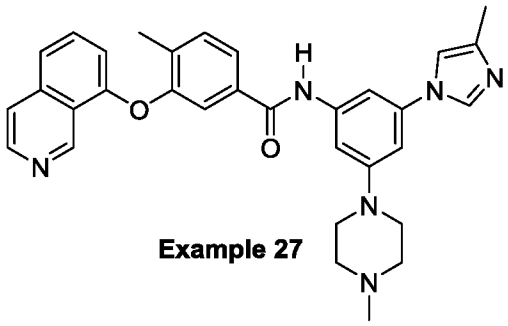


Example 7 ,

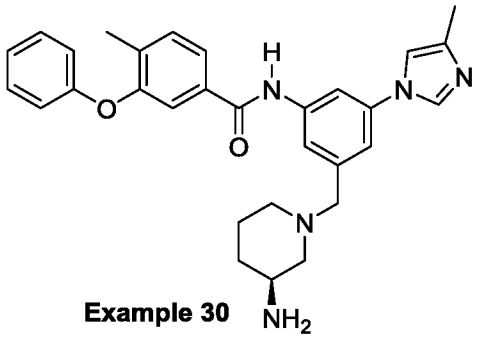


Example 19 ,



Example 27

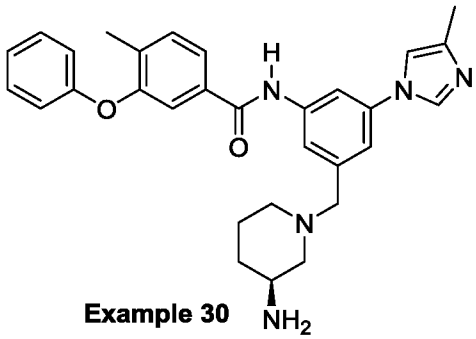
and



Example 30 ,

or a salt, solvate, prodrug or polymorph thereof.

37. The compound:



Example 30

or a salt, solvate, prodrug or polymorph thereof.

38. A compound according to claim 1 or a salt, solvate, prodrug or polymorph thereof, wherein A is selected to interact with Ser221 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

39. A compound according to claim 1 or claim 38 or a salt, solvate, prodrug or polymorph thereof, wherein Q is selected to interact with the Asp212 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

40. A compound according to any one of claims 1, 38 and 39 or a salt, solvate, prodrug or polymorph thereof, wherein Q is selected to interact with the Lys223 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

41. A compound according to any one of claims 1 and 38 to 40 or a salt, solvate, prodrug or polymorph thereof, wherein D is selected to interact with the Lys258 of a PCSK9 protein having an amino acid sequence shown in SEQ ID No 1.

42. A composition comprising a compound according to any one of claims 1 to 41 or a salt, solvate, prodrug or polymorph thereof, and a pharmaceutically acceptable excipient.

43. A composition comprising:

- a compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; and

- a statin.

44. A method for inhibiting PCSK9 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43.

45. A method for reducing LDL in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43.

46. A method for treating a disease or condition in a subject in need thereof, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43.

47. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, in the preparation of a medicament for the inhibition PCSK9 in a subject.

48. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, in the preparation of a medicament for reducing LDL in a subject.

49. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, in the preparation of a medicament for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

50. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, for inhibiting PCSK9.

51. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, for reducing LDL in a subject.

52. Use of a compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease,

cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

53. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, for use in inhibiting PCSK9.

54. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, or prodrug thereof; or a composition according to claim 42 or claim 43, for use in reducing LDL in a subject.

55. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, for use in the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

56. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, when used for inhibiting PCSK9.

57. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, when used for reducing LDL in a subject.

58. A compound according to any one of claims 1 to 41 or a pharmaceutically acceptable salt, solvate, prodrug or polymorph thereof; or a composition according to claim 42 or claim 43, when used for the treatment of a disease or condition in a subject, wherein the disease or condition is any one of the following: cardiovascular disease, cerebrovascular disease, atherosclerosis and/or their associated diseases or their symptoms.

59. A method, use or compound according to any one of claims 44 to 58, wherein the disease or condition is selected from any one of the following: stroke, heart attack, coronary artery disease and/or hypercholesterolemia.

60. A method, use or compound according to claim 59, wherein the disease or condition is hypercholesterolemia.

61. A method of preventing the protein-protein interaction between LDLR and PCSK9, the method comprising administering a compound according to any one of claims 1 to 41 or a composition according to claim 42 or claim 43 to a subject in need thereof.

62. A method, use or compound according to any one of claims 44 to 61, wherein the subject is human.

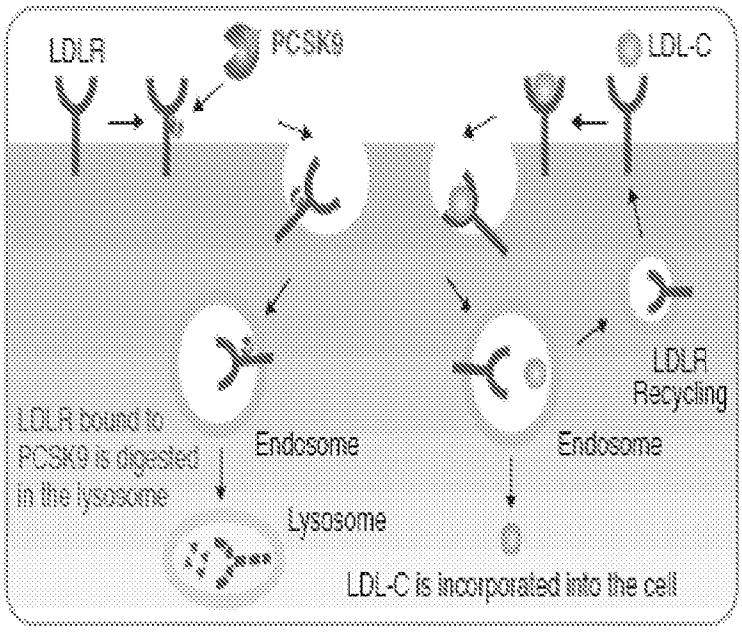


Figure 1

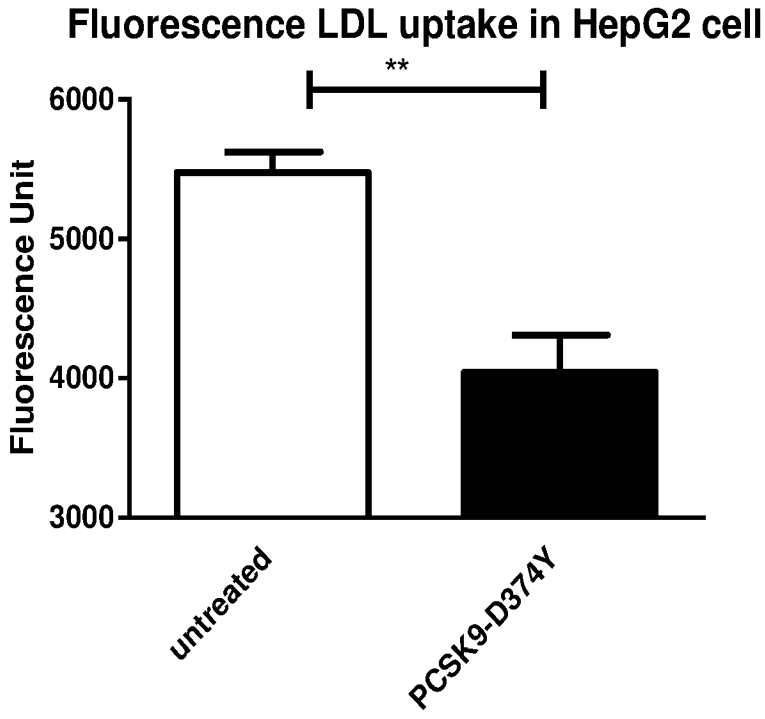


Figure 2

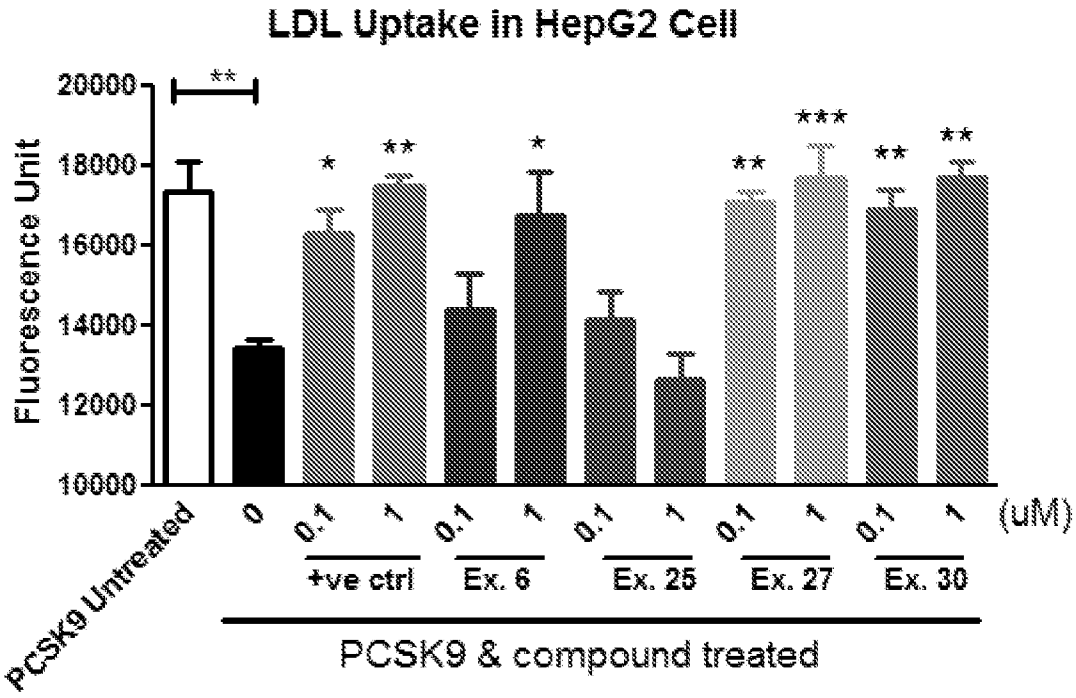

LDL Uptake in HepG2 Cell
Fluorescence Unit
20000
18000
16000
14000
12000
10000
**
*
**
*
**
***
**
**
PCSK9 Untreated
0
0.1
1
0.1
1
0.1
1
0.1
1
0.1
1
(uM)
+ve ctrl
Ex. 6
Ex. 25
Ex. 27
Ex. 30
PCSK9 & compound treated

Figure 3

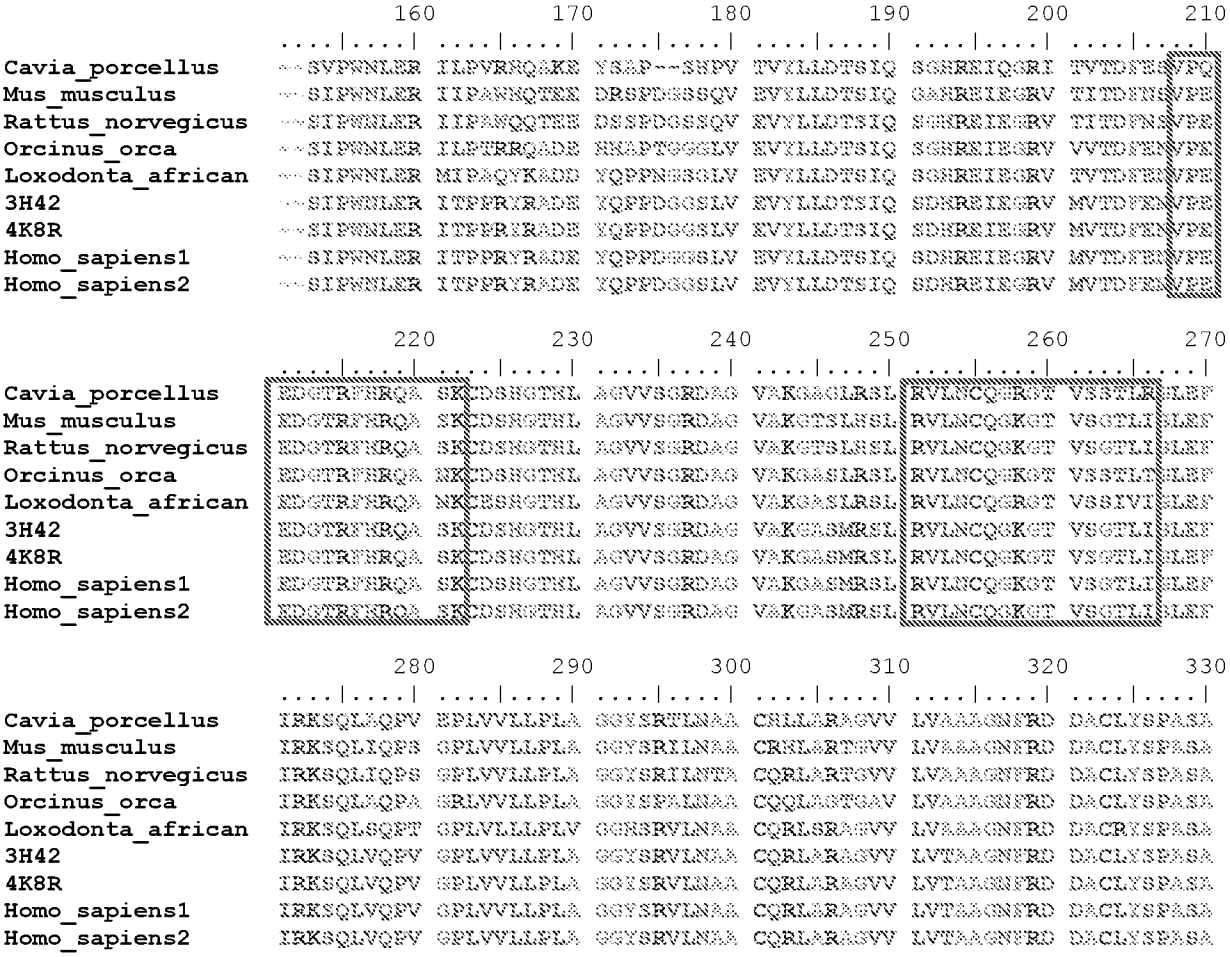

160 170 180 190 200 210
Cavia_porcellus
Mus_musculus
Rattus_norvegicus
Orcinus_orca
Loxodonta_african
3H42
4K8R
Homo_sapiens1
Homo_sapiens2
220 230 240 250 260 270
280 290 300 310 320 330

Figure 4a

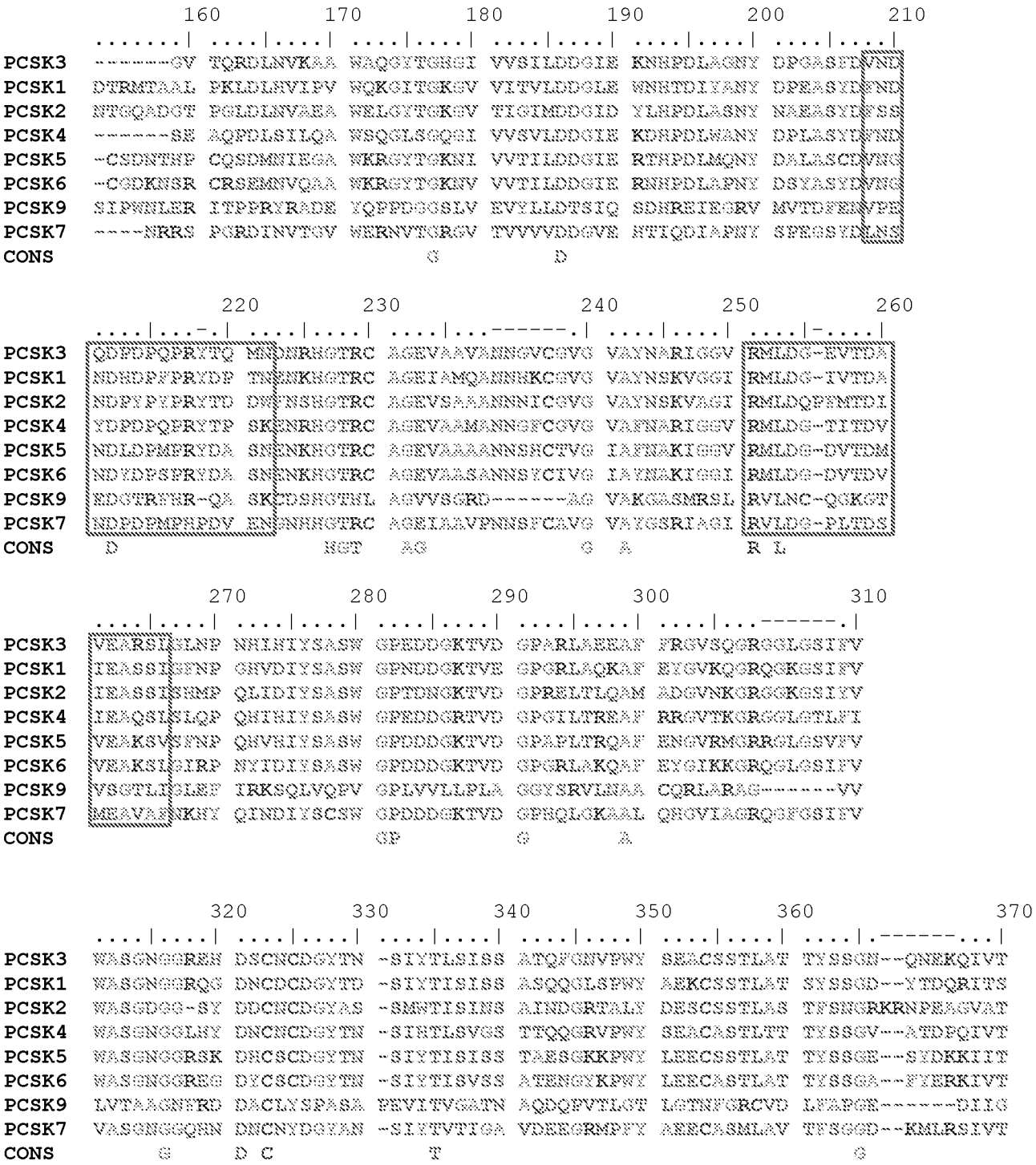


Figure 4b

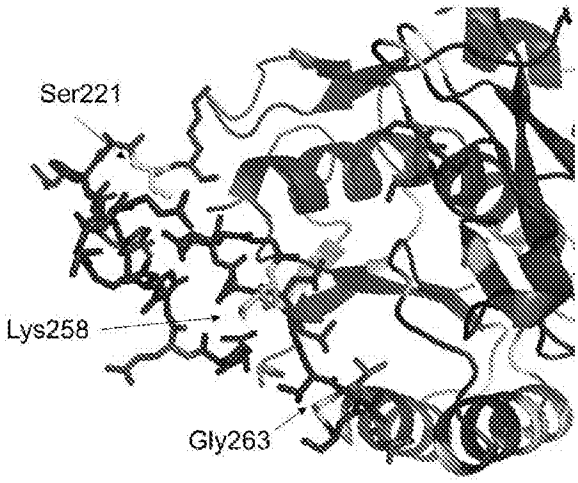


Figure 4c

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2018/050243

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

STN REGISTRY, CAPLUS: Structure search based on formula (I), molecular formula search for example 31, claim 35.

ESPACENET: Keyword search using Applicant and inventor names, "PCSK9", "LDLR" etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2018	20 April 2018

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
Email address: pct@ipaustralia.gov.au

Authorised officer

Richard Cordiner
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. +61262832162

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2018/050243**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/075869 A1 (EUROPEAN MOLECULAR BIOLOGY LABORATORY (EMBL) et al.) 08 July 2010 Abstract; Table 2A, pages 42-45; Table 7, pages 51-59; page 23, line 17 – page 27, line 30 and page 33, line 33 – page 36, line 11; page 7, line 9.	1, 38-43, 46, 49, 52-55, 58-60, 62
X	CN 101747330 A (Guangzhou Institute of Biomedicine and Health) 23 June 2010 Abstract; paragraphs [0234], [0262], [0346], [0367], [0374], [0381], [0388], and [0416], paragraphs [0138]-[0139].	1-6, 34, 38-43, 53-55, 59-60, 62
X	PONCET-MONTAGNE, G. et al, "Observed bromodomain flexibility reveals histone peptide- and small molecule ligand-compatible forms of ATAD2." Biochemical Journal, 2015, 466, 337-346. Abstract; Third paragraph, right-hand column, page 339.	1, 38-41, 53-55, 59-60, 62
X	WANG, D. et al, "Hybrid compounds as new Bcr/Abl inhibitors." Bioorganic & Medicinal Chemistry Letters, 2011, 21, 1965–1968. Abstract; Compounds 4g-4i, Table 1.	1-6, 34, 38-42, 53-55, 59-60, 62
X	DUVEAU, D. et al, "Synthesis and biological evaluation of analogues of the kinase inhibitor nilotinib as Abl and Kit inhibitors." Bioorganic & Medicinal Chemistry Letters, 2013, 23, 682–686. Abstract; Compound 2c, Scheme 1; Tables 1 and 2.	1-6, 8, 34, 38-42, 53-55, 59-60, 62
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Supplemental Box – IPC Marks

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C07D 403/12 (2006.01)

C07D 403/14 (2006.01)

C07D 403/14 (2006.01)

C07D 233/64 (2006.01)

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C07D 401/10 (2006.01)

C07D 403/10 (2006.01)

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C07D 261/08 (2006.01)

C07D 487/04 (2006.01)

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A61K 31/506 (2006.01)

A61K 31/4174 (2006.01)

A61K 31/454 (2006.01)

A61P 9/00 (2006.01)

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2018/050243**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2010/075869 A1	08 July 2010	None	
CN 101747330 A	23 June 2010	None	
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WO 2016/040305 A1	17 March 2016	None	

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.